# Organometallic Compounds in Organic Synthesis: Nucleophilic Substitution Reactions of *N*-Methylindoletricarbonyl chromium(0)

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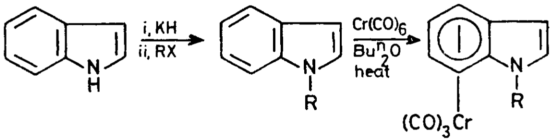
*Summary* The chromium tricarbonyl complex of *N*-methylindole undergoes nucleophilic substitution reactions with generation of 7-substituted indoles.

IN developing new methods for the regiospecific synthesis of substituted indoles,[1] we were interested in the possibility of using the chromium tricarbonyl unit to activate the aryl ring of this fused heterocycle to nucleophilic substitution. The synthetic potential of the powerful electron withdrawing effect of this group 6B element was first suggested by Trahanovsky and Card.[2] Additional studies by Semmelhack and his co-workers have elaborated on the synthetic scope and mechanistic details of this reaction.[3]



(1) (2)

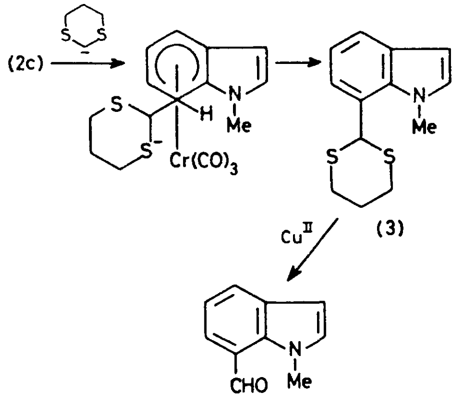
a; R = Ac
b; R = $CO_2Et$
c; R = Me

The chromium tricarbonyl complex (**2**; R = H) of indole is one of many $\eta^6$-arenetricarbonylchromium(0) complexes reported.[4,5] The new *N*-substituted complexes (**2a**)—(**2c**) were prepared by refluxing dibutyl ether solutions of the *N*-substituted indoles (**1a**)—(**1c**)[6] with an excess of chromium hexacarbonyl (1·5 equiv.) for *ca.* 5 h, and cooling and filtering off the yellow precipitates. Unchanged chromium hexacarbonyl was removed from the crude products by vacuum sublimation.[5] The air-stable complexes (**2a**) and (**2c**), obtained in 60—80% yield, were used in subsequent reactions without further purification. The chromium tricarbonyl complex of *N*-ethoxycarbonyl indole (**2b**) was obtained in only low yield (*ca.* 20% after silica gel chromatography).

Using 2-lithio-1,3-dithian as a nucleophile, complexes (**2a**) and (**2b**) underwent exclusive attack at the nitrogen protecting group at −78 °C in tetrahydrofuran (THF) with added hexamethylphosphoric triamide (HMPA). Indole and its chromium complex were the sole products isolated after quenching the mixtures with aqueous ammonium chloride.

We then focused our efforts on the chromium complex (**2c**) of *N*-methylindole, in order to overcome the problem of competing nucleophilic attack at the nitrogen protecting group.

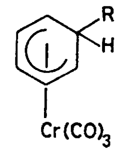
When complex (**2c**) (0·55 mmol) was added as a THF (1 ml)–HMPA (0·2 ml) solution to 2-lithio-1,3-dithian (from 1·1 mmol of Bu$^n$Li and 1·1 mmol of 1,3-dithian) in THF (4 ml) containing 0·2 ml of HMPA, rapid disappearance of the starting material was shown by t.l.c. The mixture was allowed to warm to room temperature overnight, and quenched with aqueous ammonium chloride. The isolated crude product was chromatographed on silica gel (30% ethyl acetate–hexane) to furnish exclusively the 7-substituted indole (**3**) in 41% yield.



(**4**)

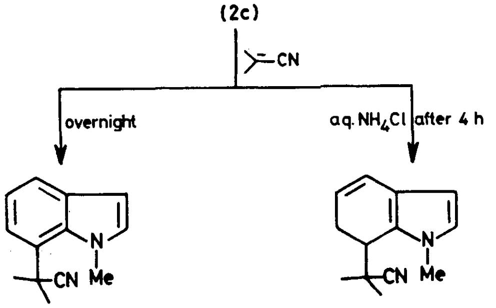
Assignment of structure (**3**) followed from 250 MHz $^1$H n.m.r. analysis of the aldehyde (**4**), obtained by copper(II) catalysed hydrolysis of the dithian (**3**) [a significant downfield shift was observed for the *N*-methyl group of (**4**) relative to the *N*-methyl group of (**1c**) owing to the deshielding effect of the formyl substituent; the aromatic region showed 2 dd and 1 t for 4-, 5-, and 6-H, and 2 d for 2- and 3-H ($J_{2,3}$ 3 Hz)].[7]

The formation of this product is at variance with the chemistry recorded by Semmelhack for the $\eta^6$-benzenechromium tricarbonyl complexes. These complexes, when treated with carbanionic reagents, afford substituted arenes only if first treated with an oxidant. If the intermediate $\eta^5$-cyclohexadienyl complexes [*e.g.*, (A)] are warmed above −30 °C, and then treated with a proton source, the starting unsubstituted arene chromium complexes are isolated.



(**A**)

The anion prepared from isobutyronitrile also reacts with (**2c**) to afford, on warming overnight at room temperature, the 7-substituted indole (**5**) in 63% yield. If this reaction is stopped after 4 h by quenching with aqueous ammonium chloride at 0 °C, however, dihydroindole (**6**) is isolated (60%) along with recovered starting material.† Again, this latter result is surprising *vis-a-vis* the chemistry of the $\eta^6$-benzenechromium tricarbonyl complexes, for treatment of the intermediate (A) with a weak acid was shown to regenerate the starting chromium complex.



(**5**) (**6**)

While nucleophilic substitution reactions in the indole series are thus possible, and these results are of some mechanistic interest, the scope of reagents which can be used is presently too limited to make this a process of general applicability.‡ The use of other nitrogen protecting groups (preferably electron withdrawing) may offer some advantages in extending this process, however.

We thank H.R.S.F. (Health Research and Services Foundation) of Pittsburgh, Pennsylvania, and the National Institutes of Health, for support and the Alfred P. Sloan Foundation for a Fellowship during 1978—1980 (to A.P.K.).

(*Received, 8th August* 1978; *Com.* 872.)

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† The preparation of the ring deuteriated dihydroindole is also possible as was shown by quenching the reaction mixture with deuterium chloride in methanol.

‡ The following reagents failed to give nucleophilic substitution products: $PhC^-HCO_2^-$, $MeC^-HCO_2Et$, $\underline{S[CH_2]_3SC}^-Me$, and cyclohexyl–N=$CHCH_2^-$.

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