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Allyl, Methallyl, Prenyl, and Methylprenyl Ethers as Protected Alcohols: Their Selective Cleavage with Diphenyldisulfone under Neutral Conditions

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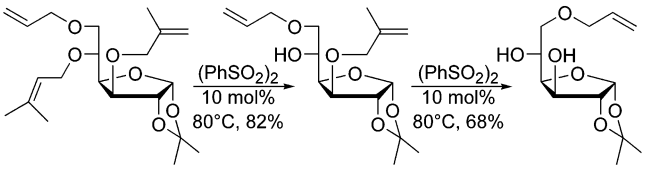
ABSTRACT



Diphenyldisulfone is a mild and efficient reagent for selective cleavage of methylprenyl (2,3-dimethylbut-2-en-1-yl), prenyl (3-methylbut-2-en1-yl), and methallyl (2-methylallyl) ethers. These reaction conditions are compatible with the presence of other protecting groups such as acetals, acetates, and allyl, benzyl, and TBDMS ethers. Exposure of 2,3-dimethylbut-2-en-1-yl and 3-methylbut-2-en1-yl ethers to diphenyldisulfone led to the formation of 2,3-dimethylbuta-1,3-diene and isoprene, respectively. 2-Methylallyl ethers undergo isomerization to 2-methylpropenyl ethers, which are easily hydrolyzed into the corresponding free alcohols and isobutyraldehyde.

The protection and deprotection of alcohols is a central theme of organic chemistry. Sophisticated synthetic schemes may fail because of protective groups that cannot be removed under suitable conditions without product decomposition. Some of the most valuable protective groups for alcohols[1] include allyl ethers, which can be cleaved under a variety of conditions.[2,3] In most cases, metal-catalyzed isomerization (Pd, Rh, Ir) of the allyl ether into the corresponding alkenyl ether and subsequent acidic hydrolysis are used to liberate the desired alcohol together with propanal.[4] The latter method can be applied to methallyl and more substituted allyl ethers. The higher the degree of substitution of the allyl ether, the slower is the transition-metal-catalyzed isomerization.[5] We report here that in the presence of a catalytic amount of diphenyldisulfone, methallyl, prenyl, and methylprenyl ethers are cleaved readily, the fastest reaction occurring with the most substituted allyl systems. Significantly, allyl ethers are not affected. These reactions are initiated by the benzenesulfonyl radical formed from thermal homolysis of $(PhSO_2)_2$.[6]

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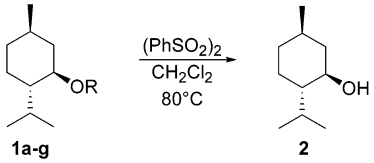
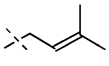
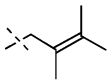
This discovery permits the cleavage of alkyl-substituted allyl ethers under neutral conditions, without heavy metals and with a useful reactivity sequence, i.e., methylprenyl > prenyl > methallyl ≫ allyl. Furthermore, other protected alcohols such as silyl ethers, esters, and benzyl ethers are not affected under these conditions.

Scheme 1. Deprotection of Menthol Derivatives **1a**−**g** by Diphenydisulfone



Menthol derivatives **1a**−**g** (Table 1) were prepared following standard procedures.[7] All compounds **1a**−**g** remained unchanged in CH_2Cl_2 after 24 h at 80 °C. In the presence of 10 mol % $(PhSO_2)_2$, allyl ether **1a**, benzyl ether **1e**, silyl ether **1f**, and acetate **1g** were not affected by heating to 80 °C. In contrast, the methyl-substituted allyl ethers **1b**, **1c**, and **1d** were cleaved, and menthol was isolated nearly quantitatively after aqueous workup.[8]

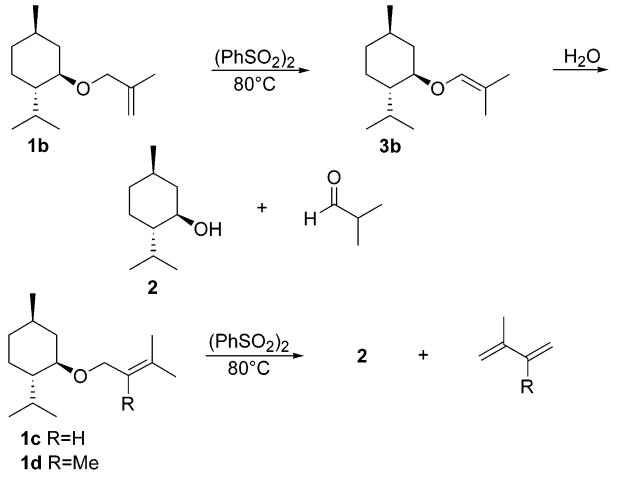
Table 1. Approximate Half-Life of **1a**−**g** in Wet CD_2Cl_2 at 80 °C in the Presence of 10 Mol % $(PhSO_2)_2$[a]

1a	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**
R: 				Bn	*t*-BuMe$_2$Si	Ac
N.R.	120 h	21 h	6 h	N.R.	N.R.	N.R.

[a] N.R. = no reaction.

In the case of **1b**, isomerization into alkenyl ether **3b** (Scheme 2) could be monitored by ^{1}H NMR. On addition of 1 mol of water **3b** was hydrolyzed at 80 °C into **2** and isobutyraldehyde. In the cases of **1c** and **1d**, no isomerized ethers could be detected during the reactions as **1c** and **1d** underwent fast 1,4-eliminations with formation of isoprene and 2,3-dimethylbutadiene, respectively, together with menthol. The reactivity sequence was methylprenyl > prenyl > methallyl ≫ allyl.

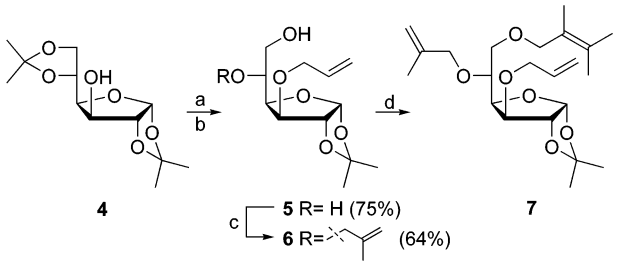
Scheme 2. Diphenyldisulfone-Catalyzed Cleavage of Methallyl (**1b**)-, Prenyl (**1c**)-, and Methylprenyl (**1d**)-Protected Menthol Derivatives



Deprotection of methylprenyl ether **1d** was examined with hydrogen abstraction agents such as hexa-*n*-butylditin and benzoyl peroxide at 80 °C in CD_2Cl_2. Benzoyl peroxide deprotects methylprenyl ether **1d** approximately four times more slowly (half-life 23 h) than diphenyldisulfone (half-life 6 h). With $(Bu_3Sn)_2$ we observed only traces of deprotected menthol **2** after prolonged heating.

As a test for the usefulness of these new reactions, we prepared the D-glucofuranoside derivative **7** according to David's method using dibutyltin oxide (Scheme 3).[13]

Scheme 3. Synthesis of D-Glucofuranoside Derivative **7**[a]



[a] (a) Allyl bromide, NaH, Bu_4NI, THF;[9] (b) H_2SO_4, 50 °C, MeOH/CH_2Cl_2;[10] (c) methallyl iodide,[11] Bu_2SnO, toluene, reflux methylprenyl bromide, NaH, Bu_4NI[12] (82%).

Compound **7** stayed unchanged upon heating to 80 °C in CH_2Cl_2 (sealed tube). In the presence of 10 mol % $(PhSO_2)_2$ in CH_2Cl_2 and at 80 °C, 1,4-elimination occurred giving **6** + 2,3-dimethylbutadiene (Scheme 4). The reaction was

(4) (a) Gent, P. A.; Gigg, R. *J. Chem. Soc., Chem. Commun.* **1974**, 277−278. (b) Gigg, R.; Conant, R. *J. Chem. Soc., Perkin Trans. 1* **1973**, *17*, 1858−1863. (c) Boullanger, P.; Chatelard, P.; Descotes, G.; Kloosterman, M.; Van Boom, J. H. *J. Carbohydr. Chem.* **1986**, *5*, 541−559. (d) Bieg, T.; Szeja, W. *J. Carbohydr. Chem.* **1985**, *140*, C7−C8. (e) Oltvoort, J. J.; Van Boeckel, C. A. A.; De Koning, J. H.; Van Boom, J. H. *Synthesis* **1981**, *4*, 305−308. (f) Chandrasekhar, S.; Reddy, C. R.; Rao, R. J. *Tetrahedron* **2001**, *57*, 3435−3438.

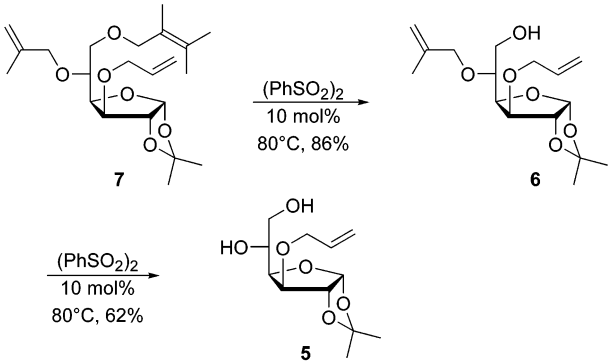
(5) (a) Guibé, F. *Tetrahedron* **1998**, *54*, 2967−3042. (b) Guibé, F. *Tetrahedron* **1997**, *53*, 13509−13556.

(6) (a) Bartmann, E. A. *Synthesis* **1993**, 490−496. (b) Tsunooka, M.; Higuchi, T.; Fujii, M.; Tanaka, M.; Murata, N. *Kogyo Kagaku Zasshi* **1970**, *73*, 596−600. See also: Kobayashi, M.; Tanaka, K.; Minato, H. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2906−2909.

(7) (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224. (b) Alonso, E.; Ramon, D. J.; Yus, M. *Tetrahedron* **1997**, *53*, 14355−14368. (c) Pansare, S. V.; Malusare, M. G.; Rai, A. N. *Synth. Commun.* **2000**, *30*, 2587−2592. (d) Kim, S.; Kee, I. S. *Tetrahedron Lett.* **1990**, *31*, 2899−2900.

(8) Only **1b** is deprotected on treating mixtures **1a** + **1b**, **1e** + **1b**, **1f** + **1b** and **1g** + **1b** under similar conditions. Similarly, only **1c** or **1d** is deprotected when mixed with **1a**, **1e**, **1f**, or **1g**. Same observations were made when cyclohexane was used as solvent.

Scheme 4. Deprotection of D-Glucofuranoside Derivative **7**

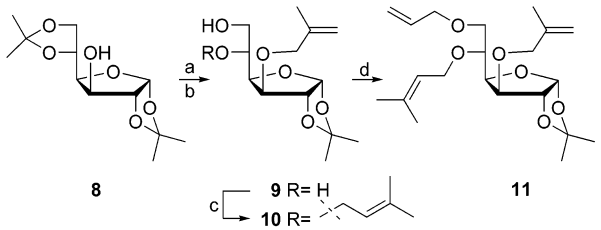


complete in 26 h, and **6** could be isolated in 86% yield. Further heating to 80 °C liberated diol **5** (isolated in 62% yield) together with isobutyraldehyde (aqueous workup).

After further heating to 80 °C in the presence of 10 mol % $(PhSO_2)_2$, the allyl ether of **5** remained intact (24 h; 95% recovery of **5**).

The same selectivity order of deprotection was observed with D-glucofuranoside **11** prepared as outlined in Scheme 5.

Scheme 5. Synthesis of D-Glucofuranoside Derivative **11**[a]

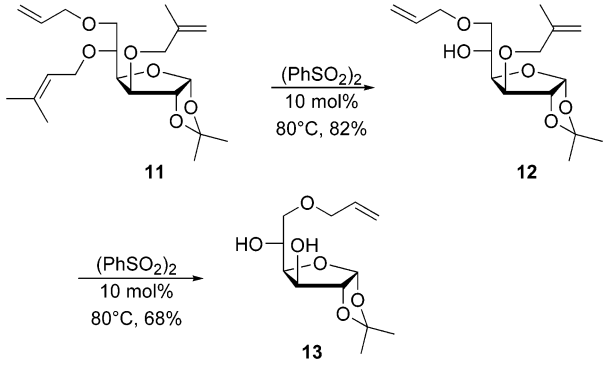


[a] (a) Methallyl chloride, NaH, Bu_4NI, THF,[14] 92%; (b) H_2SO_4 1 M, 50 °C, MeOH, CH_2Cl_2,[10] 71%; (c) prenyl bromide, Bu_2SnO, toluene, reflux;[13] (d) allyl bromide, NaH, Bu_4NI, THF,[9] 92%.

Upon heating of **11** to 80 °C in the presence of 10 mol % $(PhSO_2)_2$, 1,4-elimination of the prenyl group occurred, giving **12** and isoprene (Scheme 6). The reaction was finished after 28 h and **12** could be isolated in 82% yield. Further heating of **12** to 80 °C liberated diol **13** in 68% yield.

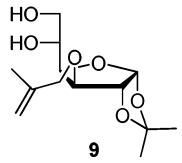
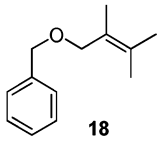
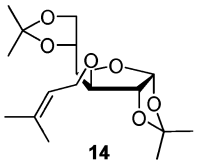
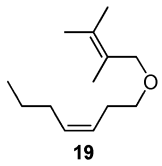
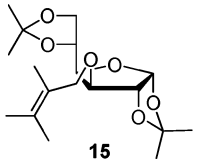
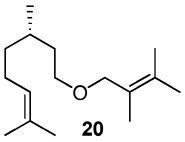
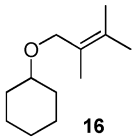
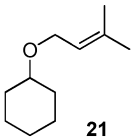
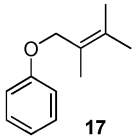
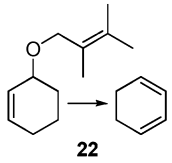
To test further the practicability of our new deprotection method, we synthesized allylic ethers **9** and **14**−**22**. Ethers **9** and **14**−**21** were easily cleaved on heating at 80 °C in the

Scheme 6. Deprotection of D-Glucofuranoside Derivative **11**



presence of 10 mol % of diphenyldisufone. However, allylic ether **22** gave exclusively cyclohexa-1,3-diene resulting from a 1,4-elimination (Table 2).

Table 2. RO-Allyl Ethers **9** and **14**−**21** Are Cleaved into Corresponding Alcohols ROH in the Presence of 10 Mol % Diphenyldisulfone in CH_2Cl_2 at 80 °C

Allylic ether	Isolated yield	Allylic ether	Isolated yield
 **9**	61%	 **18**	86%
 **14**	93%	 **19**	88%
 **15**	96%	 **20**	82%
 **16**	84%	 **21**	85%
 **17**	83%	 **22**	-

The mechanism of the isomerization of the methallyl ethers **23** might involve the formation of oxyallyl radical **24** (Scheme 7), as this isomerization was inhibited by radical scavenging agents such as TEMPO. Both 1,4-elimination **1c** → **2** + isoprene and **1d** → **2** + 2,3-dimethylbutadiene might

(9) Li, J.; Wang, J.; Hui, Y.; Chang, C.-W. T. *Org. Lett.* **2003**, *5*, 431−434.
(10) Turks, M.; Katkevica, D.; Smits, H.; Bizdena, E. *Collect. Symp. Ser.* **1999**, *2*, 268−272.
(11) Bunce, R. A.; Herron, D. M.; Johnson, L. B.; Kotturi, S. V. *J. Org. Chem.* **2001**, *66*, 2822−2827.
(12) Cennan, E. L.; Chen, X. *J. Am. Chem. Soc.* **1989**, *111*, 5787−5792.
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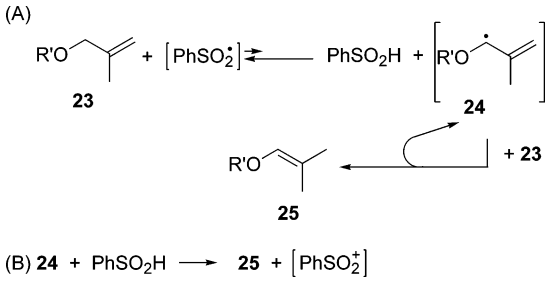
Scheme 7. Possible Mechanisms of Deprotection of Methallyl, Prenyl, and Methylprenyl Ethers in the Presence of Diphenyldisulfone



imply the intermediacy of alkyl-substituted allyl radical intermediates, as both reactions were also inhibited by TEMPO. These radical intermediates might undergo fast heterolysis[15] that competes with other intermolecular hydrogen transfers required for the allyl → alkenyl isomerization. Allyl silyl ethers have been isomerized into corresponding enol silyl ethers in the presence of radical-chain initiators and arenethiols as polarity reversal catalysts.[16] In our case (**23** → **25**) $PhSO_2H$ could play the role of polarity reversal catalyst (mechanism B in Scheme 7).

The reactivity sequence methylprenyl > prenyl > methallyl ≫ allyl can be explained invoking a direct hydrogen abstraction mechanism, the energy barrier of which depends on the ionization energy of the alkene (the more electron-rich the alkene,[17] the better it stabilizes charge-transfer configurations of the transition states, the $PhSO_2^{\bullet}$ radical being an electrophilic species.[18,19]

It should be noticed that bond dissociation enthalpies for the allyl C−H bond are not significantly different between propene and 2-methylpropene.[21] No doubt more work is required to limit the number of possible mechanisms of the reaction disclosed in this report.

Methylprenyl, prenyl, and methylallyl ethers become valuable protected forms of alcohols, as they can be cleaved under mild conditions that do not require acid, base, or heavy metal reagents or catalysts.

Acknowledgment. We thank the Swiss National Science Foundation (Grant 2000-20100002/1) and the Office Federal de l'Education et de la Sciences (Grant COI. 0071, COST D13/010/01) for financial support. We thank also Mr. Martial Rey, Franscico Sepúlveda, and Srinivas Reddy Dubbaka for technical help.

Supporting Information Available: General procedures and spectral and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049135Q

(14) Shing, T. K. M.; Leung, G. Y. C. *Tetrahedron* **2002**, *58*, 7545−7552.

(15) See, e.g.: (a) Glatthar, R.; Spichty, M.; Grugger, A.; Batra, R.; Damm, W.; Mohr, M.; Zinse, H.; Giese, B. *Tetrahedron* **2000**, *56*, 4117−4128. (b) Peukert, S.; Batra, R.; Giese, B. *Tetrahedron Lett.* **1997**, *38*, 3507−3510; Peukert, S.; Giese, B. *Tetrahedron Lett.* **1996**, *37*, 4365−4368. (c) Horner, J. H.; Taxil, E.; Newcomb, M. *J. Am. Chem. Soc.* **2002**, *124*, 5402−5410. Newcomb, M.; Miranda, N. *J. Org. Chem.* **2004**, in press.

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(19) A referee suggested that $PhSO_2^{\bullet}$ might react as DDQ and take an electron from the oxygen atom,[20] followed by α-deprotonation giving an oxyallyl cation intermediate that is hydrolyzed into the corresponding alcohol and aldehyde. Although the proposal cannot be rejected at this stage, it seems to us that it does not explain the chemoselectivity observed, especially the nonreaction of allyl ethers.

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