Organic LETTERS

Copper-Catalyzed Ligand-Free Amidation of Benzylic Hydrocarbons and Inactive Aliphatic Alkanes

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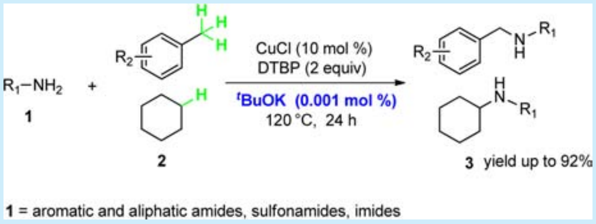
Supporting Information

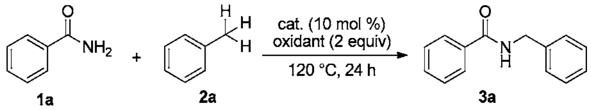
ABSTRACT: An efficient copper-catalyzed amidation of benzylic hydrocarbons and inactive aliphatic alkanes with simple amides was developed. The protocol proceeded smoothly without any ligand, and a wide range of *N*-alkylated aromatic and aliphatic amides, sulfonamides, and imides were synthesized in good yields.



Nitrogen-containing compounds have attracted much attention owing to the high prevalence of C−N bonds in pharmaceuticals, agrochemicals, polymers, etc.[1] Presently, C−H activation is noted as an efficient and highly atom-economic method for the formation of various chemical compounds. The amidation of sp^3 C−H bonds of hydrocarbons with amide compounds provides an efficient route to produce *N*-alkyl amide derivatives. In the reported methods, the amidations were usually performed by using nitrene-type derivatives as the nitrogen sources.[2,3] Recently, great progress has been made in the direct amidation of C−H bonds by employing a simple amide/imide via C−H/N−H cross-coupling.[4,5] Among them, secondary benzylic hydrocarbons have often been used as good coupling partners.[5a−g] However, the amidation of primary benzylic hydrocarbons as well as inactive aliphatic alkanes is rare.[5h−k] Inspired by previous works, we herein report a general method for the C−N bond formation via C−H/N−H cross-coupling of amides/imides with both primary benzylic hydrocarbons and inactive aliphatic alkanes to afford the corresponding products in good yields.

To begin our study, we chose the benzamide **1a** and toluene **2a** as model substrates. The reaction was initially studied with DTBP as an oxidant without any catalyst. No desired product was detected after heating at 120 °C for 24 h under N_2 in a Schlenk tube (Table 1, entry 1). When Cu_2O (10 mol %) was used as the catalyst, product **3a** was obtained in 57% yield (entry 2). Encouraged by this result, a number of other Cu catalysts, including CuI, CuCl, $[MeCN]_4Cu(I)PF_6$, $CuCl_2$, $CuSO_4{\cdot}H_2O$, and $Cu(OTf)_2$ were investigated (entries 3−8). The results showed that CuCl displayed the highest catalytic activity for this reaction (entry 4). Next, we screened other oxidants, TBHP, DCP, and $K_2S_2O_8$ were inefficient for the coupling of primary benzylic C−H bonds with benzamide (entries 9−11). When the reaction was performed under air, the yield dropped to 25% (entry 12). Further, the effect of a base (^{t}BuOK) was studied. When 20 mol % of ^{t}BuOK was added, the product was obtained in 15% yield only, with most of the starting materials recovered (entry 13). To our surprise, when the base was reduced to a very small amount of 0.001 mol %, an 84% yield of product was collected (entry 14). Slightly increasing the amount of base resulted in a lower yield with incomplete conversion of the starting materials (entry 15).

Table 1. Optimization of the Reaction Conditions[a]



entry	cat. (10 mol %)	oxidant (2 equiv)	additive (0.001 mol %)	yield (%)[b]
1		DTBP		0
2	Cu_2O	DTBP		57
3	CuI	DTBP		55
4	CuCl	DTBP		61
5	$[MeCN]_4Cu(I)PF_6$	DTBP		55
6	$CuCl_2$	DTBP		35
7	$CuSO_4{\cdot}H_2O$	DTBP		20
8	$Cu(OTf)_2$	DTBP		10
9	CuCl	TBHP		trace
10	CuCl	DCP		trace
11	CuCl	$K_2S_2O_8$		0
12	CuCl	DTBP		25[c]
13	CuCl	DTBP	^{t}BuOK	15[d]
14	CuCl	DTBP	^{t}BuOK	84
15	CuCl	DTBP	^{t}BuOK	69[e]
16	CuCl	DTBP	^{t}BuOK	74[f]
17		DTBP	^{t}BuOK	0
18	CuCl	DTBP	$CuCO_3{\cdot}Cu(OH)_2$	84

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (2.0 mL), cat (10 mol %), oxidant (1.0 mmol), additive (0.001 mol %), 120 °C, 24 h, under N_2. [b]Isolated yield. [c]Under air. [d]^{t}BuOK (20 mol %). [e]^{t}BuOK (0.002 mol %). [f]^{t}BuOK (0.0005 mol %).

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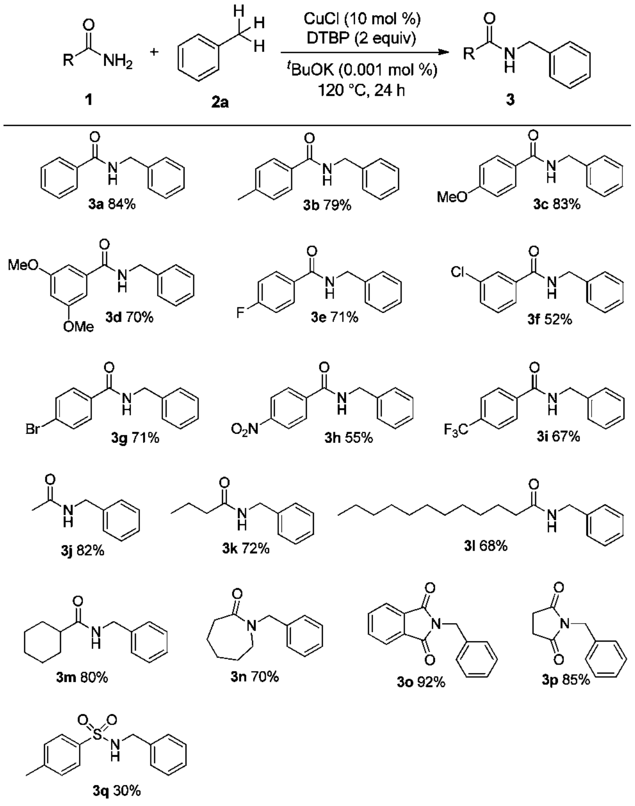
When the base was reduced to 0.0005 mol %, byproduct *N*-methylbenzamide was detected in 15% yield and the desired product was obtained in 74% yield (entry 16). These results demonstrated that only a very small amount of base is needed to promote this reaction and a higher loading of base led to a suppression of this reaction (entries 13, 15). When the reaction was performed without CuCl, the reaction did not proceed (entry 17). It showed that ^{t}BuOK might have worked as a promoter to assist copper to catalyze this reaction. It was interesting to find that 0.001 mol % of $CuCO_3{\cdot}Cu(OH)_2$ could also promote the reaction to produce **3a** in the same yield of 84% (entry 18). $CuCO_3{\cdot}Cu(OH)_2$ might have acted as a base, which assisted the promotion of this reaction.

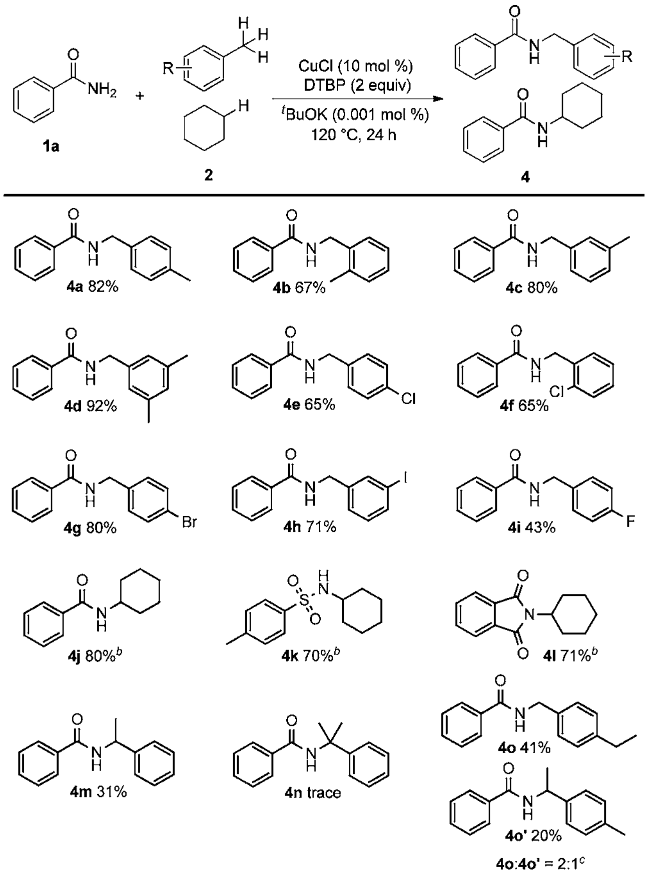
With the optimized reaction conditions in hand, we then explored the substrate scope. As shown in Scheme 1, a wide range of amides could afford the corresponding products in moderate to good yields. Benzamides containing electron-donating groups such as Me and OMe underwent the reaction to give good yields (**3b**−**3d**). Halide substituents could be well tolerated (**3e**−**3g**). Additionally, benzamides bearing strong electron-withdrawing groups, such as CF_3 and NO_2, produced the amidation products in slightly lower yields (**3h**−**3i**). Besides aromatic amides, aliphatic amides were also suitable for this method (**3j**−**3n**). Caprolactam could be smoothly transformed to the corresponding product **3n** in 70% yield. Notably, the long-chain lauroicacidamide gave a satisfactory yield of 68% (**3l**). We also applied the optimal conditions to the coupling of imides and sulfonamides with toluene. Phthalimide offered product **3o** in an excellent yield of 92%. Unfortunately, a low yield was obtained with *p*-toluenesulfonamide, and the remaining compositions of the reaction mixture were *N*-benzyl-*N*-methyl-*p*-toluenesulfonamide and *N*-methyl-*p*-toluenesulfonamide.

Scheme 1. Substrate Scope of Amides, Sulfonamides, and Imides[a]



[a]Conditions: **1** (0.5 mmol), **2a** (2.0 mL), CuCl (10 mol %), DTBP (1.0 mmol), ^{t}BuOK (0.001 mol %), 120 °C, 24 h, under N_2.

Scheme 2. Substrate Scope of Primary Benzylic Hydrocarbons and Inactive Aliphatic Alkanes[a]

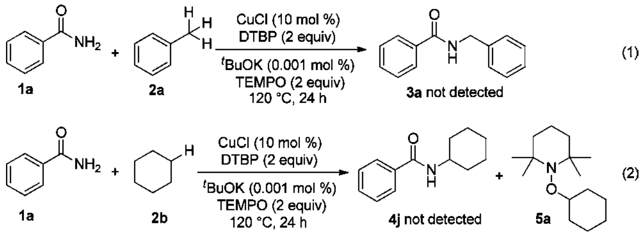


[a]Conditions: **1a** (0.5 mmol), **2** (2 mL), CuCl (10 mol %), DTBP (1.0 mmol), ^{t}BuOK (0.001 mol %), 120 °C, 24 h, under N_2. [b]DTBP (1.5 mmol), 36 h. [c]The ratio and yield were determined by ^{1}H NMR of the crude reaction mixture with CH_3NO_2 as the internal standard.

Substrate scope studies were also carried out on other benzylic hydrocarbons and inactive aliphatic alkanes with benzamide. Results were disclosed in Scheme 2. First, *p*-, *m*-, and *o*-xylenes were explored (**4a**−**4c**). They underwent the reaction to give good yields of the corresponding amidation products (67−82%). To our delight, mesitylene could couple with benzamide to give an excellent yield of 92% (**4d**). A series of halogen-containing toluene were tested. The results showed that halogens could be well tolerated in this N-alkylation reaction (**4e**−**4i**), providing a great opportunity for further synthetic manipulations. *p*-Fluorotoluene gave a lower yield than other halogen-containing toluene. Cyclohexane was selected as the model inactive aliphatic alkane, and it worked as a good partner with benzamide, *p*-toluenesulfonamide, and phthalimide to give the corresponding products in yields of 80%, 70%, and 71%, respectively (**4j**−**4l**). Compared to primary benzylic hydrocarbons or inactive aliphatic alkanes, a lower yield was obtained with a secondary benzylic hydrocarbon (31%, **4m**), and the yield of a tertiary benzylic hydrocarbon was at a trace level (**4n**). Next, the selectivity of primary and secondary benzylic hydrocarbons was tested using 4-ethyltoluene. The result showed that the ratio of **4o** and **4o′** was 2:1. Additionally, our optimized reaction conditions were not suitable for intramolecular amidation, as 2-methylbenzamide failed to produce isoindolin-1-one with most of the starting materials recovered in the solvent of benzene.

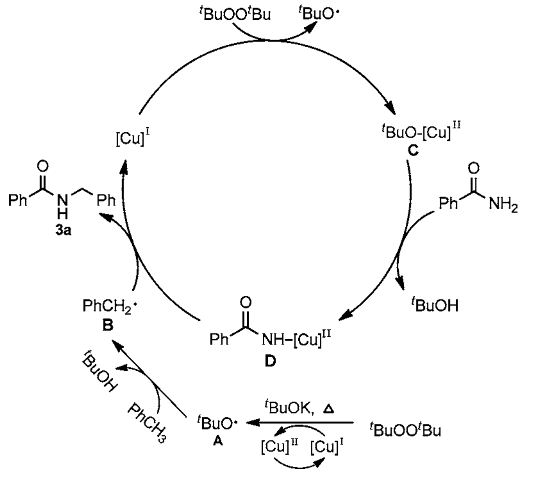
To study the mechanism, control experiments were carried out (Scheme 3). When 2 equiv of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) was added to the reaction under the standard conditions, no desired product was detected in the reaction mixture of eqs 1 and 2. Notably, the radical scavenger completely suppressed the reaction, and the reaction mixture of eq 2 offered product **5a** (determined by GC−MS), which implied a radical process was involved in the amidation coupling.

Scheme 3. Radical Trapping Experiments



Based on our experimental results and previous reports,[6] a possible mechanism is depicted in Scheme 4. First, benzyl radical **B** is formed by abstracting hydrogen from toluene by **A**, which is generated from DTBP under heating with the aid of $[Cu]^I$ and base.[7] DTBP works with $[Cu]^I$ to give the copper(II) alkoxide **C**. Metathesis of **C** with benzamide regenerates intermediate **D**, which combined with the benzyl radical **B** to give the desired product **3a** with release of $[Cu]^I$.

Scheme 4. Proposed Mechanism



In conclusion, we have developed a copper-catalyzed amidation of primary benzylic hydrocarbons and inactive aliphatic alkanes. This method is ligand-free and promoted with an extremely low amount of base. Aromatic and aliphatic amides, sulfonamides, and imides are suitable substrates for this transformation to afford desired coupling products in moderate to good yields. Further investigations into the mechanistic details and possible synthetic applications are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02063.

Experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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