

Communications to the Editor

Phenylation of Carbanions by π -(Chlorobenzene)chromium Tricarbonyl

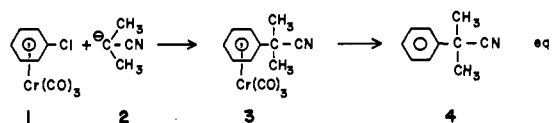
Sir:

The nucleophilic character of aromatic rings provides the driving force in the most important methods for attachment of carbon units to the rings, in Friedel-Crafts acylation and alkylation reactions. Successful reaction with the reverse polarity, that is, nucleophilic substitution on the aromatic ring, is a favorable process only when powerful electron withdrawing substituents sufficiently reduce the electron density of the ring. The introduction and removal of such activating substituents is often a cumbersome and inefficient procedure, which accounts for the fact that nucleophilic addition is seldom used as a method for attachment of carbon units in the synthesis of aromatic natural products.¹ Yet cases arise where the desired product would result directly from combination of a stabilized carbanion and an aromatic ring.² We encountered such a problem in a total synthesis^{3,4} and were led to consider new techniques for the activation of aryl rings toward attack by carbanions. We wish to report preliminary studies employing the chromium tricarbonyl unit as an activating substituent which point to a useful technique for syntheses.⁵

The concept is based on the observation that π -(chlorobenzene)chromium tricarbonyl (**1**)⁶ undergoes substitution of methoxyl for chlorine under mild conditions, approximately as readily as *p*-chloronitrobenzene.⁷ More recent studies further delineated the activating effect of the chromium tricarbonyl unit in reactions of **1** with amine and oxygen nucleophiles.⁸ With reactive carbanions, however, important side reactions involving preferential attack at chromium or at carbon monoxide were anticipated based on many examples of alkyllithium addition to the carbonyl ligand in metal carbonyl complexes,⁹ and our results with

alkyllithium addition to π -benzenechromium tricarbonyl.¹⁰

The overall process we have observed is exemplified by the reaction of complex **1** with the anion of isobutyronitrile (**2**), followed by cleavage of the intermediate π -(alkylbenzene)chromium tricarbonyl complex (**3**). The remarkable activating effect of the chromium tricarbonyl unit is apparent in the rapid (25°/20 hr) conversion of **1** to **3**, compared to no reaction between chlorobenzene and **2** at 25° over a similar period. Complex **3** is isolated by adding water and ether to the reaction mixture and washing with aqueous acid. The ether layer contains **3** in high purity (>95% pure, 78% yield); sublimation at 120° (0.001 Torr) affords a pure sample of mp 121–123° in 51% yield. The complex is characterized by a multiplet from δ 5.2–5.7 (5 H) and a singlet at δ 1.74 (6 H) in the pmr spectrum, strong carbon monoxide absorption at 1980 and 1910 cm^{-1} in the ir spectrum (CHCl_3), and a molecular ion of m/e 281.0146 (calcd for **3** with ^{52}Cr , 281.0144). Removal



of the chromium tricarbonyl group is quantitative under conditions (iodine, ether, 0°)⁷ unlikely to interfere with other functional groups. In all other examples reported here, the intermediate complex parallel with **3** is not isolated; the crude product is oxidized with iodine to give the free organic ligand.

Table I displays a series of simple examples which produce yields that are moderate to high. In each case, the anion is generated below 0° from the appropriate organic acid and lithium diisopropylamide¹¹ in tetrahydrofuran and a solution of π -(chlorobenzene)-chromium tricarbonyl (**1**) in tetrahydrofuran is added at low temperature (−78 to −20°). After 15–20 hr at 25°, the mixture is partitioned between water and ether, and the aqueous layer is extracted several times with ether. Excess iodine is added to the combined ether layers and allowed to stand for 1 hr at 25°. Removal of the excess iodine with aqueous sodium bisulfite solution leaves a green aqueous solution and a nearly colorless ether solution. After removal of the ether, the product is isolated by short path distillation or crystallization. Unless otherwise noted, yields are based on isolated material.

A variety of other reactive anions failed to give significant quantities of the desired phenylation products in preliminary experiments. Failures include the

complexes; see E. O. Fischer and A. Maasböl, *Angew. Chem., Int. Ed. Engl.*, **3**, 580 (1964), and many later references.

(10) M. F. Semmelhack and H. T. Hall, to be submitted for publication.

(11) Prepared according to the procedure used by H. Wynberg, *Tetrahedron Lett.*, 3001 (1971).

(1) A process which is overall equivalent to nucleophilic aromatic substitution is the attack of a nucleophile on a transient benzyne species; cf., R. Hoffmann, "Dehydrobenzene and Cycloarynes," Academic Press, New York, N. Y., 1967, p 100 ff.

(2) The benzyne approach has been used in a total synthesis of lysergic acid: M. Julia, F. LeGoffic, J. Igolen, and M. Baillarge, *Tetrahedron Lett.*, 1569 (1969).

(3) M. F. Semmelhack, B. C. Chong, and L. D. Jones, *J. Amer. Chem. Soc.*, **94**, 8629 (1972).

(4) M. F. Semmelhack, R. D. Stauffer, and T. D. Rogerson, *Tetrahedron Lett.*, 4519 (1973).

(5) A few examples of anionic attack on metal-coordinated arenes have been observed. For examples, see (a) π -arenemanganese tricarbonyl cation, P. J. C. Walker and R. J. Mawby, *Inorg. Chem.*, **10**, 404 (1971); *J. Chem. Soc., Dalton Trans.*, 632 (1973); (b) π -(fluorobenzene)chromium tricarbonyl, D. A. Brown and J. R. Rajo, *J. Chem. Soc. A*, 40 (1966), and L. Tchissambou, G. Jaouen, and R. Dabard, *C. R. Acad. Sci., Ser. C*, **274**, 806 (1972); (c) π -(chloroarene)cyclopentadienyliron cation, A. Nesmeyanov, N. Vol'kenau, and I. Bolesova, *Dokl. Akad. Nauk SSSR*, **175**, 606 (1967); (d) bis- π -areneiron dication, J. F. Helling and D. M. Braitsch, *J. Amer. Chem. Soc.*, **92**, 7207 (1970), and references therein; (e) π -benzenechromium tricarbonyl, R. J. Card and W. S. Trahanovsky, *Tetrahedron Lett.*, 3823 (1973).

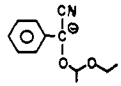
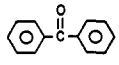
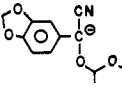
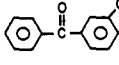
(6) W. Strohmeier, *Chem. Ber.*, **94**, 2490 (1961); see also ref 7.

(7) B. Nicholls and M. C. Whiting, *J. Chem. Soc.*, 551 (1959).

(8) J. F. Bunnett and H. Herrmann, *J. Org. Chem.*, **36**, 4081 (1971).

(9) Attack on metal-coordinated carbon monoxide by alkyllithium reagents is a general method for the preparation of carbene-metal

Table I. Reactions of π -(Chlorobenzene)chromium Tricarbonyl with Carbanions

Anion	Product	% yield
$-\text{C}(\text{CH}_3)_2\text{CN}$	$\text{PhC}(\text{CH}_3)_2\text{CN}$	85–90 ^a
$-\text{C}(\text{CH}_3)_2\text{CO}_2\text{Et}$	$\text{PhC}(\text{CH}_3)_2\text{CO}_2\text{Et}$	71
$-\text{C}(\text{CH}_3)_2\text{CO}_2^-$	$\text{PhC}(\text{CH}_3)_2\text{CO}_2\text{H}$	63 ^b
$-\text{CH}(\text{CO}_2\text{Et})_2$	$\text{PhCH}(\text{CO}_2\text{Et})_2$	51 ^c
		88 ^d
		90 ^{d,e}

^a This yield is from quantitative glpc analysis; a representative isolated yield is ca. 70%. ^b The acid was isolated as the methyl ester. ^c The solvent is hexamethylphosphoric triamide instead of tetrahydrofuran. ^d After the usual iodine oxidation, the cyanohydrin-acetal unit was removed by sequential treatment with acid and base: G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, **93**, 5286 (1971). ^e The product has mp 55–56°, lit. mp 55° (W. Borsche, *Ann.*, **526**, 1 (1936)) and 57° (Ramart-Lucas and J. Hoch, *Bull. Soc. Chim. Fr.*, **5**, 987 (1938)).

lithium salts of 1,3-dithiane, 2-methyl-1,3-dithiane, *tert*-butyl acetate, acetophenone, 5,6-dihydro-2,4,4,6-tetramethyl-4*H*-1,3-oxazine, and acetonitrile. We suspect that primary and secondary carbanions are less efficient because the postulated product chromium complex (parallel with **3**) bears relatively acidic protons (benzylic)¹² and protonates the starting carbanion. With certain of the substrates tested, this process would undoubtedly lead to rapid self-condensation.

The anion of diethyl malonate reacts only slowly with complex **1** in tetrahydrofuran. Raising the temperature to reflux leads to serious side reactions, apparently from decomposition of **1** or an intermediate. However, polar aprotic solvents such as hexamethylphosphoric triamide (HMPA) have an accelerating effect on the reaction and lead to generally simpler product mixtures. With HMPA as solvent, diethyl malonate anion reacts to completion with **1** after 24 hr at 50°, and diethyl phenylmalonate is obtained in 51% yield.

Preliminary results indicate that the dependence of reactivity on leaving group for the series of different π -(halobenzene)chromium tricarbonyl complexes is similar to that observed in classical nucleophilic aromatic substitution.¹³ As displayed in Table II, π -(iodobenzene)chromium tricarbonyl¹⁴ shows no reaction toward malonate anion under conditions where complex **1** reacts to a small extent and π -(fluorobenzene)chromium tricarbonyl¹⁵ is nearly completely converted. The higher reactivity of the fluoro complex (**5**) leads to much higher yields than can be obtained from **1**, with malonate anion, for example (entries 2 and 6, Table II). The anion of *tert*-butyl α -methylthiopropionate reacts only very slowly with **1** at 25° in THF but reacts to completion within 15 hr at 25° with complex **5**. In this case, the reaction mixture (after




(12) W. S. Trahanovsky and R. J. Card, *J. Amer. Chem. Soc.*, **94**, 2897 (1972).

(13) Cf., J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958).

(14) G. A. Razuvaev, G. G. Petruchoy, A. N. Artemov, and N. I. Sirotkin, *J. Organometal. Chem.*, **37**, 313 (1972).

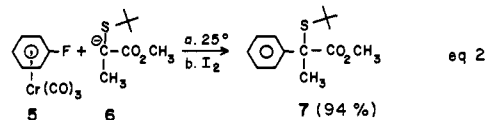
(15) Prepared according to the general method reported in ref 7, but using the recycling technique of Strohmeier (ref 6) and longer reaction times (15–30 hr), the yield of complex **5** raised to 60%.

Table II. Reactions of Diethyl Sodiomalonate with π -(Halobenzene)chromium Tricarbonyl Complexes

Complex	Entry	Conditions ^a	% phenylmalonate yield ^b
 (1)	1	25°, 48 hr	5
	2	50°, 24 hr	51
	3	25°, 48 hr	0 (very low conversion)
 (5)	4	25°, 48 hr	63
	5	50°, 0.5 hr	72
	6	50°, 20 hr	>95

^a All reactions are run in HMPA using 2 molar equiv of diethyl sodiomalonate. ^b All yields are by quantitative glpc.

oxidation with iodine) contains two products in approximately equal amounts, *tert*-butyl 2,2-diphenylpropionate and *tert*-butyl 2,2-bis(methylthio)propionate. With the related anion **6**, reaction with complex **5** proceeds smoothly to give (after oxidation), methyl α -phenyl- α -(*tert*-butyl)propionate (**7**) in 94% yield (eq 2).



Experiments to further define the scope and limitations of the chromium tricarbonyl unit as an activating group in "phenylation" of anions are under study; the mechanism¹⁶ of the reaction appears more complicated than that for classical nucleophilic aromatic substitution and may lead to unique applications.¹⁷

(16) M. F. Semmelhack and H. T. Hall, *J. Amer. Chem. Soc.*, **96**, 7092 (1974).

(17) We wish to thank Professor T. Traylor for making us aware of the results in ref 7 and gratefully acknowledge support of this work by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

(18) Fellow of the Alfred P. Sloan Foundation (1972–1974) and recipient of the Camille and Henry Dreyfus Teacher-Scholar Grant (1973–1978).

M. F. Semmelhack,*¹⁸ H. T. Hall

Baker and Olin Laboratories of Chemistry, Cornell University
Ithaca, New York 14850

Received June 27, 1974

Intermediates in the Reaction of Carbanions with π -(Chlorobenzene)chromium Tricarbonyl

Sir:

In the preceding paper, we reported the phenylation of carbanions *via* π -(halobenzene)chromium tricarbonyl complexes.¹ As illustrated by the specific example of isobutyronitrile anion (**1**) and π -(chlorobenzene)chromium tricarbonyl (**2**), a plausible pathway for the reactions is attack by the carbanion to form a π -(alkylcyclohexadienyl)chromium tricarbonyl anion (*i.e.*, **3**) followed by irreversible loss of halide anion to

(1) M. F. Semmelhack and H. T. Hall, *J. Amer. Chem. Soc.*, **96**, 7091 (1974).