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(5) This and the subsequent new compounds were characterized by full spectroscopic and analytical means.

(6) Dehydrogenation of the intermediate dihydropyridazaprostacyclins by disproportionation or by DDQ resulted in destructive reactions. Pyridazines have previously been prepared usually from cis-unsaturated 1,4-dicarbonyl systems[7] or by wasteful disproportionations of dihydropyridazines.[7,8]

(7) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds", 3rd ed., Wiley, New York, 1976, pp 392 and references cited therein.

(8) B. G. Zimmerman and H. L. Lochte, *J. Am. Chem. Soc.*, **60,** 2456 (1938).

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(10) ^{1}H NMR (220 MHz, $CDCl_3$): **15,** τ 3.03 (s, 1 H, H-7), 4.36 (m, 2 H, H-13, H-14); **17a,b,** τ 2.68 (s, 0.5, H-7 meta to *N*-oxide),[11] 3.20 (s, 0.5 H, H-7 para to *N*-oxide),[11] 4.28 (m, 2 H, H-13, H-14).

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(12) 6,9-Pyridazaprostacyclin showed higher potency than PGE_1 but less than PGI_2 in inhibiting platelet aggregation and dilating the isolated perfused cat coronary artery.[13]

(13) Tests on platelet aggregation were carried out in Professor J. B. Smith's laboratories at the Cardeza Foundation, Thomas Jefferson University, Philadelphia, Pa. 19107. The biological studies with the cat coronary artery were performed in Professor A. M. Lefer's laboratories, Department of Physiology, Thomas Jefferson University, Philadelphia, Pa. 19107.

(14) This research was supported by the National Institutes of Health (Heart, Lung and Blood Institutes, HV-E2931) and Merck Sharp & Dohme, U.S.A., and Ono Pharmaceutical, Japan. ^{1}H NMR spectra were obtained at the Middle Atlantic Regional NMR Facility (NIH No. RR542) at the University of Pennsylvania directed by Dr. G. McDonald.

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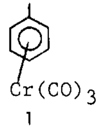
Metalation of Arenechromium Tricarbonyl Complexes and Electrophilic Trapping of the Complexed Phenyllithium Intermediate

Sir:

Proton abstraction from aromatic rings by strong base (metalation) is a method of direct activation of a ring carbon atom as a nucleophile.[1] Simple arenes can be metalated under special conditions,[1,2] but alkylarenes undergo preferential side-chain metalation (benzylic carbanion).[3] Recent developments suggest that functionalized arenes can allow efficient, selective, and preparatively useful metalation ortho to the functional group.[1c,4]

The chromium tricarbonyl unit forms π complexes with arenes, and perturbs the reactivity of the arene ligand in several distinct ways,[5] including enhanced acidity of benzylic C–H bonds[6] and the arene ring C–H bonds.[7] Preliminary observations suggest that π-(benzene)chromium tricarbonyl and bis(benzene)chromium can be directly metalated with alkyllithium reagents in low yield.[7b-d] We have been interested in generating intermediates such as **1** and **2**, because subsequent reaction with carbon electrophiles would produce directly π-arenechromium tricarbonyl complexes with elaborated substituents, useful in further nucleophilic substitution via the addition/oxidation method.[8,9]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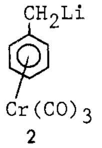
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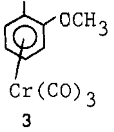
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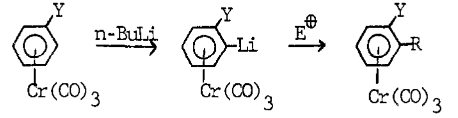
Table I. Electrophilic Quenching of the *o*-Lithio π-(Arene)chromium Tricarbonyl Complexes


(1)

entry	group Y	group E^+	product, % yield[a] (% recovered starting material)
1	H	CO_2	$-CO_2CH_3$,[b] 72 (0)
2	H	CH_3COCH_3	$-CH(OH)(CH_3)_2$, 29 (60)
3	H	CH_3OSO_2F	$-CH_3$,[c] 91 (2)
4	H	PhCHO	$-CH(OH)Ph$, 60 (0)
5	H	$(CH_3)_3SiCl$	$-Si(CH_3)_3$, 94 (0)
6	H	I_2	$-I$,[d] 76 (<5)
7	OCH_3	CH_3OSO_2F	$-CH_3$,[c] 65 (5)
8	OCH_3	CO_2	$-CO_2CH_3$,[b] 86 (0)
9	OCH_3	CH_3COCH_3	$-C(OH)(CH_3)_2$, 85 (<10)
10	OCH_3	PhCHO	$-CH(OH)Ph$,[e] 94 (0)
11	OCH_3	$(CH_3)_3SiCl$	$-Si(CH_3)_3$,[f] 70 (0)
12	F	CH_3OSO_2F	$-CH_3$,[c] 68 (30)
13	F	CO_2	$-CO_2CH_3$,[b] 99 (0)
14	F	CH_3COCH_3	$-C(OH)(CH_3)_2$, 85 (15)
15	F	PhCHO	$-CH(OH)Ph$,[e] 57 (0)
16	F	$(CH_3)_3SiCl$	$-Si(CH_3)_3$,[f] 46 (0)
17	Cl	CH_3OSO_2F	$-CH_3$,[c] 81 (6)
18	Cl	CO_2	$-CO_2CH_3$,[b] 98 (0)
19	Cl	CH_3COCH_3	$-C(OH)(CH_3)_2$, 67 (28)
20	Cl	PhCHO	$-CH(OH)Ph$,[e] 71 (0)
21	Cl	$(CH_3)_3SiCl$	$-Si(CH_3)_3$,[f] 49 (0)

[a] Unless otherwise noted, the chromium complexes were crystallized and fully characterized with ^{1}H NMR and combustion analysis. [b] The methyl ester complex was obtained by treatment of an ethereal solution of the crude carboxylic acid with diazomethane. [c] This yield was determined by GLC analysis of the free arenes after oxidative decomplexation (ceric ammonium nitrate, 25 °C). [d] The product containing π-(benzene)chromium tricarbonyl (<5%) which is difficult to remove efficiently. Recrystallization provides pure product, 54% yield. [e] The product was a mixture of diastereoisomers; the yield is for the mixture. [f] The 2,6-disilylated product was observed, 10–20% yield.

The investigation in our laboratory began with the observation that, while *tert*-butyllithium added to the π system of the arene ligand,[9,10] *n*-butyllithium acted as a base, producing a species (presumably **1**) which reacted with excess iodine to give iodobenzene (71% yield). Under optimum conditions (*n*-butyllithium, THF, tetramethylethylenediamine, −78 °C, 0.3 h), **1** was formed with high efficiency and could be trapped by addition of 1 mol equiv of iodine and other electrophiles (Table I). Under these conditions, the arene–chromium bond is maintained (eq 1). Complex **1** showed a contrast with phenyllithium in reaction with acetone; addition to the carbonyl group was a minor process (29%), while proton abstraction from the acetone accounted for 60% of the material.[11] In general, the ligand can be detached from the chromium in high yield by treatment with excess iodine or with cerium(IV) at 25 °C.[9]

Treatment of π-(anisole)chromium tricarbonyl[12] with *n*-butyllithium (ether, −35 °C, 0.5 h) produced a yellow solution of **3**, which is stable for many hours at −20 °C, but decomposes slowly at higher temperature. Entries 7-11 (Table I) display the results of reaction with representative electrophiles. Acetone reacted by addition to the carbonyl group. With methylating agents such as methyl iodide (instead of methyl fluorosulfonate, entry 7), three products are detected after removing the chromium: anisole (25%), *o*-methylanisole (30%), and 2,6-dimethylanisole (30%). This mixture is consistent with rapid proton transfer during methylation.[13] Attempts to alkylate **3** with simple primary alkyl sulfonate esters failed. However, overall alkylation can be achieved in good yield by

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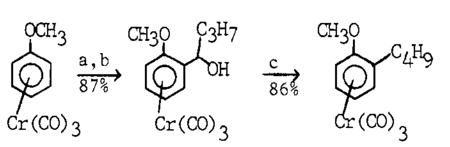


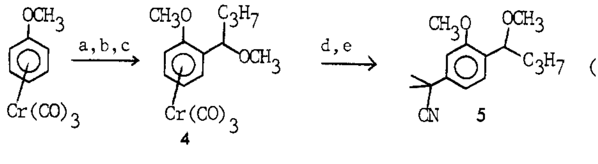
(2)

a. n-BuLi b. C_3H_7CHO c. Et_3SiH, CF_3CO_2H

the three-step procedure in eq 2, making use of the ionic hydrogenation method.[14]

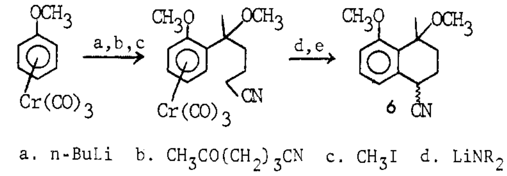
Metalation of π-(fluorobenzene)chromium tricarbonyl with *n*-butyllithium (ether, −78 °C, 0.5 h) produced a clear yellow solution which turned red with obvious decomposition above −20 °C. Entries 12-16 (Table I) display the results of reaction with electrophiles. Similarly, π-(chlorobenzene)chromium tricarbonyl reacted smoothly with *n*-butyllithium (ether, −35 °C, 0.3 h) to give a yellow solution stable below −20 °C, which led to the products presented in Table I, entries 17-21). With both the fluorobenzene and chlorobenzene complexes, reaction with acetone occurred by preferential addition to the carbonyl group, but proton transfer is significant (entries 14 and 19) leading to recovered starting complex. The product with benzaldehyde is a mixture of diastereoisomers, separable by chromatography, in a ratio of ~60:40.

The carbonyl addition products (entries 4, 9, 10, 14, 15, 19, and 20 and eq 2) are particularly important, since it is generally not possible to form chromium tricarbonyl complexes of arenes bearing electronegative substituents (halogen, oxygen) in a benzylic position using the direct thermal reaction with chromium hexacarbonyl. Simple applications are presented in eq 3 and eq 4. In the first example, π-(anisole)chromium tricarbonyl was substituted once by reaction with an electrophilic carbon and again by nucleophilic addition/oxidation, both with complete regiospecificity. Complex **4** was obtained in a yield of 53%, and the final product (**5**) was isolated in 65% yield, contaminated with a trace of the free arene from **4**.[15] In the latter example (eq 4), a simple annelation of anisole is achieved, in a yield of 50% in the second step for tetralin derivative **6** (characterized as a mixture of diastereoisomers).[16]



(3)

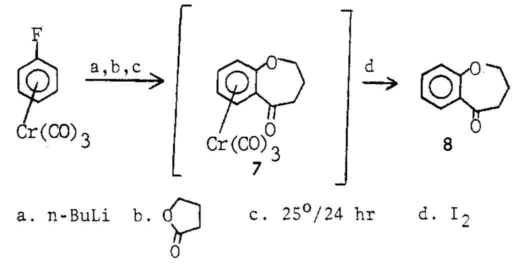
a. n-BuLi b. C_3H_7CHO c. CH_3I d. $LiC(CH_3)_2CN$ e. I_2



(4)

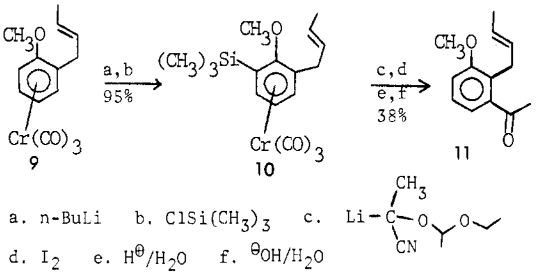
a. n-BuLi b. $CH_3CO(CH_2)_3CN$ c. CH_3I d. $LiNR_2$ e. I_2

Similarly, cyclization can occur through halide displacement after initial metalation. Acylation of π-(*o*-lithiofluorobenzene)chromium tricarbonyl with γ-butyrolactone was followed by spontaneous (25 °C, 24 h) fluoride displacement to give complex **7** (not isolated). Oxidation with excess iodine liberates heterocycle **8**, in a yield of 48% overall (eq 5).



(5)

Direct ring metalation of alkyl-substituted arenes is generally not efficient, owing to preferential abstraction of a benzylic hydrogen; in toluene, the kinetic acidity of the methyl protons is higher than the acidity of the ring protons by a factor of 150.[17] However, coordination with the chromium tricarbonyl unit appears to enhance the acidity of the ring protons more than the benzylic protons. For example, treatment of π-(toluene)chromium tricarbonyl with *n*-butyllithium (1.1 mol equiv, −78 °C, ether) followed by addition of CO_2, methylation with diazomethane, and decomplexation (cerium) produces a mixture of methyl toluates (ortho:meta:para, 10:45:45) in 53% yield and methyl phenylacetate in 13% yield. The effect is more dramatic with π-[(2-butenyl)anisole]chromium tricarbonyl (**9**)[18] where metalation/silylation proceeds with complete selectivity for the hydrogen ortho to methoxy. This procedure is useful for two reasons: first, the direct thermal reaction between chromium hexacarbonyl and arenes fails to give good yields of π-(arene)chromium tricarbonyl complexes when the arene has a 1,2,3 substitution pattern as in **10**, and, second, the trimethylsilyl substituent is a useful directing group[19] for the addition/oxidation sequence, easily removed during isolation (eq 6).[20] In this way, the arene complex **9** led to the 1,2,3-substitution pattern, in **11**, regiospecifically.[4]



(6)

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(4) For ortho metalation of (a) anisole derivatives, see R. C. Ronald, *Tetrahedron Lett.*, 3973 (1975), and references therein; (b) 2-phenyloxazolines, see A. Meyers and E. Mihelich, *J. Org. Chem.*, **40**, 3158 (1975), and references therein; (c) benzaldehyde imines, see F. E. Ziegler and K. W. Fowler, *ibid.*, **41**, 1564 (1976); (d) phenylpyrazoles, see A. Marxer and M. Siegrist, *Helv. Chim. Acta*, **57**, 1988 (1974); (e) benzamides, see P. Beak and R. A. Brown, *J. Org. Chem.*, **42**, 1823 (1977).

(5) For a discussion, see M. F. Semmelhack, *Ann. N.Y. Acad. Sci.*, **295**, 36 (1977).

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(7) For examples, see (a) E. Elschenbroich and F. Stohler, *Chimia (Aaran)*, **28**, 730 (1974); (b) A. Nesmeyanov and N. E. Kolobova, *Izv. Acad. Nauk SSSR, Ser. Khim.*, 2665 (1968); (c) C. Elschenbroich, *J. Organomet. Chem.*, **14**, 157 (1968); (d) M. D. Rausch, *Pure Appl. Chem.*, **30**, 523 (1972).

(8) While this work was in progress, the details were published for generation of complex 1 by trans metalation from a π-(mercuriobenzene)chromium tricarbonyl complex and trapping with electrophiles: M. D. Rausch and R. E. Gloth, *J. Organomet. Chem.*, **153**, 59 (1978).

(9) M. F. Semmelhack, H. T. Hall, M. Yoshifuji, and G. Clark, *J. Am. Chem. Soc.*, **97**, 1247 (1975).

(10) The first observation of the behavior we have been studying was reported in 1973: R. J. Card and W. Trayhanovsky, *Tetrahedron Lett.*, 3823 (1973).

(11) Reaction of 1 with acetone-d_6, an attempt to show the pathway of proton transfer, led to carbonyl addition as the major product, presumably owing to a (potentially useful) hydrogen/deuterium isotope effect. The recovered π-(benzene)chromium tricarbonyl (8%) from this reaction did bear deuterium (mass spectral analysis) to the extent of 0.920 deuterium/molecule.

(12) The arene complexes used as starting materials in this work are known[5] and were prepared by heating at reflux a dioxane solution of the arene and chromium hexacarbonyl.

(13) For other examples of ortho metalation of π-(anisole)chromium tricarbonyl and the occurrence of 2,6-disubstituted products, see R. J. Card, Ph.D. Thesis, Iowa State University, 1973.

(14) For a review, see D. N. Kursanov, Z. N. Parnes, and N. M. Loim, *Synthesis*, 633 (1974).

(15) A sample of **5** was obtained by preparative GLC and characterized by ^{1}H NMR, IR, and mass spectral data.

(16) The mixture of diastereoisomers **6** was obtained in high purity by column chromatography and characterized by ^{1}H NMR, IR, and mass spectral data.

(17) A. Streitwelser, Jr., and D. W. Boerth, *J. Am. Chem. Soc.*, **100**, 755 (1978).

(18) Complex **9** was prepared by reaction of *o*-(2-butenyl)anisole with chromium hexacarbonyl in dioxane at reflux in 90% yield, with no evidence of double-bond isomerization (^{1}H NMR) in either position or geometry.

(19) M. F. Semmelhack, G. Clark, R. Farina, and M. Saeman, unpublished work.

(20) For acid-promoted removal of trimethylsilyl groups from arenes, see C. Eaborn, *J. Organomet. Chem.*, **100**, 43 (1975).

(21) We gratefully acknowledge support of this work by the National Science Foundation (CHE 76-01112). We also thank Dr. Robert Farina and Dr. Glenn Clark for preliminary experiments which contributed to the development of the project.

(22) National Science Foundation Graduate Fellow, 1976–1979.

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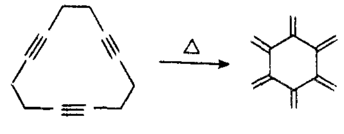
Tricyclobutabenzene

Sir:

Recently there have been several reports on the preparation of 6-radialene (**2**) utilizing high-temperature reaction conditions.[1] In one instance, pyrolysis of 1,5,9-cyclododecatriyne (**1**) at 650 °C has led to the isolation of 6-radialene and it has been suggested that this isomerization may occur via the intermediacy of tricyclobutabenzene (**3**).[2] Thus far, however, all attempts to isolate **3** have been unsuccessful. The perfluoro analogue of **3** has been prepared by a cyclotrimerization reaction and it is a stable, crystalline material (mp 135–136 °C) which shows no evidence for any bond alternation in the central ring.[3]



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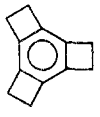

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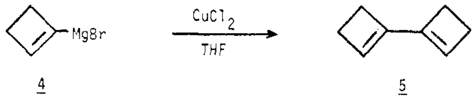
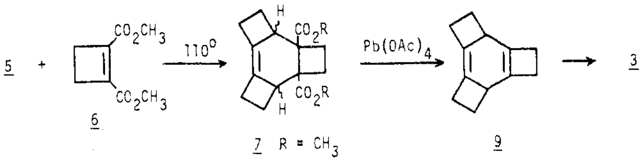
Several years ago we developed a Diels–Alder route to benzocyclobutene and annelated derivatives[4] which has proved to be extremely useful for the preparation of bis- and trisannelated benzenes[5] as well as annelated naphthalenes and anthracenes.[6] In this approach substantial ring strain may be built into the reacting partners of an initial [2 + 4] cycloaddition which is then accompanied by some relief of strain while establishing the cyclic framework of the molecule in a single step. The final aromatization profits from the resonance energy gained by the system and, most importantly, this final step can be carried out under relatively mild conditions (<40 °C).

Lüttke and Heinrich have worked out an elegant preparation of α,α'-dicyclobutenyl (**5**) by the copper chloride promoted coupling of 1-cyclobutenylmagnesium bromide (**4**).[7] This diene is extremely sensitive to acid and oxygen so that appropriate precautions must be taken to prevent its decomposition. After adding 1 equiv of anhydrous copper(II) chloride to a freshly prepared THF solution of the Grignard reagent **4** at 30 °C, the mixture is stirred at room temperature for 1 h and hydrolyzed, and the diene **5** steam distilled along with THF. After dilution of the distillate with pentane, drying over $MgSO_4$, and evaporation of the solvent, the nearly pure diene (mp ~5 °C) is obtained in 41% overall yield from 1-bromocyclobutene.[8]



4 5

The diene **5** is immediately combined with 1 equiv of dimethyl cyclobutene-1,2-dicarboxylate (**6**),[9] sealed in a glass tube, and heated to 110 °C for 12 h. Analysis of the crude Diels–Alder adduct by VPC[10] showed two peaks at 7.0- (19%) and 9.2- (81%) min retention time. Each peak was isolated by preparative VPC and mass spectral analysis showed both to have a parent ion at *m/e* 276 and almost identical fragmentation patterns. The 100-MHz NMR spectra of these two components were very similar with a sharp downfield singlet (6 H) appearing at δ 3.68 for the minor component and 3.64 for the major one. In the upfield region both spectra showed a number of poorly resolved multiplets (14 H). It is presumed that these two peaks represent the endo and exo Diels–Alder adducts, as similar epimers have been observed in other cycloaddition reactions of **6**.[5a,11] After chromatography on silica gel there was obtained 0.61 g (47%) of this mixture of epimers which was then hydrolyzed by treatment with potassium hydroxide in refluxing aqueous methanol. Acidification afforded a nearly quantitative yield of diacid **8**, mp 163–168 °C.



7 R = CH_3
8 R = H

Treatment of the diacid **8** with 2 equiv of lead tetraacetate in dimethyl sulfoxide, with pyridine added to scavenge the acetic acid generated, led to a mildly exothermic reaction accompanied by copious gas evolution. The temperature was maintained at 25–40 °C and, after the gas evolution had ceased (~15 min), the reaction mixture was poured into water and extracted with ether. The ether extracts were dried over $MgSO_4$ and evaporated and the crude product chromatographed on silica gel, eluting with hexane, to provide 2.2 mg (0.5%)[12] of a white solid, mp 141–142 °C. The ^{1}H NMR of this material showed one sharp singlet at δ 3.12. This peak position compares very well with the observed values of δ 3.08 for benzo[1,2:3,4]dicyclobutene[5a] and 3.12 for the cyclobutyl protons of [1,2:3,4]dicyclobuta[5,6]cyclopentabenzene.[13] No peaks were found at either δ 2.30 or 5.31 where the singlets for **1** and **2**, respectively have been reported. The ^{13}C NMR spectrum of **3** showed singlets at δ 138.5 and 29.6 and in the proton-coupled spectrum the upfield singlet splits into a triplet with J = 138.0 Hz. Once again these values correlate very well with the related bisannelated systems.[14]

Analysis of **3** by VPC[15] showed a major peak (96%) at 5.25-min retention time as well as a minor one (4%) at 3.1-min retention time. GC-mass spectrometry of the major peak gave *m/e* (rel intensity) 158 (1.0, M + 2), 157 (13.5, M + 1), 156 (100.0, parent ion), 141 (37.6, M − 15), 128 (19.0, M − 28), and 115 (25.9, M − 41). A high resolution mass spectrum showed the parent ion at *m/e* 156.0932 (calcd for $C_{12}H_{12}$, 156.0939). Whereas Boekelheide does report peaks at *m/e* 141 and 128 for 6-radialene, he also observes only a low intensity parent ion[1c] where this peak is the most intense for compound **3**. As he further points out and as we have also observed, peaks at M − 15 and M − 28 are quite characteristic of benzocyclobutene fragmentation. GC-mass spectrometry of the minor peak showed a parent ion at *m/e* 158 which we take to be good evidence for the dihydro precursor **9**.

The UV spectrum of **3** (isooctane) shows λ_{max} 269 nm (ϵ 170), 265 (sh, 190), 262 (210), 258 (195), 254 (195), 251 (sh, 170), 247 (sh, 150), 222 (5600), and 201 (25 500). The three

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