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Catalyzed Imidation of Tertiary Amines by Simple Copper Salts

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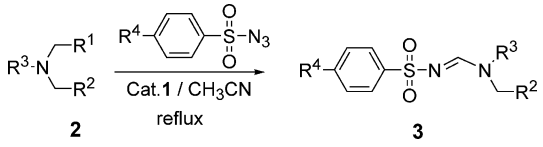
Copper salt catalyzed imidation of tertiary amines by using sulfonyl azides as the nitrogen source was achieved with moderate to high yields. Formation of the carbon–nitrogen bond occurred chemoselectively with the use of a simple and inexpensive catalyst under moderate conditions, with a simple workflow, and with easy preparation of the nitrogen precursors.

Introduction

Construction of C–N bonds catalyzed by transition-metal complexes is a fascinating methodology for processing many natural products, biologically active compounds, and many interesting organic molecules.[1] Therefore, to increase the applications of this methodology, we studied catalyzed amidation reactions of cyclic ethers.[1l] Although a series of studies on catalyzed inter- or intramolecular amidation reactions by transition-metal complexes have demonstrated that the method could effectively form carbon–nitrogen bonds in systems with sp^2 C–H bonds of benzene,[1i,1j] aromatic heterocycles,[1k] and sp^3 C–H bonds of cyclohexane and alkyl aromatics,[1c–1h] the amidation reactions of tertiary amines with azide as a nitrogen source are not reported in the literature.[2–4] We envisioned that tertiary amine substrates could function in the same way as cyclic ethers for a new approach to carbon–nitrogen bond formation. Recently, we found by chance that cuprous chloride could activate the imidation reaction of tertiary amines with sulfonyl azides as the nitrene source to give nonamidation products in good yields. Meanwhile, Li and coworkers reported the synthesis of sulfonyl amidines through a diethyl azodicarboxylate activated elimination reaction of both the α- and β-hydrogen atoms of tertiary amines.[3a] In this paper, we processed the intermolecular imidation of saturated C–H bonds of tertiary amines catalyzed by simple copper salts by using sulfonyl azides as the nitrene source (Scheme 1). The imidation reaction of tertiary amines catalyzed by a simple and inexpensive catalyst with the use of easily prepared nitrogen precursors is not known.



2 3

Scheme 1. Copper salt catalyzed imidation of tertiary amines.

Results and Discussion

We initially investigated the reaction of triethylamine with 4-methylbenzenesulfonyl azide in the presence of $Cu(OAc)_2$ in acetonitrile. However, the resulting tosylimidoformamide was isolated in 52% yield. This prompted us to undertake further investigation, and it was finally found that the reaction of *p*-toluenesulfonyl azide with triethylamine in CH_3CN in the presence of CuCl could afford the tosylimidoformamide in 88% yield (Table 1, Entry 2). Subsequently, we found TsN=NTs in the control experiment, and the reaction of *N*,*N*-diethyl-*N*-phenylamine with *p*-toluenesulfonyl azide in CH_3CN in the presence of TsN=NTs could afford *N*-ethyl-*N*-phenyl-*N*′-tosylimidoformamide. On the basis of the experimental results and combined with literature findings,[3–7] we speculated that an enamine may be formed in this system, as in the work by Li.[3a] A tentative mechanism was proposed as follows (Scheme 2). Firstly, *p*-toluenesulfonyl azide is decomposed in the presence of the copper salt to form the nitrene, and then it couples to

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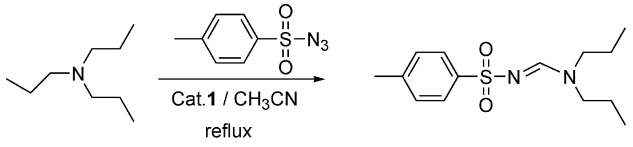
give TsN=NTs. Secondly, triethylamine undergoes nucleophilic addition to form TsN=NTs and forms an adduct. Thirdly, the adduct undergoes intramolecular hydrogen transfer to form an ion pair consisting of an imine cation and TsNH–TsN$^-$. The nitrogen anion abstracts the β-hydrogen of the nitrogen atom of triethylamine to generate the enamine to form TsNH–NHTs. Finally, the enamine reacts with *p*-toluenesulfonyl azide through a 1,3-dipolar cycloaddition and produces triazoline, which is unstable and releases one molecule of CH_2N_2 to afford the product *N*,*N*-diethyl-*N*′-tosylimidoformamide.

Table 1. Optimization of reaction conditions.[a]

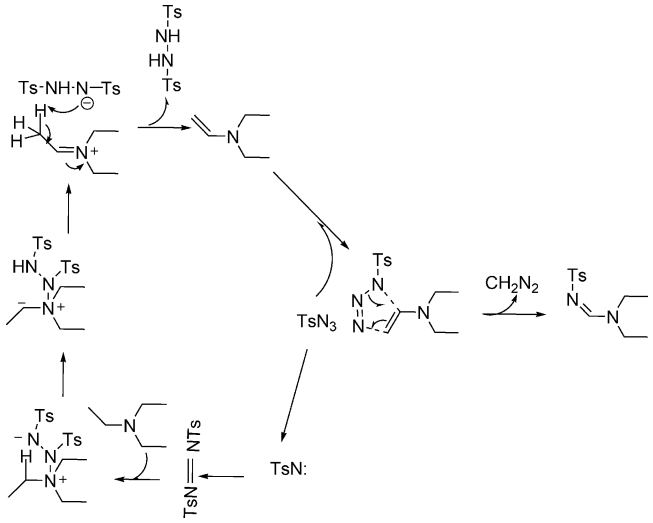


2b **3b**

Entry	Catalyst **1**	Solvent	Equiv. of R–N_3	Yield [%][b]
1	$Cu(OAc)_2$	CH_3CN	3	52
2	CuCl	CH_3CN	3	88
3	$CuCl_2$	CH_3CN	3	53
4	$CuBr_2$	CH_3CN	3	66
5	CuI	CH_3CN	3	48
6	$Cu(acac)_2$	CH_3CN	3	31
7	$Cu(CF_3SO_3)_2$	CH_3CN	3	5
8	$Cu(CH_3CN)^+ClO_4^-$	CH_3CN	3	trace
9	$Hg(OAc)_2$	CH_3CN	3	15
10	$InCl_3$	CH_3CN	3	trace
11	$ZnCl_2$	CH_3CN	3	trace
12	$CoCl_2$	CH_3CN	3	22
13	$FeSO_4$	CH_3CN	3	20
14	$AgNO_3$	CH_3CN	3	10
15	CuCl	CH_2Cl_2	3	trace
16	CuCl	CH_3OH	3	trace
17	CuCl	THF	3	trace
18	CuCl	Toluene	3	trace
19	CuCl	CH_3CN	1	57
20	CuCl	CH_3CN	2	63
21	CuCl	CH_3CN	5	88
22[c]	CuCl	CH_3CN	3	88
23[d]	CuCl	CH_3CN	3	68
24[e]	CuCl	CH_3CN	3	45
25[f]	CuCl	CH_3CN	3	80

[a] Unless otherwise noted, all reactions were carried out with a molar ratio **2b**/catalyst **1**/benzyltriethylammonium chloride (TEBA), 1:0.2:0.1 under reflux for 8 h. [b] Yield of isolated product. [c] Molar ratio **2b**/catalyst, 1:0.3. [d] Molar ratio **2b**/catalyst, 1:0.1. [e] Molar ratio **2b**/catalyst, 1:0.05. [f] Molar ratio **2b**/catalyst, 1:0.3, without TEBA.

To evaluate the catalytic efficiency of various catalysts, the reaction of tertiary amines with *p*-toluenesulfonyl azide as the nitrene source was studied by using different catalysts with acetonitrile as the solvent (molar ratio of substrate/*p*-toluenesulfonyl azide, 1:3). The results are summarized in Table 1. It is noticeable that several catalysts, namely, ruthenium(II) porphyrins, rhodium acetate, manganese prophyrin, $InCl_3$, $Hg(OAc)_2$, $ZnCl_2$, $FeSO_4$, $AgNO_3$, $CoCl_2$, copper acetate, $Cu(OTf)_2$, $Cu(acac)_2$, $Cu(hfac)_2$, CuI, CuCl, and $CuCl_2$, have been employed, but only cupric salt was found to be effective in the intermolecular *C*-imidation of tertiary amines. $InCl_3$, $ZnCl_2$, rhodium acetate, manganese prophyrin, and ruthenium(II) porphyrin catalysts were found to be poor catalysts for this intermolecular imidation reaction, and only a trace amount of **3b** was found under similar conditions. In contrast, the similar reactions with $Hg(OAc)_2$, $CoCl_2$, $FeSO_4$, or $AgNO_3$, respectively, as catalysts gave **3b** in evidently lower yields (Table 1, Entries 9, 12–14).

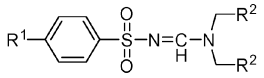
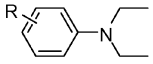
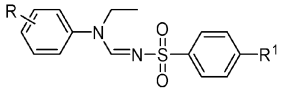
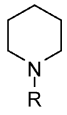
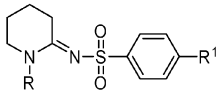
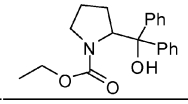
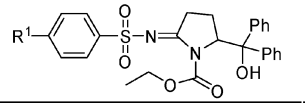


Scheme 2. Tentative mechanism for the imidation of tertiary amines with TsN_3 as the nitrogen source.

To examine the versatility of the cupric salt catalyst, a variety of tertiary amine derivatives were treated with selected sulfonyl azides as the nitrogen source. Table 2 clearly shows that adipose tertiary amines are more reactive and give excellent yields (Table 2, Entries 1, 2, 6, 7), and tertiary amines containing electron-donating groups (Table 2, Entries 15, 22) are more reactive and give better yields (66, 70% yield, respectively) of the products. Similarly, tertiary amine derivatives with electron-withdrawing substituents (Table 2, Entries 12–14, 16, 19–21, 23) were found to be less reactive than the corresponding substrates containing electron-donating groups (Table 2, Entries 15, 22). However, nitrogen heterocycles with electron-withdrawing substituents (Table 2, Entries 27–30) give the corresponding products in trace amounts. In the same way, the reactivity of substrates suffering from steric hindrance (*ortho* substituted, long chain) was low or only starting materials were recovered under strictly identical conditions.

The solvent effect on the *C*-imidation was also studied. Some of solvents were surveyed to ascertain the effect of the reaction medium on the yield. Among these solvents studied, acetonitrile and 1,4-dioxane were found to be more effective for this reaction under reaction conditions similar tot hose used with dichloromethane and toluene.

Table 2. CuCl-catalyzed imidation of **2a**–**IV**.[a]

Entry	Tertiaryamine	Product		Yield [%][b]
1	**2a–j** 		**3a**, R^1 = Me, R^2 = Me	96
2			**3b**, R^1 = Me, R^2 = Et	88
3			**3c**, R^1 = Me, R^2 = *n*Pr	50
4			**3d**, R^1 = Me, R^2 = CH_2OAc	30
5			**3e**, R^1 = Me, R^2 = CH_2OH	24
6			**3f**, R^1 = OMe, R^2 = Me	82
7			**3g**, R^1 = OMe, R^2 = Et	90
8			**3h**, R^1 = OMe, R^2 = *n*Pr	55
9			**3i**, R^1 = OMe, R^2 = CH_2OAc	34
10			**3j**, R^1 = OMe, R^2 = CH_2OH	27
11	**2k–x** 		**3k**, R^1 = Me, R = H	54
12			**3l**, R^1 = Me, R = *p*-Cl	54
13			**3m**, R^1 = Me, R = *p*-F	61
14			**3n**, R^1 = Me, R = *m*-Br	46
15			**3o**, R^1 = Me, R = *p*-MeO	66
16			**3p**, R^1 = Me, R = *p*-NO_2	–
17			**3q**, R^1 = Me, R = *p*-COOH	49
18			**3r**, R^1 = OMe, R = H	59
19			**3s**, R^1 = OMe, R = *p*-Cl	58
20			**3t**, R^1 = OMe, R = *p*-F	65
21			**3u**, R^1 = OMe, R = *m*-Br	54
22			**3v**, R^1 = OMe, R = *p*-MeO	70
23			**3w**, R^1 = OMe, R = *p*-NO_2	–
24			**3x**, R^1 = OMe, R = *p*-COOH	55
25	**2y–II** 		**3y**, R^1 = Me, R = $CH_2C_6H_5$	48
26			**3z**, R^1 = OMe, R = $CH_2C_6H_5$	43
27			**3l**, R^1 = Me, R = $COCH_3$	–
28			**3ll**, R^1 = OMe, R = $COCH_3$	–
29	**3III–IV** 		**3III**, R^1 = Me	–
30			**3IV**, R^1 = OMe	–

[a] All reactions were carried out under reflux for 8 h with a molar ratio **2**/$R^1C_6H_5SO_2N_3$/CuCl/TEBA, 1:3:0.2:0.1. [b] Yield of isolated product.

By using compound **2b** as the substrate, the effect of temperature on the imidation reaction was examined. It was found that the imidation reaction was best performed at 82 °C. When the temperature was decreased to 20 °C, the yield of the product decreased to a trace amount.

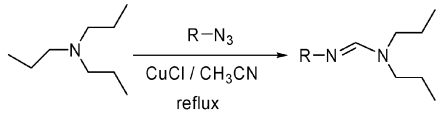
The reaction of the effect of azide[8] was carried out by using several different azides under strictly identical conditions. We noticed that the imidation of sulfonyl azides with electron-donating groups in the *para* position have moderate to high yields (88–90%) (Table 3, Entries 1, 2); however, a sulfonyl azide with an electron-withdrawing substituent in the *para* position (Table 3, Entry 3) gave 20% of the corresponding *p*-nitrophenylsulfonylimidoformamide product; azides lacking the sulfonyl group (Table 3, Entries 4–7) gave only trace amounts of products.

In this work, the imidation of tertiary amines with sulfonyl azides as the imidation reagents was conducted in acetonitrile at reflux in the presence of a copper salt catalyst (20%), and the corresponding tosylimidoformamide derivatives were obtained. Several tertiary amine derivatives were employed to demonstrate the imidation universality of simple copper salt catalyzed intermolecular reactions (Table 2).

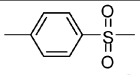
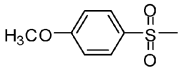
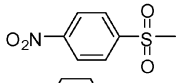
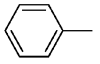
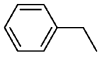
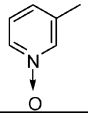
Conclusions

In summary, we have developed an efficient procedure for the direct imidation of tertiary amines catalyzed by simple copper salts to form the corresponding tosylimidoformamide by using sulfonyl azides as the nitrogen source. The method was shown to be applicable to a broad range of tertiary amines (such as tertiary amines with carboxyl and hydroxy groups) and has advantages such as the requirement for a simple and inexpensive catalyst, moderate conditions, simple workflow, easy preparation of the nitrogen

Table 3. Effect of azide on the imidation.[a]



2b

Entry	R	Yield [%][b]
1		88
2		90
3		20
4		–
5		–
6		–
7		–

[a] All reactions were carried out under reflux for 8 h with a molar ratio **2b**/R-N_3/CuCl/TEBA, 1:3:0.2:0.1. [b] Yield of isolated product.

precursors, moderate to high yields, and chemoselectivity. The imidation reaction proceeds only at the sp^3 carbon atom of the tertiary amines. We are currently investigating the scope and applications of this reaction and the pharmacological activity of the products.

Supporting Information (see footnote on the first page of this article): General procedure for the imidation of tertiary amines; characterization data, including ^1H and ^{13}C NMR spectra.

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