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Novel ring contraction of dioxepanes to tetrahydropyrans. Reaction of dioxepanes with trimethylsilyl trifluoromethanesulfonate

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Abstract

Reaction of 5-methylene-1,3-dioxepanes derived from oxaphospholanes and paraformaldehyde with trimethylsilyl trifluoromethanesulfonate in the presence of a base yielded novel, *exo* formyl tetrahydropyran derivatives in good yields. © 2000 Elsevier Science Ltd. All rights reserved.

Cyclic ethers are important compounds for the synthesis of natural products. Because their synthetic utility in the formation of tetrahydropyrans appears promising, many reports on the synthesis of substituted derivatives of tetrahydropyrans have appeared. Typical recent methods include acid-catalyzed cyclization of epoxy alcohols,[1] acid-catalyzed cyclization of terminal alkenols,[2] Pd-catalyzed intramolecular 1,4-dialkoxyalkylation of terminal dienals,[3] and reaction of hydroxyallylsilane with aldehydes in the presence of TMSOTf.[4] However, there is no report on the synthesis of tetrahydropyrans by ring contraction of seven-membered cyclic acetals (dioxepanes). Recently, we have reported a general synthesis of 5-methylene-1,3-dioxepanes (**1**) from oxaphospholanes with paraformaldehyde.[5] These results prompted us to investigate the reactivity of these relatively unknown compounds. We report herein a completely different strategy for the formation of six-membered cyclic ethers (tetrahydropyrans) from *exo*-methylene-dioxepanes.

Substituted 5-methylene-1,3-dioxepanes (**1**) were previously synthesized by the reaction of oxaphospholanes with paraformaldehydes.[5] Since oxaphospholane was easily hydrolyzed to give the corresponding diphenylphosphine oxide, we first tried a one-pot synthesis of **1**. Treatment of methylenetriphenylphosphorane obtained from methyltriphenylphosphonium bromide and sodium hydride with styrene oxide followed by the addition of paraformaldehyde afforded **1a** in 56% yield (Scheme 1). Other reactions were carried out in a similar manner (Table 1).

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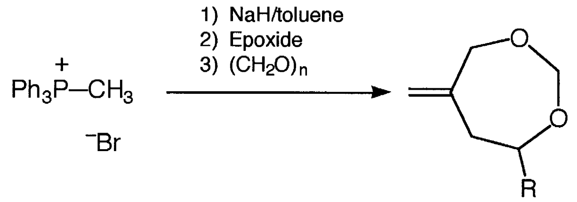


1

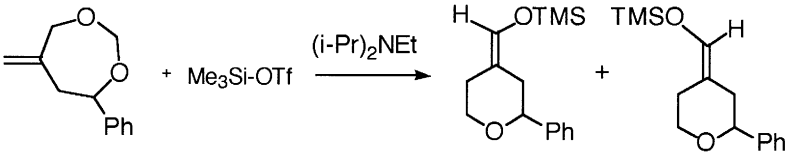
Scheme 1.

Table 1
One-pot synthesis of 5-methylene-1,3-dioxepanes **1**

Epoxide R	Conditions Time/h	Temp.	Product (Yield/%) 1	
Ph	1	reflux	**1a**	56
Me	3	reflux	**1b**	33
Et	3	reflux	**1c**	52
Bu	2	reflux	**1d**	56
CH_2=CH-CH_2OCH_2	6	reflux	**1e**	55
m-Cl-C_6H_4	1	reflux	**1f**	58

By using this improved method, dioxepanes **1** were synthesized in large scale and can be used for further investigation.

Since the dioxepanes **1** are acetals, we first attempted the acid hydrolysis of **1** in the hope of obtaining diols. By using catalytic amount of HCl, trifluoromethanesulfonic acid, and trifluoroacetic acid, dioxepanes **1** led to unidentified polymeric mixtures. Thus, some other new reaction must be devised for their synthetic use. Gassman et al. found that the reaction of acetals with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of diisopropylethylamine gave vinyl enol ethers in good yields.[6] In view of these results, we then applied this method to dioxepanes. Dioxepane (**1a**) was treated with TMSOTf in the presence of diisopropylethylamine at room temperature to give the corresponding six-membered cyclic silyl enol ether (*E*:*Z*=1:1) (Scheme 2, Table 2).



1 **2a** **2a'**

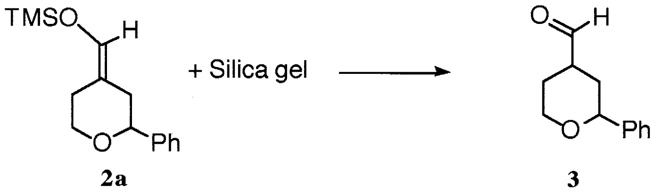
Scheme 2.

When this silyl enol ether **2a** was treated with trifluoroacetic acid, 4-formyl-tetrahydropyran (**3**) was obtained quantitatively (*trans*:*cis*=3:1). These isomers were easily separated by using gel HPLC (Scheme 3).

How do we account for the formation of **2**? Gassman et al. reported that the reaction of acetals with TMSOTf followed by the addition of diisopropylethylamine afforded the corresponding vinyl ethers in good yields. In view of this result, we proposed the following mechanism. Initial attack of **1** with TMSOTf resulted in the formation of an oxonium ion intermediate (**4**), which was further attacked by a

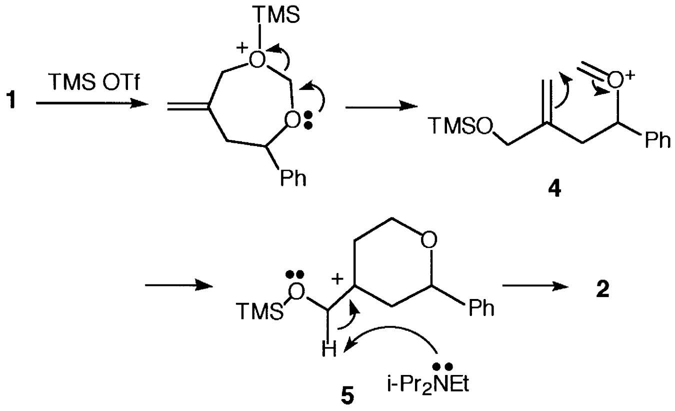
Table 2
Reaction of 5-methylene-1,3-dioxepanes **1** with TMSOTf[7]

1	R	Conditions Time/h	Temp.	Base (eq)	Product (Yield/%) **2**		(*E*:*Z*)
1a	Ph	1	reflux	0.5	**2a**	0	
1a	Ph	3	reflux	1	**2a**	10	1:1
1a	Ph	3	reflux	2	**2a**	77	1:1
1b	Me	6	reflux	2	**2b**	40	1:1
1c	Et	1	reflux	2	**2c**	35	1:1
1d	Bu	3	reflux	2	**2d**	69	1:1



Scheme 3.

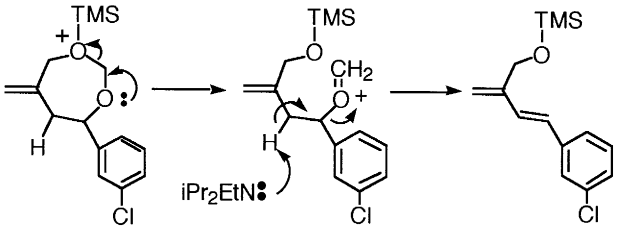
double bond to give six-membered cyclic carbocation (**5**), which finally produced the silyl enol ether, **2**, by abstraction of a proton with diisopropylethylamine (Scheme 4).



Scheme 4.

To confirm this reaction mechanism, we carried out this reaction by using **1** with an electron-withdrawing group. Treatment of **1f** with TMSOTf in the presence of diisopropylethylamine resulted in the formation of diene **3** (13%) along with **2f** (42%), which confirmed the presence of oxonium ion intermediate **4** (Scheme 5).

The present reaction is quite different from others. Gonzalez et al. have reported the synthesis of 3-deoxy-3-nitroheptoseptanosides by the reaction of 1,4-dioxepanes with nitromethane in the presence of potassium fluoride as catalyst.[8] Fukuzawa et al. reported the effective transformation of aldoximes of 1,3-dioxepanes to nitriles by dehydration in the presence of scandium(III) triflate.[9] However, there is no report on the ring contraction from methylene-1,3-dioxepanes.



1f **4** **3**

Scheme 5.

Since there are numerous natural products containing a tetrahydropyran moiety,[10] the present method provides another approach to the synthesis of tetrahydropyrans. We are currently continuing further investigation on the reaction and synthetic application of these compounds.

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7. Satisfactory mass spectra were obtained for all the new compounds. Separation of **2** and **2′** was unsuccessful. Selected ^{1}H and ^{13}C data of **2** and **3**. Compounds **2a** and **2a′**: ^{1}H NMR (CDCl$_3$) δ=1.98 (t, 2H, J=13 Hz, C*H*H), 2.07 (m, 1H, C*H*H), 2.22 (br s, 2H, CH$_2$), 2.33 (m, 1H, C*H*H), 2.73 (d, 1H, J=13 Hz, C*H*H), 2.98 (d, 1H, J=13 Hz, C*H*H), 3.53 (br t, 2H, J=12 Hz, C*H*H), 4.17 (m, 2H, C*H*H), 4.26 (br d, 2H, J=8 Hz, PhCH), 6.18 (s, 2H, =CH), 7.24–7.42 (m, 12H, Ph). ^{13}C NMR (CDCl$_3$) δ=25.98 (CH$_2$), 30.12 (CH$_2$), 33.73 (CH$_2$), 38.26 (CH$_2$), 68.51 (OCH$_2$), 69.55 (OCH$_2$), 79.91 (CH), 81.15 (CH), 116.87, 116.98, 125.70, 125.85, 127.29, 128.16, 132.01, 132.11, 142.42, 142.51 (Ph). Compound **3** (*trans* form): ^{1}H NMR (CDCl$_3$) δ=1.58 (q, 1H, J=13 Hz, C*H*H), 1.65 (dq, 1H, J=4, 13 Hz, C*H*H), 1.90 (br d, 1H, J=13 Hz, C*H*H), 2.08 (br d, 1H, J=13 Hz, C*H*H), 2.63 (tt, 1H, J=4, 13 Hz, CH), 3.61 (dt, 1H, J=2, 13 Hz, OC*H*H), 4.24 (dd, 1H, J=4, 13 Hz, OC*H*H), 4.38 (dd, 1H, J=2, 13 Hz, PhCH), 9.62 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$) δ=25.50 (CH$_2$), 33.23 (CH$_2$), 48.17 (CH), 67.37 (OCH$_2$), 78.77 (PhCH), 125.59, 127.53, 128.21, 141.79 (Ph), 201.85 (CHO).
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