First Example of Epibromohydrin as an Acetone Equivalent

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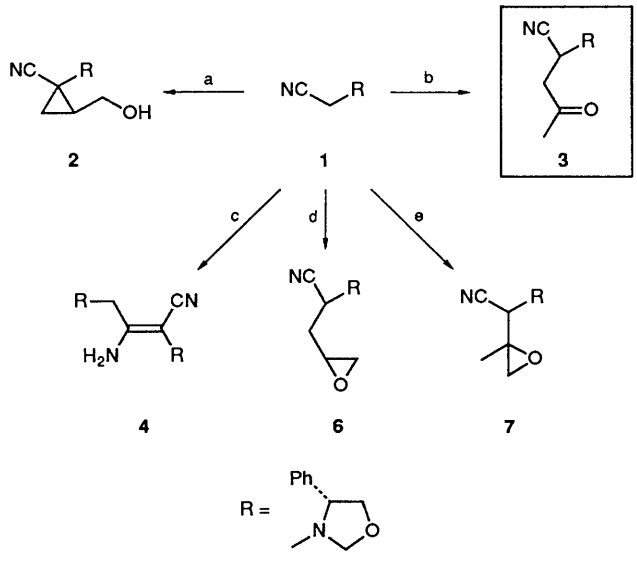
In the presence of lithium diisopropylamide at low temperature, the anion of the amino nitrile **1** is alkylated with epibromohydrin to give an acetonyl derivative **3**; allene oxide is invoked as the reactive intermediate.

As part of a programme dealing with the alkylation of aminoacetonitrile derivatives using 1,2-dielectrophiles to generate cyclopropane derivatives,[1] we investigated the reaction of (*R*)-3-cyanomethyl-4-phenyloxazolidine **1** with epibromohydrin (EBH) in the presence of strong base. While the optimum conditions[1] for formation of the desired cyclopropane derivative **2** required sequential treatment of **1** in THF at −70 °C with 1 equiv. of LDA/HMPA, then EBH, followed by a second equiv. of LDA/HMPA, we were intrigued to find that when these conditions were varied significant amounts of the derivative **3** were produced (Scheme 1), in which a three-carbon unit had been introduced as an acetonyl function.‡

We have studied the formation of the ketone **3**, and three factors appear to be essential for its production in good yield. (a) A very low temperature (−110 °C) gives highest yields and reaction selectivity. Warmer reaction conditions (*e.g.* −70 °C) result in a diminished yield of **3**, increased recovery of unchanged **1**, and the production of the cyclopropane **2** and the dimer **4** in the mixture. (b) The base must be LDA. No other strong base examined§ gave measurable yields of **3**. (c) While the reaction proceeds satisfactorily in THF alone, the addition of stoicheiometric quantities of chelating tertiary diamines (TMEDA, 1,4-dimethylpiperazine) improves the yield. In contrast, the presence of strongly dissociating agents (crown ether, HMPA) supresses the formation of **3** entirely. Under optimum conditions (see Experimental section) the yield of isolated **3** is 75%.

We have considered the mechanistic processes which would allow EBH to act in an unprecedented fashion as an acetonyl equivalent, and our observations are consistent with the intermediacy of the highly reactive allene oxide **5**. The oxiranylmethyl derivative **6**, formed by alkylation of **1** with EBH under 'normal' conditions (1 equiv. of LDA/HMPA, THF, −70 °C),[2] is not a precursor of **3**, being transformed only into cyclopropane **2** even under ketone-optimized conditions (LDA/TMEDA, THF, −110 °C). This suggests that modification of EBH to some other reactive electrophilic species takes place *before* interaction with the anion of **1**. The reaction yield is maximized when the ratio of LDA:EBH is 1:1, after allowing one extra equiv. of LDA for amino nitrile deprotonation, and when both are present in excess over synthon **1**. The nature of the halide leaving group influences the yield of **3**, which varies I ≈ Br > Cl > F, and drops virtually to zero with epifluorohydrin.

Strong base–epoxide interaction is often characterised by β-deprotonation followed by rearrangement to give an allylic alcohol,[3] a process favoured by the presence of dissociative agents such as HMPA.[4] We believe that under our conditions, however, α-deprotonation is (at least partially) achieved, on account of the presence of a reasonable leaving group on the β-carbon. The net result is, therefore, base-induced dehydro-



Scheme 1 a = i, LDA/HMPA, THF, −70 °C; ii, EBH, THF; iii, LDA/HMPA, THF, −70 °C; b = with EBH in THF, added to 3LDA/HMPA, THF, −110 °C; c = LDA/TMEDA, −70 °C, low yield (see ref. 1); d = i, LDA/HMPA, THF, −70 °C; ii, EBH, THF; e = i, 2LDA/TMEDA, THF, −110 °C; ii, CH_3COCH_2Br, THF

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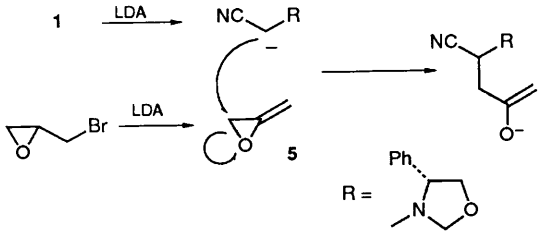
‡ Poor stereochemical induction (d.e. <10%) is observed in the formation of the new chiral centre for the transformation **1** to **3**, in contrast with previous results for **1** to **2** (d.e. 62% at C-1).
§ NaH, NaHMDS, KHMDS, *tert*-BuLi, *sec*-BuLi, lithium 2,2,6,6-tetramethylpiperidine amide.

halogenation to produce allene oxide.* This species is reactive[5] at temperatures too low for other nucleophilic reactions to proceed at reasonable rates, such as those which give rise to **2**, **4**, or **6**. Indeed, the low temperature is necessary to maintain some degree of control over the reaction selectivity of **5**, which condenses with the anion of **1** to give the enolate of **3**, itself liberated after work-up under protonic conditions (Scheme 2).



Rearrangement of EBH to bromoacetone, conceivably an alternative alkylating agent, is ruled out since the anion of **1** reacts with bromoacetone first at the carbonyl centre to produce the epoxide **7** as a mixture of stereoisomers (Scheme 1). Although allene oxide could rearrange to cyclopropanone, which might then behave as the reactive electrophile, the energy barrier for this transformation[6] in combination with the velocity of the observed acetonylation reaction at such a low temperature leads us to disfavour this possibility and propose allene oxide as the electrophile.

We are currently considering the implications of glycidyl halides as allene oxide precursors and investigating the scope of this novel acetonylation reaction.†

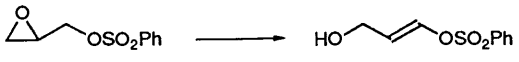
Experimental

THF was distilled under argon from sodium–benzophenone. Diisopropylamine, 1,4-dimethylpiperazine and epibromohydrin were distilled before use. The amino nitrile **1** was prepared as reported previously.[2] All solutions were prepared and manipulations carried out under nitrogen. *J* Values are in Hz.

3-(1-*Cyano*-3-*oxobutyl*)-4-*phenyloxazolidine* **3**.—A solution of **1** (0.25 g, 1.33 mmol) and epibromohydrin (275 μl, 3.21 mmol) in THF (6 ml) was added dropwise over 30 min to a solution of LDA [prepared from commercial 1.6 mol dm^{-3} butyllithium solution in hexane (2.5 ml, 4.00 mmol) and diisopropylamine (560 μl, 4.00 mmol)] and 1,4-dimethylpiperazine (540 μl, 4.00 mmol) in THF (6 ml) held at −110 °C. The mixture was left at −110 °C for 1 h, then at −70 °C for 4 h, and was finally quenched with saturated aqueous ammonium chloride (10 ml). The mixture was warmed to room temperature, the organic phase collected and the aqueous phase washed with dichloromethane (3 × 5 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to leave an oil which was subjected to flash chromatography on silica gel (heptane–EtOAc, 60:40) to separate the diastereoisomers of **3** (absolute stereochemistry not determined) in roughly equal amounts, total yield 0.24 g (75%). First stereoisomer, oil; R_F 0.47; ν_{max}/cm^{-1} 1720 and 2230; $\delta_H(CDCl_3$, 200 MHz): 1.80 (3 H, s), 2.55 (1 H, dd, *J* 6.2 and 18), 2.70 (1 H, dd, *J* 8.2 and 18), 3.70 (1 H, dd, *J* 8.2 and 6.2), 4.20 (1 H, dd, *J* 8.0 and 6.5), 4.40 (2 H, m), 4.55 (1 H, d, *J* 4.2), 4.80 (1 H, d, *J* 4.2) and 7.40 (5 H, m); $\delta_C(CDCl_3$, 50 MHz): 29.6 (q), 45.2 (t), 48.6 (d), 63.0 (d), 75.1 (t), 86.8 (d), 117.7 (s), 126.7, 127.4, 128.8 (each d), 141.5 (s) and 202.4 (s); *m/z* (CI): 244 (M^+, 34), 218 (24), 214 (43), 201 (40), 187 (36), 171 (14), 156 (19), 118 (98), 104 (100) and 91 (93).

Second stereoisomer, oil; R_F 0.38; ν_{max}/cm^{-1} 1715 and 2230; $\delta_H(CDCl_3$, 200 MHz) 2.10 (3 H, s), 2.85 (2 H, d, *J* 7.2), 3.70 (1 H, t, *J* 8.5), 4.05 (1 H, dd, *J* 8.5 and 7.2), 4.15 (1 H, t, *J* 7.2), 4.30 (1 H, d, *J* 7.2), 4.50 (1 H, d, *J* 2.5), 4.80 (1 H, d, *J* 2.5) and 7.35 (5 H, m); $\delta_C(CDCl_3$, 50 MHz) 29.5 (q), 45.6 (t), 46.2 (d), 65.3 (d), 74.0 (t), 82.5 (d), 116.3 (s), 127.5, 128.4, 128.7 (each d), 136.7 (s) and 202.3 (s); *m/z* (CI): indistinguishable from first stereoisomer.

* The competing β-deprotonation reaction also occurs under these conditions as verified by treating EBH with LDA/TMEDA in THF at −110 °C in the absence of any other nucleophile, which gave a high conversion into bromoallyl alcohol. Thus if LDA and EBH are premixed at −110 °C then **1** is added, even with an extra equiv. of LDA, no trace of **3** is formed. The β-deprotonation reaction explains the requirement for an excess of LDA and EBH over **1** for higher yields of **3**. Furthermore, there is a fine balance between the nucleofugal and electron withdrawing properties of the leaving group, for the use of glycidyl benzenesulphonate in place of EBH gave no **3**, furnishing only the allylic alcohol, the product of a β-deprotonation process:



† At the request of a referee we disclose that preliminary investigations show that acetonylation of other amino nitrile and ketone substrates occurs under the conditions described in lower (and as yet unoptimized) yield.

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