Rearrangement of 2-(Arylmethoxy)methyl-2-oxazolines *via* Lithium Azaenolates: a Facile Synthetic Route to *ortho*-Methylmandelic Acid Derivatives

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2-(Arylmethoxy)methyl-2-oxazolines, on treatment with LDA in THF at low temperature, rearrange to afford products which are hydrolysed to *ortho*-methylmandelic acids or α-(1-methyl-2-naphthyl)glycolic acid.

2-(Alkoxy)methyl-2-oxazolines, on treatment with LDA in THF at low temperature, give the stable lithium azaenolates, which can react with electrophiles to yield α-substituted products.[1] However, 2-(benzyloxy)methyl-2-oxazoline **1a**, when subjected to analogous conditions unexpectedly gave **2a**. While [2,3] sigmatropic rearrangements of 2-(allyloxy)-methyl-2-oxazolines *via* the lithium azaenolates are well documented[2] and those of benzyl allyl ethers[3] and benzyl cyanomethyl ethers[4] *via* α-carbanions have been reported, the reactions of the closely related 2-(benzyloxy)methyl-2-oxazolines have attracted little attention. In addition, the utility of the oxazoline moiety has been realized in a variety of synthetic applications.[5] We therefore investigated this novel rearrangement of 2-(arylmethoxy)methyl-2-oxazolines *via* the lithium azaenolates **4** furnishing highly functionalized 2-[α-hydroxy-α-(substituted aryl)]methyl-2-oxazolines that can be precursors to α-hydroxy-α-(*ortho*-methyl-substituted aryl)acetic acids.

The substrates, **1a–f**, **6** and **8**,† were prepared from 2-chloromethyl-4,4-dimethyl-2-oxazoline and the corresponding alcohols in the presence of 50% NaOH and tetrabutylammonium bromide in THF in good yields (76–93%). The oxazolines **1a–d** and **6** were treated with LDA (1.2 equiv.) at −75 °C, allowed to react at the same temp. for the time indicated in Table 1. 2-[α-Hydroxy-α-(*ortho*-tolyl)]methyl-2-oxazolines, **2a–d** and **7**,† were formed exclusively as the major products and were isolated by washing the crude materials with *n*-hexane (Table 1, entries 1–5). The ^{1}H NMR spectra of the crude materials demonstrated that in most cases the rearranged products accounted for more than 90% of the products. However, the reaction of **1e** with 1.2 equiv. of LDA produced a mixture of compounds in which [1,2] Wittig rearrangement products predominated over the expected **2e**. When **1f** was treated with 1.2 equiv. of LDA, the reaction resulted principally in the recovery of the starting material. Use of 2.2 equiv. of the base did not improve the reaction, but again afforded mixtures including a large quantity of polymers, in which **2f** was a minor constituent. Attempted isolation of **2e** and **2f** failed. It should be noted that **1e** and **1f** have electron-withdrawing substituents at the 4-position of the benzene rings, while the other substrates bear electron-releasing groups at the *para*- or *ortho*-positions, although both **1d** and **6** bear groups of deactivating nature. The rearrangement proceeded as expected with the lithium azaenolate derived from **8** (Table 1, entry 8). Thus, **8** afforded a mixture of **9** and **10** in a ratio of 1.6:1. From the mixture, **9**† was isolated in 45% yield, whereas isolation of **10** was unsuccessful despite its comparative stability. However, **10** could be purified to such an extent that allowed the characterization by ^{1}H and ^{13}C NMR spectroscopy.‡ It is highly plausible that **10** is an intermediate to **9**.

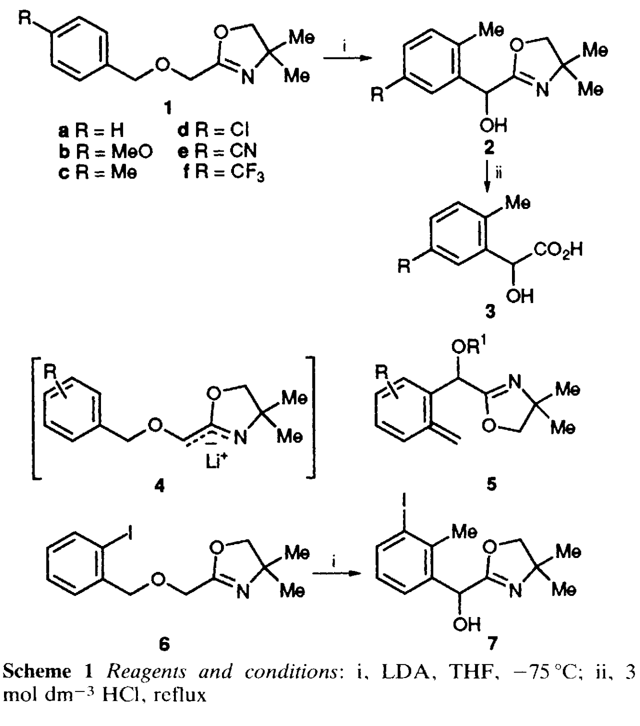
Table 1 Rearrangement of 2-(arylmethoxy)methyl-2-oxazolines[a] and the hydrolysis of the products

	Substrate			Rearrangement product	Hydrolysis product
Entry	No.	R	Reaction time/h	No. yield (%)[b]	No. yield (%)
1	**1a**	H	3.5	**2a** (70)	**3a**[6] (77)
2	**1b**	MeO	4.5	**2b** (62)	**3b** (97)
3	**1c**	Me	3.5	**2c** (65)	**3c** (95)
4	**1d**	Cl	3.5	**2d** (77)	**3d** (97)
5	**6**	—	3	**7** (50)	— ([e])
6	**1e**	CN	5.7	**2e** ([d])	**3e** ([e])
7	**1f**	CF_3	23[c]	**2f** ([d])	**3f** ([e])
8	**8**	—	3.5	**9** and **10**[f] (95)	**11**[g] (86)

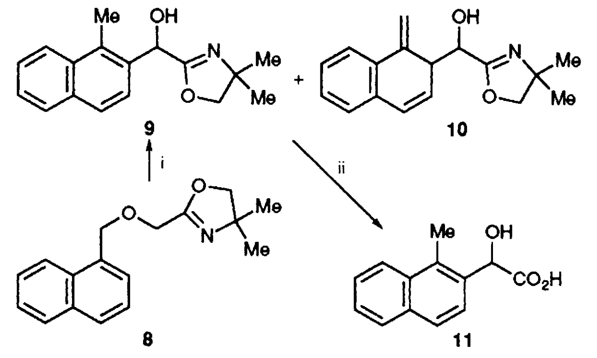
[a] Reactions were carried out by adding a solution of the substrates in THF to a solution of LDA (1.2 equiv.) in THF at −75 °C and stirring at the same temp. in 6–20 mmol scales. [b] The isolation procedure has not yet been optimized. [c] In this case, 2.2 equiv. of LDA was used. [d] Not isolated. [e] The hydrolysis was not performed. [f] The ratio of **9** to **10** was 1.6:1 by ^{1}H NMR. [g] A mixture of **9** and **10** in a ratio of 3.3:1 was used in the hydrolysis.

Hydrolyses of the products were performed by heating to reflux with 3 mol dm^{-3} HCl for 5–6.5 h. The α-hydroxy carboxylic acids, **3a**,[6] **3b–d** and **11**,† were isolated in good to excellent yields (Table 1). When a mixture of **9** and **10** was subjected to hydrolysis, **11** was obtained as a single product (Table 1, entry 8).

Although the mechanistic aspect of the rearrangement has not yet been clarified, some comments on this subject would be appropriate. By analogy with the rearrangement of benzyl allyl ethers[3] and the substituent effects found in the present reactions that are similar to those reported on the Sommelet–Hauser rearrangement of ammonium ylides,[7] we presume that a similar mechanism holds in this system in favour of a concerted [2,3]-sigmatropic rearrangement of the azaenolates to form intermediates **5** (R^1 = Li), which give the products presumably by a proton dissociation–recombination process. In support of this assumption, the amount of **5b** (R^1 = H),§ detected in quenched samples of the reaction mixture decreased as the reaction proceeded and after 4.5 h only a trace amount of **5b** was left, while **2b** was the major constituent. The ^{1}H NMR spectra of the crude materials obtained from the



Scheme 1 *Reagents and conditions*: i, LDA, THF, −75 °C; ii, 3 mol dm^{-3} HCl, reflux



Scheme 2 *Reagents and conditions*: i, LDA, THF, −75 °C; ii, 3 mol dm^{-3} HCl, reflux

reactions of **1b–e** exhibited a trace of absorptions of ABX pattern ascribable to benzyl methylene and adjacent methine proton resonances.¶ This seems to indicate the presence of by-products that have resulted from the competing [1,2] Wittig rearrangement.[3,7]

In summary, the rearrangement of 2-(arylmethoxy)methyl-2-oxazolines with electron-releasing substituents on the aromatic rings *via* the lithium azaenolates, combined with the subsequent hydrolysis of the products, provides a ready access to α-hydroxy-α-(*ortho*-methyl-substituted aryl)acetic acids. This approach is attractive because of its operational simplicity and its potential applicability to a variety of substrates. It has been found[8] that the corresponding π-excessive heteroaromatic derivatives and a 1,3-oxazine derivative undergo analogous reactions.

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Footnotes

† All new compounds gave satisfactory microanalytical and spectral (^{1}H, ^{13}C NMR) data.

‡ *NMR data* for **10**: δ_H (400 MHz; CDCl$_3$; SiMe$_4$) 1.20 (3H, s, 4-Me), 1.22 (3H, s, 4-Me), 3.51 (1H, dd, *J* 5.4 and 6.8 Hz, 2′-H), 3.68 (1H, d, *J* 8.3 Hz, 5-H), 3.92 (1H, d, *J* 8.3 Hz, 5-H), 4.09 (1H, d, *J* 6.8 Hz, α-H), 5.16 (1H, br s, C=CH_2), 5.67 (1H, br s, C=CH_2), 6.00 (1H, dd, *J* 5.4 and 9.8 Hz, 3′-H), 6.57 (1H, d, *J* 9.8 Hz, 4′-H), 7.03 (1H, m, Ph), 7.18 (2H, m, 6′- and 7′-H) and 7.50 (1H, m, Ph); δ_C (100 MHz; CDCl$_3$; SiMe$_4$) 28.23 (CMe_2), 28.36 (CMe_2), 47.82 (2′-CH), 66.87 (4-C), 70.46 (α-CH), 79.84 (5-CH$_2$), 116.22 (C=CH$_2$), 124.21 (CH aromatic), 126.73 (3′-CH), 126.86 (CH aromatic), 127.88 (CH aromatic), 128.41 (CH aromatic), 129.33 (4′-CH), 132.38 (C aromatic), 133.04 (Ca aromatic), 141.74 (*C* = CH$_2$) and 165.34 (2-C).

§ An approximate ratio of **2b** : **5b** was 4 : 1 as determined by ^{1}H NMR spectroscopy (400 MHz; CDCl$_3$).

¶ These peaks could be assigned to the benzyl methylene and adjacent methine protons of 4,4-dimethyl-2-[1-hydroxy-2-(substituted phenyl)]ethyl-2-oxazolines; *e.g.* ^{1}H NMR spectrum (400 MHz; CDCl$_3$; SiMe$_4$) of a sample obtained from the reaction of **1b** exhibited peaks of AB part at δ 2.93 (dd, J_{AB} 13.6, J_{AX} 6.8 Hz) and 3.03 (dd, J_{AB} 13.6, J_{BX} 4.8 Hz), and X part at δ 4.47 (dd, J_{AX} 6.8, J_{BX} 4.8 Hz).

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