The γ-Valerolactone (GVL) as Innoxious Reaction Media for the Synthesis of 2-Aryl-2*H*-Indazoles *via* C-N and N-N Bond Formation under Cu(I)-Catalyzed Ligand and Base Free Conditions

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ABSTRACT

An efficient method for N-arylation and N-N bond formation has been developed using an innoxious reaction medium, γ-valerolactone (GVL), as both a solvent and a ligand. The strategy involves utilizing CuI as a catalyst under conditions free of external ligands and bases. Various aldehyde and amine derivatives with different functional groups were investigated, resulting in the production of 2-aryl-2*H*-indazole compounds with yields ranging from 75% to 93%. This study highlights the effectiveness of GVL, a solvent derived from biomass, as a reaction medium and ligand in a multi-component reaction.

Introduction

The utilization of toxic solvents in organic transformations remains a serious environmental concern,[1] although solvents are accountable for the preparation of valuable products in the pharmaceutical sector and fine chemical industries.[2] According to the 'Green Chemistry' concept, the preferences of solvents for the development of novel chemical transformations depend upon their relevancy and the amounts of waste produced.[3] Recently, the innoxious solvents produced from fossil resources or obtained from biomass resources[1–4] have been cited as the most potential reaction medium. However, during the continuous efforts in developing green solvents from biomass[5] to synthesize heterocyclic compounds under mild reaction conditions,[6] we have directed our effort toward γ-valerolactone (GVL) as reaction media for the investigation of novel chemical transformations. GVL can be synthesized from biomass-derived levulinic acid *via* catalytic hydrogenation using a suitable metal catalyst.[7] GVL has accomplished physico-chemical characteristics, including a high boiling point (207 °C), and research has indicated that it has comparable properties to surrogate classic polar aprotic solvents, such as DMF, DMAc, acetone, and NMP.[1a,b] Due to its high potential and nontoxic nature, a series of organic

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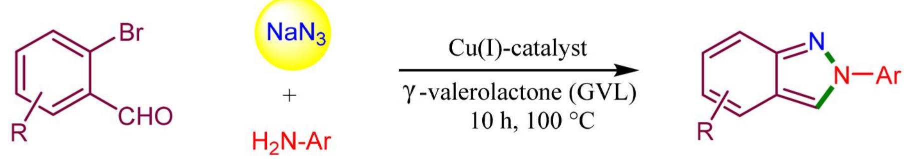
transformations including C-C and C-heteroatom bond formation reactions have been successfully demonstrated.[1a]

N-Heterocycles are witnessed as crucial building blocks and important pharmacophores in medicinal chemistry and drug-discovery research.[8] Among the scaffolds, the indazole derivatives exhibit widespread and immense pharmacological activities[9] and their contribution to biological properties includes anti-microbial,[10] anti-inflammatory,[11] anti-tumor,[12] anti-depressants,[13] and anti-fungal,[14] activities. Apart from these biological actions, the indazole derivatives are found to reveal the inhibitors of viral polymerase,[15] VEGFR (vascular endothelial growth factor receptor),[16] HIV protease,[17] poly(ADP-ribose)polymerase,[18] and also witnessed as estrogen receptor β agonists,[19] glucokinase activators,[20] and farnesoid X receptor antagonists.[21]

Due to the high biological importance, several procedures are reported for synthesizing indazole derivatives. The synthesis of 1*H*-indazoles has garnered more attention due to their high thermodynamic stability;[22] whereas, relatively a less number of protocols are described for the preparation of 2*H*-indazoles. Among the reported methods,[23] the remarkable approaches refer to the selective *N*2-alkylation reaction of 1*H*-indazoles with alkyl 2,2,2-trichloroacetimidates in the presence of Cu(II)-catalyst to afford 2-alkyl-2*H*-indazoles;[24] the reaction between arylhydrazines and 2-bromobenzyl bromides through successive *N*-benzylation, *N*-arylation and oxidation under the influences of Pd(II)-catalysis;[23b] the 1,2,2,3,4,4-hexamethylphosphetane catalyzed deoxygenative N-N bond construction and heterocyclization reaction of *ortho*-nitrobenzaldimines to achieve the corresponding 2*H*-indazoles;[25] the Cu-catalyzed multicomponent reaction between 2-halobenzamides or 2-bromobenzaldehydes, sodium azides and primary amines to obtain 2*H*-indazoles;[26] the tri-*n*-butylphosophine mediated reductive cyclization of *ortho*-imino-nitrobenzene derivatives, which are availed *in situ* by the reaction of *ortho*-nitrobenzaldehydes and amines to derive 2*H*-indazole molecules;[27] the Cadogen heterocyclization and intramolecular N-N bond formation of *ortho*-nitrobenzylidene amines using reductive cyclization under the influences of Mo(VI)-catalyst to deliver the 2*H*-indazole compounds;[28] the C-H functionalization of acylated azobenzenes under the influences of Pd(II)-catalyst to produce these scaffolds;[29] the reaction of sydnones and arynes through a [3 + 2] dipolar cycloaddition to isolate the 2*H*-indazoles;[30] and the Pd-catalyzed intramolecular *N*-arylation of *N*-aryl-*N*-(*o*-bromobenzyl)hydrazines in order to synthesize the 2-aryl-2*H*-indazoles.[31] It was found that all the developed methods were investigated using traditional solvents like DMF,[23c] DMSO,[23b,26b] PhMe,[25,28a,31] alcohols,[26a,27,28b,29] 1,4-dioxane,[24] and THF[30] etc., and none of the reported methods utilized the biomass-derived solvents toward the consecutive C-N and N-N bond formation for the preparation of indazole derivatives. Considering its nontoxic nature, here we have employed the GVL as reaction medium and ligand for the multicomponent reaction between 2-bromobenzaldehydes, sodium azide, and aniline derivatives to drive the transformation toward the formation of 2*H*-indazoles under the influence of Cu(I)-as catalyst (Scheme 1). The novelty of this work stems from the utilization of a distinct solvent derived from biomass resources. Previous literature has predominantly described C-N bond forming reactions in traditional solvents such as DMSO or DMF, which are known to have harmful effects. However, in order to overcome these adverse effects and promote sustainability, we have employed a green solvent in this transformation. This innovative use of a biomass-derived solvent marks a significant advancement toward environmentally friendly and sustainable chemical processes. GVL (a biomass-derived solvent), which acts as a ligand and



Scheme 1. Cu(I)-catalyzed N-N bond formation in GVL for the synthesis of 2-aryl-2*H*-indazoles.

could form a complex. This novel approach facilitates the reaction, leading to increased reaction rates and improved efficiency.

Materials and methods

Materials

All consumables and chemicals were received from commercial vendors such as SD fine chemicals, SRL, TCI, HI Media and were employed in the reactions directly as received, and specified if purified. Reactions were carried out in 5 mL round bottom flask fitted with magnetic stirrer. The solvents used for purification and extraction processes were distilled before use. Thin-layer chromatography (TLC silica gel 60 G F_{254}) was performed using TLC plates procured from Merck. The products were identified under UV light (λ 254 nm) and identified by immersing TLC plates in $KMnO_4$ solution or observed upon heating. The final compounds were obtained 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 300 (75) and 600 (151) MHz were used for recording ^{1}H and ^{13}C NMR spectra using $CDCl_3$ as solvent. The solvent peaks were observed at $\delta_{H/C}$ 7.26/77.28 ($CDCl_3$) using TMS as a reference. The coupling constants (J [Hz]) have been considered as such from the spectra without taking the average. Splitting patterns are represented as br (broad), m (multiplet), q (quartet), t (triplet), d (doublet), and s (singlet).

Methods

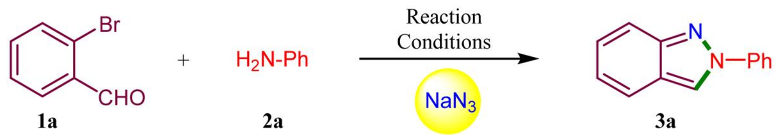
General method for the multicomponent process toward the synthesis of 2-aryl-2H-indazoles

2-bromobenzaldehydes **1a-d** (1.0 mmol), anilines **2a-k** (1.1 mmol) and sodium azide (1.5 mmol) were taken in 5 mL round bottommed flask, then CuI (0.1 mmol) and GVL (0.75 mL) were added to the mixture. The mixture was stirred for 10 h at 100 °C in RB flask equipped with the reflux condenser. The reaction progress was monitored by TLC (SiO_2, EtOAc/Hexane 1:3, v:v). The obtained crude reaction mixture was diluted with 10 mL of ethylacetate and 10 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 1:10, v:v) to afford the 2-aryl-2*H*-indazoles **3a**-**n** in excellent yields.

Results and discussions

Our study was commenced with the screening of reaction conditions for the formation of 2-aryl-2*H*-indazoles. To perform these experiments, we used the compounds 2-bromobenzaldehyde **1a**, aniline **2a** and sodium azide (NaN_3). Initially, a reaction was conducted between 1.0 mmol of **1a**, 1.1 mmol of **2a**, and 1.5 mmol of NaN_3 in the presence of 10 mol% $Pd(OAc)_2$ in DMF as solvent at 80 °C for 10 h, which delivered unsatisfactory outcomes with no product formation (Table 1, Entry 1). Similar results were observed, when the reactions were performed in the presence of 10 mol% $Pd(OAc)_2$ using 20 mol% $P(o\text{-}Tol)_3$ as a ligand (Table 1, Entry 2), and 10 mol% $Pd(PPh_3)_2Cl_2$ (Table 1, Entry 3). Next, the Pd-complexes were replaced with Cu(II)-complex as a catalyst both in the absence and presence of ligand (Table 1, Entries 4 and 5). In these experiments, the 2-phenyl-2*H*-indazole (**3a**) was identified as the product in 39% and 47% yields, respectively. The formation of the product **3a** can be assumed to be the result of a condensation reaction between the aldehyde-group in **1a** and amine-group in **2a**, *N*-arylation in the presence of Cu(I)-catalyst, and finally the intramolecular N-N bond formation reaction. Inspired by these observations, we further attempted to improve the yield of product **3a**. In this regard, 10 mol%

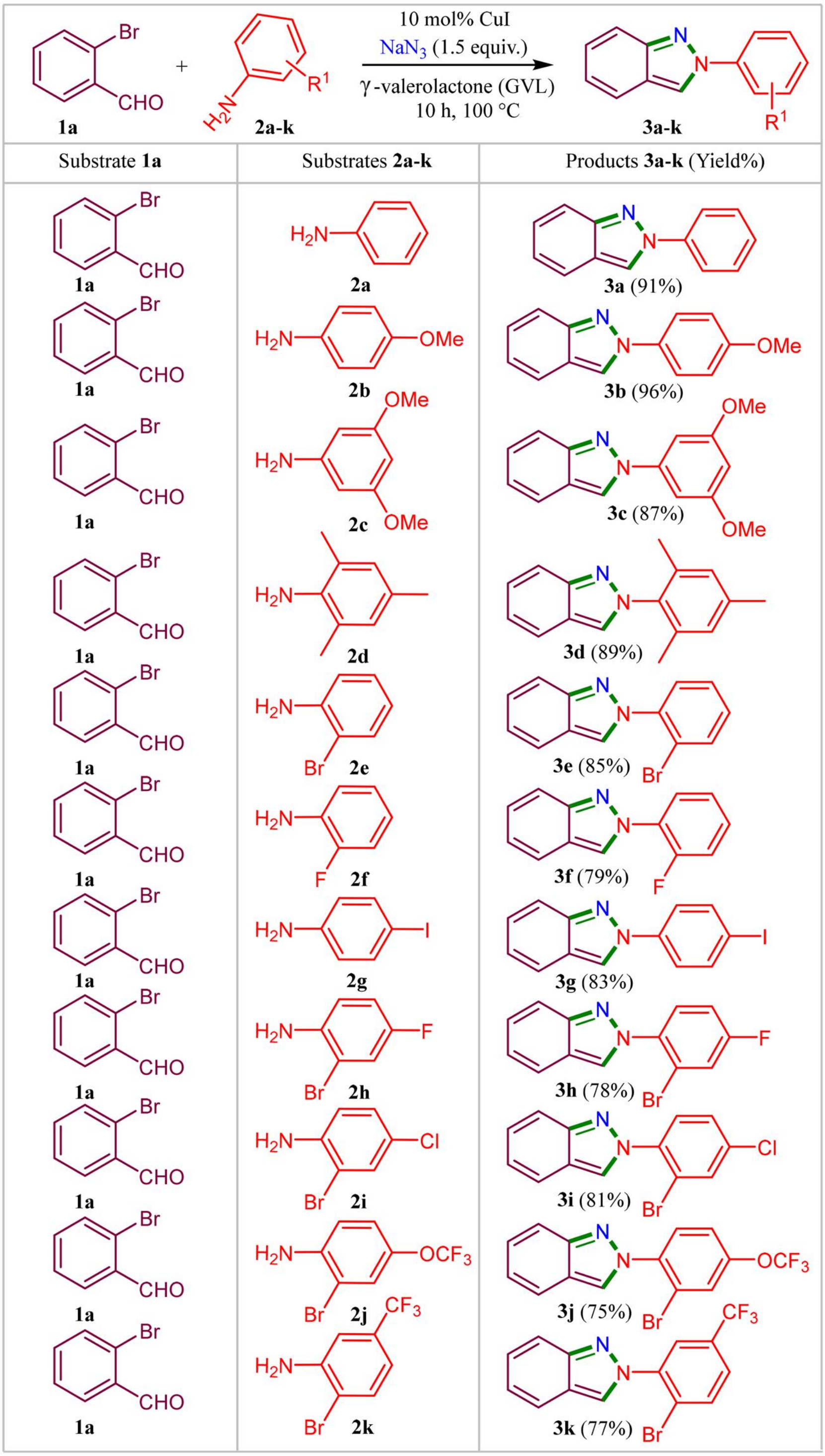
Table 1. Optimization for the synthesis of 2-phenyl-2*H*-indazole[a].



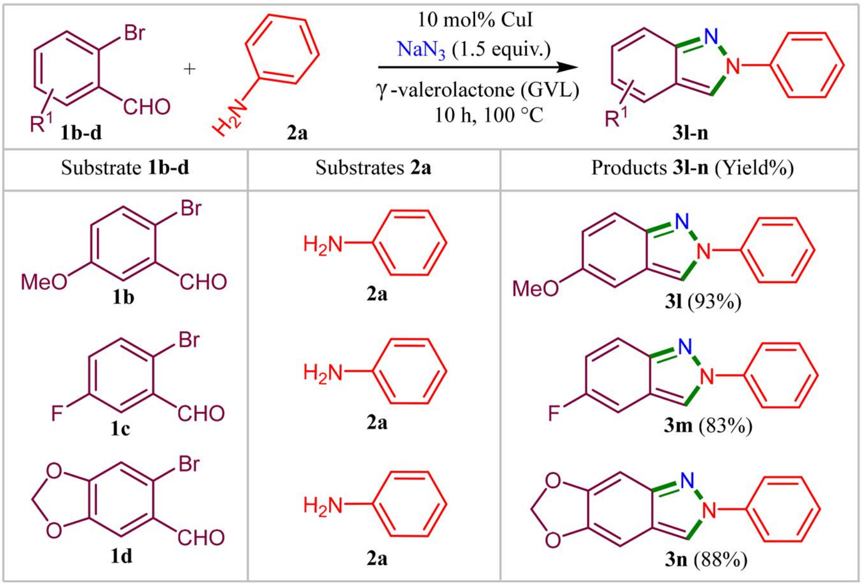
Entry	Catalyst/Ligand	Solvent	T (°C)	t (h)	Yield (%) **3a**[b]
1	$Pd(OAc)_2$/-	DMF	80	10	0
2	$Pd(OAc)_2$/P(o-Tol)$_3$	DMF	100	14[c]	0
3	$Pd(PPh_3)_2Cl_2$/-	DMF	80	10	0
4	$Cu(OAc)_2$/-	DMF	110	10	39
5	$Cu(OAc)_2$/1,10-phenanthroline	DMF	100	15	47
6	CuI/-	DMF	100	10	83
7	CuI/-	DMSO	100	10	85
8	CuI/-	MeCN	100	10	81
9	CuI/-	NMP	100	10	52
10	CuI/-	1,4-dioxane	100	10	54
11	CuI/-	THF	100	10	49
12	CuI/-	PhMe	80	10	<5
13	CuI/-	Ethylene glycol	80	10	<5
14	CuI/-	GVL	100	10	91
15	CuI//1,10-phenanthroline	GVL	100	10	81
16	CuI/DMEDA	GVL	100	12	79
17	CuI/TMEDA	GVL	100	10	85
18	CuI/Thiophene-2-carboxylic acid	GVL	100	10	63
19	CuI/2-picolinic acid	GVL	100	14	67
20	CuI/-	GVL	100	10[d]	61
21	CuI/-	GVL	100	10[e]	88
22	CuI/-	GVL	130	10	86
23	CuI/-	GVL	50	10	<5
24	CuI/-	GVL	100	15	83
25	CuI/-	GVL	100	7	68

[a]All reactions were carried out using 1.0 mmol **1a**, 1.1 mmol **2a** and 1.5 mmol sodium azide using 10 mol% catalyst and 10 mol% ligand in 0.75 mL solvent. [b]Isolated yields. [c]Reaction was carried out using 10 mol% catalyst and 20 mol% ligand. [d]Reaction was carried out using 5 mol% catalyst. [e]Reaction was carried out using 15 mol% catalyst.

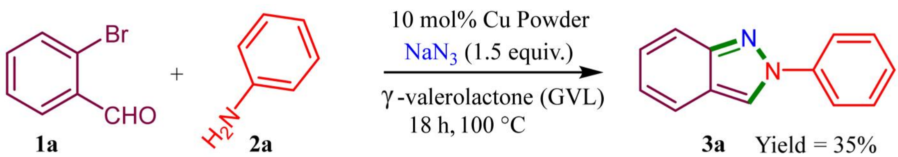
CuI was screened as a catalyst, which interestingly delivered product **3a** in 83% yield under the influence of DMF as solvent at 100 °C in 10 h (Table 1, Entry 6). To develop the reactivity of substrates **1a** and **2a** in different reaction media, a series of solvents were examined (Table 1, Entries 6–14). Among the tested reaction media (DMF, DMSO, MeCN, NMP, 1,4-dioxane, THF, toluene, ethylene glycol, and GVL), the solvents DMF, DMSO and MeCN revealed similar outcomes of this transformation (Table 1, Entries 6–8) in terms of reactivity and reaction yields of the product **3a**; whereas, the solvents NMP, 1,4-dioxane and THF (Table 1, Entries 9–11) delivered moderate yields of the product **3a** and the solvents PhMe, ethylene glycol (Table 1, Entries 12–13) showed inactivity for this transformation under similar reaction conditions. These experiments displayed that the GVL as solvent exhibited higher compatibility for this transformation, which produced slightly higher yield of the product **3a** (Table 1, Entry 14). Next, the effect of a series of ligands was screened in the presence of Cu(I)-catalyst under the influence of GVL as solvent (Table 1, Entries 15–19), which led to the conclusion that there are no additional advantages of using ligands as the yields of the product **3a** remain lower than the ligand-free conditions. Further, the significance of the amounts of the catalyst, temperature and reaction time for this transformation was studied (Table 1, Entries 20–25). It was observed that a 5 mol% catalyst loading diminished the yield of product **3a** (Table 1, Entry 20), whereas using 15 mol% catalyst loading resulted in the similar yield of the product **3a** (Table 1, Entry 21). On the other hand, variations in temperature and time lead to unsatisfactory results (Table 1, Entries 22–25). After optimization of the reaction conditions, it has been revealed that the best yield of the product **3a** was found when



Scheme 2. Cu(I)-catalyzed synthesis of 2-aryl-2*H*-indazoles using various amines in GVL as solvent.



Scheme 3. Cu(I)-catalyzed synthesis of 2-aryl-2*H*-indazoles using various aldehydes in GVL as solvent.



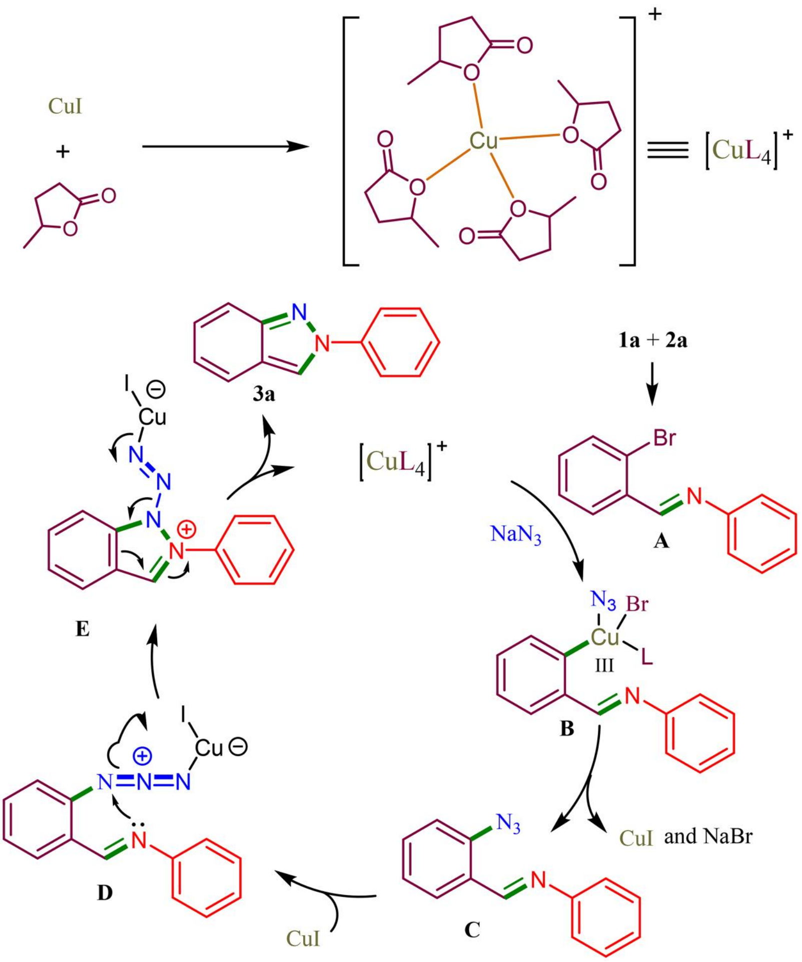
Scheme 4. Cu Powder catalyzed synthesis of 2-aryl-2*H*-indazole in using GVL as solvent.

the multicomponent reaction between **1a**, **2a**, and sodium azide (NaN_3) was carried out in the presence of 10 mol% CuI at 100 °C in 10 h under the influence of GVL (0.75 mL) as solvent (Table 1, Entry 14) and the use of a reflux condenser was employed to overcome any limitations associated with the small volume of solvent.

After optimizing reaction conditions, we attempted to investigate the substrate scope using the same synthetic protocol. To serve this purpose, a series of aromatic amines **2** are exposed in the multicomponent reaction with 2-bromobenzaldehyde **1a** and sodium azide (NaN_3). The obtained results are presented in Schemes 2 and 3.

It was observed that functional groups like methoxy (-OMe), and methyl (-Me) incorporated in different positions of aromatic amines are found to be effective in establishing efficient transformation with the formation of products **3b**-**d** in excellent yields ranging from 87–96%. On the other hand, electron-deficient substituents such as bromo (-Br), chloro (-Cl), fluoro (-F), iodo (-I), trifluoromethyl (-CF_3) and trifluoromethoxy (-OCF_3) groups embedded on aromatic rings either in mono- or disubstituted patterns showed comparatively low efficiency to yield the corresponding products **3e**-**k** in high yields ranging from 75–85%. The observed facts on the formation of products **3** in slightly lower yields may be explained due to the presence of electron deficient groups on the amine component, which may resist the formation of N-N bonds (Scheme 2). Additionally, the aromatic aldehydes **1b**-**d** are also investigated under the developed conditions, which resulted in the generation of products **3l**-**n** in yields ranging from 83–93%. These experiments showed good functional group tolerance on aromatic aldehydes for this described multicomponent reaction (Scheme 3).

To further explore the reactivity of the substrates with copper powder, we conducted a reaction between **1a** and **2a** using 10 mol% copper powder in GVL as the solvent. Surprisingly, the



Scheme 5. Plausible mechanism for the Cu(I)-catalyzed multicomponent reaction in GVL.

reaction yielded the desired product **3a**, but with a lower yield of 35% (Scheme 4). However, we observed the appearance of two additional spots on the TLC plate, which might be the spots of the biphenyl product and the coupling product of *ortho* hydrogen of aniline with bromine of benzaldehyde but these were not observed when using copper iodide, indicating the occurrence of unwanted side reactions. Additionally, it was noticed that the reaction time was significantly longer compared to using copper iodide. One possible explanation for this difference in behavior between copper iodide and copper powder is their varying reactivity. Copper iodide, being a compound, possesses a more controlled reactivity, ensuring the desired product forms without any significant interference from side reactions. On the other hand, copper powder consists of many small particles, providing a larger surface area for potential reactions to occur. This increased surface area can lead to the initiation of unwanted reactions, leading to the formation of the additional spots observed in the experiment. Moreover, the slower reaction rate observed when using copper powder compared to copper iodide can be attributed to the smaller particle size of the powder. The increased surface area exposed by the copper powder particles allows for a higher number of reactant collisions, causing a delay in the overall reaction progress. This delay results in a longer reaction time compared to the reaction conducted with copper iodide, where the reaction takes place at a faster rate due to the controlled reactivity of a compound. In conclusion, the increased surface area and reactivity of the particles can explain the unexpected appearance of

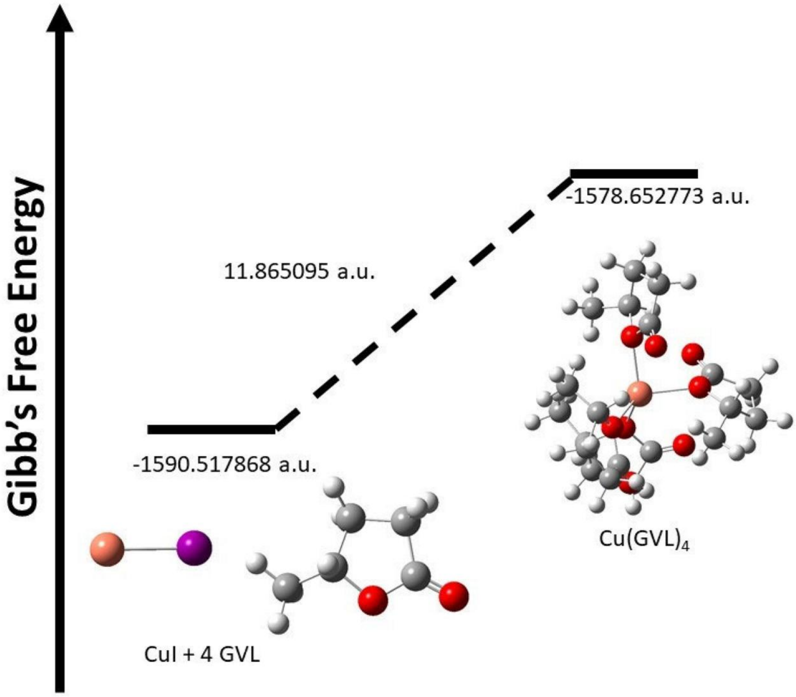


Figure 1. The DFT predicted energy profile diagram for the formation of the copper-GVL complex is shown here along with the B3LYP computed molecular structures.

additional spots and the longer reaction time observed when using copper powder. These factors contribute to the initiation of unintended side reactions and the slower progression of the desired reaction, ultimately affecting the final outcome of the experiment.

The γ-valerolactone (GVL) plays a dual role by working as a solvent and ligand in the reaction. As a solvent, GVL provides a medium for the reaction to take place by dissolving the reactants and facilitating their interaction. As a ligand, GVL can coordinate with metal ions, such as copper, forming a complex. This coordination occurs through the lone pair of electrons on the oxygen atom situated in five-membered ring of GVL. The oxygen atom of GVL acts as a Lewis base, donating its lone pair of electrons to the Lewis acid, which is the metal ion. In the reaction mechanism, the GVL coordinates with the metal ion, typically through an oxygen-metal coordination bond. This coordination bond stabilizes the reactive intermediates, enhances the reactivity of the metal ion, and ultimately influences the overall reaction pathway. Furthermore, GVL could play a role as ligand to influence the selectivity in the formation of product in the reaction. The coordination of GVL to the metal ion can affect the electronic environment around the metal-center, which leading to the different reactivity patterns and preferences toward the potential mechanistic pathway. Overall, by simultaneously acting as a solvent and a ligand, the GVL enhances the reaction by providing a suitable environment for the reaction to occur and influencing the reactivity and selectivity through its coordination with the metal ion.

A plausible mechanism for the formation of product **3a** is represented in Scheme 5. To explain the mechanism, the imine molecule **A** is generated by the reaction between substrates **1a** and **2a**. Then, the $[CuL_4]^+$-catalyzed N-arylation reaction of compound **A** with sodium azide (NaN_3) delivers the arylazide molecule **C** followed by the formation of oxidative addition intermediate **B**. The efficiency of the Cu(I)-catalyzed N-arylation reaction can be explained by the complex formation of Cu(I) with GVL to enhance the stabilization of the active catalyst and that induces the effectiveness of the cross-coupling reaction. Then, the cyclization of Cu(I)-azide complex **D** using

N-N bond formation may result the intermediate five-membered N-heterocycle **E**, which is formed *via* the release of an active Cu(I)-catalyst and the extrusion of molecular nitrogen, and obtained the expected product **3a**.

In order to gain better insights into the formation of a copper complex with GVL, we attempted to conduct a DFT analysis. This analysis provides a clear understanding for the generation of copper and GVL complex. At the B3LYP[32,33] level of theory, we performed optimization and frequency calculations for the structures of CuI, GVL, and the copper-GVL complex. We also attempted the calculations of activation energies for the formation of the copper-GVL complex from CuI and GVL. We utilized advanced computational methods, such as the B3LYP method (Becke, LYP) and the 6–31 g* Pople's Gaussian basis set\cite{pople} for C, H, N, and O. We used the LANL2DZ basis set for iodine and copper, with the assistance of the Gaussian 09 (G09) quantum chemistry package (g09). Harmonic vibrational frequencies of the electronic ground state were extracted by diagonalizing the B3LYP force field calculated at the same level of theory. We performed both structure optimization and harmonic frequency calculations for CuI, GVL, and the copper-GVL complex using the DFT level of theory and the G09 quantum chemistry tool. None of the CuI, GVL, or copper-GVL complex exhibited any imaginary frequencies, indicating their stability. The lowest harmonic vibrational frequencies for CuI, GVL, and the copper-GVL complex are 241, 122, and 16 cm^{-1}, respectively. The activation energy for the formation of the copper-GVL complex from Cu-I and 4 GVL molecules is 11.865095 a.u., which confirms the formation of the copper-GVL complex. The energy profile diagram for the formation of complex from the reactants CuI and GVL is illustrated in Figure 1 along with all the structures.

Conclusion

A ligand and base free Cu(I)-catalyzed multicomponent reaction between 2-bromobenzaldehydes, arylamines and sodium azide was described toward the synthesis of 2-aryl-2*H*-indazoles under the influences of *γ*-valerolactone (GVL) as biomass-derived solvent. The developed approach proved as efficient protocol for a series of functional groups embedded on both aldehyde and amine components to yield 2-aryl-2*H*-indazole derivatives in high to excellent yields. The biomass-derived solvent *γ*-valerolactone (GVL) was found to be highly efficient for this transformation, which performs as a suitable surrogate of a series of conventional solvents.

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Author contributions

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

Disclosure statement

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

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