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Zinc-Catalyzed N-Alkylation of Aromatic Amines with Alcohols: A Ligand-Free Approach

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Abstract: An efficient zinc-catalyzed N-alkylation reaction of aromatic amines was achieved using aliphatic, aromatic, and heteroaromatic alcohols as the alkylating reagent. A variety of aniline derivatives, including heteroaromatic amines, underwent the N-alkylation reaction and furnished the corresponding monoalkylated products in good to excellent yields. The application of the reaction is also further demonstrated by the synthesis of a 2-phenylquinoline derivative from acetophenone and 2-aminobenzyl alcohol. Deuterium labeling experiments show that the reaction proceeds via a borrowing hydrogen process.

Keywords: Zinc, Ligand-free approach, N-Alkylation, Quinoline, Borrowing hydrogen

Introduction

Amines and their products are highly valuable compounds in biological and synthetic chemistry.[1] Particularly, N-alkylamines have broad applications in pharmaceuticals, agrochemicals, a ligand for catalysis, and biologically active compounds (See Figure 1).[2] Traditionally, N-alkylated amines are prepared by treating amines with alkyl halides in the presence of a stoichiometric amount of bases[3a-b] or by reductive amination protocols.[3c-d] Meanwhile, transition metal-catalyzed N-alkylation reaction of amines using alcohol as an alkylating agent via borrowing hydrogen or hydrogen autotransfer method has emerged as an excellent alternative and environmentally-benign approach in organic synthesis.[4a-d] Notably, the use of alcohol as the alkylating agent makes the reaction greener as it affords only water as the byproduct.[4e-h] Mechanistically, the reaction proceeds via dehydrogenation of alcohol, giving carbonyl compound, which then undergoes reaction with a nucleophile such as an amine to give imine. Subsequent reduction of the imine with the borrowing hydrogen affords the corresponding alkylated product.[5] In this context, several homo- and heterogeneous catalytic systems based on Ru, Rh, Ir, Pd, Pt, Mn, Fe, Cr, Co, Ni, have been developed to prepare the N-alkylated amines in an efficient manner.[6-8] Although the reported catalyst systems are quite effective, most of the homogeneous based catalytic systems were designed using a combination of a metal salt and precious organic ligand, which sometimes may require multistep synthesis.[6-8] On the other hand, heterogeneous based metal catalysts also suffer from high catalyst loading, selectivity, and harsh reaction conditions.[9-10] Thus, the development of low-cost metal catalysts[11] or efficient catalytic systems with high turnover numbers under mild reaction conditions[12] toward the synthesis of N-alkylation reaction is highly desirable and always remains in demand.

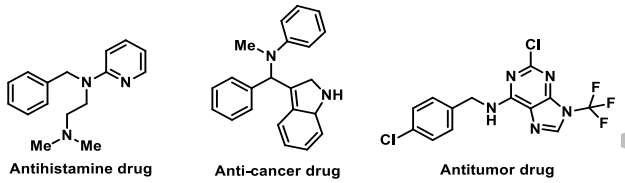
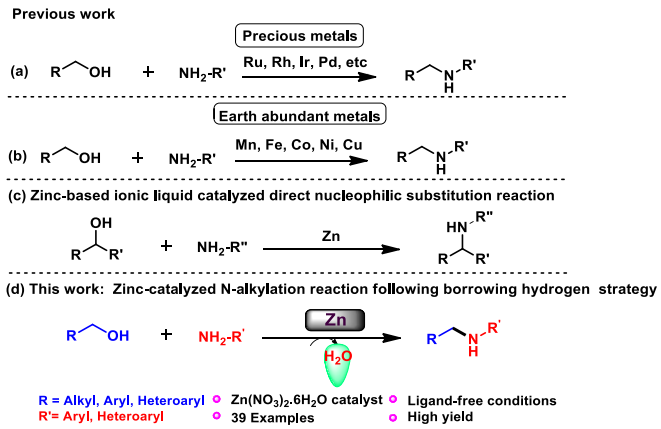


Figure 1. Representative examples of pharmaceutically important N-alkylated amine moieties

In recent years, zinc-catalyzed alkylation reactions using alcohol as the alkylating agent for constructing C-C and C-N bonds have attracted much interest in organic synthesis.[13] For instance, a zinc-based ionic liquid was used as a catalyst for the direct

nucleophilic substitution reaction of alcohols with amine that proceeds via a carbocation intermediate.[14] Subsequently, heterogeneous catalyst ($PdZn/Al_2O_3$)[15] was also developed for the N-alkylation reaction of various amines. In the meantime, visible-light induced nanocomposite ($Pd/ZnIn_2S_4$)[16] catalyst was introduced for the alkylation of amines and α-hydrogen of ketones with alcohols to construct C-N and C-C bonds. However, these reports required either a particular solvent system (ionic liquid) or other metals such as palladium as a co-catalyst. Until now, the application of simple zinc salts in the N-alkylation reaction of amines are yet to be developed.

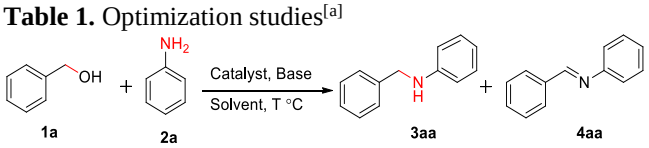
Recently, we reported a Zn based MOF[17] as a heterogeneous catalyst for C-C bond formation reactions. Inspired by these reports and our interest in search of a less expensive catalytic system for coupling reactions[18] prompted us to explore the possibility of using less expensive zinc salts in the N-alkylation reaction. Herein, we report a zinc-catalyzed N- and C-alkylation reactions using alcohols as the alkylating agent. To the best of our knowledge, this is the first report on zinc-catalyzed N-alkylation of amines under ligand-free conditions following borrowing hydrogen strategy (Scheme 1). N-Alkylation reactions employing first-row transition metal salts as catalyst have rarely been studied[19] and remained unexplored.



Scheme 1. Metal-catalyzed N-alkylation of amines with alcohols

Results and Discussion

Table 1. Optimization studies[a]



Entry	Catalyst	Solvent	Yield(%)[c]	
			3aa	**4aa**
1[b]	$Zn(NO_3)_2.6H_2O$/bpy	toluene	55	26
2[b]	$Zn(NO_3)_2.6H_2O$/phen	toluene	93	2
3[b]	$Zn(NO_3)_2.6H_2O$/PPh_3	toluene	28	46
4	$Zn(NO_3)_2.6H_2O$	toluene	100 (98)[d]	0
5	$ZnCl_2$	toluene	92	0
6	$Zn(CH_3COO)_2$	toluene	85	9
7	Zn dust	toluene	55	10
8[e]	$Zn(NO_3)_2.6H_2O$	toluene	88	5
9[f]	$Zn(NO_3)_2.6H_2O$	toluene	23	7
10	$Zn(NO_3)_2.6H_2O$	1,4-dioxane	25	15
11	$Zn(NO_3)_2.6H_2O$	THF/ MeCN[g]	22	6
12	-	toluene	55	6
13[h]	$Zn(NO_3)_2.6H_2O$	toluene	28	2

[a]All the reactions were carried out using **1a** (1.50 mmol), **2a** (1.00 mmol), Zn catalyst (7.50 - 15.0 mol%), *t*-BuOK (1.00 mmol) using 1.50 mL of solvent at 140 ° C for 36 h under nitrogen atmosphere. [b]Zn catalyst 7.5 mol% and ligand 7.50 mol% were used. [c]GC Yield. [d]Isolated Yield. [e]10.0 mol% of $Zn(NO_3)_2.6H_2O$ was used. [f]Reaction was carried out at 100 ˚C. [g]THF:MeCN (1:1) ratio. [h]Without *t*-BuOK. [i]bpy = 2,2'-bipyridine, Phen = 1,10-phenanthroline, PPh_3 = triphenylphosphine

We started our investigation by choosing benzyl alcohol (**1a**) and aniline (**2a**) as model substrates in the presence of $Zn(NO_3)_2.6H_2O$ (7.5 mol%) as the catalyst, 2,2'-bipyridine as ligand (7.5 mol%) *t*-BuOK (1.0 equiv.) as base and toluene as solvent. At 140 °C for 24 h, the reaction afforded the desired product **3aa** in 55% yield along with (*E*)-N-benzylidene aniline (**4aa**) in 26% yield (Table 1, entry 1). To increase the product yield of **3aa**, the reaction conditions were optimized by changing ligands, solvents, bases, and temperature (Table 1 and Supporting Information, Tables 1–3). To our surprise, the reaction provided the desired product **3aa** in 98% isolated yield in the absence of any phosphine or nitrogen ligands (entry 4). The reaction is highly selective and affords only monoalkylated product. Among the variety of Zn sources (entry 4-7) that we tested, $Zn(NO_3)_2.6H_2O$ was found to give the highest yield. Notably, lowering the catalyst loading of $ZnNO_3.6H_2O$ from 15 mol% to 10 mol% reduced the product yield to 88% (entry 8). The present catalytic reaction is highly solvent and temperature-dependent. Decreasing the reaction temperature from 140 to 100 °C led to low yield (entry 9). Similarly, toluene appears to be the most effective solvent under the optimized reaction conditions. Other polar and coordinating solvents such 1,4-dioxane and acetonitrile were less active (entry 10, 11). It is noteworthy to mention that the reaction also proceeds in the absence of either zinc salts or base but affords the desired product only in moderate yield (entry 12, 13). Based on these studies, we chose $ZnNO_3.6H_2O$ (15 mol%) as the catalyst, *t*-BuOK (1.0 equiv.) as a base, and toluene as solvent at 140 °C as the standard

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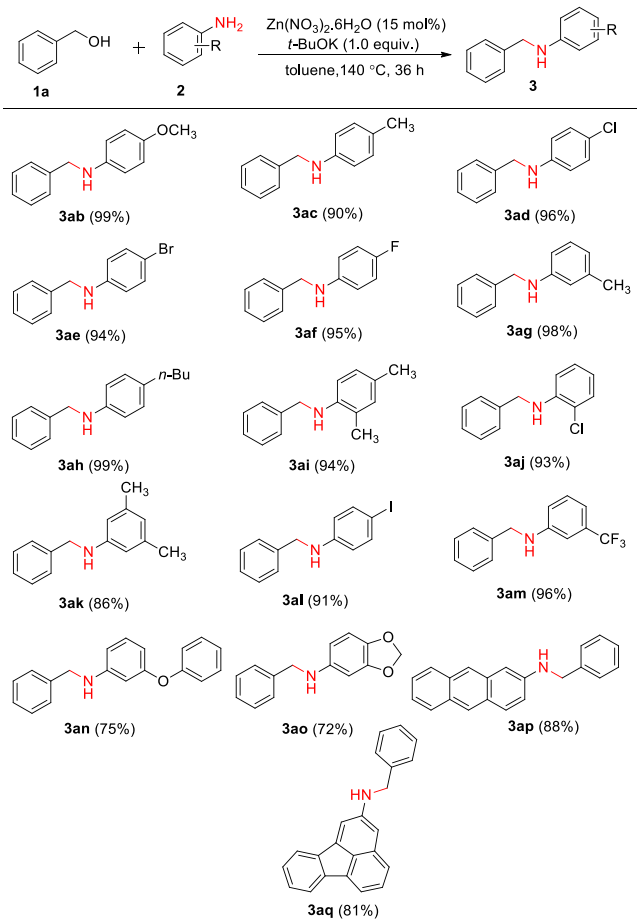
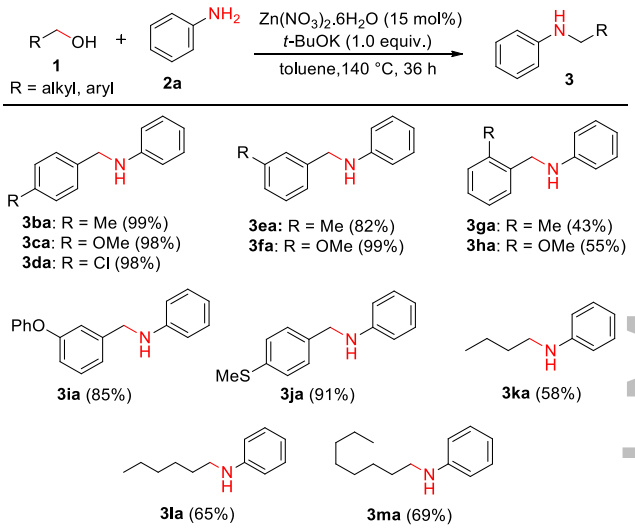
reaction conditions for the N-alkylation reaction of anilines.

Under standard reaction conditions, the scope of the aromatic amines **2** with benzyl alcohol (**1a**) in the N-alkylation reaction was examined. Scheme 2 depicts that aromatic amines bearing both electron donating and withdrawing substituents are compatible with the present reaction. Thus, the reaction of 4-methoxyaniline (**2b**) and *p*-toluidine (**2c**) with **1a** gave **3ab** and **3ac** in 99 and 90% yields, respectively. Halogen substituted aromatic amines (**2d-f**) also participated well in the reaction affording the products **3ad-af** in high yields. Similarly, aromatic amines (**2g-l**) bearing substituents at the *ortho*-, *meta*- and *para*-position also gave the desired products **3ag-al** in good to high yields. Amines containing pharmaceutically active substituents such as trifluoromethyl- (**2m**), phenoxy- (**2n**), and 1,3-dioxole (**2o**) also worked very well and furnished the desired products **3am-ao** in 96, 75 and 72% yields. Encouragingly, anthracene- (**2p**) and fluoranthene (**2q**) amines also gave the corresponding products **3ap** and **3aq** in good yields.



Scheme 2. Scope of Amines. [a]Reaction conditions: **1a** (1.50 mmol), **2b-q** (1.00 mmol), $Zn(NO_3)_2.6H_2O$ (15.0 mol%), *t*-BuOK (1.00 mmol) using toluene (1.50 mL) as the solvent at 140 °C for 36 h under nitrogen atmosphere. [b]Isolated Yield.

Next, we examined the scope of several benzyl alcohols (**1b-m**) with aniline (**2a**) (Scheme 3). In general, the reaction proceeded in high yield with benzyl alcohols (**1b-f**) containing substituents at *para*- and *meta*-position. On the other hand, benzyl alcohols containing *ortho*-substituents such as methyl (**1g**) and methoxy **(1h)** gave the desired products **3ga** and **3ha** in 43 and 55% yields, respectively. Gratifyingly, phenoxy- (**1i**) and methylthio-substituted (**1j**) benzyl alcohols also participated in the reaction and afforded the respective products **3ia** and **3ja** in 85 and 91% yields. The present catalytic reaction conditions were also successfully applied to more challenging aliphatic alcohols. To our delight, *n*-butanol (**1k**), *n*-hexanol (**1l**), and *n*-octanol (**1m**) worked well and gave the corresponding products **3ka-ma** in 58-69% yields. It is noteworthy to mention that secondary aryl amines and primary aliphatic amines did not provide any desired alkylated products **3** under the optimized reaction conditions.



Scheme 3. Scope of Alcohols. [a]Reaction conditions: **1b-m** (1.50 mmol), **2a** (1.0 mmol), $Zn(NO_3)_2.6H_2O$ (15.0 mol%), *t*-BuOK (1.0 mmol) using toluene (1.50 mL) as the solvent at 140 °C for 36 h under nitrogen atmosphere. [b]Isolated yield.

Alcohols and amines containing N-heteroaromatics such as pyridine, pyrimidine, pyrazine and thiophene moieties were also subjected to the N-alkylation reaction (Scheme 4) and the corresponding products (**3na-av**) were obtained in 67-98% yields. Notably, chloro- (**2w**), bromo- (**2x**) and iodo (**2y**) substituted aminopyridines furnished the desired products **3aw, 3ax** and **3ay** in 86, 92 and 86% yields.

To further extend the scope of the reaction, we performed a C-alkylation reaction of acetophenone (**5**) using **1a** as the alkylating agent (Scheme 5).[20a-e] Promisingly, the reaction proceeded smoothly and yielded the desired alkylated product **6** in 81% yield. In a similar fashion, a 2-phenylquinoline **8** was also synthesized from **5** and 2-amino benzyl alcohol (**7**) in 92% yield (Scheme 6).[20f-i]

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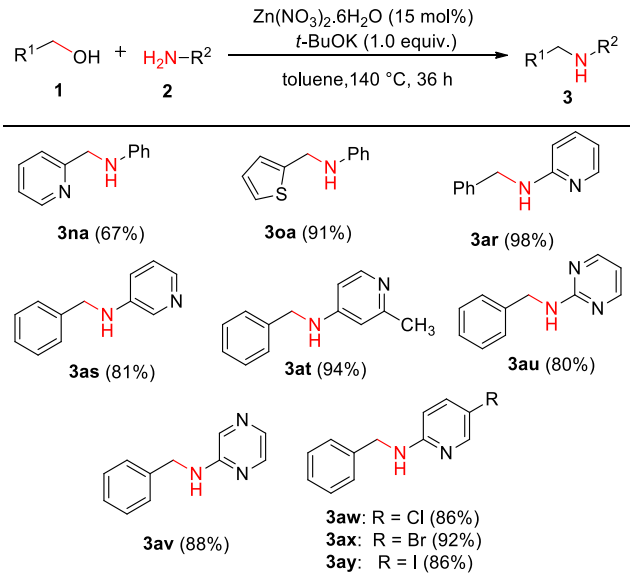
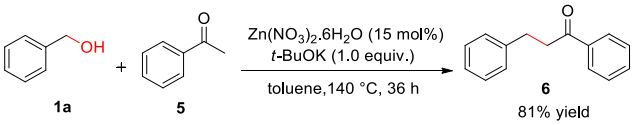
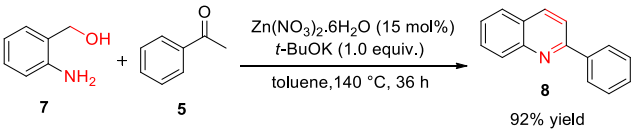


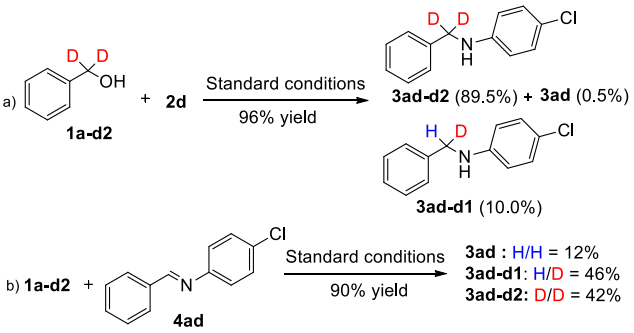
Scheme 4. Scope of Heteroaromatic Substrates. [a]Reaction conditions: **1** (1.50 mmol), **2** (1.0 mmol), $Zn(NO_3)_2.6H_2O$ (15.0 mol%), *t*-BuOK (1.0 mmol) using toluene (1.50 mL) as the solvent at 140 ˚C for 36 h under nitrogen atmosphere, [b]Isolated Yield.



Scheme 5. C-Alkylation of acetophenone (**5**) with benzyl alcohol (**1a**)



Scheme 6. Synthesis of 2-phenylquinoline (**8**)



Scheme 7. Mechanistic study

Further, deuterium labeling experiments were performed (Scheme 7) to understand the nature of the mechanism. Under standard reaction conditions, the reaction of isotopically enriched deuterated benzyl alcohol **1a-d2** with 4-chloro aniline (**2d)** afforded fully deuterated product **3ad-d2** in 89.5% yield along with **3ad-d1** in 10% (Scheme 7a).[21] The relative yields were determined by ^{1}H NMR spectroscopy. Besides, a reduction of imine **4ad** with **1a-d2** was also investigated (Scheme 7b). The desired product **3ad-d1**, along with **3ad-d2** and **3ad**, was obtained in ratio 46, 42, and 12%, respectively. The formation of **3ad-d2** in the imine reduction process is probably attributed to the reversibility in the imine formation.[21] These results are consistent with the literature reports[21a-b] on D/H exchange, although the reduction of **4ad** with H_2 failed to yield the desired product under standard reaction conditions. Based on these studies, we believe that the present catalytic reaction proceeds via borrowing hydrogen or hydrogen auto-transfer process[21] and not through carbocation intermediate. It also appears that zinc nitrate in the presence of potassium *tert*-butoxide oxidizes the benzyl alcohol and also reduces imine during the catalytic cycle. Furthermore, the outcome of the reaction in the absence of metal catalyst is also highly intriguing (Table 1, entry 12). The exact mechanistic pathway of the reaction remains uncertain at present, but we assume that the reaction may follow a transition-metal-free hydrogen autotransfer pathway as described by Wang et al. in 2019.[22]

Conclusion

In summary, we have developed an efficient N-alkylation reaction of amines with alcohols using relatively inexpensive and commercially available, earth-abundant zinc nitrate as the catalyst. The reaction is selective and affords the monoalkylated amines in good to high yields. The present reaction is compatible with various aliphatic, aromatic, and heteroaromatic alcohols and also proceeded smoothly with aryl and heteroaryl amines. The yield of the reaction is comparable with the other reported first-row transition metal catalysts.[21a-b, 8f] The application of the reaction is successfully extended toward the C-alkylation reaction of ketone and quinoline synthesis. Deuterium labeling experiments confirm that the present catalytic process proceeds via a borrowing hydrogen/hydrogen auto-transfer (HAT) mechanism. The scope of the zinc-catalyzed C-alkylation reaction is currently investigated in our laboratory.

Experimental Section

General procedure for N-alkylation of amines with alcohols: A sealed tube (15 mL) containing *t*-BuOK (1.00 mmol), and $Zn(NO_3)_2.6H_2O$ (15.0 mol%) was evacuated and purged with nitrogen gas three times. Then, alcohol (1.50 mmol), amine (1.00 mmol), and toluene (1.50 mL) were added under a nitrogen atmosphere. The reaction mixture was stirred at 140 ºC for 36 h. After completion of the reaction, the mixture was cooled to room temperature diluted with water 5.0 mL and extracted with

dichloromethane (3 × 5 mL). The resultant organic layer was dried over anhydrous Na_2SO_4, and the solvent was concentrated under reduced pressure. The crude mixture was purified on a silica gel column using hexane/ethyl acetate as eluent to provide the desired product **3**.

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FULL PAPER

Zinc-Catalyzed N-Alkylation of Aromatic Amines with Alcohols: A Ligand Free Approach

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