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The Pummerer-type reaction mediated ring-opening of 2-alkyl substituted 1-[(2-methoxyethoxy)methoxy]-2-(phenylsulfinyl)cyclopropanes

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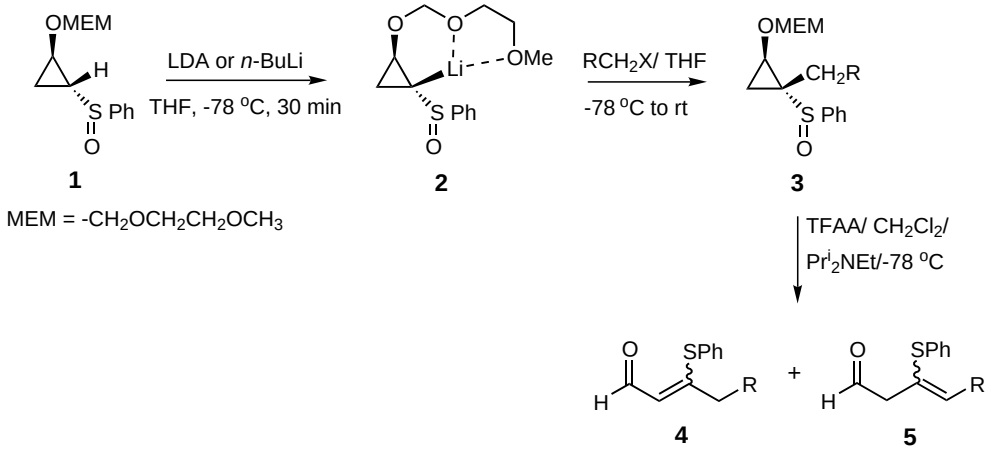
Abstract—α-Lithiated 1-[(2-methoxyethoxy)methoxy]-2-(phenylsylfinyl)cyclopropane reacted smoothly with alkylating agents to afford the corresponding α-alkylated cyclopropylsulfoxides, which underwent the Pummerer-type reaction mediated ring-opening at low temperature (−78°C) by employing TFAA/Pr^i_2NEt/CH_2Cl_2 to give mixtures of β-(phenylthio)-α,β- and γ,δ-unsaturated aldehydes.

Vicinally donor–acceptor substituted cyclopropanes are of interest due to their synthetic utilities as three-carbon building blocks via ring-opening reactions.[1] Ring-cleavage of these types of cyclopropanes can be usually accomplished by Lewis acid,[2] thermal[3] or oxidation conditions.[4] In connection with our ongoing interest in developing new synthetic methods based on vicinally *O*,*S*-disubstituted cyclopropanes,[5] we report herein that the α-sulfinyl carbanion **2** derived from *trans*-1-[(2-methoxyethoxy)methoxy]-2-(phenylsulfinyl)-cyclopropane (**1**)[6] could be alkylated to give the corresponding alkylated products **3**, which smoothly underwent the Pummerer-type mediated ring-opening reaction to give mixtures of α,β- and γ,δ-unsaturated aldehydes **4** and **5** (Scheme 1).

The α-sulfinyl carbanion **2** could be generated from *trans*-cyclopropylsulfoxide **1** (as a 1:1.5 mixture of diastereomers) by treatment with either *n*-butyllithium or lithium diisopropylamide in THF at −78°C for 1 h.



1 **2** **3** **4** **5**

Scheme 1.

Keywords: Pummerer reactions; cyclopropanes; sulfoxides; lithiation; α-sulfinyl carbanions; unsaturated aldehydes; ring-cleavage.

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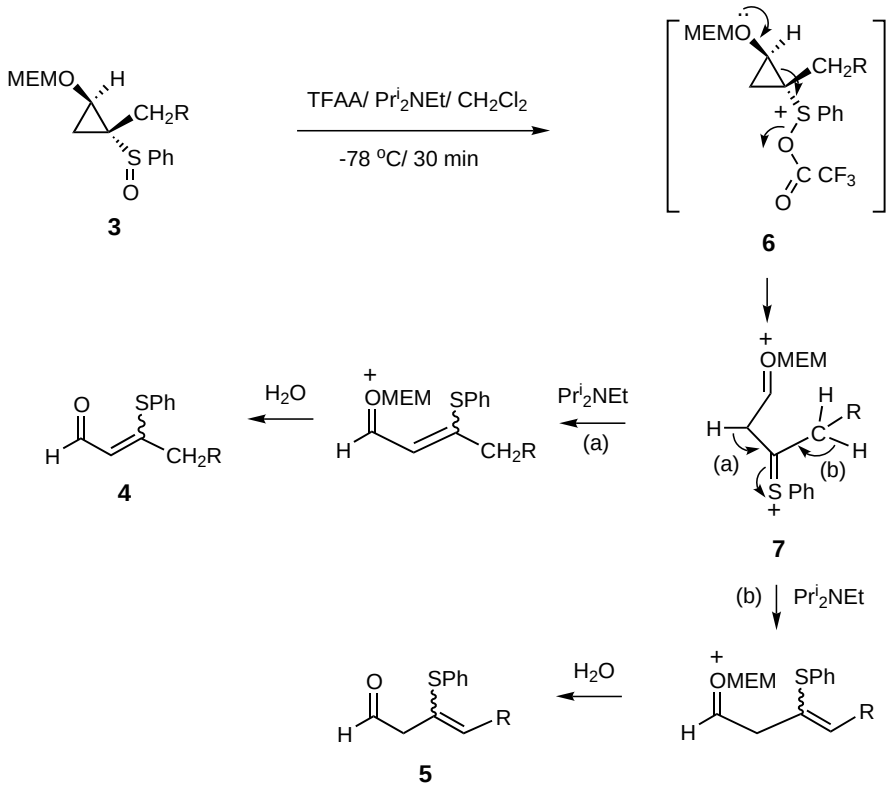
Quenching of the pale yellow solution of the expected carbanion **2** with a saturated aqueous ammonium chloride solution led to the recovery of *trans*-cyclopropylsulfoxide **1** in good yield.[7] The retention of the configuration at the α-carbon adjacent to the sulfinyl group implied that the structure of the anion **2** was as shown in Scheme 1, in which the complexation between lithium and oxygen atoms of the MEM group was assumed to occur. The reaction of the anion **2** with methyl iodide (1.1 equiv.) at −78°C at room temperature overnight provided the expected methylated cyclopropylsulfoxide **3a** in 70% yield as a 1:1 mixture of diastereomers, due to the chirality on sulfur. The *trans*-stereochemistry of **3a** was determined unambiguously by NOE experiments.[8] The alkylation of the anion **2** with other alkylating agents afforded moderate yields of the alkylated products **3b–g** as diastereomeric mixtures, as listed in Table 1.

Treatment of **3a** with 2 equiv. of trifluoroacetic anhydride (TFAA) in dichloromethane in the presence of *N*,*N*-diisopropylethylamine at −78°C for 30 min followed by quenching of the reaction mixture with an aqueous saturated sodium hydrogen carbonate solution

Table 1. Preparation of compounds **3** and their Pummerer-type mediated ring-opening employing TFAA/Pr^i_2NEt/CH_2Cl_2 at −78°C

	3		**4** and **5**	
RCH_2X	**3** (diastereomeric ratio)[a,b]	% Yield[c]	Ratio of **4** (*E*:*Z*): **5** (*E*:*Z*)[b,d]	% Yield[c]
CH_3I	**3a**, R = H (1:1)	70	**4a**, 100 (70:30)	62
n-$C_6H_{13}Br$	**3b**, R = C_5H_{11} (1:1:3)	62	**4b**, 79 (63:37):**5b**, 21 (20:80)	83
n-$C_7H_{15}Br$	**3c**, R = C_6H_{13} (1:1:4)	59	**4c**, 86 (79:21):**5c**, 14 (35:65)	75
n-$C_{11}H_{23}Br$	**3d**, R = $C_{10}H_{21}$ (1:3.7)	60	**4d**, 78 (78:22):**5d**, 22 (26:74)	84
n-$C_{15}H_{31}Br$	**3e**, R = $C_{14}H_{29}$ (1:1.3)	60	**4e**, 74 (75:25):**5e**, 26 (12:88)	77
$PhCH_2Br$	**3f**, R = Ph (1:1.3)	65	**4f**, 84 (68:32):**5f**, 16 (36:64)	69
$PhCH{=}CHCH_2Br$	**3g**, R = PhCH=CH (1:1.2)	63	–[e]	–[e]

[a] Determined by integration of the -OCH_2O- resonances in the ^1H NMR spectra (300 MHz) of the isolated products.
[b] All products were fully characterized by spectral data (IR; ^1H and ^{13}C NMR; MS) and elemental analyses.
[c] Yields of purified products by preparative thin-layer chromatography (PLC, SiO_2).
[d] Measured by the integration of the resonances of the aldehyde protons. The stereochemistries of (*E*)- and (*Z*)-isomers of both compounds **4** and **5** were determined by NOE experiments.
[e] A complex mixture of products was obtained.



Scheme 2.

at the same temperature provided **4a** in 62% yield after preparative thin-layer chromatography (PLC) as a 70:30 mixture of (*E*)- and (*Z*)-isomers. On the other hand, the reaction of **3b** with TFAA/Pr^i_2NEt in CH_2Cl_2 under the same conditions afforded a mixture of the expected α,β- and β,γ-unsaturated aldehydes **4b** and **5b**, respectively, in 83% isolated yield as a mixture of (*E*)- and (*Z*)-isomers. Likewise, under the standard conditions, the cyclopropylsulfoxides **3c–f** furnished mixtures of **4c–f** and **5c–f** in moderate to good yields (Table 1). PLC separation of the mixtures of **4b–f** and **5b-f** gave pure **4b–f** in 57–66% yields.[9] Unfortunately, β,γ-unsaturated aldehydes **5b–f** could not be obtained in pure forms.

A probable mechanistic pathway for the formation of unsaturated aldehydes **4** and **5** depicted in Scheme 2 was proposed involving the Pummerer-type reaction mediated ring-opening of cyclopropyl-sulfoxide **3**. Thus, trifluoroacetylation of **3** gave an intermediate **6**, which underwent spontaneous ring-cleavage at −78°C leading to a thionium intermediate **7**. Subsequent deprotonation of **7** with *N*,*N*-diisopropylethylamine via pathways (a) and (b) afforded the α,β- and β,γ-unsaturated aldehydes **4** and **5**, respectively, with the thermodynamically more stable isomer **4** as the major product.

In summary, we have demonstrated the Pummerer-type reaction mediated ring-opening of α-alkylated 1-[(2-methoxyethoxy)methoxy]-2-(phenylsulfinyl)cyclopropanes **3**, which are vicinally donor–acceptor cyclopropanes, to give mixtures of unsaturated aldehydes **4** and **5**. To our knowledge, this is the first report for the ring-opening of the cyclopropane ring containing vicinal *O*,*S*-substituents under the Pummerer conditions at low temperature (−78°C).

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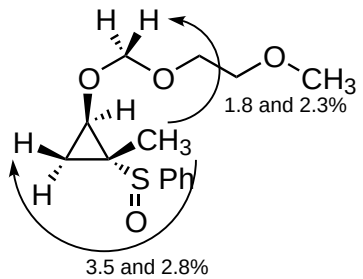
6. The starting cyclopropylsulfoxide **1** could be readily obtained by oxidation ($NaIO_4$/MeOH/H_2O, 0°C to room temperature, overnight) of *trans*-1-[(2-methoxyethoxy)-methoxy]-2-(phenylsufanyl)cyclopropane, which was prepared according to the known procedure: Tanaka, K.; Uneme, H.; Matsui, S.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2965–2972.
7. Comparable yields of the recovered starting material **1** obtained from both lithiation conditions were observed. Occasionally, bond-cleavage of the phenylsulfinyl group leading to butyl phenyl sulfoxide occurred when compound **1** was lithiated by employing butyllithium at −78°C.
8. Irradiation of the methyl groups alpha to the phenylsulfinyl group of each diastereomer resulted in 2.8 and 3.5% enhancements of the cyclopropyl protons (δ 0.77 and 0.87 ppm) *cis* to the methyl groups, as well as 2.3 and 1.8% enhancements of one proton of -OCH_2O- group of each diastereomer.



9. For the preparation of 3-(phenylthio)-2-alkenal, see: Ogawa, A.; Takeba, M.; Kawakami, J.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1995**, *117*, 7564–7565 and Kuniyasu, H.; Ogawa, A.; Sonoda, N. *Tetrahedron Lett.* **1993**, *34*, 2491–2494.