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RING-OPENING FLUORINATION OF α,β-EPOXY SULFOXIDES: A NOVEL SYNTHESIS OF α-FLUOROKETONES[1]

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Treatment of α,β-epoxy sulfoxides (sulfinyl oxilanes) with KHF_2 and $BF_3\cdot OEt_2$ in $CHCl_3$ gave α-fluoroketones in moderate to good yields.

KEYWORDS α,β-epoxy sulfoxide; α-fluoroketone; fluorination; KHF_2

Recently, α-fluoroketones have been used as key substances for preparation of fluorine-containing medicines and agricultural chemicals.[2] There are many approaches to preparing α-fluoroketones.[3] The most convenient method is oxidation of α-fluoro alcohols, which usually are synthesized from epoxides by the reaction with HF or modified HF.[4] Recently, Shimizu et al. reported that SiF_4 was an effective fluorinating agent; SiF_4 and additives (R_4NF, H_2O, and/or R_3N) formed hypervalent fluorosilane, so nucleophilicity of the fluoride anion was increased.[5] In some cases, α-halo- or α-cyano-epoxides are directly converted into α-fluoroketones with $AgBF_4$;[6] however, $AgBF_4$ is quite expensive.

On the other hand, we have reported new methods for synthesizing α-substituted ketones through α,β-epoxy sulfoxides.[7] For example, treatment of α,β-epoxy sulfoxides with $MgCl_2$ in refluxing 2-propanol gave α-chloroketones in good yields.[7c] We thought that this technology could be extended to a synthesis of α-fluoroketones.

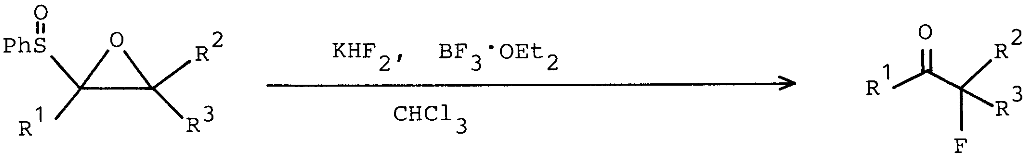
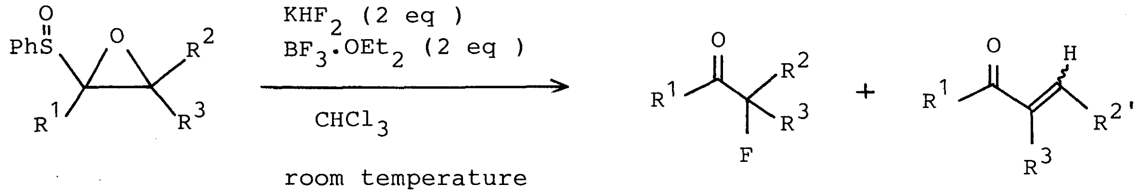


Chart 1

At first we examined the reaction of α,β-epoxy sulfoxides with Olah's reagent (HF·Pyridine); however, it gave low yield of desired α-fluoroketones with plenty of by-products. In order to increase the nucleophilicity of fluoride anion and to activate ring-opening of the epoxy group, and to trap the eliminated sulfinyl group, we tested the use of MF and BF_3OEt_2, and finally found that a combination of KHF_2 and $BF_3\cdot OEt_2$ was the reagent of choice for the desired reaction (Chart 1).

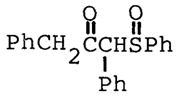
The choice of solvent was very critical; among the solvent examined, the best was $CHCl_3$ as its polarity and lipophilicity were suitable for this system. At the surface of solid KHF_2, $BF_3\cdot OEt_2$ may form BF_4^-, which dissolves into $CHCl_3$.

Table I. Ring-Opening Fluorination of α,β-Epoxy Sulfoxides with KHF_2 and $BF_3{\cdot}OEt_2$



Entry	R_1	R_2	R_3		Time (h)	Product(%)a) α-Fluoroketone	 Enone	 Other
1	$PhCH_2$	CH_3	CH_3		1	66.3	19.0	-b)
2	$PhCH_2$	CH_3	C_2H_5		1	72.1	15.0c)	-
3	$PhCH_2$	CH_3	C_3H_7		1	62.1	13.2c)	-
4	$PhCH_2$	$-(CH_2)_5-$			1	38.2	52.8	-
5	$n\text{-}C_7H_{15}$	CH_3	CH_3		1	80.4	18.2	-
6	$n\text{-}C_7H_{15}$	CH_3	C_3H_7	Le)	1	57.2	28.3c)	-
				Pe)	1	58.0	17.6c)	-
7	$n\text{-}C_7H_{15}$	$-(CH_2)_5-$			0.5	50.7	41.8	-
8	$(CH_3)_2CH(CH_2)_2$	CH_3	C_2H_5	Le)	0.5	51.0	42.9c)	-
				Pe)	0.5	50.3	35.1c)	-
9	cyc-Hexyl	CH_3	CH_3		0.25	62.0	24.7	-
10	cyc-Hexyl	$-(CH_2)_5-$			0.25	39.3	49.3	-
11	$PhCH_2$	Ph	H	Le)	0.25	0	0	85.0d)
				Pe)	0.5	0	0	76.6d)
12	$PhCH_2$	C_5H_{11}	H	Le)	12	37.2	18.4	-
				Pe)	50	-	-	65.3f)

a) Isolated yield. b) Not investigated. c) Exo methylene compound: vinyl-H (2H) appeared on NMR. d) Rearranged product as shown on the right. e) Diastereomers of the α,β-epoxy sulfoxides; the polar one was called P and the less-polar one was called L. See ref 7a. f) Starting material was recovered.



$PhCH_2C(=O)CH(Ph)S(=O)Ph$

As shown in Table I, β-monosubstituted α,β-epoxy sulfoxides showed low reactivity, giving α-fluoroketones (entry 12). β-Phenyl-substituted α,β-epoxy sulfoxide gave only the rearranged compound (entry 11). β,β-Disubstituted α,β-epoxy sulfoxides gave α-fluoroketones in good yields. However, spiro-cyclic β,β-disubstituted α,β-epoxy sulfoxides gave α-fluoroketones in low yields and enones in modest yields (entry 4, 7, and 10). These results may be interpreted as follows: the ring strain of spiro-cyclic epoxy sulfoxides is stronger than that of β,β-disubstituted acyclic ones, so in spiro-cyclic epoxy sulfoxides the ring-opening rate is faster than the fluorination rate and large amounts of the enones are obtained.

The following is a typical experiment: In a 5-ml ETFE-bottle (Teflon resin), $BF_3 \cdot OEt_2$ (34 µl; 0.28 mmol) was added to a suspension of 22 mg (0.28 mmol) of KHF_2 in $CHCl_3$ (1 ml) at room temperature under N_2 and the mixture was stirred for 5 min. A solution of 2,3-epoxy-3-methyl-1-phenyl-2-(phenylsulfinyl)butane$^{7a)}$ (32 mg; 0.14 mmol) in 1.5 ml of $CHCl_3$ was added to the mixture. After stirring for 1 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$, and extracted with ether. The organic layer was separated and washed with brine, dried over $MgSO_4$ and the solvent was evaporated. The product was purified by silica-gel preparative TLC to give 3-fluoro-3-methyl-1-phenyl-2-butanone (16.7 mg; 66%) as a colorless oil.

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