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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

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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.

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

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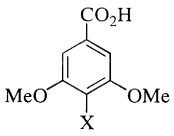
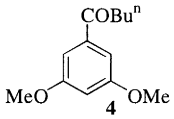
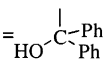
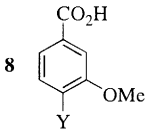
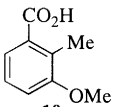
organolithium reagents, the hydrolysis of the amide posed difficulties and the yield of the carboxylic acid was very poor. Initially, we tried the direct metalation of 3,5-dimethoxy benzoic acid with Schlosser's super base, LIC–KOR,[9] followed by treatment with methyl iodide but the reaction did not yield any useful product. However, when butyl lithium (4 equiv.) was added to a pretreated mixture of 3,5-dimethoxy benzoic acid and KO^{t}Bu (4 equiv.) in THF at −78°C followed by quenching with D_2O, 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/ *n*-BuLi	D_2O	**2** X = D	98 (2)	92
	"	MeI	**3** X = Me	92 (8)[a]	80
	only *n*-BuLi	--	 **4**	--	95
	KOBu^t/ *n*-BuLi	Ph_2CO	**5** X = 	60 (40)	55[b](89)
	"	$ClCO_2Et$	**6** X = -CO_2Et	25(75)	20[b](67)
	"	OHC=CH$_2$	X = -CH(OH)-CH=CH_2 **7**	48(52)	44[b](69)
	"	MeI	**9** Y = Me	70(30)	60
 **8** Y = H	*sec*-BuLi/ TMEDA[7]	MeI	**9** +  **10** (1 : 4)		
	KOBu^t/ *n*-BuLi	OHC=CH$_2$	Y = -CH(OH)-CH=CH_2 **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^{t}Bu (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^{t}Bu 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^{t}Bu (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 conditions[7](*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. Meyers[14] 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 metabolities like selerotiorin and mitorubrin.[16] Although this relatively simple acid **3** has been synthesised in moderate yields by other routes[17] 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^{t}Bu (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. NH_4Cl (3 mL) and washed with Et_2O (5 mL). The aq. layer was acidified with 2N HCl. The white precipitate obtained was extracted with Et_2O (2×5 mL), dried over anhyd. Na_2SO_4. The solvent was removed in vacuo and the residue was recrystallised ($CHCl_3$/Et_2O) to give methylated product **3** as a white crystalline solid (0.086 g, 80%). Mp 212–214°C (lit.[11] 210–216°C), ^{1}H NMR (DMSO-d_6): 2.05 (s, 3H), 3.83 (s, 6H), 7.13 (s, 2H), 13.0 (br s, 1H).

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10. Compound **4**: ^{1}H 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; ^{1}H 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; ^{1}H 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; ^{1}H 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).
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