



Friedel–Crafts reaction of indoles with *N*-silyl-*N,O*-acetal catalyzed by $\text{Cu}(\text{OTf})_2$ in the presence of TMSCl leading to indolyl primary amines

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Abstract—A catalytic amount of copper(II) trifluoromethanesulfonate ($\text{Cu}(\text{OTf})_2$) in the presence of trimethylchlorosilane (TMSCl) effectively promoted the aminomethylation of indoles bearing a variety of functional groups with a *N*-silyl-*N,O*-acetal in good to excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

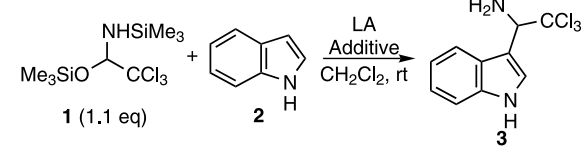
The syntheses and reactions of indoles have been extensively studied because a number of their derivatives constitute basic units in natural products and biologically active substances.¹ On the other hand, Lewis acid-mediated Friedel–Crafts reactions are efficient methods for the direct introduction of a functional group onto heterocyclic compounds such as indoles.² Among these, aminoalkylation is quite a powerful tool for the synthesis of heterocycles bearing an aminomethyl group. Although the aminomethylation of indoles with imines in the presence of Lewis or protonic acids is already known,³ Lewis acid-catalyzed aminomethylation utilizing *N,O*-acetals, which function as an imine precursor, has only been reported for a few examples.^{4–6} In these cases, however, the produced amines are limited to secondary or tertiary amines due to the stability of the starting imine, and further require a cleavage of the protecting group on the nitrogen atom in order to produce primary amines, which are more useful synthetically.^{5,6} Moreover, more than a stoichiometric amount of Lewis acid is needed to complete the reaction.⁵ We report here that a catalytic amount of copper(II) trifluoromethanesulfonate ($\text{Cu}(\text{OTf})_2$) in the presence of trimethylchlorosilane (TMSCl) promotes the aminomethylation of a variety of indoles with a *N*-silyl-*N,O*-acetal, leading to indolyl primary amines.

The reaction of a *N*-silyl-*N,O*-acetal⁷ having a trichloromethyl group (**1**, 1.1 equiv.) with indole **2a** was chosen as an initial example (run 1). It was carried out in dichloromethane at room temperature for 72 h (until the indole disappeared, as shown by TLC analysis) in the presence of a stoichiometric amount of $\text{BF}_3 \cdot \text{OEt}_2$ to produce the desired primary amine product, 1-(indol-3-yl)-2,2,2-trichloroethylamine (**3a**), in 65% yield, along with a trace amount of a dimer.^{5c} The present reaction was optimized in the presence of other Lewis acids, and the results are summarized in Table 1. Although typical Lewis acids provided the same product in moderate yields (runs 2–4), they were required stoichiometrically. Interestingly, $\text{Cu}(\text{OTf})_2$ and triflic acid (TfOH) effectively catalyzed the aminoalkylation, while each yield decreased slightly (runs 5 and 6). It should be emphasized that, when 1 equiv. of TMSCl was added to the reaction mixture using $\text{Cu}(\text{OTf})_2$,⁸ the reaction proceeded smoothly and the yield of **3a** was dramatically improved to 90% (run 8). Only 0.05 equiv. of $\text{Cu}(\text{OTf})_2$ functioned effectively in the presence of TMSCl for the catalytic imino Friedel–Crafts reaction to proceed in high yield (run 9). Surprisingly, TMSCl (0.5 equiv.) less than 1 equiv. required a longer reaction time to complete the reaction (run 10).

To clarify the generality of this catalytic reaction, several indole derivatives were treated with the acetal, the results being listed in Table 2.⁹ In all cases, a catalytic amount (0.05–0.2 equiv.) of $\text{Cu}(\text{OTf})_2$ doping TMSCl (1 equiv.) was enough to complete these reactions. Treatment of *N*-protected or 2-substituted indoles with acetal **1** produced the expected primary amines **3a–c** in

Keywords: *N,O*-acetals; Friedel–Crafts reactions; indoles; primary amines.

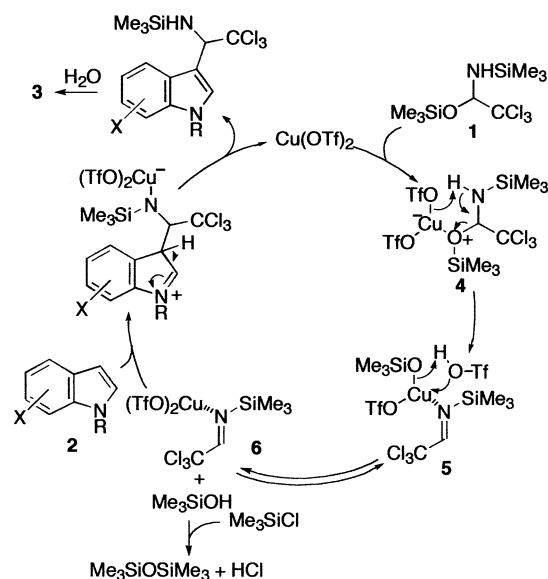
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Table 1. Effect of Lewis acids and additive


Run	LA (equiv.) + Additive (equiv.)	Time (h)	Yield (%) ^a
1	BF ₃ ·OEt ₂ (1)	72	65
2 ^b	TiCl ₄ (1)	0.3	56
3	AlCl ₃ (1)	0.2	67
4	TMSOTf (1)	72	62
5	Cu(OTf) ₂ (0.2)	7	33
6	TfOH (0.2)	72	51
7	BF ₃ ·OEt ₂ + TMSCl (each 1)	1.5	90
8	Cu(OTf) ₂ (0.2) + TMSCl (1)	4	90
9	Cu(OTf) ₂ (0.05) + TMSCl (1)	20	84
10	Cu(OTf) ₂ (0.2) + TMSCl (0.5)	53	89
11	TMSCl (1)	10	NR ^c

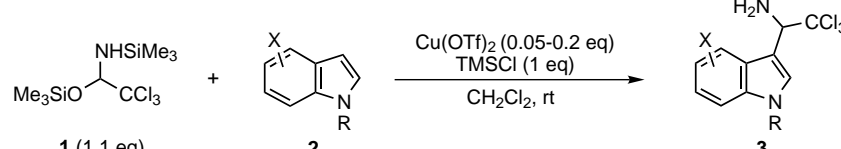
^a Isolated yields based on indole.^b Reaction was carried out at 0°C.^c NR = no reaction.

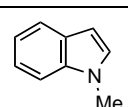
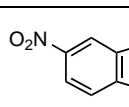
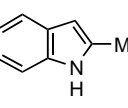
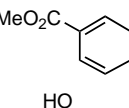
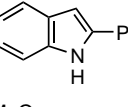
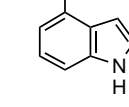
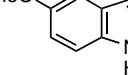
good yields (runs 1–3). Similarly, indoles bearing an electron-releasing group also produced the amine **3d**, but in a moderate yield (run 4). Although indoles with an electron-withdrawing group, such as the nitro or ester group, required a longer reaction time, the expected amines were obtained in 81 and 83% yields, respectively (runs 5 and 6). It is noted that even an indole derivative with OH and NH units, which seem to deactivate the Lewis acid, caused the catalytic

**Scheme 1.** Plausible mechanism for Cu(OTf)₂-TMSCl catalyzed aminomethylation of indoles **2** with *N,O*-acetal **1** leading to primary amine derivative **3**.

aminomethylation to run smoothly, furnishing the corresponding indole derivative **3g** (run 7).¹⁰ Unfortunately, those indoles where the pyrrole units involve electron-withdrawing substituents, such as a benzene-sulfonyl or carbomethoxy group, did not produce the corresponding primary amines.

A plausible mechanism of the Cu(OTf)₂-TMSCl catalyzed aminomethylation of indoles is shown in Scheme 1. First, coordination of Cu(OTf)₂ to an oxygen atom

Table 2. Cu(OTf)₂-catalyzed aminomethylation of indoles with *N,O* acetal


Run	Indole	Cu(OTf) ₂ (eq)	Time (h)	Yield ^a (%)	Run	Indole	Cu(OTf) ₂ (eq)	Time (h)	Yield ^a (%)
1		0.2	7	3a 74	5		0.2	52	3e 81
2		0.2	4	3b 72	6		0.2	48	3f 83
3		0.2 0.05	4 30	3c 83 70	7		0.2 0.1	2 6	3g 76 75
4		0.2	6	3d 61					

^a Isolated yields based on indoles **2**.

of the acetal **1** would form a cationic complex **4**, where cleavage of the C–O bond and abstraction of a proton by a triflate ion simultaneously occur to give the *N*-silylimine **5**, Cu(OTf)OSiMe₃ and TfOH. A subsequent equilibrium would generate a silanol¹¹ and the imine complex **6**, composed of the imine and Cu(OTf)₂. Moreover, indoles would attack the intermediate **6** to produce the corresponding amine **3** along with the regenerated catalyst. In this system, the Lewis acid plays a dual role, first to dissociate Me₃SiO⁻ and subsequently to activate the intermediate imine. The role of TMSCl is not clear at present; however, we assume that TMSCl would trap the in situ generated silanol to drive the equilibrium to completion, given that the use of less than 1 equiv. of TMSCl required a prolonged reaction time (see run 10 in Table 1). On the other hand, the role of the trichloromethyl group on complex **6** would facilitate an attack from nucleophiles as indoles, because this strong electron-withdrawing substituent increases in an electrophilic nature of imine carbon.

Thus far, we have demonstrated that the aminomethylation of a variety of indoles with an *N,O*-acetal was catalyzed by Cu(OTf)₂ in the presence of TMSCl as an activator leading to indolyl primary amines. The present aminoalkylation is a convenient method for indoles containing various functional groups without the need to protect NH and/or OH. In addition, this method would be available for synthesis of 3-indolyl glycine derivatives because the trichloromethyl group is easily hydrolyzed by an alkaline solution to produce the carboxylic acid. Further investigation into the reaction of *N,O*-acetals with aromatics other than indoles is now in progress.

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9. **Typical procedure:** *N,O*-Acetal **1** (0.55 mmol), indole **2** (0.5 mmol) and TMSCl (0.55 mmol) were successively mixed together in CH₂Cl₂ (5 mL) at room temperature with stirring under an Ar atmosphere. After 3 min, Cu(OTf)₂ (0.05–0.2 equiv.) was added, and the reaction mixture was stirred until all of the indole was consumed, as shown by TLC. After the usual work-up, the residue was separated on silica gel (hexane/AcOEt = 2/1) to afford the products **3**. All new compounds were fully characterized, the details will be published elsewhere. Data for selected compound **3f**: mp 168.5–169.9°C (colorless crystals from AcOEt–hexane); ¹H NMR (300 MHz, DMSO-*d*₆) δ 2.78 (brs, 2H), 3.84 (s, 3H), 5.04 (s, 1H), 7.46 (d, 1H, *J* = 8.5 Hz), 7.69 (s, 1H), 7.72 (d, 1H, *J* = 8.5 Hz), 8.46 (s, 1H), 11.07 (brs, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 55.3, 65.4, 101.3, 108.3, 111.2, 111.7, 112.0, 125.7, 127.4, 130.5, 153.3, 161.0; MS (FAB): *m/z* 323, 321 (M⁺+H), 203 (M⁺–CCl₃); Anal. calcd for C₁₂H₁₁Cl₃N₂O₂: C, 44.82; H, 3.45; N, 8.71. Found: C, 45.10; H, 3.53; N, 8.54%.
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