Metal- and Hazardous Reagent-Free Transamidation Process: the $NH_2OH \bullet HCl$ Promoted *N*-Formylation and *N*-Acylation Reaction under Solvent-Less Conditions

Elangbam Pinky Devi[a], Kamal Kant[a], Dhananjaya Kaldhi[a], Susanta Ghanta[b], Ragini Sengupta[c], Nabil Al-Zaqri[d], Virender Singh[e], and Chandi C. Malakar[a]

[a]Department of Chemistry, National Institute of Technology Manipur, Langol, Imphal 795004, Manipur, India; [b]Department of Chemistry, National Institute of Technology, Agartala, Barjala, Jirania 799046, Tripura, India; [c]Institute for Photon Science and Synchrotron Radiation (IPS), Karlsruhe Institute of Technology (KIT), Hermann-von-Helmholtz-Platz 1, 76344 Eggenstein-Leopoldshafen, Germany; [d]Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia; [e]Department of Chemistry, Central University of Punjab, Bathinda 151001, Punjab, India

ABSTRACT

An efficient transamidation process has been described under solvent-less conditions. The transformation has been accomplished by employing $NH_2OH \bullet HCl$ as a reagent and amines as substrates. The developed method is achieved in the absence of metals and hazardous reagents. A series of amines were explored to obtain the *N*-formylation and *N*-acylation reactions with excellent yields (81-96%) of products. The DFT analysis was also performed, which provides a clear understanding of the described *N*-formylation process. The postulated mechanism is well supported by the control experiments.

Introduction

In the magical realm of organic chemistry, the C-N bond forming transformations are topics of interest.[1a-e] Among these transformations, the transamidation process has been witnessed as one of the useful C-N bond forming reaction in organic synthesis for preparation of amide derivatives.[1f] These structural motifs are comprehensively employed for the synthesis of organic intermediates,[2] pharmacologically active molecules,[3] and exhibited enormous applications in agrochemicals,[4] and material sciences.[5] A series of marketed drug molecules embedded with these moieties are endorsed as widely used pharmaceuticals (Figure 1). Hence, the synthesis of formamide and acetamide functional groups containing molecules remains one of the most explored thematic areas in organic synthesis. The traditional approaches for their preparation refer to the acid-amine coupling reactions, which normally rely on the unstable reagents and rigorous reaction conditions. Subsequently, the base promoted methods are also described for the transamidation process; however, these protocols are associated with a longer reaction time and produce low yields of products. To circumvent these deviations, a spectrum of transamidation processes were developed using transition metal-catalysts such as Fe,[6] Ce,[7a] La,[7b] B,[7c] Zr,[7d] Pd,[8] Ni,[9] Cu,[10] Co,[11] Ru,[12] Au,[13] Ir,[14] Zn[15]-complexes and employing a metal-catalysed electrochemical approach.[10c] Nevertheless, the metal-catalyzed methods suffer from the high cost of catalysts and associated

CONTACT Chandi C. Malakar chdeepm@gmail.com; cmalakar@nitmanipur.ac.in Department of Chemistry, National Institute of Technology Manipur, Langol, Imphal - 795004, Manipur, India.

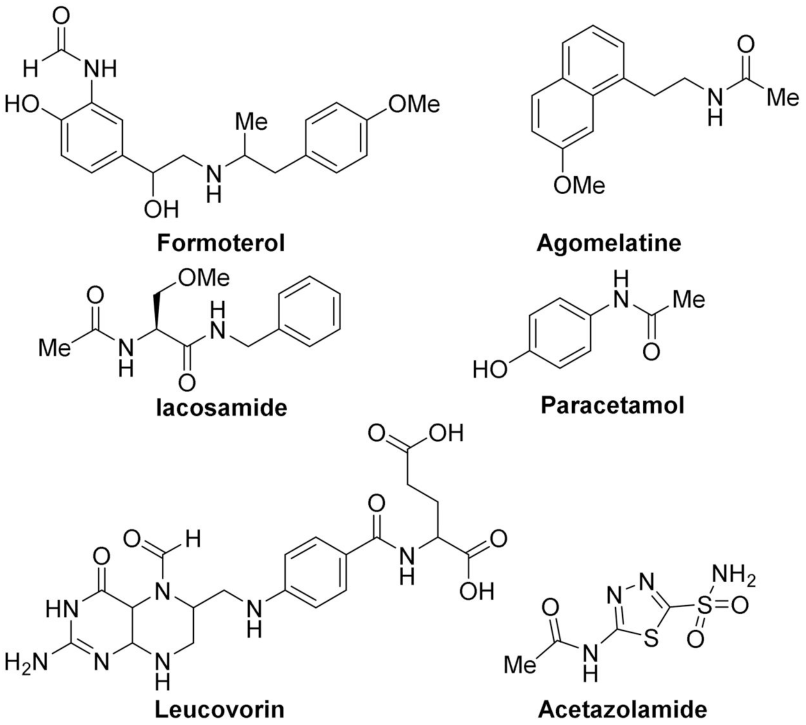


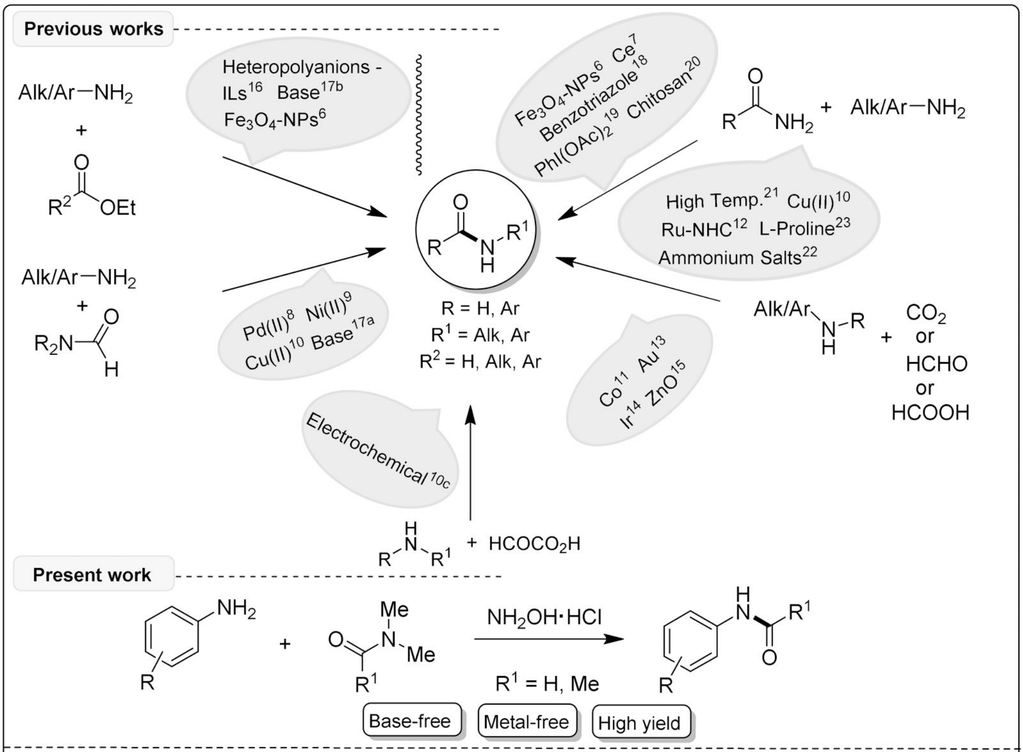
Figure 1. Selected pharmaceuticals containing *N*-acyl and *N*-formyl groups.

environmental risk by the disposal of metals. Alternatively, a series of metal-free transamidation approaches using amide derivatives or aldehyde sources are developed toward circumventing the associated drawbacks of the previously reported methods.[16–2 3] On the other hand, the transamidation reaction of DMF mostly relies on the metal (Pd, Ni, Co, Cu) catalytic processes. Thus, the development of an effective transamidation protocols of DMF using metal-free and solvent-less conditions are highly desirable. Here, we report a $NH_2OH\bullet HCl$ mediated *N*-formylation and *N*-acetylation of amines using DMF (*N*, *N*-dimethylformamide) and DMA (*N*, *N*-dimethylacetamide) under solvent-less conditions (Scheme 1). The reported method represents a metal-free and solvent-less protocol that tolerates a series of substrates and DMF as a greener formylating agent.

Materials and methods

Materials

All required chemicals were acquired from reputed vendors such as Sigma-Aldrich, SD fine chemicals, Merck, Alfa-Aesar and HI Media. These chemicals were utilized in the reactions directly as purchased and mentioned if purified. All reactions were carried out in 10 mL round bottom flask fitted with a magnetic stirrer. The solvents employed toward purification and extraction processes were carefully distilled before use. Thin-layer chromatography (TLC) was carried out on TLC plates procured from Merck. The products were observed by immersing TLC plates in $KMnO_4$ solution and checked by UV light (λ 254 nm) or visualized upon heating. The final compounds were afforded by purification through Flash column chromatography. All HRMS spectra were recorded by Agilent instrument 6545 QTOF LC/MS (EI-QTOF in MeCN). The Brucker NMR spectrometer 400 (100) MHz was used for recording ^1H and ^{13}C NMR spectra using $CDCl_3$ as solvent. The solvent peaks appeared at $\delta_{H/C}$ 7.26/77.28 ($CDCl_3$) using TMS as reference. The coupling constants (J [Hz]) have been considered as such from the spectra without



Fe_3O_4-Citric acid[6a]; $Fe(OH)_3@Fe_3O_4$[6b]; CeO_2[7]; $Pd(OAc)_2$[8]; Ni(quin)$_2$[9]; Cu(quin)$_2$[10a]; $Cu(OAc)_2$[10b]; $Cu(OAc)_2$, $NiCl_2$[10c]; $CuCl_2$[10d]; Co_3O_4-NPs[11]; Ru-NHC[12]; Au-CNT[13]; [Cp*Ir$_2$]$_2$[14]; ZnO[15]; [PyPS]$_3$PW$_{12}$O$_{40}$[16]; KO^{t}Bu[17a-b]; Benzotriazole[18]; PhI(OAc)$_2$[19]; Chitosan[20]; 150 °C[21]; NH_4I[22a]; NH$_2$OH•HCl[22b]; L-Proline[23].

Scheme 1. Strategies toward *N*-acylation and *N*-formylation processes.

taking average. Splitting patterns are represented as br (broad), m (multiplet), q (quartet), t (triplet), d (doublet), and s (singlet).

Methods

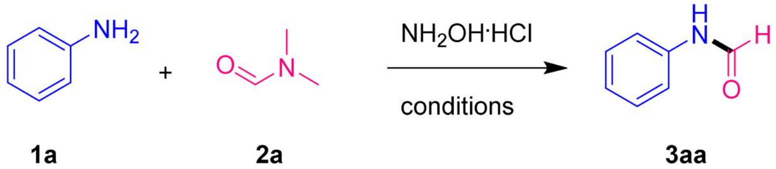
General method for the N-formylation and N-acetylation process

Anilines **1a-q** (1.0 mmol) were placed in 2 mL reaction flask, then hydroxylamine hydrochloride (1.1 mmol) and dimethyl formamide (**2a**) or dimethyl acetamide (**2b**) (30 mmol) were added to the mixture. Next, the reaction container was stired for 10 h at 100 °C. When, the transformation was completed (the advancement of the reaction was observed on TLC; SiO_2, EtOAc/Hexane 30:70). After, completion of the reaction, obtained crude mixture was diluted with 15 mL of ethyl acetate and 20 mL of water. The solution was then extracted with EtOAc (3 × 10 mL). The collected organic layers were washed with brine solution (3 × 10 mL) and dried over anhydrous Na_2SO_4. Finally, the crude product was purified by column chromatography (SiO_2, EtOAc/Hexane 30:70) to receive the expected *N*-aryl formamides or *N*-aryl acetamides **3** and **4** in excellent yields.

Results and discussions

Having surveyed the importance of these scaffolds, we have attempted to develop the metal-free and efficient protocol for the *N*-formylation approach. To establish the feasible protocol, our

Table 1. Screening of the reaction conditions for the synthesis of *N*-phenylformamide (**3aa**).[a]

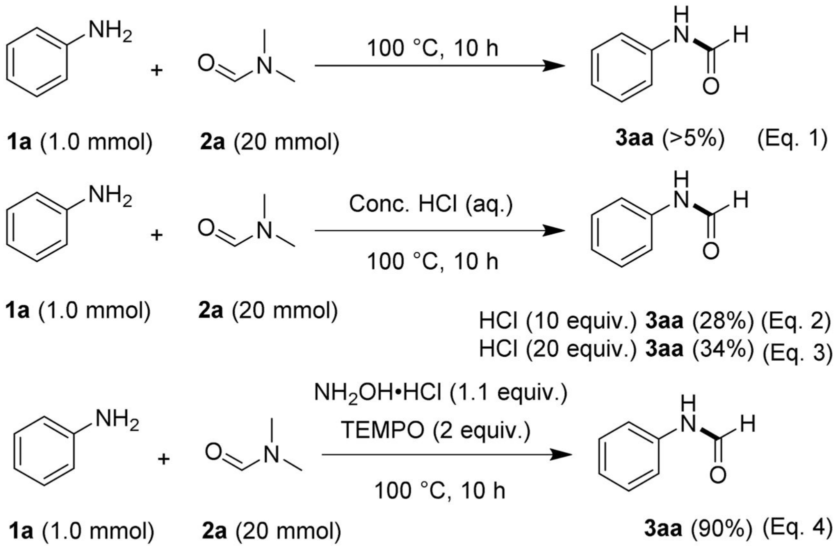


Entry	Catalyst [Mol %]	Additive [equiv.]	Solvent	Temp [°C]	Time [h]	3aa, Yield%[b]
1	KI (5)	TBHP (3)	DMSO	100	10	73
2	I_2 (10)	TBHP (3)	DMSO	100	10	70
3	TBAI (10)	TBHP (3)	DMSO	100	10	75
4	NIS (10)	TBHP (3)	DMSO	100	10	61
5	–	TBHP (3)	DMSO	100	10	72
6	KI (20)	–	DMSO	100	10	76
7	–	–	DMSO	100	10	92
8	–	–	Neat	100	10	94[c]
9	–	–	Neat	120	10	86[c]
10	–	–	Neat	70	16	47[c]

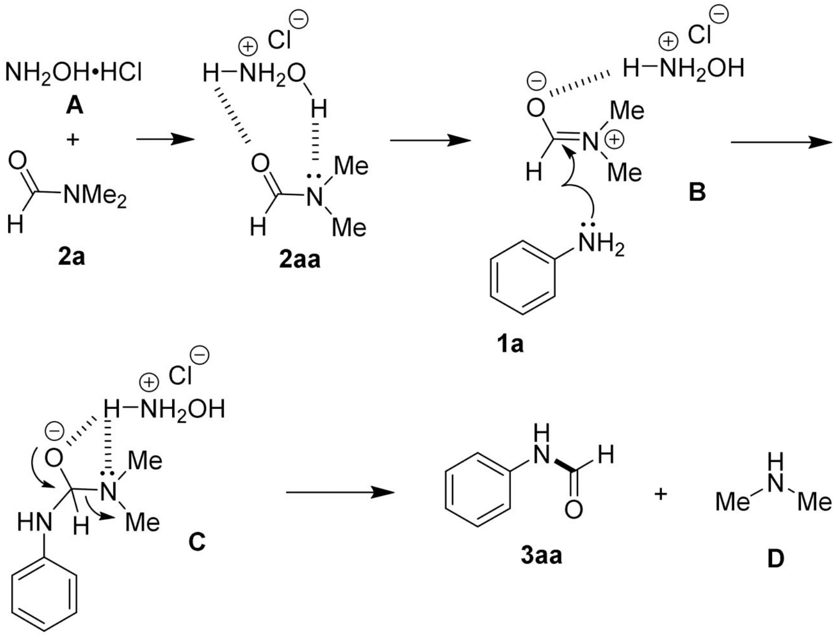
[a] Unless otherwise indicated: All reactions were performed using 1.0 mmol **1a**, 20 mmol of **2a** and 1.1 mmol of hydroxylamine hydrochloride. [b] Isolated yields. [c] Reactions were carried out using 30 mmol of DMF.

experimental work commenced with aniline (**1a**) as the model substrate. Initially, a reaction was performed between aniline (**1a**) and *N*, *N*-dimethyl formamide (**2a**) in the presence of 5 mol% KI, 1.1 mmol of NH_2OH•HCl and 3.0 mmol of *tert*-butylhydroperoxide (TBHP) in DMSO as solvent at 100 °C for 10 h (Table 1, Entry 1). Interestingly, it was observed that the reaction delivered the corresponding *N*-phenyl formamide (**3aa**) in 73% yield. Inspired by these results, the KI was replaced with 10 mol% of I_2 as catalyst, which delivered the product **3aa** in 70% yield under identical reaction conditions (Table 1, Entry 2). Next, we investigated the catalytic activities of tetrabutylammonium iodide (TBAI) and *N*-iodosuccinamide (NIS). It was revealed that both TBAI and NIS showed satisfactory catalytic efficiencies with the formation of product **3aa** in 75% and 61% yields respectively (Table 1, Entries 3-4). To understand the role of catalyst and additive, the reactions were carried out in their absence (Table 1, Entries 5-6). The performed experiments described that the transformation is not dependent upon the influences of catalyst and additive to afford the product **3aa** in good yield. Hence, if the reaction between **1a** and **2a** was performed using 1.1 mmol of NH_2OH•HCl in DMSO as solvent at 100 °C for 10 h (Table 1, Entry 7), the corresponding product **3aa** can be isolated in 92% yield. Moreover, the necessity of DMSO as solvent was verified by conducting a reaction between **1a** and **2a** under the influences of 1.1 mmol of NH_2OH•HCl at 100 °C for 10 h (Table 1, Entry 8). Surprisingly, it was observed that the corresponding *N*-phenyl formamide can be formed in 94% yield. After screening the role of catalyst, additive, and solvent, the effects of temperature and time were examined for this transformation. These investigations lead to the unsatisfactory results (Table 1, Entries 9-10). After, the successful screening of the reaction conditions, it was described that the maximum yield (94%) of the product **3a** can be obtained, when 1.0 mmol of aniline (**1a**) and 30 mmol of *N*, *N*-dimethyl formamide (**2a**) were reacted in the presence of 1.1 mmol of NH_2OH•HCl at 100 °C for 10 h (Table 1, Entry 8) and these parameters were considered as the optimal conditions for further reactions.

Having investigated the standard reaction conditions, we attempted to understand the mechanism of this transformation using suitable control experiments. Initially, we have performed the reaction of **1a** and **2a** in the absence of NH_2OH•HCl to realize the unreacted starting material with un-identification of the required product **3aa** (Scheme 2, Equation 1). In another experiment, we have executed the reaction by replacing the hydroxylamine hydrochloride with hydrochloric acid (10 equiv.) and observed the formation of the expected product **3aa** in 28% yield



Scheme 2. Control experiments for the transamidation process.

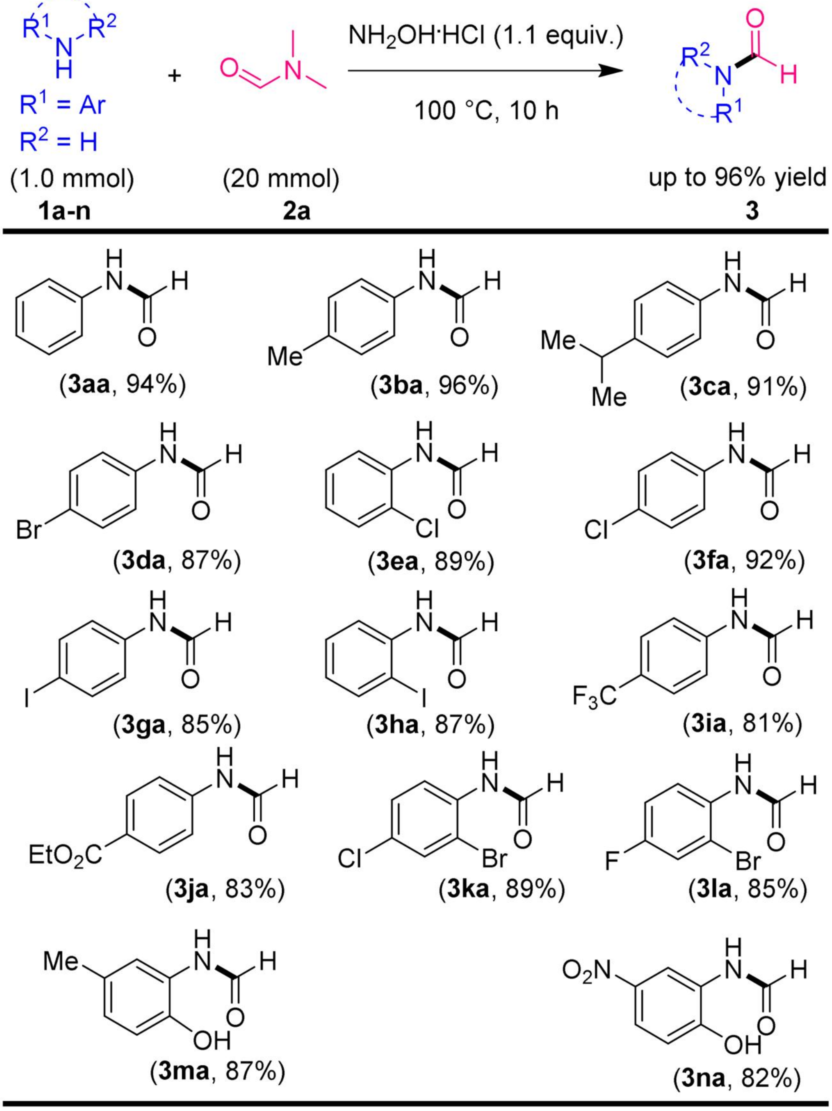


Scheme 3. Proposed mechanism for the *N*-formylation processes.

(Scheme 2, Equation 2). It was also found that the yield of the product was enhanced up to 34%, when 20 equiv. of hydrochloric acid was loaded as reagent (Scheme 2, Equation 3). To investigate the involvement of the radical pathway, the reaction of **1a** and **2a** was performed with a radical scavenger (TEMPO, 2,2,6,6-Tetramethylpiperidinyloxy), which resulted the similar yield (90%) of the product **3aa** (Scheme 2, Equation 4) that proves no involvement of the radical mechanism.

Based on the literature reports and control experiments, a plausible mechanism was proposed in Scheme 3.[17,21,24] It may be assumed that in the first step, the coordination of *N*-protonated hydroxyl amine **A** and *N*, *N*-dimethyl formamide (**2a**) induces the enhancement of the positive charge on N-atom that leading to the formation of intermediate **B** followed by the generation of transition state **2aa**. This phenomenon reinforces the nucleophilic attack of -NH_2 group of aniline (**1a**) into the carbonyl carbon of intermediate **B** to deliver the unstable intermediate **C**, which followed by the cleavage of *N*, *N*-dimethyl amine (**D**) produces the desired product *N*-phenylformamide (**3aa**).

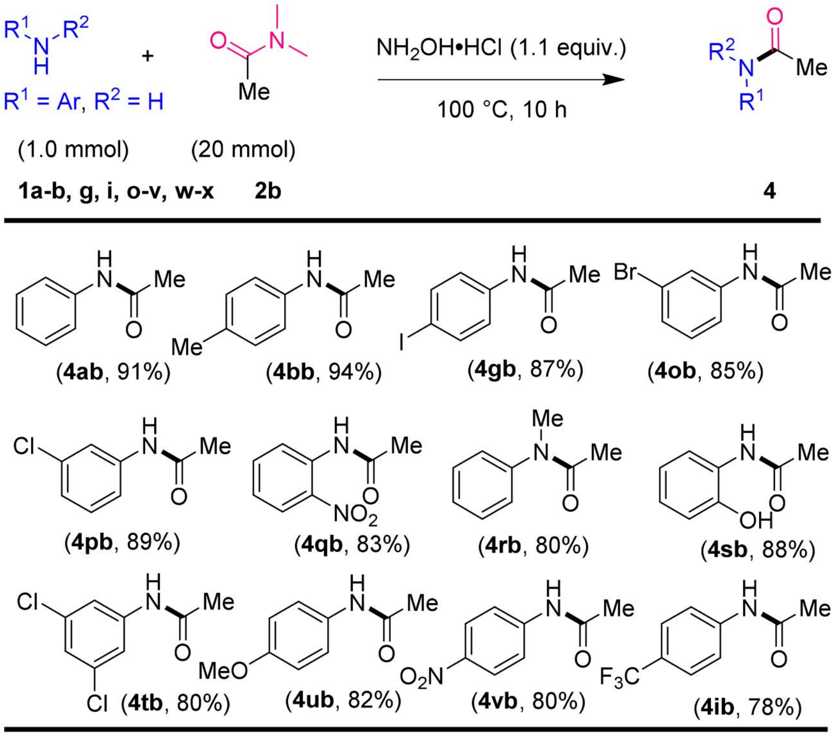
With the effective optimal reaction parameters in hand, we then tried to examine the substrate scope of this established *N*-formylation process. To serve this purpose, a series of aniline derivatives embedded with electron-releasing functional groups such as alkyl groups (Me, ^{i}Pr) and electron-deficient moieties such as halides (F, Cl, Br, I), trifluoromethyl (CF_3), ester (CO_2Et), hydroxyl (OH), and nitro (NO_2) substituents were tested under the developed reaction conditions. It has been observed that irrespective of the electronic nature of the substituents, all substrates were participated smoothly in this transformation to generate the *N*-formylated compounds **3** in excellent yields and regioselectivity. However, the aniline derivatives containing



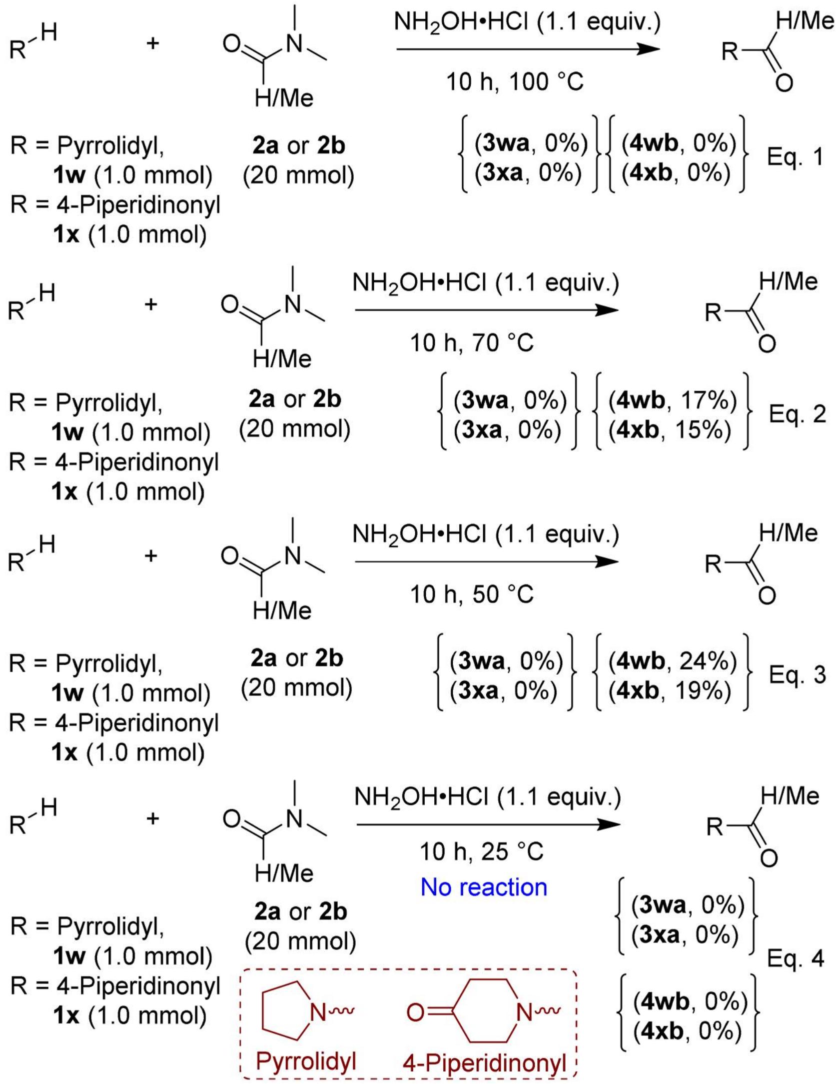
Scheme 4. Substrate scope of the developed *N*-formylation process.

electron-poor functional groups delivered yields of the expected products slightly lower than the anilines containing electron-donating moieties. It is noteworthy to mention that the final *N*-formylated compounds **3** exist in rotameric forms (Scheme 4). The regioselectivity of the formylation reaction also play a crucial role. In the developed process, the formation of *O*- or *C*-formylated products were not identified. The major facts behind this findings might be associated to the nucleophilicity factor. In case of amine derivatives like aniline, the nitrogen atom of -NH_2 group can donate the electron pair readily to the electrophilic formylating reagent. Thus, the *N*-formylation process is highly feasible in comparison to the *C*-formylation of the aromatic ring of aniline derivatives, which is due to the bare nucleophilic character of the C(sp^2)-atom of the aromatic ring. This hypothesis was further examined using anisole and 1,2-dimethoxybenzene as the substrates, which resulted no conversion toward the formation of *C*-formylation products using these developed conditions. On the other hand, unlike the *C*-formylation process, the formation of *O*-formylation products were desired due to the better nucleophilic character of the oxygen-atom. Thereby, phenol was exposed as substrate under the developed method. The obtain results indicated that after 16 h of the reaction time no conversion of phenol was found. To validate this fact, the competition between *N*-formylation/*N*-acetylation and *O*-formylation/*O*-acetylation processes were studied using the 2-aminophenol as the substrate. These experiments resulted in the exclusive formation of *N*-formylation and *N*-acetylation products; whereas, the formation of *O*-formylation and *O*-acetylation compounds are not at all observed during this reaction.

In order to extend the scope of this described method, the feasibility of the *N*-acetylation process has been examined. It was found that when *N*, *N*-dimethylformamide (**2a**) was replaced with *N*, *N*-dimethylacetamide (**2b**) under the developed conditions, a series of anilines **1** were transformed into the corresponding *N*-acetylated compounds **4ab**, **4bb**, **4gb**, **4ob-4vb**, **4ib**, **4wb**, **4xb** in high yields ranging from 78-94% (Scheme 5). To gain further insight of the developed protocol, we have examined the reactivity of *N*-methyl aniline (**1r**) as a secondary aromatic amine and



Scheme 5. Extended substrate scope toward *N*-acetylation process.



Scheme 6. Reactivity of aliphatic amines.

2-aminophenol (**1s**) under the standard conditions. It was revealed that both substrates such as 2° amine (*N*-methyl aniline) and 2-aminophenol participated smoothly in this transformation to accomplish the final *N*-acetylation products **4rb** and **4 sb** in yields 80% and 88% respectively. The experimental observations revealed that both electron-rich and electron-poor anilines were tolerated good to deliver the corresponding anilide derivatives in high yields. Whereas, electron-donating substrates lead to the formation of products in slightly higher yields than the electron-poor anilines (Scheme 5).

Having expanded the scope of a series of primary and secondary aromatic amines for the formation of corresponding products, we aimed to examine the reactivity of aliphatic amines under the described reaction conditions. In this regard, it was experienced that when the aliphatic amines such as pyrrolidine (**1w**) and 4-piperidone (**1x**) were exposed to the standard conditions at 100 °C, no expected *N*-formylation or *N*-acetylation processes were accomplished (Scheme 6, Equation 1) and hence, the required products were not observed, rather a combination of unidentified side products were found on TLC that lead to the formation of a complex reaction mixture. Thus, it was assumed that the developed protocol restricts the conversion of aliphatic amines into the corresponding products. This findings lead to the attention on the credentials of the proposed mechanism for this transformation. To understand the reluctant behavior of aliphatic amines, the proposed mechanism was reviewed carefully. It was observed that the efficiency of this transformation might be dependent upon two major factors, which are associated to the nucleophilicity of amines and the stability of transition state **C** (Scheme 3). Moreover, it could be assumed that the feasibility of the formation of transition state **C** and its stability is higher with aromatic amines in comparison to the aliphatic amines. With this hypothesis, regardless on the significance of the nucleophilicity of aromatic and aliphatic amines, the reactions of pyrrolidine (**1w**) and 4-piperidone (**1x**) were conducted in the presence of *N*, *N*-dimethyl formamide (**2a**) and *N*, *N*-dimethyl acetamide (**2b**) under standard conditions at 70 °C, 50 °C, and 25 °C to examine the effects on the stability of transition state **C** toward the formation of corresponding products. Surprisingly, the obtained results revealed that when the reactions were performed at 70 °C, the corresponding products **4wb** and **4xb** were observed in 17% and 15% yields respectively; whereas, the corresponding *N*-formylated compounds **3wa** and **3xa** were not formed (Scheme 6, Equation 2). Further, a slight improvement of the yields (**4wb**: 24%, **4xb**: 19%) were found, if the reaction temperature is diminished to 50 °C and similar observations were recorded in case of *N*-formylation process (Scheme 6, Equation 3). Nevertheless, the transformations remain inactive if the reactions were carried out at 25 °C (Scheme 6, Equation 4). Thus, these observations lead us to state that the mechanistic pathway of the developed protocol is more associated to the stability of the transition state **C** than the nucleophilicity of the amines.

The salient features of this developed protocol may be associated with its novelty over previous reported methods in terms of solvent-less reaction conditions, the use of non-hazardous reagents like hydroxylamine hydrochloride to assist the formylation and acetylation processes using *N*, *N*-dimethyl formamide and *N*, *N*-dimethyl acetamide under simple conditions. A broad range of aromatic amines could be transformed into the formylated and acetylated products with high yields; whereas, the aliphatic amines remain inefficient for this transformation and deliver very low yields of products at 50 °C and 70 °C reaction temperatures. Additionally, the *C*-formylation and *O*-formylation processes are not accomplished using this method.

In order to gain better insights, we have attempted to conduct DFT analysis which provides a clear understanding about the generation of *N*-formylation product. At the B3LYP[25-27] level of theory, the optimization of structures (reactants, intermediates, transition states, and products) and their frequency calculations have been performed. Calculations of activation energies are attempted for the whole chemical pathway for the formation of *N*-formylation reaction product from aniline (**1a**) and *N*, *N*-dimethyl formamide (**2a**) in the presence of $NH_2OH•HCl$. Numerous ab initio computations have been carried out using sophisticated computing techniques such as the B3LYP [25–27] approach and 6-31 + g** Pople's basis sets [28] with the use of Gaussian 16 (G16) quantum chemistry software.[29] At the B3LYP level of theory and utilizing the 6-31 + g** Pople's Gaussian basis set,[29] the equilibrium electronic ground state of the reactants (**1a**, **2a**, and NH_2OH), intermediate (IM1(B)), transition states (TS-I (**2aa**), and TS-II (**C**)), and products (**3aa** and **D**) structures have been optimized. By diagonalizing the B3LYP force field computed using the same level of theory, the harmonic vibrational frequencies [30–31] of the electronic ground states of the relevant molecules are recovered. For the whole reaction route, the transition states[32–33] (TS-I and TS-II) have been performed, and their associated harmonic vibrational frequencies have also been determined. We have used the G16 quantum chemistry programme to carry out structural optimization calculations as well as harmonic frequency calculations for all the reactants, intermediates, transition states, and products. The reactants (**1a**, **2a**, and NH_2OH), intermediate (IM1 (**B**)) and products (**3aa** and **D**) do not have any negative frequencies. This confirm the stability of the molecular structures. The lowest harmonic vibrational frequencies for the **1a**,

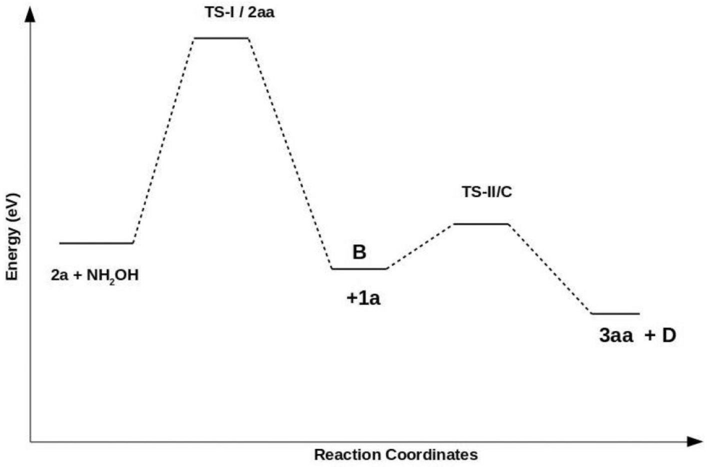


Figure 2. The DFT predicted energy profile diagram for the formation of the *N*-formylation reaction product (**3aa**) from aniline (**1a**) and *N*, *N*-dimethyl formamide (**2a**) in the presence of $NH_2OH \bullet HCl$ is shown here.

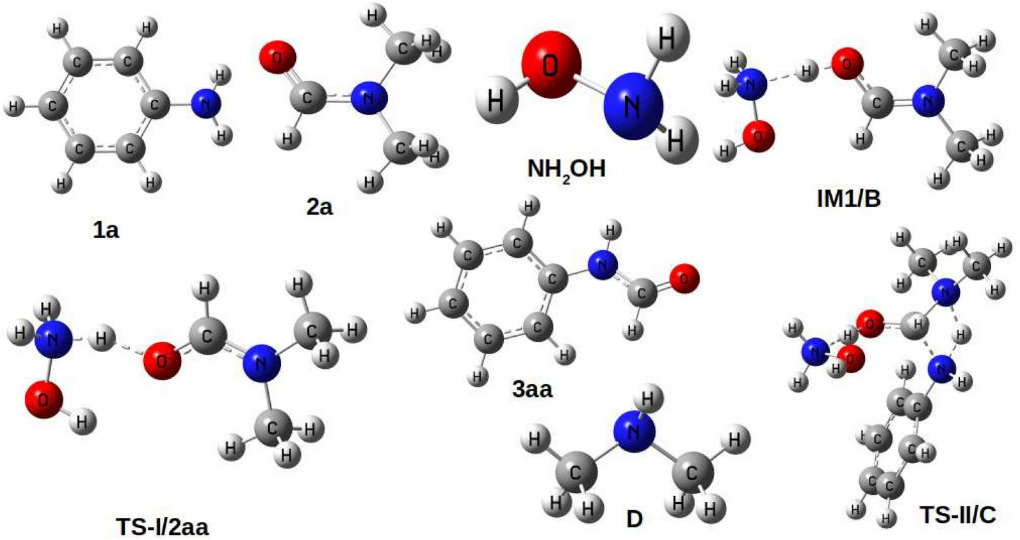


Figure 3. The B3LYP computed molecular Structure for the **1a**, **2a**, NH_2OH, **2aa**, **B**, **C**, **3aa** and **D** are shown here.

2a, NH_2OH, **B**, **3aa** and **D** are 220, 107, 440, 43, 70 and 237 cm^{-1}, respectively. All the transition states (TS-I (**2aa**) and TS-II (**C**)) have only one imaginary frequency. This suggest the confirmation of the transition states. The imaginary frequencies for the TS-I and TS-II are 33i and 1549i cm^{-1}, respectively. The activation energy for the formation of intermediate **B** (IM1) from **2a** and NH_2OH is 231.67 Kcal/mole. The activation energy for the formation of the products (**3aa** and **D**) is 32.53 Kcal/mole. The energy profile diagram for the formation of products (**3aa** and **D**) from the reactants (**1a**, **2a** and NH_2OH) is illustrated in Figure 2 and all the structures are shown in Figure 3. The activation energy is very high (231.67 Kcal/mole) for the formation of **B** from **2a** and NH_2OH, and very low (32.53 Kcal/mole) for the formation of products **3aa** and **D**. Thus, the reaction between **B** and **1a** is very fast and the formation of **B** from **2a** and NH_2OH is very slow. These theoretical observations are well supported by the experimental outcomes.

Conclusion

In conclusion, we have described the efficient methods toward *N*-formylation and *N*-acetylation processes. The developed reactions were promoted by hydroxylamine hydrochloride to deliver the corresponding products with excellent yields and selectivity. The reported amidation processes were accomplished using metal-free and base-free conditions under relatively mild reaction conditions. The results of the DFT analysis comply well with the experimental observations.

Acknowledgements

CCM appreciates the Science and Engineering Research Board (SERB), New Delhi for financial supports in the form of research grants (CRG/2020/004509 and ECR/2016/000337). KK and DK are grateful to the Ministry of Education (MoE), New Delhi for fellowship supports. The authors extend their appreciation to the Researchers Supporting Project number (RSP2023R396), King Saud University, Riyadh, Saudi Arabia.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

The manuscript was written through contributions of all authors and all authors have given approval to the final version of the manuscript.

References

1. (1a) L. Wang, N. Liu, and B. Dai, "Metal-free site-selective C–N bond-forming reaction of polyhalogenated pyridines and pyrimidines," *RSC Advances* 5, no. 100 (2015): 82097. (1b) M.L. Deb, C. Das, B. Deka, P.J. Saikia, and P.K. Baruah, "Hydrogen-Bond-Catalyzed Arylation of 3-(Aminoalkyl)indoles via C–N Bond Cleavage with Thiourea under Microwave Irradiation: An Approach to 3-(α,α-Diarylmethyl)indoles," *Synlett* 27, no. 20 (2016): 2788. (1c) J. Zhang, M. Jiang, C.S. Wang, K. Guo, Q. -X. Li, C. Ma, S.-F. Ni, G.Q. Chen, Y. Zong, H. Lu, L.-W. Xu, and X. Shao, "Transition-metal free C–N bond formation from alkyl iodides and diazonium salts via halogen-atom transfer," *Nature Communications* 13, no. 1 (2022): 7961.(1d) N. Al-jaar, M.M. Ibrahim, E.A. Younes, M. Al-Noaimi, K.A. Abu-Safieh, B.F. Ali, K. Kant, N. Al-Zaqri, R. Sengupta, and C.C. Malakar, "Strategies towards the Synthesis of 2-Ketoaryl Azole Derivatives using C-H Functionalization Approach and 1,2-Bis-Nucleophile Precursors," *Asian Journal of Organic Chemistry* 12, no. 4 (2023): e202300036. (1e) R. Gujjarappa, N. Vodnala, and C.C. Malakar, "Comprehensive Strategies for the Synthesis of Isoquinolines: Progress Since 2008," *Advanced Synthesis and Catalysis* 362, no. 22 (2020): 4896. (1f) M. Nasrollahzadeh, N. Motahharifar, A.M. Aghbolagh, M. Sajjadi, M. shokouhimehr, and R.S. Varma, "Recent advances in N-formylation of amines and nitroarenes using efficient (nano)catalysts in eco-friendly media," *Green Chemistry* 21, no. 19 (2019): 5144.
2. (a) B. L. Bray, "Large-Scale Manufacture of Peptide Therapeutics by Chemical Synthesis," *Nature Reviews. Drug Discovery* 2, no. 7 (2003): 587–593. doi:10.1038/nrd1133 (b) R. C. Larock, Comprehensive Organic Transformations, 2nd ed. (New York: Wiley-VCH, 1999)
3. (a) A.M. Larson, J. Polson, R.J. Fontana, T.J. Davern, E. Lalani, L.S. Hynan, J.S. Reisch, F.V. Schiødt, G. Ostapowicz, A.O. Shakil, and W.M. Lee, "Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study" *Hepatology* 42, no. 6 (2005): 1364. (b) K.M. Tramposch, X. Nair, G.J. Gendimenico, G.B. Tetrault, S. Chen, I. Kiss, G. Whiting, and R.J. Bonney, "The pharmacology of a novel topical retinoid, BMY 30123: comparison with tretinoin," *Journal of Pharmacy and Pharmacology* 44, no. 5 (1992): 379-86. (c) F.R. Batchelor, F.P. Doyle, J.H.C. Nayler, and G.N. Rolinson, "Synthesis of Penicillin: 6-Aminopenicillanic Acid in Penicillin Fermentations," *Nature* 183, no. 4656 (1959): 257.
4. A. R. Kniss, "Long-Term Trends in the Intensity and Relative Toxicity of Herbicide Use," *Nature Communications* 8, no. 1 (2017): 14865. doi:10.1038/ncomms14865
5. M. K. Ghosh, and K. L. Mittal, *Polyimides Fundamentals and Applications* (New York: Marcel Dekker, 1996).

6. (a) M. Arefi1, M. K. Miraki, R. Mostafalu, M. Satari, and A. Heydari, “Citric Acid Stabilized on the Surface of Magnetic Nanoparticles as an Efficient and Recyclable Catalyst for Transamidation of Carboxamides, Phthalimide, Urea and Thiourea with Amines under Neat Conditions,” *Journal of the Iranian Chemical Society* 16, no. 2 (2019): 393–400. (b) M. Arefi, and A. Heydari, “Transamidation of Primary Carboxamides, Phthalimide, Urea and Thiourea with Amines Using Fe(OH)3@Fe3O4 Magnetic Nanoparticles as an Efficient Recyclable Catalyst,” *RSC Advances* 6 (2016): 24684–24689. doi:10.1007/s13738-018-1523-8
7. (a) M. Tamura, T. Tonomura, K. Shimizu, and A. Satsuma, “Transamidation of Amides with Amines under Solvent-Free Conditions Using a CeO_2 Catalyst,” *Green Chemistry* 14, no. 3 (2012): 717–24. (b) S. Li, T. Rajeshkumar, J. Liu, L. Maron, and X. Zhou, “La-Catalyzed Decarbonylation of Formamides and Its Applications,” *Organic Letters* 25, no. 1 (2022) 163–68.(c) X. Chen, Y. Yang, H. Wang, and Z. Mo, “Cooperative Bond Activation and Catalytic CO2 Unctionalization with a Geometrically Constrained Bis(Silylene)-Stabilized Borylene,” *Journal of the American Chemical Society* 145, no. 12 (2023) 7011–7020.(d) D. K. Yoo, and S. H. Jhung, “*N*-Formylation of Amines with CO_2 by Using Zr-Based Metal-Organic Frameworks: Contribution of Defect Sites of MOFs to *N*- Formylation,” *Applied Catalysis A: General* 659 (2023): 119170. doi:10.1039/c2gc16316k
8. D.-W. Gu, and X.-X. Guo, “Synthesis of *N*-Arylcarboxamides by the Efficient Transamidation of DMF and Derivatives with Anilines,” *Tetrahedron* 71, no. 48 (2015): 9117–9122. doi:10.1016/j.tet.2015.10.008
9. R. B. Sonawane, N. K. Rasal, and S. V. Jagtap, “Nickel-(II)-Catalyzed *N*-Formylation and *N*-Acylation of Amines,” *Organic Letters* 19, no. 8 (2017): 2078–2081. doi:10.1021/acs.orglett.7b00660
10. (a) R.B. Sonawane, N.K. Rasal, D.S. Bhange, and S.V. Jagtap, “Copper-(II) Catalyzed N-Formylation and N-Acylation of Aromatic, Aliphatic, and Heterocyclic Amines and a Preventive Study in the C-N Cross Coupling of Amines with Aryl Halides,” *ChemCatChem* 10, no. 17 (2018): 3907. (b) M. Zhang, S. Imm, S. Bähn, L. Neubert, H. Neumann, and M. Beller, “Efficient Copper(II)-Catalyzed Transamidation of Non-Activated Primary Carboxamides and Ureas with Amines,” *Angewandte Chemie International Edition* 51, no. 16 (2012): 3905. (c) D.-Z. Lin, and J.-M. Huang, “Electrochemical N-Formylation of Amines via Decarboxylation of Glyoxylic Acid,” *Organic Letters* 20, no. 7 (2018): 2112. (d) V. Kumar, S. Dhawan, R. Bala, S.B. Mohite, P. Singh, and R. Karpoormath, “Cu-catalysed transamidation of unactivated aliphatic amides,” *Organic and Biomolecular Chemistry* 20, no. 34 (2022): 6931. (e) Z.-M. Zheng, N. Chen, M.-S. Dai, and S.-L. Zhang, “Base-Controlled Chemoselective Reaction of High-Valent Cu(III)-CF3 Compounds with Anilines: Access to Formamides or Hydrazines,” *Advanced Synthesis and Catalysis* 365, no. 8 (2023): 1262.
11. A. P. Marjani, S. A. Hosseini, Z. Shokri, and N. Maleki, “Co_3O_4 Nanoparticles Prepared by Oxidative Precipitation Method: An Efficient and Reusable Heterogeneous Catalyst for *N*-Formylation of Amines,” *Research on Chemical Intermediates* 43, no. 1 (2017): 413–422. doi:10.1007/s11164-016-2631-7
12. M. Nirmala, G. Prakash, P. Viswanathamurthi, and J. G. Malecki, “An Attractive Route to Transamidation Catalysis: Facile Synthesis of New *o*-aryloxide-*N*-Heterocyclic Carbene Ruthenium(II) Complexes Containing Trans Triphenylphosphine Donors,” *Journal of Molecular Catalysis A: Chemical* 403 (2015): 15–26. doi:10.1016/j.molcata.2015.03.015
13. N. Shah, E. Gravel, D. V. Jawale, E. Doris, and I. N. N. Namboothiri, “Carbon Nanotube–Gold Nanohybrid Catalyzed *N*-Formylation of Amines by Using Aqueous Formaldehyde,” *Chemcatchem.* 6, no. 8 (2014): 2201–2205. doi:10.1002/cctc.201402225
14. O. Saidi, M. J. Bamford, A. J. Blacker, J. Lynch, S. P. Marsden, P. Plucinski, R. J. Watson, and J. M. J. Williams, “Iridium-Catalyzed Formylation of Amines with Paraformaldehyde,” *Tetrahedron Letters* 51, no. 44 (2010): 5804–5806. doi:10.1016/j.tetlet.2010.08.106
15. M. Hosseini-Sarvari, and H. Sharghi, “ZnO as a New Catalyst for *N*-Formylation of Amines under Solvent-Free Conditions,” *The Journal of Organic Chemistry* 71, no. 17 (2006): 6652–6654. doi:10.1021/jo060847z
16. (a) R. Fu, Y. Yang, J. Zhang, J. Shao, X. Xia, Y. Ma, and R. Yuan, “Direct Oxidative Amidation of Aldehydes with Amines Catalyzed by Heteropolyanion-Based Ionic Liquids under Solvent-Free Conditions *via* a Dual-Catalysis Process,” *Organic & Biomolecular Chemistry* 14, no. 5 (2016): e202200997, 1784–1793. (b) T. A. Gokhale, S. C. Gulhane, and B. M. Bhanage, “Highly Selective Catalyst-Free Oxidative Synthesis of *N* -Formamides from C_2 - and C_3 -Feedstocks,” *European Journal of Organic Chemistry* 26, no. 1 (2022) doi: 10.1039/C5OB02376A
17. (a) Z. Tan, Z. Li, Y. Ma, J. Qin, and C. Yu, “Potassium tert-Butoxide Prompted Highly Efficient Transamidation and Its Coordination-Radical Mechanism,” *European Journal of Organic Chemistry* 2019, no. 28 (2019): 4538–4545. doi:10.1002/ejoc.201900666 (b) P. Nad, K. Gupta, A. Sen, A. Mukherjee, “Mechanistic Understanding of KO^tBu-Mediated Direct Amidation of Esters with Anilines: An Experimental Study and Computational Approach,” *Chemistry - an Asian Journal* 17, no. 21 (2022) e202200800.
18. T. B. Nguyen, L. Ermolenko, M.-E T. H. Dau, A. Al-Mourabit, “Hydrogen Bond Organocatalysis of Benzotriazole in Transamidation of Carboxamides with Amines,” *Heterocycles* 88, no. 1 (2014): 403–416. doi:10.3987/COM-13-S(S)41

19. R. Vanjari, B. K. Allam, K. N. Singh, “Hypervalent Iodine Catalyzed Transamidation of Carboxamides with Amines,” *RSC Adv.* 3, no. 6 (2013): 1691–1694. doi:10.1039/C2RA22459C
20. S. N. Rao, D. C. Mohan, S. Adimurthy, “Chitosan: An Efficient Recyclable Catalyst for Transamidation of Carboxamides with Amines under Neat Conditions,” *Green Chemistry* 16, no. 9 (2014): 4122–4126. doi:10.1039/C4GC01402B
21. J. Yin, J. Zhang, C. Cai, G.-J. Deng, H. Gong, “Catalyst-Free Transamidation of Aromatic Amines with Formamide Derivatives and Tertiary Amides with Aliphatic Amines,” *Organic Letters* 21, no. 2 (2019): 387–392. doi:10.1021/acs.orglett.8b03542
22. (a) J. Chen, J. Jia, Z. Guo, J. Zhang, and M. Xie, “NH_4I-Promoted *N*-Acylation of Amines *via* the Transamidation of DMF and DMA under Metal-Free Conditions,” *Tetrahedron Letters* 60, no. 21 (2019): 1426–1429. (b) C. L. Allen, B. N. Atkinson, J. M. J. Williams, “Transamidation of Primary Amides with Amines Using Hydroxylamine Hydrochloride as an Inorganic Catalyst,” *Angewandte Chemie International Edition* 51, no. 6 (2012) 1383–1386. doi:10.1016/j.tetlet.2019.04.040
23. S. N. Rao, D. C. Mohan, S. Adimurthy, “L-Proline: An Efficient Catalyst for Transamidation of Carboxamides with Amines,” *Organic Letters* 15, no. 7 (2013): 1496–1499. doi:10.1021/ol4002625
24. D. G. Ramírez-Vázquez, O. Viñas-Bravo, R. Martínez-Pascual, L. Pérez-Picaso, K. V. Castro-Cerritos, “DMF·HCl as a Versatile and Straightforward *N*- and *O*-Formylating Agent,” *Synthetic Communications* 51, no. 4 (2021): 585–592. doi:10.1080/00397911.2020.1844901
25. A. D. Becke, “Density-Functional Thermochemistry III. The Role of Exact Exchange,” *The Journal of Chemical Physics* 98, no. 7 (1993): 5648–5652. doi:10.1063/1.464913
26. C. Lee, W. Yang, R. G. Parr, “Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density,” *Physical Review. B, Condensed Matter* 37, no. 2 (1988): 785–789. doi:10.1103/physrevb.37.785
27. S. Ghanta, “Pyrene Radical Cation and the Diffuse Interstellar Band at 4430 Å: A Theoretical Survey,” *Journal of Molecular Structure* 1191 (2019): 32–42. doi:10.1016/j.molstruc.2019.04.067
28. R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople, “Self-Consistent Molecular Orbital Methods. XX. A Basis Set for Correlated Wave Functions,” *The Journal of Chemical Physics* 72, no. 1 (1980): 650–654. doi:10.1063/1.438955
29. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, et al. *Gaussian16 Revision C.01* (Wallingford, CT: Gaussian Inc., 2016).
30. S. Ghanta, “Photophysics and Photostability of Pyrimidine Molecule and Its Radical Cation: A Theoretical Study,” *Molecular Physics* 114, no. 20 (2016): 2958–2973. doi:10.1080/00268976.2016.1211767
31. S. Ghanta, “Theoretically Predicted Fox-7 Based New High Energy Density Molecules,” *Journal of Molecular Structure* 1118 (2016): 28–33. doi:10.1016/j.molstruc.2016.03.094
32. (a) M. S. Manna, C. K. Das, and S. Ghanta, “Design of C-H-N-O Based New Hetero-Cyclic High Energy Density Molecules: A Theoretical Survey,” *Structural Chemistry* 32, no. 3 (2021): 1095–1104. (b) C. K. Patel, R. Gujjarappa, K. Kant, S. Ghanta, V. Singh, A. K. Kabi, N. Al-Zaqri, C. C. Malakar, “Copper-Catalyzed $C(sp^3)$-Functionalization and Annulation of 2-Bromoaryl Oximes with Active Methylene Compounds towards Synthesis of Isoquinoline *N*-Oxides,” *Advanced Synthesis and Catalysis* 365 (2023). doi:10.1002/adsc.202300217
33. S. Ghanta, “Design of Derivatives of FOX-7-Based New Four-Member Heterocyclic Insensitive High Energy Density Molecules: A Theoretical Prospectives,” *Journal of Molecular Modeling* 29, no. 1 (2023): 18. doi:10.1007/s00894-022-05414-2