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$CuCl/CCl_4$-Promoted Convenient Synthesis of Sulfonyl Amidines from Tertiary Amines and Sulfonyl Azides

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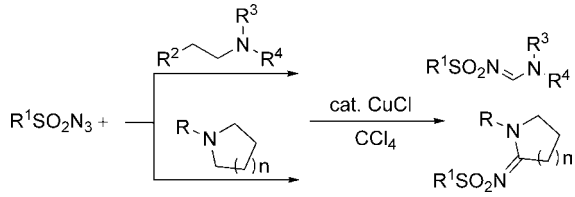
ABSTRACT



Promoted by $CuCl/CCl_4$, a variety of sulfonyl azides and tertiary amines were successfully coupled to give sulfonyl amidine derivatives in good to excellent yields. A possible mechanism for this reaction is discussed.

Amidine derivatives have been widely applied in medicinal and synthetic chemistry due to their structural specialties.[1] Furthermore, substituted amidines are key intermediates for the synthesis of many heterocyclic compounds and metal complexes.[2] Traditional methods for the preparation of amidine derivatives involved several tedious steps of functional group transformation from the not readily accessible starting materials.[3] Therefore, the development of more efficient methods for the synthesis of amidine derivatives is still in high demand. Recently Chang reported a new route for the synthesis of amidines via copper-catalyzed tandem reactions of sulfonyl azides, alkynes, and amines either intermolecularly or intramolecularly.[4] We and others also reported that DEAD or TsN═NTs could promote the formation of sulfonyl amidine derivatives through the oxidative dehydrogenation[5,6] of tertiary amines.[7] Despite the advantages, it should be noted that the byproduct 2H-DEAD or TsNHNHTs incurred inconvenience in isolation and purification of the amidines.[7b,c] More recently, Wang reported the synthesis of sulfonyl amidines from aliphatic tertiary amines and sulfonyl azides in the presence of $FeCl_3$.[8] Herein, we wish to report a more expedient and general method for the synthesis of sulfonyl amidine derivatives from

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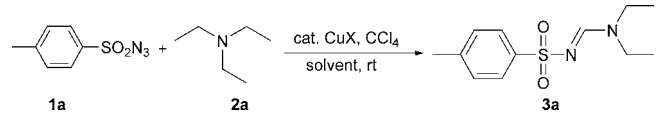
a broad spectrum of tertiary amines and sulfonyl azides employing a CuCl/CCl_4 system.

Carbon tetrachloride was frequently used as a solvent. Except the Appel reaction which involved PPh_3/CCl_4-promoted the transformation of an alcohol into an alkyl chloride,[9] carbon tetrachloride was rarely used as a reactant since it is normally very stable.[10] Due to the inherent similarity in tertiary phosphine and tertiary amine in several aspects, we speculate that the chemical interaction or reaction might occur between CCl_4 and tertiary amine. We first examined the reaction between 10 mmol of triethylamine and CCl_4 each. As expected, a considerable amount of white water-soluble solid identified as $Et_3N{\cdot}HCl$ was generated after several hours under room temperature and chloroform could be detected by GC−MS from the reaction system (see the Supporting Information). According to these results, we guess *N*,*N*-diethylethenamine may be produced. Based on our and others' previous works,[7,8] 1 mmol of TsN_3, with the expectation of capturing the in situ formed *N*,*N*-diethylethenamine, was added to the mixture of 2 mmol of triethylamine and 4 mL of CCl_4. To our delight, sulfonyl amidine **3a** was indeed obtained albeit in 53% yield even in the absence of any catalyst. This prompted us to undertake further experiments to find effective conditions for the synthesis of the sulfonyl amidine derivatives.

The optimization of the reaction conditions for the formation of **3a** was done by screening several solvents and copper catalysts. The results are summarized in Table 1. As can be seen, even in the absence of a catalyst, the reaction could proceed smoothly in all of the solvents examined and the desired product can be obtained in low to moderate yields at room temperature in 15−36 h (entries 1−7). In comparison, the result obtained by use of CCl_4 both as the solvent and reagent was better (entry 8). Interestingly, it was found that the reaction time can be shortened by adding a catalytic amount of copper sources in CCl_4. Several copper catalysts such as CuCl, CuBr, CuI, $CuSO_4$, $Cu(OAc)_2$, $CuBr_2$, $Cu(NO_3)_2{\cdot}3H_2O$, and copper powder were tested (entries 9−16). CuCl and $Cu(NO_3)_2{\cdot}3H_2O$ gave the best results. Thus, the standard reaction condition was established as using 0.2−0.3 mol % of CuCl relative to sulfonyl azides, 3 equiv of triethylamine, and CCl_4 as both the solvent and reactant.

Table 1. Synthesis of **3a** under Various Conditions[a]

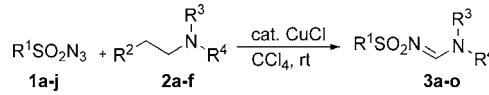


1a **2a** **3a**

entry	solvent	cat.	time (h)	yield[b] (%)
1	THF		36	41
2	CH_3CN		36	38
3	CH_2Cl_2		15	51
4	$CHCl_3$		36	48
5	diethyl ether		36	18
6	toluene		36	34
7	dioxane		36	38
8[c]	CCl_4		36	63
9[c]	CCl_4	CuCl	10	71
10[c]	CCl_4	$Cu(NO_3)_2{\cdot}3H_2O$	13	72
11[c]	CCl_4	CuBr	14	59
12[c]	CCl_4	CuI	14	47
13[c]	CCl_4	Cu	15	54
14[c]	CCl_4	$CuSO_4$	13	69
15[c]	CCl_4	$Cu(OAc)_2$	12	52
16[c]	CCl_4	$CuBr_2$	15	62

[a] *p*-Toluenesulfonyl azide (1 mmol), triethylamine (3 mmol), and CCl_4 (1.3 mmol) in solvent (4 mL) under room temperature in the presence/absence of 0.2−0.3% equiv of copper catalyst until otherwise noted. [b] Isolated yields based on TsN_3. [c] CCl_4 (4 mL) was used as the solvent and reactant.

Table 2. CuCl-Catalyzed Synthesis of Sulfonyl Amidine Derivatives from Acylic Tertiary amines and Sulfonyl Azides[a]



1a-j **2a-f** **3a-o**

entry	R^1	R^2; R^3; R^4	yield[b] (%)
1	4-$CH_3C_6H_4$ (**1a**)	H; Et; Et (**2a**)	**3a**; 71
2	4-$CH_3OC_6H_4$ (**1b**)	H; Et; Et (**2a**)	**3b**; 66
3	Ph (**1c**)	H; Et; Et (**2a**)	**3c**; 73
4	4-ClC_6H_4 (**1d**)	H; Et; Et (**2a**)	**3d**; 62
5	3-$NO_2C_6H_4$ (**1e**)	H; Et; Et (**2a**)	**3e**; 67
6	4-$Pr^iC_6H_4$ (**1f**)	H; Et; Et (**2a**)	**3f**; 74
7	4-$CH_3C_6H_4CH_2$ (**1 g**)	H; Et; Et (**2a**)	**3g**; 61
8	2-naphthyl (**1 h**)	H; Et; Et (**2a**)	**3h**; 65
9	2,4,6-$(CH_3)_3C_6H_2$ (**1i**)	H; Et; Et (**2a**)	**3i**; 61
10	$CH_3(CH_2)_3$ (**1j**)	H; Et; Et (**2a**)	**3j**; 84
11[c]	**1a**	Et; Bu; Bu (**2b**)	**3k**; 66
12[d]	**1a**	H; Me; Et (**2c**)	**3l**:**3a**; 46:15
13	**1a**	H; Pr^i; Pr^i (**2d**)	**3m**; 76
14	**1a**	H; Et; *c*-hexyl (**2e**)	**3n**; 65
15[e]	**1a**	H; Et; Ph (**2f**)	**3o**; 34

[a] Sulfonyl azide (1 mmol), tertiary amine (3 mmol), CuCl (0.2−0.3% mmol), CCl_4 (4 mL) under room temperature until otherwise noted (see the Supporting Information). [b] Isolated yields based on the sulfonyl azides. [c] **2b** (4 mmol), 70 °C. [d] **2c** (6 mmol). [e] 70 °C, 30 h, K_2CO_3 (1 mmol).

As shown in Table 2, various substituted sulfonyl azides and acylic tertiary amines were investigated to expand the scope and generality of this reaction system. Aromatic

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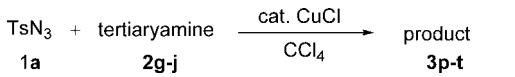
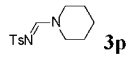
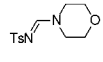
Table 3. CuCl-Catalyzed Synthesis of Sulfonyl Amidine Derivatives from the Cylic Tertiary Amines and **1a**[a]



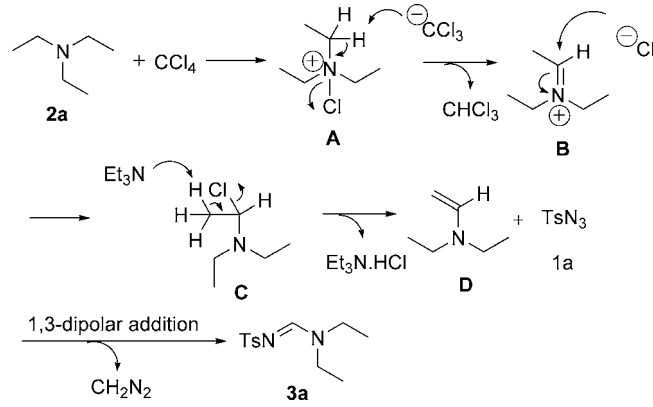
entry	tertiaryamine	product	yield (%)[b]
1	 **2g**	 **3p**	76
		 **3q**	10
2	 **2h**	 **3r**	86
3	 **2i**	 **3s**	53
4[c]	 **2j**	 **3t**	41

[a] **1a** (1 mmol), tertiary amine (6 mmol), CuCl (0.2−0.3% mmol), CCl_4 (4 mL) until otherwise noted (see the Supporting Information). [b] Isolated yields based on the sulfonyl azides. [c] **2j** (4 mmol).

sulfonyl azides with either electron-donating or electron-withdrawing groups at the aryl worked well as the substrates, and the corresponding products were obtained in good to excellent yields. 2-Naphthalenesulfonyl azide can participate in the coupling substrate well (entry 8). The substituents such as methoxy, chloro, nitro, and isopropyl remained intact in the reaction (entries 2, 4, 5, and 6). Benzylsulfonyl azide and butylsulfonyl azide also reacted smoothly (entries 7 and 10). Several types of aliphatic acyclic tertiary amines can be used in this study. When *N*,*N*-diethylmethylamine was used as the starting material, the ratio of products obtained from ethyl and methyl was about 75:25 in 61% total yield (entry 12). For *N*,*N*-diethylcyclohexylamine or *N*,*N*-diisopropylethylamine, the corresponding product was formed from hydrogen abstraction from the ethyl group (entries 13 and 14). This result indicated that the dehydrogenation occurred regioselectively at the ethyl group, whereas the α-hydrogen locating at the cyclohexyl and isopropyl remained almost intact although two types of α-hydrogens adjacent to the nitrogen atom were present. When *N*,*N*-diethylaniline was used as the substrate, the desired product was not obtained under the standard reaction conditions. Fortunately, **3o** can be obtained in 34% yield with the assistance of K_2CO_3 (entry 15).

Several cyclic tertiary amines were also investigated under our standard conditions (Table 3). For *N*-ethylpiperidine, the major product was produced by elimination of the hydrogens from the ethyl group (entry 1). Interestingly, when *N*-methylpiperidine or *N*-methylpyrrolidine was used as the substrate, the products resulting from the hydrogen abstraction from cyclic α-carbon were obtained predominantly (entries 2 and 3). When *N*-ethylmorpholine was used as the substrate, the yield of the product resulting from the hydrogen abstraction from ethyl was relatively lower and some unidentified products were obtained (entry 4).

Scheme 1. Proposed Mechanism



According to the literature[7b,c,8,9] and the experimental results, a possible mechanism was postulated in Scheme 1. First, the reaction initiates with the formation of the ammonium salt ion pair **A**, from which the trichloromethyl anion abstracts an α-hydrogen of triethylamine to form chloroform, which can be detected by GC−MS, and liberate chloride ion. Then the chloride ion undergoes nucleophilic addition to **B** to form chlorinated triethylamine **C**. With the assistance of another molecule of triethylamine, **C** undergoes E2 reaction, losing HCl and being transformed into enamine **D**. Subsequent 1,3-dipolar cycloaddition between **D** and TsN_3 **1a** followed by release of one molecule of CH_2N_2 finally gives rise to product **3a**. The enamine **D** and CH_2N_2 can be captured by 2,4-dinitrophenylhydrazine and benzoic acid, respectively (see the Supporting Information).

In summary, the CCl_4-promoted dehydrogenation of tertiary amines in the presence/absence of cuprous chloride is established. The in situ formed enamines underwent a subsequent tandem reaction with sulfonyl azides thus affording sulfonyl amidine derivatives. This work is characterized by employing readily accessible starting materials and operational simplicity, which provided a preferable way to the synthesis of sulfonyl amidine derivatives. Further investigation including mechanism, scope, and synthetic application of this system is in progress.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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