Selective Conversion of 2-Mercaptoalkanols to Thiirans with Orthocarbonates

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(Received September 9, 1987)

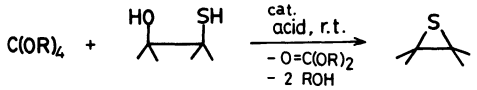
Synopsis. Tetraalkyl orthocarbonates **1** were demonstrated to serve as potent cyclodehydrating agents for 2-mercaptoalkanols **2** to give the corresponding thiirans in good yields in acid-catalyzed reactions in aprotic solvents. Effects of catalysts, solvents, and alkyl substituents of **1** were examined. Activity of the acid catalysts depended on their acidity (pK_a), and the strong Lewis acid BF_3·OEt_2 also had high catalytic activity. Effects of solvents and alkyl substituents of **1** were little observed.

Tetraalkyl orthocarbonates **1** have extensively been studied as useful reagents capable of reacting with both nucleophiles and electrophiles.[1,2] Especially, the characteristic reactions via carbenium ions under acidic conditions are of interest among the various reactions of **1**. Reactions with protic compounds such as phenols and carboxylic acids gave *O*-alkylation products.[1,3] We have recently utilized the acid-catalyzed alcohol-exchange reaction of **1** with some diols to obtain spiroorthocarbonates in good yields.[4] Although **1** is known to readily react with water to afford dialkyl carbonate and two moles of alcohol,[1,2,5] there is no report on the use of **1** as a dehydrating agent except for only one example of conversion of succinic acid to succinic anhydride.[3a]

In our continuing studies on the chemistry of **1**,[4] we have found that **1** is quite a potent cyclodehydrating agent for 2-mercaptoalkanols to thiirans under acidic conditions. A recent report of Evans et al. on the cyclodehydration of mercaptoalkanols to thiacycloalkanes with 1,3,2-dioxaphospholane derivatives,[6] also prompted us to report our recent results on the dehydration.

Results and Discussion

Orthocarbonate **1**, which is commercially available (R=Me) or easily prepared (R=Et and Bu^n),[7,8] was examined as a dehydrating agent in the acid-catalyzed reaction with 2-mercaptoethanol (**2a**), which often resists dehydration[9] and easily affords polymer of the product thiiran in the presence of a strong acid.[10] When **1** was mixed with an equimolar amount of **2a** in the presence of an acid catalyst such as *p*-toluenesulfonic acid (TsOH), thiiran was formed in more than 95% yield (by NMR) along with a dialkyl carbonate and an alkanol (Eq. 1). Without such an acid no reaction took place. The results examined for catalysts, solvents, and alkyl substituents of **1** are summarized in Table 1.



(1)

Using TsOH as the catalyst, the reaction (**1a**, Run 1) was completed within a few minutes, being too fast to monitor the reaction progress, unlike the case of trichloroacetic acid (TCA, Run 4) or acetic acid (AcOH, Run 5). This conversion was very clean, and the reaction gave only thiiran, dimethyl carbonate, and methanol (ratio, 1:1:2) without any by-products. TsOH monohydrate could also be used with slightly excess amount of **1** and similar products were obtained. Catalytic activity of the acids used clearly depended on their acidities: pK_a values were correlated with the effectiveness; accordingly, a strong Lewis acid (boron trifluoride etherate BF_3·OEt_2) was also a highly active one. All aprotic solvents listed could be used as they showed no detectable difference in the reaction progress. No serious difference was confirmed in the reaction efficiency among three orthocabonates **1a**—**1c** used.

Isolation of thiiran was attempted by distilling the reaction mixture (from **1a**, **2a**, and TsOH), but thiiran (bp 56 °C) was obtained in 67% yield as a mixture with methanol (bp 65 °C) and dimethyl carbonate (bp 90 °C). Part of thiiran still remained in the reaction mixture along with a small amount of white thiiran polymer, which appeared as a

Table 1. Acid-Catalyzed Cyclodehydration of 2-Mercaptoethanol (**2a**) to Thiiran[a] with Tetraalkyl Orthocarbonates (**1**)

Run	Orthocarbonate **1**, C(OR)$_4$		Acid catalyst mol%	pK_a	Solvent	Temp	Time/min
1	R=Me,	**1a**	TsOH[b](2.0)	−7	$CDCl_3$	RT[c]	<3
2	Et,	**1b**	TsOH(4.6)		Benzene	RT	<5
3		**1b**	TsOH(3.6)		$CDCl_3$	RT	<5
4		**1b**	TCA[d](11)	0.66	CCl_4	RT	ca. 40
5		**1b**	AcOH(31)	4.56	Benzene	RT	ca. 3 days
6		**1b**	AcOH(31)		$CDCl_3$	60—70 °C	ca. 15
7		**1b**	BF_3·OEt_2(12)		CCl_4	RT	<3
8	R=Bu^n,	**1c**	TsOH(10)		$CDCl_3$	RT	<3
9		**1b**[e]	TsOH·H_2O(3.0)		$CDCl_3$	RT	<5

a) Yield of thiiran was quantitative (more than 95% by NMR). b) *p*-Toluenesulfonic acid. c) Room temperature. d) Trichloroacetic acid. e) Excess amount of **1b** (1.2 equiv) was used.

Table 2. Acid-Catalyzed Cyclodehydration of 2-Mercaptoalkanols (2) with Tetraalkyl Orthocarbonates (1)

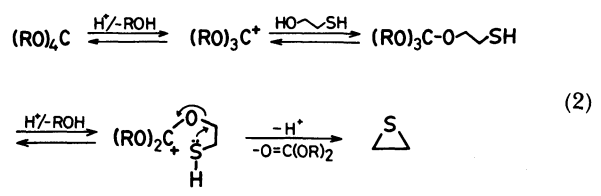
Entry	Substrate 2		Orthocarbonate 1: $C(OR)_4$	Solvent	Product 3		Yield/%
1		2a	R=Me	$CDCl_3$		3a	95[b]
2			Me	*m*-Xylene			67[b,c]
3			^{n}Bu	None			30[d]
4		2b	Me	$CDCl_3$		3b	77[b]
5[e]		2c	Me	$CDCl_3$		3c	80[b]
6[e]		2c′	Me	CH_2Cl_2			63[f]
7		2d	Et	$CDCl_3$		3d	97[g]
8			Me	CH_2Cl_2			78[d]

a) Reaction with 1—3 mol% of TsOH within 10 min. at room temperature. b) NMR yield. c) A mixture of **3a**, methanol and dimethyl carbonate. d) Isolated yield by distillation. e) Mixture of **2c** and **2c′** (ratio=3:2, by ^{1}H NMR) was used. f) The yield was determined by GC and NMR.

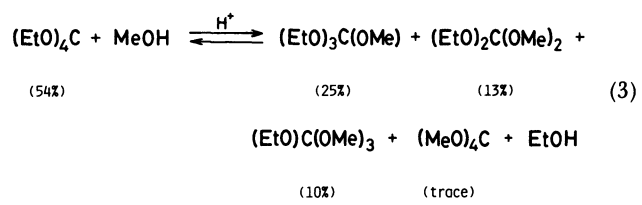
broad peak around δ 2.3 in ^{1}H NMR. Thereby, considering the formation of by-products having higher boiling points than 90 °C, use of butyl derivative **1c** instead of **1a** eventually made the isolation of thiiran possible (Table 2, Entry 3), although the yield was low (30%).

Furthermore, a few 2-mercaptoalkanols **2b**, **2c**, and **2d** were examined and in every case it was demonstrated that the corresponding thiirans were obtained in high yields (Table 2). Bicyclic thiiran **3d** was isolated in 78% yield by distillation, while 2-phenylthiiran **3c** was obtained in 63% yield by purification with chromatography (silica gel/hexane).

The rational reaction mechanism does not involve a simple acid-catalyzed dehydration process, because the reaction hardly proceeded without **1**. Therefore, the reaction should be completed via the alcohol-exchange equilibrium[2] followed by intramolecular thiiran cyclization to eliminate a dialkyl carbonate only as a leak process, as shown in Eq. 2. This mechanism can be supported by the following two experimental results: (i) to a mixture of **1b** and methanol is added a catalytic amount of TsOH and the system reaches a certain equilibrium of alcohol-exchange and (ii) **1** does not interact with any sulfhydryl groups, since 1,2-ethanedithiol did not react with **1a** in the presence of TsOH at all under the same conditions (^{1}H NMR study). Therefore, formation of 2,2-dialkoxy-1,3-oxathiolane as an intermediate is unlikely, although monocyclic and spirocyclic orthocarbonates are the main products in the reactions of tetraalkyl orthocarbonates with an equimolar and two equimolar amounts of diols, respectively.[4]



(2)



(3)

Thus, in this paper the orthocarbonate **1** is suggested to be a useful dehydrating agent for 2-mercaptoalkanols to thiirans in the acid-catalyzed reactions. This method is of advantage of its easy procedure and short reaction time under mild conditions.

Experimental

^{1}H NMR spectra were recorded on a JEOL JMN-PMX60 spectrometer using tetramethylsilane (TMS) as the internal standard in deuteriochloroform. Gas chromatography was carried out with a Shimadzu GC 4CPF equipped with FID detector and a data processor (column: PEG-20M, 3 m; carrier: N_2, 30 mL min^{-1}). Catalysts (extra pure grade) were used as received without further purification, except for TsOH which was dehydrated by heating its monohydrate at 100 °C for 6 h under reduced pressure. All solvents were dried before use by usual methods. Preparation of 2-mercaptoalkanols (**2b**, **2c**, and **2d**) was carried out according to the reported method from corresponding oxiranes.[11] Commercial **2a** was available. Orthocarbonates **1b** and **1c** were synthesized according to Sakai's method using tetrachlorostannane ($SnCl_4$),[8] while **1a** was obtained from Aldrich. The products were identified by GC, ^{1}H NMR, and boiling points in comparison with their authentic samples.[12]

Reaction of 2 with 1. (a) NMR Scale Method. An example using **2a** and **1a**. A mixture of **2a** (0.39 g, 0.5 mmol) and slightly excess **1a** (0.70—0.75 g, 0.52—0.55 mmol) in $CDCl_3$ (200 μL) was subjected to measurement of ^{1}H NMR (t=0). Then, to the reaction mixture was added TsOH (ca. 2 mg) at room temperature. After mixing, ^{1}H NMR was recorded promptly (within five min) and further at some intervals in order to monitor the reaction. ^{1}H NMR indicated quantitative conversion of **2a** to thiiran within

three minutes.

(b) Preparative Scale Procedure. An example using **1a** and **2d**. To a mixture of **2d** (800 mg, 6.1 mmol) and **1a** (910 mg, 6.69 mmol) in dichloromethane (5 mL) was added TsOH (monohydrate, 23 mg, 2 mol%) in one portion at room temperature. The mixture was stirred and solid TsOH was soon dissolved. The **2d** smoothly disappeared (by GC) in a few minutes, and then triethylamine (a few drops) was added and evaporated. The resulting residue was carefully distilled using a microdistillation apparatus to give **3d** as colorless oil. Yield 540 mg (78%), bp 100 °C (bath temp)/25 mmHg (1 mmHg=133.322 Pa). Purity ≥95% by GC. Lit,[12] bp 71.5 °C/21 mmHg. ^{1}H NMR ($CDCl_3$) δ=1.45 (4H, m, CH_2), 2.15 (4H, m, CH_2), 3.20 (2H, m, CH). **3a**: bp 50—60 °C (lit,[12] 56 °C); ^{1}H NMR (CCl_4) δ=2.31 (s, CH_2). **3b**: ^{1}H NMR ($CDCl_3$) δ=1.52 (3H, d, J=2.8 Hz, CH_3), 2.12 (1H, d, J=2.7 Hz, H^a or H^b of CH_2), 2.50 (1H, d, J=3.0 Hz, H^b or H^a), 2.93 (1H, m, CH). **3c**: ^{1}H NMR ($CDCl_3$) δ=2.55 (1H, dd, J=0.7 and 2.7 Hz, H^a or H^b of CH_2), 2.74 (1H, dd, J=0.7 and 3.3 Hz, H^b or H^a), 3.79 (1H, t, J=3.0 Hz, CH), 7.17 (5H, s, phenyl).

TsOH-Catalyzed Reaction of 1b with Methanol. To a mixture of **1b** (95 mg, 0.49 mmol) and 20 μL of methanol (0.49 mmol) in 200 μL of dry benzene in a NMR tube was added anhydrous TsOH (6 mg). The resulting mixture was subjected to measurement of ^{1}H NMR and GC. The product structures were estimated by reference to the fast alcohol-exchange equilibrium.[2] The ratio of these products was determined by ^{1}H NMR integration and GC peak area (see Eq. 3).

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