

Regioselectivity Control in Alkylation Reactions of Indolyl Ambident Anion

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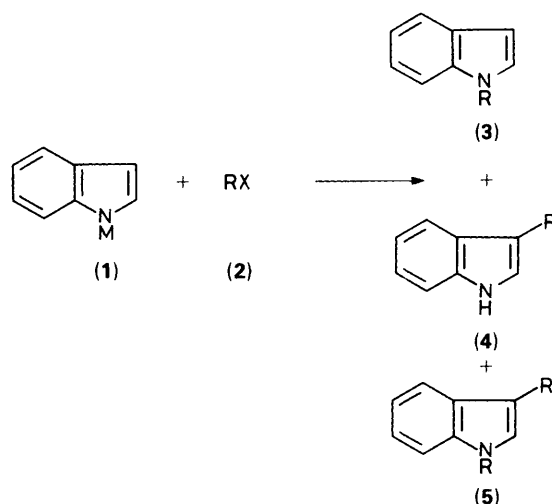
The regioselectivity of *N*- and *C*-3(β)-alkylations of indolylmetal salts was studied under various conditions. The effect of counter metal ion is crucial in determining the regioselectivity. In tetrahydrofuran, exclusive *N*-alkylation occurred with the potassium salt, but the extent of *C*-3-alkylation increased with the sodium and lithium salts and became predominant with the magnesium bromide salt. However, *N*-alkylation was favoured generally in more polar solvents and for alkyl toluene-*p*-sulphonates it was favoured even with magnesium bromide salts. The reactivity and regioselectivity of the alkylations were correlated with the calculated electron density of the indolyl anion and with ^{13}C n.m.r. chemical shifts of the metal salts.

The reaction site of ambident anions is influenced delicately by many factors such as the structure of the anion itself, the metal counter-ion, the alkylating reagent, and the reaction conditions: the homogeneity of the system, solvent, concentration of reagents, and temperature *etc.*¹⁻¹⁰ Regioselective *N*- or *C*-alkylation of the important nitrogen heterocycle derivatives pyrrolylmetal and indolylsodium salts is desirable. However, the reactions of these metal salts with allyl and alkyl halides generally afford *N*- and *C*-alkylation products nonregioselectively.^{11,12} In order to clarify the factors governing regiocontrol and to find regioselective conditions, we have investigated the alkylation of the indolylmetal salts (1) under various conditions using several metal counter-ions, nonpolar and polar solvents, and various alkylating agents. These results are discussed on the basis of ^{13}C n.m.r. chemical shift values of the salts and the calculated electron density in comparison with those for pyrrolylmetal salts (9).¹¹

Results

The results of the reactions of indolylmetal salts (1) with butyl iodide and allyl bromide in tetrahydrofuran (THF) are summarized in Scheme 1 and Table 1. The regioselectivity of the *N*- or *C*-alkylation depended markedly upon the metal counter-ion. In the case of the potassium salt, the *N*-alkylation product (3) was almost exclusively formed in high yields (entries 1 and 6). Sodium and lithium counter-ions resulted in a mixture of *N*- and *C*-alkylation. Magnesium bromide as the counter-ion gave predominantly the *C*-alkylation product (98%) with the more reactive allyl bromide. Similarly, on addition of AlCl_3 to the system, the *C*-alkylation product (4) (98%) with butyl toluene-*p*-sulphonate (tosylate) was formed, although in low yield (entry 5). Thus the reactivity and regioselectivity of the indole derivatives (1) are similar to those of the pyrrolyl system (9).¹¹ In the reactions of the indolylsodium salt (1b) with various alkyl iodides, the proportion of *C*-alkylation product increased slightly in order $\text{Me} (15\%) < \text{Et} (24\%) < \text{Pr}^n (30\%) \sim \text{Bu}^n (30\%)$. The *C*-alkylation products became the major products with allyl (55%) and benzyl (59%) iodides.

When the leaving group of the substituted butyl derivative



Scheme 1. For (1): a, M = K; b, M = Na; c, M = Li; d, M = MgBr; e, M = Al.

varied from TsO^- to Br^- and I^- , the *C*-alkylation products (4) and (5) increased considerably [$\text{TsO}^- (4\%) < \text{Br}^- (6\%) < \text{I}^- (30\%)$], in accordance with the softness of these leaving groups. A similar tendency was observed for (1c) with lithium as the counter-ion.

The addition of polar solvents, *e.g.* dimethylformamide (DMF), dimethyl sulphoxide (DMSO), and hexamethylphosphoric triamide (HMPA) (30% with respect to THF) in the reaction of (1b) with butyl iodide resulted in exclusive *N*-alkylation, similar to the results reported for (9) by Hobbs *et al.*¹¹ *N*-Alkylation was favoured also by lowering the concentration of (1) and the reaction temperature. However, MgBr as counter-ion gave the *C*-alkylation product (4) almost exclusively even in the presence of DMF (95%).

The electron densities at the α - and β -sites of the anions of (1) and (9) were calculated by the CNDO/2 method as shown in Figure 1. ^{13}C n.m.r. chemical shifts of the salts (1) and (9) are summarized in Table 2.

Table 1. Effect of metal ion on reactions of indolylmetal salts (1) with RX^a

Entry	RX	Metal	Product ratio			% Yield ^b
			(3)	(4)	(5)	
1	Bu ⁿ I	K	97	1	2	84
2	Bu ⁿ I	Na	70	20	10	87
3	Bu ⁿ I	Li	25	60	15	83
4	Bu ⁿ I	MgBr				0
5 ^d	Bu ⁿ OTs	Al ^c	2	98	0	10
6	CH ₂ =CHCH ₂ Br	K	93	1	6	85
7	CH ₂ =CHCH ₂ Br	Na	65	20	15	87
8	CH ₂ =CHCH ₂ Br	Li	34	55	11	67
9	CH ₂ =CHCH ₂ Br	Mg	2	90	8	27

^a In THF at 20 °C for 16 h; [C₈H₆NM]₀ = 0.1 mol/100 ml [C₈H₆NM]:[RX] = 1:1 molar ratio. ^b Total isolated yield. ^c In this run, aluminium chloride (0.03 mol) was added to reagent (1d) (M = MgBr). ^d To a mixture of butyl tosylate (Ts; 0.10 mol) and CuI (20 mol % to butyl tosylate) in THF (50 ml) cooled to -30 °C, (1e) was added.

Table 2. ¹³C N.m.r. chemical shifts (δ) of indolylmetal salts (1) and N-pyrrolylmetal salts (9) in THF^a (atom numbering as in Figure 1)

M	Salt (1)		Salt (9)	
	C-2	C-3	C-2	C-3
H	123.7	100.9	118.1	108.2
K	130.7	97.4	126.9 ^b	104.4 ^b
Na	131.2	98.3	127.2	105.0
Mg	131.0	99.5	125.0	105.9

^a N-Indolyl- (1) or N-pyrrolylmetal (9) reagent, 0.1 mol in 60 ml.

^b Reagent (9), 0.1 mol in THF (60 ml) + DMF (30 ml).

Table 3. The product ratios in remetallation-alkylations with BuⁿI

	Metal	Product ratio			% Yield ^b
		(3)	(4)	(5)	
Before ^c	Na	70	20	10	87
After	Li	68	10	22	72
Before ^d	Li	25	60	15	83
After	Na	24	35	41	74

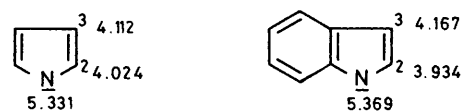
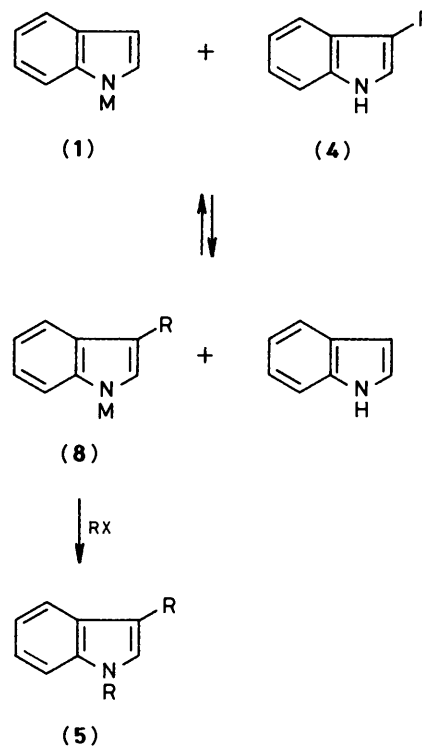
^a In THF at 20 °C for 16 h; [C₈H₆M]₀ = 0.1 mol/100 ml; [C₈H₆M]:[RI] = 1:1 molar ratio. ^b Total isolated yield. ^c See entry 2, Table 1. ^d See entry 3, Table 1.

Discussion

In order to obtain further information about the reaction pathway, a mixture of the products (3), (4), and (5) obtained from the reaction of (1b) and (1c) with butyl iodide was remetallated, and again treated with butyl iodide. The changes in the product ratios of (3), (4), and (5) before and after the remetallation-alkylation are shown in Table 3.

Remetallation by lithium hydride or sodium hydride followed by realkylation increased the amount of (5) at the expense of (4). No change was observed in the amount of (3). The results indicate that the dialkylated product (5) is formed *via* the C-monoalkylindolylmetal salt (8), formed by the metallation of the NH of (4), and that (5) is not produced directly from the N-alkyl product (3). As shown in Schemes 1 and 2, the C-alkylated product (4) is directly produced upon alkylation of (1). On the other hand, only (3) is initially formed as the N-alkylation product on N-alkylation of (1).

In the reaction of the pyrrolylmetal salt (9) with alkyl iodides,

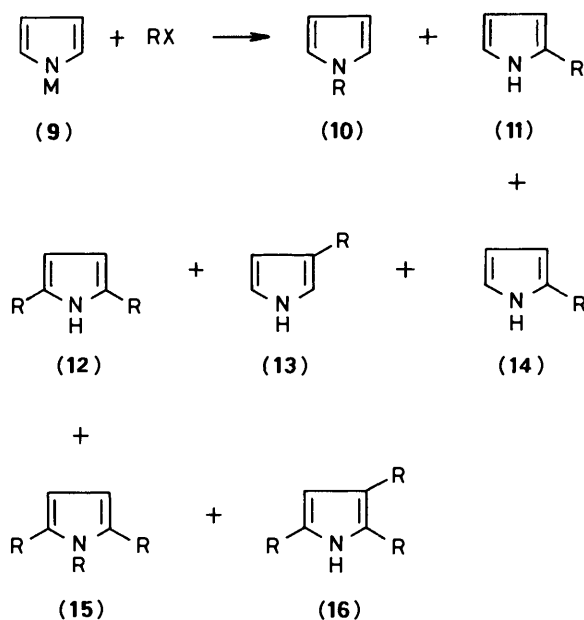
**Figure 1.** Electron density of pyrrole and indole anion by the CNDO/2 method.**Scheme 2.**

the N-alkylation product (10), and the C-alkylation products (11) and (12) were obtained as major products together with trace amounts of (13), (14), (15), and (16) as shown in Scheme 3. Among these products, only (10) can be regarded as the initial N-alkylation product.

The ratios of N-monoalkylation [*i.e.*, the amount of (3) or (10)] to total C-alkylation (other products) in the reaction of (1) and (9) with alkyl halides or alkyl tosylates revealed that C-alkylation occurs more readily in the reaction of (9) than (1) as shown in Table 4. The extent of C-alkylation for (9) may reflect the higher electron density at the carbon atoms in (9) than (1). The ratios of the total electron density at carbon and nitrogen of (1) and (9) were calculated to be 0.274 and 0.822 respectively, the ratio being much higher for (9) than for (1). The greater extent of C-alkylation of (9) than of (1) can be explained by this higher electron density ratio.

A closer look at the regioselectivity in the C-alkylation indicates that the alkylation of (9) occurs mainly on the α-site, but that of (1) occurs mainly on the β-site. The calculated electron density for both (1) and (9) is higher at the β-site than at the α-site, but the difference between the α- and the β-sites is higher in (1) than (9). For the carbon atoms in (1) the electron is localized more at the β-site than the α-site owing to the stabilizing effects of the benzene ring. This may lead to the predominant C-3 (β)-alkylation of (1), whereas the C-2 (α)-alkylation of (9) occurs more readily but not selectively.

The ¹³C n.m.r. chemical shifts for the α- and β-carbon atoms of (9) and (1) are shown in Table 2. The β-C resonance of (9) is shifted to higher field by 0.9–1.5 p.p.m. on changing the counter-ion from MgBr to Na or K. In contrast, the chemical



Scheme 3.

occur at the position of the highest electron density, namely at nitrogen.

The addition of a polar solvent or a lower reaction temperature favours *N*-alkylation because of dissociation of the nitrogen-metal bond by the stronger solvation of the counter-ion. The foregoing results indicate that the alkylation reactions can be understood in terms of an S_N2 reaction of the $C\cdots C\cdots N$ ambident anion with alkyl halides or tosylates. Both (1) and (9) seem to react by a similar fundamental mechanism.

It would be interesting to know the ratio of α - to β -alkylation in the pyrrolylmetal salts to determine what influence the metal counter-ion has. However, the amounts of β -alkylation product are too small for a detailed discussion.

In summary, the factors controlling the regioselectivity in the alkylation of (1) and (9), having K, Na, Li, or MgBr as the counter-ion, with alkyl halides or tosylates can be summarized as follows.

(i) The counter-ions play an important role in determining the regioselectivity and reactivity of the $C\cdots C\cdots N$ ambident anion of (1) or (9) with alkyl halides or tosylates.

(ii) The *C*-alkylation products were favoured with the more covalently bonded organometallic compounds, with increased softness of alkyl and leaving groups,¹³ with the use of less basic solvents, and with lower reaction temperatures.

(iii) The regioselectivity of (1) and (9) at the α - and the β -site can be correlated with the calculated electron density ratio at

Table 4. Comparison of *N*- and *C*-alkylations in the reaction of indolylmetal salts (1) and pyrrolylmetal salts (9) with RX or ROTs^a

RX	Metal	<i>T</i> /°C	Indole		Pyrrole	
			% <i>N</i> -R (3)	% <i>C</i> -R (4) + (5)	% <i>N</i> -R (10)	% <i>C</i> -R (11)–(16)
Bu ⁿ I	K	20	97	3	100	0
Bu ⁿ I	Na	20	70	30	50	50
Bu ⁿ I	Li	20	25	75	4	96
CH ₂ =CHCH ₂ Br	K	20	93	7	—	—
CH ₂ =CHCH ₂ Br	Na	20	65	35	17	83
CH ₂ =CHCH ₂ Br	Li	20	34	66	Trace	99
CH ₂ =CHCH ₂ Br	Mg	20	2	98	0	100
Bu ⁿ OTs	K	–30 to 20	100	0	100	0
Bu ⁿ OTs	Na	–30 to 20	96	4	80	20
Bu ⁿ OTs	Li	–30 to 20	74	26	17	83
Bu ⁿ OTs	Mg	–30 to 20	—	—	Trace	99

^a In THF at 20 °C for 16 h; [C₄H₄NM]₀ = 0.1 mol/100 ml, [C₈H₆NM]₀ = 0.1 mol/100 ml, [C₄H₄NM] or [C₈H₆NM]:[RX] or [ROTs] = 1:1 molar ratio.

shift for α -C of (9) having MgBr as the counter-ion appeared 2.2 p.p.m. to higher field than that with Na as the counter-ion. These results suggest that the interaction between the N anion of (9) and the counter-ion is tight, in the order K < Na < MgBr, and hence, the electron density at the α -C of the pyrrole ring increases in this order.

The chemical shift for the α -C varies little with change in counter-ion for (1), reflecting the calculated lower electron density at the α -position. The β -C resonance, however, is shifted to higher field by 2.1 and 1.2 p.p.m. for K and Na, respectively, with respect to MgBr as counter-ion, similar to results for (9). These changes in chemical shifts at the β -carbon atom are considered to reflect the change in free ionic nature of the metal salts. Because the total electron density on the anion was highest with potassium as counter-ion, the chemical shifts of the β -carbon atoms appeared at the highest field. In the alkylation of the free ionic salts, the reaction is considered to

carbon and nitrogen, and the ¹³C n.m.r. chemical shifts of the salts. Thus, *N*- and *C*-alkylation of (1) and (9) can be controlled by selecting appropriate conditions.

Experimental

¹H and ¹³C N.m.r. spectra were recorded on Jeol spectrometers: model MH-100 for ¹H in CCl₄ and model FX 90-A for ¹³C in CDCl₃, and chemical shifts (δ) are given in p.p.m. from tetramethylsilane as an internal standard. Products were analysed quantitatively with a Yanagimoto gas chromatograph model G-2800 using 4 ft packed columns of 25% PEG 20M on Chromosorb W or 5% SE 30 on Chromosorb W, with comparison with authentic samples.^{11–14} Indolylmetal salts (1) and pyrrolylmetal salts (9) were prepared by the reported procedures.^{11–12}

Reaction of the Salts (1) or (9) with Alkyl Halides RX.—To a stirred mixture of the alkyl iodide (0.1 mol) and THF (50 ml) the salt (1) or (9) (0.1 mol) in THF (100 ml) was added dropwise under nitrogen at room temperature. An exothermic reaction occurred. After completion of the addition, the mixture was stirred for 16 h at room temperature. The organic layer was separated after hydrolysis with 3M NH₄Cl (100 ml), and the aqueous layer was extracted with diethyl ether (2 × 100 ml). The combined organic layers were washed with saturated aqueous NaCl (30 ml) and then water, then dried (Na₂SO₄), and distilled. The products were identified by comparing their i.r., mass, and n.m.r. spectra with reported data.^{11–14}

Reaction of the Salts (1) or (9) with Alkyl Tosylates.—The reactions were carried out at –30 °C. After completion of the addition, stirring was continued for 16 h at 0–20 °C.

Remetallation–Alkylation.—The NH group of the product (4) prepared by the reaction of (1b) with butyl iodide was lithiated with LiH and then treated with butyl iodide. To LiH (0.55 g, 0.07 mol) and THF (50 ml), the mixture of products (3), (4), and (5) (entry 2, Table 1) (17.3 g, 0.10 mol) in THF (50 ml) was added dropwise with stirring under nitrogen. After completion of the addition, the system was heated under reflux for about 2 h in order to complete the metallation. Butyl iodide (12.8 g, 0.07 mol) in THF (30 ml) was slowly added to the remetallated system. After completion of the addition, stirring was continued for a further 16 h at room temperature. The products were isolated by work-up similar to that used for alkyl iodides. The remetallation with NaH was carried out similarly.

CNDO Calculations.—CNDO calculations were carried out on a FACOM M-200 computer at Nagoya University Computation Center. The geometries of the indolyl and pyrrolyl anions required for the CNDO/2 calculation¹⁷ were estimated from values based on microwave spectroscopy (for

pyrrole)¹⁸ and X-ray diffraction studies (for indole)¹⁹ in conjunction with standard bond length and angles.

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