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Ethylation of the Indole Dianions by Alkyl Methyl Ethers

Yuji Naruse,* Kenji Kido, and Satoshi Inagaki

Department of Chemistry, Gifu University,
1-1 Yanagido, Gifu 501-11 Japan

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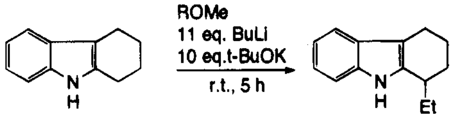
In the course of our studies focusing on the regioselective deprotonation of indole derivatives,[1] we have observed α-ethyl byproducts (e.g., the tetrahydrocarbazole derivative **1**[2] in the case of 1,2,3,4-tetrahydrocarbazole[3]). At first sight, the byproducts appear to originate from the nucleophilic addition of the α-deprotonated intermediate to ethylene generated in situ from diethyl ether or tetrahydrofuran, respectively.[4] To our surprise, however, the same byproducts were obtained when methyl propyl ether, *tert*-butyl methyl ether, and other alkyl methyl ethers were employed as the solvent. Thus, a new explanation is warranted.



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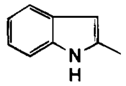
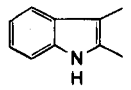
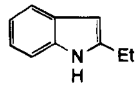
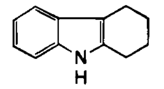
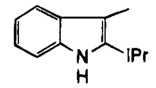
(1)

The yield was fair to moderate with a variety of alkyl methyl ethers (Table 1). Longer reaction time did not improve the yield. The ethylated products were also obtained for the other indole derivatives that possess the secondary center at the α-position. However, no reactions have occurred in the case of the 2-methyl- and 2-isopropylindoles.

To probe the reaction mechanism, labeling experiments were performed. Quenching by heavy water or methanol-*d* led to no incorporation of deuterium. However, reaction in butyl trideuteriomethyl ether gave predominantly 1-(1,1,2,2-tetradeuterioethyl)-1,2,3,4-tetrahydrocarbazole according to ^{13}C NMR and MS analyses.[5]

Ziegler reported that butyllithium reacts with dimethyl ether to give a mixure of pentane, hexane, heptane, and octane.[6] These products came from the sequential addition of carbene to the organolithiums. In our case, however, the ethyl adduct was obtained predominantly and the indoles with longer alkyl chains were obtained only in small amounts.[7] We have performed the calculations of the thermal stabilities of the model compounds, ω-alkenyllithiums with dimethyl ether and 1-alkenes with methoxymethyllithium at the 3-21G level.[8] However, no advantages in energy were observed for the C_2-elongated anion. Thus, the mechanism involving sequential carbene insertion to the dianion appears to be only as a minor bypass.

Table 1. Ethylation by Alkyl Methyl Ethers

indole	ROMe	Yield/%
	Bu	0
		0
		59
	Pr	60
	i-Pr	27
	Bu	55
	i-Bu	24
	s-Bu	19
	t-Bu	17
	neo-Pent	35
	n-Hex	45
	Bu	0

The ethyl group incorporated seemed to be originated from ethylene insersion to the anion intermediate, the same as in the cases of alkyl ethyl ethers.[4,9] Treatment of methyl butyl ether with BuLi−*t*-BuOK[10] at 0 °C for 40 min generated ethylene, which was ascertained by trapping with Br_2.[11]

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(1) Naruse, Y.; Ito, Y.; Inagaki, S. *J. Org. Chem.* **1991**, *56*, 2256.

(2) Pausacker, K. H. *J. Chem. Soc.* **1950**, 621. See also: Wakamatsu, T.; Hara, H.; Ban. Y. *Heterocycles* **1977**, *8*, 335.

(3) Preparation of indoles, see: Tietze, L.-F.; Eicher, T. In *Reaktionen und Synthesen im organisch-chemischen Praktikum*; Georg Thieme Verlag: Stuttgart, 1981. Japanese translation by: Takano, S.; Ogasawara, K. Nankodo: Tokyo, 1983; pp 309−310, M-4a.

(4) Naruse, Y.; Ito, Y.; Inagaki, S. Manuscript in preparation.

(5) Data: ^{13}C NMR ($CDCl_3$) δ 26.6 (m), 10.9 (quint); MS (EI,70 eV) *m/e* (rel int) 204 (22), 203 (17), 171 (36), 170 (100).

(6) Ziegler, K.; Gellert, H. G. *Liebigs Ann. Chem.* **1950**, *567*, 185. For review: Maercker, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 972.

(7) To a stirred solution of 1,2,3,4-tetrahydrocarbazole (0.17 g, 1.0 mmol) in *i*-BuOMe (10 mL) was added BuLi (1.7 M in hexane, 6.5 mL, 11 mmol), followed by *t*-BuOK (1.1 g, 10 mmol). After 5 h, the reaction mixture was poured into saturated $NaHCO_3$ (aq) and extracted with ether (3 × 20 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by column chromatography on silica gel. There were three spots on TLC analysis (Merck No. 5715). The second highest product (R_f = 0.50, hexane−ether, 1:1) was **1** (49 mg, 24%), and the lowest (R_f = 0.44) was the recovery of 1,2,3,4-tetrahydrocarbazole (0.10 g, 59%). The highest R_f portion was collected (12 mg), which was subjected to GC−MS analysis (EI, 70 eV). This fraction was separated into four major peaks. First peak: *m/e* (rel int) 221 (6), 213 (10), 212 (6), 200 (7), 199 (32), 198 (13), 185 (8), 184 (24), 183 (10), 182 (8), 171 (22), 170 (100), 169 (25), 168 (36), 167 (21); second peak: 228 (16), 227 (20), 213 (17), 199 (17), 198 (100), 197 (18), 196 (7), 184 (24), 183 (11), 182 (14), 171 (10), 170 (63), 169 (25), 168 (35), 167 (23); third peak: 281 (5), 279 (5), 242 (9), 241 (29), 240 (4), 228 (5), 227 (6), 213 (17), 212 (78), 211 (12), 199 (18), 198 (100), 197 (19), 184 (13), 183 (18), 182 (22), 180 (10), 170 (41), 169 (23), 168 (35), 167 (34), 166 (10); fourth peak: 279 (8), 242 (6), 241 (8), 228 (7), 227 (18), 226 (7), 225 (5), 213 (8), 212 (23), 199 (6), 198 (24), 197 (8), 196 (7), 185 (5), 184 (11), 183 (11), 182 (10), 171 (18), 170 (100), 169 (25), 168 (31), 167 (35), 166 (10). We thus assigned the first peak as 1-propyl-1,2,3,4-tetrahydrocarbazole, the second as 1-butyl-1,2,3,4-tetrahydrocarbazole, and the third as 1-pentyl-1,2,3,4-tetrahydrocarbazole, respectively.

(8) Gaussian 92 Program, Revision C: Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. Gaussian, Inc. Pittsburgh PA, 1992; Hehre, W. J.; Radom, L. Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

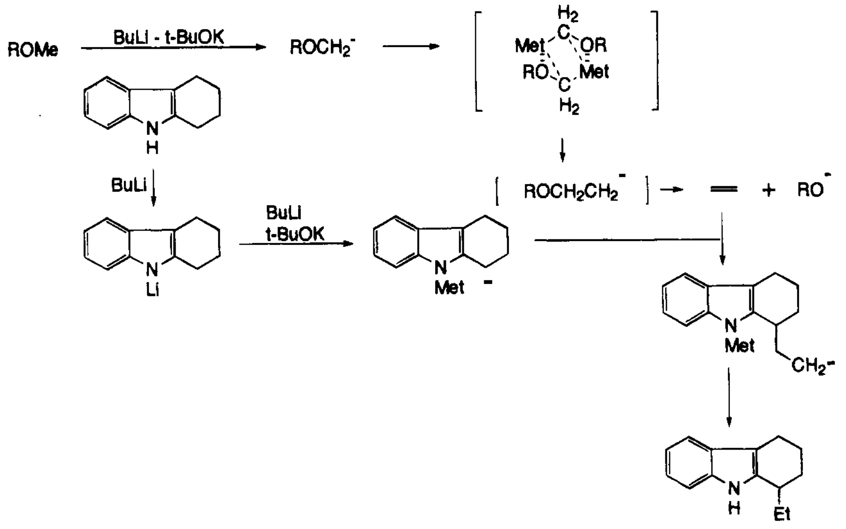
(9) Bartlett, P. D.; Tauber S. J.; Weber, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 6362. Bartlett, P. D.; Goebel, C. V.; Weber, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 7425. Spialter, L.; Harris, C. W. *J. Org. Chem.* **1966**, *31*, 4263.

(10) Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9. Schlosser, M.; Choi, J. H.; Takagishi, S. *Tetrahedron* **1990**, *46*, 5633. For review: Schlosser, M. In *Modern Synthetic Methods*; Scheffold, R., ed.; Verlag Helvetica Chimica Acta: Basel, 1992; Vol. 6, pp 227−272. Schlosser, M. *Organometallics in Synthesis*; John Wiley and Sons: Chichester, 1994; pp 1−166.

(11) A mixture of *s*-BuLi−*t*-BuOK deprotonated *tert*-butyl methyl ether to afford *tert*-butoxymethylide,[12] which was reported as irreproducible, affording only low yields with byproducts.[13]

0022-3263/95/1960-8334$09.00/0

Scheme 1 Proposed Mechanism of the Ethylation



Now we can illustrate the reaction mechanism as follows: the first deprotonation of the indole side chain occurred by BuLi−*t*-BuOK reagent.[1,4,14] On the other hand, the alkoxymethylide was generated from the methyl ether by the superbase. It was transformed into ethylene. Although we have no evidence for the detailed mechanism of this transformation, it is assumed that the dimeric alkoxymethylide should decompose heterogeneously to a carbenoid and alkoxide−organometallic complex.[15] The carbenoid might insert into the carbon−metal bond to give β-alkoxyethylide, which was cleaved into ethylene and alkoxide.[16,17] Addition of ethylene led to the C_2-elongated anion, which was terminated by abstracting proton from the solvent. Oligomerization avoided due to low reactivity of primary anion to ethylene.[6,7,9]

Supporting Information Available: Experimental procedure, ^{1}H and ^{13}C NMR and GC−MS spectra of the products, and calculation of the model anions (13 pages).

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(12) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1983**, *24*, 3165.

(13) Lehmann, R.; Schlosser, M. *Tetrahedron Lett.* **1984**, *25*, 745: Note 14.

(14) Inagaki, S.; Nishizawa, Y.; Sugiura, T.; Ishihara, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 179.

(15) Reaction of methyl ether and cyclohexene with butyllithium afforded norcarane. Hoberg, H. *Liebigs Ann. Chem.* **1962**, *656*, 1.

(16) Olah reported that treatment of Meerwein reagent (trimethyloxonium tetrafluoroborate) with sodium hydride yielded ethyl methyl ether not by intramolecular Stevens rearrangement, but in the course of the intermolecular alkylation. In our system, however, the process involving oxonium ylide formation by carbene and ether should be unlikely. Olah, G. A.; Diggweiler, H.; Felberg, J. D. *J. Org. Chem.* **1984**, *49*, 2112. See also: Rimmelin, P.; Taghavi, H.; Sommer, J. *J. Chem. Soc., Chem. Commun.* **1985**, 250. Rimmelin, P.; Brenner, A.; Fischer, K.; Sommer, J. *J. Chem. Soc., Chem. Commun.* **1986**, 1497. Jackson, J. E.; Bertsch, F. M. *J. Am. Chem. Soc.* **1990**, *112* , 9085.

(17) A reviewer proposed that the ethyl ether should have survived after workup if it was generated *in situ* as the ethylene source. However, treatment of butyl methyl ether with BuLi−*t*-BuOK afforded no butyl ethyl ether, which was confirmed with analysis of the crude reaction mixture by GC−MS.