

A New Synthesis of 4-Substituted Indoles *via* Tricarbonylarenechromium(0) Complexes

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Tricarbonyl-(η^6 -1-tri-isopropylsilylindole)chromium(0), lithiated selectively at C-4 by *n*-butyl-lithium-*N,N,N',N'*-tetramethylethylenediamine (TMEDA), can be substituted in good yield by a range of electrophiles; the method has been used to synthesise 4-prenylindole.

We have recently reported¹ that the lithiation² of tricarbonyl-(η^6 -*N*-protected indole)chromium(0) complexes occurs initially at C-2. If this position was trimethylsilylated, subsequent lithiation was predominantly at C-7 with minor amounts of C-4 attack. The well established importance of 4-substituted indoles³ led us to examine methods to achieve exclusive or predominant 4-lithiation and hence develop a general route to 4-substituted indoles. We now report such a method.

Since lithiation of tricarbonyl-(η^6 -1-methyl-2-trimethylsilylindole)chromium(0) (1, R¹ = Me, R² = SiMe₃) gave a

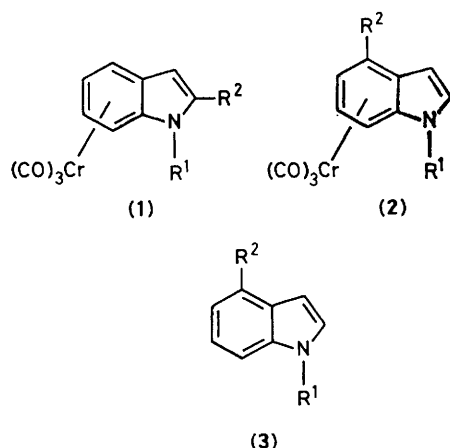
4:1 mixture of 7- and 4-lithiation,¹ the selectivity of attack is finely balanced. It was reasoned, therefore, that a bulky *N*-substituent could provide sufficient lateral protection to favour 4-deprotonation. Accordingly, the *N*-*t*-butyldimethylsilyl complex† (2, R¹ = SiMe₂Bu^t, R² = H) [m.p. 143 °C (decomp.)] was prepared in 91% yield from the indole complex⁴ with

† All new compounds had correct microanalyses and spectroscopic data.

Table 1. Synthesis of 4-substituted indoles.

Run	Electrophile	4-Substituted indole complex (2, R ¹ = SiPr ⁱ ₃)			4-Substituted indole (3, R ¹ = H)		
		R ²	Isolated yield (%)	M.p. (°C)	R ²	Isolated yield (%)	M.p. (°C)
1	Me ₃ SiCl	SiMe ₃	56	145 (decomp.)	SiMe ₃	86 ^a	65–66
2	EtO ₂ CCl	CO ₂ Et	60	134–136	CO ₂ Et	84 ^b	70–71 ^c
3	MeO ₂ CCl	CO ₂ Me	59	100–101	CO ₂ Me	81 ^a	68–69 ^d
4	PhSCl	SPh	— ^e	—	SPh	26 ^{f,g}	oil
5	Me ₂ C=CHCH ₂ Br	CH ₂ CH=CMe ₂	36 ^g	112–113.5	CH ₂ CH=CMe ₂	95 ^g	oil

^a Deprotection sequence: i, TBAF–THF, 0 °C, 10 min; ii, heat, pyridine, 2 h.¹¹ ^b Deprotection sequence: i, *hν*, air; ii, TBAF–THF, 0 °C, 10 min. ^c Lit.¹² m.p. 70–71 °C. ^d Lit.¹² m.p. 64 °C. ^e The complex was too unstable to be isolated. ^f Overall yield. ^g Deprotection sequence: i, TBAF–THF, 0 °C, 10 min; ii, *hν*, air, MeCN. ^h Estimated total yield 70%.



potassium hydride and the silyl chloride in tetrahydrofuran (THF). However, lithiation of this complex with *t*-butyllithium–*N,N,N',N'*-tetramethylethylenediamine (TMEDA) in THF and quenching with ethyl chloroformate gave a mixture of products in low yield.

The bulk of this protecting group lies principally in the *t*-butyl residue and in order to provide more spatially complete protection, we synthesised the *N*-tri-isopropylsilyl analogue^{5,6} (2, R¹ = SiPrⁱ₃, R² = H) [m.p. 138–140 °C (decomp.)] in a similar manner (90%). Alternatively, indole can be *N*-tri-isopropylsilylated⁷ (100%) and the product complexed with hexacarbonylchromium(0) (85%) as previously described.^{1,8}

Lithiation of this complex (2, R¹ = SiPrⁱ₃, R² = H) required two equivalents of *n*-butyl-lithium–TMEDA at –78 °C for 3 h. The product was quenched with trimethylsilyl chloride to give a single product (56%) after crystallisation of the crude material. The n.m.r. spectrum of this product indicated it to be a 4- or 7-silylated indole complex. Thus, H-2 (δ 7.35) and H-3 (δ 6.4) were both present and the protons of the carbocyclic ring appeared as a simple ABC system. Decomplexation of the product (*hν*, tungsten lamp, air⁹) gave the substituted indole (3, R¹ = SiPrⁱ₃, R² = SiMe₃) (93%). A nuclear Overhauser effect (n.O.e.) difference spectrum of this at 250 MHz established the precise structure. Thus, irradiation of the methyls of the trimethylsilyl group produced enhancement of *two* protons (H-3 and H-5). Irradiation of the tri-isopropylsilyl protons also produced enhancement of *two* protons (H-2 and H-7). These observations are consistent only with 4-substitution.

N.m.r. analysis of the decomplexed mother liquors from the initial work-up procedure showed the presence of predominantly 4-silylated material together with small amounts of two isomers which are tentatively assigned as the 5- and 6-silylated

species (ratio 4- : 5- : 6- *ca.* 3 : 1 : 1). In particular, no product of attack at C-2 and C-7 was detected. The total yield of 4-silylated product was thus estimated as 70%, with *ca.* 5% of each of the 5- and 6-isomers.

The lithiation–quench procedure was repeated with a series of electrophiles (Table 1) and the products were isolated in fair to good yield.

The prenylated material (2, R¹ = SiPrⁱ₃, R² = Me₂C=CHCH₂) (Table 1, run 5) was deprotected with tetrabutylammonium fluoride (TBAF) in THF (0 °C, 10 min)⁶ and decomplexed in acetonitrile (*hν*, tungsten lamp, air) to give 4-prenylindole¹⁰ (3, R¹ = H, R² = Me₂C=CHCH₂) in 95% yield (28% overall from indole).

This method offers a rapid and apparently general route to 4-substituted indoles and further development in natural product synthesis is in hand.

We thank Mr. D. Neuhaus, Imperial College, for the n.O.e. and high resolution n.m.r. experiments and the S.E.R.C. for financial support (to G. N.).

Received, 28th January 1982; Com. 089

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