

Ring opening of fluoroalkyl-containing α,β -epoxyketones by aromatic amines

V. G. Ratner* and K. I. Pashkevich

Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences,
20 ul. S. Kovalevskoi, 620219 Ekaterinburg, Russian Federation.
Fax: +7 (343 2) 44 4133

Aromatic amines cause α,β -epoxyketones containing a β -fluoroalkyl group to undergo ring opening at the α -position to give α -amino- β -hydroxyketones.

Key words: fluoroalkyl-containing α,β -epoxyketones; epoxide ring opening; fluoroalkyl-containing α -amino- β -hydroxyketones.

The reactions of epoxides with amines have long been of practical importance. From the scientific viewpoint, the most interest is attracted to the opening of the three-membered ring (in the case of asymmetric epoxides) and its stereochemistry.

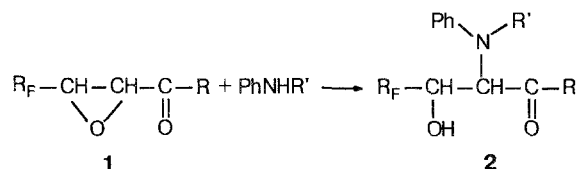
The effect of a carbonyl group conjugated with the epoxide ring on the direction of ring opening by nucleophilic reagents has been rather widely covered in the literature.¹ The reactions of aliphatic α,β -epoxyalkylketones with amines occur exclusively as a β -attack of the amine on the ring resulting in β -amino- α -hydroxyketones.^{1–3}

The purpose of the present work was to study the effect of a fluoroalkyl substituent at the β -position of α,β -epoxyalkylketones on the direction of the attack on the epoxide ring by an amine. We chose fluoroalkyl-containing *trans*- α,β -epoxyalkylketones (**1**), which were synthesized by us for the first time previously,^{4,5} as subjects of this study.

Preliminary experiments, in which compounds **1** were treated with ammonia in ethanol or benzene, showed

that, irrespective of the reaction conditions, the resulting product was a multicomponent resinous residue that could not be separated. Therefore, we used aromatic amines, which are less nucleophilic and, hence, react more selectively.

The interaction of α,β -epoxyalkylketones **1a–c** with aniline and *N*-methylaniline (Table 1) occurs when the reactants are heated in methanol or in ethanol. The reactions studied, unlike those involving aliphatic α,β -epoxyalkylketones, result exclusively in fluoroalkyl-containing α -amino- β -hydroxyketones (**2a–e**), which implies that α -opening of the epoxide ring occurs.



Generally, the direction of the attack of the amine on the epoxide ring of compounds **1** does not depend on the nature of the hydrocarbon substituent R or the

Table 1. Interaction of α,β -epoxyalkylketones **1a–c** with aromatic amines PhNHR'

Starting compound	R _F	R	R'	Reaction time/h	Reaction product	Product yield (%)	M.p./°C
1a	CF ₃	Ph	H	12	2-Anilino-4,4,4-trifluoro-3-hydroxy-1-phenyl-1-butanone (2a)	90	Oil
1a	CF ₃	Ph	Me	36	4,4,4-Trifluoro-3-hydroxy-2-(<i>N</i> -methylanilino)-1-phenyl-1-butanone (2b)	71	116–117
1b	C ₄ F ₉ ⁿ	Bu ^t	H	40	4-Anilino-6,6,7,7,8,8,9,9,9-nonafluoro-5-hydroxy-2,2-dimethyl-3-nonanone (2c)	38	60–61
1c	C ₄ F ₉ ⁿ	Ph	H	15	2-Anilino-4,4,5,5,6,6,7,7,7-nonafluoro-3-hydroxy-1-phenyl-1-heptanone (2d)	84	100–101
1c	C ₄ F ₉ ⁿ	Ph	Me	36	4,4,5,5,6,6,7,7,7-Nonafluoro-3-hydroxy-2-(<i>N</i> -methylanilino)-1-phenyl-1-heptanone (2e)	59	66–67

Note. The elemental analysis data (C, H, F, N) for all compounds obtained, **2a–e**, are within ± 0.3 % of the calculated values.

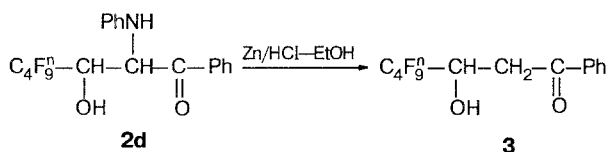
Table 2. Spectral characteristics of compounds **2a–e**

Compound	R _F	R	R'	IR, ν/cm^{-1}	^1H NMR (CDCl_3), δ , J/Hz
2a	CF ₃	Ph	H	3385 (OH, NH); 1675 (C=O)	4.49 (dq, $J_{\text{H,H}} = 5.40$, $J_{\text{H,F}} = 7.28$, 1 H, CF ₃ CH); 5.37 (d, $J_{\text{H,H}} = 5.40$, 1 H, NCH); 6.73–8.17 (m, 10 H, Ph)
2b	CF ₃	Ph	Me	3430 (OH); 1675 (C=O)	2.60 (s, 3 H, NCH ₃); 4.86 (m, 1 H, CF ₃ CH); 5.48 (d, $J_{\text{H,H}} = 10.7$, 1 H, NCH); 5.62 (d, $J = 7.0$, 1 H, OH); 6.50–7.82 (m, 10 H, Ph)
2c	C ₄ F ₉ ⁿ	Bu ^t	H	3520, 3430 (OH, NH); 1700 (C=O)	1.20 (s, 9 H, Bu ^t); 4.48 (m, 1 H, C ₄ F ₉ CH); 4.91 (d, $J = 3.52$, 1 H, NCH); 6.67–7.31 (m, 5 H, Ph)
2d	C ₄ F ₉ ⁿ	Ph	H	3290, 3200 (OH, NH); 1670 (C=O)	4.67 (m, 1 H, C ₄ F ₉ CH); 5.39 (d, $J = 3.29$, 1 H, NCH); 6.77–8.02 (m, 10 H, Ph)
2e	C ₄ F ₉ ⁿ	Ph	Me	3450 (OH); 1670 (C=O)	2.76 (s, 3 H, NCH ₃); 5.22 (m, 1 H, C ₄ F ₉ CH); 5.72 (d, $J = 8.2$, 1 H, OH); 5.84 (d, $J = 9.0$, 1 H, NCH); 6.68–8.02 (m, 10 H, Ph)

Note. Spectra of compounds **2a,c,d** were recorded in the presence of CD₃COOD.

length of the fluoroalkyl substituent R_F, although an increase in steric hindrance results in decreased yields.

The compositions and structures of compounds **2a–e** were confirmed by elemental analysis and IR and ^1H NMR data (Table 2) as well as by chemical methods. The identification of the α -substituent was based on the ability of α -heteroatomic substituents in ketones to undergo reductive elimination when treated with zinc dust. Specifically, treatment of compound **2d** with zinc in acidified ethanol gave a compound that was identified, according to TLC and IR data, as β -hydroxyketone **3** synthesized by us previously.⁶



Experimental

^1H NMR spectra were recorded on a Tesla BS-576A spectrometer (working frequency 100 MHz) using Me₄Si as the internal standard. IR spectra were recorded on a Specord IR-75 spectrophotometer in vaseline oil for solid samples and in thin layers for liquids. TLC was carried out on Silufol UV-254 plates. Chromatograms were visualized in UV light using a KMnO₄ solution and a solution of KI in glacial AcOH. Column chromatography was performed on silica gel 40/100.

Compounds **1a–c** were obtained by the procedures reported previously.^{4,5}

Interaction of α,β -epoxyalkylketones **1a–c with aromatic amines.** A mixture of compound **1a–c** (5 mmol) with an aromatic amine (6–10 mmol) was refluxed in methanol or ethanol (50 mL). The reaction was monitored by TLC. When the starting compound **1a–c** disappeared, the reaction mixture

was concentrated *in vacuo*. The residue was dissolved in ether (50 mL) and washed with dilute HCl to remove the amine completely. The ether was evaporated, and the product was purified by crystallization or by column chromatography (see Table 1).

Interaction of compound **2d with zinc.** Compound **2d** (0.92 g, 2 mmol) and zinc dust (13.08 g, 0.2 g-at.) in 95 % EtOH (50 mL) were placed in a two-neck flask equipped with a bubbler and a reflux condenser. The reaction mixture was boiled and dry HCl was passed through it. The reaction was monitored by TLC (CHCl₃ as the eluent). When compound **2d** disappeared, the reaction mixture was filtered, concentrated, and poured into water (50 mL). The precipitate that formed was filtered off to give 0.53 g (72 %) of compound **3**, m.p. 87–88 °C, which was identical to an authentic sample according to its TLC, m.p., and IR spectral data.

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