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 (10) P. M. Maitlis, "The Organic Chemistry of Palladium", Vol. II, Academic Press, New York and London, 1971, Chapter 3, p. 127.
 (11) Satisfactory NMR, IR, and mass spectra and elemental analyses were obtained for this material.
 (12) A cis isomer was not detected by NMR spectroscopic analysis.

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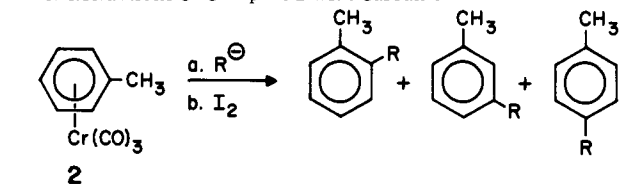
Meta-Substituted Aromatics by Carbanion Attack on π -Anisole and π -Toluenetricromium Tricarbonyl

Sir:

The addition of carbanions to η^6 -benzenetricarbonylchromium(0) proceeds under mild conditions to produce a η^5 -(alkylcyclohexadienyl)tricarbonylchromium(0) complex which can be oxidized to form the alkylbenzene.¹ This formal substitution for hydride may have special potential in the synthesis of aromatic derivatives because the activating unit [$\text{Cr}(\text{CO})_3$] is easily attached and removed, and because existing methods² of nucleophilic aromatic substitution generally require a halogen or other electronegative atom at the site of substitution. Since arene substrates will generally bear more than one hydrogen substituent, important questions arise as to whether useful regioselectivity can be attained and what the factors are which influence the site of attack.³ Here we report preliminary studies of the reaction of carbanions with complex **1**, η^6 -anisoletricarbonylchromium(0),⁶ complex **2**, η^6 -toluenetricarbonylchromium(0),⁷ and the complexes (**3**, **4**, **5**)⁸ of the dimethoxybenzenes. The results provide evidence of useful selectivities and some hints concerning the mechanism of the reactions.

The results of the reaction of η^6 -toluenetricarbonylchromium (**2**) with a variety of carbanions are displayed in Table I. In each case, equimolar amounts of anion (prepared according to standard procedures) and complex **1** were mixed at -78°C or lower under argon in tetrahydrofuran or in a mixture of THF with hexamethylphosphoric triamide (HMPA). After a short time at 0°C or below, excess iodine was added and the mixture was stirred at 25°C for 3–4 h. Conventional isolation procedures produced a crude product which was flash distilled and carefully analyzed using quantitative GLC with an internal standard. Except as noted, all products were prepared in pure form by unambiguous independent routes and were used to calibrate the GLC analysis. The distribution of products depends on the nature of the anion, except for a consistent absence of para substitution. Entries 2, 3, and 4 show that there is little effect of reaction temperature on the distribution of products and that conversion is complete after a few minutes at -78°C . With cyano- and carboalkoxy-stabilized carbanions, there is a preference toward meta substitution which increases as the size of the carbanion unit increases. Lithio-1,3-dithiane (entry 7) is much less selective, producing almost equal amounts of 1,2- and 1,3-substituted products.

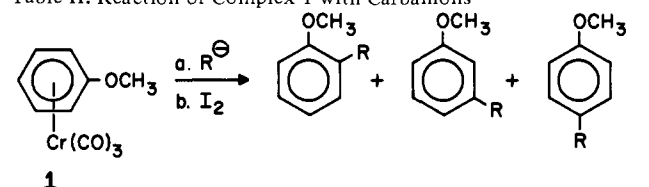
Table I. Reactions of Complex **2** with Carbanions



Carbanion	Time (min)/ temp ($^\circ\text{C}$)	Product mixture			Combined yield (%)
		Ortho	Meta	Para	
1. LiCH_2CN	5/-78 ^a	35	63	2	88
2. $\text{LiC}(\text{CH}_3)_2\text{CN}$	1.5/-100	2	96	2	52
3. $\text{LiC}(\text{CH}_3)_2\text{CN}$	1.5/-78	1	97	2	95
4. $\text{LiC}(\text{CH}_3)_2\text{CN}$	20/0	1	97	2	86
5. $\text{LiCH}_2\text{CO}_2-t\text{-Bu}$	15/0 ^b	28	72	0	89
6. $\text{LiC}(\text{CH}_3)_2\text{CO}_2-t\text{-Bu}$	10/0	3	97	0	96
7. $\text{Li}-\text{S}(\text{CH}_2)_2\text{S}$	15/0	52	46	2	94

^aThe medium was a mixture of THF/HMPA, 12.5/1. ^bThe medium was an equivolume mixture of THF and HMPA.

Table II. Reaction of Complex **1** with Carbanions^a



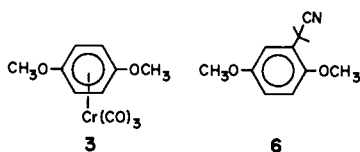
Carbanion	Medium	Product distribution			Combined yield (%)
		Ortho	Meta	Para	
1. LiCH_2CN	THF	3	97	0	38
2. $\text{LiC}(\text{CH}_3)_2\text{CN}$	THF	3	97	0	93
3. $\text{LiCH}_2\text{CO}_2-t\text{-Bu}$	THF/HMPA	6	94	0	86
4. $\text{LiCH}(\text{CH}_3)\text{CO}_2-t\text{-Bu}$	THF/HMPA	4	96	0	93
5. $\text{LiC}(\text{CH}_3)_2\text{CO}_2-t\text{-Bu}$	THF/HMPA	0	100	0	76
6. $\text{Li}-\text{C}(\text{CN})(\text{OR})\text{CH}_2\text{Ph}^b$	THF/HMPA	0	100 ^b	0	75
7. $\text{Li}-\text{S}(\text{CH}_2)_2\text{S}$	THF	10	90	0	35

^aThe complex was added to the carbanion at -78°C and held at 0°C for 15 min before quenching with excess iodine. ^bThe product is benzyl (*m*-methoxyphenyl) ketone, identified by comparison of the melting point of the semicarbazone derivative; cf. J. Levy and R. Perrot, *Bull. Chem. Soc. Fr.*, 49, 1730, 1734 (1931). It is homogeneous by GLC and ^1H NMR. $\text{R} = \text{CH}(\text{CH}_3)\text{OCH}_2\text{CH}_3$; see ref 10.

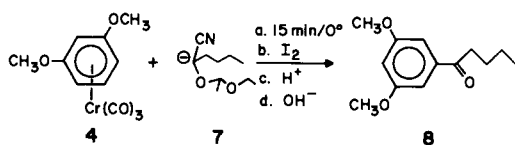
The results of the reactions of η^6 -(anisole)tricarbonylchromium (**1**) with a similar collection of anions are presented in Table II. The anisole complex is somewhat less reactive than complex **2**, and HMPA in the reaction medium is important in order to achieve complete conversion with ester enolates. For entry 6, the isolation procedures include acid and base hydrolysis,¹⁰ and the yield refers to the overall process, resulting in completely selective formation of benzyl (*m*-methoxyphenyl) ketone. Just as with complex **2**, substitution in the para position of complex **1** is apparently not favored; ortho substitution is also disfavored even with the less bulky anions (entries 1 and 3). Very reactive anions such as 2-lithio-1,3-dithiane (entry 7) gives predominant meta substitution, but the yields are low due to competitive proton abstraction, presumably from the ortho position of complex **1**.¹¹

Dialkoxyarene ligands appear to be somewhat less reactive than anisole, but smooth additions are achieved using nitrile-

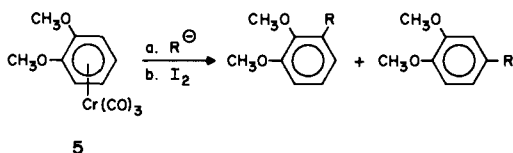
stabilized anions with HMPA as cosolvent with THF. For example, η^6 -(1,4-dimethoxybenzene)tricarbonylchromium (3) reacts with 2-lithio-2-cyanopropane to produce, after quenching with iodine, the substitution product 6 in 92%



yield.¹² No displacement of methoxyl occurred. With complex 4, obtained in 95% yield from 1,3-dimethoxybenzene, a direct route to the substitution pattern of olivetol is available. While alkylolithium reagents and 2-lithio-1,3-dithiane react with 4 predominantly by proton abstraction, the anion (7) of the cyanohydrin acetal¹⁰ of valeraldehyde adds smoothly to the arene ring. After an isolation procedure involving sequential addition of excess iodine, aqueous acid, and aqueous base, the ketone 8 was obtained in 92% yield.¹³ Hydrogenation and methyl ether cleavage produced olivetol in 73% yield overall from 1,3-dimethoxybenzene.¹⁴



The selectivity against para substitution shows up clearly in the reactions of η^6 -(1,2-dimethoxybenzene)tricarbonylchromium (5). With lithioacetonitrile, a single product, (2,3-dimethoxyphenyl)acetonitrile (9a), is obtained in 48% yield. The more sterically demanding anion, 2-lithio-2-cyanopropane, produces the 1,2,3-isomer (9b) in 85% yield, and the less crowded 1,2,4-isomer (10b) in 13% yield.



Meta substitution in the presence of an electron donor substituent is consistent with a transition state resembling a cyclohexadienyl anion,¹⁵ but the nearly complete absence of para substitution, especially in those cases where ortho substitution is significant, is unexpected. Experiments are un-

derway to provide more understanding of the selectivities observed here and the scope of the reaction as a preparative method.¹⁶

References and Notes

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- (11) The major by-product has been identified as one of the unsymmetrical isomers of dimethoxybiphenyl by mass spectrometry and ¹H NMR. A possible pathway for its formation involves proton abstraction from 1 (ortho H?) followed by attack by the resulting lithio derivative on another molecule of 1. Then iodine oxidation would give a product with the observed properties.
- (12) Physical and spectral properties of this product were identical with those of an authentic sample obtained from 2,5-dimethoxybenzyl alcohol (chlorination, displacement with cyanide, methylation).
- (13) P. Baekstrom and G. Sundstrom, *Acta Chem. Scand.*, **24**, 716 (1970).
- (14) Few of the alternative routes to olivetol involve direct substitution on a *m*-dimethoxybenzene derivative. For a recent example and leading references, see A. J. Birch and J. Slobba, *Tetrahedron Lett.*, 2079 (1976).
- (15) Assuming the transition state for addition of the anion to the arene ligand resembles the η^5 -(alkylcyclohexadienyl)tricarbonylchromium intermediate, a simple view would predict substantial charge buildup at positions ortho and para to the incoming anion. A donor substituent would more favorably sit at the meta position.
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