Anions of chalcone-epoxides†

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Treatment of chalcone-epoxide 1 with lithium tetramethylpiperidide gives two anions: enolate 3 and the remote anion 4 which upon formation, 4 adds to unreacted starting material 1 to yield the diastereoisomeric products 5 and 6.

The introduction of the epoxide moiety into organic molecules *via* nucelophilic addition is an important exercise in natural product synthesis. Further, due to the susceptibility of epoxides towards base promoted isomerizations[1] several methods have consequently been developed for the generation of oxiranyl anions.[2] The recent futile attempt to prepare lithium enolate **3** from enolizable α-ketoepoxide **1** by direct treatment with lithium diisopropylamide (LDA) which yielded, instead, alcohol **2**,[2b] evinces the influence of the epoxide functionality.[3] The reaction is yet another example of a Meerwein–Ponndorf–Verley type hydride transfer reduction[4] previously observed with non-enolizable ketones, *e.g.* benzophenone,[5] as well as certain enolizable ketones, *e.g.* α-bromo- and α-methoxyketones[6] upon treatment with a lithium amide base bearing an α-hydrogen such as LDA, which yield the corresponding alcohols.

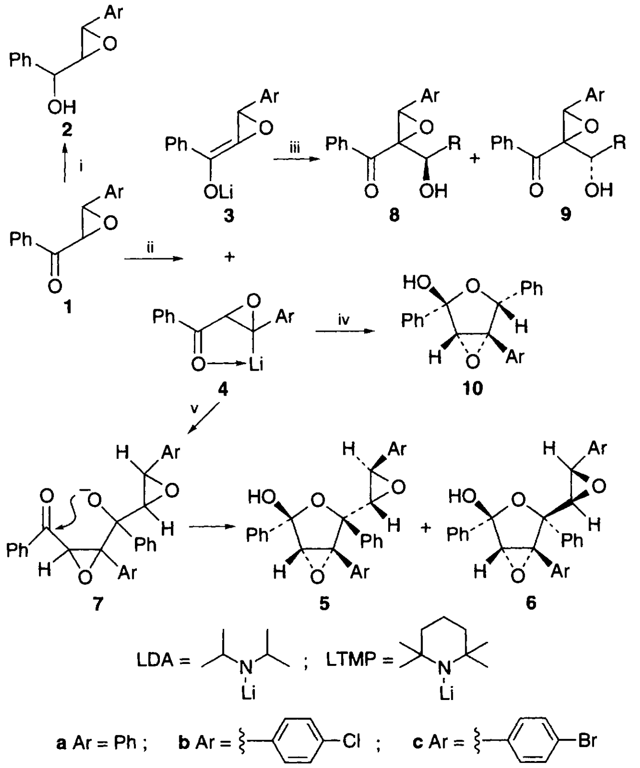
However, here we report that, upon changing the base from LDA to lithium tetramethylpiperidide (LTMP), an amide base bearing no α-hydrogen, and using conventional saturated aqueous ammonium chloride work-up, chalcone epoxide **1a** affords **5a** and **6a** in 14 and 36% isolated yields respectively (along with 42% recovered starting material) apparently *via* the remote anion **4** (Scheme 1, Table 1). Although remote β-anions are well precedented and widely used in organic synthesis,[7] the fact that anion **4** can be formed from enolizable ketone **1** is still quite noteworthy.

The structures **5a** and **6a** are deduced from their physical data which include NMR NOE experiments and X-ray analyses.‡ The compounds' isolation indicates formation of the remote β-anion **4a**, which apparently reacts with starting material **1a** in consecutive aldol fashion *via* intermediate **7a**.

Concurrent formation of α-anion **3a** was demonstrated by trapping with aldehydes to obtain the corresponding aldol products as two separable isomers, **8a** and **9a**, accompanied by epoxytetrahydrofurans **5a** and **6a**, from anion **4a**. Thus when a solution of an equimolar mixture of the starting epoxide and aldehyde[8] is introduced into a solution of preformed LTMP at −78 °C, four products, **5a**, **6a**, **8a** and **9a** are isolated as shown in Table 1.

The competitive β-hydrogen abstraction from chalcone epoxide can be substantially enhanced as clearly demonstrated by the reactions of halo-derivatives **1b** and **1c** in which a fair increase in yields of the epoxyfuran dimers has obtained over that from the parent compound **1a**.

Treatment of *p*-chloro chalcone-epoxide **1b** with LTMP, followed by proton quenching under the conditions previously described for **1a** provided epoxyfuran dimers **5b** and **6b**, with some recovered starting material, in 27, 48 and 15% isolated yields respectively. Similarly the bromo derivative **1c** gave rise to **5c** and **6c** accompanied by **1c** in 24, 45 and 19% yields. Morevoer, in these two cases it was possible to trap the β-anions, although in poor yields, with an external electrophile as illustrated by carrying out the reactions in the presence of benzaldehyde whereby furans **10b** and **10c** were isolated in 15 and 13% yields respectively,§ along with the corresponding



Scheme 1 *Reagents and conditions*: i, LDA, THF, −78 °C; ii, LTMP, THF, −78 °C; iii, RCHO; iv, PhCHO; v, **1**

Table 1 Reactions of epoxides **1a–c**

		Yield product (%)				
Starting material	Electrophile	5	6	8[a]	9[a]	10
1a	H_3O^+	14	36	—	—	—
	RCHO					
	R = Ph	12	36	11	10	—
	= 4-Me-C_6H_4	11	35	7	4	—
	= 4-Cl-C_6H_4	11	34	11	10	—
	= 4-Br-C_6H_4	11	35	11	10	—
1b	H_3O^+	27	48	—	—	—
	PhCHO	14	39	7	6	15
1c	H_3O^+	24	45	—	—	—
	PhCHO	14	32	9	6	13

[a] Structures of **8** and **9** may be interchanged.

dimers **5** and **6**, and aldol products **8** and **9**, whose respective yields are shown in Table 1. Quite notable is that the corresponding furan, **10a**, could not be detected in the analogous reaction of **1a**. The assignment of the stereochemistry of compound **10** was quite straightforward, using NMR NOE experiments. Furan **10** further proves the presence of β-anion **4**.

This work demonstrates the unique property of the keto group of the α-ketoepoxide moiety, that is, besides being easily reduced *via* hydride transfer from amide base bearing an α-hydrogen such as LDA, it is also amenable to deprotonation by lithium tetramethylpiperidide at both the α- and β-sites, to generate the respective enolate and remote β-anion, the latter being the preferred mode of reaction.

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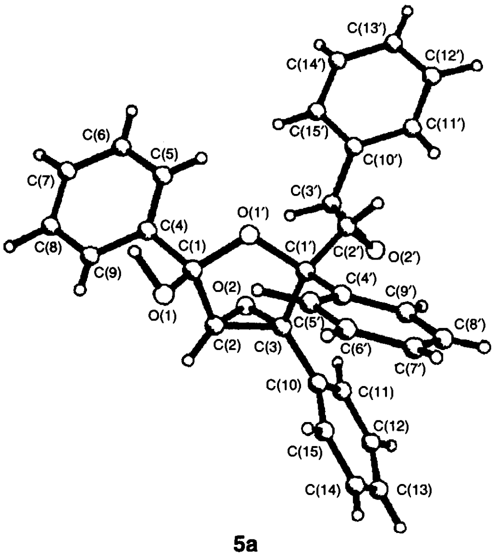
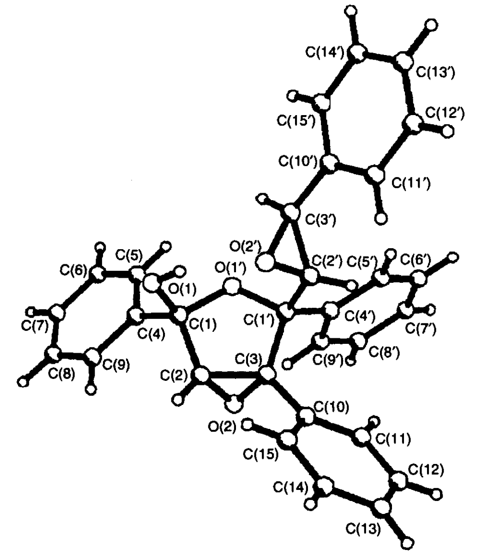


5a



6a

Fig. 1 Computer generated drawings of the final model of **5a** and **6a**. Note the difference configurations at C(1′).

Footnotes

† Part of this work was presented at the 15th International Congress of Heterocyclic Chemistry, Taipei, August 6–11, 1995.

‡ All compounds described are fully characterized by spectroscopic and elemental analyses. *Crystal data* for **5a** and **6a**: Both data sets were collected at room temperature on Siemens *R*3 m/v with Cu-Kα radiation (λ = 1.54178 Å) by using 2θ–θ scans from 3 to 110°. The crystal structures were solved by direct methods using SHELXS-86 and then all atoms except hydrogen atoms were refined anisotropically with full-matrix least-squares on F^2 using SHELXL-93. For **5a**: 0.3 × 0.4 × 0.4 mm^3 monoclinic crystal, was crystallized from methanol, space group $P2_1/n$, a = 10.573(1), b = 12.116(1), c = 18.793(3) Å and β = 104.48(1)°. With one molecule in the asymmetric unit and Z = 4, the calculated density was 1.278 g cm^{-3}. The total of 2928 independent reflections was collected [2850 observed, $|F_o| > 4\sigma(F)$] with R_{int} of 2.04%. The structure has been refined to the final R-factor of 5.32% (wR^2 = 12.52%) for all data. For **6a**: 0.4 × 0.4 × 0.6 mm^3 monoclinic crystal, was crystallized from methanol, space group $P\bar{1}$, a = 10.387(5), b = 12.667(5), c = 11.575(6) Å, α = 89.81, β = 104.48(1) and γ = 115.41°. With one molecule in the asymmetric unit and Z = 2, the calculated crystal density was 1.286 g cm^{-3}. The total of 2907 independent reflections was collected [2860 observed, $|F_o| > 4\sigma(F)$] with R_{int} of 1.93%. The structure has been refined to the final R-factor or 5.01% (wR^2 = 12.52%) for all data. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/78.

§ Other isomers of **10** were not detected.

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