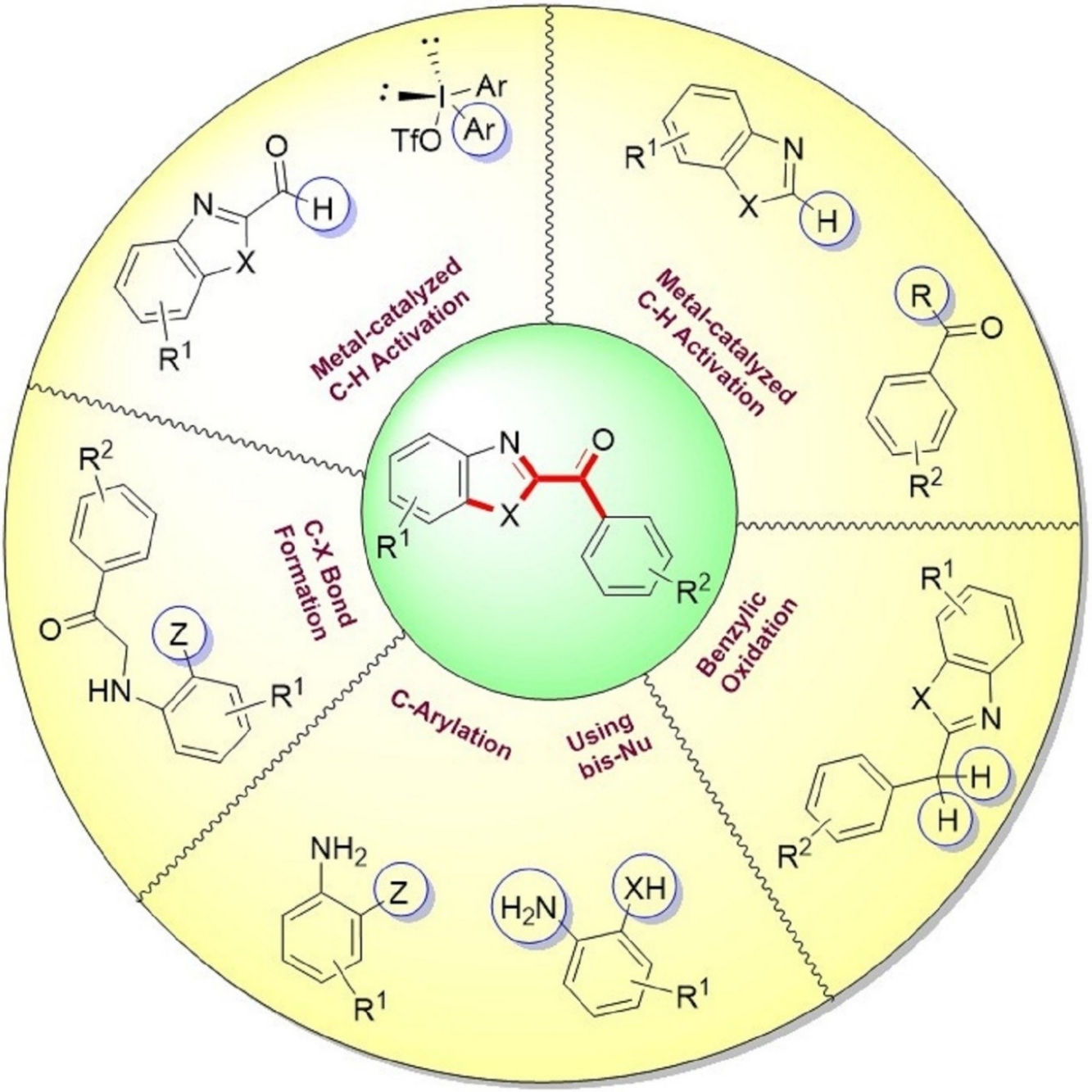
Strategies towards the Synthesis of 2-Ketoaryl Azole Derivatives using C-H Functionalization Approach and 1,2-Bis-Nucleophile Precursors

Nayyef Aljaar,*[a] Mohammad M. Ibrahim,[b] Eyad A. Younes,[a] Mousa Al-Noaimi,[a, c] Kayed A. Abu-Safieh,[a] Basem F. Ali,[b] Kamal Kant,[d] Nabil Al-Zaqri,[e] Ragini Sengupta,[f] and Chandi C. Malakar*[d]



Abstract: A spectrum of compounds attached to 2-keto aryl azole moieties are found as pivotal building blocks in medicinal chemistry and drug discovery. This is why, the collection of novel methods have been described for the synthesis of these compounds, which are of great significance among organic chemists interested towards the development of new synthetic methods in the fields of natural products, bioactive molecules and materials sciences. This review presents the important breakthrough achieved during last decade towards improvement of approaches for the synthesis of these molecules.

1. Introduction

Heterocyclic scaffolds represent as adequate building blocks and relevant structural motifs in many pharmaceutical and agro-chemical industries, and more than 60% of drug molecules contain heterocyclic building blocks.[1a] Benzothiazoles are significant classes of heterocyclic units that are found in many synthetic intermediates, natural products and biologically active compounds.[2] Among them, 2-keto aryl benzothiazoles are an important category of benzothiazole scaffolds with a wide range of biological activities such as antitumor,[3] antidiabetic,[4] antiviral,[5] inhibitors of fatty acid amide hydrolase **1**,[6] inhibitors of the antiapoptotic Bcl-2 protein 2, which inhibits cell growth and induces apoptosis in human breast and prostate cancer cell lines (Figure 1, compound **2**),[7] antiviral agents **3**,[8] inhibitors of hepatic CYP enzymes, metabolic stability, inhibition of marmoset 17β-HSD1 and 17β-HSD2 **4**,[9] potent inhibitors of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) **5**[10] (Figure 1). The imidazole rings form the vital unit in a large plethora of significant molecules, including natural products, pharmaceutical compounds and fluorescent ligands. Representative examples include antimicrobial activity,[11] antihypertensive,[12] anticancer,[13] antibroncospastic,[14] analgesic,[15] antiallergic,[16] antithrombotic[17] and as potent receptor of tyrosine kinase inhibitors.[18] A sub-group of this family is 2-keto aryl benzimidazoles that show neuroprotective and anxiolytic activity,[19] the AMG 580 [1-(4-(3-(4-(1*H*-benzo[*d*]imidazole-2-carbonyl)phenoxy)pyrazin-2-yl)piperidin-1-yl)-2-fluoropropan-1-one], a novel, and selective small-molecule antagonist with sub-nanomolar affinity for rat, primate and human PDE10 A[20] and as protective action on tissue-culture cells infected with types 1, 2, 3 poliovirus.[21] Moreover, the 2-benzoylbenzoxazoles are prevalent as biological and pharmaceutical compounds.[22] Representative examples include the fatty acid amide hydrolase inhibitor[23] and anti-proliferative activity.[24] Motivated by their importance, the synthesis of 2-keto aryl substituted (imida)(ox)thiazoles is of great interest in medicinal chemistry and drug discovery research. During the past decade, a large number of synthetic routes are described for the preparation of these compounds; nevertheless, no review article has been published yet, which summarizes all the established methods associated to the synthesis of these skeletons so far. This review highlights on the significant synthetic contributions to these heterocyclic systems.[1b]

[a] *Dr. N. Aljaar, Dr. E. A. Younes, Dr. M. Al-Noaimi, Dr. K. A. Abu-Safieh*
Department of Chemistry, Faculty of Science,
The Hashemite University, P.O. Box 330127, Zarqa 13133 (Jordan)
E-mail: nayyef@hu.edu.jo
[b] *Dr. M. M. Ibrahim, Dr. B. F. Ali*
Department of Chemistry, Faculty of Science,
Al al-Bayt University, Al-Mafraq 25113 (Jordan)
[c] *Dr. M. Al-Noaimi*
Department of Chemistry, Faculty of Science,
Kuwait University, P.O. Box 5969, Safat, 13060 (Kuwait)
[d] *K. Kant, Dr. C. C. Malakar*
Department of Chemistry
National Institute of Technology Manipur
Imphal – 795004, Manipur (India)
E-mail: chdeepm@gmail.com
cmalakar@nitmanipur.ac.in
[e] *Dr. N. Al-Zaqri*
Department of Chemistry, College of Science,
King Saud University, P.O. Box 2455, Riyadh, 11451 (Saudi Arabia)
[f] *R. Sengupta*
Institute for Photon Science and Synchrotron Radiation (IPS),
Karlsruhe Institute of Technology (KIT)
Hermann-von-Helmholtz-Platz 1,
76344 Eggenstein-Leopoldshafen (Germany)

2. Synthesis of 2-keto aryl thiazoles

Due to the great importance of annulated benzothiazoles, the synthesis of these scaffolds have been attempted by many researchers during past decades, and a number of protocols have been established for the efficient synthesis of these compounds. In contradiction of the synthesis of 2-substituted benzothiazoles, only limited number of procedures are reported towards the preparation of 2-keto aryl substituted benzothiazole derivatives. In this section, we have demonstrated the synthetic protocols for these compounds.

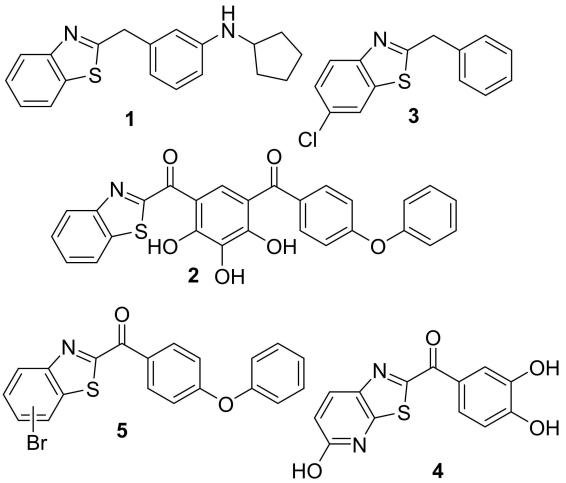
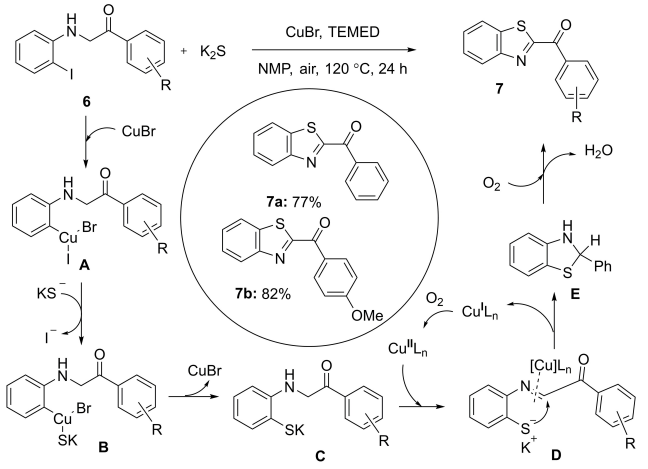


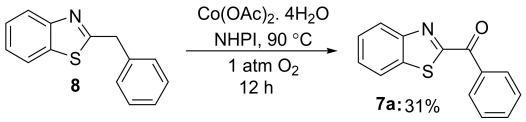
Figure 1. Biologically active 2-ketobenzothiazoles.

Liang and co-workers described the synthesis of 2-acylbenzothiazoles **7**. According to the reported method, the reaction was proceeded by coupling of benzyl substituted 2-iodoanilines **6** and potassium sulfide in the presence of 20 mol% of CuBr as catalyst, 40 mol% TEMED under aerial conditions using NMP as solvent at 120 °C for 24 h (Scheme 1).[25] The developed method employed CuBr as catalysts, both for traditional cross-coupling reaction and for oxidative cross-coupling reaction, and molecular oxygen was found to act not only as an oxidant, but also as an initiator to activate this catalytic process.

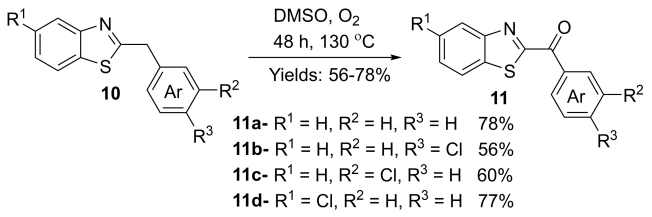
The corresponding 2-aroylbenzothiazoles **7 a** can be prepared from the oxygenation of heteroarenes **8** using a combination of cobalt(II)/*N*-hydroxypthalimide catalyst system, BuOAc as base and molecular oxygen as an oxidant. The radical reaction pathway tolerates electronically diverse benzylic C–H bonds and developed reaction conditions (1.0 mmol substrate in BuOAc or EtOAc as solvent, 90–100 °C for 12 h). The described method has been extended for gram-scale synthesis (Scheme 2).[26]



Scheme 1. CuBr-Catalyzed double C–S bond formation for the synthesis of 2-acylbenzothiazoles **7** from *N*-benzyl-2-iodoaniline **6** and K_2S.



Scheme 2. Synthesis of 2-benzoylbenzothiazole **7 a** from 2-benzylbenzo[*d*]thiazole **8**.



Scheme 3. Synthesis of 2-aroyl benzothiazoles **11** from the oxidation of 2-benzyl-1*H*-benzo[*d*]thiazoles **10**.

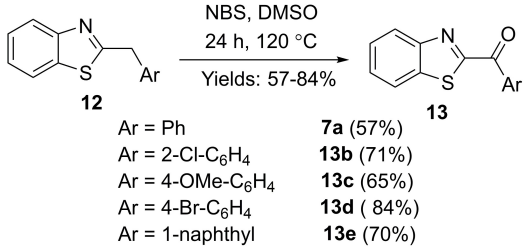
A similar but more sustainable approach towards the synthesis of 2-aroybenzothiazoles **11** could be achieved by oxidation of 2-benzyl-1*H*-benzo[*d*]thiazoles **10** using DMSO and O_2 as the terminal oxidant. This transformation represents a concise, simple and green route for the synthesis of N-heterocyclic ketones in absence of metals and additives (Scheme 3).[27]

Analogous method for the synthesis of 2-aroylbenzothiazoles **13** in moderate yield has been introduced by the selective metal-free oxidation of aryl/heteroarylmethanes **12**. The preparation of 2-aroylbenzothiazoles **13** is carried out in the presence of catalytic amounts of NBS in DMSO as solvent. In this method, the metal-free halogen based reagent (NBS) is employed as an efficient organocatalyst for developing this organic transformation (Scheme 4).[28]

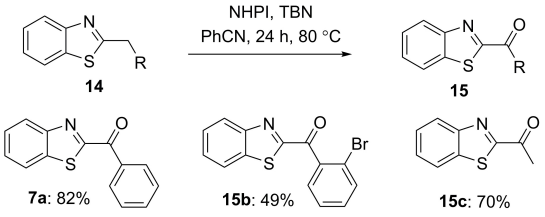
The identical approach was also found suitable for the preparation of Benzo[*d*]thiazol-2-yl(phenyl)methanone **15** from alkyl or aryl heteroarenes **14** under relatively mild conditions with moderate to high yields. This reaction affords a powerful method for overcoming the electron withdrawing effect as well as product-inhibition effects in heterobenzylic radical oxidation process (Scheme 5).[29]

Another protocol has been described for the synthesis of benzothiazoles-2-carboxaldehydes **17** starting from the oxidation of 2-methylbenzothiazoles **16** using oxygen, fluorescent lamp, TFA and iodine in ethyl acetate at 70 °C. This is the first protocol for catalytic oxidation of a methyl group attached to a heteroaromatic scaffold to form the corresponding aldehydes via homolytic cleavage of C–I bond caused by irradiation with visible light (Scheme 6).[30]

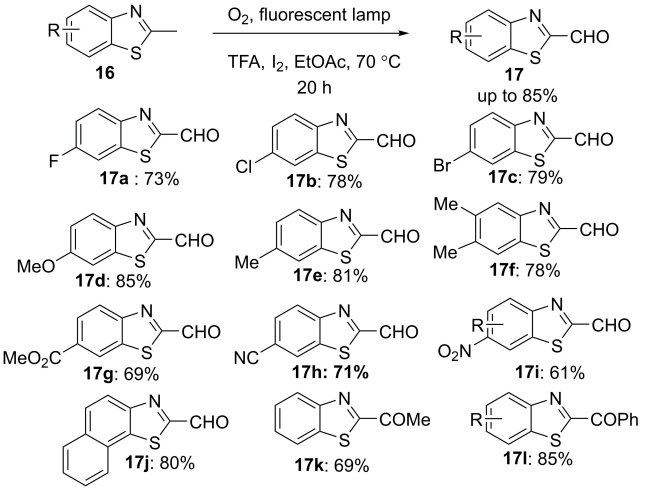
Pan and co-workers reported a successful synthesis of 2-substitutedbenzothiazoles **19** in 2019.[31] Their approach depends on the formation of *N*-formyl-2-benzoylbenzothiazolines **19** from *N*-phenacylbenzothiazolium bromides **18** in the



Scheme 4. Synthesis of 2-aroyl benzothiazoles **13** from the oxidation of aryl/heteroarylmethanes **12**.



Scheme 5. Benzo[*d*]thiazol-2-yl(phenyl)methanone **15** from alkyl or aryl hetroarenes **14**.



Scheme 6. Synthesis of benzothiazoles-2-carboxaldehydes **17** from 2-methylbenzothiazoles **16**.

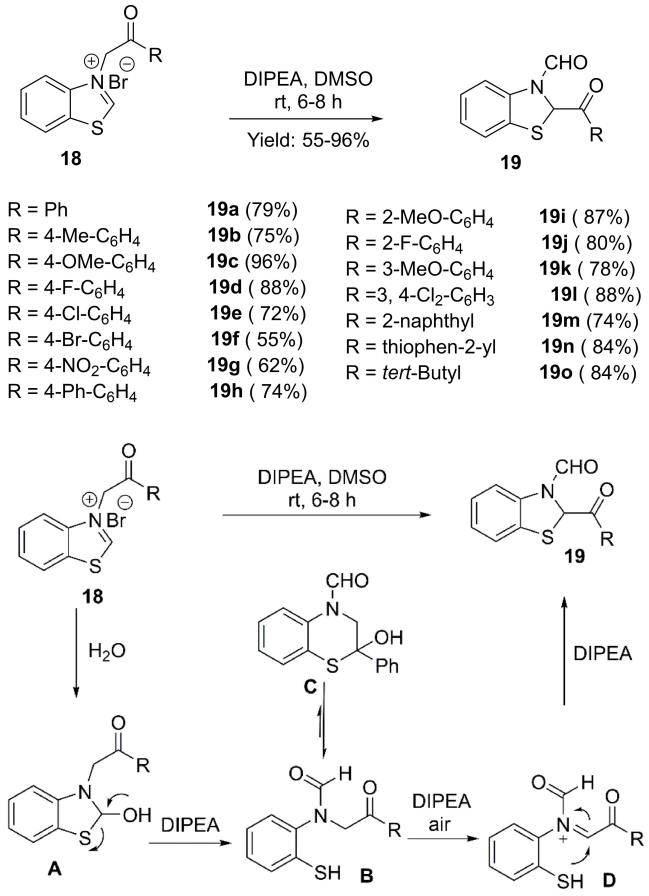
presence of DIPEA as a base in DMSO as solvent. Initially, substrate **18** hydrolyse to give **A** which generates **B** under basic conditions. In presence of air, an uncommon type of imine **D** was encountered, finally imine **D** cyclize to give desired product **19** (Scheme 7a). This report delineates an unusual aerobic hydrolysis-cascade reaction for the first reported synthesis of *N*-formyl-2-benzoyl benzothiazolines **19** (Scheme 7).[32]

A variety of synthetic procedures towards the preparation of 2-keto aryl benzothiazoles were described based on the functionalization of benzothiazoles. In this regard, Thames et al. established a suitable approach for the synthesis of 2-benzoylthiazoyl phenyl ketones **23** with high yield from the reaction of 2-trimethylsilylbenzothiazoles **21** and benzoyl chloride **22**. The substrate **21** was prepared by the reaction of n-butyllithium and benzothiazole **20** followed by the addition of trimethylchlorosilane at 75 °C (Scheme 8).[32a,b]

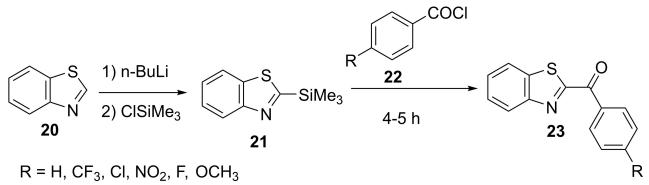
Similar approach for the preparation of 2-substituted keto aryl benzothiazole **27** moieties from 2-bromobenzothiazoles (**24**) in two steps has been shown by Kim et al. It was realized by the reaction between **24** and active zinc at room temperature in THF to afford the intermediate 2-benzothiazoleylzinc bromide **25**. Then, the reaction of intermediate **25** with acid chlorides **26** using CuI and LiCl to lead to the final product **27** (Scheme 9).[33]

A general and efficient synthesis of aroylated benzothiazoles **30** has been accomplished starting from (benzo)thiazoles **28** and acid chlorides **29** in the presence of catalytic amounts of DMAP in CH_3CN at 80 °C (Scheme 10). The established novel DMAP-mediated Regel-type direct C-2 aroylation of various 1,3-(benzo)thiazoles with a wide panel of aroyl chlorides has been employed. This general and efficient methodology allows the metal-free preparation of valuable diheteroaryl ketones, which are found in natural products and pharmaceuticals active compounds.[34]

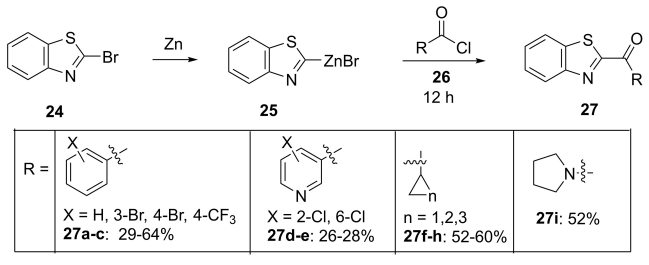
Another protocol for the synthesis of 2-benzoylbenzothiazole (**32**) with good yield was realized by irradiation of benzothiazoles (**20**), benzoylchloride (**31**) and catalytic amounts



Scheme 7. Synthesis of *N*-formyl-2-benzoylbenzothiazolines **19** from *N*-phenacylbenzothiazolium bromides **18**. Proposed mechanism for the Synthesis of *N*-formyl-2-benzoylbenzothiazolines **19** from *N*-phenacylbenzothiazolium bromides **18** according to Pan and co-workers.



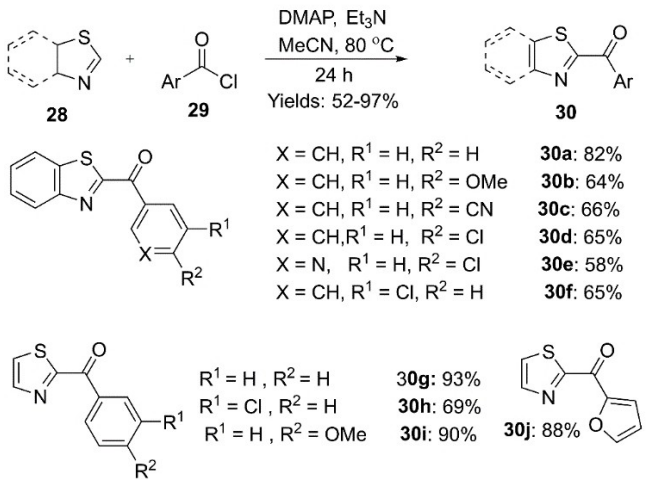
Scheme 8. Synthesis of 2-benzoylbenzothiazole **23** according to Thames and Pinkerton.



Scheme 9. Synthesis of 2-benzoylbenzothiazoles **27** according to Kim et al.

of *fac*-Ir(ppy)$_3$ in MeCN as solvent. These methods enabled the rapid synthesis of a series of Minisci-type adducts using

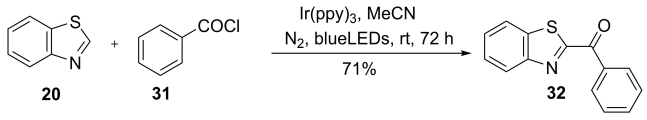
)



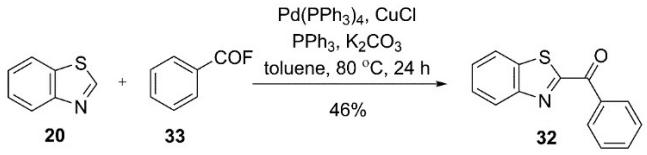
Scheme 10. Synthesis of 2-benzoylbenzothiazole **30** according to Hoarau et al.

commercially available starting materials under mild conditions (Scheme 11).[35]

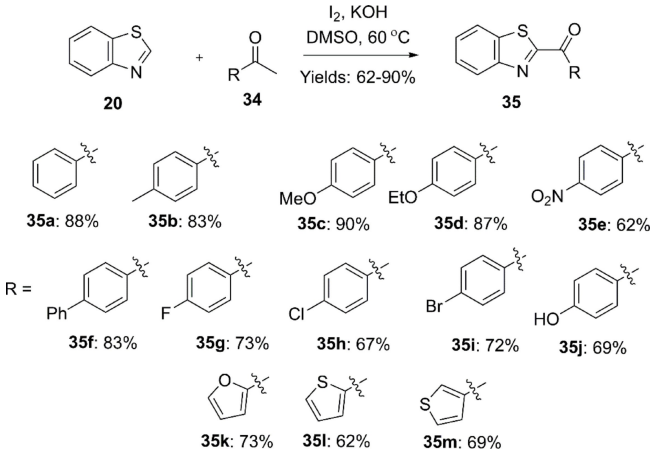
Alternative transformation available for the synthesis 2-benzoylbenzothiazole **32** was described by Sakai et al.[36]



Scheme 11. Synthesis of 2-benzoylbenzothiazole **32** according to Xu et al.



Scheme 12. Synthesis of 2-benzoylbenzothiazole **32** according to Skai. et.al.



Scheme 13. Synthesis of 2-benzoylbenzothiazole derivatives **35** according to Wu and co-workers.

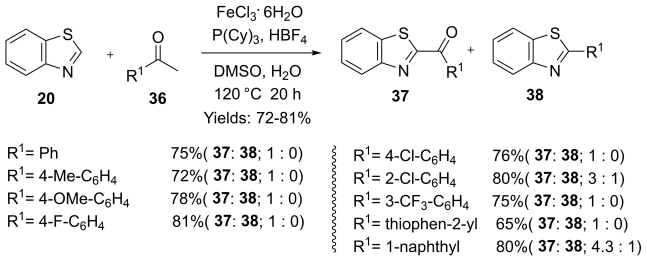
According to this development, the transformation was advanced under very mild conditions using the palladium/copper-catalyzed direct acylation of benzothiazole **20** with acyl fluoride **33**. This study represents the first example of acyl fluoride as acylating agent in C–H activation chemistry (Scheme 12).[36]

Further development for achieving 2-acyl benzoxazole derivatives **35**, refers to the I_2/KOH synergistically promoted direct ring-opening aroylation of benzothiazoles **20** using aryl ketones **34** as carbonyl sources. This protocol could provide an efficient method to synthesize 2-acylbenzathiazoles **35** through an in situ cross-trapping strategy (Scheme 13).[37]

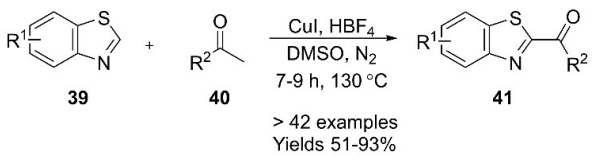
Similar and convenient procedure has been witnessed for the formation of 2-acyl benzothiazoles **37** from benzothiazoles **20** and aromatic ketones **36** catalyzed by iron salts under an atmosphere of oxygen. The solvent played an important role in this transformation and the best yield was obtained in a mixture of H_2O/DMSO as solvent. A series of functional groups were well tolerated under the established reaction conditions (Scheme 14).[38]

The transition metal-catalyzed straightforward aroylation of benzothiazoles **39** with aryl methylketones **40** has been developed for the synthesis of 2-substituted benzothiazoles **41** (Scheme 15).[39] It was proposed that under an O_2 atmosphere, the acetophenone was initially oxidized into 2-hydroxyacetophenone, via the activation of molecular oxygen by Cu(I) salt. The generated 2-hydroxyacetophenone further underwent oxidation to provide phenylglyoxal, which reacted with benzothiazoles to give the desired product.

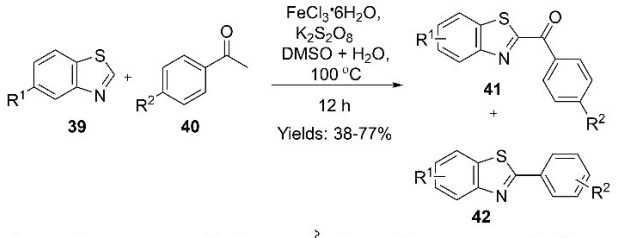
Further approaches to the synthesis 2-ketobenzothiazoles **41** have been explored by Yu and co-workers. They have developed a new procedure for the highly selective, inexpensive and non-toxic iron catalyst, which efficiently catalyzed the coupling reactions between benzothiazoles **39** and aryl ketones **40** using $K_2S_2O_8$ as an oxidant under simple conditions to yield the desired products in moderate yields (Scheme 16).[40] The use of an iron catalyst and the ratio of substrates are important for



Scheme 14. Synthesis of 2-benzoylbenzothiazole **37** and **38** according to Deng and co-workers.



Scheme 15. Synthesis of 2-benzoylbenzothiazole **41** according to Song et al.



R^1 = H, R^2 = H	70%(**42**: **41**; 1 : 3)	R^1 = H, R^2 = Cl	61%(**42**: **41**; 1 : 2)
R^1 = H, R^2 = Me	69%(**42**: **41**; 1 : 3)	R^1 = H, R^2 = Br	73%(**42**: **41**; 1 : 2)
R^1 = H, R^2 = OMe	50%(**42**: **41**; 1 : 5)	R^1 = Me, R^2 = H	75%(**42**: **41**; 1 : 3)
R^1 = H, R^2 = F	63%(**42: 41**; 1 : 3)	R^1 = OMe, R^2 = H	38%(**42**: **41**; 1 : 1.5)
		R^1 = Cl, R^2 = H	77%(**42**: **41**; 1 : 2)

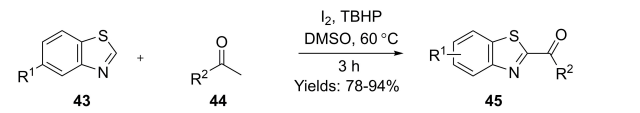
Scheme 16. Synthesis of 2-benzoylbenzothiazole **41** and **42** according to Yu and co-workers.

this conversion, and this reaction is subtle to the electronic effects of the substituents.

Similar procedure for the synthesis of 2-acylbenzothiazoles **45** has been described using aryl ketones **43** and benzothiazoles **44** in the presence of I_2 and TBHP. Acylation of the benzothiazoles is done through a series of consecutive reactions involving oxidation of aryl ketone to aryl glyoxal, ring opening of the benzothiazole followed by condensation of the amino group with the aryl glyoxal, cyclization and oxidation process. The developed route avoids the use of metals and toxic solvents (Scheme 17).[41]

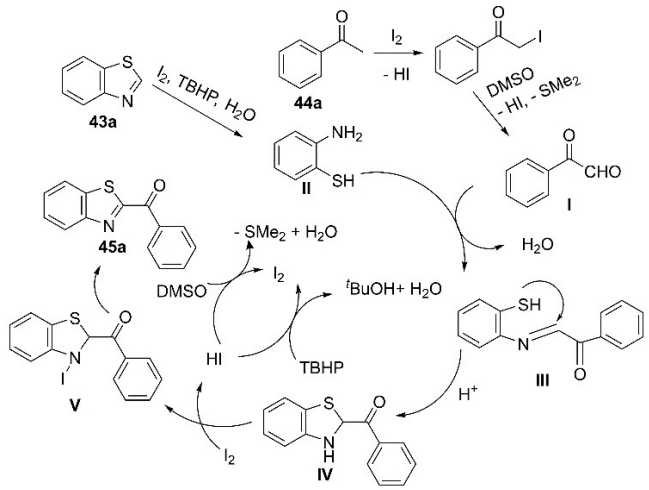
The proposed transformation begins by the conversion of acetophenone **44 a** into phenylglyoxal **I** using I_2 in DMSO as solvent via Kornblum oxidation process.[42] In this process, the byproduct HI can be oxidized using DMSO or TBHP to reproduce I_2.[43] Then, the ring opening reaction of benzothiazoles **43 a** can be realized in the presence of I_2, TBHP and water to give the 2-aminobenzenethiol **II**. Next, the condensation reaction of intermediate **I** and **II** produces imine intermediate **III** and the intermediate **IV** is produced by an intramolecular addition reaction. A subsequent substitution reaction between **IV** and I_2 produces intermediate **V**, which followed by elimination reaction generates the product **45 a** (Scheme 18).

Related procedure for the synthesis of 2-acyl benzothiazoles **48** was acheived by Weng and co-workers. They divulged a procedure for the straightforward acylation of benzothiazoles **46** with aryl aldehydes and aliphatic aldehydes **47** in DMSO as



R^1 = H, R^2 = Ph	**45a**: 85%	R^1 = 5-Cl, R^2 = 3-Br-C_6H_4	**45j**: 81%
R^1 = H, R^2 = 2-naphthyl	**45b**: 92%	R^1 = 5-Cl, R^2 = 3-Me-C_6H_4	**45k**: 87%
R^1 = H, R^2 = 4-OEt-C_6H_4	**45c**: 94%	R^1 = 5-Cl, R^2 = Ph	**45l**: 85%
R^1 = H, R^2 = 2-Me-C_6H_4	**45d**: 88%	R^1 = 5-Cl, R^2 = 4-Me-C_6H_4	**45m**: 89%
R^1 = H, R^2 = 3-Me-C_6H_4	**45e**: 91%	R^1 = 5-Cl, R^2 = 4-Br-C_6H_4	**45n**: 80%
R^1 = H, R^2 = 4-Me-C_6H_4	**45f**: 85%	R^1 = 6-OMe, R^2 = 4-OMe -C_6H_4	**45o**: 91%
R^1 = H, R^2 = 4-Br -C_6H_4	**45g**: 82%	R^1 = 6-OMe, R^2 = 4-Br -C_6H_4	**45p**: 91%
R^1 = H, R^2 = 3-Br-C_6H_4	**45h**: 80%	R^1 = 6-OMe, R^2 = 4-Me -C_6H_4	**45q**: 91%
R^1 = H, R^2 = 3-Cl-C_6H_4	**45i**: 78%		

Scheme 17. Synthesis of 2-benzoylbenzothiazole **45** according to Ablajan and co-workers.

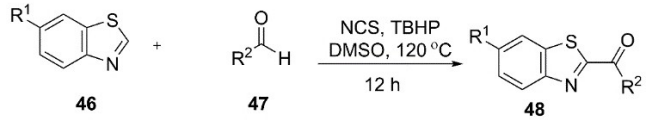


Scheme 18. Proposed mechanism for the synthesis of 2-benzoylbenzothiazole **45 a** according to Ablajan and co-workers.

solvent, which acts as a strong Lewis base and probably could promote the cleavage of bonds through hydrogen bonding interaction (Scheme 19).[44] The cheap organic catalyst NCS is used as a radical initiator reagent and TBHP as an oxidant.

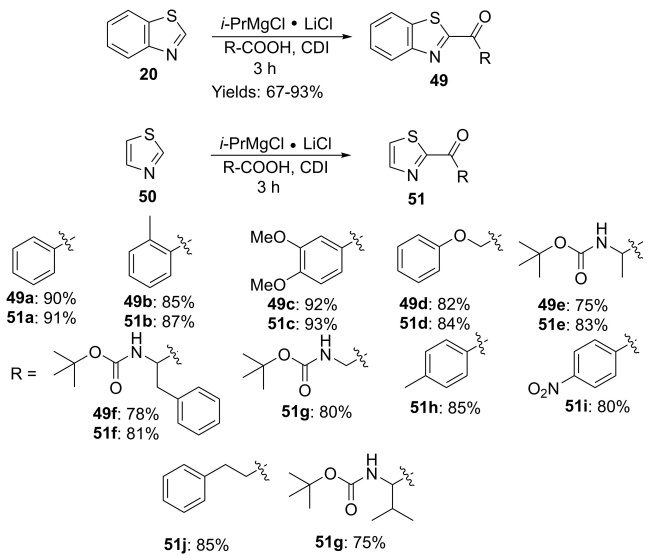
Yin and co-workers have reported a successful synthesis of 2-acyl benzothiazoles **49** and thiazoles **51** in 2019. They established a suitable and efficient method for the synthesis of these scaffolds via the reaction of benzothiazole **20** and thiazole **50** with *i*-PrMgCl·LiCl, followed by the treatment with CDI and activated carboxylic acid derivatives. Numerous substituted carboxylic acids effectively provided the chosen products in moderate to excellent yields under mild reaction conditions. This offers an alternative approach to access 2-acyl benzothiazoles/ thiazoles and supplements the acylation methods of benzothiazole and thiazole (Scheme 20).[45]

A general and efficient syntheses of 2-substituted thiazoles **53** and **54** have been achieved starting from benzothiazole **20**, thiazole **50** and 2-naphthoic acid **52** in the presence of catalytic amounts of $Pd(OAc)_2$ and $CuCl_2$/dppp using Boc_2O and $NaHCO_3$ in cyclohexane at 120 °C (Scheme 21).[46] The novel controllable palladium and copper cooperative catalytic system was established for the selective preparation of biaryls and biaryl ketones from azoles, thiazoles and carboxylic acids. In this reaction, the choice of an appropriate phosphine ligand is the key factor for high chemoselectivity.

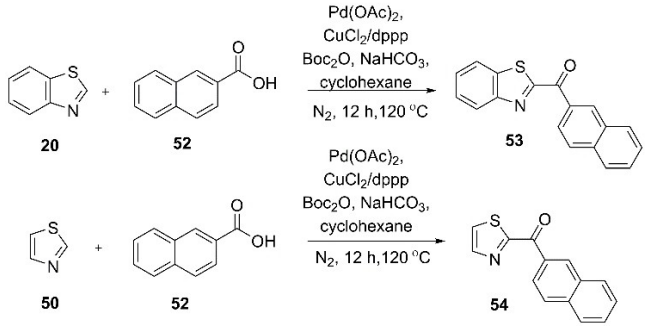


R^1= H, R^2 = Ph	**48a**: 78%	R^1 = H, R^2 = CH_2CH_3	**48c**: 22%
R^1= CH_3CO, R^2 = Ph	**48b**: 37%	R^1 = H, R^2 = $CH(CH_3)_2$	**48d**: 45%

Scheme 19. Synthesis of 2-acylbenzothiazole **48** according to Weng and co-workers.



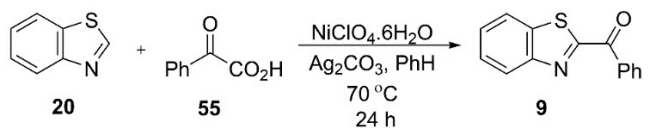
Scheme 20. Synthesis of benzothiazoles **49** and thiazoles **51** according to Yin and co-workers.



Scheme 21. Synthesis of annulated thiazoles **53**, **54** according to Chen and co-workers.

Furthermore, nickel-catalyzed ligand-free synthesis of 2-benzoylbenzothiazole **9** was afforded by the decarboxylative cross-coupling reaction of benzothiazole **20** with 2-oxo-2-phenylacetic acid **55**. This work represents the first example of decarboxylative cross-coupling reactions, in a C–H bond functionalization manner, through nickel catalysis (Scheme 22).[47]

Moreover, the cobalt(II)-catalyzed direct decarboxylative coupling of thiazole derivatives **20** and 2-oxocarboxylic acids **56** has been described through sp^2 C–H bond functionalization process. This transformation is the first example of a decarboxylative C–H functionalization reaction with cobalt catalysis, and offers an effective complementary approach towards the

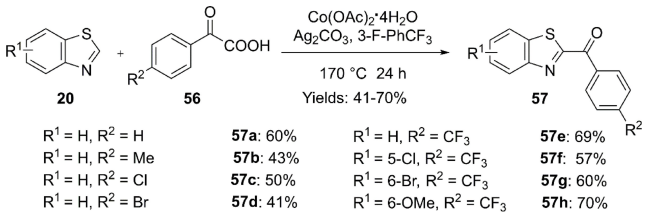


Scheme 22. Synthesis of 2-benzoyl benzothiazoles **9** according to Ge et al.

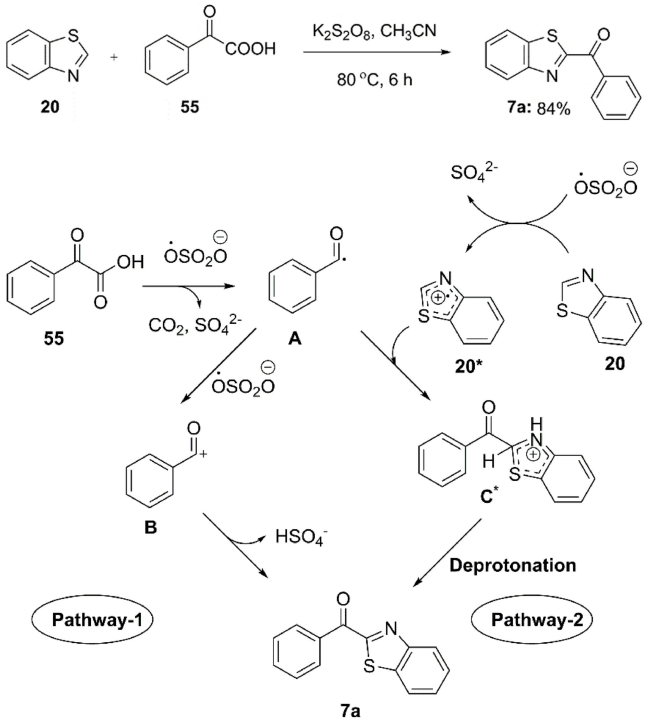
preparation of important bioactive heteroaryl ketone **57** (Scheme 23).[48]

Similar approach for the preparation of 2-benzoyl benzothiazole **7a** through the decarboxylative acylation of electron-rich pyrroles and benzothiazole **20** has been reported using arylglyoxylic acids **55** as acylating agents under silver-free, acid-free neutral conditions (Scheme 24 and 24a).[49] The protocol represents a fine advancement of Minisci acylation on electron-rich heteroarene substrates that were otherwise previously unexplored.

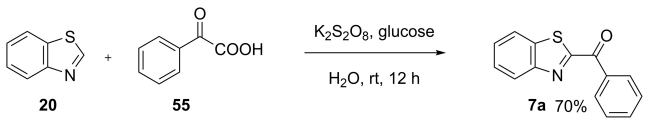
In order to overcome the problems of using higher temperature, UV light, transition metals or bases in the acylation of benzothiazoles **20** with 2-oxo-2-phenylacetic acid **55**, Laha and co-workers have demonstrated (in 2021) an analogous route towards the preparation of 2-benzoyl benzothiazole **7a.**[50] This route relies on the use of glucose as reagent for activation of persulfate at room temperature to generate SO_4^{2-} and avoiding the use of higher temperature, UV light, transition metals or bases (Scheme 25).



Scheme 23. Synthesis of 2-benzoyl benzothiazoles **57** according to Lu et al.



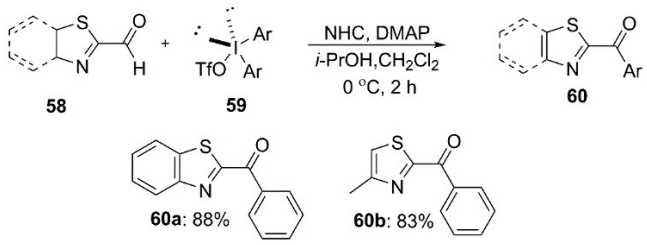
Scheme 24. Synthesis of 2-benzoyl benzothiazole **7a** according to Laha and co-workers. Proposed mechanism for the synthesis of 2-benzoyl benzothiazole **7a** according to Laha and coworkers.



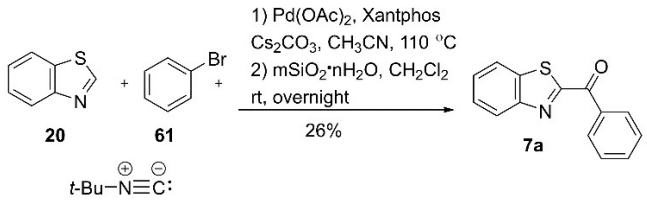
Scheme 25. Synthesis of 2-benzoyl benzothiazole **7a** according to Lu and coworkers.

Gaunt and co-workers reported another approach towards the synthesis of 2-aroyl benzothiazoles **60** by *N*-heterocyclic carbene (NHC) catalyzed reaction of thiazole-2-carboxaldehyde **58** with diaryliodonium triflate **59** (Scheme 26).[51] The protocol operates under mild conditions and involves with simple experimental method using commercially available NHC catalyst to generate a range of high-value heterocyclic scaffolds.

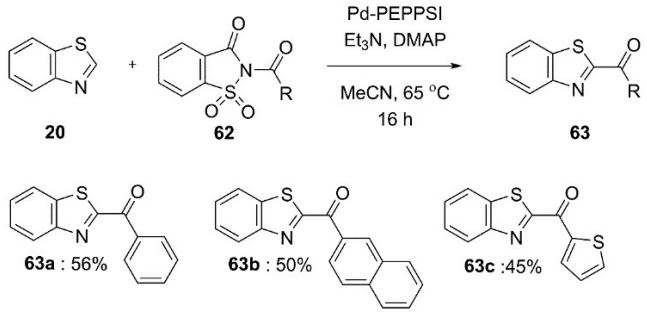
In 2015, Eycken and co-workers have disclosed a novel, simple, efficient and useful protocol for the Pd-catalyzed Csp^2-H functionalization of benzothiazole **20** and bromobenzene **61** via isocyanide insertion for the synthesis of 2-benzoyl benzothiazole **7a**. The broad substrate scope, readily available starting



Scheme 26. Synthesis of 2-aroylbenzothiazole **60** according to Gaunt and co-workers.



Scheme 27. Synthesis of 2-benzoylbenzothiazole **9** according to Eycken and co-workers.



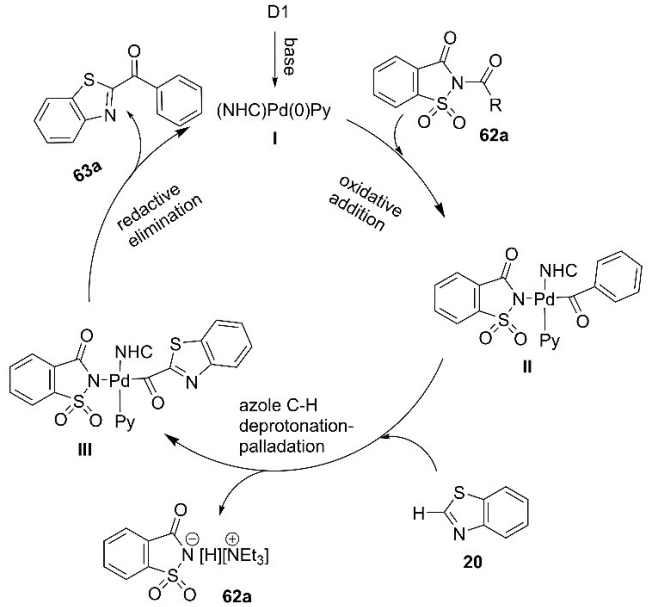
Scheme 28. Synthesis of 2-keto-(hetero)aryl benzothiazole **63** according to Gandhi and co-workers.

materials, relatively mild reaction conditions and good yields makes this method synthetically useful (Scheme 27).[52]

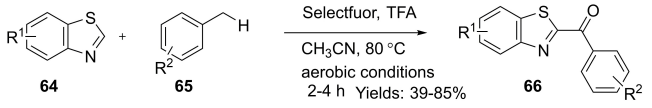
Recently, Gandhi and co-workers presented a route for the synthesis of 2-keto-(hetero)aryl benzothiazoles **63**, which is established based on the Pd-NHC catalyzed C–H acylation of benzothiazoles **20** and *N*-benzoylsaccharin **62** (Scheme 28).[53] They have demonstrated that various benzoxazoles, benzothiazoles, and N-methylbenzimidazoles were selectively transformed into the corresponding 2-acylated products in high selectivity with synthetically suitable yields. High functional group tolerance and wide substrate scope accomplished an attractive method to access 2-acylated azole derivatives. Experimental studies show that the high reactivity of the pyrene Pd-NHC system is likely due to non-covalent interaction of complexes with the substrates.

The mechanism of the Pd-NHC-catalyzed direct C–H acylation,[54] initiates by the generation of complex **II** via oxidative addition of *N*-acylsaccharin **62a** to a triggered palladium complex **I**. The base eliminates acidic proton from **20** and produces the intermediate **III**, which finally undergoes reductive elimination to form the desired product **63a** (Scheme 29).

More recently, Weng and co-workers reported a very interesting protocol for the synthesis of 2-aroyl benzothiazoles **66** involving the direct C2-arylacylation of 2*H*-benzothiazoles **64** with methyl arenes **65** *via* oxidation using Selectfluor (Scheme 30).[55] This arylacylation reaction tolerates a broad range of functional groups giving a library of arylacylated products in yields ranging from 39–81%. Moreover, the direct coupling of 2*H*-benzothiazoles without pre-functionalized substrates and avoiding transition-metal catalysts represents this protocol as practical approach for the synthesis of C2-arylacylated 2*H*-benzothiazoles.



Scheme 29. Proposed mechanism for Pd-NHC-catalyzed straightforward C–H acylation.

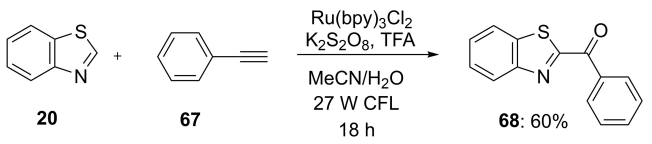


R^1 = H, R^2 = H	**66a**: 85%	R^1 = 6-NO_2, R^2 = 3-H	**66n**: 39%
R^1 = H, R^2 = 4-Me	**66b**: 81%	R^1 =5-Cl, R^2 = H	**66o**: 63%
R^1 = H, R^2 = 3-Me	**66c**: 74%	R^1 = 6-CN, R^2 = H	**66p**: 68%
R^1 = H, R^2 = 2-Me	**66d**: 63%	R^1 = 5-$COCH_3$, R^2 = H	**66q**: 66%
R^1 = H, R^2 = 4-Cl	**66e**: 58 %	R^1 = 6-OMe, R^2 = 4-H	**66r**: 75%
R^1 = H, R^2 = 3-Cl	**66f**: 60%	R^1 = 7-OMe, R^2 = H	**66s**: 70%
R^1 = H, R^2 = 2-Cl	**66g**: 47%	R^1= 5-Cl, R^2 = 4-Me	**66t**: 67%
R^1 = H, R^2 = 4-Br	**66h**: 56%	R^1 = 6-OMe, R^2 = 4-Me	**66u**: 70%
R^1 = H, R^2 = 3-Br	**66i**: 55%	R^1 = 5-Cl, R^2 = 4-Cl	**66v**: 63%
R^1 = H, R^2 = 2-Br	**66j**: 45%	R^1 = 6-OMe, R^2 = 4-Cl	**66w**: 65%
R^1 = H, R^2 = 4-F	**66k**: 57%	R^1 = 5-Cl, R^2 = 4-Br	**66n**: 53%
R^1 = H, R^2 = 3-F	**66l**: 61%	R^1 = 6-OMe, R^2 = Br	**66x**: 61%
R^1 = H, R^2 = 2-F	**66m**: 50%	R^1 = 5-Cl, R^2 = 4-F	**66y**: 45%
		R^1 = 6-OMe, R^2 = 4-F	**66z**: 50%

Scheme 30. Synthesis of 2-benzoylbenzothiazoles **66** *via* Selectfluor oxidation.

In 2018, Shah and co-workers described a Ru(II)-catalyzed reaction between benzothiazole **20** and phenylacetylene **67** for the preparation of 2-benzoyl benzothiazole **68** (Scheme 31).[56] The optimal procedure involves the use of 2.0 mol% of Ru (II) as the catalyst, 3.0 mmol of $K_2S_2O_8$ as an oxidant, 1.0 mmol TFA in CH_3CN/H_2O as solvent under photoredox catalysis. This route demonstrated for the first time use of arylacetylenes as precursors of acyl radicals in the acylation reaction of *N*-heteroarenes.

Most current processes for accessing 2-acyl benzothiazoles molecules are achieved by acylation of benzothiazoles with a carbonyl compound under organo- or metal-catalysis, either sequentially or in one-step process. The most accepted drawbacks to these methods are the requirement of costly organic catalysts or heavy transition metals, and frequently restricted by the availability of properly substituted benzothiazoles. To



Scheme 31. Synthesis of 2-benzoylbenzothiazole **68** developed by Shah et al. under photoredox catalysis.

R^1 = H, R^2 = H	**71a**: 81%	R^1 = 5-Cl, R^2 = 4-F	**71i**: 80%
R^1 = H, R^2 = 4-Me	**71b**: 80%	R^1 = 4-Cl, R^2 = H	**71j**: 65%
R^1 = H, R^2 = 4-OMe	**71c**: 78%	R^1 = 4-Cl, R^2 = 4-Me	**71k**: 66%
R^1 = H, R^2 = 4-F	**71d**: 82%	R^1 = 4-Cl, R^2 = 4-F	**71l**: 62%
R^1 = H, R^2 = 4-NO_2	**71e**: 86 %	R^1 = 4-Cl, R^2 = 3-Me	**71m**: 60%
R^1 = H, R^2 = 3-CH_3	**71f**: 75%	R^1 = 6-Me, R^2 = 4-Me	**71n**: 79%
R^1 = 5-Cl, R^2 = H	**71g**: 81%	R^1 = 6-Me, R^2 = 4-OMe	**71o**: 63%
R^1 = 5-Cl, R^2 = 4-CH_3	**71h**: 56%	R^1 = 6-Me, R^2 = 4-F	**71p**: 80%

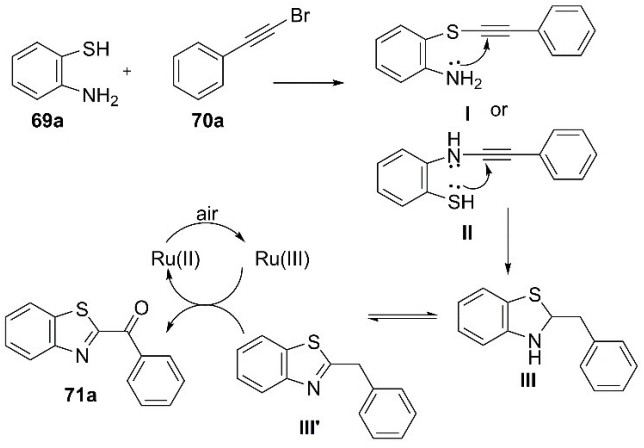
Scheme 32. Synthesis of 2-benzoylbenzothiazoles **71** according to Zhang and co-workers.

conquer such disadvantages, the cyclization reactions between 2-amino(thio)phenols and 1,1-dibromoethenes or phenacyl bromide were recently received much attention.

Zhang and co-workers have described the use of $RuCl_3 \cdot 3H_2O$ catalyzed tandem reaction of alkynyl bromides **70** with 2-aminothiophenols **69** mediated by water to represent a suitable synthesis of 2-benzoylbenzothiazoles **71** (Scheme 32).[57] Furthermore, the Ru(III)-catalyst could be readily recovered and efficiently reused up to three times. This is the first report in which 2-aryl benzothiazoles have been synthesized from alkynyl bromides through a Ru(III)/air promoted tandem process mediated by water. A comprehensive study about the possible mechanism of the reaction was achieved, giving proof for the following proposed mechanism (Scheme 33). Initially, the condensation of **69a** and **70a** gives an alkynylthiophenyl amine (**I**) or alkynylaminothiophenol (**II**), that is quickly converted by intramolecular cyclization to give 2-benzylbenzothiazole (**III**). Then, the Ru(III)/air assisted oxidation of the benzylic methylene moiety of **III** affords 2-benzothiazyl ketone **71** to accomplish the tandem process. Meanwhile, the in situ produced Ru(II) could be oxidized back to Ru(III) by air to complete the catalytic cycle.

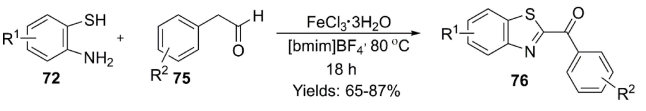
Similar to what was suggested by Zhang et al. in 2011,[57] Fan et al. also described an environmentally and economically sustainable preparation of 2-benzoylbenzothiazoles **74**, **76** starting from alkynyl bromides **73**,[58a] phenylacetaldehdes **75**[58b] and 2-amino(thio)phenols **72** in the presence of catalytic amounts of $FeCl_3 \cdot 6H_2O$ in $[bmim]BF_4$ at 80 °C (Scheme 34). The developed synthetic protocol has advantages such as high efficiency, mild reaction conditions, recyclable catalyst and benign solvent.

Wang and co-workers have reported an one-pot tandem reaction of 1,1- dibromoethenes **78** with 2-amino(thio)phenols **77** promoted by TBAF$\cdot 3H_2O$ and $RuCl_3$ (5%) under aerial conditions for the synthesis of heteroaryl ketones **79** (Scheme 35).[59] It seems to be the first report in which the heteroaryl ketones are synthesized in straightforward manner from 1,1-dibromoethenes. This new method includes several cascade reactions in one-pot and uses economically efficient



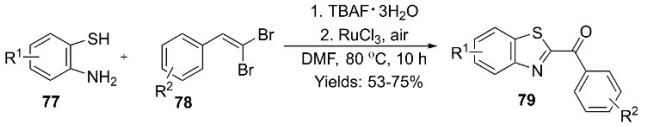
Scheme 33. Proposed reaction mechanism for the synthesis of 2-benzoylbenzothiazoles **71** according to Zhang and co-workers.

R^1 = H, R^2 = H	**74a**: 81%	R^1 = 5-Cl, R^2 = 4-F	**74g**: 81%
R^1 = H, R^2 = 4-Br	**74b**: 81%	R^1 = 5-Cl, R^2 = 4-CH_3	**74h**: 81%
R^1 = H, R^2 = 4-Me	**74c**: 84%	R^1 = 4-Cl, R^2 = 3-Me	**74i**: 62%
R^1 = H, R^2 = 4-OMeF	**74d**: 80%	R^1 = 6-Me, R^2 = 4-F	**74j**: 79%
R^1 = H, R^2 = 4-NO_2	**74e**: 87%	R^1 = 7-Me, R^2 = 4-Me	**74k**: 78%
R^1 = 5-Cl, R^2 = H	**74f**: 80%	R^1 = 7-Me, R^2 = 3-OMe	**74l**: 76%



R^1 = H, R^2 = H	**76a**: 82%	R^1 = 4-Cl, R^2 = H	**76j**: 74%
R^1 = H, R^2 = 4-OMe	**76b**: 83%	R^1 = 4-Cl, R^2 = 4-Me	**76k**: 76%
R^1 = H, R^2 = 4-Me	**76c**: 80%	R^1 = 4-Cl, R^2 = 4-F	**76l**: 68%
R^1 = H, R^2 = 4-F	**76d**: 79%	R^1 = 4-Cl, R^2 = 3-Me	**76m**: 66%
R^1 = H, R^2 = 3-Me	**76e**: 75%	R^1 = 4-Cl, R^2 = 4-Br	**76n**: 65%
R^1 = 5-Cl, R^2 = H	**76f**: 87%	R^1 = 6-Me, R^2 = 4-F	**76o**: 75%
R^1 = 5-Cl, R^2 = 4-F	**76g**: 79%	R^1 = 6-Me, R^2 = 4-Me	**76p**: 76%
R^1 = 5-Cl, R^2 = 4-Me	**76h**: 85%	R^1 = 6-Me, R^2 = 3-NO_2	**76q**: 82%
R^1 = 5-Cl, R^2 = 3-Me	**76i**: 77%		

Scheme 34. $FeCl_3$•$3H_2O$-Catalyzed synthesis of 2-benzoylbenzothiazoles **74** and **76**, using $[bmim]BF_4$ as solvent.



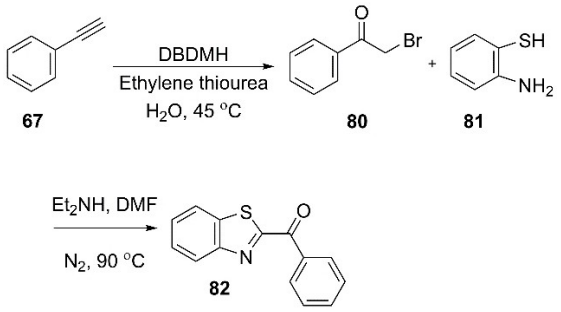
R^1 = H, R^2 = H	**79a**: 65%	R^1 = 5-Cl, R^2 = 4-F	**79g**: 68%
R^1 = H, R^2 = 4-Me	**79b**: 56%	R^1 = 4-Cl, R^2 = H	**79h**: 57%
R^1 = H, R^2 = 4-Me	**79c**: 65%	R^1 = 4-Cl, R^2 = 4-Me	**79i**: 56%
R^1 = H, R^2 = 4-NO_2	**79d**: 75%	R^1 = 6-Me, R^2 = 4-Me	**79n**: 58%
R^1 = 5-Cl, R^2 = H	**79e**: 63 %	R^1 = 6-Me, R^2 = 4-OMe	**79o**: 53%
R^1 = 5-Cl, R^2 = 4-CH_3	**79f**: 64%	R^1 = H, R^2 = 3-Me	**79p**: 59%

Scheme 35. Synthesis of 2-benzoylbenzothiazoles **79** promoted by TBAF · $3H_2O$ and catalytic $RuCl_3$ under aerial conditions.

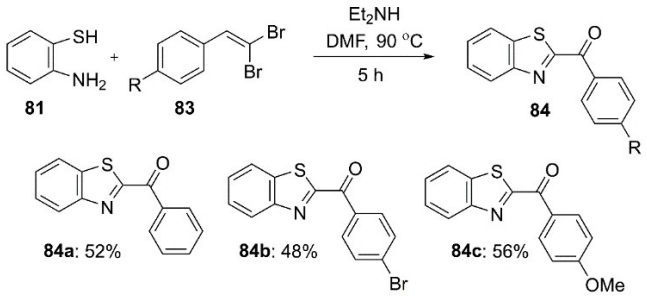
reagents to generate molecular complexity under mild conditions.

Recently, He and co-workers established a greener protocol for the synthesis of 2-benzoyl benzothiazole **82** in 52% yield. The domino reaction initiated by the preparation of phenacyl bromide **80** via the reaction between phenylacetylene **67** and DB DMH, using ethylene thiourea as catalyst in water followed by the addition of 2-amino(thio)phenols **81** (Scheme 36).[60] The α-mono-haloketones were obtained in aqueous acetone at 45 °C; additionally, the α,α'-dihalo ketones were formed in pure water as the sole solvent at room temperature.

He and co-workers have reported the practical and efficient methodology for the cyclization reaction between 2-amino(thio)phenol **81** and α,α-dihaloketones **83** as the substrates, affording 2-keto(hetero)aryl benzox(thi)azoles **84** in moderate to very good yields (Scheme 37).[47] Various functional groups are tolerated under the reaction conditions, resulting in a wide range of substituted 2-keto(hetero)aryl benzox(thi)azoles. This protocol has circumvented some drawbacks found in the method developed by Wang and co-workers,[61] which requires a corrosive and moisture-sensitive $RuCl_3$ in the catalytic oxidation; and whereas, protocol described by He[46] delivers a large amounts of side products.



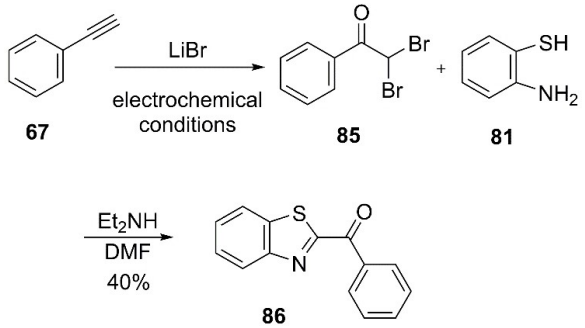
Scheme 36. Synthesis of 2-benzoylbenzothiazoles **82** promoted by Et_2NH.



Scheme 37. Synthesis of 2-benzoylbenzothiazoles **84** according to He and co-workers.

Lei and co-workers presented a similar method for the synthesis of 2-benzoyl benzothiazole **9** with 40% yield in two steps. It was started by the electrochemical oxidation of phenylacetylene **67** to afford 2,2-dibromo-1-phenylethan-1-one **85**, which followed by the cyclization reaction with 2-amino-thiophenol **81** in the presence of diethylamine leading to the formation of final product **86** (Scheme 38).[62] The electrochemical oxidative functionalization of aryl alkynes for the synthesis of α,α-dibromoacetophenones **85** has been achieved with an undivided cell under mild conditions.

Another route to the synthesis of 2-keto arylbenzothiazoles **88** and 2-arylbenzothiazoles is the condensation reaction

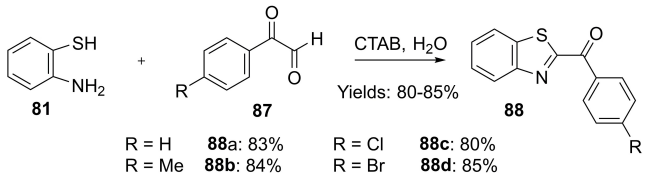


Scheme 38. Synthesis of 2-benzoylbenzothiazoles **86** promoted by Et_2NH.

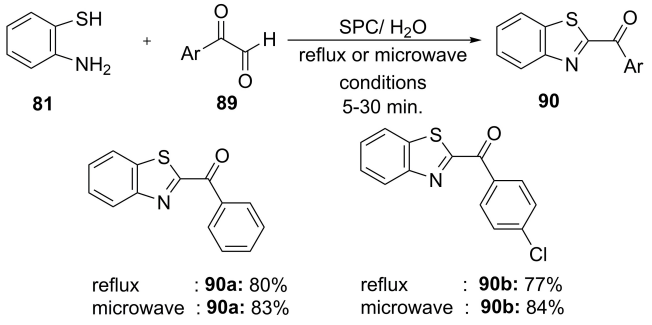
between 2-aminothiophenols and aldehydes. A collection of the contributions is presented here. The condensation reaction between 2-aminothiophenol **81** and arylformyl aldehydes **87** in the presence of cetyltrimethyl ammonium bromide CTAB in water derived the final product **88** (Scheme 39).[63] This present protocol features simple work-up, environmentally benign conditions, high yields with alkyl aldehyde, no requirement of extra oxidants and use of the catalytic amounts of the cheap catalyst.

Similar to what was suggested by Su in 2010,[63] Mahdavi and co-workers[64] reported in 2012 the condensation reaction of arylformylaldehyde **89** with 2-aminothiophenol **81** in the presence of SPC in water for the preparation of 2-arylformylbenzothiazoles **90**. The reactions were attempted under reflux conditions within 230–250 minutes to obtain the good yields of products (Scheme 40). However, when the same reaction was performed under microwave irradiation, it gave better yields of products in shorter reaction time.

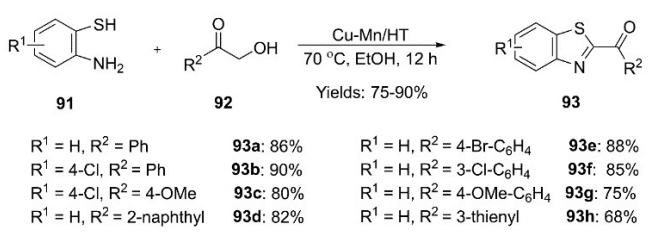
A closely related route to prepare 2-acylbenzothiazoles **93** was established by Zhao and co-workers in 2018. Their approach depends upon the use of Cu–Mn/HT catalyst for the preparation of 2-acylbenzothiazoles **93** from α-hydroxyacetophenone **92** and 2-aminothiophenol **91** in EtOH as solvent



Scheme 39. Synthesis of 2-benzoylbenzothiazoles **88** using catalytic amount of CTAB.



Scheme 40. Synthesis of 2-benzoylbenzothiazoles **90** using SPC under reflux and microwave conditions.



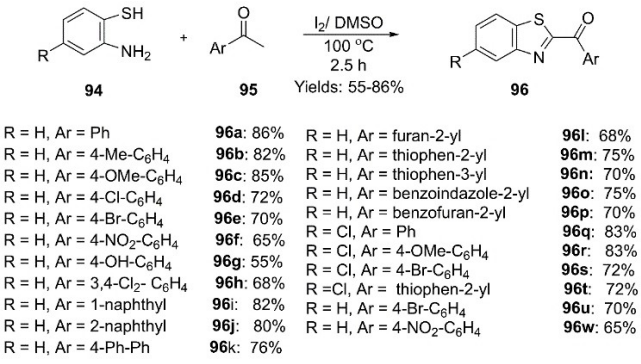
Scheme 41. Synthesis of 2-acylbenzothiazoles **93** using Cu–Mn/HT.

using O_2 as green oxidant (Scheme 41).[65] The mechanochemically prepared catalyst exhibited high catalytic activity and recyclability towards the synthesis of 2-acylbenzothiazoles and quinoxalines under aerobic conditions in green reaction medium like ethanol.

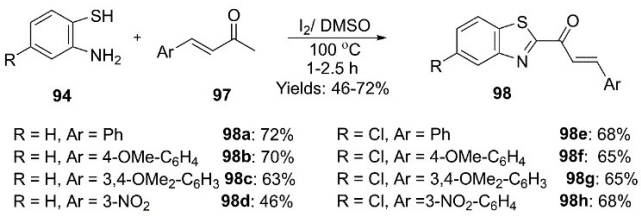
A general and well-established domino process for the preparation of 2-acylbenzothiazoles **96** and **98** has been accomplished starting from 2-aminothiophenols **94**, and aromatic ketones **95** or unsaturated methyl ketones **97** in the presence of I_2 in DMSO at 100 °C (Scheme 42 and 43).[66] This domino transformation involves three mechanistically different reactions (iodination, Kornblum oxidation, and heterocyclization reaction). Also, the protocol could provide a simple and efficient method to synthesize 2-acylbenzathiazoles, in which a metal, base and ligand are not required.

Telvekar and co-workers established a simple, mild and efficient aerobic reaction conditions using copper (II) catalyzed domino protocol for the synthesis of 2-aroylbenzothiazoles **99**. The annulation reaction of 2-aminobenzenethiols **81** and aryl ketones **95** using Cu-catalyst in ethanol as solvent afforded the desired compound **110** (Scheme 44).[67] This route uses inexpensive copper salt, economic and environmentally friendly molecular oxygen as the oxidant. Several functional groups were well tolerated and leading to moderate to good yields of the products.

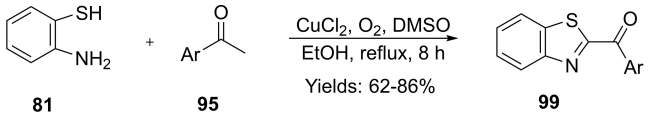
Furthermore, the direct one pot condensation reaction of 2-aminobenzenethiols **100** with methyl ketones **101** using $TsNBr_2$ as reagent in DMSO/H_2O as solvent has been established for the synthesis of 2-aceylbenzothiazoles **102** (Scheme 45).[68] The reaction was achieved starting from aromatic ketones via the generation of an aryl gloxal intermediate, which upon further



Scheme 42. Synthesis of 2-arylbenzothiazoles **96** starting from **95** and **96** using I_2/DMSO as reagent.



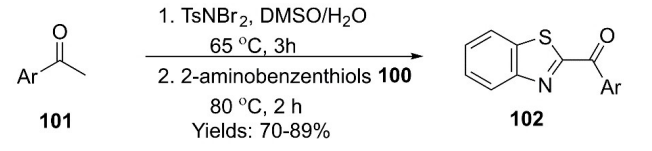
Scheme 43. Synthesis of 2-arylbenzothiazoles **98** starting from **94** and **97** using I_2/DMSO as reagent.



81 95 99

Ar = Ph	**99a**: 86%	Ar = 4-NO_2-C_6H_4	**99g:** 62%
Ar = 4-Me-C_6H_4	**99b**: 83%	Ar = 3,5-OMe_2-C_6H_3	**99h:** 62%
Ar = 4-Me-C_6H_4	**99c**: 85%	Ar = 2-naphthyl	**99i:** 70%
Ar = 4-OMe-C_6H_4	**99d**: 85%	Ar = pyridin-2-yl	**99j**: 80%
Ar = 4-Cl-C_6H_4	**99e**: 82%	Ar = pyridin-3-yl	**99k**: 75%
Ar = 4-Br-C_6H_4	**99f**: 78%	Ar = thiophen-2-yl	**99l**: 78%

Scheme 44. $CuBr_2$ Catalyzed Synthesis of 2-arylbenzothiazoles **99**.



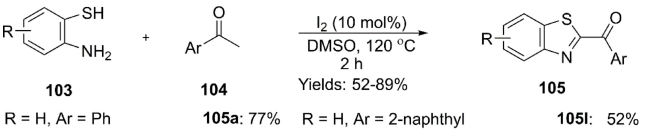
101 102

Ar = Ph	**102a**: 87%	Ar = 4-OEt-C_6H_4	**102g:** 83%
Ar = 4-Me-C_6H_4	**102b**: 83%	Ar = 2,4-OMe_2-C_6H_3	**102h:** 70%
Ar = 4-OMe-C_6H_4	**102c**: 89%	Ar = 2-naphthyl	**102i:** 78%
Ar = 2-OMe-C_6H_4	**102d**: 80%	Ar = 4-F-C_6H_4	**102j**: 84%
Ar = 4-Cl-C_6H_4	**102e**: 75%	Ar = 2-Cl-C_6H_4	**102k**: 70%
Ar = 4-Br-C_6H_4	**102f**: 82%	Ar = 2-NO_2-C_6H_4	**102l**: 80%

Scheme 45. $TsNBr_2$ Promoted Synthesis of 2-arylbenzothiazoles **102.**

condensation reaction with 2-aminobenzenethiol, produces the corresponding heterocyclic skeleton. The aromatic ketones are initially treated with $TsNBr_2$ in DMSO at 65 °C for 3 h and the crude reaction mixture was then subjected with 2-aminobenzenethiol at 80 °C to afford the final compound.

More recently, Ma and co-workers described the I_2-catalyzed domino annulation of aromatic methyl ketones **104** and 2-aminobenzenethiols **103** under metal-free reaction conditions (Scheme 46).[69] Under these developed conditions, the versatile synthetic approach not only produced the 2-aroyl benzothiazoles **105**, but also afforded the 2-arylbenzothiazoles selectively by varying the oxidants and solvents. Using DMSO as the oxidant and solvent, the 2-aroyl benzothiazoles were selectively afforded, while the reaction mediated by $PhNO_2$ delivered the 2-aryl benzothiazoles.



103 104 105

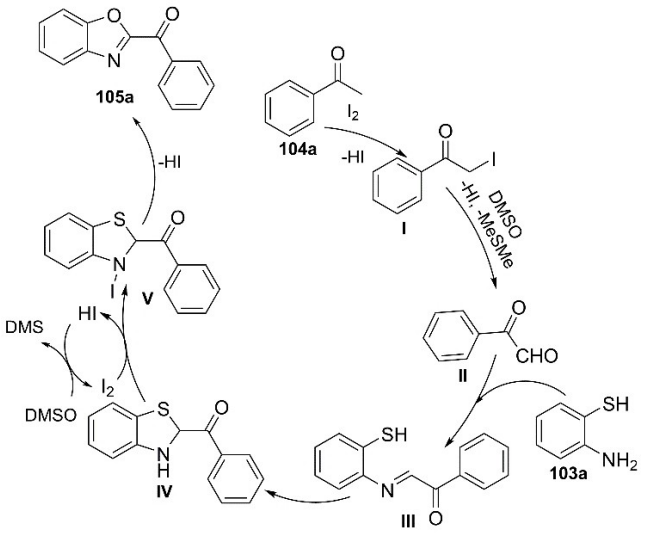
R = H, Ar = Ph	**105a**: 77%	R = H, Ar = 2-naphthyl	**105l**: 52%
R = H, Ar = 2-OMe-C_6H_4	**105b**: 70%	R = H, Ar = thiophen-2-yl	**105m**: 53%
R = H, Ar = 2-OH-C_6H_4	**105c**: 70%	R = H, Ar = benzothiophen-2-yl	**105n:** 59%
R = H, Ar = 2-Cl-C_6H_4	**105d**: 67%	R = H, Ar = benzofuran-2-yl	**105o**: 48%
R = H, Ar = 3-OMe-C_6H_4	**105e**: 70%	R = H, Ar = 1*H*-indol-2-yl	**105p**: 62%
R = H, Ar = 4-F-C_6H_4	**105f**: 69%	R = 6-Cl, Ar = Ph	**105q**: 53%
R = H, Ar = 4-Me-C_6H_4	**105g**:75%	R = 6-Cl, Ar = 4-F-C_6H_4	**105r**: 89%
R = H, Ar = 4-NH_2-C_6H_4	**105h**: 72%	R = 6-Cl, Ar = 3,5-F_2-C_6H_3	**105s**: 75%
R = H, Ar = 3,5-OMe_2-C_6H_3	**105i**: 61%	R =6-Cl, Ar = 2-naphthyl	**105t**: 81%
R = H, Ar = 3,4-Me_2-C_6H_3	**105j**: 68%	R = 6-Cl, Ar = benzothiophen-2-yl	**105u**: 70%
R = H, Ar = 3,5-F_2-C_6H_3	**105**k: 52%		

Scheme 46. Synthesis of 2-arylbenzothiazoles **105** starting from **103** and **104** using I_2/DMSO.

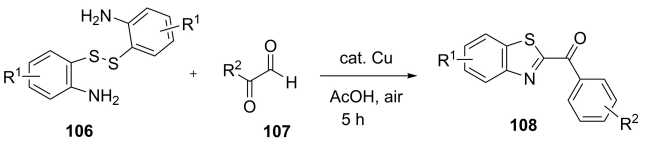
The reaction mechanism, which was supported by control experiments and previous literature reports,[70] involves initially the formation of the intermediate **I** by the activation of acetophenone **104 a** using I_2 in the presence of DMSO, which then undergoes oxidation using Kornblum oxidation to give the phenylglyoxal intermediate **II**. This intermediate undergoes condensation with 2-aminobenzenethiol **103 a** to afford the iminium intermediate **III**. Next, spontaneous cyclization of intermediate **III**, followed by oxidation that catalyzed by iodine in the presence of DMSO gives the intermediate **V**. Elimination of HI from intermediate **V** afforded the final 2-benzoylbenzothiazoles **105 a** (Scheme 47).

Another protocols for the synthesis of 2-acylbenzothiazoles relied on the use of 2,2′-disulfanediyldianilines instead of using 2-aminobenzenethiols as substrates. The copper-catalyzed reaction between 2,2′-disulfanediyldianilines **106** and aldehydes **107** for the synthesis of 2-aroyl benzothiazoles **108** and 2-acylbenzothiazoles is established (Scheme 48).[71] This process is developed based on the activation of disulfide bond accompanied by C–H bond activation of neighboring imine functionality. The scope and the restrictions of this method have been established on several functionalized substrates with good to excellent yields.

Related to what was proposed by Srogl in 2010,[72] Deng and co-workers have reported $Cu(OTf)_2$-catalyzed tandem syn-



Scheme 47. Proposed mechanism for the synthesis of 2-benzoylbenzothiazole **105 a** according to Ma and co-workers.

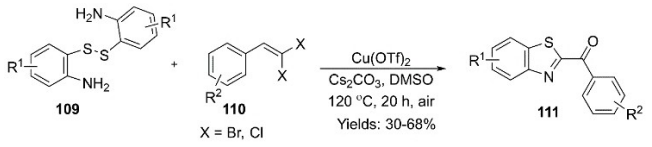


R^1 = 6-OMe, R^2 = H **108a**: 66%
R^1 = 5-CN, R^2 = H **108b**: 69%
R^1 = Br, R^2 = H **108c**: 85%

Scheme 48. Copper-catalyzed synthesis of 2-arylbenzothiazoles **108**.

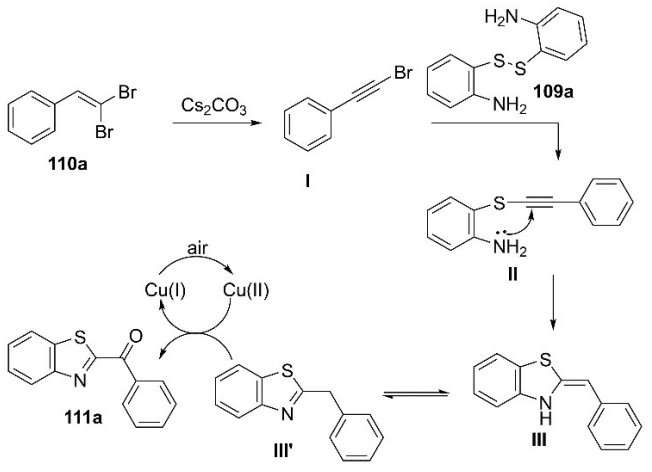
thesis of 2-acylbenzothiazoles **111** via the reaction of 2,2′-disulfanediyldianilines **109** with β,β-dihalidestyrenes **110** using Cs_2CO_3 as base in DMSO at 120 °C for 20 h under aerial conditions (Scheme 49).[72] In addition, a variety of different dihalidestyrenes and diphenyldisulfanes were efficiently transformed into the corresponding 2-acylbenzothiazole derivatives in the presence of $Cu(OTf)_2$. It is noteworthy that the developed method is applicable for the long-chain 1,1-dibromohept-1-ene derivatives to convert these into 2-hexylbenzo[*d*]thiazoles in moderate yields.

Established on the obtained results and literature evidences,[57,58] the authors proposed a plausible mechanism for the synthesis of the 2-acylbenzothiazoles **111a** (Scheme 50). The initial reaction of substrate **109a** with base would produce the intermediate **I**. Subsequently, the condensation reaction between intermediate I and **110a** could afford the intermediate **II**, which followed by an intramolecular cyclization delivers the intermediate **III**. Finally, the Cu(II)-catalyst would oxidize the intermediate **III'** to afford the target product **111a** together with the Cu(I)-species. The Cu(I)-species would then be oxidized by air to retrigger the Cu(II)-catalyst to complete the catalytic cycle.



R^1 = H, R^2 = H	**111a**: 68%	R^1 = H, R^2 = 2-OH	**111j**: 58%
R^1 = H, R^2 = 4-Me	**111b**: 31%	R^1 = H, R^2 = 3-OMe	**111k**: 64%
R^1 = H, R^2 = 4-NMe_2	**111c**: 30%	R^1 = H, R^2 = 3-Cl	**111l**: 61%
R^1 = H, R^2 = 4-CN	**111d**: 53%	R^1 = H, R^2 = 2-thiophen-2-yl	**111m**: 58%
R^1 = H, R^2 = NO_2	**111e**: 57 %	R^1 = H, R^2 = 2-furan-2-yl	**111n**: 64%
R^1 = H, R^2 = 2-OCH_3	**111f**: 64%	R^1 = H, R^2 = C_6H_{11}	**111o**: 50%
R^1 = H, R^2 = 4-F	**111g**: 52%	R^1 = 5-Cl, R^2 = 4-OMe	**111p**: 65%
R^1 = H, R^2 = 2-Br	**111h**: 57%	R^1 = 4-Me, R^2 = 4-OMe	**111q**: 62%
R^1 = H, R^2 = 2-F	**111i**: 38%		

Scheme 49. Synthesis of 2-benzoylbenzothiazoles **111** promoted by $Cu(OTf)_2$ under aerobic conditions.



Scheme 50. Plausible mechanism for the synthesis of 2-benzoylbenzothiazoles **111** promoted by $Cu(OTf)_2$ under aerobic conditions.

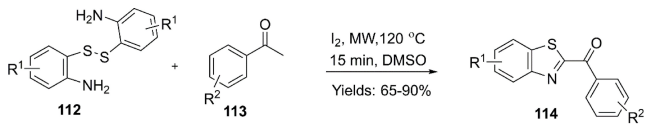
More recently, Yu and co-workers have described the Microwave assisted synthesis of 2-acylbenzothiazoles **114** and bibenzo[*b*][1,4]thiazines from disulfanediyldianilines **112** and aryl methyl ketones **113** using I_2/DMSO or I_2/MeCN reagent systems, respectively (Scheme 51).[73] The reaction was switchable by simply changing the reaction conditions (I_2/MeCN or I_2/DMSO) without the involvement of hazardous oxidants and additional activating reagents.

Wu and co-workers have developed four interesting domino pathways to prepare 2-acylbenzothiazoles **120** using acylethenes **115**, arylacetylene **116**, 2-hydroxy aromatic ketones **117** and carbinols **118** in reaction with 2-aminobenzenethiols **119** (Scheme 52).[74] The protocols embodied four diverse reaction pathways. It delivered adverse synthetic routes to access **120**, which should be of great significant in the field of combinational chemistry and organic synthesis methodology.

The reaction mechanism for the developed cross-coupling reaction has been proposed by Wu and co-workers. This mechanism summarizes various control experiments and previous works which were performed.[75] First, styrene (**115a**) or phenylacetylene (**116a**) was converted into 2-iodo-1-phenylethanone (**I**) by successive iodination and oxidation in I_2/IBX or NIS. Then, the molecule **I** was further converted into phenylglyoxal (**II**) in DMSO. The carbinol **118a** was oxidized by IBX to produce acetophenone (**I'**), which was proceeded by successive iodination and oxidation to give phenylglyoxal (**II**). Furthermore, 2-hydroxy-1-phenylethanone **117a** was simply oxidized to phenylglyoxal (**II**) by oxidant IBX. Lastly, phenylglyoxal (**II**) reacted with molecule **119a** via consecutive condensation reaction, Michael addition, and oxidative dehydrogenation to afford the desired product **120a** (Scheme 53).

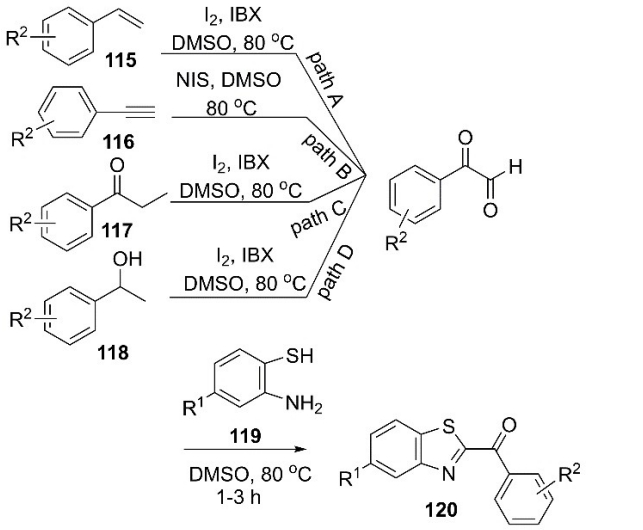
Analogous to what was proposed by Wu in 2012,[76] Shah and co-workers reported (in 2014) an efficient metal-free iodine promoted oxidative amidation of 2-aminobenzenethiol **81** with terminal alkenes **121** both at high temperatures and at room temperature, to afford the synthesis of 2-acyl benzothiazoles **122** (Scheme 54).[76] A simple experimental protocol, low catalyst loading, the stoichiometric quantity of the reactants, and the wide substrate scope are some of the benefits represented for the developed process.

Recently, Sheng and co-workers, developed a more general and greener protocol for the synthesis of metal-free diketones **125** containing benzothiazole backbone and a tunable copper-catalyzed method for the synthesis of 2-aroyl benzothiazoles



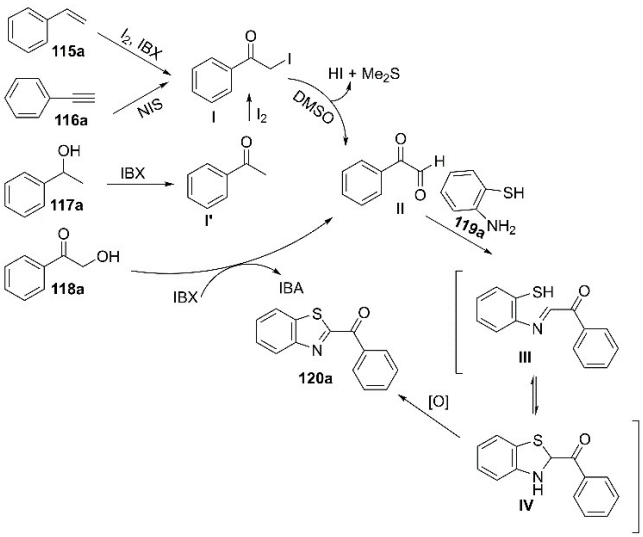
R^1 = H, R^2 = H	**114a**: 88%	R^1 = H, R^2 = 2,5-OMe_2	**114i**: 67%
R^1 = H, R^2 = 4-Me	**114b**: 89%	R^1 = H, R^2 = 3-OMe	**114j**: 83%
R^1 = H, R^2 = 4-OMe	**114c**: 90%	R^1 = H, R^2 = 3-Br	**114k**: 78%
R^1 = H, R^2 = 4-F	**114d**: 75%	R^1 = 6-OMe, R^2 = H	**114l**: 89%
R^1 = H, R^2 = 4-Cl	**114e**: 78 %	R^1 = 5-Cl, R^2 = H	**114m**: 79%
R^1 = H, R^2 = 4-I	**114f**: 83%	R^1 = H, R^2 = furan-2-yl	**114n**: 65%
R^1 = H, R^2 = 4-NO_2	**114g**: 79%	R^1 = 6-OMe, R^2 = 4-OMe	**114o**: 89%
R^1 = H, R^2 = 4-CN	**114h**: 76%	R^1 = 5-Cl, R^2 = 4-OMe	**114p**: 79%

Scheme 51. Microwave assisted synthesis of 2-benzoylbenzothiazoles **114**.

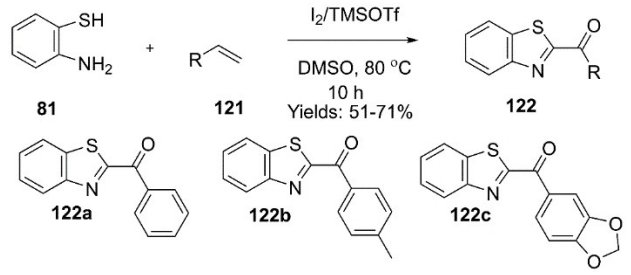


		path A	path B	path C	path D
R^1 = H, R^2 = H	**120a:**	75%	62%	75%	75%
R^1 = H, R^2 = 4-Me	**120b**:	56%	55%	80%	80%
R^1 = H, R^2 = 4-Br	**120c:**	64%	60%	72%	78%
R^1 = H, R^2 = 4-OMe	**120d**:	63%	58%	-----	----
R^1 = H, R^2 = 4-*i*-Pr	**120e**:	66 %	----	-----	----
R^1 = H, R^2 = 4-Me	**120f**:	73%	----	----	----
R^1 = H, R^2 = 2-Me	**120g**:	62%	----	----	----
R^1 = H, R^2 = 4-Cl	**120h**:	67%	----	78%	----
R^1 = H, R^2 = 2,4-Me	**120i**:	63%	----	----	----
R^1 =-H, R^2 = 3-Br	**120j**:	63%	----	----	----
R^1 =-H, R^2 = 4-CN	**120k**:	50%	----	----	----
R^1 = H, R^2 = 4-F	**120l**:	----	----	80%	----
R^1 =H, R^2 = 2-OMe	**120m**:	----	----	----	----
R^1 =Cl, R^2 = H	**120n**:	82%	63%	82%	72%
R^1 =Cl, R^2 = 4-OMe	**120o**:	65%	45%	----	----
R^1 = Cl, R^2 = 4-Br	**120p**:	60%	60%	68%	80%

Scheme 52. Pathways for the synthesis of 2-benzoylbenzothiazoles **120** according to Wu and co-workers.



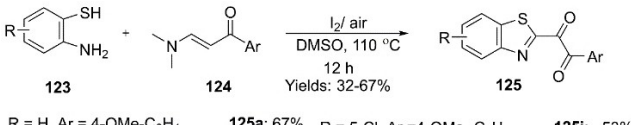
Scheme 53. Mechanism for the synthesis of 2-benzoylbenzothiazoles **120** according to Wu and co-workers.



Scheme 54. Iodine promoted synthesis of 2-acylbenzothiazoles **122** according to Shah and co-workers.

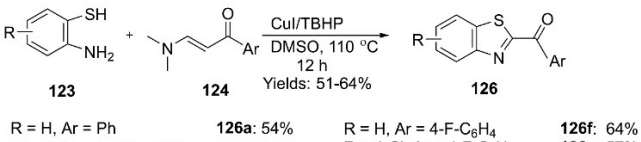
126 by employing simple enaminones **124** and 2-aminothiophenols **123** as starting materials (Scheme 55 and 56).[77] This protocol not only represented as a new methods for the synthesis of these useful heterocyclic molecules, but more importantly disclosed the novel reactivity possessed by enaminones via the rarely noticed C–C double bond activation.

More recently, Wu and co-workers have disclosed a novel synthesis of 2-acylbenzothiazoles **129** through the cyclization reaction between aryl-substituted acetonitriles **128** and 2-aminobenzenethiols **127** catalyzed by $AlCl_3$ and sequential oxidation by I_2 (Scheme 57).[78] The best reaction conditions were determined by stirring a mixture of **127** (0.5 mmol) and **128** (1.5 mmol) in the presence of $AlCl_3$ (0.6 mmol), I_2 (0.6 mmol), KI (0.75 mmol), and K_3PO_4 (0.5 mmol) in DMF (2.0 mL) at 90°C under aerobic conditions for 12 h. Using the optimized reaction conditions in hand, the authors have synthesized several derivatives of **129** from easily accessible starting materials under simple reaction conditions.



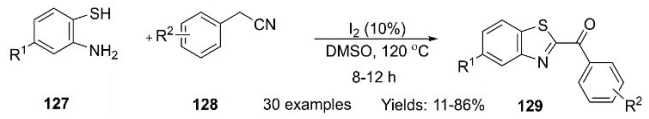
R = H, Ar = 4-OMe-C_6H_4	**125a**: 67%	R = 5-Cl, Ar =4-OMe- C_6H_4	**125j**: 53%
R = H, Ar = 4-OMe-C_6H_4	**125b**: 66%	R =5-Cl , Ar = 4-N(Me)$_3$-C_6H_4	**125k**: 66%
R = H, Ar = 2-Me-C_6H_4	**125c**: 57%	R = 5-Cl, Ar = 2-Me-C_6H_4	**125l**: 53%
R = H, Ar = 3, 4-OMe$_2$-C_6H_4	**125d**: 54%	R = 5-Cl, Ar = 2-thiophen-2-yl	**125m**: 54%
R = H, Ar = Ph	**125e**: 55%	R = 5-Cl, Ar =2-naphthyl	**125n**: 66%
R = H, Ar = 4-Cl-C_6H_4	**125f**: 45%	R = 6-Me, Ar =4-OMe- C_6H_4	**125o**: 59%
R = H, Ar = 4-CF_3-C_6H_4	**125g**: 32%	R = 6-Me, Ar = 2-Me-C_6H_4	**125p**: 53%
R = H, Ar = 2-thiophen-2-yl	**125h**: 57%	R = 6-Me, Ar = Ph	**125q**: 63%
R = H, Ar = 2-naphthyl	**125i**: 66%		

Scheme 55. Metal-free synthesis of 2-acylbenzothiazoles using I_2/air in DMSO.



R = H, Ar = Ph	**126a**: 54%	R = H, Ar = 4-F-C_6H_4	**126f**: 64%
R = H, Ar = 4-OMe-C_6H_4	**126b**: 51%	R = 4-Cl, Ar = 4-F-C_6H_4	**126g**: 57%
R = H, Ar = 4-Me-C_6H_4	**126c**: 53%	R = 4-Cl, Ar = 4-CF_3-C_6H_4	**126h**: 52%
R = H, Ar = 3, 4-OMe$_2$-C_6H_3	**126d**: 54%	R = H, Ar = 2-thiophen-2-yl	**126i**: 48%
R = H, Ar = 4-Cl-C_6H_4	**126e**: 57%	R = H, Ar = 2-naphthyl	**126j**: 52%

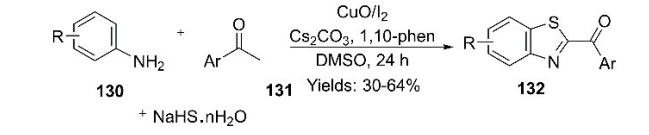
Scheme 56. Tunable CuI/TBHP assisted synthesis of 2-acylbenzothiazoles **126**.



Scheme 57. $AlCl_3$-Assisted reaction of **127** and **128** for the synthesis of 2-acylbenzothiazoles **129**.

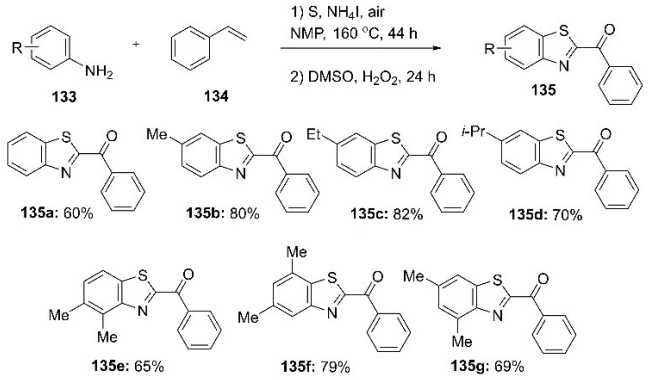
Another possible reaction accessible for the synthesis of 2-acylbenzothiazoles **132** was described by Wu and co-workers. According to the developed method, the reaction was proceeded via a combination of CuO-catalyzed cascade reactions in one pot using very readily available anilines **130** and aromatic ketones **131** (Scheme 58).[79] The reaction sequence not only supplied a novel method for constructing complex molecules, but also provided a typical example for logical and sustainable synthesis of these molecules.

In 2018, Ding and co-workers reported a three-component synthesis of 2-aroylbenzothiazoles **135** from aryl amines **133**, styrenes or aryl acetylene **134** and elemental sulfur in 1-methylpyrrolidin-2-one (NMP) (Scheme 59).[80] The C–S bond formation was realized *via* direct sulfuration of aromatic amine C–H bond. Elemental sulfur was used as the sulfur source as



R = H, Ar = Ph	**132a**: 54%	R = H, Ar = 2-thiophen-2-yl	**132l**: 50%
R = H, Ar = 4-Me-C_6H_4	**132b**: 51%	R = H, Ar =2-naphthyl	**132m**: 53%
R = H, Ar = 4-F-C_6H_4	**132c**: 37%	R = H, Ar = 2-furan-2-yl	**132n**: 48%
R = H, Ar = 4-Cl-C_6H_4	**132d**: 42%	R = H, Ar = 2-benzofuran-2-yl	**132o**: 44%
R = H, Ar = 4-OMe-C_6H_4	**132e**: 57%	R = H, Ar = 4,5- OEtO-C_6H_3	**132p**: 64%
R = H, Ar = 4-OEt-C_6H_4	**132f**: 55%	R = 5-Cl, Ar = Ph	**132q**: 53%
R = H, Ar = 4-NO_2-C_6H_4	**132g**: 57%	R = 5-CF_3, Ar = Ph	**132r**: 52%
R = H, Ar = 4-OH-C_6H_4	**132h**: 57%	R = 5-Me, Ar = Ph	**132s**: 62%
R = H, Ar = 4-Ph-C_6H_4	**132i**: 46%	R = 5-F, Ar = Ph	**132t**: 30%
R = H, Ar = 4-OMe-C_6H_4	**132j**: 57%	R = 5-NO_2, Ar = Ph	**132u**: 30%
R = H, Ar = 4-OMe-C_6H_4	**132k**: 57%	R = 5-Me, Ar = 4-Me-C_6H_4	**132v**: 30%

Scheme 58. CuO-Catalyzed reaction of **130** and **131** for the synthesis of 2-acylbenzothiazoles **132**.

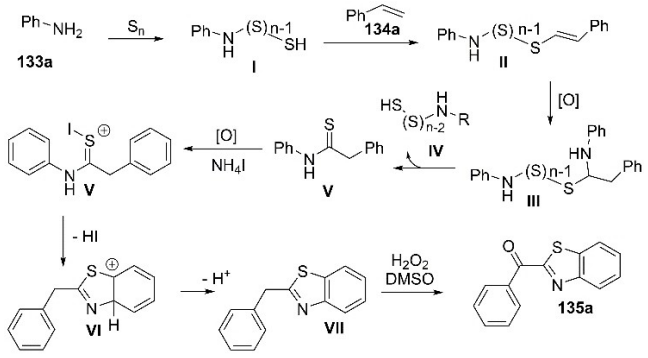


Scheme 59. Synthesis of 2-acylbenzothiazoles **135** using three component reaction according to Deng and co-workers.

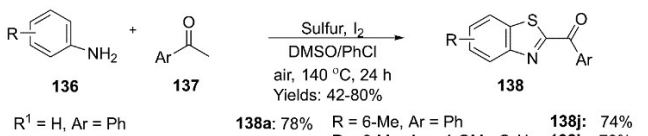
well as efficient oxidant to accomplish the transformation. The addition of NH_4I could significantly improve the yield of the desired product.

After several control experiments and previous reports,[81] a reasonable mechanism was proposed by authors, which suggested that the aniline **133 a** reacted with elemental sulfur to produce an intermediate **I**. The addition of intermediate **I** to styrene **134 a** delivers the intermediate **II**, which followed by the coupling with **133 a** gives intermediate **III**. Consequently, S–S bond cleavage of **III** occurs to release the intermediate **IV** and thioamide **V**. Further, the oxidative cyclization of **V** affords the final product **135 a**, which proceeded probably with the assistance of iodine salt (Scheme 60).

More recently, Phan and co-workers[82] have revealed a metal-free sequential transformation that proceeds in the presence of molecular iodine, similar to what was proposed by Wu in 2018,[81] using anilines **136**, acetophenones **137** and elemental sulfur (Scheme 61). The developed procedure involves the reaction of aniline **136**, with excess acetophenones **137** and elemental sulfur in the presence of iodine as the catalyst and in a mixture of DMSO/PhCl as oxidizing agent and solvent. The mixture was stirred for 24 h at 140 °C, and a diversity of 2-aceylbenzothiazoles **138** could be delivered in 42–80% yields. The advantages of this domino synthesis are represented as easily available starting materials, inexpensive, non-toxic, easy handling, and abundant elemental sulfur as building block and transition metal-free reaction conditions.



Scheme 60. Reaction mechanism for the synthesis of 2-acylbenzothiazoles **135** using three component reaction according to Deng and co-workers.

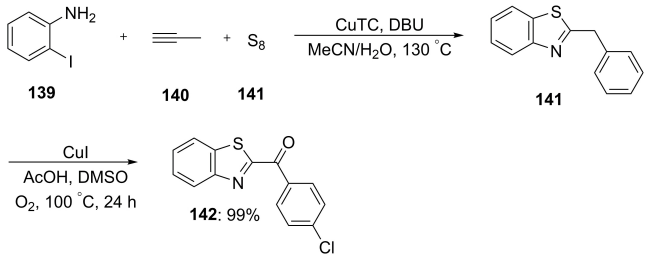


R^1 = H, Ar = Ph	**138a**: 78%	R = 6-Me, Ar = Ph	**138j**: 74%
R = H, Ar = 4-OMe-C_6H_4	**138b**: 80%	R = 6-Me, Ar = 4-OMe-C_6H_4	**138k**: 78%
R = H, Ar = 3-OMe-C_6H_4	**138c**: 77%	R = H, Ar= 2-thiophen-2-yl	**138l**: 61%
R = H, Ar = 4-Cl	**138d**: 63%	R = 5-Me, Ar = 3-OMe-C_6H_4	**138m**: 75%
R = H, Ar = 3-Cl	**138e**: 72%	R = 5-Cl, Ar = 4-Br-C_6H_4	**138n**: 48%
R = H, Ar = 4-Br-C_6H_4	**138f**: 54%	R = 6-OMe, Ar = 4-Br-C_6H_4	**138o**: 57%
R = H, Ar = 4-NO_2-C_6H_4	**138g**: 42%	R = 6-Me, Ar = 3- OMe-C_6H_4	**138p**: 64%
R = H, Ar = 2-OH-4-Me-C_6H_3	**138h**: 53%	R = 6-Me, Ar = NO_2	**138q**: 52%
R = H, Ar = 2-Cl-C_6H_4	**138i**: 61%	R = 5-Cl, Ar = Ph	**138r**: 59%

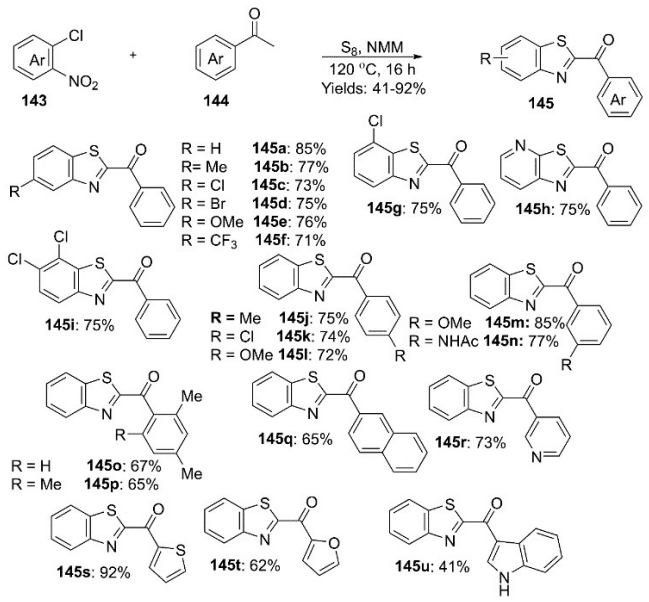
Scheme 61. I_2-Catalyzed the reaction of **136** and **137** for the synthesis of 2-acylbenzothiazoles **138**.

In 2018 Jiang, Wu and co-workers have developed a highly regioselective procedure for the synthesis of 2-arylbenzothiazoles and 2-acylbenzothiazoles **142**. They have reported that 2-benzylbenzothiazoles **141**, which are generated by the copper-catalyzed cyclization of 2-haloanilines **139**, elemental sulfur and terminal alkynes **140**, undergoes Cu-catalyzed oxygenation at the benzylic position (Scheme 62).[83] This route employs a concise synthetic method to assemble a molecular framework in one pot, where different types of 2-substituted benzothiazole are prepared using triple bonds as one-carbon synthons in different reaction systems.

Further approach towards the preparation of 2-aroylbenzothiazoles **145** in moderate to good yields was achieved by a three-component redox condensation reaction of 2-halonitrobenzenes **143**, acetophenones **144**, elemental sulfur, and *N*-methylmorpholine as base at 120 °C for 24 h (Scheme 63).[84] The selection of *N*-methylmorpholine as base is important for the achievement of this transformation, and was found to be mainly suitable for this reaction. The elemental sulfur was found to play dual roles as nucleophilic building block and redox moderating agent to accomplish electronic requirement of this process. The transformation involves, formation of three new bonds (two C–S and one C=N) without addition of oxidizing or reducing agents or catalyst for coupling-reaction.



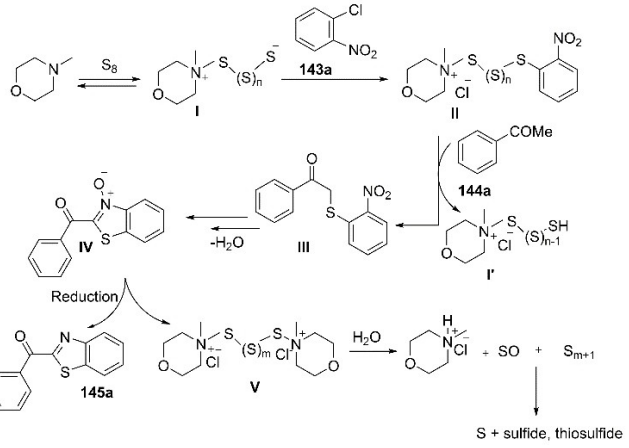
Scheme 62. CuI-Catalyzed formation of 2-acylbenzothiazoles **142** according to Wu and co-workers.



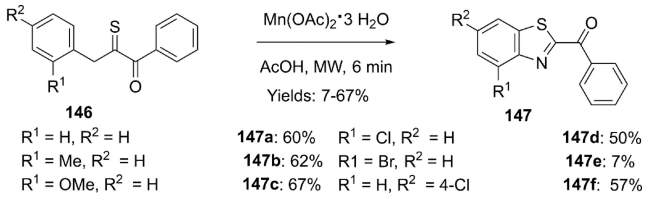
Scheme 63. Synthesis of 2-aroylbenzothiazoles **145** by the reaction of 2-halonitrobenzenes **143**, acetophenones **144** and elemental sulfur.

Suggested mechanism for the formation of 2-aroylbenzothiazoles **145** involves the initiation of ammonium polysulfide zwitterion **I** by the reaction of sulfur with *N*-methylmorpholine. The nucleophilic aromatic substitution of zwitterion **I** on 2-chloronitrobenzene **143a** would lead to the formation of intermediate **II**. With the help of electron withdrawing effects of the aromatic nitro group, the S–S bond next to the aromatic ring of **II** would be capable of nucleophilic attack on acetophenone **144a** to afford sulfide intermediate **III** and a homologue of zwitterion **I**. Triggered by both benzoyl group and aryl sulfide group, the methylene group of sulfide **III** could undergo condensation reaction readily with the aromatic nitro group which leading to the formation of nitrone **IV**. The reduction of intermediate **IV** would provide the product **145a** along with the formation of double-zwitterion **V**. Hydrolysis of **V** by water would release partially elemental sulfur and lead to the oxygenated sulfur compounds ("SO") and *N*-methylmorpholinium hydrochloride (Scheme 64).

Furthermore, the transition metal-catalyzed *S*-arylation protocol was used for the preparation of sulfur heterocycles. Zou and co-workers established a method for the synthesis of 2-aroyl benzothiazoles **147**, based on the $Mn(OAc)_2 \cdot 3H_2O$-catalyzed intramolecular C–S cross-coupling reaction of the α-benzoylthioformanilide **146** (Scheme 65).[85] Major advantages of this protocol are the use of manganese triacetate as a new reagent to replace potassium ferricyanide or bromine for radical



Scheme 64. The plausible mechanism for the synthesis of 2-benzoylbenzothiazoles **145a** by the coupling of 2-chloronitrobenzenes **143a**, acetophenone **144a** and elemental sulfur.

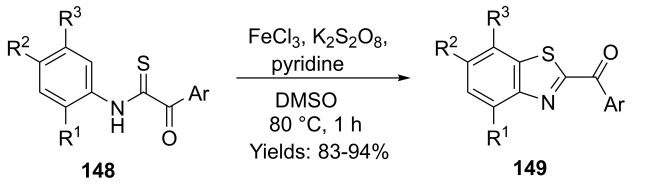


Scheme 65. Mn-Catalyzed formation of 2-aroylbenzothiazoles **147** using microwave irradiation.

cyclization of substituted thioformanilides. The desired 2-substituted 2-aroylbenzothiazoles **147** are produced in 6 minutes under microwave irradiation.

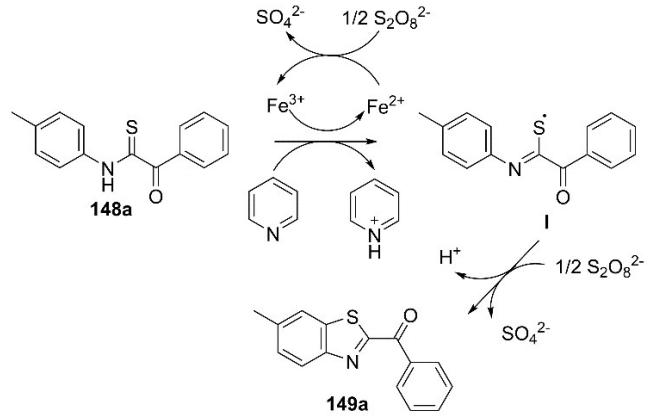
Similar to previously discussed intramolecular C–S cross-coupling reaction of the α-benzoylthioformanilide **146** catalyzed by Mn(III),[85] the new method begins by using Fe(III) with the substrate *N*-benzoylbenzothioamides **148** to form 2-aroylbenzothiazoles **149** (Scheme 66).[86] The developed method involves an efficient synthesis of 2-benzoylbenzothiazoles **149** via intramolecular C(Ar)–H/S–H activation and C–S bond formation catalyzed by $FeCl_3$ under mild reaction conditions in the presence of optimized conditions (0.50 mmol of **148**, 0.05 mmol $FeCl_3$, 0.50 mmol $K_2S_2O_8$) to prepare a series of desired products **149**, in reasonable to very good yields after 1 h of reaction time at 80 °C.

Based on previous reports[87] and control experiments, a plausible reaction mechanism was proposed. At first, the Fe^{3+}-catalyst oxidizes the *N*- benzoylbenzothioamide **148a** to produce thionyl radical intermediate **I**, and Fe^{3+} ion reduces to Fe^{2+}. The oxidant $K_2S_2O_8$ re-oxidizes Fe^{2+} into Fe^{3+} to continue the reaction. Ring closure reaction of intermediate **I**, followed by the oxidation in the presence of $K_2S_2O_8$, afforded the targeted compound **149a**. (Scheme 67).



R^1 = H, Cl
R^2 = H, F, Cl, Br, Me, OMe, OEt
R^3 = H, Cl, Me, OMe
Ar = Ph, 4-Me-C_6H_4, Furan-2-yl, Thiophen-2-yl, 2-Cl-C_6H_4, 4-Br-C_6H_4, 4-OMe-C_6H_4, 4-Cl-C_6H_4, 4-^{t}Bu-C_6H_4

Scheme 66. Fe-Catalyzed formation of 2-aroylbenzothiazoles **149** from *N*-benzoylbenzothioamides **148**.



Scheme 67. Plausible reaction mechanism for the synthesis of 2-aroylbenzothiazoles **149**.

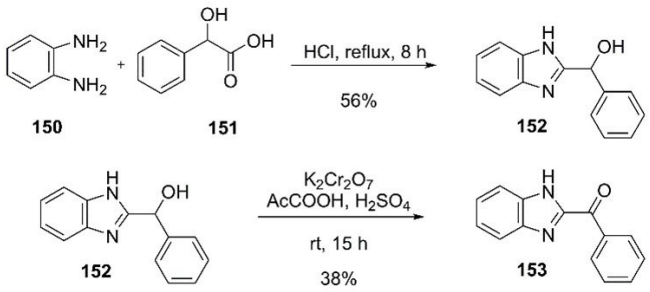
3. Synthesis of 2-keto annulated imidazoles

Due to the significant contribution of annulated imidazoles in the field of natural products, pharmacological applications and many clinical applications, the synthesis of these compounds is of great interest. Here, we will demonstrate the important synthetic protocols according to the starting materials, reaction conditions under which they are synthesized.

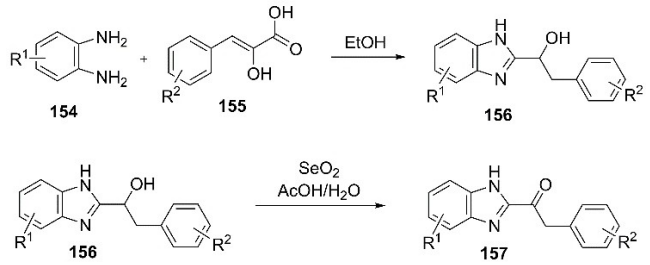
In 1963, Wallis and O'Sullivan described the use of $K_2Cr_2O_7$/CH_3COOH, H_2SO_4 as an efficient oxidizing medium to convert 2-(α-hydroxybenzyl)benzimidazoles **152** to 2-benzoylbenzimidazoles **153** with 37% yield.[21] The compound **152** was prepared by the condensation of *o*-phenlenediamine **150** with mandelic acid **151** in acidic solution (Scheme 68). The influence of compounds **153** on type 1 and 2 viruses is negligible. However, the compounds **153** exhibit small protection against type 3 virus. Although the reported methods are important and have been extensively used over past years, these protocols have serious restrictions, like the use of strong oxidizing agents in the presence of strong acids.

Similar approach for the synthesis of 2-aroylbenzimidazoles was achieved by Dirngerger and co-workers in 1967. Their method relied on the condensation of 2-hydroxy-3-phenylacrylic acid **155** with *o*-phenlenediamine **154** under reflux conditions in ethanol to afford the 1-(1*H*-benzo[d]imidazol-2-yl)-2-phenylethanol **156** (Scheme 69).[88] Then, the compounds **156** were oxidized using SeO_2 in refluxed ethanol and acetic acid for 60 h to give the final products 1-(1*H*-benzo[d]imidazol-2-yl)-2-phenylethanone **157**.

Similar to what was proposed by O'Sullivan in 1963[21] and Dinbeger in 1967,[88] Ishii and co-workers in 1990 represented



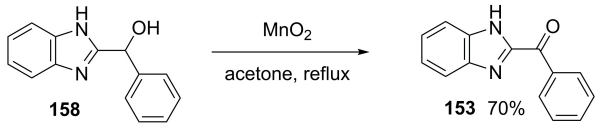
Scheme 68. Synthesis of 2-aroylbenzothiazoles **153** according to Wallis and O'Sullivan.



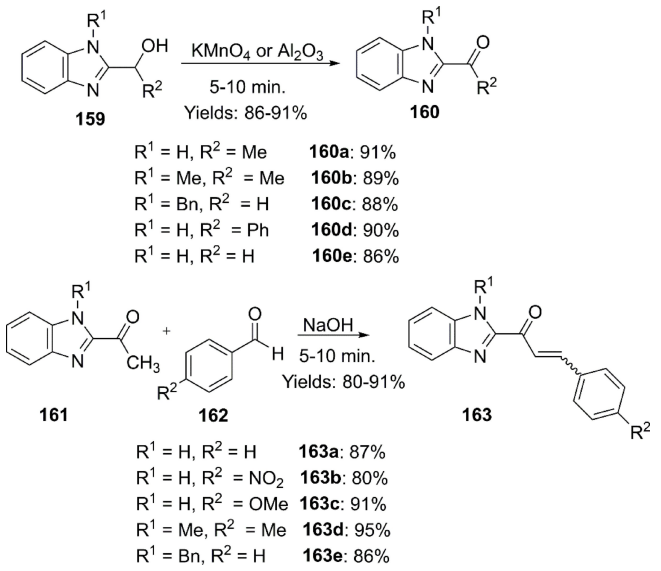
Scheme 69. Synthesis of 1-(1*H*-benzo[d]imidazol-2-yl)-2-phenylethanone **157** according to Dinberger and co-workers.

another route for the synthesis of 2-aroylbenzimidazole **153** in 76.5% yield, through the oxidation of 2-(α-hydroxybenzyl)benzimidazoles **158** in acetone (Scheme 70).[89]

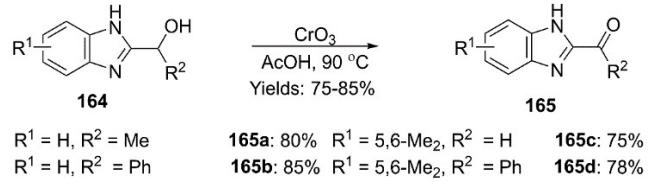
Furthermore, Dupy and co-workers employed the same route using $KMnO_4$ or neutral alumina as oxidizing agent



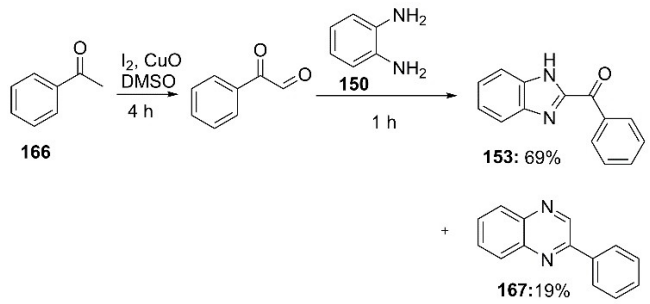
Scheme 70. Synthesis of 2-aroylbenzothiazoles **153** using activated MnO_2.



Scheme 71. Synthesis of 2-ketoaryl(alkyl)benzimidazole **160** and 1-(1*H*-benzo[d]imidazol-2-yl)-3-phenylpropan-1-one **163** according to Dubey and co-workers.



Scheme 72. Synthesis of 2-aroylbenzothiazoles **165** using CrO_3.



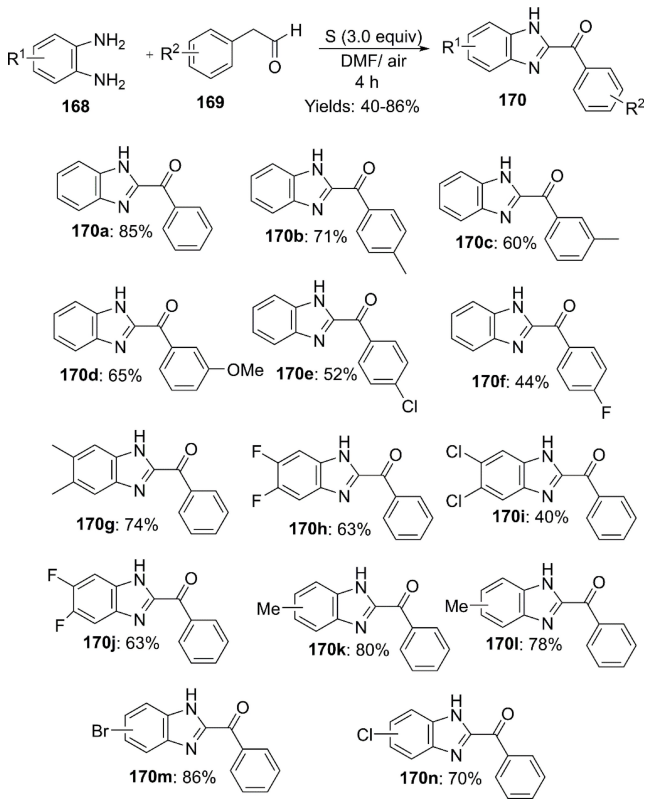
Scheme 73. The unexpected formation of 2-benzoylbenimidazole **153** according to Wu and co-workers.

instead of $K_2Cr_2O_7$,[21] or SeO_2,[88] or MnO_2,[89] for the synthesis of 2-ketoaryl(alkyl)benzimidazole **160** from 1-alkyl/aralkyl-2-(α-hydroxyalkyl/aryl)benzimidazoles **159** under solvent free conditions. In this study, the 1-(1*H*-benzo[*d*]imidazol-2-yl)-3-phenylpropan-1-one derivatives **163** were synthesized through the reaction of **161** with benzaldehydes **162** using NaOH as base (Scheme 71).[90]

The 1-(1*H*-benzo[*d*]imidazol-2-yl)-2-phenylethanol **164** can simply be transformed into 2-ketoaryl(alkyl)benzimidazoles **165**, similar to what was shown in earlier Schemes 69–73 for the Oxidation of **164**. In this example, the CrO_3 was used in place of $K_2Cr_2O_7$, SeO_2, MnO_2, $KMnO_4$ (Scheme 72).[91]

Furthermore, when the reaction was performed between *o*-phenylenediamine **150** and acetophenone **166** in the presence of I_2/CuO/DMSO that delivered the unexpected product 2-benzoylbenzimidazole **153**, instead of the expected 2-phenylquinoxaline **167** (Scheme 73).[92] However, this protocol is convenient for one-pot synthesis of quinoxaline from simple ketones and 1,2-diamines. This route underwent towards the preparation of substituted quinoxalines **167** via a successive iodination, Kornblum oxidation and cyclization in the presence of I_2/CuO/DMSO.

Recently, Huang and co-workers have reported a new cascade reaction between *o*-phenylenediamines **168** and phenylacetaldehydes **169** towards (1*H*-benzo[*d*]imidazol-2-yl)(phenyl)methanones **170** (Scheme 74).[93] The best reaction conditions consist in mixing equivalent amounts of **168** and **169** in the presence of S_8 (3.0 equiv) as catalyst, DMF as solvent



Scheme 74. Elemental sulfur-promoted formation of various 2-aroylbenzothiazoles **170**.

under aerial conditions for 20 h at 60 °C. By this procedure, a series of 2-aroylbenzimidazoles **170** were obtained in 40–86% yields. The 2-aroylbenzimidazoles **170** was collected by the oxidative rearrangement of 2-benzylbenzimidazoles using a combination DMF/S_8.

Control experiments conducted in the presence of a radical scavengers 2,2,6,6-tetramethyl-1-piperidinyl (TEMPO) revealed that a radical pathway is not involved in the reaction. The GC-MS measurements showed that 2-benzyl-1*H*-benzo[*d*]imidazoles **B** was formed during the reaction. Based on these control experiments the mechanism is depicted in Scheme 75. Initially, the reaction mechanism involves the condensation of *o*-phenylenediamines **168** with phenylacetaldehydes **169** to form a schiff base **A**, which followed by ring closure afforded the compound **B**. The intermediate **B** was then oxidized to give the corresponding 2-benzoylbenztiazole **170.**

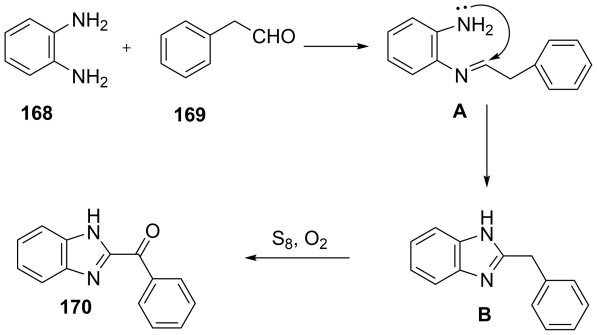
During the course of recent decades, a number of routes using oxidation of 2-benzylbenzimidazoles for the synthesis of 2-ketoaryl benzimidaoles have been developed. A collection of the contributions is presented here.

In 1996, Alcalde and co-workers have reported a SeO_2 catalyzed oxidation of 5,6-dimethyl-2-pyridyl-1*H*-benzimidazole **173** to 5,6-dimethyl-2-(4-pyridylcarbonyl)-1H-benzimidazoles **174** with 38% yield.[94] The 5,6-dimethyl-2-pyridyl-1*H*-benzimidazole **173** was prepared by the condensation of *o*-phenylenediamine **171** with pyridylcarboxylic acid **172** in the presence of PPA at 170–180 °C (Scheme 76).[95]

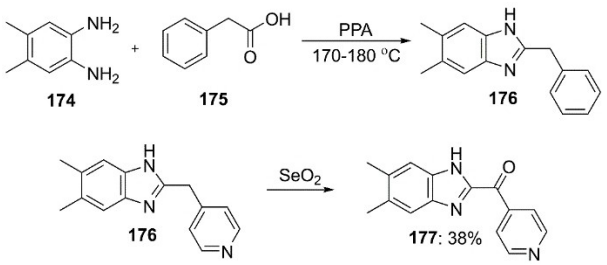
In 2013, Grimaud and co-workers have employed the Pd-catalyzed oxidation of 2-benzyl benzoimid(thia)zoles **175/176** under aerobic conditions to afford the corresponding 2-aroylbenzoimid(thia)azoles **177/178** in good yields (Scheme 77).[96] The results revealed that uses of palladium acetate as a catalyst instead of Cs_2CO_3 has little effect and even gives, in some cases, much lower yields.

In 2017, Stahl and co-worker have established an accessible approach for the synthesis of 2-(hetero)aryl ketones **180** from 2-benzylbezimidazoles **179** in the presence of cobalt(II)/*N*-hydroxypthalimide as catalyst in BuOAc ester as solvent under oxygen atmosphere at 90 °C for 12 h (Scheme 78).[26] This result indicates that the use of Co/NHPI catalyst promotes the benzylic aerobic oxygenation reactions using radical-mediator. The robustness of the protocol was shown in the large-scale preparation of 2-(hetero)aryl ketones.

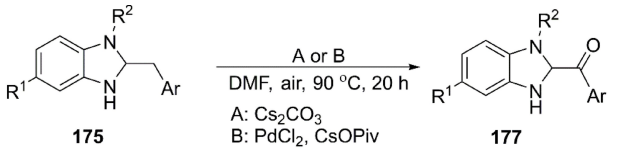
In the same year 2017, Xu and co-workers have developed a metal-free oxidation for the synthesis of 2-benzoylbenzimidazole **153** from readily available 2-benzylbenzimidazole **181**



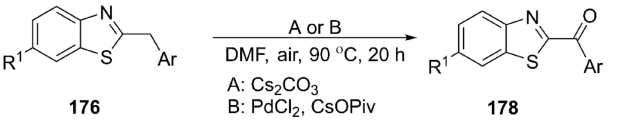
Scheme 75. Plausible mechanism for the synthesis of (1H-benzo[d]imidazol-2-yl)(phenyl)methanones **170**.



Scheme 76. SeO_2-Promoted formation of 5,6-dimethyl-2-(4-pyridylcarbonyl)-1*H*-benzimidazoles **174**.

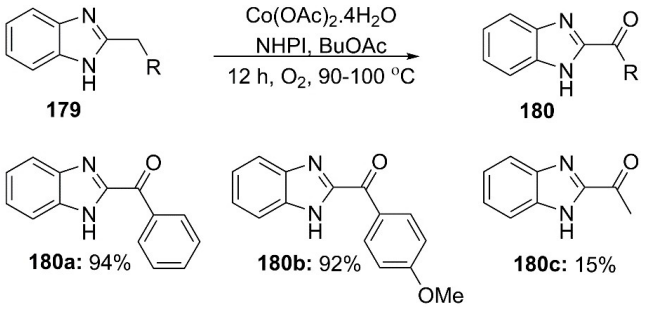


		Yield A%	Yield B%
R^1 = H, Ar = Ph, R^2 = H	**177a**	21	9
R^1 = H, Ar = 3,4-OMe_2-C_6H_3, R^2 = H	**177b**	19	46
R^1 = Cl, Ar = 4-Me-C_6H_4, R^2 = H	**177c**	71	54
R^1 = COPh, Ar = Ph, R^2 = H	**177d**	73	37
R^1 = NO_2, Ar = Ph, R^2 = H	**177e**	29	20
R^1 = Me, Ar = 2-thiophenyl, R^2 = H	**177f**	52	29
R^1 = H, Ar = 3,4-OMe_2-C_6H_3, R^2 = Et	**177g**	90	67
R^1 = H, Ar = 4-Me-C_6H_4, R^2 = 4-*t*-Bu$C_6H_4CH_2$	**177h**	84	74
R^1 = H, Ar = 4-Me-C_6H_4, R^2 = tosyl	**177i**	0	0



		Yield A%	Yield B%
R^1 = H, Ar = Ph	**178a**	58	71
R^1 = H, Ar = 2-thioph**enyl**	**178b**	54	19
R^1 = H, Ar = 4-F-C_6H_4,	**178c**	49	0
R^1 = Cl, Ar = Ph	**178d**	46	73
R^1 = Cl, Ar = 3,4-OMe_2-C_6H_3	**178e**	48	71

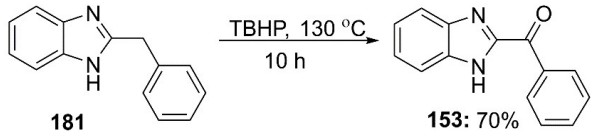
Scheme 77. Synthesis of 2-(hetero)aryl ketones **177**, **178** from 2-benzylbezimid(thi)azoles **175**, **176** using Cs_2CO_3 or $PdCl_2$.



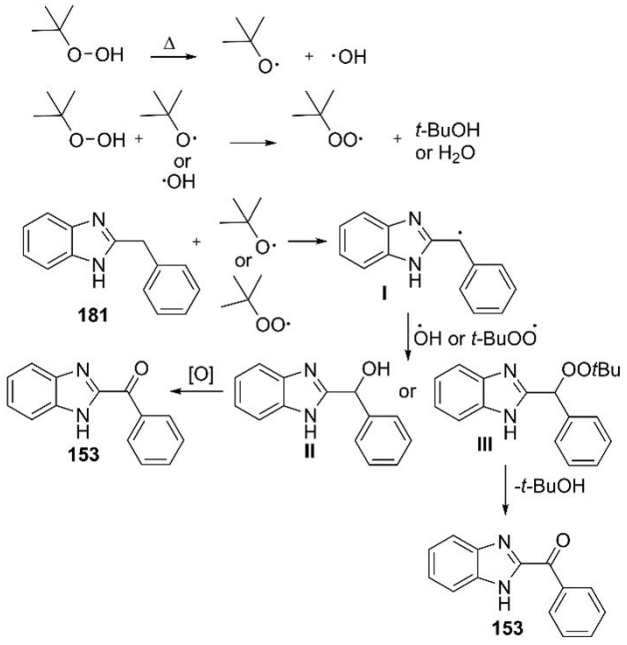
Scheme 78. 2-(hetero)aryl ketones **180** from 2-benzylbezimidazoles **179** using cobalt(II)/*N*-hydroxypthalimide catalyst.

using *tert*-butyl hydroperoxide (TBHP) at 130 °C (Scheme 79).[97] The radical-based reaction pathways tolerate on several benzylic C–H bonds that affording the required product in good to excellent yields.

Based on several control experiments, the authors proposed a mechanistic pathway for the preparation of 2-benzoylbenzimidazole from 2-benzylbenzimidazole (Scheme 80). Initially, the oxygen-based radicals generated from the cleavage of TBHP. When the radical is formed, the intermediate **I** is generated by the abstraction of H from substrate **181**. The radical intermediate **I** can either react with OH radical or COO^{t}Bu radical to give the oxygenated intermediate **II** or **III**. The intermediate **II** either undergo elimination of one molecule of *t*-BuOH to afford the ketone **153**, or oxidized the benzyl alcohol **III** to give the desired aryl ketone product **153.**



Scheme 79. Synthesis of 2-benzoylbenzimidazole **153** using TBHP according to Xu and co-workers.



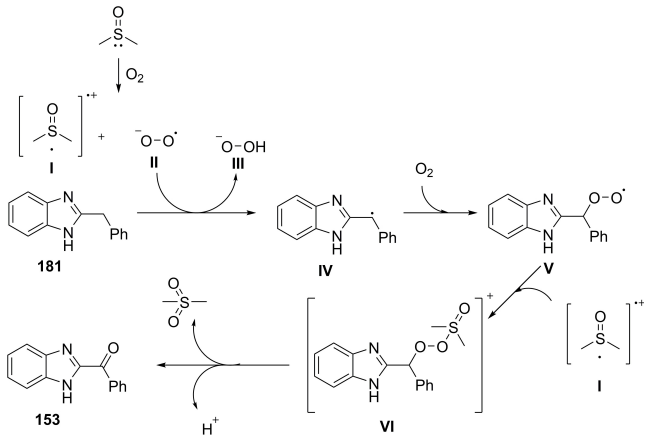
Scheme 80. Proposed mechanism for the Synthesis of 2-benzoylbenzimidazole **153** according to Xu and co-workers.

Furthermore, Liu and co-workers established another protocol for the synthesis of 2-benzoylbenzimidazole **153** through the direct oxygenation of 2-benzylbenzimidazole **181** using DMSO and O_2 as terminal oxidant (Scheme 81).[27] In addition, this method can be performed in a gram scale with good reaction efficiency. This selective oxygenation reaction of heterobenzylic methylene group can be achieved using DMSO, which plays an important role in this transformation.

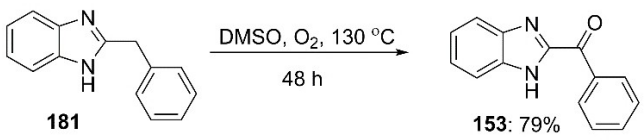
Based on control experiments and previous reports,[98] the proposed reaction mechanism can be started with the oxidation of DMSO using O_2 to generate intermediate **I** and **II**. Subsequently, 2-benzylbenzimidazole **181** can be oxidized by **II** to afford the intermediate **III** and the free radical **IV**. Further oxygenation of **IV** with O_2 gives the intermediate **V**, which reacts with the intermediate **I** to deliver the intermediate **VI**. Finally, the 2-benzoylbenzimidazole **153** and dimethyl sulfone were obtained by the O–O bond cleavage of the intermediate **VI** (Scheme 82).

In 2022, Li and co-workers have developed an efficient synthesis of 2-benzoylbenzimidazole **153** starting from 2-benzylbenzimidazole **181** in the presence of catalytic amounts of *rac*-Mn complex and H_2O_2 as an oxidant in CH_3CN at room temperature for 1 h (Scheme 83).[99] This developed route has opened a new horizon using a benign oxidant with unique level of functional group tolerance.

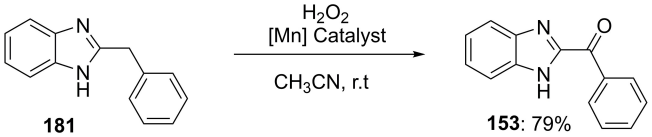
More recently in 2022, Liu and co-workers have disclosed a novel protocol for the synthesis of 2-aroylbenzimidazoles **183** from 2-arylbenzimidazoles **182** using palladium as catalyst and H_2O as only oxygen donor (Scheme 84).[100] The source of oxygen atom presented into the product is from water molecule, which is confirmed by MS-analysis using the ^{18}O



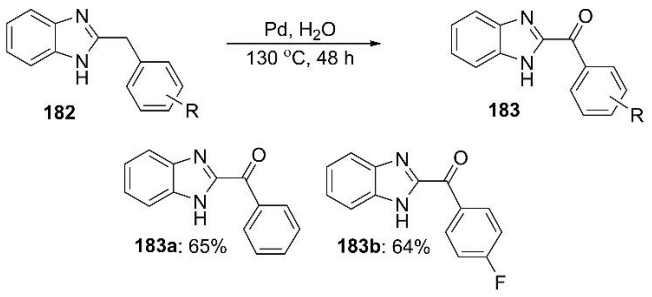
Scheme 82. Plausible mechanism for the formation of 2-benzoylbenzimidazole **153**.



Scheme 81. Synthesis of 2-benzoylbenzimidazole **153** using DMSO and O_2 as terminal oxidant.



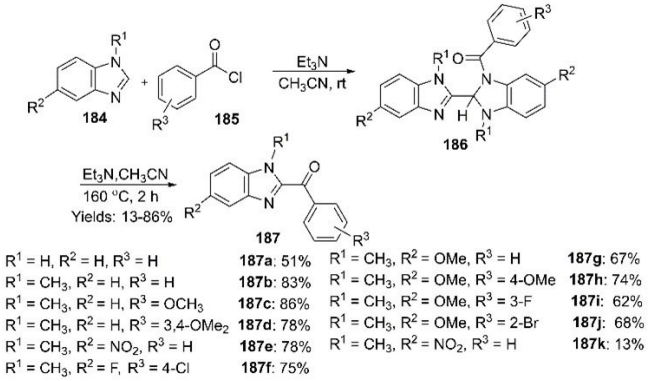
Scheme 83. Synthesis of 2-benzoylbenzimidazole **153** using *rac*-Mn complex and H_2O_2 as oxidant.



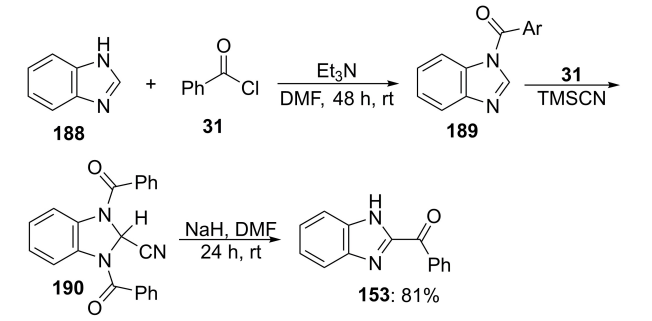
Scheme 84. Synthesis of 2-benzoylbenzimidazole **183** using Pd-catalyst and water as source of oxygen.

labeled water molecule (H_2O^{18}). The developed benzylic oxidation does not require other oxidant and hydrogen acceptors.

The functionalization of benzimidazoles is another route for the synthesis of 2-keto aryl(alkyl)benzimidazoles. In 1983, Yatsimirskii and co-wokers have reported the synthesis of 2-acylbenzimidazoles **187** from 3-benzoyl-2-(1-methyl-2-benzimidazolyl)-4-benzimidazolines **186** by heating in the presence of triethylamine. The compound **186** has been prepared by the reaction of benzimidazoles **184** with benzoyl chlorides **185** at room temperature in the presence of triethylamine and CH_3CN as solvent (Scheme 85).[101]



Scheme 85. Direct acylation of benzimidazoles according to Yatsimirskii and co-workers.



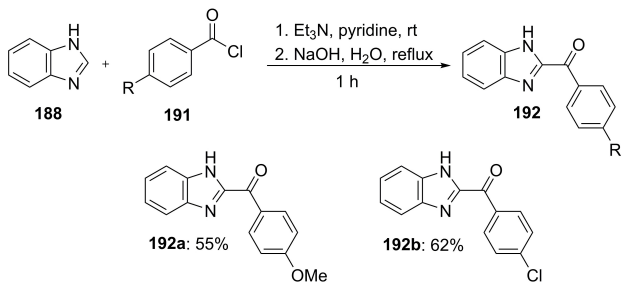
Scheme 86. The rearrangement reaction of **190** with NaH/DMF to give 2-benzoylbenzimidazole **153**.

A similar route was established by Gibson and Jois in 1994. Their approach depends upon the acylation of benzimidazole **188** with acyl chloride **31** using triethylamine in DMF to give 1-acylbenzimidazole **189**, which are reacted in the next step with another molecule of **31** using TMSCN to give the 2-cyano-1,3-dibenzoyl-2,3-dihydrobenzimidazole **190**. Then, the base-induced rearrangement of **190** afforded 2-benzoylbenzimidazole **153**. The presence of radical-ion intermediates during the rearrangement reaction of **190** in the presence of NaH/DMF was proven by CIDNP and ESR (Scheme 86).[102]

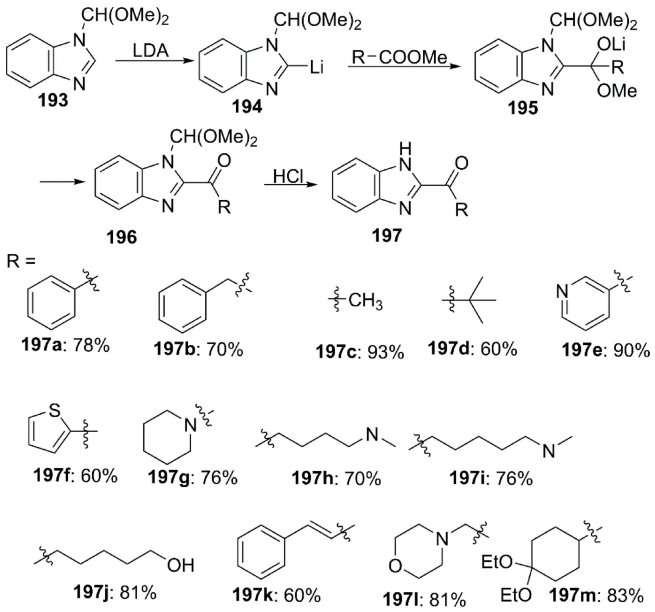
The benzimidazole **188** can be easily functionalized with acyl chlorides **191**, similar to what was shown in Schemes 86 and 87. In this case, the NaOH was used instead of NaH as base (Scheme 87).[103]

To overcome the drawback of using acid chlorides; in 2005, Wu and co-workers have established a new protocol for the synthesis of 2-acylbenzimidazoles through the functionalization of benzimidazoles with ester, lactones, and lactams. The reaction initiates with deprotonation of benzimidazoles **193** with LDA to give the 2-lithiated product **194** followed by the addition of esters delivers the hemiacetal intermediate **195** and then the protected 2-acylbenzimidazoles **196**. Treatment of **196** with acid gives the deprotected 2-acybenzimidazoles **197** (Scheme 88).[104] In addition, this reaction could be performed in one-pot by the reaction of *o*-phenylenediamine **150** with triethyl formate. After removal of volatile byproducts by distillation, the products **153** could be afforded in 76% yields by lithiation, and acylation followed by deprotection (Scheme 89).

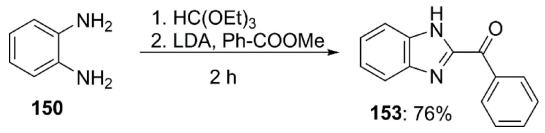
In 2016, Song and co-workers disclosed the first C–N bond formation reaction by the use of Cu-catalyzed aerobic oxidative decarboxylative acylation of benzimidazoles. The reaction of 2-halogenated phenylacetic acid **199** with benzimidazoles **198** under the use of $Cu(OAc)_2$, CuBr delivered the fused 11*H*-benzo[4,5]imidazo[1,2-*a*]indol-11-one **200**, and *N*-benzoylated benzimidazoles **201**, respectively (Scheme 90).[105] The annulation route is relied upon a domino reaction pathway through an aromatic nucleophilic substitution followed by an oxidative acylation. In both cases, phenylacetic acids **205** played as a novel benzoylation reagent.



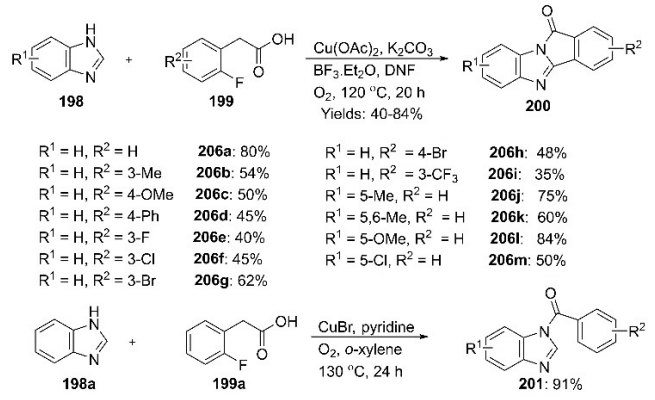
Scheme 87. Direct acylation of benzimidazoles according to Yurttas and co-workers.



Scheme 88. Acylation of benzimidazoles according with ester according to Miller and co-workers.



Scheme 89. One pot synthesis of 2-acylbenzimidazole **153** according to Miller and co-workers.



Scheme 90. Synthesis of 11*H*-benzo[4,5]imidazo[1,2-a]indol11-one **200**, N-benzoylated benzimidazoles **201** according to Song and co-workers.

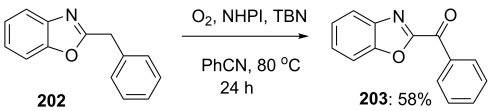
4. Synthesis of 2-keto annulated oxazoles.

The annulated oxazoles form the vital core structure in a large and a wide variety of natural products, and display various biological and pharmaceutical properties. Among them 2-aroylbenzoxazoles are specific class of compounds, which have been found to exhibit a series of biological activities. Consequently, numerous synthetic routes to these skeletons have been reported and which are summarized in previous review.[22] Here, we highlight the synthetic routes described for these important compounds from 2019 to 2022.

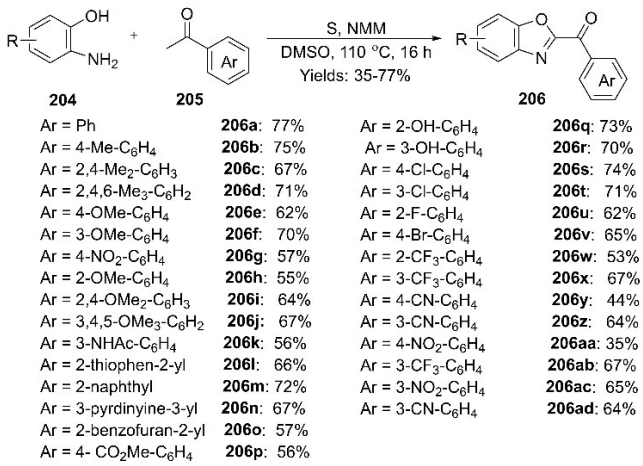
In 2021 Kang and co-workers, reported the synthesis of 2-benzoylbenzoxazole **203** from the oxidation of 2-benzylbenzoxazole **202** using NHPI-^{t}BuONO catalyst in the presence of oxygen in benzonitrile at 80 °C for 24 h (Scheme 91).[29]

Moreover, in 2021, Nguyen and co-workers established a very interesting route for the synthesis of 2-benzoylbenzoxazoles **206** involving the straightforward Willgerodt type benzoxazolation and methylene oxidation, which was promoted by elemental sulfur in DMSO. The best reaction condition consists of stirring a mixture of *o*-aminophenols **204** (1 equiv) with acetophenones **205** (1.2 equiv) in the presence of NMM (0.5 equiv) as additive, S_8 (1 equiv) as oxidant and DMSO as an oxidant, and solvent at 110 °C for 16 h (Scheme 92).[106] Furthermore, these methods are found to be cheapest and most convenient protocol to afford a collection of 2-benzoylbenzoxazoles.

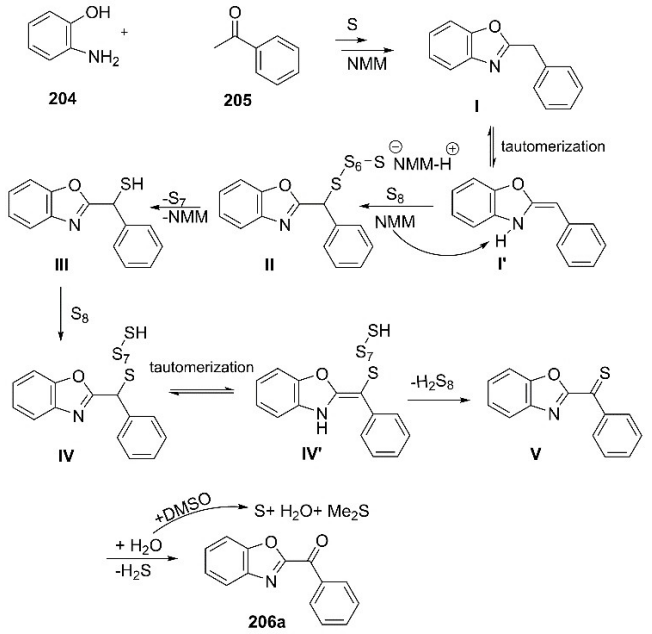
Relied on the control experiments conducted by these authors and previous reports,[107] a reasonable reaction mechanism was proposed (Scheme 93). Initially, the 2-benzylbenzoxazole **I** is provided by Willgerodt-type of reaction between 2-aminophenol **204** and acetophenone **205**. Tautomerization of **I** to **I'** facilitated by the presence of benzoxazole and phenyl moiety, and followed by the reaction with S_8 in NMM afforded the intermediate **II**. Then, extrusion of sulfur from **II** occurs and the oxidation of thiol **III** to thione **V** may be realized, which would proceed *via* the formation of polysulfide **IV** and its tautomer **IV'**. Finally, the hydrolysis of thione **V** would lead to the formation of products **206a** by the exchange of sulfur-atom with oxygen.[108]



Scheme 91. Synthesis of 2-benzoylbenzoxazole using NHPI-^{t}BuONO catalyst.



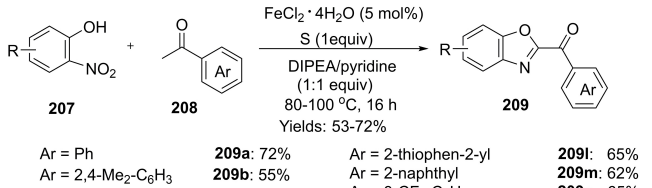
Scheme 92. Scope of methyl Aryl ketones for the synthesis of 2-benzoylbenzoxazoles **206**.



Scheme 93. Plausible mechanism for the formation of 2-benzoylbenzoxazole **210a**.

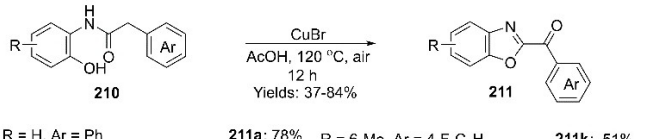
More recently, the same group has disclosed the synthesis of 2-benzoylbenzoxazoles **209** from the reaction of 2-nitrophenols **207** and acetophenones **208** in the presence of tertiary amine and Fe/S catalyst generated *in situ* from simple $FeCl_2 \cdot 4H_2O$ and S_8 (Scheme 94).[109] In addition, this protocol employs an inexpensive and readily available starting materials such as *o*-nitrophenols, acetophenones and methylquinoline analogues with a high degree of structural diversity. The condensed products 2-benzoylbenzoxazoles and 2-quinolylbenzoxazoles were obtained in reasonable yields with water as the only byproduct at 80 °C.

Almost at the same time in 2021, Yunyum and co-workers described their findings in the synthesis of 2-acylbenzoxazoles **211** *via* the Cu(I)-catalyzed tandem benzoxazole annulation and C(sp^3)-H oxygenation, employing *N*-(*o*-hydroxyphenyl) **210** as starting materials (Scheme 95).[110] In addition, the synthesis of



Ar = Ph	**209a**: 72%	Ar = 2-thiophen-2-yl	**209l**: 65%
Ar = 2,4-Me_2-C_6H_3	**209b**: 55%	Ar = 2-naphthyl	**209m**: 62%
Ar = 2,4,6-Me_3-C_6H_2	**209c**: 58%	Ar = 3-CF_3-C_6H_4	**209n**: 65%
Ar = 3,4,5-OMe_3-C_6H_2	**209d**: 68%	Ar = 2-benzofuran-2-yl	**209o**: 66%
Ar = 4-OMe-C_6H_4	**209e**: 53%	Ar = 4-CF_3-C_6H_4	**209p**: 68%
Ar = 3-OMe-C_6H_4	**209f**: 55%	Ar = 2-CF_3-C_6H_4	**209q**: 63%
Ar = 4-F-C_6H_4	**209g**: 62%	Ar = 3-CN-C_6H_4	**209r**: 65%
Ar = 3-Cl-C_6H_4	**209h**: 61%	Ar = 4-CN-C_6H_4	**209s**: 62%
Ar = 4-Cl-C_6H_4	**209i** : 53%	Ar = 3-NO_2-C_6H_4	**209t**: 54%
Ar = 4-Br-C_6H_4	**209j**: 63%	Ar = 4-CO_2Me-C_6H_4	**209u**: 59%
Ar = 3-NHAc-C_6H_4	**209k**: 57%		

Scheme 94. Fe/S-Catalyzed synthesis of 2-acylbenzimidazole **209** according to Nguyen and co-workers.



R = H, Ar = Ph	**211a**: 78%	R = 6-Me, Ar = 4-F-C_6H_4	**211k**: 51%
R = 7-Me, Ar = 4-Me-C_6H_4	**211b**: 53%	R = 6-Me, Ar = 2-thiophen-2-yl	**211l**: 49%
R = 6-Me, Ar = 2,4-Me_2-C_6H_3	**211c**: 67%	R = 5-Cl, Ar = 2-thiophen-2-yl	**211m**: 47%
R = 5-Me, Ar = 2,4,6-Me_3-C_6H_2	**211d**: 62%	R = H, Ar = 2-thiophen-2-yl	**211n**: 51%
R = 5-F, Ar = 4-OMe-C_6H_4	**211e**: 40%	R = 6-Me, Ar = 4-Cl-C_6H_4	**211o**: 61%
R = 5-Cl, Ar = 3-OMe-C_6H_4	**211f**: 53%	R = 6-Me, Ar = 4- OMe-C_6H_4	**211p**: 54%
R = 5-Br, Ar = 4-NO_2-C_6H_4	**211g**: 56%	R = 5-Cl, Ar = 4- F-C_6H_4	**211q**: 61%
R = H, Ar = 4-F-C_6H_4	**211h**: 83%	R = 5-Cl, Ar = 4- Cl-C_6H_4	**211r**: 63%
R = H, Ar = 4-Cl-C_6H_4	**211i**: 84%	R = 5-Cl, Ar = 4- OMe-C_6H_4	**211s**: 37%
R = H, Ar = 4-OMe-C_6H_4	**211j**: 45%		

Scheme 95. One pot synthesis of 2-acylbenzoxazoles **211** according to Yunyum and co-workers.

2-acyl benzoxazole **211** is of special advantages, due to the use of air as an oxygen atom source, low cost of copper catalyst as well as the attractive conversion of the stable C(sp^3)-H bonds, which make the synthetic approach efficient for the preparation of these valuable heterocyclic motives with environmentally benign operations.

5. Conclusion

2-Ketoaryl azole derivatives have occupied an important position in pharmaceutical research. Among these molecules, the 2-ketoaryl benzothiazoles, 2-ketoaryl benzimidazoles and 2-ketoaryl benzoxazoles derivatives exhibit a series of pharmacological properties such as antidiabetic, antitumor, antiviral, antimicrobial, anticancer, antihypertensive, analgesic, antibroncospastic, antiallergic, antithrombotic properties and as a potent receptor of tyrosine kinase. Over the past decades, the attempts on progress towards synthesis of these scaffolds have developed a number of useful synthetic protocols. This review represents numerous exceptional approaches, which are contributed from synthetic chemists across the globe using reliable methodologies and easily accessible substrates. A series of potential synthetic tools including C–H functionalization, intermolecular cyclization and multicomponent reactions for the generation of C–C and C-heteroatom units are described. Despite the outstanding breakthrough during last years, there are still many scope for further investigation in this field with regard to the preparation of medicinally important compounds. These opportunities could led to realize the future challenges which might expedite the application of these transformations towards the synthesis of novel molecules.

Acknowledgements

Dr. Al-jaar gratefully acknowledges the financial and research support from Chemistry Department, The Hashemite University. CCM appreciates Science and Engineering Research Board (SERB), New Delhi for financial support in the form of research grants (CRG/2020/004509 and ECR/2016/000337). The authors extend their appreciation to the Researchers Supporting Project number

(RSP2023R396), King Saud University, Riyadh, Saudi Arabia. The authors are grateful to all the coworkers whose names appeared in the references.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Keywords: 2-Ketoaryl azoles · C–H Activation · Catalysis · Cyclization · Heterocycles

[1] a) K. C. Majumdar, S. K. Chattopadhyay, *Heterocycles in Natural Product Synthesis*, Wiley-VCH: Weinheim, Germany, **2011**; b) X.-X. Guo, D.-W. Gu, Z. Wu, W. Zhang, *Chem. Rev.* **2015**, *115*, 1622.

[2] a) A. Irfan, F. Batool, S. A. Zahra Naqvi, A. Islam, S. M. Osman, A. Nocentini, S. A. Alissa, *Med. Chem.* **2020**, *35*, 265; b) L. Racané, L. Ptiček, G. Fajdetić, V. Tralić-Kulenović, M. Klobučar, S. Kraljević Pavelić, M. Perić, H. Č. Paljetak, D. Verbanac, K. Starčević, *Bioorg. Chem.* **2020**, *95*, 103537; c) P.-C. Diao, W.-Y. Lin, X.-E. Jian, Y.-H. Li, W.-W. You, P.-L. Zhao, *Eur. J. Med. Chem.* **2019**, *179*, 196; d) D. W. Kneller, J. Agniswamy, A. K. Ghosh, I. T. Weber, *Biochem. Biophys. Res. Commun.* **2019**, *519*, 61; e) Y. Takamatsu, M. Aoki, H. Bulut, D. Das, M. Amano, V. R. Sheri, L. C. Kovari, H. Hayashi, N. S. Delino, A. K. Ghosh, H. Mitsuya, *Antimicro. Agents Chemother.* **2019**, *63*, 372; f) I. A. Y. Ghannam, E. A. Abd El-Meguid, I. H. Ali, D. H. Sheir, A. M. Kerdawy, *Bioorg. Chem.* **2019**, *93*, 103373; g) S. Zehra, M. Shavez Khan, I. Ahmad, F. Arjmand, *J. Biomol. Struct. Dyn.* **2019**, *37*, 1863; h) T. Batsalova, D. Basheva, K. Bardarov, V. Bardarov, B. Dzhambazov, I. Teneva, *Chemosphere* **2019**, *218*, 93; i) X. Huang, E. Meggers, *Acc. Chem. Res.* **2019**, *52*, 833; j) S. Kanie, R. Nakai, M. Ojika, Y. Oba, *Bioorg. Chem.* **2018**, *80*, 223; k) Y.-Q. Wang, Z.-M. Weng, T.-Y. Dou, J. Hou, D.-D. Wang, L.-L. Ding, L.-W. Zou, Y. Yu, J. Chen, H. Tang, G.-B. Ge, *Int. J. Biol. Macromol.* **2018**, *120*, 1944; l) J. J. Day, D. L. Neill, S. Xu, M. Xian, *Org. Lett.* **2017**, *19*, 3819; m) K. S. Mohamed, A. A. Fadda, *Heterocycles* **2015**, *91*, 1937; n) M. Taha, N. H. Ismail, *RSC Adv.* **2016**, *6*, 3003.

[3] W. Skinner, F. Gualtiere, G. Brody, A. Fieldsteel, *J. Med. Chem.* **1971**, *14*, 546.

[4] E. Meltzer-Mats, G. Babai-Shani, L. Pasternak, N. Urisky, T. Getter, O. Viskind, J. Eckel, E. Cerasi, H. Senderowitz, S. Sasson, A. Gruzman, *J. Med. Chem.* **2013**, *56*, 5335.

[5] a) T. D. Bradshaw, S. Wrigley, D. F. Shi, R. J. Schulz, K. D. Paull, M. F. G. Stevens, *J. Cancer* **1998**, *77*, 745; b) F. Gualtiere, G. Brody, A. H. Fieldsteel, W. A. Skinner, *J. Med. Chem.* **1971**, *14*, 546.

[6] a) M. J. Myllymaki, S. M. Saario, A. O. Kataja, J. A. Castillo-Melendez, T. Nevalainen, R. O. Juvonen, T. Jarvinen, Koskinen, *J. Med. Chem.* **2007**, *50*, 4236; b) M. Seierstad, J. G. Breitenbucher, *J. Med. Chem.* **2008**, *51*, 7327; c) K. Otrubova, C. Ezzili, D. L. Boger, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4674.

[7] G. Tang, Z. Nikolovska-Coleska, S. Qiu, C. Yang, J. Guo, S. Wang, *J. Med. Chem.* **2008**, *51*, 717.

[8] W. A. Skinner, F. Gualtiere, G. Brody, A. H. Fieldsteel, *J. Med. Chem.* **1971**, *14*, 546.

[9] A. Spadaro, M. Frotscher, R. W. Hartmann, *J. Med. Chem.* **2012**, *55*, 2469.

[10] M. Komiya, S. Asano, N. Koike, E. Koga, J. Igarashi, S. Nakatani, Y. Isobe, *Chem. Pharm. Bull.* **2013**, *61*, 1094.

[11] a) S. N. A. Bukhari, M. Jasamai, I. Jantan, *Mini-Rev. Med. Chem.* **2012**, *12*, 1394; b) L. Mercs, M. Albrecht, *Chem. Soc. Rev.* **2010**, *39*, 1903.

[12] a) W. C. Lumma, W. C. Randall, E. L. Cresson, J. R. Huff, R. D. Hartman, *J. Med. Chem.* **1983**, *26*, 357; b) E. Muler-Schweinitzer, J. R. Fozard, *J. Pharmacol.* **1997**, *120*, 1241.

[13] a) S. Banerjee, E. B. Veale, C. M. Phelan, S. A. Murphy, G. M. Tocci, L. J. Gillespie, D. O. Kelly, J. M. Frimannsson, T. Gunnlaugsson, *Chem. Soc. Rev.* **2013**, *42*, 1601; b) G. Gasser, I. Ott, N. Metzler-Nolte, *J. Med. Chem.* **2011**, *54*, 3; c) M. O. Contour-Galcera, L. Poitout, C. Moinet, B. Morgan, T. Gordon, P. C. Roubert, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 741.

[14] P. A. Bonnet, F. Michel, C. Laurent, E. Sablayrolles, J. C. Rechencq, M. Mani, J. P. Boucard, *J. Med. Chem.* **1992**, *35*, 3353.

[15] a) R. S. Keri, M. R. Patil, S. A. Patil, S. Budagumpi, *Eur. J. Med. Chem.* **2015**, *89*, 207; b) T. Melo, *Curr. Org. Chem.* **2005**, *9*, 925.

[16] a) W. Sun, M. Wang, Y. Zhang, L. Wang, *Org. Lett.* **2015**, *17*, 426. b) B. Narasimhan, D. Sharma, P. Kumar, *Med. Chem. Res.* **2012**, *21*, 269.

[17] R. O. Bora, B. Dar, V. Pradhan, M. Farooqui, *Mini-Rev. Med. Chem.* **2014**, *14*, 355.

[18] M. H. Kim, A. L. Tsuhako, E. W. Co, D. T. Aftab, F. Bentzien, J. Chen, W. Cheng, S. Engst, L. Goon, R. R. Klein, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4979.

[19] D. Sharma, B. Narasimhan, P. Kumar, V. Judge, R. Narang, E. De Clercq, J. Balzarini, *J. Enzyme Inhib. Med. Chem.* **2009**, *24*, 1161.

[20] H. Chen, D. Lester-Zeiner, J. Shi, S. Miller, C. Glaus, E. Hu, N. Chen, J. Able, C. Biorn, J. Wong, J. Ma, K. Michelsen, G. D. Hill, T. Kazules, H. Hannah Dou, S. Talreja, X. Zhao, A. Chen, S. Rumfelt, K. Roxanne, K. Hu Ye, R. Oliver, O. R. Thiel, T. Williamson, C. Davis, A. Porter, D. Immke, J. R. Allen, J. Treanor, *J. Pharmacol. Exp. Ther.* **2015**, *352*, 327.

[21] D. G. O'Sullivan, A. K. Wallis, *Nature* **1963**, *198*, 1270.

[22] N. Aljaar, R. Gujjarappa, M. Al-Refai, M. Shtaiwi, C. C. Malakar, *J. Heterocycl. Chem.* **2019**, *56*, 2730.

[23] a) M. J. Myllymäki, S. M. Saario, A. O. Kataja, J. A. CastilloMelendez, T. Nevalainen, R. O. Juvonen, T. Järvinen, A. M. P. Koskinen, *J. Med. Chem.* **2007**, *50*, 4236; b) M. Seierstad, J. G. Breitenbucher, *J. Med. Chem.* **2008**, *51*, 7327; c) M. J. Myllymaeki, H. Kaesnaenen, A. O. Kataja, M. Lahtela-Kakkonen, S. M. Saario, A. A. Poso, A. M. P. Koskinen, *Eur. J. Med. Chem.* **2009**, *44*, 4179; d) A. Minkkilae, S. M. Saario, T. Nevalainen, *Curr. Top. Med. Chem.* **2010**, *10*, 828.

[24] J. Chen, C.-M. Li, J. Wang, S. Ahn, Z. Wang, Y. Lu, J. T. Dalton, D. D. Miller, W. Li, *Bioorg. Med. Chem.* **2011**, *19*, 4782.

[25] X. Zhang, W. Zeng, Y. Yang, H. Huang, Y. Liang, *Org. Lett.* **2014**, *16*, 876.

[26] D. P. Hruszkewycz, K. C. Miles, O. R. Thiel, S. S. Stahl, *Chem. Sci.* **2017**, *8*, 1282.

[27] Y. Zhang, Y. Yue, X. Wang, K. Wang, Y. Lou, M. Yao, K. Zhuo, Q. Lv, J. Liu, *Asian J. Org. Chem.* **2018**, *7*, 2459.

[28] S. Guha, G. Sekar, *Chem. Eur. J.* **2018**, *24*, 14171.

[29] H. Wang, J. Liu, J.-P. Qu, Y.-B. Kang, *J. Org. Chem.* **2020**, *85*, 3942.

[30] Y. Nagasawa, Y. Tachikawa, E. Yamaguchi, N. Tada, T. Miura, A. Itoh, *Adv. Synth. Catal.* **2016**, *358*, 178.

[31] S. C. Sahoo, S. Pan, *Org. Lett.* **2019**, *21*, 6208.

[32] a) B. F. Thames, F. H. Pinkerton, *J. Heterocycl. Chem.* **1971**, *8*, 257; b) C. Boga, R. Stengel, R. Abdayem, E. Del Vecchio, L. Forlani, P. E. Todesco, *J. Org. Chem.* **2004**, *69*, 8903.

[33] S. Park, K. Lee, S. Kim, *Bull. Korean Chem. Soc.* **2014**, *35*, 1848.

[34] P. Lassalas, F. Marsais, C. Hoarau, *Synlett* **2013**, *24*, 2233.

[35] R. Chang, J. Fang, J. Q. Chen, D. Liu, G. Q. Xu, P. F. Xu, *ACS Omega.* **2019**, *4*, 14021.

[36] Y. Ogiwara, Y. Iino, N. Sakai, *Chem. Eur. J.* **2019**, *25*, 6513.

[37] Q. Gao, X. Wu, F. Jia, M. Liu, Y. Zhu, Q. Cai, A. Wu, *J. Org. Chem.* **2013**, 2792.

[38] S. Liu, R. Chen, H. Chen, G.-J. Deng, *Tetrahedron Lett.* **2013**, *54*, 3838.

[39] Q. Feng, Q. Song, *Adv. Synth. Catal.* **2014**, *356*, 2445.

[40] J. Wang, X.-Z. Zhang, S.-Y. Chen, X.-Q. Yu, *Tetrahedron* **2014**, *70*, 245.

[41] B. Wang, Q. Zhang, Z. Guo, K. Ablajan, *Synthesis* **2020**, *52*, 3058.

[42] M. B. Floyd, M. T. Du, P. F. Fabio, L. A. Jacob, B. D. Johnson, *J. Org. Chem.* **1985**, *50*, 5022.

[43] a) A. Monga, S. Bagchi, A. Sharma, *New J. Chem.* **2018**, *42* 1551; b) H.-X. Wang, T.-Q. Wei, P. Xu, S.-Y. Wang, S.-J. Ji, *J. Org. Chem.* **2018**, *83*, 13491; c) A. Ilangovan, G. Satish, *J. Org. Chem.* **2014**, *79*, 4984.

[44] W.-X. Xu, F.-X. Ye, X.-H. Liu, J.-Q. Weng, *Tetrahedron Lett.* **2020**, *61*, 151807.

[45] T. Huang, X. Wu, Y. Yu, L. An, X. Yin, *Tetrahedron Lett.* **2019**, *60*, 1667.

[46] K. Xiang, S. Zhang, L. Liu, T. Huang, Z. Tang, C. Li, K. Xu, T. Chen, *Org. Chem. Front.* **2021**, *8*, 2543.

[47] K. Yang, C. Zhang, P. Wang, Y. Zhang, H. Ge, *Chem. Eur. J.* **2014**, *20*, 7241.

[48] K. Yang, X. Chen, Y. Wang, W. Li, A. A. Kadi, H.-K. Fun, H. Sun, Y. Zhang, G. Li, H. Lu, *J. Org. Chem.* **2015**, *80*, 11065.

[49] J. K. Laha, M. Kaur Hunjan, S. Hegde, A. Gupta, *Org. Lett.* **2020**, *22*, 1442.

[50] J. K. Laha, M. K. Hunjan, *Chem. Commun.* **2021**, *57*, 8437.

[51] Q. Y. Toh, A. McNally, S. Vera, N. Erdmann, M. J. Gaunt, *J. Am. Chem. Soc.* **2013**, *135*, 3772.

[52] U. K. Sharma, N. Sharma, J. Xu, G. Song, E. V. Van der Eycken, *Chem. Eur. J.* **2015**, *21*, 4908.

[53] S. Karthik, T. Gandhi, *Org. Lett.* **2017**, *19*, 5486.

[54] H. Wu, Y. Li, M. Cui, J. Jian, Z. Zeng, *Adv. Synth. Catal.* **2016**, *358*, 3876.

[55] Q. Lu, X. T. Sun, Y. L. Kong, J. C. Liu, B. Chen, J. Q. Weng, *Tetrahedron Lett.* **2021**, *75*, 153184.
[56] S. Sultan, M. A. Rizvi, J. Kumar, B. A. Shah, *Chem. Eur. J.* **2018**, *24*, 10617.
[57] X. Fan, Y. He, S. Guo, X. Zhang, *Aust. J. Chem.* **2011**, *64*, 1568.
[58] a) L. Cui, Y. He, X. Fan, *Chin. J. Chem.* **2012**, *30*, 992; b) X. S. Fan, Y. He, Y. Y. Wang, Z. K. Xue, X. Y. Zhang, J. J. Wang, *Tetrahedron Lett.* **2011**, *52*, 899.
[59] X. Fan, Y. He, X. Zhang, S. Guo, Y. Wang, *Tetrahedron* **2011**, *67*, 6369.
[60] C. Wu, X. Xin, Z.-M. Fu, L.-Y. Xie, K.-J. Liu, Z. Wang, W. Li, Z.-H. Yuan, W.-M. He, *Green Chem.* **2017**, *19*, 1983.
[61] J. Jiang, H. Zou, Q. Dong, R. Wang, L. Lu, Y. Zhu, W. He, *J. Org. Chem.* **2016**, *81*, 51.
[62] D. Wang, Z. Wan, H. Zhang, A. Lei, *Adv. Synth. Catal.* **2021**, *363*, 1022.
[63] X.-L. Yang, C.-M. Xu, S.-M. Lin, J.-X. Ding, J.-C. Wu, H.-Y. Sua, *J. Braz. Chem. Soc.* **2019**, *21*, 37.
[64] A. Shokrolahi, A. Zali, M. Mahdavi, *Phosphorus Sulfur Silicon Relat. Elem.* **2012**, *187*, 535.
[65] X. Meng, X. Bi, C. Yu, G. Chen, B. Chen, Z. Jing, P. Zhao, *Green Chem.* **2018**, *20*, 4638.
[66] Y.-P. Zhu, M. Lian, F.-C. Jia, M.-C. Liu, J.-J. Yuan, Q.-H. Gao, A.-X. Wu, *Chem. Commun.* **2012**, *48*, 9086.
[67] J. K. Mali, D. A. Mali, V. N. Telvekar, *Tetrahedron Lett.* **2016**, *57*, 2324.
[68] D. C. Loukrakpam, P. Phukan, *ChemistrySelect* **2019**, *4*, 3180.
[69] R. Ma, Y. Ding, R. Chen, Z. Wang, L. Wang, Y. Ma, *J. Org. Chem.* **2020**, *86*, 310.
[70] a) S. Mohammed, R. A. Vishwakarma, S. B. Bharate, *J. Org. Chem.* **2015**, *80*, 6915; b) O. Ravi, A. Shaikh, A. Upare, K. K. Singarapu, S. R. Bathula, *J. Org. Chem.* **2017**, *82*, 4422.
[71] J. Hyvl, J. Srogl, *Eur. J. Org. Chem.* **2010**, 2849.
[72] Z.-L. Zhou, T. Fang, R.-Y Tang, X.-G. Zhang, C.-L. Deng, *Synlett* **2014**, *25*, 255.
[73] Y. Qi, X. Gu, X. Huang, G. Shen, B. Yang, Q. He, Z. Xue, M. Du, L. Shi, B. Yu, *Chin. Chem. Lett.* **2021**, *32*, 3544.
[74] Y.-P. Zhu, F.-C. Jia, M.-C. Liu, Y. Wu, *Org. Lett.* **2012**, *14*, 4414.
[75] a) C. Zhu, T. Akiyama, *Synlett.* **2010**, 2345; b) M. Y. Wu, X. Hu, Y. F. Liao, G. J. Deng, *Org. Lett.* **2012**, *14*, 2722; c) A. J. Blacker, M. M. Farah, M. I. Hall, S. P. Marsden, O. Saidi, J. M. J. Williams, *Org. Lett.* **2009**, *11*, 2039; d) K. Bahrami, M. M. Khodaei, F. Naali, *J. Org. Chem.* **2008**, *73*, 6835; e) V. V. Zhdankin, *J. Org. Chem.* **2011**, *76*, 1185; f) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299; g) K. C. Nicolou, T. Montagnon, P. S. Baran, Y. L. Zhong, *J. Am. Chem. Soc.* **2002**, *124*, 2245; h) N. Kornblum, J. W. Powers, G. J. Anderson, W. J. Jones, H. O. Larson, O. Levand, W. M. Weaver, *J. Am. Chem. Soc.* **1957**, *79*, 6562; i) H. F. Jiang, H. W. Huang, H. Cao, C. R. Qi, *Org. Lett.* **2010**, *12*, 5561.
[76] R. Deshidi, S. Devari, B. A. Shah, *Eur. J. Org. Chem.* **2015**, *2015*, 1428.
[77] J.-P. Wan, Y. Zhou, Y. Liu, S. Sheng, *Green Chem.* **2016**, *18*, 402.
[78] S. Zhang, S. Wang, Y. Leng, Y. Wu, *Tetrahedron Lett.* **2021**, *79*, 153300.
[79] W. J. Xue, Y. Q. Guo, F. F. Gao, H. Z. Li, A. X. Wu, *Org. Lett.* **2013**, *15*, 890.
[80] J. Jiang, G. Li, F. Zhang, H. Xie, G.-J. Deng, *Adv. Synth. Catal.* **2018**, *360*, 1622.
[81] a) Y. N. Cheng, J. Yang, Y. P. X. Qu, *Org. Lett.* **2012**, *14*, 98; b) X. Y. Qian, S. Q. Li, J. S. Song, H. C. Xu, *ACS Catal.* **2017**, *7*, 2730; c) V. Reg, S. M. Soria-Castro, J. E. Argüello, A. B. Peñéñorg, *Tetrahedron Lett.* **2009**, *50*, 4720; d) F. M. Moghaddam, D. Zargarani, *J. Sulfur Chem.* **2009**, *30*, 507; e) N. K. Downer-Riley, Y. A. Jackson, *Tetrahedron* **2008**, *64*, 7741.
[82] T. V. Huynh, K. V. Doan, N. T. K. Luong, D. T. P. Nguyen, S. H. Doan, T. T. Nguyen, N. T. S. Phan, *Adv. Synth. Catal.* **2020**, *362*, 18423.
[83] Y. Huang, D. Yan, X. Wang, P. Zhou, W. Wu, H. Jiang, *Chem. Commun.* **2018**, *54*, 1742.
[84] T. B. Nguyen, K. Pasturaud, L. Ermolenko, A. Al-Mourabit, *Org. Lett.* **2015**, *17*, 2562.
[85] X.-J. Mu, J.-P. Zou, R.-S. Zeng, J.-C. Wu, *Tetrahedron Lett.* **2005**, *46*, 4345.
[86] X. Feng, Q. Wang, Z.-B. Huang, D.-Q. Shi, *Adv. Synth. Catal.* **2014**, *4*, 54719.
[87] H. Wang, L. Wang, J. Shang, X. Li, H. Wang, J. Gui, A. Lei, *Chem. Commun.* **2012**, *48*, 76.
[88] H. Zellner, G. Zellner, F. Koppl, J. Dirnberger, *Monatsh. Chem.* **1967**, *98*, 643.
[89] K. Kohata, Y. Kawamonzen, T. Odashima, H. Ishii, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3398.
[90] P. K. Dubey, C. R. Kumar, B. Babu, *Indian J. Chem.* **2003**, *42B*, 3128.
[91] Y. Q. Ge, J. Jia, H. Yang, X. T. Tao, J. W. Wang, *Dyes. Pigments* **2011**, *88*, 344.
[92] M. Lian, Q. Li, Y. Zhu, G. Yin, A. Wu, *Tetrahedron* **2012**, *68*, 9598.
[93] Z. Zhan, H. Ma, X. Cui, P. Jiang, J. Pu, Y. Zhang, G. Huang, *Org. Biomol. Chem.* **2019**, *17*, 5148.
[94] E. Alcalde, M. Gisbert, J. M. Pons, L. Perez-Garcia, *Tetrahedron* **1996**, *52*, 15197.
[95] E. Alcalde, I. Dinarés, L. Pérez-García, T. Rota, *Synthesis* **1992**, 395.
[96] A. Dos Santos, L. El Kaim, L. Grimaud, *Org. Biomol. Chem.* **2013**, *11*, 3282.
[97] J. Tan, T. Zheng, Y. Yu, K. Xu, *Adv. Synth. Catal.* **2017**, *7*, 15176.
[98] a) J. De Houwer, B. K. A. Tehrani, B. U. W. Maes, *Angew. Chem. Int. Ed.* **2012**, *51*, 2745; b) H. Sterckx, J. D. Houwer, C. Mensch, I. Caretti, K. A. Tehrani, W. Herrebout, A. S. V. Doorslaer, B. U. W. Maes, *Chem. Sci.* **2016**, *7*, 346; c) J. Liu, X. Zhang, H. Yi, C. Liu, R. Liu, H. Zhang, K. Zhuo, A. Lei, *Angew. Chem. Int. Ed.* **2015**, *54*, 1261; d) B. A. Steinhoff, S. R. Fix, S. S. Stahl, *J. Am. Chem. Soc.* **2002**, *124*, 766.
[99] J. Zhou, M. Jia, M. Song, Z. Huang, A. Steiner, Q. An, J. Ma, Z. Guo, Q. Zhang, H. Sun, C. Robertson, J. Bacsa, J. Xiao, C. Li, *Angew. Chem. Int. Ed.* **2022**, *61*, e202205983.
[100] J. Zhang, J. Du, C. Zhang, K. Liu, F. Yu, Y. Yuan, B. Duan, R. Liu, *Org. Lett.* **2022**, *24*, 1152.
[101] B. L. Khristich, A. M. Simonov, E. N. Shepelenko, V. A. Yatsimirskii, *Chem. Heterocycl. Compd.* **1983**, *19*, 87.
[102] H. R. Yajnanarayana, Y. H. R. Joist, H. W. Gibson, *Macromolecules* **1994**, *27*, 2912.
[103] S. Demirayak, I. Kayagil, L. Yurttas, *Eur. J. Med. Chem.* **2011**, *46*, 411.
[104] K. Asakawa, J. J. Dannenberg, K. J. Fitch, S. S. Hall, C. Kadowaki, S. Karady, S. Kii, K. Maeda, B. F. Marcune, T. Mase, R. A. Miller, R. A. Reamer, D. M. Tschaen, *Tetrahedron Lett.* **2005**, *46*, 5081.
[105] S. Mai, Y. Zhao, Q. Song, *Org. Biomol. Chem.* **2016**, *14*, 8685.
[106] L. A. Nguyen, Q. A. Ngo, P. Retailleau, T. B. Nguyen, *Adv. Synth. Catal.* **2021**, *11*, 2098.
[107] R. Okazaki, N. Tokitoh, *Acc. Chem. Res.* **2000**, *33*, 625.
[108] a) M. Byrn, M. Calvin, *J. Am. Chem. Soc.* **1966**, *88*, 1916. b) M. Cohn, H. C. Urey, *J. Am. Chem. Soc.* **1938**, *60*, 679.
[109] L. A. Nguyen, T. T. T. Nguyen, Q. A. Ngo, T. B. Nguyen, *Org. Biomol. Chem.* **2021**, *19*, 6015.
[110] T. Zhi, Z. Baoli, W. Jieping, W. Chaoli, L. Yunyum, *Chin. J. Org. Chem.* **2021**, *41*, 4780.