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REGIOSELECTIVE LITHIATION OF Π-(ARENE)CHROMIUM TRICARBONYL COMPLEXES

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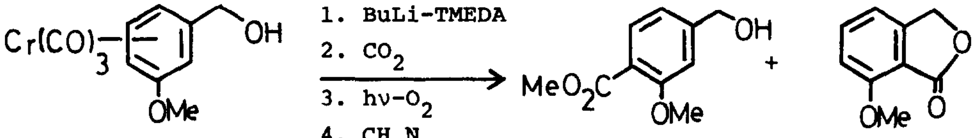
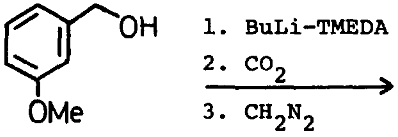
Summary: Chromium tricarbonyl complexes of 3-methoxybenzyl alcohol and related compounds were selectively lithiated at the 4-position in contrast to the corresponding metal free arene compounds. The resulting 4-lithio complexes were converted to the 4-substituted arene compounds in moderate to excellent yields through the reactions with proper electrophiles and subsequent demetalation.

The 3-methoxybenzyl alcohol and related compounds have been shown to be lithiated mostly at the 2-position of the aromatic ring due to the stabilization of the carbon-lithium bond by an intramolecular coordination between the lithium and the proximal oxygen atoms1), 2). With the π-(arene)chromium tricarbonyl complexes of these aromatic compounds, the lithiation is further accelerated by the enhancement of the acidity of the aromatic ring protons3). However, its regioselectivity is different from that with the corresponding metal free arene compounds. This report provides evidences on this lithiation of the chromium complexes (see Table).

(3-Methoxybenzyl alcohol)chromium tricarbonyl complex, 1 4), mp. 109-110°C, was treated with 2eq. of n-butyllithium and tetramethylethylenediamine (TMEDA) in ether at -78°C for 2h, and then with a large excess of solid carbon dioxide to give the carboxylated products. The crude product mixture was demetalated by air oxidation (sunlight exposure) and methylated with diazomethane. After purification, two products, methyl 4-hydroxymethyl-2-methoxybenzoate 2 (77%) and 7-methoxyphthalide 3 (23%), were obtained in overall yield of 71% (eq. 1). On the other hand, 3-methoxybenzyl alcohol itself was lithiated preferentially at the 2-position to give the phthalide 3 as a major product after carboxylation and methylation1) (eq. 2).



1 2 (ratio; 77:23) 3 eq. 1

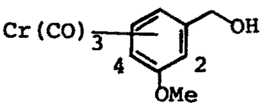
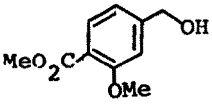
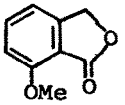
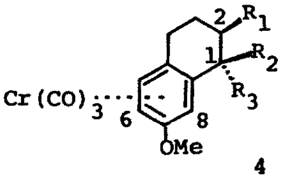
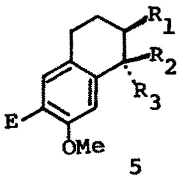
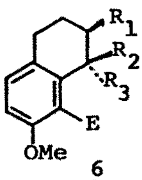
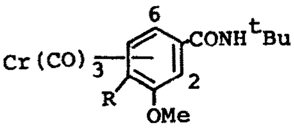
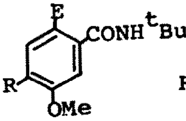
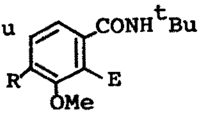


2 + 3 (ratio; 10:90) eq. 2

When the hydroxymethyl group is fixed by a rigid conformation as in 1,2,3,4-tetrahydro-7-methoxy-1-naphthol, the effect of the chromium coordination on the regioselectivity would be of more interest. In fact, endo-(1,2,3,4-tetrahydro-7-methoxy-1-naphthol)chromium tricarbonyl complex 4 (R_1=R_2=H, R_3=OH), mp. 120-121°C, prepared from lithium aluminum hydride reduction of (3,4-dihydro-7-methoxy-1(2H)-naphthalenone)chromium tricarbonyl complex$^{5)}$, gave exclusively 1,2,3,4-tetrahydro-7-methoxy-6-methoxycarbonyl-1-naphthol (5, E=CO_2Me) in a similar reaction sequence (entry 2), in contrast to the result with the parent 1,2,3,4-tetrahydro-7-methoxy-1-naphthol (100% formation of 6, E=CO_2Me)$^{1)}$. When the electrophile was changed from carbon dioxide to other carbonyl and silyl compounds (entry 3-6), the yield was greatly improved to be practically quantitative$^{6)}$. The high regioselectivity of this lithiation is explained by the steric hindrance of the coordinated bulky chromium tricarbonyl group, which would affect more critically the more crowded 8-position (or 2-position of 1) than the 6-position of 4 (or 4-position of 1). This steric effect seems to exceed the stabilization effect of the hydroxymethyl oxygen on the preferential formation of the 8-lithio compound, since a diastereomeric exo-chromium complex$^{7)}$ 4 (R_1=R_3=H, R_2=OH), mp. 90-91°C, still shows the predominant formation of 6-methoxycarbonylated product under the same reaction conditions (entry 9).

These two reactions (with and without chromium complexation on lithiation) are supplemented each other and provide useful tool in organic synthesis of arene compound having various substituents at the different position.

Table; Electrophilic quenching of the lithio π-(arene)chromium tricarbonyl complexes

Entry	(Arene)chromium tricarbonyl complex	Electrophile (E)	Products and Formation ratio		Isolated yield %
1	 1	CO_2	 2  3	77:23	71
	 4		 5  6		
2	$R_1=R_2=H$, $R_3=OH$	CO_2	$E=CO_2Me$	100:0	65
3	$R_1=R_2=H$, $R_3=OH$	Me_3SiCl	$E=SiMe_3$	100:0	96
4	$R_1=R_2=H$, $R_3=OH$	p-MeO-C_6H_4CHO	E=CH(OH)C_6H_4-OMe(p)	100:0	90
5	$R_1=R_2=H$, $R_3=OH$	o-$C_6H_4(CO_2Me)_2$	E=CO-C_6H_4-CO_2Me(o)	100:0	91
6	$R_1=R_2=H$, $R_3=OH$	Me(CH$\underset{E}{=}$CMe)COCl	E=CO-CMe=CHMe	100:0	82
7	R_1=Me, R_2=H, R_3=OH	CO_2	$E=CO_2Me$	100:0	63
8	R_1=CH(OH)Me, R_2=H, R_3=OH	CO_2	$E=CO_2Me$	100:0	55
9	$R_1=R_3=H$, $R_2=OH$	CO_2	$E=CO_2Me$	86:14	52
	 7		 8  9		
10	R=H	CO_2	$E=CO_2Me$	50:50	44
11	R=OMe	CO_2	$E=CO_2Me$	60:40	52

The chromium complexes of meta-oxygenated-N-tert-butylbenzamides 7 were lithiated at both the ortho positions (at C-6 and C-2) of the amido group to produce 8 and 9 in a nearly equal ratio (entry 10 and 11)[8]. Although the selectivity was not high in these cases, the former products could not be obtained by direct metalation of the free arenes[2].

We are actively investigating the limitation of this reaction and synthetic utility to natural polyhydroxylated anthraquinone derivatives such as fallacinal[9] and ω-hydroxyemodin[10], and also natural phenolic compounds.

References and Notes

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2. m-Oxygenated N-substituted benzamides, piperonal cyclohexylimine, dimethylacetal of m-oxygenated benzaldehydes and 2-(3-methoxyphenyl)-4,4-dimethyl-2-oxazoline are also directly lithiated in a similar manner via an intramolecular coordination. Amide: P. Beak and R. A. Brown, J. Org. Chem., 42, 1823 (1977); J. E. Baldwin and K. W. Bair, Tetrahedron Lett., 2559 (1978); I. Forbes, R. A. Pratt, and R. A. Raphael, ibid., 3965 (1978); S. O. de Silva, I. Ahmad, and V. Snieckus, ibid., 5107 (1978) and references cited therein. Imine: F. E. Ziegler and K. W. Fowler, J. Org. Chem., 41, 1564 (1976). Dimethylacetal: H. Plaumann, B. A. Keay, and R. Rodrigo, Tetrahedron Lett., 4921 (1979). Oxazoline: A. I. Meyer and E. D. Mihelich, J. Org. Chem., 40, 3158 (1975).
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4. The (arene)chromium tricarbonyl complexes used as starting materials were prepared by refluxing a heptane:dibutyl ether solution of a proper arene and chromium hexacarbonyl under nitrogen in a Strohmeier type apparatus[11] and characterized spectroscopically.
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7. The exo-chromium complex was prepared from the endo-compound by treatment with conc. sulfuric acid in dichloromethane: S. Top, A. Meyer, and G. Jaouen, Tetrahedron Lett., 3537 (1979).
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