



Pergamon

Tetrahedron Letters 41 (2000) 3157–3160

TETRAHEDRON
LETTERS

Selective *para* metalation of unprotected 3-methoxy and 3,5-dimethoxy benzoic acids with *n*-butyl lithium–potassium *tert*-butoxide (LIC–KOR): synthesis of 3,5-dimethoxy-4-methyl benzoic acid

Surajit Sinha, Bhubaneswar Mandal and Srinivasan Chandrasekaran *

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

Received 6 December 1999; revised 7 February 2000; accepted 21 February 2000

Abstract

The potassium salt of 3-methoxy and 3,5-dimethoxy benzoic acids undergoes deprotonation at the position *para* to the carboxylate group selectively when treated with LIC–KOR in THF at -78°C and it has been extended to the synthesis of 3,5-dimethoxy-4-methyl benzoic acid. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: alkylation; carboxylic acids; metalation.

The directed *ortho*-lithiation of substituted benzenes with organolithium reagents is a powerful method for the preparation of synthetically useful aryllithium intermediates.^{1,2} There are a number of carboxylic acid derivatives such as amides, esters, α -amino alkoxides, oxazolines, acetals, imidazolidines, imidazoles and cyclohexylimines which are widely used for *ortho*-lithiation. The use of *N,N*-diethylbenzamide as a powerful *ortho*-directing group has found widespread application.³

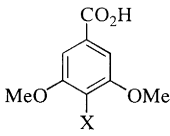
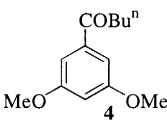

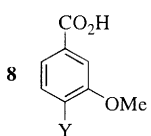
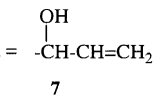
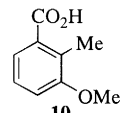
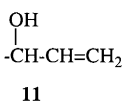
Direct metalation of lithium benzoate with an additional equivalent of organolithium reagent leads to addition rather than metalation, providing a useful synthesis of ketones.⁴ Direct lithiation in the position *ortho* to the carboxylic acid group is known only in a few special cases.⁵ While lithiation *ortho* to the carboxylic acid group has been achieved in the case of pyridine carboxylic acid using LTMP,⁶ this reagent does not work with benzene carboxylic acids. Recently, Mortier has reported a successful, direct *ortho*-lithiation of benzoic acid using *sec*-BuLi/TMEDA in THF at -90°C .⁷ Schlosser has shown that the super base, LIC–KOR, generated from *n*-BuLi and potassium *tert*-butoxide prefers to lithiate adjacent to inductive electron-withdrawing groups and is more sensitive to steric hindrance than to metal coordination ability.⁸

During the course of our synthetic studies we required reasonable amounts of 3,5-dimethoxy-2-methyl benzoic acid. Although *N,N*-diethyl-3,5-dimethoxy-2-methyl benzamide could be prepared using

* Corresponding author.

organolithium reagents, the hydrolysis of the amide posed difficulties and the yield of the carboxylic acid was very poor. Initially, we tried the direct metalation of 3,5-dimethoxy benzoic acid with Schlosser's super base, LIC-KOR,⁹ followed by treatment with methyl iodide but the reaction did not yield any useful product. However, when butyl lithium (4 equiv.) was added to a pretreated mixture of 3,5-dimethoxy benzoic acid and KO^tBu (4 equiv.) in THF at -78°C followed by quenching with D₂O, the deuterated product **2** (deuterium at the *para*-position relative to carboxylic acid) was isolated in 92% yield. The disappearance of the triplet for the *para* proton at δ 6.73 and the molecular ion at m/z 183 confirmed the incorporation of deuterium at the 4-position of 3,5-dimethoxy benzoic acid. This interesting observation prompted us to study the behaviour of 3,5-dimethoxy benzoic acid towards Schlosser's base, LIC-KOR and its subsequent reaction with suitable electrophiles. The results obtained in this area are presented in Table 1.

Table 1

Substrate	Base	Electrophile	Product	Ratio Product/ Substrate	Yield (%)
 1 X = H	KOBu ^t / <i>n</i> -BuLi	D ₂ O	2 X = D	98 (2)	92
	"	MeI	3 X = Me	92 (8) ^a	80
	only <i>n</i> -BuLi	--	 4	--	95
	KOBu ^t / <i>n</i> -BuLi	Ph ₂ CO	5 X = 	60 (40)	55 ^b (89)
	"	ClCO ₂ Et	6 X = -CO ₂ Et	25(75)	20 ^b (67)
 8 Y = H	"	OHC-CH=CH ₂	X =  7	48(52)	44 ^b (69)
	"	MeI	9 Y = Me	70(30)	60
	<i>sec</i> -BuLi/ TMEDA ⁷	MeI	9 +  10 (1 : 4)		
	KOBu ^t / <i>n</i> -BuLi	OHC-CH=CH ₂	Y =  11	--	34 ^b (75)

* all the reactions were done in THF; a) conversion was 15% when ether was used as solvent; b) isolated as the methyl ester; Yield in parenthesis is based on recovered starting material.

When the metalated intermediate generated from 3,5-dimethoxy benzoic acid **1** [on treatment with

KO^tBu (4 equiv.)/*n*-BuLi (4 equiv.) in THF at -78°C] was allowed to react with methyl iodide, 3,5-dimethoxy-4-methyl benzoic acid **3** was isolated as the only product in 80% yield. To our knowledge this is the first report of selective *para* metalation of a benzoic acid derivative. The direct deprotonation of 3,5-dimethoxy benzoic acid did not take place either with excess *n*-BuLi or KO^tBu alone or with preformed LIC–KOR, indicating prior formation of potassium salt of the carboxylic acid was required. Interestingly, when the potassium salt was first prepared by reaction of the acid **1** with KO^tBu (1.1 equiv.) in THF under argon at -78°C followed by treatment with *n*-BuLi (3 equiv.) and methyl iodide there was no reaction. This pointed to the fact that *n*-BuLi alone was not able to deprotonate the potassium salt. In another experiment the reaction of carboxylic acid **1** was carried out with only *n*-BuLi (2.5 equiv.) at room temperature followed by quenching with methyl iodide. Instead of the desired product of alkylation, the butyrophenone derivative **4**¹⁰ was the only product obtained in excellent yield. Therefore it became apparent that the potassium salt of acid **1** is deprotonated at the *para*-position only in the presence of super base LIC–KOR.

The reaction was then extended to quenching with other electrophiles. When the *para*-metalated intermediate derived from **1** was treated with benzophenone the alcohol **5**¹¹ was isolated in 55% yield. There was no indication of any *ortho*-substituted product. When ethyl chloroformate was used the *para*-substituted product **6**¹² was isolated in 20% yield. Similarly when acrolein was used as the electrophile in this reaction the corresponding *para* substituted alcohol **7**¹³ was obtained in 44% yield.

Interestingly, when benzoic acid or 4-methoxy benzoic acid was treated with LIC–KOR under similar conditions followed by quenching with methyl iodide no reaction was observed. However, 3-methoxy benzoic acid **8** gave the *para* methylated carboxylic acid **9** in 60% yield (under similar conditions LIC–KOR 4 equiv., THF, -78°C , followed by MeI). The same carboxylic acid **8** on treatment under Mortier's conditions⁷(*sec*-BuLi/TMEDA, THF, -90°C and MeI) gave a mixture of *para*- and *ortho*-substituted products **9** and **10** (20:80), respectively. From this study it is clear that the 3-methoxy group is necessary to stabilise the *para*-metalated intermediate. It is worth mentioning that 3-methoxy aryl oxazolidines on treatment with either *n*-BuLi or *sec*-BuLi/TMEDA have been shown to give a mixture (63:37) of both the *ortho*- and *para*-products. Meyers¹⁴ has also reported that 3,5-dimethoxy aryl oxazolidines on deprotonation gave a mixture of *ortho*- and *para*-products in which *ortho*-product was the major component. When acrolein was used in the reaction of 3-methoxy benzoic acid, the corresponding substituted product **11**¹⁵ was obtained in 34% yield.

3,5-Dimethoxy-4-methylbenzoic acid has been used in the synthesis of certain fungal metabolites like selerotiorin and mitorubrin.¹⁶ Although this relatively simple acid **3** has been synthesised in moderate yields by other routes¹⁷ we report the first directed *para*-metalation of unprotected 3,5-dimethoxy benzoic acid for achieving this goal. We believe that the directed *para* metalation of unprotected 3-methoxy benzoic acids with LIC–KOR will find useful application in organic synthesis.

Typical experimental procedure: To a stirred solution of KO^tBu (0.246 g, 2.19 mmol) in THF (5 mL) was added a solution of 3,5-dimethoxy benzoic acid (0.100 g, 0.55 mmol) in THF (5 mL) at -78°C under argon followed by the addition of *n*-BuLi (1.37 mL, 2.19 mmol, 1.6 M in hexanes). After stirring for 40 min at -78°C , methyl iodide (70 μL , 1.10 mmol) was added and the reaction mixture was stirred for 1 h (-78°C) and then was allowed to warm to room temperature. It was quenched with aq. NH₄Cl (3 mL) and washed with Et₂O (5 mL). The aq. layer was acidified with 2N HCl. The white precipitate obtained was extracted with Et₂O (2 \times 5 mL), dried over anhyd. Na₂SO₄. The solvent was removed in vacuo and the residue was recrystallised (CHCl₃/Et₂O) to give methylated product **3** as a white crystalline solid (0.086 g, 80%). Mp $212\text{--}214^{\circ}\text{C}$ (lit.¹¹ $210\text{--}216^{\circ}\text{C}$), ¹H NMR (DMSO-*d*₆): 2.05 (s, 3H), 3.83 (s, 6H), 7.13 (s, 2H), 13.0 (br s, 1H).

Acknowledgements

We are grateful to the Department of Science and Technology, New Delhi, for financial support.

References

1. Gilman, H.; Morton, J. W. *Org. React.* **1954**, *8*, 258.
2. (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1; (b) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306; (c) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
3. (a) Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823; (b) Clark, R. D.; Repke, D. B.; Kilpatrick, A. T.; Brown, C. M.; Mackinnon, A. C.; Clague, R. U.; Spedding, M. *J. Med. Chem.* **1989**, *32*, 2036; (c) De Silva, S. O.; Reed, J. N.; Billedeau, R. J.; Wang, X.; Norris, D. J.; Snieckus, V. *Tetrahedron* **1992**, *48*, 4863.
4. (a) Jorgenson, M. J. *Org. React.* **1970**, *18*, 1; (b) Ahn, T.; Cohen, T. *Tetrahedron Lett.* **1994**, 203.
5. (a) Davies, G. M.; Davies, P. S. *Tetrahedron Lett.* **1972**, 3507; (b) Knight, D. W.; Nott, A. P. *J. Chem. Soc., Perkin Trans. I* **1981**, 1125; (c) Knight, D. W.; Nott, A. P. *ibid* **1983**, 791; (d) Gammill, R. B.; Hyde, B. R. *J. Org. Chem.* **1983**, *48*, 3863; (e) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron Lett.* **1985**, 1777.
6. Florence, M.; Francois, T.; Queguiner, G. *Tetrahedron Lett.* **1999**, 5483.
7. Mortier, J.; Moyroud, J.; Bennetau, B.; Cain, P. A. *J. Org. Chem.* **1992**, *59*, 4042.
8. Maggi, R.; Schlosser, M. *J. Org. Chem.* **1996**, *61*, 5430.
9. (a) Katsoulos, G.; Schlosser, M. *Tetrahedron Lett.* **1993**, 6263; (b) Schlosser, M. *Angew. Chem., Int. Ed.* **1998**, *110*, 1496.
10. Compound **4**: ^1H NMR (CDCl_3): 0.95 (t, $J=7.5$ Hz, 3H), 1.40 (m, 2H), 1.65 (m, 2H), 2.92 (t, $J=7.2$ Hz, 2H), 3.83 (s, 6H), 6.65 (t, $J=2.0$ Hz, 1H), 7.12 (d, $J=2.0$ Hz, 2H).
11. Methyl ester of compound **5**: mp 151.6–152.8°C; ^1H NMR (CDCl_3): 3.46 (s, 6H), 3.92 (s, 3H), 7.25 (m, 12H).
12. Methyl ester of compound **6**: mp 99–101°C; ^1H NMR (CDCl_3): 1.37 (t, $J=7.1$ Hz, 3H), 3.86 (s, 6H), 3.92 (s, 3H), 4.42 (q, $J=7.1$ Hz, 2H), 7.24 (s, 2H).
13. Methyl ester of compound **7**: mp 71–73°C; ^1H NMR (CDCl_3): 3.82 (s, 6H), 3.92 (s, 3H), 5.07 (dt, $J_1=7.0$, $J_2=1$ Hz, 1H), 5.19 (dt, $J_1=11$, $J_2=1$ Hz, 1H), 5.30 (s, OH), 5.65 (m, 1H), 6.13 (m, 1H), 7.25 (s, 2H).
14. (a) Meyers, A. I.; Avila, W. B. *Tetrahedron Lett.* **1980**, 3335; (b) Shimano, M.; Meyers, A. I. *Tetrahedron Lett.* **1997**, 5415.
15. Methyl ester of compound **11**: ^1H NMR (CDCl_3): 2.75 (br s, OH), 3.92 (s, 6H), 5.17 (d, $J=10.40$ Hz, 1H), 5.30 (d, $J=17.18$ Hz, 1H), 5.45 (d, $J=4.7$ Hz, 1H), 6.06 (m, 1H), 7.40 (d, $J=7.8$ Hz, 1H), 7.55 (s, 1H), 7.64 (d, $J=7.8$ Hz, 1H).
16. Chong, R.; King, R. R.; Whalley, W. B. *J. Chem. Soc. [C]* **1971**, 3566.
17. (a) Briggs, D. R.; Whalley, W. B. *J. Chem. Soc., Perkin Trans. I* **1976**, 1382; (b) Manchand, P. S.; Townsend, J. M.; Belica, P. S.; Wong, H. S. *Synthesis* **1980**, 409; (c) Asahina, Y.; Asano, J. *Ber. Dtsch. Chem. Ges.* **1933**, *66[B]*, 687; (d) Charlesworth, E. H.; Robinson, R. *J. Chem. Soc.* **1934**, 1531; (e) Fujikawa, F.; Kobayashi, T. *J. Pharm. Soc. Jpn.* **1944**, *64*, 7; (f) Wessely, F.; Swoboda, J.; Guth, V. *Monatsh. Chem.* **1964**, *95*, 649; (g) Tyman, J. H. P. *J. Chem. Soc., Perkin Trans. I* **1973**, 1639.