Received: November 29, 2013 | Accepted: December 21, 2013 | Web Released: December 28, 2013 CL-131116

N-Aminomethylation vs. *C*-Aminomethylation of Indole and Pyrrole with an *N*,*O*-Acetal Controlled by the Hardness of a Counter Ion of an Iminium Compound

Norio Sakai,* Hidetoshi Okano, Kazuyori Shimamura, and Takeo Konakahara
Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science (RIKADAI), Noda, Chiba 278-8510

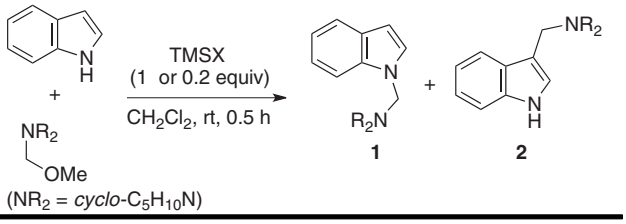
(E-mail: sakachem@rs.noda.tus.ac.jp)

Under relatively strong Lewis acidic conditions (a softer counter ion) using TMSOTf and TMSI, the aminomethylation of indole or pyrrole with a typical *N*,*O*-acetal preferentially produced the kinetically favored *N*-aminomethylated indole or pyrrole derivative. Use of a relatively weak Lewis acid (a harder counter ion), such as TMSCl and TMSBr, preferentially produced the thermodynamically favored *C*-aminomethylated indole and pyrrole derivative.

Because indole and pyrrole constitute the basic skeleton of natural products and biologically active substances, developing the regioselective introduction of a functional group onto these skeletons with an ambident nucleophilic point remains a fundamentally important and central pursuit in organic synthesis.[1,2] Among these efforts, aminoalkylation with imines,[3] *N*,*O*-acetals,[4,5] or *N*,*N*-aminals[6] in the presence of a Lewis acid constitutes a straightforward and practical method to achieve this goal. Thus far, the common aminomethylation of indole or pyrrole derivatives with *N*,*O*-acetals in the presence of a typical organosilicon Lewis acid such as chlorotrimethylsilane (TMSCl) regioselectively took place at either the 3- or 2-position (*C*-aminomethylation), respectively.[6e,6f] However, as an unconventional example, we reported that with a Lewis acid, $Hf(OTf)_4$ promoted the regioselective *N*-aminomethylation of an indole derivative, preferentially producing the kinetically stable *N*-aminomethylated indole derivative instead of the thermodynamically stable 3-aminomethylated indole.[7] Therefore, we anticipated that in this aminomethylation the hardness (basicity) of a counter anion of the iminium compound, which is derived from an *N*,*O*-acetal, would control the product ratio of the *N*-aminomethylation vs. the *C*-aminomethylation of an indole, and actually attempted the regioselective aminomethylation of either indole or pyrrole with an *N*,*O*-acetal in the presence of an organosilicon Lewis acid series (e.g., TMSCl, TMSBr, TMSI, and TMSOTf). Thus, we have obtained new results, in which an iminium intermediate with a softer counter anion (a weakly basic anion) undertook an aminomethylation onto the harder nitrogen position of indole or pyrrole; to a certain extent, these results correlated with the principle of the hard and soft acids and bases (HSAB).[8,9] In this letter, we report these results.

Initially, the regioselective aminomethylation of indole with an *N*,*O*-acetal, 1-(methoxymethyl)piperidine, prepared from piperidine, methanol, and paraformaldehyde in the presence of both K_2CO_3 and Na_2SO_4,[7] was performed with four types of organosilicon Lewis acids (1 equiv) at room temperature in CH_2Cl_2; the results are summarized in Table 1.[10] In all cases, indole was consumed within 30 min to produce three types of indole derivatives **1**, **2**, and **3**. Compounds **1** and **2** were characterized as the *N*-aminomethylated and *C*-aminomethylated indole derivatives, respectively. Compound **3** was characterized as the 1,3-disubstituted indole derivative. The hardness of a counter ion directly controlled the product ratio of the aminomethylated indole. In other words, when the strength of the Lewis acid increased, the product ratio of the kinetically stable 1-aminomethylated indole **1** increased, but the formation of the thermodynamically stable 3-aminomethylated indole **2** remarkably decreased. Interestingly, when this aminomethylation was also subjected to the conditions with a catalytic amount (0.2 equiv) of a Lewis acid, a similar tendency for the product ratio was observed. Moreover, this tendency was maintained when the reaction time was prolonged.[11]

Table 1. Selective aminomethylation of indole with an *N*,*O*-acetal by organosilicon Lewis acids



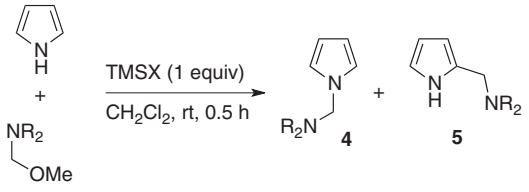
Entry	TMSX	Conversion /%[a,b]	Product ratio[a,c]		
			1	**2**	**3**[d]
1	TMSCl	86 (63)	8 (14)	77 (59)	15 (27)
2	TMSBr	85 (81)	19 (19)	65 (59)	16 (22)
3	TMSI	96 (77)	36 (52)	53 (23)	11 (25)
4	TMSOTf	95 (90)	60 (62)	37 (20)	3 (18)

[a]0.2 equiv of TMSX is in parentheses. [b]Based on indole. [c]Ratio was calculated by NMR. [d]Compound **3**: 1,3-disubstituted indole.

Then, when the aminomethylation of pyrrole was performed with the same organosilicon Lewis acids, a similar tendency toward the product ratio was observed (Table 2). As the strength of four types of organosilicon Lewis acids increased, the product ratio of *N*-aminomethylated pyrrole **4** increased more than that of *C*-aminomethylated pyrrole **5**. The formation of a mixture of 1,2-disubstituted pyrrole **6** and 2,5-disubstituted pyrrole **7** was also observed. Unfortunately, neither compound could be cleanly isolated from the mixture. When the aminomethylation was conducted with 0.2 equiv of a Lewis acid series, contrary to expectations, cases with TMSCl and TMSBr afforded disubstituted pyrroles as a major product. However, the cases with TMSI and TMSOTf produced *N*-aminomethylated pyrrole **4** with a relatively high selectivity.

To understand the effect to regioselectivity of a counter anion of each iminium compound, several control experiments

Table 2. Selective aminomethylation of pyrrole with an *N*,*O*-acetal by organosilicon Lewis acids



NR_2 = *c*-$C_5H_{10}N$

Entry	TMSX	Conversion /%[a,b]	Product ratio[a,c]		
			4	**5**	**6** + **7**[d]
1	TMSCl	100 (93)	5 (11)	83 (38)	12 (51)
2	TMSBr	98 (94)	15 (30)	68 (23)	17 (47)
3	TMSI	89 (100)	46 (70)	32 (19)	22 (11)
4	TMSOTf	98 (100)	68 (75)	26 (16)	6 (9)

[a]0.2 equiv of TMSX is in parentheses. [b]Based on pyrrole. [c]Ratio was calculated by NMR. [d]A mixture of 1,2-disubstituted pyrrole **6** or 2,5-disubstituted pyrrole **7**.

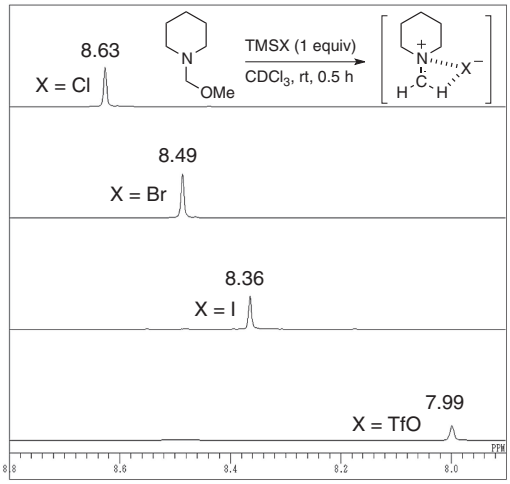
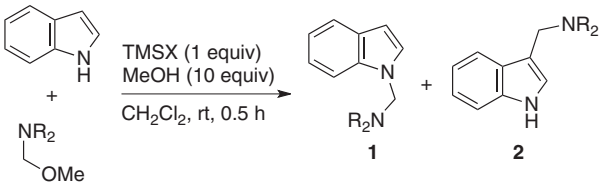


Figure 1. Observation of the chemical shift of the methylene protons on each iminium compound by ^{1}H NMR.

were then examined. First, a chemical shift of the corresponding methylene peak of each iminium compound, generated in situ from the *N*,*O*-acetal and Lewis acid, was measured by ^{1}H NMR (Figure 1). In all cases, a single peak derived from the methylene proton was observed at 8.0–8.6 ppm. The observed shift was in agreement with the results of the chemical shifts of diethylmethyleneammonium salts, $Et_2N^+{=}CH_2X^-$ (X = Cl, Br, I, and OTf) in CD_3CN by Mayr and Würthwein.[12,13] Based on the strength of the chemical shift, in this aminomethylation the triflate anion behaved as a relatively soft base. These results showed that relatively hard anions such as Cl^- and Br^- formed a strong hydrogen bond with methylene protons, which led to a downfield shift of the proton. In other words, we are convinced that the methylene portion became a softer electrophile, which preferentially led to *C*-aminomethylation at the softer 3- or 2-position carbon on indole or pyrrole, respectively. In turn, in cases with relatively soft counter anions, such as TfO^- and I^-, the methylene moiety became an even harder electrophile, which

Table 3. Aminomethylation of indole with an *N*,*O*-acetal in the presence of MeOH



NR_2 = *c*-$C_5H_{10}N$

Entry	TMSX	Conversion /%[a]	Product ratio[b]		
			1	**2**	**3**[c]
1	TMSCl	99	ND	100	ND
2	TMSBr	91	ND	100	ND
3	TMSI	99	3	95	2
4	TMSOTf	99	ND	100	ND

[a]Based on indole. [b]Ratio was calculated by NMR. [c]Compound **3**: 1,3-disubstituted indole.

resulted into preferential *N*-aminomethylation at the harder nitrogen atom on indole and pyrrole.

Also, when aminomethylation of indole was carried out in the presence of excess methanol (10 equiv) in the hopes that strong solvation would separate the iminium cation from the counter anion, the aminomethylation was completed within 0.5 h to selectively produce thermodynamically stable indole **2** (Table 3).[14] These results showed that the electrophilicity of each iminium compound became identical by the insertion of methanol between the iminium cation and the counter anion.[15]

In the selective aminomethylation of either indole or pyrrole having an ambident nucleophilic position with an *N*,*O*-acetal in the presence of organosilicon Lewis acid series, we observed a new tendency.[16] As the hardness of a counter ion on an iminium salt decreased, the kinetically stable *N*-aminomethylated products preferentially formed (*N*-aminomethylation), and, in turn, as the hardness of a conjugate anion on an iminium salt increased, a thermodynamically stable 3- or 2-aminomethylated indole or pyrrole preferentially formed (*C*-aminomethylation). Also, we observed that each counter anion undertook a strong interaction with the methylene protons of the iminium intermediate.

This work was partially supported by a grant from the Japan Private School Promotion Foundation supported by MEXT. The authors thank Mr. Hiroaki Hori (Tokyo University of Science) for his assistance with the experiments. The authors also thank Shin-Etsu Chemical Co., Ltd., for the gift of chlorosilane.

References and Notes

1 a) J. S. Glasby, *Encyclopedia of the Alkaloids*, Plenum Press, New York, **1975**. doi:10.1007/978-1-4615-8729-3. b) R. J. Sundberg, *Indoles*, Academic Press, San Diego, **1996**.

2 For selected reviews for preparations or reactions of indoles, see: a) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195. b) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489. c) J. Barluenga, F. Rodríguez, F. J. Fañanás, *Chem.—Asian J.* **2009**, *4*, 1036. d) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875. e) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873. f) M.

Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Synlett* **2005**, 1199. g) G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045.

3 a) G. A. Olah, *Friedel–Crafts Chemistry*, Wiley-Interscience, New York, **1973**. b) P. Thirupathi, S. S. Kim, *J. Org. Chem.* **2010**, *75*, 5240. c) I. Alonso, J. Esquivias, R. Gómez-Arrayás, J. C. Carretero, *J. Org. Chem.* **2008**, *73*, 6401. d) M. Soueidan, J. Collin, R. Gil, *Tetrahedron Lett.* **2006**, *47*, 5467. e) B. Jiang, Z.-G. Huang, *Synthesis* **2005**, 2198. f) S. Saaby, P. Bayón, P. S. Aburel, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 4352. g) A. Janczuk, W. Zhang, W. Xie, S. Lou, J. Cheng, P. G. Wang, *Tetrahedron Lett.* **2002**, *43*, 4271. h) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817. i) S. Saaby, X. Fang, N. Gathergood, K. A. Jørgensen, *Angew. Chem., Int. Ed.* **2000**, *39*, 4114. j) T. Huang, C.-J. Li, *Tetrahedron Lett.* **2000**, *41*, 6715.

4 a) W.-I. Lee, J.-W. Jung, J. Jang, H. Yun, Y.-G. Suh, *Tetrahedron Lett.* **2013**, *54*, 5167. b) A. E. Hartman, C. L. Brophy, J. A. Cupp, D. K. Hodge, T. J. Peelen, *J. Org. Chem.* **2009**, *74*, 3952. c) C.-S. Ge, Y.-J. Chen, D. Wang, *Synlett* **2002**, 37. d) T. Billard, B. R. Langlois, *J. Org. Chem.* **2002**, *67*, 997. e) M. P. DeNinno, C. Eller, J. B. Etienne, *J. Org. Chem.* **2001**, *66*, 6988. f) R. Pedrosa, C. Andrés, J. M. Iglesias, *J. Org. Chem.* **2001**, *66*, 243. g) D. Ferraris, T. Dudding, B. Young, W. J. Drury, III, T. Lectka, *J. Org. Chem.* **1999**, *64*, 2168. h) T. Chiba, I. Saitoh, M. Okimoto, T. Tanase, S. Yano, *J. Org. Chem.* **1999**, *64*, 2516.

5 a) N. Sakai, A. Sato, T. Konakahara, *Synlett* **2009**, 1449. b) N. Sakai, J. Asano, Y. Kawada, T. Konakahara, *Eur. J. Org. Chem.* **2009**, 917. c) N. Sakai, J. Asano, Y. Shimano, T. Konakahara, *Tetrahedron* **2008**, *64*, 9208. d) N. Sakai, J. Asano, Y. Shimano, T. Konakahara, *Synlett* **2007**, 2675. e) N. Sakai, M. Hirasawa, T. Hamajima, T. Konakahara, *J. Org. Chem.* **2003**, *68*, 483. f) N. Sakai, T. Hamajima, T. Konakahara, *Tetrahedron Lett.* **2002**, *43*, 4821.

6 a) B. E. Love, *J. Org. Chem.* **2007**, *72*, 630. b) S. Piper, N. Risch, *Synlett* **2004**, 1489. c) H.-J. Grumbach, B. Merla, N. Risch, *Synthesis* **1999**, 1027. d) D. Ferraris, B. Young, T. Dudding, W. J. Drury, III, T. Lectka, *Tetrahedron* **1999**, *55*, 8869. e) H. Heaney, G. Papageorgiou, R. F. Wilkins, *Tetrahedron* **1997**, *53*, 2941. f) H. Heaney, G. Papageorgiou, R. F. Wilkins, *J. Chem. Soc., Chem. Commun.* **1988**, 1161.

7 N. Sakai, K. Shimamura, R. Ikeda, T. Konakahara, *J. Org. Chem.* **2010**, *75*, 3923.

8 a) T.-L. Ho, *Chem. Rev.* **1975**, *75*, 1. b) R. G. Pearson, *J. Chem. Educ.* **1968**, *45*, 581. c) R. G. Pearson, J. Songstad, *J. Am. Chem. Soc.* **1967**, *89*, 1827. d) R. G. Pearson, *J. Am. Chem. Soc.* **1963**, *85*, 3533.

9 For selected papers of regioselective reaction with ambifunctional nucleophilic compounds, see: a) A. L. Kurts, N. K. Genkina, A. Macias, L. P. Beletskaya, O. A. Reutov, *Tetrahedron* **1971**, *27*, 4777. b) R. Gompper, *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 560. c) W. S. Murphy, D. J. Buckley, *Tetrahedron Lett.* **1969**, *10*, 2975. d) W. J. Le Noble, H. F. Morris, *J. Org. Chem.* **1969**, *34*, 1969. e) F. E. Henoch, K. G. Hampton, C. R. Hauser, *J. Am. Chem. Soc.* **1969**, *91*, 676.

10 General procedure for the aminomethylation of indole or pyrrole with an *N*,*O*-acetal: To a freshly distilled CH_2Cl_2 solution (1.0 mL) was successively added an *N*,*O*-acetal (0.5 mmol), indole or pyrrole (0.5 mmol), and a organosilicon Lewis acid (0.5 mmol) under a nitrogen atmosphere. The resulting solution was stirred for 0.5 h at room temperature. The reaction was then quenched with a saturated aqueous solution of Na_2CO_3 (5 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was quantified by NMR measurement ($CDCl_3$) to determine the product ratio of each aminomethylated product with tetrachloroethane as an internal standard. If necessary, the crude product was purified by silica gel chromatography (hexane-AcOEt). Spectral data for a novel compound, 1-(piperidin-1-ylmethyl)-1*H*-pyrrole (**4**) colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34–1.39 (m, 2H), 1.55–1.59 (m, 4H), 2.45–2.47 (m, 4H), 4.62 (s, 2H), 6.15 (t, 1H, $J = 2.0$ Hz), 6.67 (t, 1H, $J = 2.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.7, 25.8, 51.2, 71.8, 107.7, 121.6; MS (ESI) m/z: 165 $[M + H]^+$; HRMS (ESI): Calcd for $C_{10}H_{17}N_2$: 165.1392, Found: 165.1382.

11 See Supporting Information. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

12 H. Mayr, A. R. Ofial, E.-U. Würthwein, N. C. Aust, *J. Am. Chem. Soc.* **1997**, *119*, 12727.

13 In ^{13}C NMR measurement, the corresponding methylene carbon peaks were detected as 162.4 ($X = Cl^-$), 160.7 ($X = Br^-$), and 157.9 ppm ($X = I^-$), respectively. These shift values had a good correlation with the proton values. However, when the counter ion was a triflate anion, the methylene carbon (164.9 ppm) was remarkably shifted to a lower magnetic field side. There is no clear explanation for this result, see ref 12.

14 N. Kornblum, P. J. Berrigan, W. J. Le Noble, *J. Am. Chem. Soc.* **1963**, *85*, 1141.

15 One reviewer pointed out that the presence of excess amounts of MeOH might produce the reversible reaction in the formation of the iminium compound, which led to increase the amount of *C*-aminomethylation. The discussion may be correct, but we have no clear results for this discussion. However, when a similar aminomethylation of indole with an *N*,*O*-acetal was carried out in other solvents, such as CH_3CN, dioxane, and toluene, the same result to the product ratio shown in Table 1 was observed in each case. The only case with MeOH that has a strong solvation led to a selective *C*-aminomethylation. Consequently, we assume that solvation of the iminium intermediate by a protic solvent, MeOH affected the product ratio.

16 When the aminomethylation of indole with an *N*,*O*-acetal was performed with Brønsted acids, the same tendency to the product ratio was observed; TfOH: **1**:**2**:**3** = 76:20:4, HCl (4 mol L^{-1} in dioxane): **1**:**2**:**3** = 1:98:1. In this context, we cited a related paper, in which alkylation and dimerization of indole could be controlled by removal of protic acids, see: M. J. Earle, R. A. Fairhurst, H. Heaney, *Tetrahedron Lett.* **1991**, *32*, 6171.

