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Preliminary communication

NEW SUBSTITUTION REACTIONS ON INDOLE PROMOTED BY THE $Cr(CO)_3$ UNIT

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Summary

Indole derivatives form complexes with the $Cr(CO)_3$ unit at the 6-membered ring. Addition of reactive carbon nucleophiles occurs at the coordinated ring with strong preference for C-4 and, in a few cases, for C-7. Oxidation of the intermediate cyclohexadienyl anionic complexes produces substituted indoles in good yield. Complexes of *N*-methylindoline and benzofuran also undergo the addition/oxidation sequence preferentially at C-4. Changes in the substituents at C-3 and the nitrogen atom in the indole complexes influences the regioselectivity so that either C-4 or C-7 substitution can be observed. The selectivity is correlated with EHT calculations on free indole and complexes indole.

The indole skeleton appears widely in biologically-active molecules, with carbon substituents invariably at C-3 and commonly at C-2 and C-4. Electrophilic reactions occur with good selectivity at C-3 [1], metalation can activate C-2 [2] and less general methods have been employed to add carbon units at C-4 [3]. We wish to report that the tricarbonylchromium complexes of N-protected indoles (complexes **2**—**8**), *N*-methylindoline (**9**), and benzofuran (**10**) are excellent substrates for the addition/oxidation method [4] of substitution by reactive carbon nucleophiles; that electronic factors strongly direct attack to C-4 and C-7; and that steric factors conveniently allow either C-4 or C-7 to be favored [5].

A preliminary survey of the reactivity of η^6-(*N*-methylindole)tricarbonylchromium (**2**) [6] η^6-(*N*-methylindoline)tricarbonylchromium (**9**) [8] and η^6-(benzofuran)tricarbonylchromium (**10**) [9] was carried out. In each case, the set of anions which added successfully (Table 1) is similar to the set which adds to η^6-benzenetricarbonylchromium itself [4]. Ketone enolates fail to add (<20%), while ester enolates, cyano-stabilized carbanions, and 2-lithio-1,3-

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TABLE 1

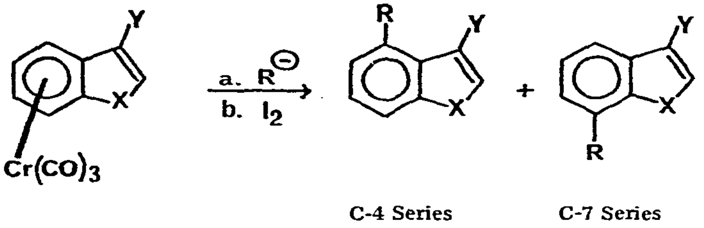
SUBSTITUTION OF INDOLE, INDOLINE, AND BENZOFURAN COMPLEXES

Entry	Complex anion [a]	Product ratio C-4/C-7	Combined yield (%) [f]
1	2/A	97/3 [b]	73
2	3/A	100/0 [b]	82
3	4/A	98/2 [b]	95
4	9/A	71/29 [d]	(89) [g]
5	10/A	73/27 [b]	71
6	5/A	57/43 [b]	86
7	6/A	17/83 [b]	82
8	7/A	95/5 [b]	78
9	8/A	100/0 [b]	94 [i]
10	2/B	75/25 [c]	43
11	2/C	99/1 [d]	92
12	2/D	14/86 [d]	68
13	2/E	16/84 [e]	43
14	9/D	100/0 [e]	61 [g]
15	10/B	63/37 [c]	55
16	10/D	86/14 [d]	42
17	6/F	33/67 [b]	64

[a] Anions A, B, C, and F were generated using lithium diisopropylamide as base (1.05 mol-eq, −78°C, THF) while anions D and E were prepared using n-butyllithium as base (1.05 mol-eq, −30°C, THF). [b] The complex was added to the anion in THF at −78°C; after 0.5 h, excess iodine (5 mol-eq) in THF was added and the mixture was warmed slowly to 25°C and allowed to stir for several hours. The products were isolated through standard extraction/chromatography procedures. [c] The reaction was carried out at 0°C in THF/HMPA (5/1) for 0.5 h. [d] THF/HMPA (5/1), −78°C, 0.5 h. [e] THF/HMPA (1/1), 0°C, 0.5 h. [f] The yields are based on weighed amounts of combined substituted indoles after simple chromatographic purification. All products were obtained in pure form and identified by comparison of spectral and chromatographic data except where noted. [g] This yield refers to the mixture of substituted indolines which was obtained after chromatography. The mixture was directly dehydrogenated and the product indoles were separated and identified. [h] The 5% yield of by-product includes at least two substituted indoles, not identified in detail. [i] N-Methylindole was recovered (29%); the yield is based on the amount converted.

dithiane give excellent results. Very reactive anions ($LiCH_2SPh$, n-BuLi) lead primarily to metalation at C-7 [10,11].

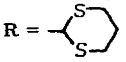
The parent indole complex (1) is easily converted into a series of N-protected versions through deprotonation with NaH. We find N-protection of 1, especially silylation, to proceed with greater efficiency than the corresponding reactions on indole [12]. For example, 1 is treated with NaH (30% excess) in THF at 25°C for 15 min (gas evolution); then t-butyldiphenylsilyl chloride (30% excess) is added. After 15 min, 4 is obtained in 64% yield using the usual extraction procedures and rapid chromatography. Addition of 2-lithio-2-methylpropionitrile (A) is complete within 1.0 h at −78°C in THF or mixtures of THF/HMPA; then addition of excess iodine (25°C, several h) provides the substituted indoles. Selectivity in four simple cases (entries 1—3, 9) is >97% for C-4, with the remainder (0—3%) at C-7 [13]. The less bulky analog, lithioacetonitrile (B) reacts with 2 under the same conditions as A but with lower selectivity (entry 10). On the other hand, 2-lithio-1,3-dithiane and 1-lithio-3-(trimethylsilyl)-2-propene show a strong preference for C-7 giving after oxidation, a mixture of substitution at C-7/C-4 ≅ 6/1 (entries 12,



Series of complexes:

1: X = NH, Y = H
2: X = NMe, Y = H
3: X = NCH_2Ph, Y = H
4: X = $NSiPh_2$-t-Bu, Y = H
5: X = NMe, Y = Me
6: X = NMe, Y = CH_2SiMe_3
7: X = $NSiPh_2$-t-Bu, Y = CH_2SiMe_3
8: X = NCO_2-t-Bu, Y = H
9: X = NMe, Y = H (2,3-dihydro-)
10: X = O, Y = H

Series of anions:

A: R = $C(CH_3)_2CN$
B: R = CH_2CN
C: R = $C(CH_3)_2CO_2$-t-Bu
D: R = 
E: R = $CH_2CH{=}CHSiMe_3$
F: R = $CH(CH_3)CN$

Structure numbering: the products are labelled with the number of the complex and the letter of the anion from which they are derived, followed by the number for the position of substitution (4 or 7).

13) [13,18]. Ester enolates generally parallel the selectivity of cyano-stabilized anions; t-butyl-2-lithioisobutyrate adds almost exclusively at C-4 (entry 11) [13]. It has been noted that the selectivity in addition to substituted arenetricarbonylchromium complexes, correlates with the pattern of coefficients in the LUMO for the free arene [15]. Extended Hückel Calculations [20] on indole and the indoletricarbonylchromium complex [21] are summarized in Fig. 1. Consistent with the observed selectivity, the larger coefficients appear at C-4 and C-7 [22].

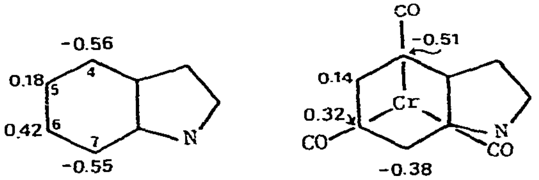
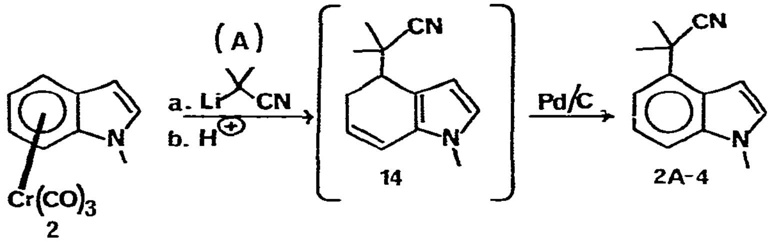


Fig. 1. Coefficients for LUMO in indole and indole-$Cr(CO)_3$.

The indoline complex 9 gives the C-4 product with both 2-lithio-2-methylpropionitrile and 2-lithio-1,3-dithiane (entries 4, 14). Since the conversion of indolines to indoles can be efficient [23], results in entries 12 and 14 point to general processes of substitution by 2-lithio-1,3-dithiane and related anions at either C-4 or C-7. With benzofuran complex **10**, all anions tested showed selectivity for C-4, ranging from 2/1 to greater than 6/1 (entries 5, 15, 16) [13]. Again, the selectivity is slightly higher with tertiary carbanions compared to primary.

Important questions in considering the regioselectivity in the two-step addition/oxidation reaction include whether kinetic control is operating and whether the iodine oxidation procedure influences the position of attachment of the nucleophile. No direct evidence for kinetic control is available, but in these and other examples [19, 24], variation in reaction temperature (—78°C/0.5 h to 25°C/1 h) and medium (THF, THF/HMPA, etc.) has no significant effect on the distribution of isomers. In the reaction of anion A with complex 2 an alternate isolation procedure with excess trifluoroacetic acid at —78°C in place of iodine, led to dihydroindoles (89% yield; tentative structure 14) [8] which were dehydrogenated to indoles (Pd/C, 150°C, 6 h, 80% yield). A mixture of C-4/C-7 derivatives (2A-4/2A-7) was obtained in the ratio 97/3, identical to the products from iodine oxidation [13].



The balance between electronic effects and steric effects is delicate in the indole system. With the *N*-methyl-3-methylindole complex (5) anion A produces the C-4 and C-7 isomers in in the ratio of 4/3 (86% yield), suggesting steric hindrance to addition at C-4 (compare Table 1, entries 1 and 6). The larger trimethylsilylmethyl substituent at C-3 (in **6**) further disfavors C-4, so that C-7 is preferred by 6/1 (82% yield, entry 7). With the less bulky anion, 2-lithiopropionitrile, the steric hindrance from C-3 is less effective and **6** reacts at C-4 and C-7 in the ratio 1/2 (64% yield, entry 17). The reverse effect can be achieved by increasing the size of the N-protecting group. In the extreme case of complex 7, with the t-butyldiphenylsilyl group, anion A adds at C-4 to the extent of 95% (73% yield, entry B).

More cases must be examined before the full pattern of selectivity in additions to these complexes is clear, but useful selectivity for C-4 and C-7 is now established.

Acknowledgement. We gratefully acknowledge a research grant from the National Science Foundation (CHE 7905561), as well as preliminary results and helpful discussion from Dr. Herbert Mühle (Sandoz, Basle) during a stay in Princeton. NMR studies were carried out at Princeton at a facility provided in part by NSF and expertly supervised by Ms. Mary Baum and through the NMR Service Centers at the University of Pennsylvania (360 MHz) and Yale University (270 MHz).

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5 A preliminary report [6] demonstrated that two carbon nucleophiles add to complex 2, but erroneously claimed that the oxidation step is unnecessary, that substitution only at C-7 is observed, and that the range of anions is very limited. The sources of the misconceptions are now understood and a discussion will be presented in the full paper describing this work. We thank Professor Kozikowski for his cooperation and suggestions in clearing up this matter.

The question as to whether an oxidation step is necessary is complicated by two facts: first, adventitious air during the isolation procedures can serve as the oxidizing agent, thereby promoting the well-precedented [4] addition/oxidation sequence without deliberate oxidation. Second, with excess alkyllithium reagents, a new mechanism operates which leads to substitution for hydrogen without oxidation [7]. We have shown that this special mechanism does not apply with the carbanions employed in our work.

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8 Complex 9 was prepared by heating 1-methylindoline with $Cr(CO)_6$ (60% molar excess) in dioxane for three days. Crystallization from a mixture of ether/hexane/chloroform (6/3/1) produced yellow crystals, 65% yield, m.p. 113—115°C. Satisfactory ^1H NMR, ^{13}C NMR, IR, and high resolution MS data were obtained.

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11 Quenching with CO_2 and methylation with diazomethane gave a mixture of the 7-carbomethoxy derivative and the 2-carbomethoxy derivative (ratio 3/2, 45% yield).

12 Complex 1 and the complexes from 3-methyl- and 3-(trimethylsilylmethyl)-indole have been converted to a variety of *N*-methyl, *N*-benzyl, *N*-acyl, and *N*-silyl derivatives by a simple procedure employing sodium hydride in THF at 25°C. In contrast, N-protection of indoles often requires special techniques to avoid competing reaction at C-3. For example, phase-transfer techniques (V.O. Illi, Synthesis, 387 (1979) 1) and crown ether chelation (E.S. Santaniello, C. Farachi, and F. Ponti, Synthesis, 617 (1979).

13 The structures of 2A-4 and 2A-7 are pivotal in this work. We have established them by analysis of NMR spectral data and by correlation with material from alternative synthesis. For 2A-4, ^1H NMR($CDCl_3$, 270 MHz): δ 1.85(s, 6H, CH_3), 3.67 (s, 3H, NCH_3), 6.71 (dd, 1H, H_3, J_{23} = 3.2 Hz, J_{37} = 0.7 Hz), 7.00 (d, 1H, H_2, J = 3.2 Hz), 7.03 (dd, 1H, H_5, J_{56} = 7.5 Hz, J_{57} = 1.4 Hz), 7.11 (t, 1H, H_6, $J_{56} \cong J_{67} \cong$ 7.5 Hz), 7.20 (d of br s, 1H, H-7 collapses to dd, J 7.5 Hz and 1.4 Hz, upon irradiation at δ 6.71 (H-3)). The cross-ring coupling H-3/H-7 is precedented [14]. ^{13}C NMR ($CDCl_3$): δ 27.7, 32.8, 36.1, 100.2, *109.4*, 115.1, 121.2, 124.8, 124.9, 128.7, 132.3, 137.1. The definitive signal is at 109.4, assigned to C-7; for indole itself, the absorption due to C-7 is well-separated from other signals, at 109.0 ppm [15]. Given the substituent chemical shift (SCS) values of the 2-cyano-2-propyl group [16], the 7-substituted product (2A-7) would show no signals between 100 and 115 ppm. Starting from 4-chloroindole [17], *N*-methyl-4-carbomethoxyindole was prepared. Reduction with $LiAlH_4$ produced the 4-hydroxymethyl derivative, and the hydroxyl group was replaced by a cyano unit to give 2B-4. Monomethylation (lithium diisopropylamide, MeI) produced 2F-4, and dimethylation gave 2A-4 which was identical in all respects with the major product obtained from addition of anion A to complex 2.

The structures in the 7-substituted series are based on analysis of the ^1H NMR spectra of the 7-(1,3-dithian-2-yl) derivative 2D-7 and of the 7-formyl derivative obtained from 2D-7. The patterns of absorption due to the aromatic H are particularly revealing. In each case, H-3 appears at δ 6.55 as a sharp doublet, J_{23} = 3.1 Hz; H-5 at 7.18 as a t, $J_{45} = J_{56}$ = 7.6 Hz; and H-6 and H-4 each as a dd (7.64 and 7.80), J_{46} = 1.4 Hz. This pattern is also consistent with 2D-4, except for the absence of additional coupling of H-3 expected if H were present at C-7. The 7-formyl derivatives was converted to 2F-7 by conventional steps and shown to be different from 2F-4, prepared (above) from 4-chloroindole. The ^{13}C NMR spectrum of 2D-7 shows the absence of a peak due to C-7 calculated to appear at about δ 109 if the 1,3-dithianyl unit were attached at C-4, as in 2D-4. In addition, product 2D-4 (Table 1, entry 15) shows ^{13}C NMR 25.5, 32.4, 32.8, 49.9, 99.6, *109.4*, 118.4, 121.6, 126.5, 128.7, 130.7 ppm.

For product 2C-4: ^1H NMR ($CDCl_3$, 90 MHz): δ 1.31 (s, 9H), 1.64 (s, 6H), 3.69 (s, 3H), 6.50 (d, 1H, J = 3.2 Hz), 6.93 (d, 1H, J = 3.2 Hz), 7.0—7.2 (m, 3H). ^{13}C NMR($CDCl_3$): δ 26.2, 27.8, 32.7, 47.1, 79.9, 100.8, 108.0, 115.1, 121.2, 126.3, 127.7, 137.0, 137.8, 170.9. IR($CHCl_3$): 2795(w), 1710(s), 1367(s), 1300(s), 1287(s), 1148(s), 1120(s) cm^{-1}. Mass spectral mol.wt.: 273.1732; $C_{17}H_{23}NO_2$ calcd.: 273.1729.

Products from complex 10: The structures of the products from addition/oxidation to complex 10 are based on ^1H and ^{13}C NMR spectra. Each product (10A-4, 10A-7, 10D-4, 10D-7) was isolated by silica gel chromatography and fully characterized. Critical data for 4-substituted products include the typical splitting pattern for H-5/H-6/H-7, the long range coupling of 0.9 Hz of H-7 and H-3, and the presence of a ^{13}C NMR signal at 110—112. In the complete series of methylbenzofurans, the ^{13}C NMR signal for C-7 varies in the range δ 109 (for C-4 methyl) to 11.6 ppm (for C-6 methyl), except for the C-7 methyl isomer itself (δ 121.5 ppm): N. Platzer, J.-J. Basselier, and P. Demerseman, Bull. Chem. Soc. France, (1974) 905.

Complex 5: This was prepared by reaction of skatole with $Cr(CO)_6$ (208 h, dioxane at reflux) followed by *N*-methylation (CH_3I, NaH, THF). It was obtained as an orange crystalline solid in 92% yield based on skatole, m.p. 138—140°C and was fully characterized.

Complexes 6 and 7: Reaction of 3-(trimethylsilylmethyl)indole with $Cr(CO)_6$ as usual gave the corresponding $Cr(CO)_3$ complex in 84% yield, m.p. 100°C dec. It was converted to 7 by reaction with t-butylchlorodiphenylsilane and sodium hydride in THF (92% yield, m.p. 155—158°C). Complex 6 had m.p. 122—123°C.

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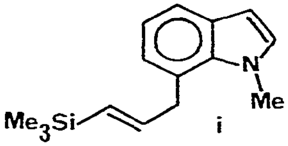
16 The SCS values for the substituents involved in this study were determined from the ^{13}C NMR spectrum of the corresponding monosubstituted benzene. For example, 2-phenyl-2-methylpropionitrile was used to obtain values for the effect of the 2-cyano-2-propyl group on the ^{13}C NMR chemical shifts for *o*, *m*, and *p* carbons. It has been shown that ^{13}C NMR chemical shifts for the isomeric methylindoles can be predicted using SCS values for the methyl group obtained from toluene [14].

17 We are grateful to Dr. H. Mühle and the Sandoz Company (Basle) for a generous gift of 4-chloroindole. Details of the preparation of 2A-4 will be presented in the full report of this work.

18 The product mixture from anion E and complex 2 is complicated by the possible formation of regioisomers at the allylic unit. Tentative structure assignment for the major products as i and ii (ratio 5/3/1, respectively) is based on ^{13}C NMR, ^1H NMR, and mass spectral data. Attack at the γ-position of the allyl anion in the major isomer is indicated by a *trans* vicinal H—H coupling constant of 20 Hz for the olefinic H, as well as by the pattern of olefinic signals. Substitution at C-7 is postulated based on calculation of SCS values from appropriate models. Chemical correlation has not been completed.



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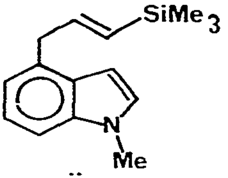

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20 We wish to thank Mr. Daniel Iverson for his assistance with the EHT calculations. The program, installed in the Mislow collection at Princeton, is the package EXTHUC (E.B. Moore et al., QCPE, No. 11, 1965, p.64), obtainable from the Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, Bloomington, Indiana 47401.

21 Calculations were performed with three conformations of the $Cr(CO)_3$ unit. The conformation shown is calculated to be of lowest energy, about 2 kcal/mol more stable than two alternative eclipsed conformations. The variation in pattern of coefficients with conformation for the LUMO which is heavily centered on the indole ligand is very small; full details will be published in due course. Efforts have been made to correlate selectivity in addition to arenetricarbonylchromium complexes with conformational preferences of the $Cr(CO)_3$ unit: see (a) A. Solladie-Cavallo and G. Wipff, Tetrahedron Lett., (1980) 3047; (b) A. Solladie-Cavallo and J. Suffert, Org. Mag. Resonance, 14 (1980) 426; (c) T.A. Albright and B.K. Carpenter, Inorg. Chem., 19 (1980) 3092.

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