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Ethylation by Ethyl Ethers in the Presence of Organometallic Bases: Reactions of Hydrocycloalk[*b*]indoles

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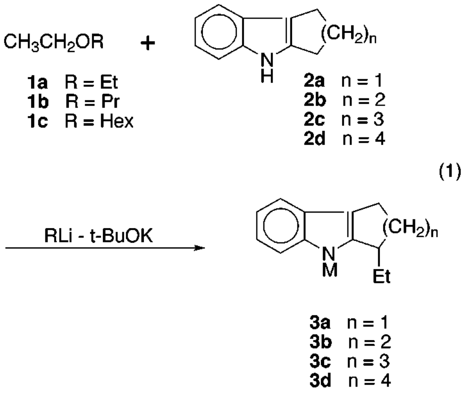
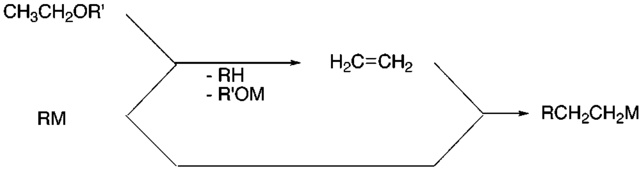
Alkyllithiums are well-known to decompose ethyl ethers to generate ethylene, which inserts into the Li−C bond of the still unreacted alkyllithiums (Scheme 1).[1,2] We found an interesting extension of the reactions while we attempted to optimize the reaction conditions of the functionalization of indoles via the C,N-dianions in diethyl ether.[3] The ethylene generated from ethyl ethers by a complex of organometallic bases (RM) was found to transfer to the carbanions (AM) generated in the same pot, but not to the unreacted organometallics (RM) (Scheme 2). Here we report the ethylation of hydrocycloalk[*b*]indoles by ethyl ethers in the presence of organometallic complex bases (eq 1).



During the optimization of the deprotonation conditions of the indoles in diethyl ether, we obtained the ethylated product when the reaction mixture was not treated with any ethylating reagents. For example, treatment with 1,2,3,4-tetrahydrocarbazole **2b**[4] with BuLi and subsequently with *t*-BuOK[5] at room temperature in diethyl ether **1a** produced the ethyl derivative

Scheme 1



Scheme 2

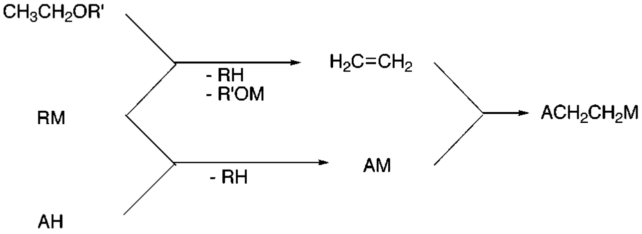


Table 1. Ethylation by Ethyl Ethers

entry	ether	indole	RLi	product	yield/%
1	**2a**	**2a**	BuLi	**3a**	55
2	**1a**	**2b**	BuLi	**3b**	80
3	**1a**	**2b**	MeLi/LiBr	**3b**	45[a]
4	**1a**	**2b**	*s*-BuLi	**3b**	66[a]
5	**1a**	**2b**	*t*-BuLi	**3b**	60[a]
6	**1a**	**2b**	PhLi	**3b**	38[a]
7	**1b**	**2b**	BuLi	**3b**	62
8	**1c**	**2b**	BuLi	**3b**	75
9	**1a**	**2c**	BuLi	**3c**	46
10	**1a**	**2d**	BuLi	**3d**	44[a]

[a] The reaction time was 4 h.

3b.[6] The reaction was regioselective. Further elongation by the sequential insertion of ethylene was not observed. The use of a large excess of the bases improved the yield to 80%.[7] The ethylation similarly occurred in the other ethyl ethers (**1b**, **1c**). A variety of hydrocycloalk[*b*]indoles (**2a**−**d**) were ethylated irrespective to the methylene length of the side chain of the indole ring. The alkyllithiums employed in the ethylation include MeLi/LiBr, *n*-, *s*-, and *t*-BuLi, and PhLi. Each ethylation reaction proceeded in fair to good yields and with high regioselectivity. The results were summarized in Table 1.

Labeling experiments were performed to probe the reaction mechanism. Quenching of the reaction in diethyl ether by deuterium oxide or methanol-OD gave no deuterated products. This result suggests that the β-metalloethyl group of the first insertion product should be transformed into the ethyl group by M−H exchange[8] possibly with the unreacted ethyl ether or *N*-metallo-1,2,3,4-tetrahydrocarbazole (Scheme 3) prior to the quench-

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[2] For review, see: Maercker, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 972.

[3] (a) Inagaki, S.; Nishizawa, Y.; Sugiura, T.; Ishihara, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 179. (b) Naruse, Y.; Ito, Y.; Inagaki, S. *J. Org. Chem.* **1991**, *56*, 2256.

[4] Preparation of starting 2,3-dialkylated indoles: Tietze, L. F.; Eicher, T. *Reaktionen und Synthesen im organisch-chemischen Praktikum*; Georg Thieme Verlag: Stuttgart, 1981. Japanese translation: Takano, S.; Ogasawara, K. Nankodo: Tokyo, 1983; pp 309−310, M-4a.

[5] For the BuLi-*t*-BuOK complex base, see: Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9. Schlosser, M. In *Modern Synthetic Methods Vol. 6*; Scheffold, R., Ed.; Verlag Helvetica Chimica Acta: Basel, 1992; pp 227−272; Schlosser, M. *Organometallics in Synthesis*; John Wiley and Sons: Chichester, 1994; pp 1−166.

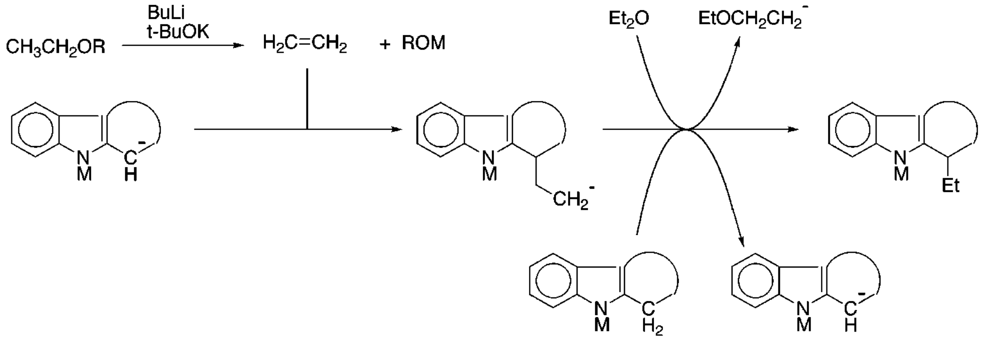
[6] Pausacker, K. H. *J. Chem. Soc.* **1950**, 621. See also: Wakamatsu, T.; Hara, H.; Ban, Y. *Heterocycles* **1977**, *8*, 335.

[7] Physical data for 1-ethyl-1,2,3,4-tetrahydrocarbazole **3b** picrate: mp 141.5−142.8 °C (lit.[6] mp 142 °C); TLC R_f 0.33 (Merck 5715 plate, hexanes−ether 5:1); IR (neat) 3417.8, 3053.7, 2929.3, 1467.5, 1362.0, 1328.9, 1297.9, 1236.1, 1153.3, 1009.3, 741.7 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (br. s, 1H), 7.46 (d, $J = 6.7$ Hz, 1H), 7.26 (d, $J = 7.7$ Hz, 1H), 7.03−7.14 (m, 2H), 2.74−2.85 (m, 1H), 2.65−2.72 (m, 2H), 1.97−2.03 (m, 2H), 1.70−1.89 (m, 2H), 1.48−1.63 (m, 2H), 1.01 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 137.8, 135.7, 127.7, 121.0, 119.0, 117.9, 110.4, 110.2, 35.3, 28.5, 27.4, 21.8, 21.2, 11.5. MS (EI, 70 eV) 199(29), 170(100, $M^+ -$ Et), 168(31).

[8] Maercker, A.; Troesch, J. *J. Organomet. Chem.* **1975,** *102*, C1. Maercker, A.; Passlack, M. *Chem. Ber.* **1982**, *115*, 540. Maercker, A.; Stoetzel, R. *J. Organomet. Chem.* **1983**, *254*, 1.

10.1021/jo9813080 CCC: $18.00

Scheme 3



ing. This is consistent with the single ethylation. The reaction of 1,2,3,4-tetrahydrocarbazole in diethyl ether-d_{10} afforded the product with the deuterated ethyl group. GC−MS and ^{1}H and ^{13}C NMR analyses showed that the introduced ethyl group was a mixture of CD_2CD_2H and CD_2CD_3.[9] The third β-deuterium in CD_2CD_3 and the hydrogen in CD_2CD_2H should be transferred from the ether and the carbazole, respectively.

The mechanism of the reaction is illustrated in Scheme 3. First the C,N-dianions of the indole are generated by a sequential treatment of BuLi−*t*-BuOK in diethyl ether. The deprotonation occurs exclusively at the α-position of the 2-alkyl side chain due to the stability of the cross-conjugated C,N-dianions (six π-electron/four p-orbital systems) relative to the linear-conjugated ones.[3,10] Subsequently, the ethylene generated in situ by β-elimination from diethyl ether inserts itself into the C−M bond of the dianions.[11] The reaction is terminated by the abstraction of a proton from the unreacted diethyl ether of *N*-metallocarbazole. The ethylation occurs at the α-position of the 2-alkyl side chain in a highly regioselective manner. No multiple insertion of ethylene molecules takes place.

Experimental Section

General Methods. Hydrocycloalk[*b*]indoles were prepared by a manner similar to that described in the literature.[4] Diethyl ether was distilled from sodium benzophenone ketyl. The other reagents were commercial products and used as received.

Typical Procedure for the Ethylation: Preparation of 1-Ethyl-1,2,3,4-tetrahydrocarbazole 3b. To a solution of 1,2,3,4-tetrahydrocarbazole **2b** (0.34 g, 2.0 mmol) in diethyl ether (30 mL) was added BuLi (1.6 M in hexane, 15 mL, 22 mmol), followed by *t*-BuOK (2.2 g, 20 mmol) under Ar. The mixture turned bright orange. After being stirred for 5 h at rt, the resulting suspension was poured into saturated aqueous $NaHCO_3$ and extracted with ether. The combined extracts were washed with water and dried over Na_2SO_4. Concentration in vacuo and purification by column chromatography on silica gel (Merck 9385, eluent: hexane−ethyl acetate 6:1) afforded **3b** (0.32 g, 1.6 mmol, 80%).

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Supporting Information Available: Characterization data for **3a**, **3c**, and **3d** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(9) Assignment of the ethyl group was performed as follows: The product with diethyl ether-d_{10} showed peaks at *m*/*e* 203 (21, C_2D_4H) and 204 (20, C_2D_5) for M^+ (relative intensities (%) to the mother peak of *m*/*e* 170), whereas only the peak *m*/*e* 204 for the M^+ was observed with the authentic sample with CD_2CD_3. ^{13}C NMR spectra of the crude product showed an overlapping multiplet at δ 26.4 ppm and a quintet large in intensity at δ 10.8, while the authentic sample possesses the weak signals of a quintet at δ 26.4 and a heptaplet at δ 10.8 in the aliphatic region. Thus, we concluded that the peak at higher field should be CD_2H with NOE enlargement by proton saturation. No significant change was observed in the aromatic region.

(10) Inagaki, S.; Hirabayashi, Y. *Chem. Lett.* **1982**, 709. Inagaki, S.; Kawata, H.; Hirabayashi, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3724. Inagaki, S.; Iwase, K.; Goto, N. *J. Org. Chem.* **1986**, *51*, 362.

(11) To avoid ethylation, the reaction mixture should be cooled immediately after generation of the dianion.