

## Directed Metalation Reactions. Intermolecular Competition of the Carboxylic Acid Group and Various Substituents

Guénaël Ameline, Michel Vaultier, and Jacques Mortier\*

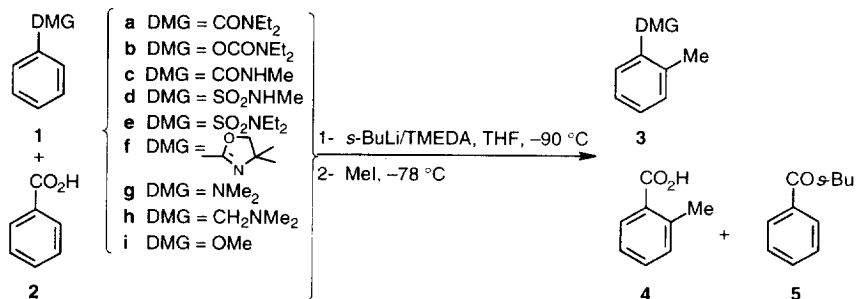
Université Rennes-I, Groupe de recherches de physicochimie structurale associé au CNRS.

Avenue du Général Leclerc, 35042 Rennes Cedex, France

Phone: (33) 2 99 28 16 91. Fax: (33) 2 99 28 69 55. E-mail: jacques.mortier@univ-rennes1.fr


**Abstract:** Intermolecular competition between equimolar amounts of benzoic acid and substituted aromatics (PhCONEt<sub>2</sub>, PhOCONEt<sub>2</sub>, PhCONHMe, PhSO<sub>2</sub>NHMe, PhSO<sub>2</sub>NEt<sub>2</sub>, phenyloxazoline, PhNMe<sub>2</sub>, PhCH<sub>2</sub>NMe<sub>2</sub>, and PhOMe) establishes the carboxylic acid group to be of intermediate capacity in directing metalation. Copyright © 1996 Published by Elsevier Science Ltd

The methodology associated with ortho-lithiation of aromatics is an important synthetic tool.<sup>1</sup> Since a number of biological compounds contain aromatic systems with a methoxy or hydroxy substituent along with various amine, carboxylic acid, carboxamide, and sulfonamide substituents, a knowledge of the relative ortho-directing abilities of the various substituents toward metalation is of great utility in planning the synthesis of such compounds. Because of our interest in the metalation of *unprotected* benzoic acid **2**,<sup>2,3</sup> we desired to explore the relative metalations between this species and monosubstituted benzenes **1** containing CONEt<sub>2</sub>, OCONEt<sub>2</sub>, CONHMe, SO<sub>2</sub>NHMe, SO<sub>2</sub>NEt<sub>2</sub>, oxazoline, NMe<sub>2</sub>, CH<sub>2</sub>NMe<sub>2</sub>, and OMe.



In the literature, with *sec*-butyllithium/*N,N,N',N'*-tetramethyl-1,2-ethylenediamine (*s*-BuLi/TMEDA) as the base and at -78 °C, the secondary amide has been reported to be a less efficient director than the oxazoline for intermolecular competition and the oxazoline in turn is less efficient than the tertiary amide with *n*-BuLi as the base.<sup>1a,4</sup> However the secondary amide is a more powerful ortho-director than the tertiary amide in intramolecular competition.<sup>5,6</sup> We have recently reported intramolecular competition between the carboxylic acid and methoxy, chloro, fluoro, or diethylamido functions in ortho- and para-substituted benzoic acids which demonstrates that the carboxylic acid group has an intermediate capacity in directing metalation.<sup>2a,c</sup> We now wish to report lithiations of 1:1 mixtures of monosubstituted benzenes **1a-i** and benzoic acid **2** with 2 equiv of the 1:1 *s*-BuLi/TMEDA complex at -90 °C in THF which establish that the carboxylic acid function follows a similar behavior in competitive intermolecular directing ortho-lithiation. The lithio salts were trapped by addition of methyl iodide at -78 °C and the relative ratios of methylated compounds are given in Table 1.

**Table 1. Intermolecular competition between substituted benzenes **1a-i** and benzoic acid (**2**) for 2 equiv of *s*-BuLi/TMEDA**

	DMG	% Yield, <sup>a</sup>		% Yield, <sup>a</sup>		% Yield, <sup>a</sup>
		Methylated Products		Starting Materials		1,2-Add. Product
		<b>3</b>	<b>4</b>	<b>1</b>	<b>2</b>	<b>5</b>
<b>a</b>	CONEt <sub>2</sub>	68	4	27	89	5
<b>b</b>	OCONEt <sub>2</sub>	61	4	29	87	6
<b>c</b>	CONHMe	72 <sup>b</sup>	12	27 <sup>c</sup>	80	4
<b>d</b>	SO <sub>2</sub> NHMe	60 <sup>d</sup>	12	30	80	7
<b>e</b>	SO <sub>2</sub> NEt <sub>2</sub>	75	12	19	67	8
<b>f</b>		75	13	20	73	3
<b>g</b>	NMe <sub>2</sub>	< 1 <sup>e</sup>	60	92	32	6
<b>h</b>	CH <sub>2</sub> NMe <sub>2</sub>	< 1 <sup>e</sup>	60	95	23	8
<b>i</b>	OMe	< 1 <sup>e</sup>	64	94	20	8

<sup>a</sup> Yields represent pure material from flash chromatography and/or recrystallization (silica gel, heptane-ethylacetate). <sup>b</sup> Product was *N,N*-dimethyltoluamide. 3.3 Equiv of *s*-BuLi/TMEDA was used. <sup>c</sup> Recovered as the *N,N*-dimethylbenzamide. <sup>d</sup> 3.3 Equiv of *s*-BuLi/TMEDA was used. <sup>e</sup> **1g-i** were not deprotonated when treated alone with *s*-BuLi/TMEDA at -90 °C.

As seen from the competition experiments, benzoic acid **2** does not compete effectively with the benzamides **1a,c**, the sulfonamides **1d,e**, the oxazoline **1f**, and the carbamate **1b**. While **1a-f** underwent efficient lithiations under the above conditions, **2** gave mixtures of *o*-toluic acid **4** and  $\alpha$ -methylbutyrophenone **5**.<sup>2a,c,d,7</sup> Reaction of benzoic acid and *N,N*-dimethylaniline **1g**, *N,N*-dimethylbenzylamine **1h** or anisole **1i** gave predominantly *o*-toluic acid **4**, which was isolated in moderate yields. Interpretation of the results must take into account steric and inductive effects that affect aggregation and complexation of the alkylolithium and formation of the ortho-lithiated species.<sup>1a,b</sup> Development of this metalative approach for synthesis is currently in progress.

## REFERENCES AND NOTES

- Reviews: (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1-105. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933. (c) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epszajn, J. *Adv. Heterocyclic Chem.* **1991**, *52*, 187-304.
- (a) Mortier, J.; Moyroud, J.; Bennetau, B.; Cain, P. A. *J. Org. Chem.* **1994**, *59*, 4042-4044. (b) Moyroud, J.; Guesnet, J. L.; Bennetau, B.; Mortier, J. *Tetrahedron Lett.* **1995**, *36*, 881-884. (c) Bennetau, B.; Mortier, J.; Moyroud, J.; Guesnet, J. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1265-1275. (d) Moyroud, J.; Guesnet, J.-L.; Bennetau, B.; Mortier, J. *Bull. Soc. Chim. Fr.* **1996**, *133*, 133-141.
- First examples of conjugate additions of organolithium reagents to *unprotected* 1- and 2-naphthalene carboxylic acids: Plunian, B.; Mortier, J.; Vaultier, M.; Toupet, L. *J. Org. Chem.* **1996**, *61*, 5206-5207.
- Meyers, A. I.; Lutomski, K. *J. Org. Chem.* **1979**, *44*, 4464-4466.
- Beak, P.; Tse, A.; Hawkins, J.; Chen, C.-W.; Mills, S. *Tetrahedron* **1983**, *39*, 1983-1989.
- The advantage of the tertiary amide over other directors has been attributed to complexation by the amide function: Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34-46.
- Ketone **5** was not obtained when **1a,c** and **1f** were treated alone with *s*-BuLi/TMEDA at -90 °C.