

1-(2-OXAZOLINYLY) INDOLES¹

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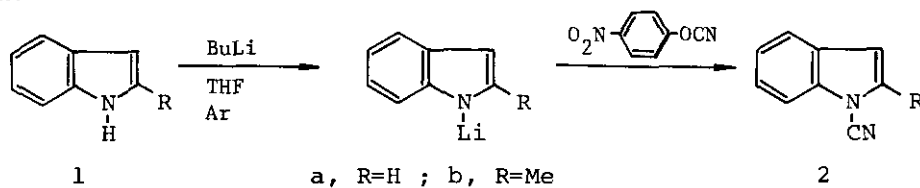
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Abstract — Utilization of 1-(2-oxazolinyl)indoles,
prepared from 1-cyano compounds, to the synthesis of
2-substituted indoles was investigated.

While the ortho-lithiation of 2-oxazolinylaromatics has been well documented as an elegant methodology in synthetic chemistry,² the reaction has never been explored with indole derivatives. Then, it would be expected that regioselective lithiation of an indole having reactive group(s) could be realized efficiently with 1-(2-oxazolinyl)indoles under compatible reaction conditions. Very recently, superiority of 1-methoxy group in indole, among other directing groups, for selective lithiation and consequent functionalization of 2-position of indole ring has been reported by Somei *et al.*³ We now wish to describe the preliminary studies on the synthesis and reactions of 1-(2-oxazolinyl)indoles, prepared from hitherto unknown compounds, 1-cyanoindoles.

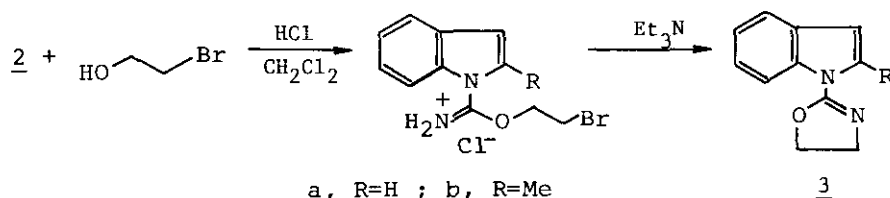
Cyanation of 1-lithioindole, obtained from indole (1a) and *n*-BuLi (1.1 equiv.) in tetrahydrofuran (THF) at -80°C for 30 min *in situ*, with *p*-nitrophenylcyanate (1.2 equiv.)⁴ as a cyanating agent at -70°C for 3 h under argon afforded exclusively 1-cyanoindole (2a) in 70 % yield,⁵ after purification of the product by flash chromatography.⁶ Under similar conditions, 1b produced 2b in the yield of 50 %.⁵ (Scheme 1)

Scheme 1



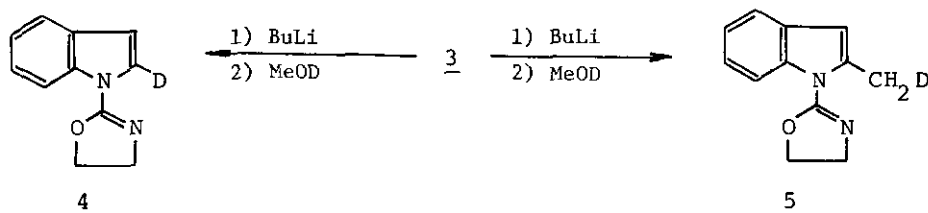
A solution of 2 and ethylene bromohydrin (1.5 equiv.) in dichloromethane (CH_2Cl_2) was saturated with dry hydrogen chloride under ice-cooling, then refluxed for 2 h (3a) or stood at 5°C for 48 h (3b). After concentration of the reaction mixture *in vacuo*, the residue was redissolved in CH_2Cl_2 and treated with excess triethylamine at -70°C for 1 h (3a) or 3 h (3b). After usual work-up, 3 was obtained in 81.5 % (3a) and 69.5 % (3b) yield, respectively.⁷ (Scheme 2)

Scheme 2



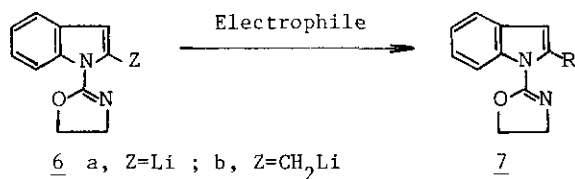
To estimate the directing effect of 2-oxazolinyl group in 3 on lithiation, 3 was reacted with BuLi at -80°C for 30 min under argon, then deuterized by the addition of MeOD. Deuterioindoles (4,5) thus formed were characterized by ^1H -nmr and high resolution mass (Hrms) spectra, after isolation by flash chromatography in the yields of 90 % (4) and 83 % (5), respectively.⁸ (Scheme 3)

Scheme 3



These results revealed that 2-oxazolinyll group had a remarkable effect on regioselective lithiation of 3 under fairly mild conditions as expected. Next, the reaction of lithioindole (6) with some electrophiles was briefly investigated, using the THF solution of 6 prepared by the procedure described above. Results are summarized in Table I.

Table I. Reaction of lithioindole with electrophiles



Li-indole	electrophile	React. Condition		R	Product (<u>7</u>) ⁹	
		temp.(°C)	time(h)		mp(°C)	Yield(%)
<u>6a</u>	MeI	-80	20	Me	51-2	31
<u>6a</u>	PhCH ₂ Br	-80	20	PhCH ₂	oil	28
<u>6a</u>	CH ₂ =CHCH ₂ Br	-80	20	CH ₂ =CHCH ₂	oil	20(80) ^{a)}
<u>6a</u>	1)Me ₂ NCHO	-80	0.5			
	2)NaBH ₄	-50	1.5	CH ₂ OH	101-1.5	37
<u>6b</u>	PhCH ₂ Br	-80	20	PhCH ₂ CH ₂	95-6	69
<u>6b</u>	PhCOOMe	-80	4			
		r.t.	20	PhCOCH ₂	145-6	14
<u>6b</u>	"	-40-r.t.	20	"	"	45 ^{b)}
<u>6b</u>	1)Me ₂ NCHO	-80--50	0.5			
	2)NaBH ₄	-50	1.5	CH ₂ CH ₂ OH	oil	44

a) CuBr·SMe₂(1.1 equiv.)¹⁰ was added to the solution of 6a at -80°C.

b) *tert*-BuOK(1.6 equiv.) was added to the solution of 6b at -40°C.

Finally, 2-oxazolinyll group in 3 was efficiently removed upon heating with 5 % potassium hydroxide-ethanol (70°C, 20 h for 3a ; 80°C, 44 h for 3b) to

afford parent indole in the yields of 83 % (1a) and 30 % (1b), respectively. Further application of the present procedure to the synthesis of 2-substituted indoles are now in progress.

REFERENCES AND NOTES

1. A part of this work has been presented at The 110th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, August, 1990.
2. B. E. Maryanoff, "The Chemistry of Heterocyclic Compounds", Vol. 45, ed. by A. Weissburger and E. C. Taylor, John Wiley & Sons, Inc., New York, 1986, pp.963-1017 ; A. I. Meyers and E. D. Mihelich, *Angew. Chem., Int. Ed. Engl.*, 1976, 15 270.
3. T. Kawasaki, A. Kodama, T. Nishida, K. Shimizu, and M. Somei, *Heterocycles*, 1991, 32, 221, and references cited therein.
4. E. Vowinkel and H. -J. Baese, *Chem. Ber.*, 1974, 107, 1213.
5. 2a: bp 69-70°C (0.26 Torr, bath temp.). Ir (neat) cm^{-1} : 2250 (CN). $^1\text{H-Nmr}$ (CDCl_3) δ : 6.54 (1H, d, $J=3.5$), 7.06 (1H, d, $J=3.5$), 7.22 (1H, t, $J=7.3$), 7.24 (1H, t, $J=7.3$), 7.42 (1H, d, $J=7.3$), 7.51 (1H, d, $J=7.3$). Ms m/z : 142 (M^+). Anal. Calcd for $\text{C}_9\text{H}_6\text{N}_2$: C, 76.04; H, 4.25; N, 19.71. Found: C, 76.16; H, 4.19; N, 19.55.
2b: mp 71.5-72.5°C (from $i\text{-Pr}_2\text{O}$). Ir (Nujol) cm^{-1} : 2236 (CN). $^1\text{H-Nmr}$ δ : 2.49 (3H, s), 6.32 (1H, s), 7.22-7.29 (2H, m), 7.46-7.48 (2H, m). Ms m/z : 156 (M^+). Anal. calcd for $\text{C}_{10}\text{H}_8\text{N}_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 77.09; H, 5.10; N, 17.91.
6. Flash chromatography was performed on Wakoh-gel C-300 and hexane : ethyl acetate = 10 : 1 as an eluant.
7. Yields were based on 2 consumed. 3a: bp 107-108°C (0.1 Torr, bath temp.). Ir (neat) cm^{-1} : 1677. $^1\text{H-Nmr}$ (CDCl_3) δ : 4.06 (2H, t, $J=9$), 4.49 (2H, t, $J=9$), 6.58 (1H, d, $J=3.4$), 7.21 (1H, t, $J=8$), 7.31 (1H, t, $J=8$), 7.54-7.58 (2H, m), 8.27 (1H, d, $J=8$). Ms m/z : 186 (M^+). Anal.

- Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.06; H, 5.43; N, 14.89. 3b: mp 51-52°C (from $i\text{-Pr}_2O$). Ir (Nujol) cm^{-1} : 1665. $^1H\text{-Nmr}$ ($CDCl_3$) δ : 2.29 (3H, d, $J=1$), 4.04 (2H, t, $J=9$), 4.46 (2H, t, $J=9$), 6.30 (1H, s), 7.14-7.22 (2H, m), 7.43 (1H, d, $J=8$), 8.13 (1H, d, $J=8$). Ms m/z : 200 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.17; H, 6.13; N, 14.19.
8. 4: Ir (neat) cm^{-1} : 1674. $^1H\text{-Nmr}$ ($CDCl_3$) δ : 3.98-4.20 (2H, dt, $J=2, 9$), 4.45-4.67 (2H, dt, $J=2, 9$), 6.59 (1H, s), 7.19-7.32 (2H, m), 7.53-7.63 (1H, m), 8.21-8.32 (1H, m). Hrms Calcd for $C_{11}H_9N_2OD$: 187.08742. Found: 187.08554. 5: Ir (Nujol) cm^{-1} : 1665. $^1H\text{-Nmr}$ ($CDCl_3$) δ : 2.58 (2H, d, $J=1$), 3.95-4.17 (2H, dt, $J=2, 9$), 4.42-4.64 (2H, dt, $J=2, 9$), 6.32 (1H, d, $J=1$), 7.11-7.23 (2H, m), 7.40-7.49 (1H, m), 8.07-8.18 (1H, m).
9. Satisfactory elemental analyses and/or Hrms data were obtained with all new compounds. Structures were also characterized by spectral data (ir, $^1H\text{-nmr}$).
10. C. R. Ellefson, J. Org. Chem., 1979, 44, 1533.

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