1-(2-OXAZOLINYL)INDOLES[1]

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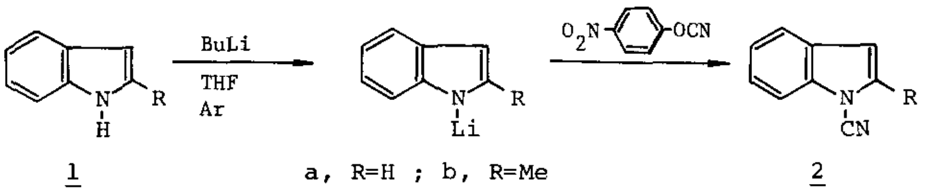
Abstract —— Utilization of 1-(2-oxazolinyl)indoles, prepared from 1-cyano compounds, to the synthesis of 2-substituted indoles was investigated.

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.

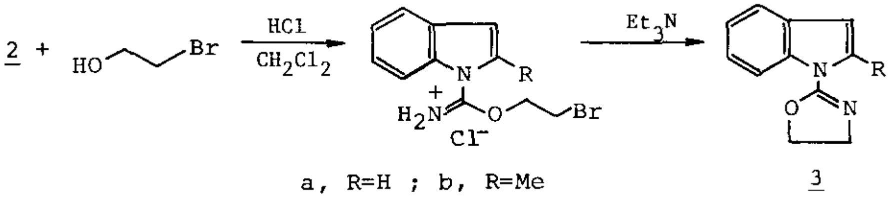
Cyanation of 1-lithioindole, obtained from indole (1a) and n-BuLi (1.1 equiv.) in tetrahydrofuran (THF) at -80°C for 30 min *in situ*, with p-nitrophenylcyanate (1.2 equiv.)[4] as a cyanating agent at -70°C for 3 h under argon afforded exclusively 1-cyanoindole (2a) in 70 % yield,[5] after purification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

Scheme 1



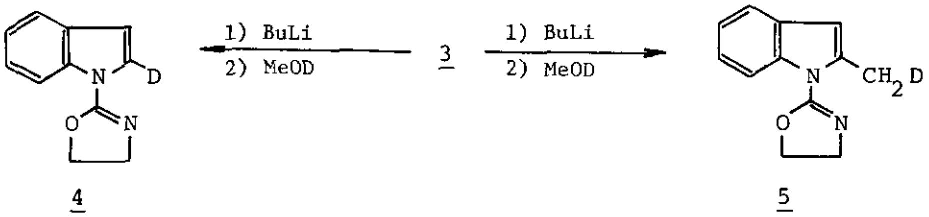
A solution of 2 and ethylene bromohydrin (1.5 equiv.) in dichloromethane (CH_2Cl_2) was satuarated with dry hydrogen chloride under ice-cooling, then refluxed for 2 h (3a) or stood at 5°C for 48 h (3b). After concentration of the reaction mixture in vacuo, the residue was redissolved in CH_2Cl_2 and 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



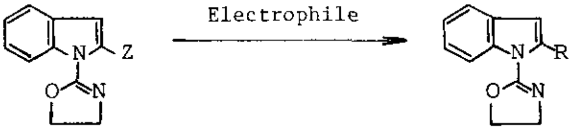
To estimate the directing effect of 2-oxazolinyl group in 3 on lithiation, 3 was reacted with BuLi at -80°C for 30 min under argon, then deuterized by the addition of MeOD. Deuterioindoles (4,5) thus formed were characterized by ^{1}H-nmr and high resolution mass (Hrms) spectra, after isolation by flash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

Scheme 3



These results revealed that 2-oxazolinyl 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



6 a, Z=Li ; b, $Z=CH_2Li$ 7

		React. Condition		Product $(7)^9$		
Li-indole	electrophile	temp.(°C)	time(h)	R	mp(°C)	Yield(%)
6a	MeI	-80	20	Me	51-2	31
6a	$PhCH_2Br$	-80	20	$PhCH_2$	oil	28
6a	$CH_2=CHCH_2Br$	-80	20	$CH_2=CHCH_2$	oil	20(80)[a)]
6a	1)Me_2NCHO	-80	0.5			
	2)$NaBH_4$	-50	1.5	CH_2OH	101-1.5	37
6b	$PhCH_2Br$	-80	20	$PhCH_2CH_2$	95-6	69
6b	PhCOOMe	-80	4			
		r.t.	20	$PhCOCH_2$	145-6	14
6b	"	-40-r.t.	20	"	"	45[b)]
6b	1)Me_2NCHO	-80--50	0.5			
	2)$NaBH_4$	-50	1.5	CH_2CH_2OH	oil	44

a) $CuBr \cdot SMe_2$(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-oxazolinyl 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.
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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}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 $C_9H_6N_2$: 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 $i\text{-}Pr_2O$). Ir (Nujol) cm^{-1}: 2236 (CN). ^{1}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 $C_{10}H_8N_2$: 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}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. <u>3b</u>: mp 51-52°C (from i-Pr_2O). Ir (Nujol) cm^{-1}: 1665. ^{1}H-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. <u>4</u>: Ir (neat) cm^{-1}: 1674. ^{1}H-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. <u>5</u>: Ir (Nujol) cm^{-1}: 1665. ^{1}H-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, ^{1}H-nmr).

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