Communications

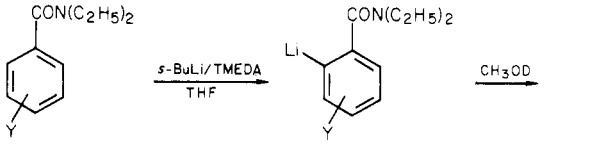
Ortho Metalations. Advantage of the Amide Functions

Summary: A series of metalations of substituted *N,N*-diethylbenzamides by *sec*-butyllithium/tetramethylethylenediamine in tetrahydrofuran at −100 °C shows the tertiary amide function to be superior to sulfonamide, oxazoline, methoxy, (dimethylamino)methyl, chloro, carboxyl, and methyl groups in directing lithiation to an adjacent position in intramolecular competitions. The *N*-methyl amide is found to be somewhat better than the *N,N*-diethylamide group in the same competition.

Sir: The well-known metalations of aromatic carbon–hydrogen bonds which are ortho to relatively inert or deactivated functions have been supplemented recently by reports that lithiations can be achieved by deprotonations adjacent to functions which are susceptible to nucleophilic addition.[1-3] The hierarchy of different functions in directing ortho metalation clearly is important for the development of synthetic methodology. We wish to report competitive intramolecular lithiations of substituted benzamides with *sec*-butyllithium/tetramethylethylenediamine (*s*-BuLi/TMEDA) in tetrahydrofuran which establish that the secondary and tertiary amide functions are superior to other common functions in directing ortho lithiation.

Reaction of the substituted diethylbenzamides **1–11** as shown in Scheme I for 1–20 min at the temperatures indicated followed by addition of methanol-*d* and product

Scheme I[a]

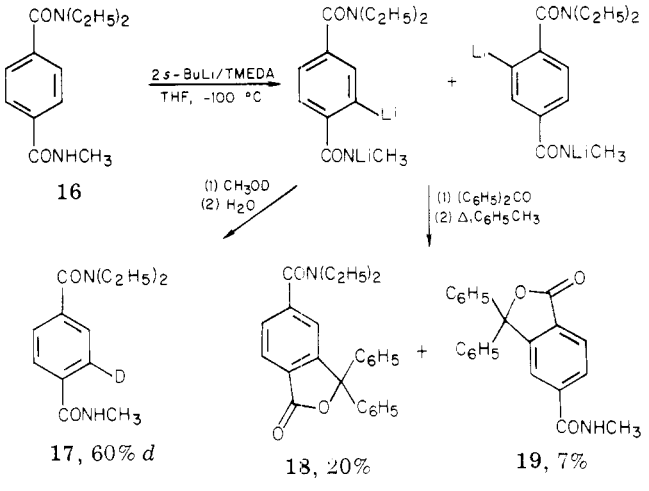


1–11

1,[b] Y = *o*-oxazoline
2,[c] Y = *p*-$SO_2N(C_2H_5)_2$
3, Y = *p*-SO_2NHCH_3
4, Y = *p*-CO_2H
5, Y = *p*-$CH_2N(CH_3)_2$
6,[d] Y = *o*-OCH_3
7, Y = *m*-CH_3
8, Y = *p*-CH_3
9, Y = *o*-Cl
10, Y = *m*-Cl
11, Y = *p*-Cl

[a] At −100 °C, unless otherwise noted. [b] −78 °C. [c] 43% d_1. [d] −78 or −45 °C.

Scheme II



17, 60% *d* 18, 20% 19, 7%

isolation gives compounds in 56–94% yield in which the position adjacent to the amide is 67–99% deuterated. The incorporation of deuterium was confirmed by ^1H NMR spectroscopy and mass spectrometry while its location was established by ^{13}C NMR spectroscopy.[4] In the case of **10** metalation and trapping occur between the chloro and amide functions, a result similar to that reported previously for the *m*-methoxy substituent.[3a] The product from **7** appears to be a 2:1 mixture of 6- and 2-deuterio-*m*-toluamides. In the cases of the oxazoline **1**, the diethylsulfonamide **2**, the methylsulfonamide **3**, and the chloride **11**, the position of lithiation was confirmed chemically by trapping

(1) Groups long known to be effective in directing ortho metalation include ethers and amines: J. M. Mallan and R. L. Bebb, *Chem. Rev.*, **69**, 693 (1969); M. Schlosser, "Struktur und Reaktivität polarer Organometalle", Springer-Verlag, West Berlin, 1973, p 143; D. W. Slocum and D. I. Sugarman, *Adv. Chem. Soc.*, **No. 130**, 222–247 (1974); H-P. Abicht and K. Issleib, *Z. Chem.*, 17, 1 (1977).

(2) Related ortho metalations which involve initial deprotonation or addition include: (a) secondary amides; W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964); A. Marxer, H. R. Rodriguez, J. M. McKenna, and H. M. Tsai, *ibid.*, **40**, 1427 (1975); J. E. Baldwin and K. W. Bair, *Tetrahedron Lett.*, 2559 (1978), and references cited therein; (b) secondary thioamides; J. J. Fitt and H. W. Gschwend, *J. Org. Chem.*, **41**, 4029 (1976); (c) secondary sulfonamides; H. Wantanabe, R. L. Gay, and C. R. Hauser, *ibid.*, **33**, 900 (1968); (d) tertiary dimethylamides; L. Barsky, H. W. Gschwend, J. McKenna, and H. R. Rodriguez, *ibid.*, **41**, 3651 (1976), and references cited therein; (e) isonitriles; H. M. Walborsky and P. Ronman, *ibid.*, **43**, 731 (1978); (f) benzyl alcohols; N. Meyer and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **17**, 521 (1978); (g) secondary anilides; W. Fuhrer and H. W. Gschwend, *J. Org. Chem.*, **44**, 1133 (1979).

(3) Groups which are potentially susceptible to nucleophilic addition but which efficiently direct lithiation to ortho positions include: (a) diethyl and higher tertiary amides; P. Beak, G. R. Brubaker, and R. F. Farney, *J. Am. Chem. Soc.*, **98**, 3621 (1976); P. Beak and R. A. Brown, *J. Org. Chem.*, **42**, 1823 (1977); S. O. de Silva, J. N. Reed, and V. Snieckus, *Tetrahedron Lett.*, 5099 (1978); S. O. de Silva and V. Snieckus, *ibid.*, 5103 (1978); S. O. de Silva, I. Ahmad, and V. Snieckus, *ibid.*, 5107 (1978); (b) oxazolines; H. W. Gschwend and A. Hamdan, *J. Org. Chem.*, **40**, 2008 (1975); A. I. Meyers and E. D. Mihelich, *ibid.*, **40**, 3158 (1975); A. Padwa, A. Ku, A. Mazzu, and S. I. Wetmore, Jr., *J. Am. Chem. Soc.*, **98**, 1048 (1976); M. S. Newman and S. Kumar, *J. Org. Chem.*, **43**, 370 (1978); T. D. Harris, B. Neuschwander, and V. Boekelheide, *ibid.*, **43**, 727 (1978); L. D. Vecchia and I. Vlattas, *J. Org. Chem.*, **42**, 2649 (1977); A. Padwa and A. Ku, *J. Am. Chem. Soc.*, **100**, 2181 (1978); A. I. Meyers and R. A. Gabel, *Tetrahedron Lett.*, 227 (1978); (c) tertiary sulfonamides; H. Wantanabe, R. A. Schwarz, C. R. Hauser, J. Lewis, and D. W. Slocum, *Can. J. Chem.*, **47**, 1543 (1969); D. W. Slocum and C. A. Jennings, *J. Org. Chem.*, **41**, 3653 (1976), and references cited therein; (d) imines which have additional activation; F. E. Ziegler and K. W. Fowler, *ibid.*, **41**, 1564 (1976); (e) pyrazoles; A. Marxer and M. Siegrist, *Helv. Chim. Acta*, **57**, 1988 (1974).

(4) All new compounds have been satisfactorily characterized by spectral and analytical methods except for 18, which was characterized by NMR and MS. In most cases as much as 15% deuteration at another aromatic carbon could go undetected. For references see G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, 1972; J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972.

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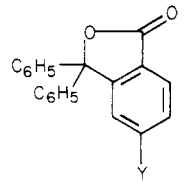
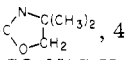
with benzophenone to give the lactones **12–15** in the yields indicated.



12, Y =  , 46%
13, Y = $-SO_2N(C_2H_5)_2$, 21%
14, Y = $-SO_2NHCH_3$, 60%
15, Y = -Cl, 60%

Reaction of *N,N*-diethyl-*N'*-methylterephthalamide (**16**) with 2 equiv of *s*-BuLi/TMEDA followed by deuteration or reaction with benzophenone gave predominantly *N,N*-diethyl-*N'*-methylterephthalamide-*3-d* (**17**) or the lactones **18** and **19**, respectively, as shown in Scheme II.[4,5] We presume the secondary amide would also take precedence over all other groups in Scheme I.[6] The superior directing ability of the amides may be rationalized in terms of associated species which are stabilized by intramolecular complexation.[1-3,7]

The high regiospecificities observed for the cases in Scheme I, in conjunction with preparative convenience, suggest amides should be the carboxylic acid derivative of choice for directing ortho lithiation. Moreover, since an amide function can be converted easily to an aldehyde, amine, alcohol, or alkyl group this approach appears advantageous for a wide variety of ortho substitutions. The secondary amide, which was reported first by Puterbaugh and Hauser to be a very good ortho-directing function,[2a] seems to be the most activating of the groups generally used, although the tertiary amide appears to be almost as effective.

It is particularly significant for the synthesis of polysubstituted aromatics that lithiation can be achieved adjacent to amides under conditions which do not affect other potentially useful functions.[2a,b,g,3a] The stability of the *o*-methoxy and *o*-chloro functions in **6** and **9** contrasts with the replacement of these or similar functions by organolithiums on reaction of the corresponding 2-aryloxazolines with alkyllithiums.[8] The directed metalation of **8** in the presence of the acidic benzylic hydrogens of the *p*-methyl group suggests useful subsequent conversions should be possible. It should be noted that we have found that the *o*-methyl group of *N,N*-diethyl-*o*-toluamide is metalated in preference to removal of the ortho proton, a result similar to that reported by Snieckus et al.[3a] Also, halogen–metal interchange occurs on attempted metalation of *N,N*-diethyl-*p*-bromobenzamide, a result which supplements the useful metalations of reactive bromo aromatics reported by Parham and co-workers.[9] Development of the metalative approach for synthesis, as well as studies of the underlying structure–stability relationships, are currently in progress.[10]

Acknowledgment. We are grateful to the National Institutes of Health and the National Science Foundation for support of this work.

Registry No. **1**, 71888-21-6; **2**, 71888-22-7; **3**, 71888-23-8; **4**, 71888-24-9; **5**, 71888-25-0; **6**, 51674-10-3; **7**, 134-62-3; **8**, 2728-05-4; **9**, 10345-79-6; **10**, 15952-65-5; **11**, 7461-38-3; **12**, 71888-26-1; **13**, 71901-99-0; **14**, 71888-27-2; **15**, 71888-28-3; **16**, 71888-29-4; **17**, 71888-30-7; **18**, 71888-31-8; **19**, 71888-32-9; 2-(3-deuterio-4-(diethylaminocarbonylphenyl))-3,3-dimethyl-2-oxazolidine, 71888-33-0; *N,N*-diethyl-2-deuterio-4-[(diethylamino)sulfonyl]benzamide, 71888-34-1; *N,N*-diethyl-2-deuterio-4-[(methylamino)sulfonyl]benzamide, 71888-35-2; *N,N*-diethyl-2-deuterio-4-carboxybenzamide, 71888-36-3; *N,N*-diethyl-2-deuterio-4-[(dimethylamino)methyl]benzamide, 71888-37-4; *N,N*-diethyl-2-methoxy-6-deuteriobenzamide, 71902-00-6; *N,N*-diethyl-2-deuterio-3-methylbenzamide, 71888-38-5; *N,N*-diethyl-2-deuterio-5-methylbenzamide, 71888-39-6; *N,N*-diethyl-2-deuterio-4-methylbenzamide, 71888-40-9; *N,N*-diethyl-2-chloro-6-deuteriobenzamide, 71888-41-0; *N,N*-diethyl-2-deuterio-3-chlorobenzamide, 71888-42-1; *N,N*-diethyl-2-deuterio-4-chlorobenzamide, 71888-43-2.

(5) The formation of **18** and **19** is taken to show that the tertiary and secondary amides are competitive in directing ortho metalations but the relative yields of **18** and **19** do not necessarily reflect the relative amounts of dilithiated precursors.

(6) The present report may be considered to extend the work of Slocum and Jennings, which established that the secondary and tertiary sulfonamide, the secondary amide, and the (dimethylamino)methyl functions are more effective at directing ortho lithiations than are methoxy, β-(dimethylamino)ethyl, dimethylamino, trifluoromethyl, and fluoro substituents.[3c]

(7) For a quantitative study see P. Beak and B. Siegel, *J. Am. Chem. Soc.*, **96**, 6803 (1974).

(8) A. I. Meyers, R. Gabel, and E. D. Mihelich, *J. Org. Chem.*, **43**, 1372 (1978); A. I. Meyers and B. E. Williams, *Tetrahedron Lett.*, 223 (1978).

(9) W. E. Parham, D. C. Egberg, Y. A. Sayed, R. W. Thraikill, G. M. Keyser, M. Neu, W. C. Montgomery, and L. D. Jones, *J. Org. Chem.*, **41**, 2628 (1976), and references cited therein.

(10) In applications of these results it should be noted that diethylamide is preferred over the dimethylamide as the latter undergoes nucleophilic addition[2d] and methyl metalation.[3a]

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Ortho Metalations. Intermolecular Competition between Various Substituents

Summary: Equimolar amounts of phenyl oxazoline and substituted aromatics ($PhCONEt_2$, PhCONHMe, $PhSO_2NMe_2$, $PhSO_2NHMe$, $PhCH_2NMe_2$) were allowed to compete with 1 equiv of butyllithium to assess a reactivity series.

Sir: The methodology associated with ortho lithiation of aromatics has become an important synthetic tool in recent years.[1] Although a number of substituents are known to activate the ortho position toward deprotonation by strong bases, there has been only one systematic examination to assess the relative "activation" abilities. Slocum and Jennings[2] described a study which showed that, relative to the methoxyl group, there are a number of substituents more or less reactive to metalation. This was done by determining the site of metalation in a series of substituted anisoles. These authors concluded that SO_2NMe_2, SO_2NHMe, CONHMe, and CH_2NMe_2 were all more reactive toward metalation than the methoxy group, but did not assess the relative metalation abilities within this group.

Because of our interest in the metalation of aryl oxazoline (**2**)[3] and the apparent ease with which this occurs, we

(1) B. J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon Press, New York, 1974; H. W. Gschwend and H. R. Rodriguez, *Org. React.*, in press; P. Beak and R. A. Brown, *J. Org. Chem.*, **42**, 1823 (1977).

(2) D. W. Slocum and C. A. Jennings, *J. Org. Chem.*, **41**, 3653 (1976).

(3) A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40**, 3158 (1975); H. W. Gschwend and A. Hamden, *ibid.*, **40**, 2008 (1975); A. Padwa and A. Ku, *J. Am. Chem. Soc.*, **100**, 2181 (1978); A. I. Meyers and R. A. Gabel, *Tetrahedron Lett.*, 227 (1978); T. D. Harris, B. Neuschwander, and V. Boekelheide, *J. Org. Chem.*, **43**, 727 (1978); L. D. Veching and I. Vlattas, *ibid.*, **42**, 2649 (1977); J. A. Hauben, J. A. Miles, and J. A. Paton, *Org. Prep. Proced.*, **11**, 27 (1979); M. S. Newman and S. Kamar, *J. Org. Chem.*, **43**, 279 (1978).

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