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N-Alkylation

Copper-Catalyzed Reductive *N*-Alkylation of Amides with *N*-Tosylhydrazones Derived from Ketones

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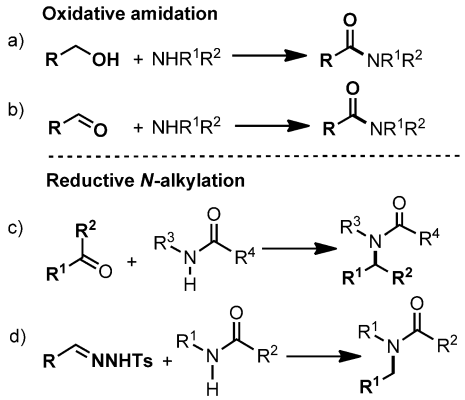
Abstract: A CuI-catalyzed reductive coupling of ketone-derived *N*-tosylhydrazones with amides is presented. Under the optimized conditions, an array of *N*-tosylhydrazones derived from aryl–alkyl and diaryl ketones could couple effectively with a wide variety of (hetero)aryl as well as aliphatic amides to afford the *N*-alkylated amides in high yields. The method represents the very few examples for reliably accessing secondary and tertiary amides through a reductive *N*-alkylation protocol.

Secondary and tertiary amides are ubiquitous motifs in natural products, synthetic bioactive compounds and materials.[1] Therefore, the development of conceptually or methodologically new approaches toward efficient and versatile synthesis of *N*-substituted amides has been a focus of contemporary organic chemistry. Traditional methods have mainly relied on the condensation of carboxylic acids or their derivatives, such as acyl chlorides, anhydrides, and esters with amines.[1b] Recent efforts have been largely devoted to a Cu-[2] and Pd-catalyzed[3] cross-coupling of aryl/alkenyl (pseudo)halides with amides. In addition, a Pd-catalyzed aminocarbonylation of aryl halides with a combination of water and isocyanides or nitriles, or a combination of CO and amines has also been demonstrated to be an alternative option.[4] Moreover, a report by Zhu[5] showed that amides could be synthesized efficiently from aryl diazonium salts and isocyanides under metal-free conditions. Such advanced methods have enabled the versatile synthesis of a rich variety of secondary and tertiary amides from aryl and alkenyl substrates.

For an amide synthesis from alkyl substrates, a direct amidation of alcohols or aldehydes with amines has been successfully established either by the Ru-,[6] Rh-,[7] Ag-,[8] and Cu-catalyzed[9] or by the oxidant-mediated[10] oxidative reactions (Scheme 1 a and b). In such transformations, alcohols and aldehydes were converted into the acyl moiety of amides. Alternatively, a transition-metal-catalyzed reductive coupling of amides with aldehyde or ketone derivatives with the assistance of stoichiometric amounts of extraneous reductants has also been investigated (Scheme 1 c).[11] Such reactions afforded the *N*-alkylated amides. However, to compare with the extensively investigated oxidative *N*-acylation, the reductive *N*-alkylation has been far less explored.



Scheme 1. Synthesis of amides from alcohol and aldehyde derivatives by oxidative amidation and reductive *N*-alkylation.

With the recent great advances in *N*-tosylhydrazone chemistry[12] involving a wide array of cross-couplings for C–C,[13] C–O,[14] C–S,[15] C–B,[16] C–P,[17] C–N,[18] and N–N[19] bond-formations, as well as our constant interests in Cu-catalyzed C–N bond-forming reactions,[20] we have previously developed a Cu-catalyzed reductive coupling of amides with aldehyde-derived *N*-tosylhydrazones[20d] (Scheme 1 d). The method provided an alternative pathway for the synthesis of *N*-alkylated amides and took advantage of carrying out the reaction by a one-pot process without the need of external reductants.

Unfortunately, when *N*-tosylhydrazones derived from ketones were employed to couple with amides, the reaction did not proceed under the identical conditions for coupling the aldehyde-derived *N*-tosylhydrazones (10 mol% of $Cu(CH_3CN)_4BF_4$, 1 mol% of nBu_4NI, and NaOH base in THF). This presumably resulted from the steric hindrance of ketones as well as the weak nucleophilic nature of amides as implied by the reported C–N bond-forming reactions of *N*-tosylhydrazones with amines.[18]

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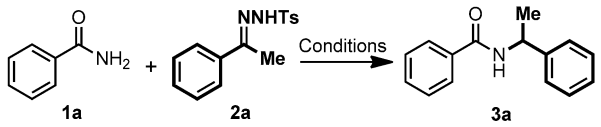
Thus, we initiated a study aimed at establishing a method for effectively coupling the ketone-derived *N*-tosylhydrazones with amides. The successful results are presented herein.

Benzamide (**1a**) and tosylhydrazone **2a** were used as the model substrates to optimize the reaction conditions (Table 1).

Table 1. Optimization of reaction conditions.



Entry	CuI [mol%]	*T* [°C]	Additive [mol%]	Yield [%][c]
1[a]	5	80	–	44
2[a]	10	80	–	56
3[a]	15	80	–	63
4[a]	20	80	–	61
5[a]	20	100	–	60
6[a]	20	70	–	49
7[a]	20	60	–	trace
8[b]	15	80	nBu$_4$NI (10)	77
9[b]	15	80	nBu$_4$NI (15)	80
10[b]	15	80	nBu$_4$NI (20)	83
11[b]	**15**	**80**	**nBu$_4$NI (25)**	**87**
12[b]	15	80	nBu$_4$NI (50)	89

[a] Reaction conditions: benzamide **1a** (0.4 mmol), *N*-tosylhydrazone **2a** (1.0 mmol), CuI (x mol%), and *t*BuOLi (2.5 mmol) in THF (5.0 mL) under argon atmosphere for 6 h. [b] Reaction conditions: benzamide **1a** (0.4 mmol), *N*-tosylhydrazone **2a** (0.6 mmol), CuI (15 mol%), *t*BuOLi (1.2 mmol), and nBu$_4$NI (mol%) in THF (5.0 mL) at 80 °C under argon atmosphere for 6 h. [c] Isolated yields.

An extensive screening of various conditions by means of a free combination of an array of copper catalysts (e.g., Cu powder, Cu(acac)$_2$, CuBr$_2$, CuOAc, CuBr, Cu(CH$_3$CN)$_4$BF$_4$, and CuI) and bases (e.g., Na$_2$CO$_3$, K$_2$CO$_3$, K$_3$PO$_4$, NaOH) showed that the reaction did not proceed or gave only a trace amount of products. In most cases, **1a** remained intact, but **2a** was decomposed to form a mixture of **4a** and **5a**[21] (Figure 1). Based

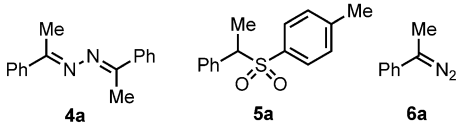
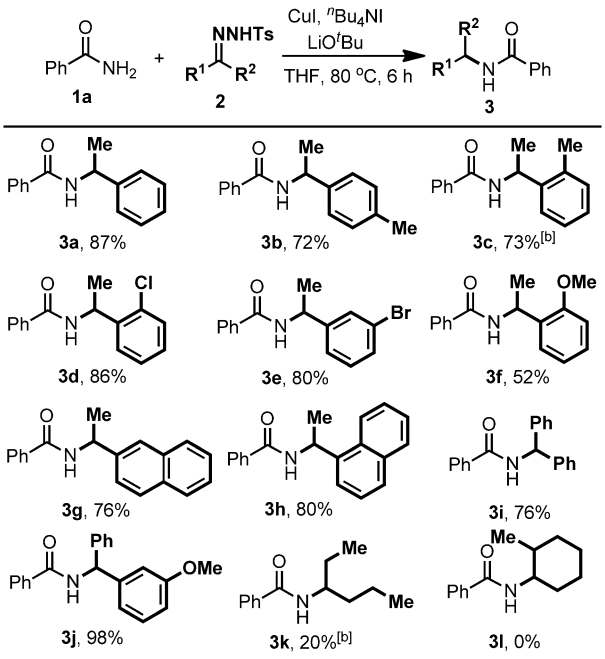


Figure 1. Structures of byproducts and a diazo intermediate.

on these observations and the proposed mechanism in our previous study,[20d] *t*BuOM (M = Li and K) was employed as base to screen the catalysts and solvents. We assumed that the use of such strong and sterically hindered bases would allow for the amide **1a** to generate an amido anion more efficiently, which could serve as a stronger nucleophilic species than **1a** itself in the reaction system. Thus, after a brief evaluation of the reaction parameters, we found that CuI and *t*BuOLi would be a promising combination. The reaction proceeded to give product **3a** in 44% yield with 5 mol% of CuI in THF at 80 °C (entry 1). Other combinations of copper catalysts and bases were ineffective (data not shown). The yield could be improved to 63% with 15 mol% of CuI loading (entry 3). However, further attempts toward improving the yield of **3a** by increasing the catalyst loading (entry 4) or varying the reaction temperature (entries 4–7) proved to be futile even in the presence of a large excess amount of **2a** (2.5 equiv) and a base (ca. 6.25 equiv). The key problems involved in this transformation are the production of side products **4a** and **5a** (Figure 1) formed through the Cu-catalyzed competitive homocoupling[21] and denitrogenation[15a] of tosylhydrazone **2a**, respectively, at a temperature higher than the boundary temperature for generating the reactive diazo intermediate **6a** (>60 °C based on the control experiment in entry 7). We then examined the effect of a phase-transfer catalyst (PTC) on the transformation, because it was found to be crucial for a Cu-catalyzed coupling of aldehyde-derived *N*-tosylhydrazones with amides.[20d] Delightedly, addition of 10 mol% of nBu$_4$NI improved substantially the reaction efficiency, the yield of **3a** could be increased to 77% (entry 8). In addition, both the molar equivalents of **2a** and *t*BuOLi base could be markedly decreased from 2.5 and 6.25 equiv to 1.5 and 3.0 equiv, respectively. A further optimization of PTC loading showed that the use of 25 mol% of nBu$_4$NI was optimal, affording **3a** in 87% yield (entry 11).

Having established the optimized conditions (Table 1, entry 11), we examined the general applicability of the method. Firstly, the reaction of benzamide (**1a**) and an array of *N*-tosylhydrazones were investigated (Table 2). The reaction

Table 2. Substrate scope by varying *N*-tosylhydrazones.[a]



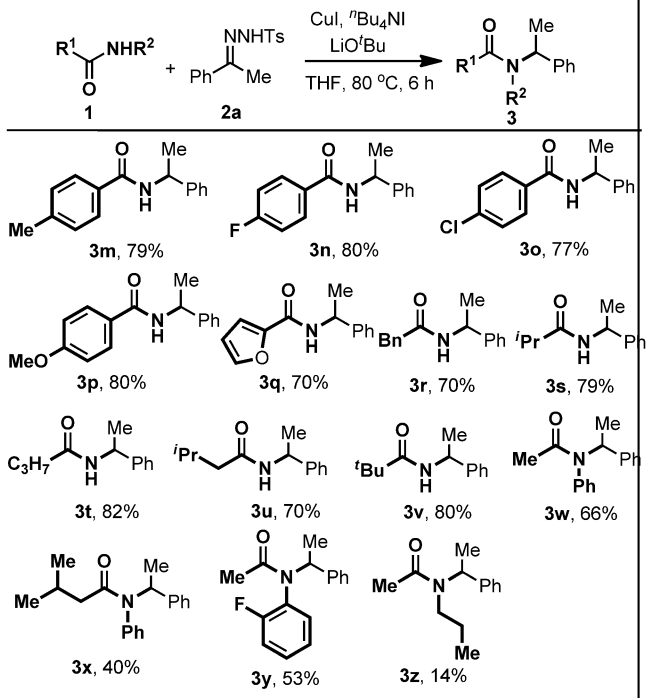
[a] Unless otherwise noted, the reaction conditions were: benzamide **1a** (0.4 mmol), *N*-tosylhydrazones (0.6 mmol), CuI (15 mol%), *t*BuOLi (1.2 mmol), nBu$_4$NI (25 mol%) in THF (5.0 mL) at 80 °C under argon atmosphere for 6 h; isolated yields. [b] The reaction was carried out at 100 °C.

proceeded well with an array of *N*-tosylhydrazones prepared from various alkyl–aryl ketones, such as acetophenone (**3a**–**3f**) and acetonaphthone derivatives (**3g** and **3h**). Notably, halogen functionalities in the aryl ring periphery were well tolerated under the conditions (**3d** and **3e**). In addition, *N*-tosylhydrazones formed from diaryl ketones were also viable substrates, affording the corresponding products in high yields (**3i** and **3j**). However, the method was incompatible with dialkyl ketone-derived *N*-tosylhydrazones (**3k** and **3l**) due to the decomposition of the corresponding *N*-tosylhydrazones under the standard conditions.

Next, the scope of amides was evaluated. A broad range of amides **1** reacted smoothly with *N*-tosylhydrazone **2a**. As shown in Table 3, aryl amides modified by electron-withdrawing (**3n** and **3o**) and -donating (**3p**) groups were coupled efficiently to afford the *N*-alkylated products in high yields. Importantly, halogen substituents remained intact under the reaction conditions. In addition, high yield was observed for a heteroaryl amide (**3q**). Moreover, the method was also exemplified to be applicable for various aliphatic amides (**3r**–**3w**), including a sterically hindered pivalamide (**3v**). We also examined the reaction of secondary amides, the results showed that the *N*-aryl-substituted amides could react with *N*-tosylhydrazone **2a** to afford the desired products in moderate to high yields (**3w**–**3y**). However, the reaction of an *N*-alkyl-modified derivative was sluggish (**3z**).

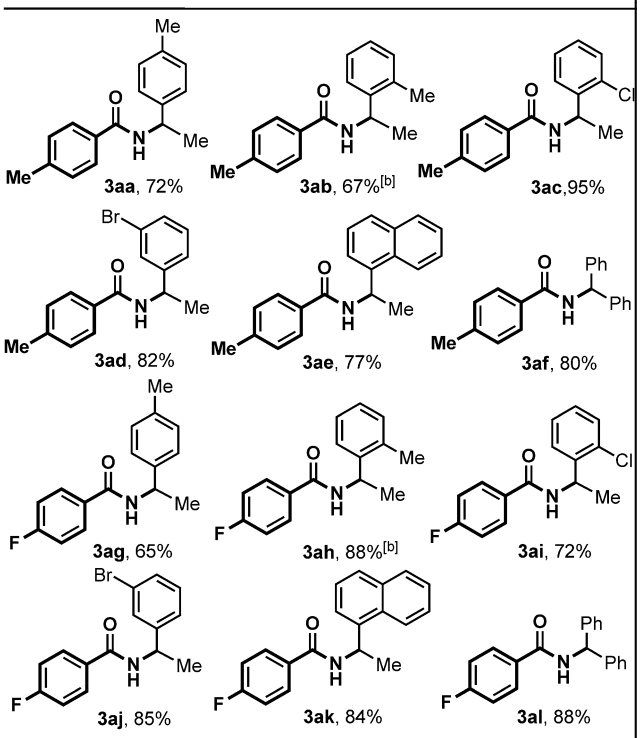
Finally, we further inspected the reaction by varying both the amide and *N*-tosylhydrazone partners to showcase the robustness of the methodology (Table 4). The results showed that the reaction proceeded uneventfully for various combinations of amides and *N*-tosylhydrazones to afford the cross-coupled products in high yields.

Table 3. Substrate scope by varying amides.[a]



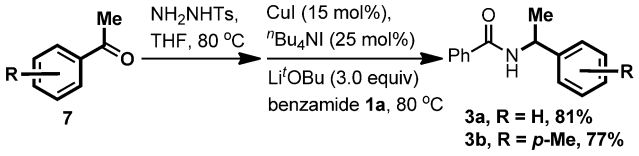
[a] Unless otherwise noted, the reaction conditions were: Amides **1** (0.4 mmol), *N*-tosylhydrazone **2a** (0.6 mmol), CuI (15 mol%), *t*BuOLi (1.2 mmol), and nBu_4NI (25 mol%) in THF (5.0 mL) at 80 °C under argon atmosphere for 6 h; isolated yields.

Table 4. Substrate scope by varying amides and *N*-tosylhydrazones.[a]



[a] Unless otherwise noted, the reaction conditions were: Amides (0.4 mmol), *N*-tosylhydrazones (0.6 mmol), CuI (15 mol%), *t*BuOLi (1.2 mmol), and nBu_4NI (25 mol%) in THF (5.0 mL) at 80 °C under argon atmosphere for 6 h; isolated yields. [b] The reaction was carried out at 100 °C.

To exemplify the straightforwardness of the methodolgy, we briefly investigated the feasibility of the reaction through a one-pot operation (Scheme 2). The reaction proceeded well without an apparent erosion of the yields as compared to the stepwise operation.



Scheme 2. *N*-alkylation of benzamide through a one-pot procedure.

In conclusion, we have developed a Cu-catalyzed reductive coupling reaction of amides with *N*-tosylhydrazones derived from ketones. This method, together with our previously established reductive coupling of amides with *N*-tosylhydrazones generated from aldehydes,[20d] have significantly expanded the substrate scope of carbonyl compounds. More importantly, to compare with the widely investigated amide synthesis through the oxidative *N*-acylation of amines with alcohols or aldehydes,[6–10] the method presented herein represents the very few examples for reductive *N*-alkylation of amides. As a result, the method would highly complement with the oxidative amidation for the flexible synthesis of amides with structural diversity.

Experimental Section

General procedure for the coupling of amides with *N*-tosylhydrazones

To a 25 mL oven-dried Schlenk tube equipped with a magnetic bar was added amide (0.4 mmol), *N*-tosylhydrazone (0.6 mmol, 1.5 equiv), CuI (15 mol%), LiO*t*Bu (1.2 mmol, 3.0 equiv), and nBu$_4$NI (25 mol%). The reaction vessel was evacuated and backfilled with argon three times. Dried THF (5.0 mL) was then injected using a syringe. The tube was sealed with a Teflon screwcap, and the resulting reaction mixture was stirred vigorously at 80 °C for 6 h. After the completion of the reaction as monitored by TLC, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 mL). The reaction mixture was washed with water for three times. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel with a mixed solvent of ethyl acetate and petroleum ether as eluent to afford product **3**.

General procedure for the one-pot reaction of amides and ketones

A mixture of ketones **7** (0.6 mmol) and $TsNHNH_2$ (0.6 mmol) in THF (5.0 mL) was stirred at 80 °C until the condensation had completed as monitored by TLC. Then, benzamide **1a** (0.4 mmol), CuI (15 mol%), LiO*t*Bu (1.2 mmol, 3.0 equiv), and nBu$_4$NI (25 mol%) were recharged in situ to the reaction vessel. The resulting mixture was then stirred vigorously at 80 °C for 6 h in the sealed vessel under argon atmosphere. After the completion of the reaction as monitored by TLC, the mixture was cooled to room temperature and diluted with ethyl acetate (20 mL). The reaction mixture was washed with water for three times. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel by using a mixed solvent of EtOAc and petroleum ether as eluent to afford product **3**.

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Keywords: amides · copper catalysts · ketones · *N*-tosylhydrazones · reductive coupling

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COMMUNICATION

***N*-Alkylation**

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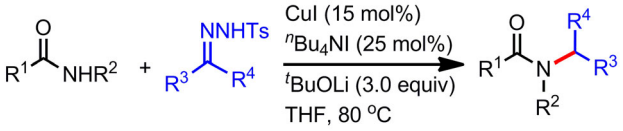
Copper-Catalyzed Reductive *N*-Alkylation of Amides with *N*-Tosylhydrazones Derived from Ketones



A CuI-catalyzed reductive coupling of ketone-derived *N*-tosylhydrazones with amides has been developed (see scheme). Under the optimized conditions, an array of *N*-tosylhydrazones derived from aryl–alkyl and diaryl ketones could couple effectively with a wide variety of (hetero)aryl as well as aliphatic amides to afford the *N*-alkylated amides in high yields. The method represents the very few examples for reliably accessing secondary and tertiary amides through a reductive *N*-alkylation protocol.