ORGANIC LETTERS

2002
Vol. 4, No. 26
4671−4672

Novel Nucleophilic Trifluoromethylation of Vicinal Diol Cyclic Sulfates

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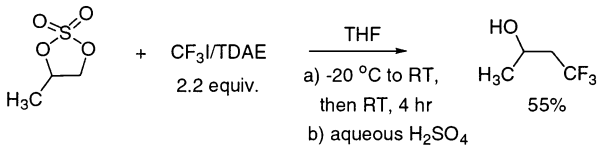
Received October 5, 2002

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 CF_3I/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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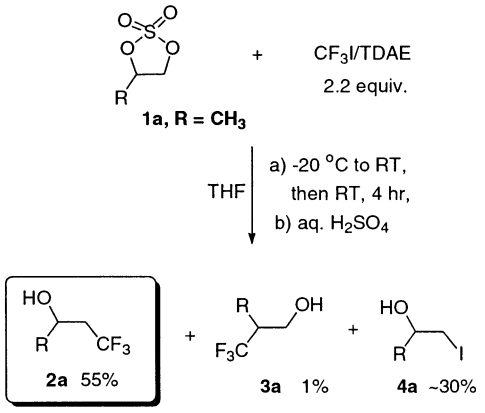
10.1021/ol0270374 CCC: $22.00
Published on Web 12/03/2002

reaction of our CF_3I/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, CH_2Cl_2, and Et_2O) 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 each case being good but limited by intervention of a competing reaction of the sulfates with the inevitably present iodide ion.

Table 1. Trifluoromethylation of Cyclic Sulfates[a]

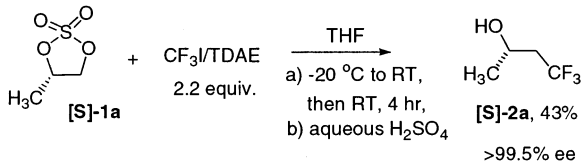
	yields of products (%)		
cyclic sulfate	**2**[b]	**3**	**4**
1b, R = H	45[14]		55
1a, R = CH_3	55[15]	1	30[16]
1a, R = CH_3	62[c]	1	e
1a, R = CH_3	56[d]	1	e
1c, R = C_2H_5	49[15]	0.5	33
1d, R = *n*-C_3H_7	51	0.2	31
1e, R = *n*-C_4H_9	50[17]	0.5	40

[a] In THF, using 2.2 equiv each of CF_3I 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 H_2SO_4. [b] 1,1,1-Trifluoro-3-alkanols were characterized by comparison of their ^1H and ^{19}F NMR spectra with those reported in the literature; references are provided. [c] Using 3 equiv each of CF_3I and TDAE. [d] Using 5 equiv each of CF_3I and TDAE. [e] Not measured.

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 "CF_3^- anion" reagent could first be prepared by adding TDAE to CF_3I 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 CF_3I/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 CF_3Br in place of CF_3I, but there was no reaction either thermally or photochemically between CF_3Br 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 ^{19}F 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' CHF_3-based method,[3] or CF_3ZnI[5] to trifluoromethylate sulfate **1a** led to no detectable trifluoromethylated products. Thus, the "trifluoromethyl anion" reagent that is derived from reduction of CF_3I 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 (CH_2) 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.

Acknowledgment. Support of this research in part by the National Science Foundation is acknowledged with thanks, and we are grateful to F-Tech, Inc., for a generous donation of trifluoromethyl iodide. We also thank Prof. Dennis Wright for his synthetic insight that led us to investigate trifluoromethylation of cyclic sulfates.

OL0270374

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