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First Efficient Synthesis of Fluorinated Glycidic Esters from Ketones

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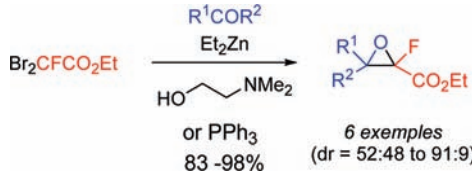
ABSTRACT



Treatment of various ketones with ethyl dibromofluoroacetate in the presence of diethylzinc and dimethylaminoethanol or triphenylphosphine provides rapid access to corresponding fluorinated glycidic esters. Simplified workup allowed first characterization of these compounds.

Because of their unique properties, organofluorine compounds have a large range of applications, especially for drug development purposes and crop protection.[1] Indeed, a large number of new pharmaceuticals incorporate one or more fluorine atoms.[2] In this context, our group is interested in developing new efficient synthesis methodologies of monofluorinated building blocks from commercially available products. We recently reported the use of ethyl dibromofluoroacetate associated with diethylzinc to achieve the synthesis of α-fluoro-α,β-unsaturated esters.[3]

Epoxides are useful intermediates in organic synthesis since C−C or C−heteroatom bonds can be created by simple nucleophilic addition. However, only a few methods of synthesis of monofluorinated epoxides have been reported: O-cyclization of α-halogeno-α-fluorohydrines,[4] fluoroalkene epoxidation,[5] Darzens reaction,[6] and tandem fluorination−cyclization of α,β-unsaturated ketones.[7] To our knowledge, only one method allowing preparation of fluorinated glycidic esters has been described, highlighting the particular instability of such compounds.[5a]

During the study of the reactivity of ethyl dibromofluoroacetate associated with diethylzinc toward ketones, we found out that the use of triphenylphosphine as additive allowed the formation of fluorinated epoxides (Table 1). Indeed, when 4 equiv of diethylzinc was added to a THF solution of benzophenone (1 equiv), triphenylphosphine (4 equiv), and ethyl dibromo fluoroacetate (2 equiv), we observed the complete conversion of the carbonyl compound and the subsequent formation of the corresponding fluorinated glycidic ester by ^{19}F NMR spectroscopy. However,

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(7) Tamura, M.; Matsukawa, Y.; Quan, H.; Mizukado, J.; Sekiya, A. *J. Fluorine Chem.* **2004**, *125*, 705.

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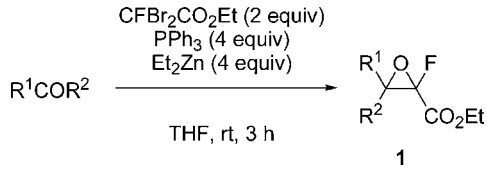
Table 1. Epoxidation Reaction Using Triphenylphosphine



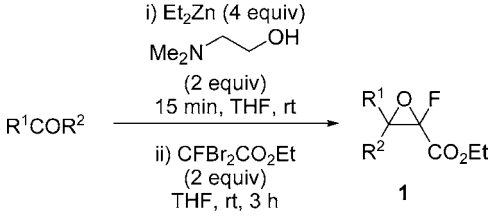
entry	R^1	R^2	conv[a] (%)	yield (%)	dr[b] (*cis*:*trans*)	product
1	Ph	Me	>99	n.d.[c]	50:50	**1a**
2	Ph	*i*Pr	>99	63	11:89	**1b**
3	Ph	*t*Bu	>99	50	>5:95	**1c**
4	Ph	Ph	>95[b]	n.d.[c]		**1d**

[a] Determined by GC. [b] Determined by ^{19}F NMR. [c] Decomposition of **1a** and **1d** was observed during purification by flash column chromatography on silica gel.

due to the large amount of triphenylphosphine remaining after classical workup and to the instability of the products during the purification process (silica gel chromatography), complete decomposition was observed in most cases, and only two fluorinated glycidic esters were purified and fully characterized.[8]

During our investigations to replace triphenylphosphine in the epoxidation procedure, we found out, after extensive investigations, that the use of ethylzinc *N*,*N*-dimethylaminoethoxide (prepared in situ from the *N*,*N*-dimethylethanolamine and diethylzinc) proved to be efficient for the formation of epoxides **1** (Table 2). For each substrate tested, 3 h after dropwise addition of ethyl dibromofluoroacetate, ^{19}F NMR spectroscopy of the reaction mixture showed complete conversion into the corresponding epoxides. Moreover, only liquid−liquid extraction workup was necessary to obtain the expected products with enough purity for characterization.[9]

Table 2. Epoxidation Reaction using *N*,*N*-Dimethylamino Ethanol

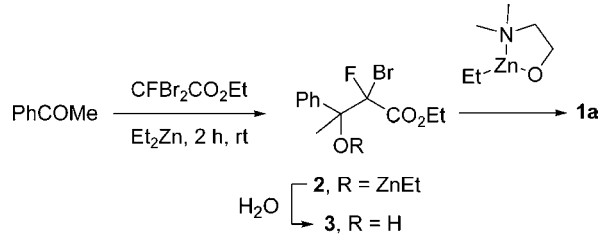


entry	R^1	R^2	conv[a] (%)	yield[b] (%)	dr[b] (*cis*:*trans*)	product
1	Ph	Me	>95	83[c]	47:53	**1a**
2	Ph	Et	>95	>95	44:56	**1e**
3	Ph	*i*Pr	>95	98[d]	9:91	**1b**
4	Ph	*t*Bu	>95	98[d]	7:93	**1c**
5	Ph	Ph	>95	>95		**1d**
6	*i*Pr	Me	>95	>95	52:48	**1f**

[a] Conversion into corresponding epoxides determined by ^{19}F NMR of reaction mixture. [b] Determined on crude mixture (based on the recovered mass) by ^{19}F and ^{1}H NMR. [c] 17% of an unknown side product after workup. [d] Purified by silica gel chromatography.

To rationalize this original reactional sequence and to elucidate the mechanism involved, several experiments were carried out. In particular, it was observed that ethyl dibromofluoroacetate is inert for days in the presence of either triphenylphosphine or ethylzinc *N*,*N*-dimethylaminoethoxyde. Next, sequential addition of diethylzinc and ethylzinc *N*,*N*-dimethylaminoethoxide to a mixture of ethyl dibromofluoroacetate and acetophenone was carried out (Scheme 1). Quenching an aliquot of the reaction mixture

Scheme 1. Sequential Epoxidation Procedure



after diethylzinc addition gave bromofluorohydrine **3** (^{19}F NMR monitoring), indicating that zinc alkoxide **2** was present in the reaction mixture. Addition of ethylzinc *N*,*N*-dimethylaminoethoxyde resulted in the formation of epoxide **1a**.

Thus, we propose a two-step pathway for the formation of epoxides, involving first a diethylzinc-mediated Reformatsky addition of ethyl dibromofluoroacetate on the ketone, followed by activation of the nucleophilicity of resulting zinc alkoxide **2** through coordination of the metal by the activating agent (Scheme 2). Indeed, it is known that zinc alkoxides can assemble as dimer in solution.[10] Hence, the zinc alkoxide **2** and ethylzinc *N*,*N*-dimethylaminoethoxyde can lead to the dimer intermediate ***I*** which is in equilibrium with the Zn-THF coordinate species ***II***. The electronic density of the oxygen atom of the alkoxide issued from **2** (thanks to this zinc alkoxide activation) is sufficiently enhanced to achieve the epoxidation process.

However, these fluorinated epoxides are highly unstable in pure form and have to be kept in most cases in solution to prevent degradation. The resulting products of degradation have not been yet identified, but according to Schlosser's work,[11] we assume that during the concentration process a self-induced rearrangement of epoxides occurs.[12]

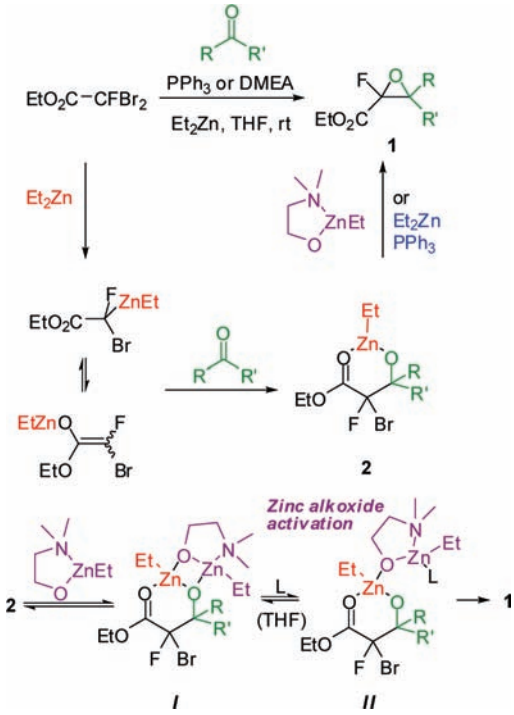
Next, we explored the reactivity of such epoxides, using compound **1b** (which is the most stable synthetized epoxide, no degradation during the purification process) as a model substrate. The ester function appeared to be more reactive than the epoxide ring toward nucleophiles. Indeed, when **1b** was subjected to *i*PrNH$_2$, amide adduct **4** was mainly formed

(8) The same sequence has been carried out from aldehydes. In all cases, the correponding epoxides could only be detected by GC-MS spectroscopy. These epoxides are particularly unstable as it has been previously shown (see ref 5a).

(9) Relative configuration of epoxide **1b** has been determinated by NOE experiment. See Supporting Information.

(10) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327.

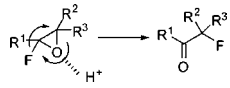
Scheme 2. Proposed Mechanism



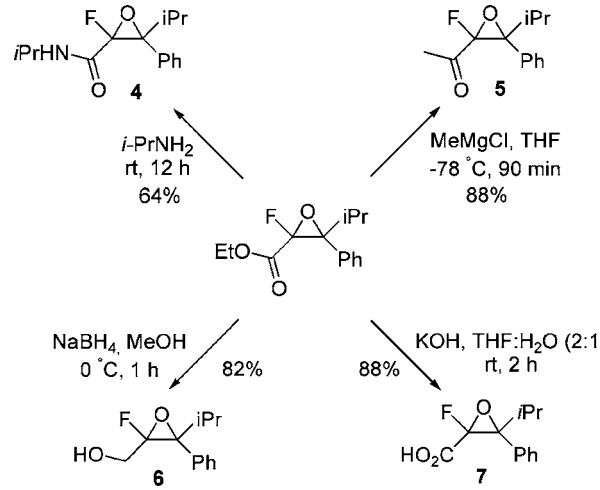
in good yield (64%). Addition of MeMgCl to **1b** led to the formation of corresponding ketone **5** in very good yield (88%). The reduction of **1b** with $NaBH_4$ led to the corresponding alcohol **6**, and the saponification using KOH furnished the very unstable acid **7** (Scheme 3).

(11) Schlosser showed that fluorinated epoxides exposed to fluoridric acid undergo a rearrangement to α-fluoroketones, see: (a) Schlosser, M.; Michel, D. *Tetrahedron* **1996**, *52*, 99. (b) Michel, D.; Schlosser, M. *Tetrahedron* **1996**, *52*, 2429.

(12) As pointed out by one of the reviewers, it appears that the rearrangement could also possibly proceed via an NIH-shift like mechanism.



Scheme 3. Epoxide Reactivity



In summary, a new and efficient methodology allowing the one-pot synthesis of α-fluorinated glycidic esters was developed based on the addition of ethyldibromo fluoroacetate to ketones using diethylzinc in the presence of an *N*,*N*-dimethylethanolamine. Further explorations, especially concerning the determination of the exact mechanism, ring-opening sequences, as well as reactivities of the new epoxides are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and complete spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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