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Copper-catalyzed carbonylation of anilines by diisopropyl azodicarboxylate for the synthesis of carbamates

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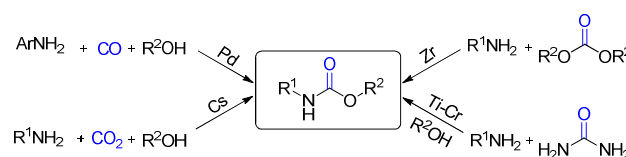
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Cu-catalyzed an efficient methodology of direct carbonylation of anilines has been developed. The N-H bond cleavage and N-C bond formation was notably achieved under solvent-free conditions and variety of carbamates were synthesized from readily available anilines using diisopropyl azodicarboxylate (DIAD) as a carbonylating source.

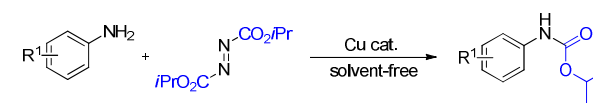
Dialkyl azodicarboxylates, as potential reagents, are very useful in organic synthesis such as Mitsunobu reaction.¹ Due to its unique structural and electronic features, azodicarboxylates are used in zwitterions intermediate reactions,² as oxidants,³ aldehydic C-H bond functionalization by hydroacylation,⁴ amination of C-H bonds,⁵ α -amination of carbonyl and cyanoacetate compounds.⁶ However, the investigation of dialkyl azodicarboxylates as carbonylating reagent is very limited.⁷

Organic carbamates are important intermediates for the synthesis of pesticides, herbicides and pharmaceutical drugs.⁸ Several methods for carbamates synthesis have been reported using *N,N'*-carbonyldiimidazole, carbamoylimidazolium salts and toxic phosgene or its derivatives.^{8c,9} The other available carbonyl sources for the synthesis of carbamates are urea, dialkyl carbonate, CO₂ and CO (Scheme 1a).¹⁰ Transition metals catalyzed poisonous CO oxidative¹¹ and reductive¹² carbonylation of amines and nitro compounds have been reported respectively. Industrially important methods are through carbonylation of amines with organic carbonates.¹³ The synthesis of carbamates have also been accomplished via Lossen, Curtius and Hofmann rearrangements.¹⁴ The limitations of these methods are due to multi step procedures, harsh reaction conditions and lack of easily available substrates. Despite these advances, the development of more convenient and alternative methods based upon other

carbonyl sources is also desirable (Scheme 1b). As part of our (a) Previous work (Different carbonyl sources)



(b) This work (DIAD as the carbonyl source)



Scheme 1 Different carbonyl sources used for the synthesis of carbamates from amines.

previous work related to carbamate synthesis,^{10d} we speculated that carbamates could be formed with the aid of dialkyl azodicarboxylate under mild reaction conditions. We selected copper as a possible catalyst because, it has robust catalytic activities.¹⁵ Cu-catalyzed direct C-N bond formation is more desirable atom-economic synthetic approach.^{15a} In this regard, Cu-catalyzed reactions of diazo compounds have gained significant achievement.^{15c} However, to the best of our knowledge copper-catalyst had never been studied in the carbonylation reaction of dialkyl azodicarboxylates. Herein, we wish to report a simple method for the synthesis of carbamates via a novel reaction by using diisopropyl azodicarboxylate (DIAD) as the carbonyl source over copper-catalyst notably under solvent-free conditions.

We initially tried to optimize the reaction conditions of aniline **1b** with DIAD **2a** by using different solvents. Gratifyingly, we observed that **1b** could be transformed into the desired carbamate **3b** in 23% yield (Table 1, entry 1) using CuI as the catalyst in THF. In addition, the effects of various organic solvents and catalysts were investigated, and we found that solvents do not play an important role in this reaction. When toluene, DMSO or DMF was used as a solvent, major change in carbonylation did not occur, but a very low yield of

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corresponding product was obtained (15-20%) (Table 1, entries 2-4). The change of different catalysts in THF further reduced the product yield (Table 1, entries 5-7). When Pd(OAc)₂ was used as a catalyst, no reaction was observed (Table 1, entry 8). We speculated that the employment of solvent-free conditions would improve the reaction yield. Delightedly, the yield of **3a** increased to 27% in the absence of solvent when the reaction was carried out in the presence of CuI at room temperature for 1 h (Table 1, entry 9). The best result was obtained when the reaction was performed in the presence of Cu(OAc)₂ (Table 1, entry 11). Further changing the catalyst loading showed less efficiency in term of yields (Table 1, entries 12-13). Furthermore, no reaction occurred in the absence of copper-catalyst (Table 1, entry 14).

After optimizing the reaction conditions, the substrate scope of the reaction was investigated (Table 2). This solvent free carbonylation was found to be a good methodology for the synthesis of carbamates. Carbonylation of aniline **1a** with DIAD **2a** gives carbamate **3a** in 81% yield (Table 2, entry 1). While, diethyl azodicarboxylate (DEAD) **2b** led to comparatively the same yield (Table 2, entry 2). Anilines substituted at the aryl ring with Me, MeO, F, Cl Br, and I were converted into the corresponding products efficiently, (Table 2, entries 3-9). However, the reaction of **1h** and **1i** was sluggish and was achieved with long reaction time at elevated temperature (Table 2, entries 10-11). When meta-substituted anilines **1j** and **1k** were employed, the corresponding products **3j** and **3k** were obtained up to 71% and 81% yields, respectively (Table 2, entries 12-13). In addition, ortho-substituted anilines **1l** and **1m** were transformed into the corresponding carbamates **3l** and **3m** in moderate yields (Table 2, entries 14-15). Moreover, the 3,4-dimethylaniline and 2,4-dimethylaniline smoothly furnished the desired products in good yields (Table 2, entries 16-17). Interestingly, when the heterocyclic analogues **1p** was subjected to the standard reaction conditions, the desired product **3p** was obtained in 30% yield (Table 2, entry 18). However, the scope of this reaction was limited to primary anilines.

Table 1 Optimization of reaction conditions^a

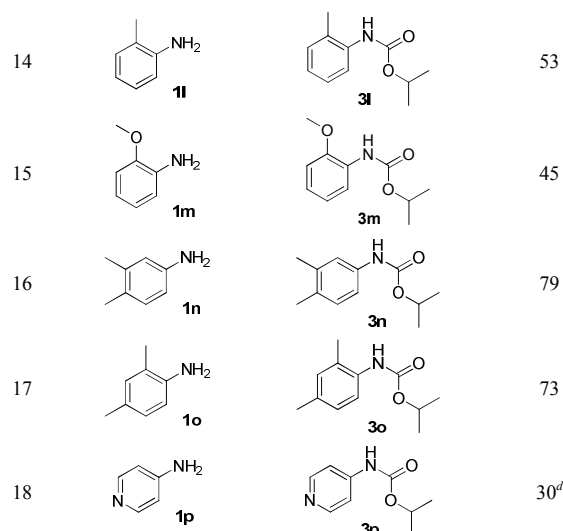
Entry	Catalyst	Solvent	Temp (°C)	Yield ^b (%)
1	CuI	THF	120	23
2	CuI	toluene	120	15
3	CuI	DMSO	120	20
4	CuI	DMF	120	18
5	CuBr ₂	THF	120	19
6	CuCl ₂	THF	120	Trace
7	Cu(NO ₃) ₂	THF	120	Trace
8	Pd(OAc) ₂	THF	120	0
9	CuI	-	RT	27
10	Cu(TFA) ₂	-	RT	21
11	Cu(OAc)₂	-	RT	75
12 ^c	Cu(OAc) ₂	-	RT	66

13 ^d	Cu(OAc) ₂	-	RT	68
14	-	-	RT	0

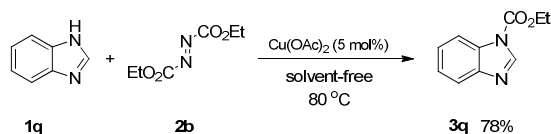
^a Reaction conditions: **1b** (0.3 mmol), **2a** (0.6 mmol) and catalyst (5 mol%) in solvent (1 ml) under Ar for 1 h. ^b Isolated yields. ^c Cu(OAc)₂ (1 mol%), ^d Cu(OAc)₂ (20 mol%).

Table 2 Cu-catalyzed carbonylation of anilines^a

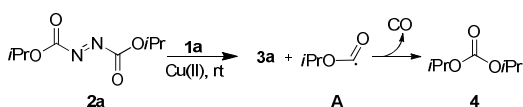
Entry	Substrate	Product	Yield ^b (%)
1	1a	3a	81
2	1a	3a'	79
3	1b	3b	75
4	1b	3b'	74
5	1c	3c	74
6	1d	3d	78
7	1e	3e	83
8	1f	3f	82
9	1g	3g	66
10	1h	3h	48 ^c
11	1i	3i	52 ^c
12	1j	3j	71
13	1k	3k	81



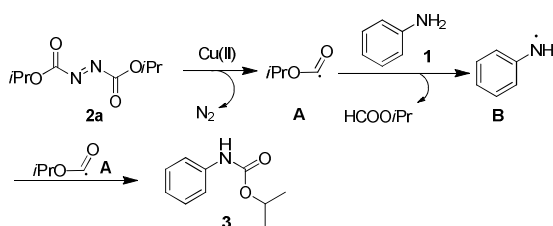
^a Reaction conditions: anilines **1** (0.3 mmol), **2** (0.6 mmol) and Cu(OAc)₂ (5 mol%) under Ar at room temperature for 1 h. ^b Isolated yields. ^c 80 °C instead of room temperature for 4 h. ^d 80 °C for 1 h. R = ⁱPr, Et.



Scheme 2 Synthetic transformation of **1q**. Reaction conditions: **1q** (0.3 mmol), DEAD **2b** (0.6 mmol) and Cu(OAc)₂ (5 mol%) under Ar at 80 °C for 1 h.



Scheme 3 Investigation of the reaction mechanism.



Scheme 4 Proposed mechanism for Cu-catalyzed carbonylation of anilines with DIAD.

To demonstrate the synthetic utility of this method, further transformation of DEAD **2b** was conducted with benzimidazole **1q** (Scheme 2). To our delight, we found that carbonylation of N-H bond functionality in **1q** proceeded smoothly in a highly selective manner at elevated temperature (80 °C) for 1 h to afford the corresponding product **3q** in 78% yield.

Cu-catalyzed mechanism of carbon and heteroatom bond formations proposed to occur through radical pathway.^{15a} Comparatively the high yields of electron-deficient anilines agreed with the high stability of electron-deficient aniline radicals as compared with electron-rich aniline radicals.¹⁶

Further, the decomposition of aliphatic azo compounds accomplished the free radicals that could be used for further transformations.^{7a,7b,17} We found that, when **1a** reacted with **2a** under standard reaction conditions, **3a** and diisopropyl carbonate **4** were formed (Scheme 3).^{7a} We believed that decomposition of **2a** would generate the oxyacyl radicals **A**,¹⁸ some of which undergo carbonylation to form carbamates, while some of them would undergo decarbonylation to generate diisopropyl carbonate.

On the basis of these studies, a possible mechanism for this C-N bond formation utilizing DIAD and aniline is proposed (Scheme 4). The N-H bond carbonylation using DIAD, the proposed mechanism is triggered by copper catalyst, first the DIAD **2a** decomposes to give the oxyacyl radicals **A**, which is supposed to abstract hydrogen from aniline **1** to generate the aminyl radical **B**.¹⁹ DIAD **2a** serves as an aniline radical initiator as well as radical trapping reagent in the reaction.²⁰ The resulting radicals **A** and **B** combine together to give corresponding carbamate **3**.

In conclusion, we have uncovered a novel method for the synthesis of carbamates by Cu-catalyzed reaction of simple anilines with commercially available diethyl or diisopropyl azodicarboxylate. The N-H bond cleavage and N-C bond formation was notably achieved under solvent-free conditions. Various electron-donating and electron-withdrawing groups on anilines are compatible with this method. The use of readily available dialkyl azodicarboxylate and an inexpensive copper-catalyst make this method mild, general and efficient, thus providing an extremely preferable protocol for the synthesis of variety of carbamates. Further studies on extending the scope of the reaction and detailed investigation into the reaction mechanism are under progress in our laboratory.

Acknowledgements

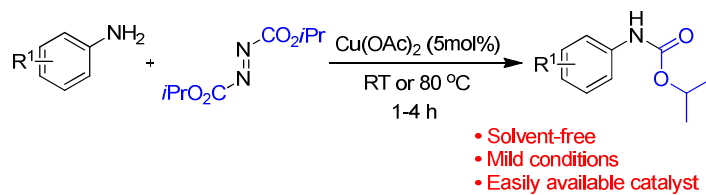
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Graphical Abstract:



Herein a simple Cu-catalyzed system for the synthesis of carbamates has been developed using anilines with diisopropyl azodicarboxylate as a carbonyl source under solvent-free conditions.