Phase-transfer-catalysed Ring Opening of Cyclohexene Oxide by Phenylacetonitrile Carbanion in the Presence of Lithium Salts†

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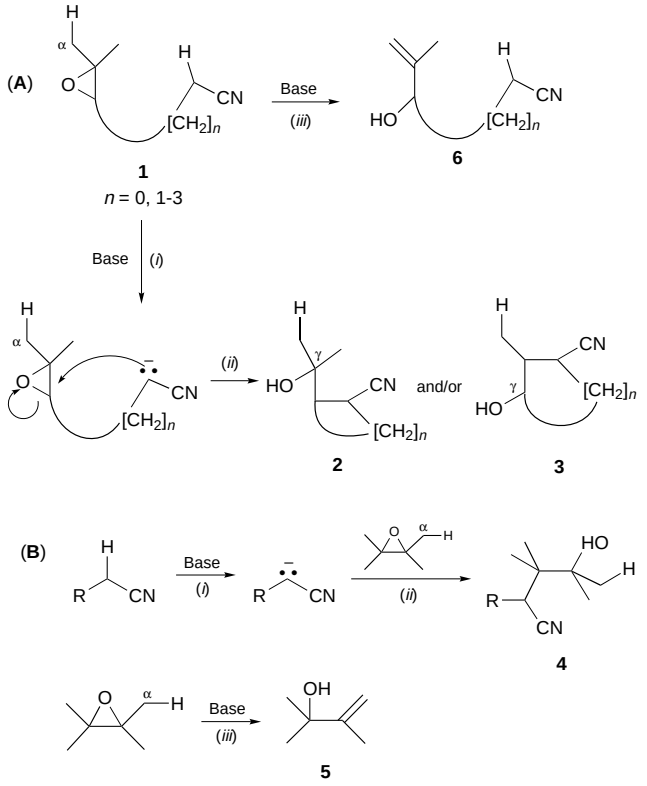
Lithium cation assisted nucleophilic ring opening of cyclohexene oxide, by phenylacetonitrile carbanions, under phase-transfer conditions giving rise to a diastereoisomeric mixture of *trans*-γ-hydroxynitriles **7** and **8** is reported.

Intramolecular cyclizations of epoxynitriles **1** and intermolecular ring openings of epoxides by alkanonitrile carbanions (Scheme 1, routes A and B), constitute an important method for the synthesis of highly reactive and versatile γ-hydroxynitriles **2–4** (Scheme 1).[1,2]

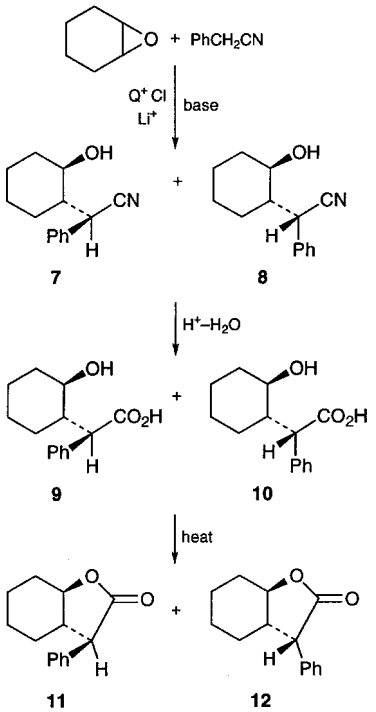


Scheme 1

Many studies indicate that, owing to the high pK_a values of nitriles[3] [CH_3CN, pK_{DMSO} = 31.3; $PhCH(CH_3)CN$, pK_{DMSO} = 23.0; $PhCH_2CN$, pK_{DMSO} = 21.9] the efficient ionization of an α-hydrogen, as an initial step [Scheme 1, step *i* in (A) or (B)], can be effected only under strongly basic conditions.[2–4] Accordingly, the oxirane opening by the resulting nucleophile (step *ii*) was usually accomplished using KNH_2 in liquid NH_3–glyme mixture,[1] $NaNH_2$ in PhH,[2] BuLi in THF–hexane, or lithium diisopropylamide in THF. In competition with path *i*, the strong base is capable of (a) elimination of the α-hydrogen, giving rise to unsaturated alcohols **5** and **6** (path *iii*) and (b) nucleophilic attack on the nitrile group as well. However, phenylacetonitriles, being of more strongly acidic nature than acetonitrile, do react satisfactorily with weaker bases.[5–7] In the search for the use of appropriate bases, *e.g.*, anhydrous K_2CO_3, Na_2CO_3, $KHCO_3$, KOH, NaOH and $KOBu^t$, still strong enough to generate a significant equilibrium concentration of carbanions, phase-transfer catalysts and crown ethers were found to be particularly useful and effective for (1) alkylation of phenylacetonitrile,[7] (2) acylation of phenylalkanenitrile,[7] (3) nucleophilic addition of sodium arylalkenenitrile carbanions to substituted *o*-propenylanisoles[8] and (4) the preparation of ethynyl-substituted phenylacetonitriles from vinylidene chloride and phenylacetonitrile derivatives.[9] There has been as yet no report of the phase-transfer-catalysed ring opening of epoxides of that type. The only related reaction recently described by Abenhaim *et al.*[10] is the ring opening of a fatty epoxide by diethyl acetamidomalonate in basic medium by phase-transfer catalysts.

Based on a concept employing weaker bases in a solid–liquid and liquid–liquid two phase system,[11] we report now phase-transfer-catalysed ring opening of cyclohexene oxide under diverse reaction conditions, by *in situ* generated potassium phenylacetonitrile (Scheme 2) affording the diastereoisomeric *trans*-2-hydroxycyclohexyl(phenyl)acetonitriles **7** and **8** in good yields (45–76%). Followed by the hydrolysis to *trans*-2-hydroxycyclohexyl(phenyl)acetic acids **9** and **10**, and cyclization to **11** and **12**, the complete reaction sequence constitutes a competitive method for the transformation of epoxides into the corresponding γ-lactones.

As shown in Table 1, we focused our attention on the reaction of **1** with phenylacetonitrile under various conditions in the presence of LiCl or $LiClO_4$ as an appropriate promoter for the epoxide opening, using benzyltriethyl-



Scheme 2

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ammonium chloride (TEBA) or tetrabutylammonium fluoride (TBAF) as a phase-transfer catalyst, and solid KOBu^t or KOH (or concentrated aqueous KOH) as a base.

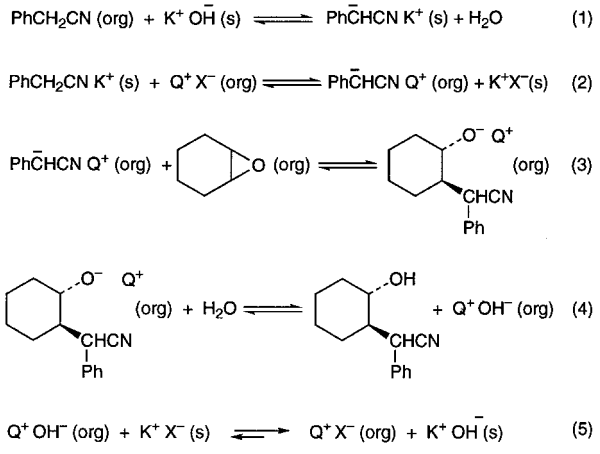
The proposed mechanism, illustrated in Scheme 3, involves as a first step initial formation of the conjugate base of phenylacetonitrile by heterogenous deprotonation with the solid KOH [eqn. (1)].

Table 1 The ring opening of 1,2-epoxycyclohexane by phenylacetonitrile carbanion in the presence of PTC, promoted by Li-cation participation[a]

Entry	Base (11 mmol)	Li salt (11 mmol)	PTC (1 mmol)	Yield (%)[d]
1	KOH[b]	LiCl	TEBA	45.0
2	KOH (50% aq.)	LiCl	TBFA	51.5
3	KOH[b]	$LiClO_4$	TBFA	76.0
4	KOH[b]	none	TEBA	<5.0
5	KOBu^t[c]	LiCl	TEBA	61.8
6	KOBu^t	$LiClO_4$	TBFA	74.2

[a]Conditions: reaction temp. 60–70 °C.; reaction time 8–10 h; cyclohexene oxide: 10 mmol. [b]Pulverized KOH. [c]The reaction was carried out under solvent-free conditions, *i.e.*, the organic phase consisted of neat organic substrates, to ensure as thorough mixing of the reacting species as possible to eliminate unfavourable solute-solvent interactions, but the isolation of the product was rather difficult [d]Yields refer to the amount of the mixture of diastereoisomer *trans*-2-hydroxycyclohexyl(phenyl)-acetic acids **9** and **10**.

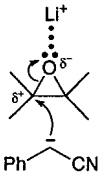
Extraction of Nu^- from the KOH surface as an ion pair with the lipophilic catalyst cation Q^+ into the organic phase is the next step [eqn. (2)] (the reaction was slower in larger quantity of PhH as a solvent). Phenylacetonitrile carbanion, being a strong nucleophile, opens up the oxirane ring in the



Scheme 3

organic phase [eqn. (3)] in a step which deserves some comments. The stereochemistry of the ring opening appears to be *trans*-diaxial, as would be expected for a mechanism involving nucleophilic attack of a carbanion from the periplanar direction. Secondly, it is facilitated by the prior addition of a Li salt which coordinates with the oxygen, and by polarizing the C—O bond as depicted in structure **13**, makes the oxirane ring more prone to the nucleophilic attack.

Electrophilic assistance of this type, based on the coordinating capacity of the metallic cations, has been presumed to play an important role in many cases.[4,10,12] A drastic decrease in the yield of **6** (to <5%) with nearly complete recovery of the starting epoxide, when the reaction is carried out in the absence of any lithium salt (Table 1, entry 4), illustrates the importance of Li^+ participation in alkali-carbanion-mediated epoxide-cleavage reactions. Furthermore, the enhanced nucleophilicity of $PhCHCN^-$ is anticipated under the PTC conditions, because of the high degree of ionic dissociation



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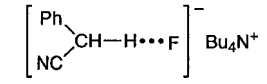

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and the lack of unfavourable nucleophile–solvent interactions.[11] It is interesting to note that, in an attempt to explore the effect of PTC catalysts, we observed the highest yield of **6** with TBFA as a catalyst and $LiClO_4$ as a metal salt promoter (76.0%, Table 1, entry 3). This is attributed to the enhanced nucleophilicty of the organic carbanion,[13] as an F^- ion, which is capable of forming strong hydrogen bonds, probably assists in proton abstraction *via* the hydrogen-bonded complex **14**.

The protonation of an alkoxide ion liberates the ion-pair Q^+ OH^- [eqn. (4)]. The favourable ion-exchange equilibrium forcing the migrations of OH^- ions out of the organic phase regenerates the catalyst[11] [eqn. (5)].

In conclusion, we have demonstrated that nucleophilic ring opening of epoxides, assisted by a Lewis-acidic Li^+ cation, may be successfully used, under PTC conditions, in organic syntheses.

Experimental

Typical Procedure for Phase-transfer-catalysed Ring Opening of Cyclohexene Oxide in the Presence of Li salt.—To a suspension of TBAF (0.31 g, 1 mmol), pulverised KOH (0.51 g, 11 mmol) and $LiClO_4$ (1.17 g, 11 mmol) in dry benzene (4 ml) a solution of phenylacetonitrile (1.17 g, 10 mmol) in benzene (2 ml) was added. After stirring for 1 h at 60 °C, cyclohexane oxide (0.98 g, 10 mmol) was added dropwise during 0.5 h, and the reaction mixture was then well stirred for an additional 8 h, cooled to room temperature and allowed to stand with stirring for 2 h. Dilution with water, extraction with benzene (15 ml) and removal of benzene *in vacuo* afforded a crude, pale yellow oil, which was without further purification saponified by the standard procedure to yield, after acidification, 1.78 g (76%) the mixture of diastereoisomeric *trans*-2-hydroxycyclohexylphenylacetic acids **9** and **10**. The crude product was crystallized from benzene–light petroleum (bp 40–70 °C) to give colourless crystals: mp 159–161 °C (lit.,[2] mp 160 °C; ν_{max}/cm^{-1} (KBr) 3259 (OH), 3061 (Aryl CH), 1678 (C=O), 768, 698 (mono-sub. Ar); δ_H (200 MHz) ($CDCl_3$) 1.06–1.75 (m, 6 H, cyclohexyl H-3; -4, -5) 1.90 (m, 2 H, cyclohexyl H-6), 2.98 (d, 1 H, *J* 3.7 Hz, *H*CCOH), 3.82 [d, 1 H, *J* 6.5 Hz, *H*C(Ph)CO_2H], 4.65 (br s, 1 H, OH), 7.30 (m, 5 H_{arom}), 12.07 (br s, 1 H, CO_2H); *m/z* 234 (3%, M^+), 216 (63), 172 (84), 136 (93), 118 (88), 91 (100), 77 (24), 44 (8) (Found: C, 71.59; H, 7.72. Calc. for $C_{14}H_{18}O_3$: C, 71.8; H, 7.7%).

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