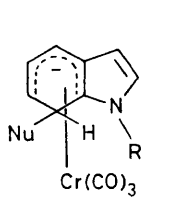
Regioselective Lithiation and Substitution of Tricarbonyl-(η^6-1-methylindole)-chromium(0): *X*-Ray Crystal Structure Analysis of Tricarbonyl-(η^6-1-methyl-2-trimethylsilyl-7-ethoxycarbonyl-indole)chromium(0)

By GORDON NECHVATAL, DAVID A. WIDDOWSON,* and DAVID J. WILLIAMS
(*Department of Chemistry, Imperial College, London* SW7 2AY)

Summary Tricarbonyl(η^6-1-methylindole)chromium(0) is lithiated by n-butyl-lithium at C-2 whereas tricarbonyl-(η^6-1-methyl-2-trimethylsilylindole)chromium(0) is lithiated predominantly at C-7, as shown by *X*-ray analysis of the derived 7-ethoxycarbonyl derivative, and the 7-lithio species is substituted in good yield by a range of electrophiles.

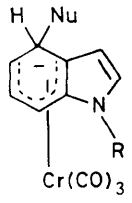
THE electronic effect of the tricarbonyl chromium unit in tricarbonyl(η^6-arene)chromium complexes is to lower the electron density on the arene ring and render it more susceptible to both nucleophilic attack[1] and deprotonation.[2] The tricarbonyl chromium moiety of indole complexes is bonded to the carbocyclic ring [as (**1**)][3] and thus creates the potential for promoting substitution in that ring, a process which is inefficient in the uncomplexed species.[4] Recently, it has been shown[5] that the *N*-protected complexes are attacked by carbanions at C-4 and C-7 of the indole nucleus, depending on the carbanion used, to generate the addition complexes (**2b**) or (**3a**). Mild oxidation of these gave the substituted indoles. As this approach results in the loss of the chromium group, we have examined the deprotonation of the *N*-protected indole complexes as a means of substitution which avoids this loss and thus gives scope for additional chromium-directed regioselective and stereospecific control.



(2)

(a) Nu = $-CMe_2CN$

(b) Nu = 

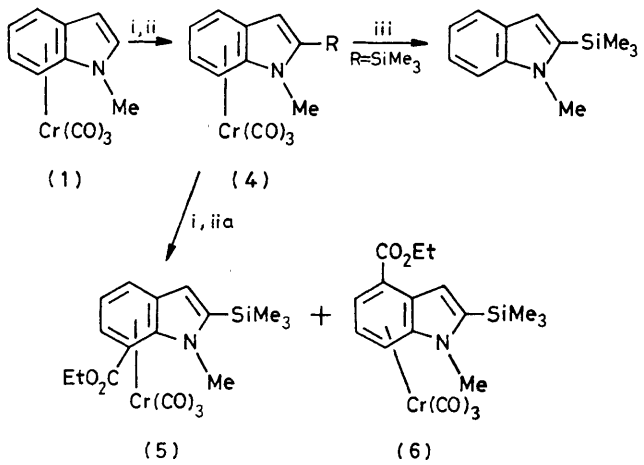


(3)

While this work was in progress, it was reported[6] that the reaction of tricarbonyl(η^6-3,3-dimethyl-1-t-butyldimethylsilylindoline)chromium(0) with n-butyl-lithium and

subsequent quenching with aldehydes gave a mixture of 4-, 5-, and 6-substituted indoline complexes with poor regioselectivity.

Reaction of tricarbonyl(η^6-1-methylindole)chromium(0)† (**1**) with n-butyl-lithium in tetramethylethylenediamine (TMEDA)–tetrahydrofuran (THF) at −78 °C produced a pale yellow solution which turned deep red when quenched with ethyl chloroformate. The product was isolated (78% after chromatography) and identified as tricarbonyl(η^6-2-ethoxycarbonyl-1-methylindole)chromium(0) (**4**, R = CO_2Et), m.p. 124 °C.‡ Uncomplexed *N*-protected indoles are deprotonated at C-2; however, this requires higher temperatures (−10 to 36 °C) and under the above conditions, 1-methylindole was unaffected. Tricarbonyl chromium complexes are known to labilise benzylic protons,[7] but activation of more remote centres, as here, has not been previously demonstrated although remote stereocontrol has been observed.[8]



SCHEME. *Reagents and conditions:* i, Bu^nLi–THF, −78 °C, TMEDA; ii, (a) $ClCO_2Et$, (b) $ClSiMe_3$; iii, *hν*.

In order to determine the second site of deprotonation, complex (**1**) was treated successively with n-butyl-lithium (−78 °C) and trimethylsilyl chloride (see Scheme). The product (**4**, R = $SiMe_3$) (m.p. 99—100 °C, 60% after chromatography) was decomplexed photochemically to give 1-methyl-2-trimethylsilylindole, spectroscopically identical with authentic material.[9] Complex (**4**, R = $SiMe_3$), generated *in situ*, was further deprotonated with n-butyl-lithium as above and quenched with ethyl chioroformate to give a ≥4 : 1 ratio (by n.m.r. spectroscopy) of tricarbonyl-(η^6-7-ethoxycarbonyl-1-methyl-2-trimethylsilylindole)-chromium(0) (**5**) (m.p. 107 °C, 67% after chromatography) and tricarbonyl(η^6-4-ethoxycarbonyl-1-methyl-2-trimethyl-silylindole)chromium(0) (**6**) (not obtained pure).

The structure of (**5**) was assigned initially by high resolution ^{1}H n.m.r. spectroscopy of the decomplexed material. The carbocyclic ring protons (δ 7·1—7·7) showed a clear vicinal ABC splitting pattern and the *N*-methyl group chemical shift (δ 4·24) suggested 7-substitution, but without authentic specimens the distinction between 4- and 7-substitution could not be made with complete certainty. We therefore undertook a single-crystal *X*-ray analysis of the complex (**5**)§ which revealed that substitution in the predominant product had indeed occurred at the 7-position (Figure).

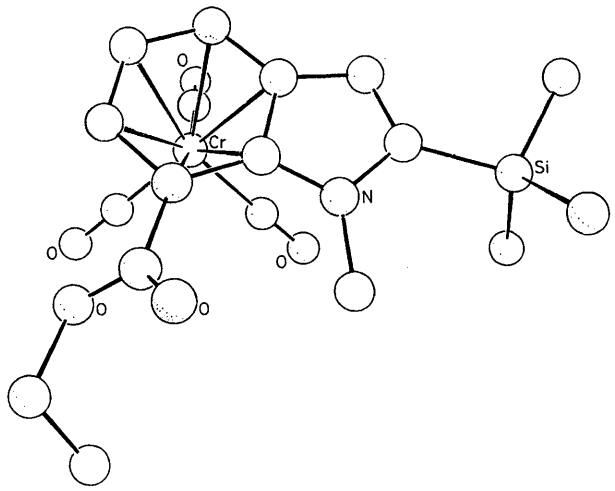


FIGURE. Crystal structure of (**5**). Bond distances: Cr–CO 1·82—1·85, Cr–Ar 2·20—2·32, C–Si 1·88, Si–Me 1·85 Å.

With the structure of (**5**) unambiguously established, the lithiated complex was treated with a series of electrophiles to give the mixtures of 7- and 4-substituted indole complexes (Table). In each case (except run 2) the 7-derivative was isolated pure and in good yield by column chromatography, although the minor 4-derivative could never be completely separated from its isomer. In all cases, the ratio of products (7- or 4-) remained approximately the same. Thus, there was no equilibration of the lithiated species during electrophilic quenching and the ratio presumably represents the ratio of kinetic deprotonation of the complex.

In runs 2 and 6, the products contain benzylic protons which could give rise to quenching of the starting anion by virtue of their acidity.[7] This may explain the slightly lower yields in these cases, but the effect is not pronounced.

Runs 3 and 4 give rise to diastereoisomeric products (**7**).[1b] N.m.r. analysis shows that there is no stereoselection and the two racemates are equally present. Run 4 also shows exclusive 1,2-addition to the unsaturated carbonyl group.

† *N*-Methylindole complex was prepared in 82% yield by heating *N*-methylindole with one equivalent of hexacarbonyl chromium in dibutyl ether and tetrahydrofuran (95 : 5) overnight, filtering through celite, concentrating the solution, and allowing to crystallise.

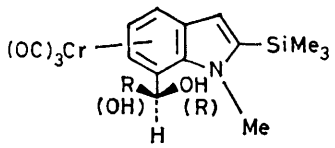
‡ All new complexes had correct microanalyses and expected spectroscopic data.

§ *Crystal data:* Crystals of (**5**) $C_{18}H_{21}CrNO_5Si$ are orthorhombic, a = 23·694(6), b = 17·616(5), c = 9·683(2) Å, U = 4042 Å^3; space-group *Pbcn*, Z = 8. Of the 2080 independent reflections ($\theta \leq 50°$) measured on a diffractometer using Cu-K_α radiation 560 were classified as unobserved. The structure was solved by the heavy atom method and refined anisotropically to give a current R = 0·051. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

TABLE. Synthesis of 7-substituted 1-methyl-2-trimethylsilylindoles

Run	Electrophile	Indole complex Yield[a], (Yield[b])/%	M.p./°C	Free indole Yield[c]/%	M.p./°C
1	$ClCO_2Et$	67 (85)	107	78	Oil
2	MeI	—[d] (64)	(117—119)[e]	—	109—110[f]
3	PhCHO	63 (83)	148 (decomp.)	89	110
4	CH_2=CHCHO	60 (74)	155 (decomp.)	92	Oil
5	PhSCl	51 (73)	135—140 (decomp.)	80	102—104
6	Me_2C=$CHCH_2Br$	43 (61)	119—119·5	77	106—107

[a] Isolated yield after chromatography. [b] Total yield of mixed isomers. [c] Yield from complex. [d] The 4/7-isomer mixture was inseparable. [e] M.p. of the mixed isomers. [f] Pure 7-isomer.



(7)

The products were readily decomplexed by photolysis with a 300 W tungsten lamp[10] to generate the parent indoles (Table). Aromatic desilylation using aqueous trifluoroacetic acid at room temperature[11] converted 1-methyl-2-trimethylsilylindole into the desilylated material in 79% yield in 2·5 h.

Modification of this chemistry to achieve predominant 4-substitution and extension to the synthesis of natural indoles is in hand.

We thank the S.R.C. for financial support (to G. N.).

(*Received, 29th April* 1981; *Com.* 410.)

[1] (a) B. Nicholls and M. C. Whiting, *J. Chem. Soc.*, 1959, 551; (b) for comprehensive reviews see, M. F. Semmelhack, *Ann. N.Y. Acad. Sci.*, 1977, **295**, 36; G. Jaouen, *ibid.*, p. 59.

[2] A. N. Nesmeyanov, N. E. Kolobova, K. N. Anisimov, and Yu. V. Makarov, *Izv. Akad. Nauk SSSR., Ser. Khim.*, 1968, 2665; *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1968, 2538; M. F. Semmelhack, J. Bisaha, and M. Czarny, *J. Am. Chem. Soc.*, 1979, **101**, 768; R. J. Card and W. S. Trahanovsky, *J. Org. Chem.*, 1980, **45**, 2555; M. Uemura, N. Nishikawa, and Y. Hayashi, *Tetrahedron Lett.*, 1980, **21**, 2069.

[3] E. O. Fischer, H. A. Goodwin, C. G. Kreiter, H. D. Simmons, K. Sonogashira, and S. B. Wild, *J. Organomet. Chem.*, 1968, **14**, 359.

[4] For a comprehensive review see 'Indoles', ed. W. J. Houlihan, Wiley, New York, 1972, part 1, ch. 1.

[5] A. P. Kozikowski, *Heterocycles*, 1981, **16**, 281; A. P. Kozikowksi and K. Isobe, *J. Chem. Soc., Chem. Commun.*, 1978, 1076.

[6] M. Fukui, Y. Yamada, A. Asakura, and T. Oishi, *Heterocycles*, 1981, **15**, 415.

[7] R. J. Card and W. S. Trahanovsky, *J. Am. Chem. Soc.*, 1972, **94**, 2897.

[8] G. Jaouen and A. Meyer, *J. Am. Chem. Soc.*, 1975, **97**, 4667.

[9] Authentic 1-methyl-2-trimethylsilylindole was prepared by lithiating *N*-methylindole by the method of D. A. Shirley and P. A. Roussel, *J. Am. Chem. Soc.*, 1953, **75**, 375 and quenching with trimethylsilyl chloride.

[10] *Cf.* G. Jaouen and R. Dabard, *Tetrahedron Lett.*, 1971, 1015.

[11] C. Eaborn, P. M. Jackson, and R. Taylor, *J. Chem. Soc. B*, 1966, 613.