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RATE AND ORIENTATION EFFECT OF TMEDA ON DIRECTED LITHIATION REACTIONS

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In view of recent reports of the ability of tetramethylethylenediamine (TMEDA) to increase the rates and yields of a number of metalation reactions,[1] examination of the effect of TMEDA upon rate and orientation of certain directed metalation reactions in the benzene series seemed desirable. Among those substituents which are known to promote ortho lithiation on a benzene ring are $-CH_2N(CH_3)_2$,[2] $-CH_2CH_2N(CH_3)_2$,[3] $-N(CH_3)_2$[4] and $-OCH_3$.[5] Metalation of such benzene derivatives by n-butyllithium without TMEDA proceeds over a relatively long period but usually in fair-to-good yield as shown in Table I.

Table I

Yield/Metalation Time Study for the Metalation of Certain Monosubstituted Benzenes[a]

Substituted Benzene	Without TMEDA			With TMEDA	
	Time (hr)[b]	Yield (%)[c]	Ref	Time (hr)[b]	Yield (%)[c]
$C_6H_5CH_2N(CH_3)_2$	18	84	2	2	60
$C_6H_5CH_2CH_2N(CH_3)_2$	11	7	3	-	0
$C_6H_5N(CH_3)_2$	12	56	4	2	55
$C_6H_5OCH_3$	21	65	5	1	55

a. Solvent system, temperature and other reaction conditions were identical to those reported in the original literature except for the addition of 1 equiv. TMEDA. Commercial n-butyllithium (Foote mineral, 15% in hexane) was used.

b. Time recorded is for maximum yield.

c. Yields based on product of condensation of the respective lithio intermediate with benzophenone, except for anisole for which condensation with dry ice was effected.

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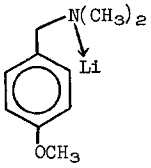
N,N-dimethylbenzylamine, β-phenethyldimethylamine, N,N-dimethylaniline and anisole were each lithiated under conditions similar to those previously reported[2-5] with the exception that one equivalent of TMEDA was added to each metalation solution. In three cases the rate of metalation was increased significantly with only a slight loss in overall yield. These results are summarized in Table I. The metalation yields were maximized by isolating the product after a series of metalation times as shown in Table II. The most important fact to be noted from Table II is that TMEDA did not much increase the yield of benzophenone condensation product with metalation times longer than 1-2 hour. β-Phenethyldimethylamine was also subjected to this time study, but no condensation product after any metalation period was ever isolated. Instead the rate of the competing elimination reaction[3b] appeared to be increased.

Table II

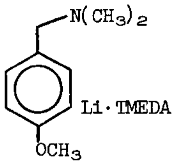
Yields of the Benzophenone Condensation Product from the Lithiation of Substituted Benzenes at Various Times

	Yield (%)		
Time (hr)	$C_6H_5CH_2N(CH_3)_2$	$C_6H_5CH_2N(CH_3)_2$	$C_6H_5OCH_3$
0.5	33	48	48
1.0	40	34	55
2.0	60	55	46
20.0	51	28	23

In addition to the above results we have discovered that the site of ring metalation in p-methoxy-N, N-dimethylbenzylamine (I) can actually be reversed through use of TMEDA. It has been reported that amine I undergoes lithiation in the absence of TMEDA at a position ortho to the amine side-chain, presumably via intermediate Ia, in 70% yield.[6] Repetition of



Ia



Ib

this procedure but with one equivalent of TMEDA added gave after 5 hours a benzophenone condensation product in 48% yield which possessed the substituent ortho to the methoxy group, i.e. which must have proceeded through an intermediate much like lithio-intermediate Ib. A small amount of material which proved to be identical to the product from this same procedure without TMEDA was also isolated.

To our knowledge these results constitute the first examples of rate acceleration in directed metalation reactions and certainly the first demonstration of orientation reversal in such reactions.[7] Potentially, the use of TMEDA offers particular synthetic utility in controlling the site of metalation in compounds containing more than one ortho-directing substituent. Added utility lies in the ability of TMEDA to increase the rates of metalation of certain monosubstituted benzenes.

References

1. M. M. Mallan and R. L. Bebb, Chem. Rev., **69**, 693 (1969).

2. a) F. N. Jones, M. F. Zinn and C. R. Hauser, J. Org. Chem., **28**, 663 (1963);
   b) F. N. Jones, R. L. Vaulx and C. R. Hauser, ibid., **28**, 3461 (1963).

3. a) N. S. Narasimhan and A. C. Ranade, Tetrahedron Letters, 603 (1966);
   b) D. W. Slocum, T. R. Engelmann and C. A. Jennings, Aust. J. Chem., **21**, 2319 (1968).

4. A. R. Lepley, W. A. Khan, A. B. Giumanini and A. G. Giumanini, J. Org. Chem., **31**, 2047 (1966); R. E. Ludt, G. P. Crowther and C. R. Hauser, J. Org. Chem., **35**, 1288 (1970).

5. D. A. Shirley, J. R. Johnson, Jr. and J. P. Hendrix, J. Organomet. Chem., **11**, 209 (1968).

6. K. P. Klein and C. R. Hauser, J. Org. Chem., **32**, 1479 (1967); N. S. Narasimhan and B. H. Bhide, Tetrahedron Letters, 4159 (1968).

7. Control of the site of lithiation of 1-methoxynaphthalene at the 2- or 8-position by use of n-BuLi·TMEDA and t-BuLi/pentane-hexane, respectively, has recently been described, cf. D. A. Shirley and C. F. Cheng, J. Organomet. Chem., **20**, 251 (1969).