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REDUCTIVE ALKYLATION OF 2-METHOXYBENZOIC ACID DERIVATIVES

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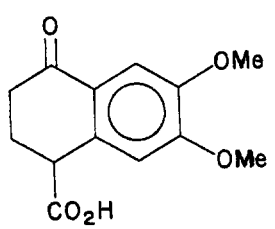
Summary: Metal-ammonia reduction followed by *in situ* alkylation of 2-methoxybenzoic acids often results in substantial loss of the methoxy substituent; reduction of the carboxylate salts or esters, however, suppresses this side reaction and good to excellent yields of desired products are then obtained.

Reductive alkylation of 2-methoxybenzoic acids may provide useful access to a wide variety of cyclohexenone derivatives.[1] It has been usefully applied recently to the synthesis of several carbocyclic natural products,[2] but unfortunately, hydrogenolysis of the 2-methoxy substituent can be a serious side-reaction (up to 90% loss).[1ab,2ab,3] In this letter we report two simple solutions to this problem, based on reduction of either benzoate salts or the corresponding esters.

Careful reduction of benzoic acid and its alkyl derivatives in liquid ammonia by lithium requires only 2.2 gram atom equivalents of metal, indicating that reduction of the substrate occurs more rapidly than the reaction of the dissolving metal with the ammonium ions generated by the addition of the acid to the ammonia. We had noted also that, in the reductive alkylation of 1[4] and 2,[2c] over-reduction occurred unless the ammonium ions, formed through ionisation of these substrates, were neutralised by the addition of KO^tBu prior to reduction. *The application of this simple expedient also suppresses methoxy loss from 2-methoxybenzoic acids.*



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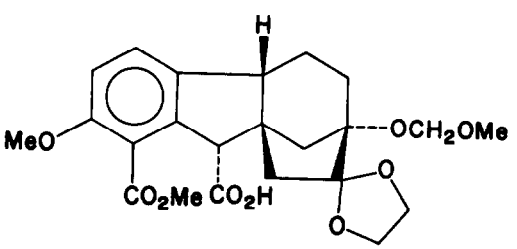


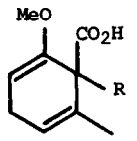
2

The choice of base is unimportant in the avoidance of hydrogenolysis, but potassium salts are generally the most soluble; the ^tBuOH which is generated also assists solubility, ensures C(1) alkylation,[5] and prevents the formation of amide ion, which might otherwise be deleterious to the reactants or products. Reduction of 2-methoxybenzoic acid itself may then be equally well effected by lithium, sodium or potassium; the addition of ^tBuOH (up to 4 equiv.) improves solubility and was essential with the first two metals. Alkylation by many halides, especially those prone to E2 elimination, is best carried out on the dilithium enediolates formed, when necessary, by the addition of anhydrous lithium bromide following the reduction.[6] A typical example follows:

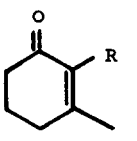
Reductive Methylation of 2-Methoxybenzoic Acid:[7] Potassium *t*-butoxide (5.6 g, 0.05 mole) was added to a stirred solution of 2-methoxybenzoic acid (7.6 g, 0.05 mole) in dry THF (50 ml), followed by *t*-butyl alcohol (4.9 ml, 0.05 mole) and liquid ammonia (dried for > 0.5 h over sodamide). The mixture was cooled to -70°C (internal temp.) and potassium metal (4.89 g, 0.125 gm atom) added in small pieces until a deep blue colour persisted for > 5 min. This was discharged by the addition of a drop of 1,3-pentadiene, then a solution of methyl iodide (15.5 ml, 0.25 mole) in THF (50 ml) was added. The ammonia was removed in a stream of nitrogen, brine (200 ml) added to the residue, and the product extracted with dichloromethane while the pH of the mixture was progressively reduced to 4 by the addition of 1M HCl. Drying (Na_2SO_4), evaporation of solvent and distillation (Kugelrohr) gave 2-methoxy-1-methylcyclohexa-2,5-diene-1-carboxylic acid (4.6 g, 84%) as a homogeneous colourless gum. IR 3400-2700, 1700 cm^{-1}. NMR δ 1.24 (3H, s), 2.80 (2H, br s), 3.52 (3H, s), 4.81 (1H, t, J 3 Hz), 5.64-5.83 (2H, m). M.s. 152.0478 (M^+-CH_4, 100%. $C_8H_8O_3$ requires 152.0473), 123 (49), 105 (98).

The methodology is equally effective for most benzoic acid derivatives and its application to 2-methoxy-6-methylbenzoic acid, for example, provides a useful and more efficient alternative[8] to the utilisation of Hagemann's ester[9] for the preparation of 3-methylcyclohex-2-enone derivatives (Table 1).

Table 1: *Reductive Alkylation of 2-methoxy-6-methylbenzoic Acid*



R	Yield[6]
Me	90%
CH_2Ph	91%
$CH_2CH_2CH=CH_2$*	87%



R	Yield†
Me[9a]	89%
CH_2Ph[9b]	93%
$CH_2CH_2CH=CH_2$[9c]	86%

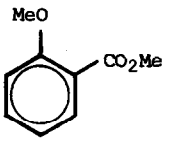
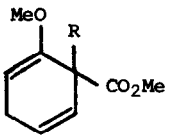
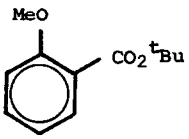
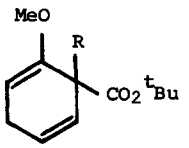
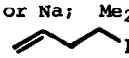
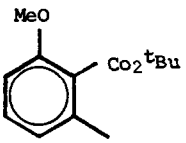
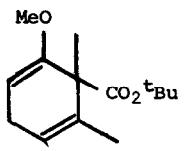
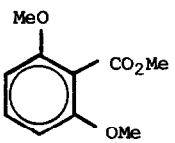
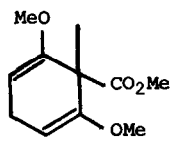
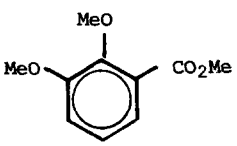
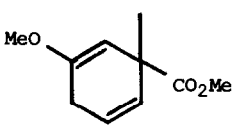
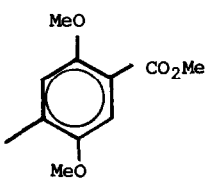
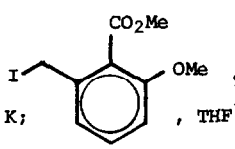
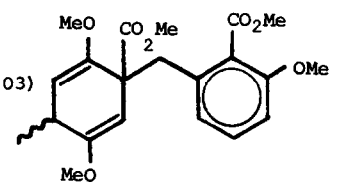
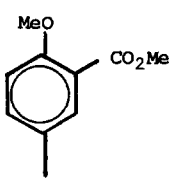
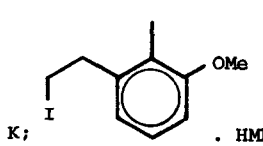
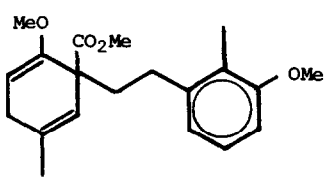
*Ammonia removed before alkylation.

†Hydrolysis/decarboxylation effected by reported procedure.[1b]

In cases where solubility of the carboxylate salt presents a serious difficulty, it may be advantageous to reduce the benzoate ester instead. This may also be preferred where retention of the carboxyl group is required, or when oxidative decarboxylation back to the aryl ring occurs readily.[10] *t*-Butyl esters may be utilised if simple decarboxylation (effected simply by trifluoroacetic acid at 50°C for 3 h) is desired. The reductions are best effected in the presence of one equivalent of *t*-butyl alcohol with potassium or sodium at -70°C, following the procedure described above for the benzoate salts.[11] Again, metathesis to the lithium enolates before alkylation is vital for many halides. A summary of results on a range of esters is indicated in Table 2. With both esters and carboxylate salts, removal of ammonia prior to alkylation may be necessary with some alkyl halides, especially more reactive ones.

Loss of 2-methoxy substituents is promoted by both 4- and 6-substituents and is unavoidable with 3-substituted derivatives (due, presumably, to steric compression), even with the application of the procedures described above. Substituents at C(5), however, retard hydrogenolysis, and a 5-methoxy substituent suppresses it completely. These complementary effects are consistent with the view that increased electron density at C(2) and C(5) in intermediate radical-anions or dianions (favoured by 3-, 4- and 6-substituents, disfavoured by 5-substituents) promotes expulsion of the 2-methoxyl, but the role of ammonium ion is still obscure.

Table 2: *Reductive Alkylation of Benzoate Esters*

Substrate	Reagents	% Yield (b.p./torr)†	Product[7]
	K; MeI	95 (92°/0.3)	
	K; CH_3CH_2I	96 (100°/0.3)	
	K or Na; MeI	96 (105°/0.2)	
	Li; MeI	73	
	K or Na; Me_2CHI	94 (135°/0.2)	
	K; 	nil	
	K; LiBr; 	60 (dec.)	
	K; MeI	96 (125°/0.1)	
	K; MeI	96 (m.p. 65°-67°)	
	K; MeI	70 (95°/0.3)	
	 K; , THF*	93 (125°/0.03)	
	 K; . HMPA*	60	

* Ammonia removed prior to alkylation.

† Kugelrohr

References and Footnotes

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5. When potassium 2-methoxybenzoate generated from KNH_2 was alkylated with methyl iodide, C(3) alkylation occurred specifically to give 2-methoxy-3-methyl-cyclohexa-1,5-diene carboxylic acid. This result was unique for this substrate and methyl iodide, however, and is ascribed to an aggregation effect. Reactive halides such as allyl and benzyl bromides gave $\sim$ 20% C(3) alkylation under these conditions with this substrate, but the other benzoates under examination were alkylated at C(1) in the normal way.

6. Cf. M. Narisada and F. Watanabe, *J. Org. Chem.*, 1973, *38*, 3887.

7. All new compounds were fully characterised by satisfactory microanalyses ($\pm$<0.3%, C,H) and/or accurate mass measurements, and N.M.R., I.R. and mass spectra.

8. Cf. J. Amupitan and J.K. Sutherland, *J. Chem. Soc. Chem. Commun.*, 1978, 852.

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10. A.J. Baker and A.C. Goudie, *J. Chem. Soc. Chem. Commun.*, 1972, 951.

11. Cf. H.J.E. Loewenthal, "Guide for the Perplexed Organic Experimentalist", Heyden, London, 1978, pp 133-138. L.N. Mander and R.J. Hamilton, *Tetrahedron Lett.*, 1981, *22*, P.W. Rabideau, D.L. Huser and S.J. Nyikos, *Tetrahedron Lett.*, 1980, *21*, 1401.

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