

Functionalization of the Methyl Group of 2-Methylindole by Direct Generation of a C,N-Dianion

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The first method for directly generating C,N-dianion from an alkyl-substituted π -excessive *N*-heterocyclic compound (2-methylindole) has been developed. It involves treatment with 3 equiv. of BuLi and 2 equiv. of Bu^tOK in a particular sequence and results in the functionalization of the 2-methyl group of the indole in a regiospecific manner.

Although it is well known that methyl groups on π -deficient *N*-heteroaromatics (pyridine and quinoline) can be metallated,¹ methods for methyl metallation of π -excessive heteroaromatics (pyrrole and indole) are much less advanced.

For *N*-substituted indoles, only one literature reference² suggested that the methyl group on C-2 was metallated, though the intermediate reacted with an electrophile not only at the C(2)-methyl but also the C(3)-ring carbon. For *N*-unsubstituted indole rings, protons were shown³ to be removed from the N-H and the alkyl side chain with the assistance of intramolecular chelation.⁴ More recently, Katritzky and Akutagawa⁵ reported a method for introducing a functional group into the 2-alkyl side chain by using carbon dioxide. The key intermediates are not C,N-dianions but C,O-dianions.

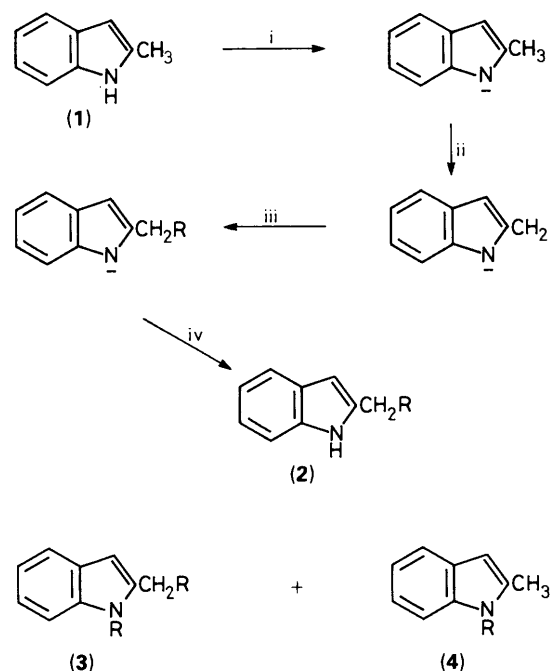
We now report direct generation of the C,N-dianion from 2-methylindole (1) and regiospecific functionalization at the methyl group. Our strategy was to find a base capable of abstracting a methyl proton from *N*-metallated (1), and the conditions necessary for regiospecific reactions to occur at the methyl carbon of the resulting C,N-dianions.

We examined various procedures for converting (1) to 2-ethylindole (2; R = CH₃) via a dianion intermediate. The best procedure was found to be the following. At ambient temperature C,N-dianion intermediate was generated by adding 3 equiv. of BuLi and then 2 equiv. of Bu^tOK in ether solution. After cooling at -70 °C, 2 equiv. of MeI was added to the dianion intermediate. 2-Ethylindole was obtained as the sole product (see Table, entry 1) in 77% yield [this compares favourably with the Katritzky-Akutagawa method⁵ (52%)]. Reversing the sequence of base treatments, under the same conditions, lowered the conversion (entry 2). Treatment of (1) firstly with 3 equiv. of Bu^tOK and then with 2 equiv. of BuLi resulted in an increase in the amount of the starting material recovered. Treatment with both bases simultaneously gave a similar result (entry 3).

The regiospecificity of the reaction is dependent on temperature. The C,N-dianions reacted exclusively at the carbanion centre with MeI at low temperature (-70 °C). At higher temperature considerable amounts of *N*-methylated by-products appeared (entry 4).

Electrophiles with a carbonyl group also gave 2-substituted indoles in good yields (entries 8 and 9). This reaction is regiospecific even at ambient temperature.

In the best procedure one of 3 equiv. of BuLi may be used for the *N*-metallation. The remaining BuLi is considered to combine with 2 equiv. of Bu^tOK to form a powerful deprotonating base complex (Schlosser base),⁶ the actual reactive species of which is unknown.⁷ The yield is dependent on the molar ratio (entry 5). The yield of (2; R = CH₃) was lowered by using 2 equiv. of BuLi and 1 equiv. of Bu^tOK. This suggests that the second-step deprotonation of the methyl group may



Scheme. Reagents and conditions: i, 3 equiv. BuLi, room temperature (r.t.); ii, 2 equiv. Bu^tOK, r.t., 0.5 h; iii, electrophile, -70 °C, 2 h; iv, H₂O, -70 °C.

require at least 2 equiv. of [BuLi/Bu^tOK] or 1 equiv. of [2BuLi/2Bu^tOK], in accordance with the results⁸ observed for the methyl metallation of anthracene derivatives by LDA/Bu^tOK base. The failure of the reversed sequence of the base treatments (entry 2) suggests that effective methyl metallation requires formation of *N*-Li rather than *N*-K. However, a combination of LDA and Bu^tOK did not give (2; R = CH₃) (entry 6). The failure of the reversed sequence of base treatments also suggests that Bu^tOH generated in the first step might quench BuLi preventing formation of sufficient [BuLi/Bu^tOK] or [2BuLi/2Bu^tOK]. We employed one more equiv. of BuLi (entry 7) in order to transform Bu^tOH into BuOLi. However, the yield was still low. Unfortunately, the properties of the active base complex still remain open to question.

The present method is the first to directly metallate the methyl group on π -excessive heteroaromatics or to generate the C,N-dianions from (1). The success resulted from particular sequence of treatments with two different bases. The C,N-dianions were found to be useful intermediates for regiospecific functionalization of methyl group resulting in higher yields than previous methods.^{5,9}

Table. Procedure and conditions for generating dianion intermediate and yield of indoles.

Entry	Base treatment ^a		Electrophile	Temp. (°C) ^b	R	Yield (%) ^c			
	1st.	2nd.				(2)	(3)	(4)	(1)
1	3BuLi	2Bu ^t OK	MeI	-70	Me	77(52) ^f	0	0	23
2	3Bu ^t OK	2BuLi	MeI	-70	Me	11	0	0	46
3	3BuLi/2Bu ^t OK		MeI	-70	Me	31	0	0	18
4	3BuLi	2Bu ^t OK	MeI	r.t.	Me	28	27	9	10
5	2BuLi	Bu ^t OK	MeI	-70	Me	21	0	0	47
6	3 LDA	2Bu ^t OK	MeI	-70	Me	0	0	0	70
7	3Bu ^t OK	3BuLi	MeI	-70	Me	16	0	0	45
8	3BuLi	2Bu ^t OK	Ph ₂ CO	r.t. ^d	Ph ₂ COH	78(67) ^f	0	0	—
9	3BuLi	2Bu ^t OK	Bu ^t NCO	r.t. ^e	Bu ^t NHCO	67(61) ^f	0	0	—

^a At ambient temperature for 30 min. ^b The temperature at which the dianion was allowed to react with electrophile for 2 h. ^c Isolated on t.l.c.

^d Reaction time is 4 h. ^e Reaction time is 30 min. ^f The yield in parenthesis reported by Katritzky and Akutagawa (ref. 5).

Experimental

Typical Procedure (Table, Entry 1).—2-Methylindole (0.131 g, 1.0 mmol) was dissolved in degassed ether (10 ml) at room temperature under a nitrogen atmosphere. Addition of butyllithium (3.0 mmol in hexane) followed by treatment with potassium t-butoxide (0.24 g, 2.0 mmol) gave a bright yellow solution. After stirring for 30 min, the reaction mixture was cooled to -70 °C. Methyl iodide (0.124 ml, 2.0 mmol) was added dropwise. The solution was kept at -70 °C for 2 h, and quenched with a few drops of water. The solution was warmed to room temperature and poured into water (30 ml). The mixture was neutralized with 1M HCl and extracted with ether (50 ml). The extract was washed with water (2 × 30 ml) and dried (Na₂SO₄). Removal of the solvent followed by purification on t.l.c. [hexane-ether (4:1)] gave 0.114 g (77%) of 2-ethylindole as yellow crystals, m.p. 42–43 °C (lit., m.p.⁵ 44.5–45.0 °C); δ_H(CDCl₃) 1.31 (3 H, t, Me), 2.47 (2 H, q, CH₂), 6.23 (1 H, s, CH), 7.07–7.53 (4 H, m, Ar), and 7.75 (1 H, br, NH).

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Paper 9/03774H

Received 4th July 1989

Accepted 5th September 1989