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Synthesis of tetrahydrofurans via silicon promoted Pummerer type reaction☆

Sadagopan Raghavan,* A. Rajender, M. Abdul Rasheed and S. Ramakrishna Reddy

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—A novel, unprecedented transformation of δ-hydroxysulfoxides into substituted tetrahydrofurans by a silicon promoted Pummerer type reaction is disclosed. The transformation is shown to be general and is brought about under very mild reaction conditions. The products with the sulfide group at the anomeric carbon provide a suitable handle to carry out further transformations.

The Pummerer rearrangement of sulfoxides is a reaction with immense synthetic potential and has proved useful for the preparation of α-substituted sulfides.[1] The Pummerer reaction has been initiated with a variety of electrophilic reagents.[2] Acetic anhydride, has been the commonly used promoter either as the solvent at reflux temperature or in combination with other solvents/co-catalysts. Some trialkylsilyl reagents have also been employed for this transformation. Miller and McKean[3] reported on the transformation of sulfoxides into α,β-unsaturated sulfides using iodotrimethylsilane and Hunig's base. The same transformation could be effected with chlorotrimethylsilane[4] in the absence of an added base on certain sulfoxides. Kita and co-workers[5] have demonstrated the use of ketene methyl *t*-butyldimethylsilyl acetal for effecting the Pummerer type rearrangement under mild conditions. Trimethylsilyltriflate and Hunig's base[6] have been employed as the reagent combination for carbon–carbon bond formation in the reaction of allyl sulfoxides with enol ethers. So also, *t*-butyldimethylchlorosilane in conjunction with DBU[7] has been employed for the transformation of sulfoxides into α-chlorosulfides. Herein, we disclose a novel, silicon promoted, unprecedented transformation of δ-hydroxy sulfoxides into substituted tetrahydrofurans[8] under very mild conditions (Eq. (1)).

R = NP^1P^2, OP, Me
Ar = Aryl

(1)

The tetrahydrofuran ring system is widely distributed in nature and has attracted the attention of the synthetic community relating to the total synthesis of natural products.[9] The stereocontrolled construction of substituted tetrahydrofurans is challenging, prompting the development of new methodologies for its efficient elaboration.[10]

In the course of the synthesis toward (±)-allosedamine (**1**), we wished to protect the hydroxy group of sulfoxide (**2a**) as its silyl ether. Treatment of **2a** with *t*-butyldimethylchlorosilane in DMF in the presence of imidazole[11] afforded a major product (60%) which was not the expected silyl ether, but the tetrahydrofuran (**3a**); the minor product (30%) turned out to be the silyl ether (**4**) (Scheme 1).

In efforts to optimize the reaction to afford the substituted tetrahydrofuran as the sole product, the bulky *t*-butyldiphenylchlorosilane was employed. Gratifyingly, the reaction proceeded cleanly to afford **3a** in 80% yield. Extension to a number of similar δ-hydroxy sulfoxides revealed the reaction to be general[12] (Table 1). An inspection of Table 1 reveals that the reaction proceeds stereoselectively to afford a single isomer

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Keywords: tetrahydrofurans; Pummerer rearrangement; sulfoxide; *t*-butyldiphenylchlorosilane.

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* Corresponding author. E-mail: purush101@yahoo.com

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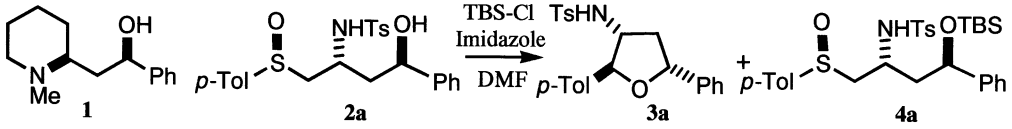
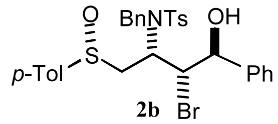
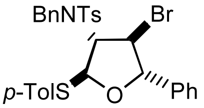
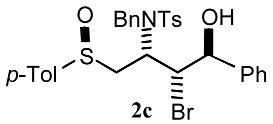
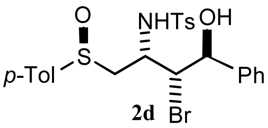
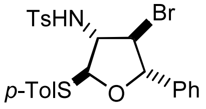
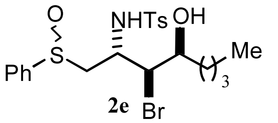
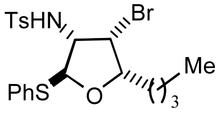
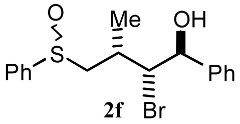
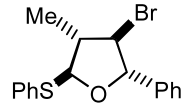
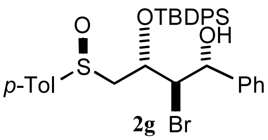
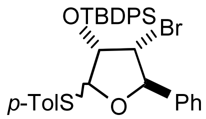
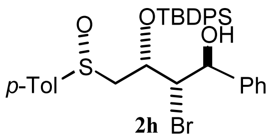
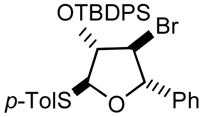


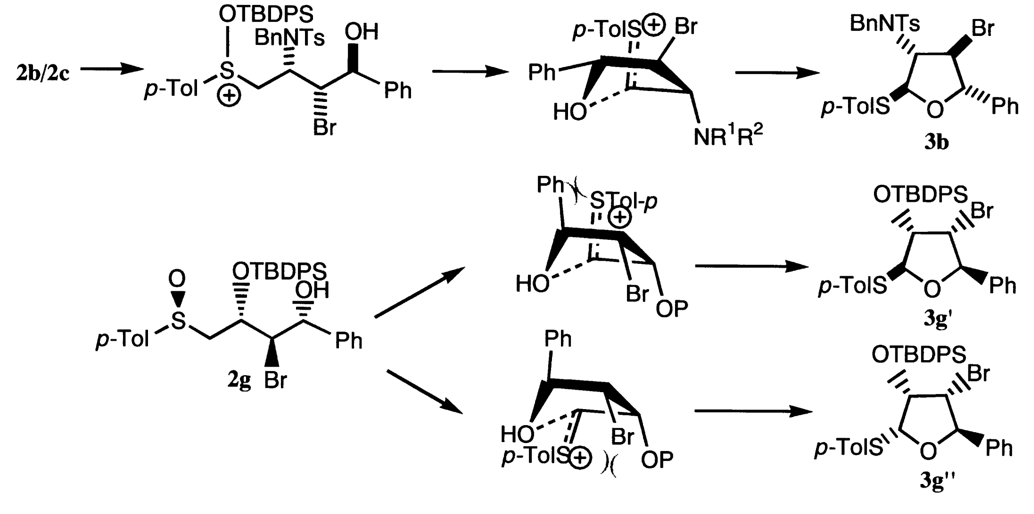
Scheme 1.

Table 1. Formation of tetrahydrofurans by silicon promoted Pummerer type reaction

Entry	Hydroxysulfoxide	Tetrahydrofuran	Yield[b] %
1	 **2b**	 **3b**	90%
2	 **2c**	**3b**	90%
3	 **2d**	 **3d**	86%
4	 **2e**	 **3e**	90%
5	 **2f**	 **3f**	93%
6	 **2g**	 **3g**	82%
7	 **2h**	 **3h**	90%

a) All reactions were done on racemic substrates on 0.2 mmol scale in the presence of 1 eq. of *t*-butyldiphenylchlorosilane and 2 eq. of imidazole in DMF as the solvent. b) Yield refers to the isolated yield.

wherein the sulfide is disposed *anti* to the substituent at C3, except sulfoxide (**2g**) which afforded an equimolar mixture of epimeric sulfides. The structure of **3b** was rigorously established by NOE experiments. Thus irradiation of the methine proton at C2 revealed NOE with the *N*-benzyl protons and C4 methine proton. Irradiation of the C5 methine proton revealed NOE with C3 methine proton (Fig. 1). The structure of the other tetrahydrofurans were assigned by comparison of their ^{1}H NMR spectra with **3b**.



Scheme 2.

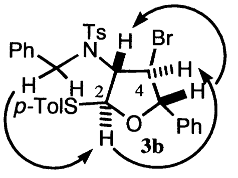


Figure 1.

The formation of tetrahydrofuran can be rationalized by coordination of the sulfoxide oxygen to silicon to afford the sulfoxonium salt, which on elimination of *t*-butyldiphenylsilyloxy group (OTBDPS) would yield the sulfonium ion which would then be attacked intramolecularly by the hydroxy group. The substituent at C3 would direct the sulfenyl moiety away from itself, to minimize steric interactions, and afford the observed product. The intermediate from **2g** would experience unfavorable steric interactions between the phenyl ring and sulfenyl moiety while the latter is oriented *anti* to the C3 OTBDPS substituent, which would probably explain for the obtention of a mixture of sulfides in this case (Scheme 2).

The intermediacy of the sulfonium ion is confirmed by the fact that the same product is obtained from reactions done individually on diastereomeric sulfoxides **2b** and **2c**. It is worthwhile to note that the sulfenyl group provides a suitable handle for further elaboration into more complex molecules.[13]

In summary we have disclosed a highly stereoselective route for the elaboration of tetrahydrofurans from δ-hydroxy sulfoxides under very mild conditions in a Pummerer like reaction. The products have a suitable handle for further manipulations.

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12. Typical experimental procedure: To the substrate (0.2 mmol) in dry DMF (0.2 mL) were added imidazole (27 mg, 0.4 mmol) followed by TBDPS-Cl (55 mg 0.2 mmol) at room temperature under N_2 atmosphere. The reaction mixture was stirred at room temperature until TLC revealed complete consumption of the starting material. The reaction mixture was diluted with ether and washed successively with water, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product mixture. Purification by column chromatography using EtOAc:hexane (1:24) afforded the pure product.
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