Tetrahedron Letters,Vol.30,No.26,pp 3373-3376,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

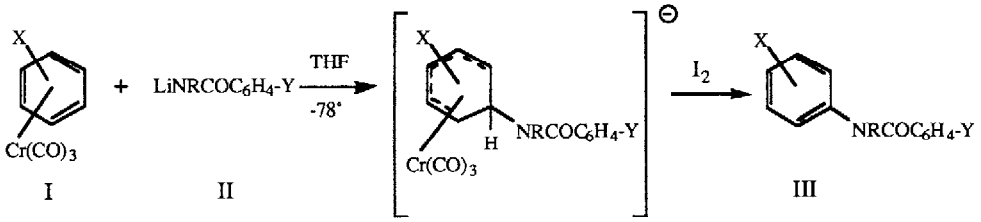
NUCLEOPHILIC ADDITION OF N-LITHIOAMIDES TO π-ARENECHROMIUM TRICARBONYL COMPLEXES. PREPARATION OF ANILINE DERIVATIVES

L. Keller,* K. Times-Marshall,† S. Behar,† and K. Richards†
Department of Chemistry
Florida International University
Miami, FL 33199 USA

SUMMARY: A simple procedure for the preparation of aniline derivatives by the nucleophilic addition of nitrogen anions to π-(arene)chromium tricarbonyl complexes is described.

Despite its importance, the number of methods for the introduction of nitrogen-bearing functional groups onto an aromatic ring is quite limited. Furthermore, almost every standard method of nitrogen-to-arenecarbon bond formation requires either electrophilic attack by nitrogen (nitration, azobenzene formation, etc.) or the use of Hofmann/Curtius/Schmidt-like rearrangements. Introduction of nitrogen as a nucleophile is limited to those very few cases where either the arene substrate is a halobenzene with several powerful electron-withdrawing substituents[1] or amines are added to a benzyne intermediate.[2]

We now wish to report that an extension of the Semmelhack method[3] of nucleophilic substitution on a π-(arene)chromium tricarbonyl complex can lead to the replacement of hydride by nitrogen on an aromatic ring resulting in the direct formation of aniline derivatives. The only reports of $Cr(CO)_3$-assisted nucleophilic substitution by nitrogen involve substitution of an amine nucleophile for fluoride in a π-(fluorobenzene)chromium tricarbonyl derivative.[4,5] The difficulty in preparing such organometallic substrates, however, is a serious limitation in developing a general synthetic method with these complexes.



I II III

Scheme 1.

We have found that the lithium salts of primary carboxamides will successfully substitute directly for hydride in π-(arene)chromium tricarbonyl complex leading to benzanilides. For example, addition of an excess of N-lithiobenzamide derivative II (Y=H) to a tetrahydrofuran solution of complex I ($X=CH_3$) at -78° followed by iodine oxidation of the intermediate cyclohexadienyl anion affords benzanilide derivative III in 93% yield.

Table 1. summarizes the experimental results for the reaction of some carboxamide anions and π-(benzene)chromium tricarbonyl derivatives. While a variety of such anions does undergo nucleophilic substitution, our results indicate that the lithium salts of primary aromatic amides add with the best yields. Entries 4-6 show that the reaction is also successful if there are substituents on the benzamide ring, but the yield is lowered somewhat if the substituent is electron-withdrawing. Entries 7 and 8 show that the substitution reaction occurs with significant regioselectivity. The *ortho:meta:para* substitution ratio is 68:26:6 in the case of π-(toluene)chromium tricarbonyl and 25:60:18 in the case of π–(anisole)chromium tricarbonyl. In each instance *para*-substitution is the least favored pathway, but the proportion of the *para* isomer is greater than that found in reactions with the same complexes when carbanion nucleophiles are employed.[3d] The *ortho:para* ratios reverse between the toluene and anisole complexes in the nitrogen series, while *meta* substitution appears always to be favored in the carbon series. Substitution by amino in fluoride-substituted complexes has already been reported.[4] Substitution for chloride (Entries 10 and 11) occurs in very low yield despite the fact that the analogous substitution occurs smoothly with carbanion nucleophiles.[3b]

Primary aliphatic carboxamide nucleophiles (Entries 13, 14,15) do add to these chromium complexes, but isolated yields are variable and generally lower than those obtained with aromatic amides. In the case of the lower molecular weight anilides, the lower yields appear to be due to significant loss of product during the extractive workup procedure. Quantitative HPLC analysis of the crude reaction mixtures in these cases shows that actual percent conversions are as high as those obtained with aromatic amide nucleophiles.

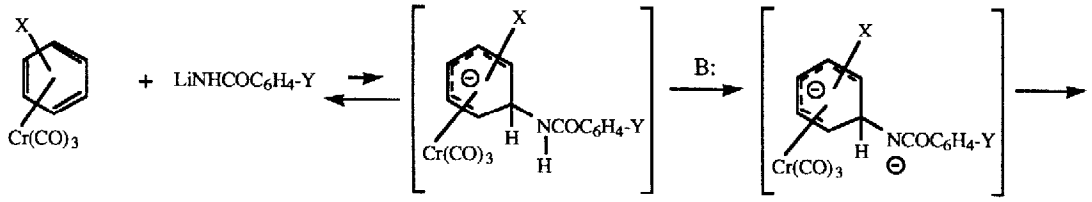
In a typical procedure, N-lithiobenzamide is prepared by the dropwise addition of 2.0 mmol of *n*-butyllithium (≈2M in hexane) at -78° under nitrogen to a solution of 2.1 mmol of benzamide in 4 ml of dry THF. After stirring for 30 min, π–(benzene)chromium tricarbonyl (0.214 g, 1.0 mmol) is added in one portion *via* a solids addition apparatus. The resulting mixture is allowed to stir for 30 min at -78° and for an additional 30 min at 0°. After cooling again to -78°, a solution of iodine (1.3 g, 5.0 mmol) in 5 ml of dry THF is added in one portion, and the reaction mixture is allowed to stir for four hours at room temperature . The reaction mixture is diluted with 100 ml of ether and washed successively with 20 ml of 10% sodium bisulfite solution, and 100 ml of saturated brine. The organic layer is dried over anhydrous magnesium sulfate and concentrated by rotary evaporation to afford 175 mg (89%) of pure benzanilide.

Entry	Arene I	Amide II		% Anilide	Comments
	X	Y	R		
1	H	H	H	89	
2	H	H	CH_3	0	
3	H	H	*n*-Bu	0	
4	H	*p*-CH_3	H	75	
5	H	*p*-OCH_3	H	81	
6	H	*m*-NO_2	H	61	
7	CH_3	H	H	93	68 *ortho*:26 *meta*:6 *para*
8	OCH_3	H	H	85	25 *ortho*:60 *meta*:18 *para*
9	H	Phthalimide		12	
10	Cl	H	H	<10	
11	Cl	H	CH_3	<10	
12	H	β-Naphthamide		80	
13	H	LiNHCO*t*-Bu		27	
14	H	LiNHCO*i*-Pr		37	
15	H	Hydrocinnamide		76	

Table 1.

Other nitrogen anions (*e.g.*, lithium diisopropylamide, N-lithioaniline, N-lithiobenzamidine, N-lithiobenzophenone imine, and N-lithio-*t*-butyl carbamate) do not afford identifiable products. In an attempt to demonstrate that substitution products may actually form in these cases but do not survive treatment with iodine, alternative methods of oxidation with Ce(IV) or O_2 were used. Isolable products could still not be found.

There are two observations which strongly suggest that the mechanism for the substitution reaction in the case of nitrogen nucleophiles differs from that which is operating in the carbon series: (1) two equivalents of base are required for complete addition of primary amide anions (see typical experimental procedure, above), and (2) anions of secondary amides do not add at all to π-(arene)chromium tricarbonyl complexes (Table 1, Entries 2,3). The mechanism which is therefore operating in the nitrogen series appears to require abstraction of a second proton from nitrogen after initial addition of the amide anion to the complex. Such an irreversible abstraction of the second proton may circumvent what is an otherwise unfavorable equilibrium in the initial addition process (Scheme 2). Such unfavorable equilibria have been observed with some of the more stable carbanions whose pK_a's are in the same range as the primary amides.[3]



Scheme 2.

Experiments to study the details of the mechanism of the nitrogen nucleophile addition are in progress. In addition, studies are presently underway on the intramolecular analog of this reaction as a means of preparing benzannulated nitrogen heterocycles by the cyclization of appropriate amidoalkylarene chromium complexes.

ACKNOWLEDGMENT. This work was supported by a grant from MBRS Program of the National Institutes of Health (RR 08205).

REFERENCES

† National Institutes of Health Minority Biomedical Research (MBRS) Undergraduate Participant

1 *cf,* J.F. Bunnett, *Quart. Reviews, Chem. Soc.*, **12**, 1 (1958).

2 *cf,* R.W. Hofmann, *Dehydrobenzene and Cycloalkynes*, Academic Press, New York, 1967.

3 (a) M.F. Semmelhack, H.T. Hall, M. Yoshifuji, and G. Clark, *J. Amer. Chem. Soc.*, **97**, 1247 (1975); (b) M.F. Semmelhack and H.T. Hall, *J. Amer, Chem. Soc.*, **96**, 7091, 7092 (1974); (c) M.F. Semmelhack, H.T. Hall, and M. Yoshifuji, *J. Amer. Chem. Soc.*, **98**, 6387 (1976); (d) M.F. Semmelhack and G. Clark, *J. Amer. Chem. Soc.*, **99**, 1675 (1977); (e) M.F. Semmelhack, G.R. Clark, R. Farina, and M. Saeman, *J. Amer. Chem. Soc.*, **101**, 217 (1979); (f) M.F. Semmelhack, G. Clark, T. Bargar, K. Hirotsu, and J. Clardy, *J. Amer. Chem. Soc.*, **101**, 3535 (1979); (g) M.F. Semmelhack, W. Seufert, and L. Keller, *J. Amer. Chem. Soc.*, **102**, 6584 (1980).

4 J.F. Bunnett and H. Hermann, *J. Org. Chem.*, **36**, 4081 (1971).

5 M.Ghavshou and D.A. Widdowson, *J. Chem. Soc., Perkin I.*, **1983**, 3065.

(Received in USA 14 April 1989)