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$Hf(OTf)_4$-Catalyzed Regioselective *N*-Aminomethylation of Indoles and Related NH-Containing Heterocycles

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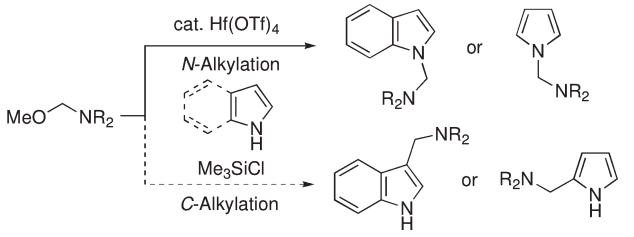

Under Lewis acidic conditions using $Hf(OTf)_4$, the aminomethylation of an indole derivative with a typical *N*,*O*-acetal preferentially produced kinetically favored *N*-aminomethylated indole derivatives instead of thermodynamically favored 3-aminomethylated indoles.

Aminoalkylation is one of the most efficient and practical methods for introduction of a nitrogen-containing functional group onto an aromatic compound, especially an electron-rich heterocycle such as indole and pyrrole.[1] In this context, a number of researchers have previously reported that a common aminomethylation of an indole derivative with an *N*,*O*-acetal and *N*,*N*-aminal in the presence of a typical Lewis acid regioselectively took place on the 3-position (*C*-alkylation)[2] and that under basic conditions or at low temperature the aminomethyl substituent was mainly introduced onto the nitrogen atom (*N*-alkylation) on indole.[3−5] We also reported the $Hf(OTf)_4$-doped Me_3SiCl-catalyzed *C*-alkylation of indoles with *N*,*O*-acetals having either a cyano group or an ester group and recognized a preferential introduction of the substituent onto the *C3*-position in indole.[6] However, during ongoing studies on the aminomethylation of nitrogen-containing heterocycles with the *N*,*O*-acetals, we found an unprecedented result: $Hf(OTf)_4$ promoted the regioselective *N*-alkylation of an indole derivative, preferentially producing the kinetically favored *N*-aminomethylated indole derivative at room temperature instead of the thermodynamically favored 3-aminomethylated indole. With but two exceptions, aminomethylation of a 3-protected indole under Lewis acidic conditions or an *N*-underivatized indole derivative under basic conditions, this type of highly regioselective *N*-aminomethylation of an indole derivative in the presence of a catalytic amount of a Lewis acid has not been reported. The success of *N*-alkylation under Lewis acidic conditions enables the use of indoles having a base-sensitive functional group, which is applied to the practical preparation of some biologically active substances such as isogramine. Herein, we report the unconventional results of this unique *N*-aminomethylation of indoles and related NH-containing heterocycles.

Initially, a series of *N*,*O*-acetals **2a**−**g** having several amino groups were prepared via the reaction of a secondary amine, methanol, and paraformaldehyde in the presence of a dehydrating reagent such as K_2CO_3 and Na_2SO_4.[7] When the reaction of indole (**1a**) with the *N*,*O*-acetal **2a** was then carried out in the presence of $Hf(OTf)_4$ in CH_2Cl_2, *N*-aminomethylation was cleanly completed within 5 min to lead to the selective preparation of indole **3aa** in 76% yield with formation of 3-substituted indole **4aa** and 1,3-disubstituted indole **5aa** (run 1 in Table 1).[7] Thus, to improve the regioselectivity of the aminomethylation, we then performed the reaction using several different Lewis/Brønsted acids. When $HfCl_4$ was used instead of $Hf(OTf)_4$, both the product yield and selectivity were reduced (run 2). In the presence of AgOTf, however, the yield of 3-aminomethylated indole was increased (run 3). With no reference to a

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(2) Selected papers and review for *C*-alkylation of indole and pyrrole with an acetal, an aminal, and a hemiacetal: (a) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *J. Chem. Soc., Chem. Commun.* **1988**, 1161. (b) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron Lett.* **1988**, *29*, 2377. (c) Fairhurst, R. A.; Heaney, H.; Papageorgiou, G.; Wilkins, R. F.; Eyley, S. C. *Tetrahedron Lett.* **1989**, *30*, 1433. (d) Katritzky, A. R.; Yang, Z.; Lam, J. N. *Tetrahedron* **1992**, *48*, 4971. (e) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1997**, *53*, 2941. (f) Gong, Y.; Kato, K. *J. Fluorine Chem.* **2001**, *108*, 83. (g) DeNinno, M. P.; Eller, C.; Etienne, J. B. *J. Org. Chem.* **2001**, *66*, 6988. (h) Yadav, J. S.; Reddy, B. V. S.; Satheesh, G. *Tetrahedron Lett.* **2004**, *45*, 3673. (i) Lindquist, C.; Ersoy, O.; Somfai, P. *Tetrahedron* **2006**, *62*, 3439. (j) Katritzky, A. R.; Lan, X.; Yang, J. Z.; Denisko, O. V. *Chem. Rev.* **1998**, *98*, 409.

(3) (a) Swaminathan, S.; Ranganathan, S.; Sulochana, S. *J. Org. Chem.* **1958**, *23*, 707. (b) Swaminathan, S.; Narasimhan, K. *Chem. Ber.* **1966**, *99*, 889. (c) Love, B. E.; Nguyen, B. T. *Synlett* **1998**, 1123. (d) Love, B. E. *J. Org. Chem.* **2006**, *72*, 630.

(4) Selected papers for *N*-alkylation of indoles with electrophiles in the presence of a base: (a) Heaney, H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 499. (b) Bergman, J.; Norrby, P.-O.; Sand, P. *Tetrahedron* **1990**, *46*, 6113. (c) Ottoni, O.; Cruz, R.; Alves, R. *Tetrahedron* **1998**, *54*, 13915. (d) Bombrun, A.; Casi, G. *Tetrahedron Lett.* **2002**, *43*, 2187. (e) Shieh, W.-C.; Dell, S.; Bach, A.; Repic, O.; Blacklock, T. J. *J. Org. Chem.* **2003**, *68*, 1954. (f) Burley, G. A.; Davies, D. L.; Griffith, G. A.; Lee, M.; Singh, K. *J. Org. Chem.* **2010**, *75*, 980.

(5) Fridkin, G.; Boutard, N.; Lubell, W. D. *J. Org. Chem.* **2009**, *74*, 5603.

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(7) See the experimental details in the Supporting Information.

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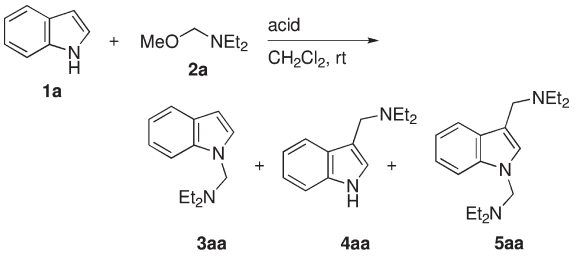
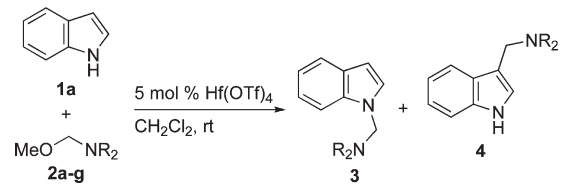
TABLE 1. Examination of the Aminomethylation of Indole



run	acid (5 mol %)	time (min)	yield[a] (%) 3aa	4aa	5aa
1	$Hf(OTf)_4$	5	(76)	6	2
2	$HfCl_4$	30	31	9	5
3	AgOTf	30	13	45	16
4	$Cu(OTf)_2$	30	47	19	11
5	$Zn(OTf)_2$	30	55	9	4
6	$In(OTf)_3$	30	72	3	6
7	$Yb(OTf)_3$	30	75	5	8
8	TfOH[b]	30	64	8	7
9	Me_3SiCl	30	5	87	3

[a]NMR(isolated) yield. [b]0.2 equiv of TfOH was used.

TABLE 2. *N*-Alkylation of Indole with Several *N*,*O*-Acetals

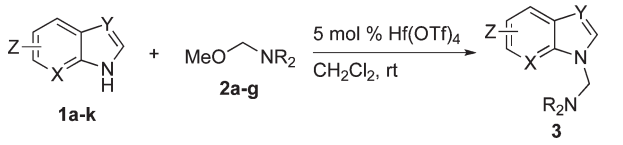


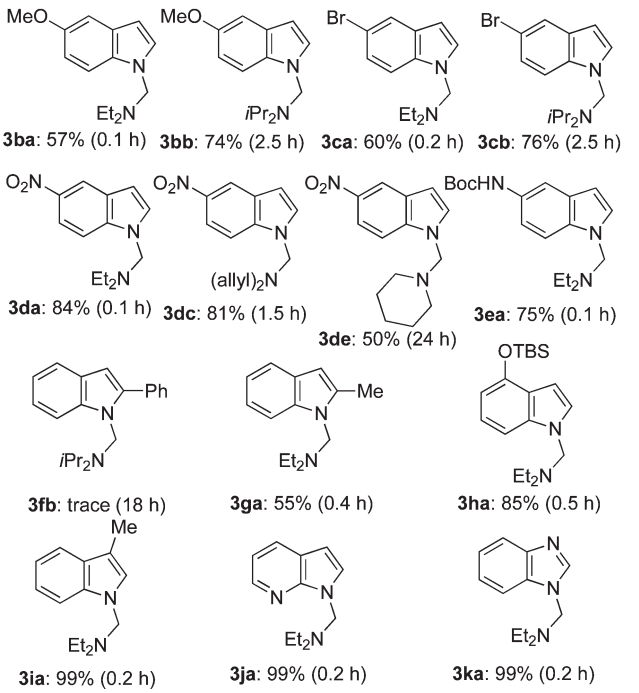
entry	R_2N		yield (%)[a] 3		4	
1	Et_2N	**2a**	76	**3aa**	6	**4aa**
2	iPr_2N	**2b**	96	**3ab**	0	**4ab**
3	$(Allyl)_2N$	**2c**	70	**3ac**	11	**4ac**
4		**2d**	59	**3ad**	7	**4ad**
5		**2e**	52	**3ae**	10	**4ae**
6	$PhCH_2(Me)N$	**2f**	66	**3af**	10	**4af**
7	Ph(Me)N	**2g**	26	**3ag**	ND	**4ag**

[a]Isolated yield.

sort of metal cation, when the number of the triflate anion was increased, both the yield and selectivity were drastically improved (runs 4−7). Thus, when 20 mol % of TfOH was used as a catalyst, the similar reaction proceeded smoothly to produce the *N*-aminomethylated indole as a major product with high regioselectivity (run 8). These results imply that the triflate anion species or TfOH functions as a key promoter of this unique aminomethylation. On the other hand, use of Me_3SiCl gave 3-aminomethylated indole **4** as a major product as well as the conventional results (run 9).[2] From the viewpoints of the handling of the catalyst and the reactivity, the reaction conditions shown in run 1 were the optimal conditions for the present aminomethylation.

TABLE 3. *N*-Aminomethylation of Indoles [a,b]



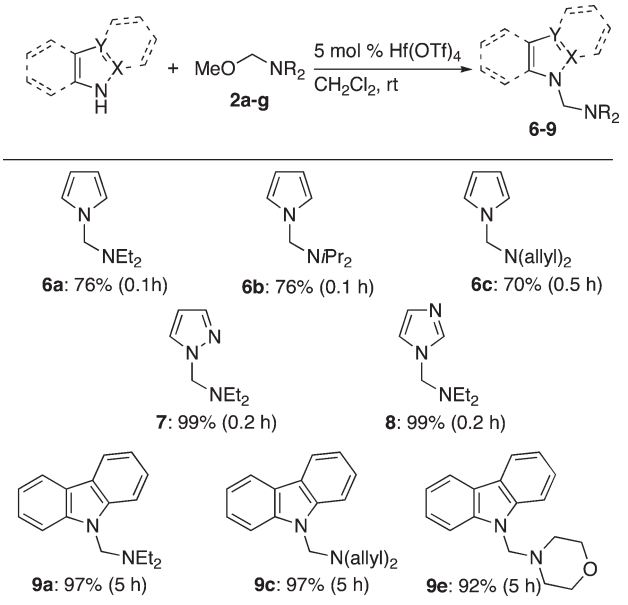


[a]Isolated yield. [b]The term "**b**" in **3ba** denotes a sort of indole, and the term "**a**" in **3ba** corresponds to a sort of *N*,*O*-acetal **2** shown in Table 2.

We next examined the effect of an amine moiety on the *N*,*O*-acetal for the aminomethylation of indole (**1a**) (Table 2). For instance, in the case of the *N*,*O*-acetals having an acyclic amino group, the corresponding *N*-aminomethylated products **3a**−**c** were regioselectively produced in good yields. Use of *N*,*O*-acetals having a cyclic amino moiety slightly reduced the yields of *N*-aminomethylated indoles **3** (entries 4 and 5). *N*,*O*-Acetal **2f** with an unsymmetrical amine produced good selectivity and practical yield. However, in the case of the *N*,*O*-acetal **2g** derived from *N*-methylaniline, the yield of product **3ag** was drastically decreased. This may have been due to the phenyl group retarding conversion into the corresponding Mannich base.

To further extend the generality of this reaction, the reaction of *N*,*O*-acetals **2a**−**g** with a variety of indoles was carried out under optimal conditions (Table 3). With the exception of *N*,*O*-acetal **2g**, most *N*-aminomethylations of indoles with a substituted group, such as a methoxy, a bromine, a nitro, or a Boc-protected amino group, proceeded smoothly to produce the corresponding derivatives in moderate to good yields. Unfortunately, in the cases of 2-substituted indoles, the yields of *N*-aminomethylated derivatives **3fb** and **3ga** were drastically reduced; in particular, use of 2-phenylindole did not give the desired product **3fb** due to the steric repulsion between a relatively bulky isopropyl group and a 2-substituted group. On the other hand, when aminomethylation of an indole possessing a TBS-protected OH

TABLE 4. ***N*-Aminomethylation of *N*-Containing Heterocycles**[a]



[a]Isolated yield.

substituent, or of 3-methylated indole was conducted, the aminomethyl group was easily introduced onto the nitrogen atom. Moreover, the present method could be applied to the quantitative *N*-aminomethylation of 7-azaindole and benzimidazole.

When the reaction of other nitrogen-containing heterocycles such as pyrrole, pyrazole, imidazole, and carbazole with several *N*,*O*-acetals was performed with 5 mol % of $Hf(OTf)_4$, it was found that unlike conventional reports using a typical silyl chloride, such as Me_3SiCl as a promoter, *N*-aminomethylation proceeded selectively to produce the desired derivatives **6**−**9** in good to excellent yields (Table 4).

To better understand the reaction pathway for aminomethylation, a time-course of thermal rearrangement of the aminomethyl moiety on the isolated indole **3aa** was monitored by ^1H NMR in CD_2Cl_2 at room temperature (Figure 1). The gradual conversion of indole **3aa** into 3-aminomethylated indole **4aa**, 1,3-diaminomethylated indole **5aa**, and indole (**1a**) was directly observed, and after 6 h, the reaction reached equilibrium (**4aa**, 12%; **5aa**, 14%; **1a**, 15%; 59% of **3aa** remained). Thus, the results of the present study show that isomerization from kinetically favored indole **3aa** into thermodynamically favored **4aa** via a consecutive dissociation−recombination of the aminomethyl group proceeded slowly under these conditions.[8,9] Also, the formation of 1,3-disubstituted indole **5aa** shows that the shift of the aminomethyl group occurred intermolecularly.[10] Moreover, to understand

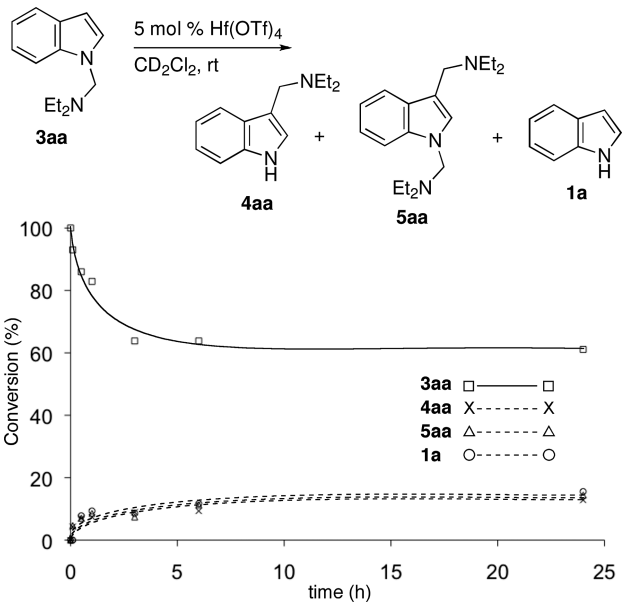
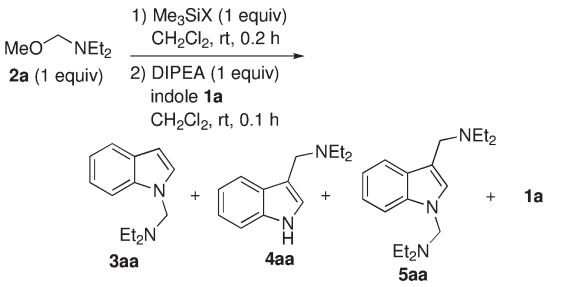


FIGURE 1. Time-course of thermal conversion of indole derivative **3aa** into indole derivatives **4aa**, **5aa**, and indole (**1a**) in the presence of 5 mol % of $Hf(OTf)_4$ by NMR monitoring.

TABLE 5. Comparison of *N*- and *C*-Alkylation in the Reaction of Indole (1a) and *N*,*O*-Acetal 2a in the Presence of Me_3SiX[a]



		product yield[a] (%)			
run	Me_3SiX	**3aa**	**4aa**	**5aa**	**1a**
1	Me_3SiOTf	46	4	2	46
2	Me_3SiCl	9	37	16	38

[a]NMR yield.

an effect of a counteranion of the Mannich base generated from the *N*,*O*-acetal **2**, aminomethylation of indole (**1a**) with the acetal **2a** was performed with Me_3SiOTf or Me_3SiCl in the presence of *N*,*N*-diisopropylethylamine (DIPEA) as a scavenger of an acid (Table 5).[11] Interestingly, the one Me_3SiOTf mainly produced *N*-aminomethylated product **3aa**, and the other Me_3SiCl gave *C*-aminomethylated indole **4aa** as a major product. The results imply that a softness of the in situ generated electrophile controls regioselectivity of this aminomethylation. In short, the alkylating reagent with a harder triflate anion favored *N1*-alkylation, and the iminium salt with a chloride ion, which is a softer anion than the triflate anion, provided *C3*-alkylation product predominantly.[9,12]

In summary, we have found that $Hf(OTf)_4$ promotes aminomethylation of indole derivatives, preferentially affording

(8) (a) When isolated product **3aa** was treated with 2 equiv of Me_3SiCl in CH_2Cl_2 at room temperature for 72 h, no shift of the aminomethyl group was observed.

(9) Several groups reported that regioselective *N1*- or *C3*-alkylation of NH-containing heterocycles depends on a softness of the leaving group of an electrophile; see: (a) Nunomoto, S.; Kawakami, Y.; Yamashita, Y.; Takeuchi, H.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 111. (b) Epling, G. A.; Kumar, A. *Synlett* **1991**, 347. (c) Bourak, M.; Gallo, R. *Heterocycles* **1990**, *31*, 447.

(10) When isolated product **3aa** in the presence of 20 mol % of $Hf(OTf)_4$ was vigorously stirred in CH_2Cl_2 at room temperature, product **4aa** was obtained in 68% yield.

the kinetically favored *N*-aminomethylated indole derivatives (*N*-alkylation product) instead of the thermodynamically favored 3-aminomethylated indoles (*C*-alkylation product). This method could be successfully extended to the *N*-alkylation of pyrroles and other related NH-containing heterocycles. Further studies by our group on the detailed reaction mechanism of this type of aminomethylation are currently ongoing.

Experimental Section

General Procedure for the $Hf(OTf)_4$-Catalyzed Aminomethylation of a Nitrogen-Containing Heterocycle with an *N*,*O*-Acetal. To a freshly distilled CH_2Cl_2 solution (2 mL) was successively added an *N*,*O*-acetal **2** (70.3 mg, 0.600 mmol), indole (70.3 mg, 0.600 mmol), and $Hf(OTf)_4$ (23.2 mg, 0.0300 mmol) under a nitrogen atmosphere. The resulting solution was stirred for 0.1 h at room temperature. The reaction was quenched with a saturated aqueous solution (2 mL) of Na_2CO_3. The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/AcOEt) to afford the corresponding product.

***N*-((1*H*-Indol-1-yl)methyl)-*N*-ethylethanamine (3aa):** colorless oil; IR (neat) 3040, 2933, 1459 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (t, 6H, J = 7 Hz), 2.60 (q, 4H, J = 7 Hz), 4.87 (s, 2H), 6.49 (d, 1H, J = 3 Hz), 7.09 (t, 1H, J = 7.5 Hz), 7.16 (d, 1H, J = 3 Hz), 7.19 (t, 1H, J = 7.5 Hz), 7.46 (d, 1H, J = 7.5 Hz), 7.61 (d, 1H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.2, 44.9, 64.1, 101.4, 109.9, 119.4, 120.7, 121.5, 128.2, 128.6, 136.8; MS (ESI) m/z 225 ($M^+ + Na^+$); HRMS (ESI) calcd for $C_{13}H_{18}N_2Na$ 225.1368, found 225.1383.

***N*-((1*H*-Pyrrol-1-yl)methyl)-*N*-ethylethanamine (6a):** colorless oil; IR (neat) 3104, 2937, 1490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (t, 3H, J = 7 Hz), 2.54 (q, 2H, J = 7 Hz), 4.72 (s, 1H), 6.14 (t, 1H, J = 2 Hz), 6.68 (t, 1H, J = 2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 45.0, 65.8, 107.8, 121.2; MS (ESI) m/z 153(M^+ + H); HRMS (FAB) calcd for $C_9H_{17}N_2$ 153.1392, found 153.1417.

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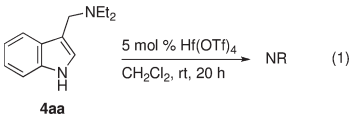
Supporting Information Available: Experimental details and spectroscopic data of the prepared compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) When the reaction was conducted with another proton scavenger such as *N*,*O*-bis(trimethylsilyl)acetamide, the desired reaction did not proceed.

(12) The reviewer commented that a shift of the aminomethyl group occurs from a kinetically favored one (*N*-alkylation) to a thermodynamically favored one (*C*-alkylation) in the presence of the catalyst. However, we have no observation from the thermodynamic product to the kinetic one through a series of experiments (eq 1).



Additionally, the same reviewer pointed out the disproportion that the case using Me_3SiCl did not undergo the thermal conversion (see ref 8). It seems that a relatively moderate Lewis acid Me_3SiCl does not lead to regeneration of the iminium species through a cleavage of the C−N bond.