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Preliminary communication

Synthesis and lithiation of tricarbonyl(methylbenzo[*b*]thiophene)chromium complexes

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Abstract

Lithiation of tricarbonyl(benzo[*b*]thiophene)chromium with Bu^nLi followed by methylation with MeI gives successively 2-methyl- and 2,7-dimethyl-substituted derivatives. Similarly, 3-, 4-, 5-, 6- and 7-methyl derivatives gave 2,3-, 2,4-, 2,5- and 2,6-dimethylbenzo[*b*]thiophenetricarbonyl complexes, whereas the 2-methyl derivative gave 2,7-dimethylbenzo[*b*]thiophenechromium tricarbonyl, selectively.

There is continuing interest in pharmaceutical applications of substituted benzo[*b*]thiophenes and benzo[*b*]furans, including dihydro compounds and condensed analogues. Particularly important are derivatives with substituents at the 7-position [1–6], which are prepared by conventional annulation procedures from substituted arenes or heteroarenes [7]. The objective of this work was to achieve regioselective functionalisation of benzo[*b*]thiophenes through the use of lithiobenzo[*b*]thiophenetricarbonylchromium complexes.

It should be noted that a number of benzo[*b*]thiophenes are deprotonated by n-butyllithium to give 2-lithiobenzo[*b*]thiophenes but dilithio species are not normally obtained; a poor yield of 2,7-dilithiobenzo[*b*]thiophene is obtained from benzo[*b*]thiophene and n-butyllithium in tetramethylethylenediamine as solvent [8]. Directed lithiation at the 7-position of 6-hydroxymethyl-3-methylbenzo[*b*]thiophene has been ascribed to a cooperative effect of the 6-substituent and the sulphur atom [9].

An important property of arenetricarbonylchromium complexes [10] is the enhanced acidity of arene hydrogens, which enables hydrogen–metal exchange to occur under conditions in which the uncomplexed substrate is unreactive [11]. Thus the carbocyclic ring of *N*-substituted tricarbony(indole)chromium complexes can be functionalised (at positions 4- or 7-) by lithiation (n-BuLi) followed by reaction with electrophiles, although complete regioselectivity is not achieved [12,13].

Preparation of tricarbonyl(methylbenzo[b]thiophene)chromium complexes

Tricarbonyl(benzo[*b*]thiophene)chromium (**1**) was prepared in 49% yield by heating benzo[*b*]thiophene and chromium hexacarbonyl in di-n-butyl ether and

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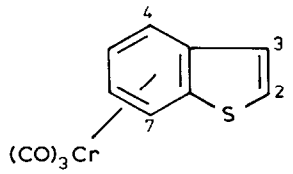
n-hexane as previously described [14]. This direct procedure was also used for yellow complexes [21 *] derived from 2- (34%), 3- (67%), 4- (26%), and 5-methylbenzo[*b*]thiophenes (26%) but proved unsatisfactory for the 6- and 7-methyl isomers [22 *], the latter were prepared [21 *], albeit in poor yields (14, 35%), from the free ligand and tricarbonyl(trispyridine)chromium(0) [18] in diethyl ether in the presence of boron trifluoride diethyl etherate at room temperature.

Lithiation / methylation of tricarbonyl(benzo[b]thiophene)chromium and its methyl derivatives

Tricarbonyl(benzo[*b*]thiophene)chromium was treated with an equimolar amount of n-butyllithium in tetrahydrofuran under conditions (−78°C) known [11] to effect hydrogen–metal exchange in monocyclic tricarbonyl(arene)chromium complexes. Methylation of the lithio derivative with methyl iodide gave tricarbonyl(2-methylbenzo[*b*]thiophene)chromium as the only product (60–70% yields in repeat experiments). Thus the propensity for hydrogen–metal exchange at the 2-position in the free ligand is unaffected by coordination, and no redirection of lithiation can be achieved. When the above reaction sequence was repeated but with a four fold molar excess of n-butyllithium, tricarbonyl(2,7-dimethylbenzo[*b*]thiophene)chromium was isolated in 27% yield from a mixture containing tricarbonyl(2-methylbenzo[*b*]thiophene)chromium and a compound believed to be a tricarbonyl(trimethylbenzo[*b*]thiophene)chromium complex (mass spectral analysis). It can be concluded that the initially formed 2-lithio compound undergoes subsequent lithiation predominantly at the 7-position.

A systematic study of the reactions of tricarbonyl(methylbenzo[*b*]thiophene)chromium complexes with an equimolar quantity of n-butyllithium in the lithiation/methylation sequence was then carried out in similar fashion. In every reaction studied the predominant product was the dimethylbenzo[*b*]thiophene complex in high yield, accompanied by trace amounts of products believed to be trimethylbenzo[*b*]thiophene complexes (mass spectral analysis). The ease of lithiation at the 2-position is manifested in the formation of orange 2,3- (94%), 2,4- (75%), 2,5- (75%), 2,6- (60%), and 2.7- (65%) dimethylbenzo[*b*]thiophene complexes [23 *] from the 3-, 4-, 5-, 6-, and 7-methylbenzo[*b*]thiophene complexes, respectively. An important result is the regioselective conversion of the 2-methylbenzo[*b*]thiophene complex into tricarbonyl(2,7-dimethylbenzo[*b*]thiophene)-chromium [24 *].

The oxidative deligation of tricarbonyl(arene)chromium complexes is widely used [19] and successful procedures for recovery of reusable carbonylchromium starting materials have been devised [20]. We are currently extending this work as an approach to the synthesis of uncomplexed 2,7-disubstituted-benzothiophenes and trisubstituted benzo[*b*]thiophene derivatives functionalised at the 7-position.



* This and other references marked with asterisks indicate notes occurring in the list of references.

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21 Satisfactory elemental analytical data were obtained. Representative ^{1}H NMR spectra (acetone-d_6): Compound **1**: δ (ppm) 5.58 (H(5)), 5.75 (H(6)), 6.62 (H(4)), 6.77 (H(7)), 7.32 (H(3)), 7.78 (H(2)); $J_{4,7}$ 0.3, $J_{3,7}$ 0.7, $J_{5,7}$ 1.0, $J_{4,6}$ 1.1, $J_{2,3}$ 5.6, $J_{4,5}$ 6.7, $J_{6,7}$ 6.8 Hz. 3-Methylbenzo[*b*]thiophenetricarbonylchromium: δ (ppm) 5.58 (H(5)), 5.76 (H(6)), 6.46 (H(4)), 6.74 (H(7)), 7.38 (H(2)); $J_{4,7} = 0.5$, $J_{5,7} = 0.9$, $J_{4,6} = 1.0$, $J_{5,6} = 6.1$, $J_{4,5} = 6.7$, $J_{6,7} = 6.9$ Hz.
22 2-Methyl- [15], 4-methyl- [16] and 6-methyl-benzo[*b*]thiophenes [17] were prepared by known methods. The 3- and 5-methyl isomers were obtained from Synthetic Chemicals (Four Ashes, UK), and 7-methylbenzo[*b*]thiophene was kindly donated by Dr R.P. Dickinson.
23 Representative ^{1}H NMR spectral data (acetone-d_6): 2,3-dimethylbenzo[*b*]thiophenetricarbonylchromium: δ (ppm) 5.56 (H(5)), 5.69 (H(6)), 6.36 (H(4)), 6.66 (H(7)); $J_{4,7}$ 0.4, $J_{4,6}$ 1.0, $J_{5,7}$ 1.1, $J_{5,6}$ 6.1, $J_{4,5} = J_{6,7}$ 6.7 Hz. 2,4-Dimethyl isomer: δ (ppm) 5.39 (H(5)), 5.71 (H(6)), 6.47 (H(7)), 7.06 (H(3)); $J_{3,7} = J_{5,7}$ 0.8, $J_{5,6}$ 6.2, $J_{6,7}$ 6.8 Hz.
24 ^{1}H NMR investigation of the crude product of lithiation/methylation indicated the absence of disubstituted tricarbonyl(benzo[*b*]thiophene)chromium complexes other than the 2,7-dimethyl isomer.