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A novel and unusual method for C—N bond formation between benzene ring and various amines

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ABSTRACT

A new approach to form C—N bond without metal catalysis was developed. 4-acetylbenzoyl isocyanate reacted with various amines through a mild method to form C—N bond. This reaction was amenable to scale-up and it afforded the corresponding products with good to excellent yields and tolerates a wide range of functional groups.

Introduction

C—N bond formation is a fundamental reaction in organic chemistry [1,2]. The reaction is highly important in the synthetic methodologies and in the preparation of pharmaceutical compounds [3]. Because of its broad applications in various fields, numerous methods have been documented in the literature for the formation of this important chemical bond [4]. Migita and co-workers firstly reported that *N*, *N*-diethylaniline was synthesized by using organotin reagent and bromobenzene as the reaction substrate, $PdCl_2(o\text{-}tolyl_3P)_2$ as the catalyst in toluene (Scheme 1, Method A) [5]. Buchwald and co-workers reported that using amines instead of highly toxic organotin reagents can also realize the coupling of C—N bonds [6,7], which was refered to as the first-generation Buchwald-Hartwig amination reaction. (Scheme 1, Method B) [8]. Hua-Jian Xu and co-workers reported that CuCl/ligand-free catalyzed *N*-arylation of aryl halides with *N*-heterocyclic compounds and alkyl amines in water. (Scheme 1, Method C) [9–11]. Yuqin Xu and co-workers reported that various *N*-aryl phosphinamides and phosphonamides were successfully prepared through the Chan-Evans-Lam reaction. (Scheme 1, Method D) [12]. Sukanya and co-workers reported that a general and practical method for direct C—H amination of 2H-indazole with a series of amines (including aliphatic primary amines, secondary amines, azoles and sulfonimides) through oxidative coupling catalyzed by organic photocatalysts. (Scheme 1, Method E) [13]. Manwika reported that a high-temperature and high-pressure continuous-flow protocol to carry out nucleophilic aromatic substitution (SNAr) of heterocycles with nitrogen nucleophiles. (Scheme 1, Method F) [14]. However, most of these reported methods used functionalized starting materials [15], expensive metal catalysts [16], and strict conditions [17].

Therefore, construction of C—N bond under mild reaction conditions are more attractive in modern synthetic chemistry [18]. Initially, we attempted synthesis of compounds containing a formyl urea structure (**I**). However, the structure of the final compound was not obtained, but rather to give a C—N coupling product (**3a**). This discovery aroused our great interest. In this study, we reported a convenient method of forming C—N bond by mild method with 4-acetylbenzoyl isocyanate as material, and it displayed wide applicability and good yield.

Results and discussion

In the initial attempt, 4-acetylbenzoyl isocyanate (**1a**) and cyclopentanamine (**2a**) were chosen as model substrates to explore the optimization of aliphatic amine reaction conditions. Second, we selected MeCN as the solvent, screening of the reaction temperature from 25 °C to 80 °C. The results indicated that raising the temperature to 70 °C increased the yield of **3a** from 26% to 85% (Table 1, entry 4). However, raising the temperature from 70 °C and 80 °C displyed no further effects on the yield (Table 1, entry 5). Third, the reaction solvents were screened. The results revealed that the yield could not be improved (Table 1, entries 6–11). To our

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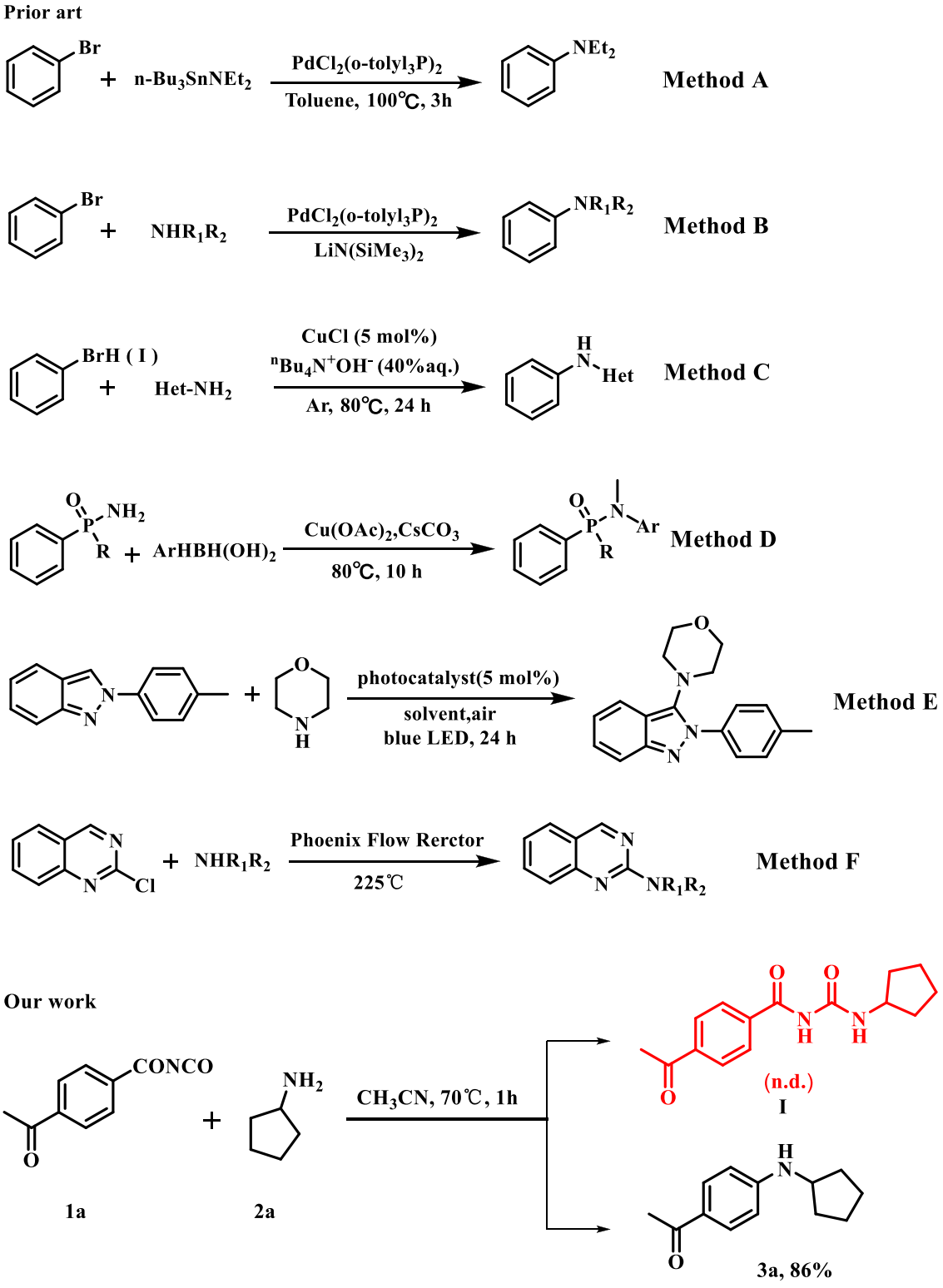
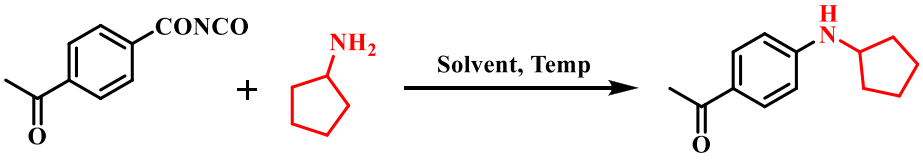


Scheme 1. Synthesis of C—N coupling products.

surprise, when we reduce the reaction time to 1 h, the desired product (**3a**) was obtained in 86% yield (Table 1, entry 12). Consequently, the standard reaction conditions used for further investigations were **1a** (1.0 equiv.) and **2a** (1.2 equiv.) in MeCN at 70 °C for 1 h (Table 1, entry 12).

With the optimized reaction conditions for C—N bond formation identified, the substrate scope was investigated to determine the generality of this method (Table 2). A series of aliphatic amines were explored and the desired C—N coupling products were obtained with 74–92% yields. The results showed that the types of aliphatic amines had little effect on the yields. These results clearly indicated that the C—N bond formation could better endure the wide variation in aliphatic amine.

Table 1
Optimization of aliphatic amine reaction conditions.

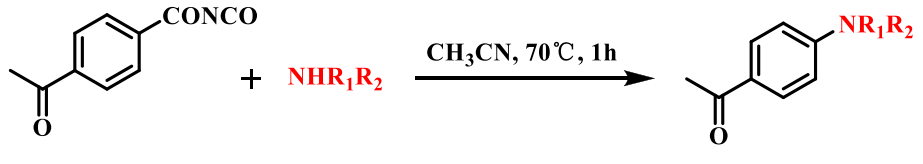


1a 2a 3a

Entry	Solvent	Temp (°C)	Time (h)	Yield [b] (%)
1	CH_3CN	r.t.	2	26
2	CH_3CN	40	2	43
3	CH_3CN	60	2	67
4	CH_3CN	70	2	85
5	CH_3CN	80	2	76
6	$ClCH_2CH_2Cl$	reflux	2	45
7	DCM	reflux	2	18
8	1,4-dioxane	70	2	68
9	THF	reflux	2	62
10	DMSO	70	2	46
11	CH_3OH	reflux	2	Trace
12	CH_3CN	70	1	**86**
14	CH_3CN	70	4	**86**

[a] Reagents and conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), solvent (5 mL) was added to the reaction system.
[b] Isolated yield.

Table 2
Substrate scope for the C—N bond formation between **1a** and aliphatic amine.



1a 2a-g 3a-g

Entry	NHR_1R_2	Product	Yield [b] (%)
1	cyclopentanamine	**3a**	92
2	cyclopropanamine	**3b**	87
3	methanamine	**3c**	74
4	pyrrolidine	**3d**	84
5	piperidine	**3e**	87
6	4-methylpiperidine	**3f**	89
7	1-methylpiperazine	**3g**	91

[a] Reagents and conditions:**1** (1.0 mmol), **2** (1.2 mmol), CH_3CN, 70 °C, 1 h.
[b] Isolated yield.

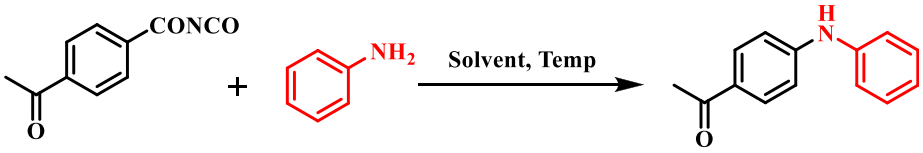
To further expand the scope of the substrates, we took aniline as an example to optimize a series of reaction conditions for aromatic amines. First, we selected CH_3CN as solvent to react at different temperatures. However, the yield decreased significantly. As the influence of solvent was crucial for the reaction, different solvents were then screened. It was found that when 1,2-dichloroethane was used as solvent, the yield was increased significantly. Then the reaction temperature was screened from 25 °C to 60 °C. The results indicated that reducing the temperature to 25 °C increased the yield of compound **3 h** to 94% (Table 3, entry 8). Thus, the optimal reaction conditions were **1a** (1 equiv.), **2h** (1.2 equiv.) in 1,2-dichloroethane at 25 °C for 2 h (Table 3, entry 8).

Under the optimized reaction conditions, we investigated the range of substrates to verify the generality of the method (Table 4). A series of substituted anilines with *ortho*-or *para*-substituents were explored and the desired C—N coupling products (**3h-p**) were obtained in 48–94% yield. Compounds **3r** was also obtained in good yields, which indicated that the reaction might be able to tolerate large groups. However, the reaction of nitro and chlorine substituted substrates **3o**, **3p** and **3q** showed an obvious decrease in yield, which indicated that this reaction is affected by electronic factors and electron-withdrawing groups are unfavorable.

Finally, we explored the substrate scope of 4-acetylbenzoyl isocyanate and its derivatives (Table 5). Under the optimized reaction conditions, all substrates with acyl groups on the benzene ring were converted into the desired C—N coupling products (**3v-x**) in 64–89% yield. However, the substrates without acyl substitution couldn't react with piperidine to obtain the C—N coupling products (**3s-u**), which indicated that the presence of acetyl groups were necessary for this reaction.

In order to explore the reaction mechanism, various control experiments were conducted. 4-Acetylbenzoyl isocyanate (**1a**) and piperidine (**2e**) were converted into the C—N coupling product (**3e**) in 87% yield under the optimised reaction conditions. When

Table 3
Optimization of aromatic amine reaction conditions.

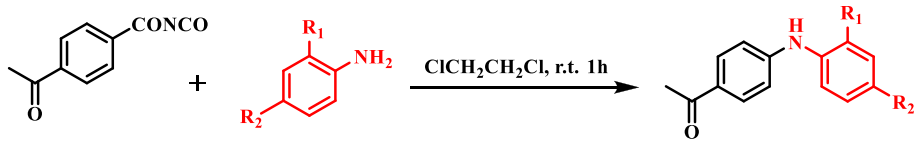


1a **2h** **3h**

Entry	Solvent	Temp (°C)	Time (h)	Yield [b] (%)
1	CH_3CN	r.t.	2	23
2	CH_3CN	40	2	26
3	CH_3CN	60	2	22
4	CH_3CN	80	2	24
5	DCM	r.t.	2	33
6	DCM	40	2	28
7	DCM	reflux	2	24
8	$ClCH_2CH_2Cl$	r.t.	2	**94**
9	$ClCH_2CH_2Cl$	40	2	88
10	$ClCH_2CH_2Cl$	60	2	87
11	$ClCH_2CH_2Cl$	r.t.	1	93
12	1,4-dioxane	r.t.	2	34
13	1,4-dioxane	40	2	29
14	1,4-dioxane	60	2	23
15	1,4-dioxane	80	2	27
16	THF	r.t.	2	45
17	THF	40	2	37
18	THF	reflux	2	44

[a] Reagents and conditions: **1a** (1.0 mmol), **2 h** (1.2 mmol), solvent (5 mL) was added to the reaction system.
[b] Isolated yield.

Table 4
Substrate scope for the C—N bond formation between **1a** and aromatic amine.



1a **2h-r** **3h-r**

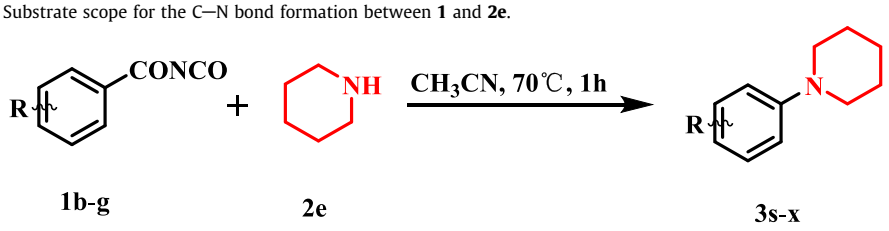
Entry	R_1	R_2	Product	Yield [b] (%)
1	**-H**	**-H**	**3h**	94
2	**-H**	**$-CH_3$**	**3i**	92
3	**$-CH_3$**	**$-CH_3$**	**3j**	89
4	**-H**	**$-CH_2CH_3$**	**3k**	92
5	**-H**	**$-CH(CH_3)_2$**	**3l**	86
6	**-H**	**$-OCH_3$**	**3m**	90
7	**-H**	**$-OCF_3$**	**3n**	88
8	**-H**	**-Cl**	**3o**	54
9	**-Cl**	**-H**	**3p**	48
10	**-H**	**$-NO_2$**	**3q**	n.d.
11	**-H**	**$-N(CH_2CH_2)_2O$**	**3r**	85

[a] Reagents and conditions:**1** (1.2 mmol), **2** (1.2 mmol), 1,2-dichloroethane, 25 °C, 1 h.
[b] Isolated yield.

the reaction was conducted in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (**TEMPO**) or butylated hydroxytoluene (**BHT**) as radical scavengers, compound **3e** was obtained in 85% and 86% yield Scheme 2, respectively, which indicated that the reaction did not proceed via a radical mechanism.

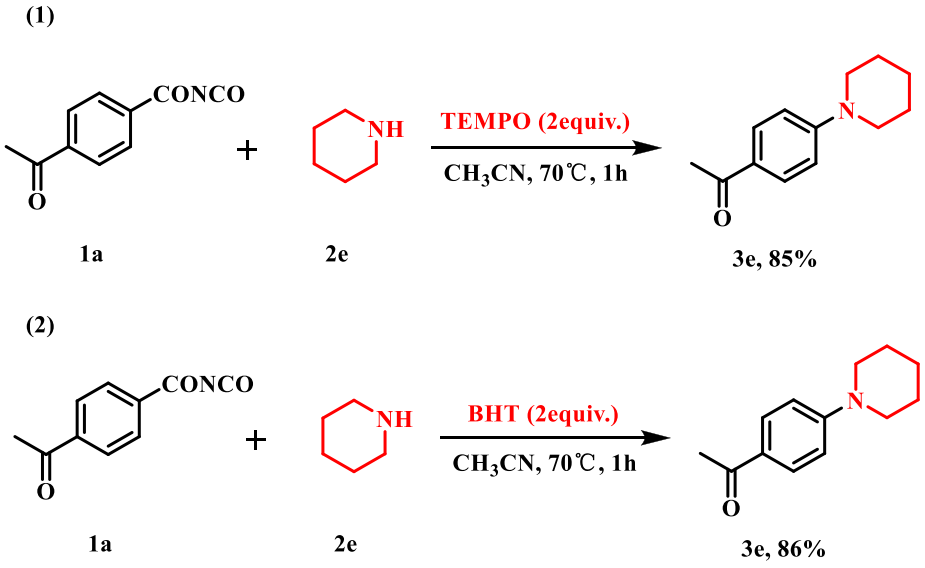
Based on our experimental results and previous investigations, a plausible mechanism was proposed (Scheme 3) [19,20]. First, intermediate **A** was formed by the reaction between benzoyl isocyanate (**1**) and amine (**2**) under acidic condition. Then intermediate **B** and **C** were formed via the tautomerism between the benzene ring and the acyl group on intermediate A. Second, the nitrogen atom on the amine attacked the carbocation on the 1-position of the benzene ring to obtain the intermediate D. Third, intermediate **E** was formed by breaking the C—N bond. Finally, intermediate **E** removed one molecule of formyl isocyanate to obtain compound **3**.

Table 5
Substrate scope for the C—N bond formation between **1** and **2e**.

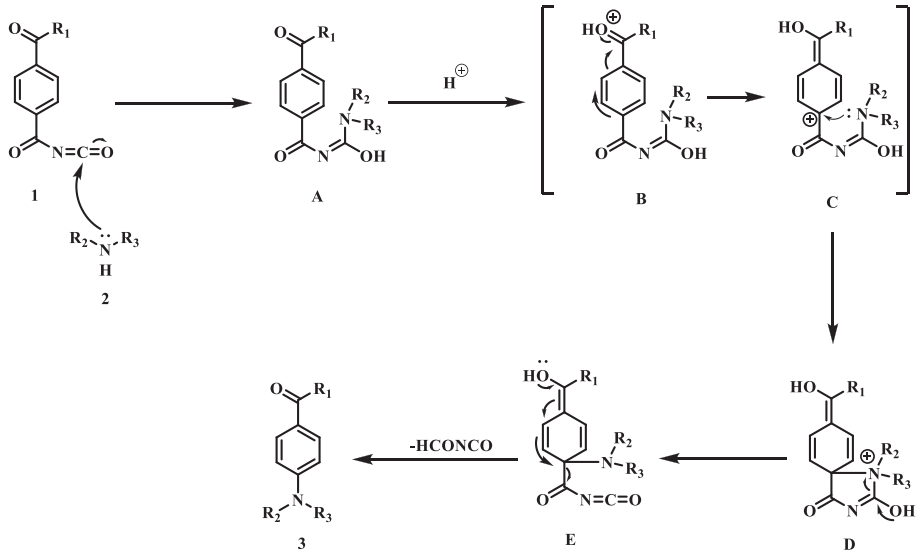


Entry	R	Product	Yield [b] (%)
1	**-H**	**3 s**	n.d.
2	***p*-NO_2**	**3 t**	n.d.
3	***p*- OCH_3**	**3u**	n.d.
4	***o*- $COCH_3$**	**3v**	89
5	***m*- $COCH_3$**	**3w**	86
6	***p*- $COCH_2CH_3$**	**3x**	64

[a] Reagents and conditions:**1** (1.0 mmol), **2e** (1.2 mmol), CH_3CN, 70 °C, 1 h.
[b] Isolated yield.



Scheme 2. Control experiments.



Scheme 3. Proposed mechanism for the formation of **3.**

Conclusion

In summary, we have developed an effective C—N bond formation method. The developed protocol provides highly attractive route to various C—N coupling products from the simple and readily available starting materials, and especially it avoids the use of any catalyst. This novel reaction works well with a wide range of substrates and mild reaction conditions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153355.

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