

Novel Nucleophilic Trifluoromethylation of Vicinal Diol Cyclic Sulfates

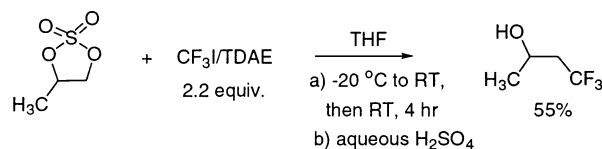
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ABSTRACT



A novel method for highly regioselective and stereospecific nucleophilic trifluoromethylation of vicinal diol cyclic sulfates, using the reagent derived from reduction of trifluoromethyl iodide by tetrakis(dimethylamino)ethylene (TDAE), is presented.

Despite the widespread interest in nucleophilic trifluoromethylation and the availability of a number of good methods for carrying out such reactions,^{1–7} there are no examples in the literature related to trifluoromethylation of epoxides. Epoxides play an important role in organic synthesis, in part because the nature of their structure and reactivity allows regio- and stereospecific carbon–carbon bond formation simultaneous with formation of an adjacent alcohol function. Especially considering the current interest in chiral synthesis, nucleophilic trifluoromethylation of epoxides would provide a unique method for preparing chiral trifluoroethylcarbinols.

Because our recently developed trifluoromethyl anion reagent^{6,7} derived from reduction of trifluoromethyl iodide by tetrakis(dimethylamino)ethylene (TDAE) has exhibited a chemical behavior/reactivity that can differ from those of

(trifluoromethyl)trimethylsilane^{1,2} and Langlois' nucleophilic trifluoromethylation methods,^{3,4} we examined its reactivity with epoxides, in particular styrene oxide. Unfortunately, the $\text{CF}_3\text{I}/\text{TDAE}$ -derived reagent *did not* undergo productive reaction with this epoxide, either alone or in the presence of Lewis acids such as TiCl_4 , BF_3 , or BPh_3 , the reactions being examined in DMF and 1,2-dimethoxyethane.

Although disappointed by these results, it occurred to us that the desired qualities of epoxides are shared by another class of vicinally functionalized electrophiles, the 1,2-diol cyclic sulfates. In 1988, Gao and Sharpless demonstrated that diol cyclic sulfates could be readily prepared from 1,2-diols,⁸ which themselves can be prepared via an asymmetric dihydroxylation of olefins.⁹ Such cyclic sulfates are apparently more reactive than epoxides and have found much synthetic utility during the last 14 years.^{10–13} After an initial

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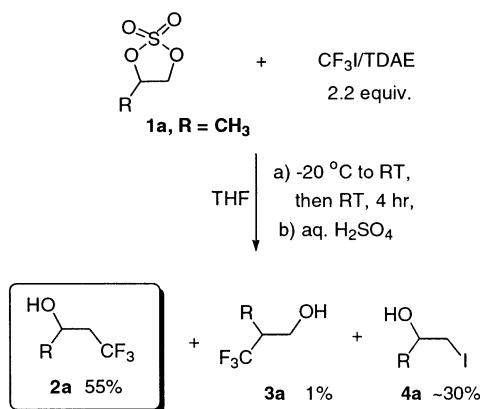
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reaction of our CF₃I/TDAE reagent with cyclic sulfate **1a**, under the usual conditions in DMF at –20 °C, resulted in formation of 8% of the desired product **2a**, a quick optimization study revealed that THF is the best solvent (from among DMF, DME, CH₂Cl₂, and Et₂O) for this reaction, with a respectable 55% yield being obtained.



The reaction proved to be general and highly regioselective, as indicated by the data in Table 1, with the yields in

Table 1. Trifluoromethylation of Cyclic Sulfates^a

cyclic sulfate	yields of products (%)		
	2 ^b	3	4
1b , R = H	45 ¹⁴		55
1a , R = CH ₃	55 ¹⁵	1	30 ¹⁶
1a , R = CH ₃	62 ^c	1	e
1a , R = CH ₃	56 ^d	1	e
1c , R = C ₂ H ₅	49 ¹⁵	0.5	33
1d , R = <i>n</i> -C ₃ H ₇	51	0.2	31
1e , R = <i>n</i> -C ₄ H ₉	50 ¹⁷	0.5	40

^a In THF, using 2.2 equiv each of CF₃I and TDAE; reagents were added at –20 °C, warmed to room temperature, and then stirred at room temperature for 4 h before hydrolysis with aqueous H₂SO₄. ^b 1,1,1-Trifluoro-3-alkanols were characterized by comparison of their ¹H and ¹⁹F NMR spectra with those reported in the literature; references are provided. ^c Using 3 equiv each of CF₃I and TDAE. ^d Using 5 equiv each of CF₃I and TDAE. ^e Not measured.

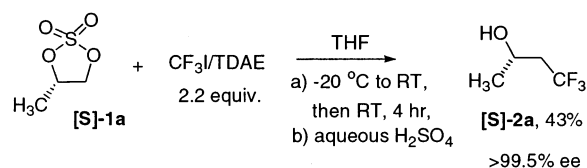
each case being good but limited by intervention of a competing reaction of the sulfates with the inevitably present iodide ion.

The reactions can be carried out by adding the TDAE to a solution of trifluoromethyl iodide and the sulfate substrate in THF at –20 °C, followed by warming to room temperature and stirring for an additional 4 h. Alternatively, the “CF₃[–] anion” reagent could first be prepared by adding TDAE to

CF₃I in THF at –20 °C. After warming the solution to room temperature, the substrate sulfate was added and stirred for 4 h at room temperature. Much the same results were obtained by either procedure, which indicates that this trifluoromethyl anion reagent has some stability in THF at temperatures up to room temperature. As indicated in Table 1, the yields of desired alcohol product **2a** could be enhanced by increasing the relative amount of CF₃I/TDAE reagent used in the reaction to 3 equiv, but additional increases did not prove to be beneficial.

In an attempt to avoid the presence of the competing iodide ion, the trifluoromethylation reaction was carried out using CF₃Br in place of CF₃I, but there was no reaction either thermally or photochemically between CF₃Br and TDAE.

The stereospecificity of the ring-opening process was demonstrated by carrying out the reaction using the (*S*)-isomer of **1a**, whereupon (*S*)-**2a** with an ee of >99.5% was obtained, as determined from the ¹⁹F spectrum of the (*R*)-2-methoxy-2-(trifluoromethyl)phenylacetate esters that were obtained from the alcohol product mixture.



Attempts to utilize either the (trifluoromethyl)trimethylsilane-based methodologies,^{1,2} Langlois' CHF₃-based method,³ or CF₃ZnI⁵ to trifluoromethylate sulfate **1a** led to no detectable trifluoromethylated products. Thus, the “trifluoromethyl anion” reagent that is derived from reduction of CF₃I by TDAE has unique reactivity characteristics that allow this particular nucleophilic trifluoromethylation reaction to occur.

Thus far, the reaction has proved to be effective only for nucleophilic trifluoromethylation of 1,2-cyclic sulfates that bear at least one primary (CH₂) group. Reactions with sulfates derived from *meso*-2,3-butanediol, *meso*-1,2-cyclopentanediol, or *meso*-tartaric esters led to no detectable products containing the trifluoromethyl group. Nor did the sulfate derived from 1,3-propanediol, which underwent strictly ring opening by iodide ion.

However, even with the observed limitations, this new aspect of nucleophilic trifluoromethylation chemistry should provide synthetic chemists with unprecedented opportunities to selectively incorporate trifluoromethyl groups into organic compounds.

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