The sulfonation of methyl and prenyl ethers of naturally occurring phenols with trimethylsilylchlorosulfonate as sulfonating agent

Philippe Petit* and Paul Bourgeois

Département de Chimie, Université des Antilles-Guyane, Campus de Fouillole BP 250, 97 157 Pointe- à-Pitre Guadeloupe, FWI

At room temperature trimethylsilylchlorosulfonate has been found to be an effective and a mild reagent for the nuclear sulfonation of some methyl and prenyl ethers of naturally occurring phenols.

Keywords: sulfonation, trimethylsilylchlorosulfonate, phenol ethers, sulfonic acids

Many plants produce biologically active metabolites, some of which are useful as, for example, insect control agents. Phenolic derivatives generally occurring in essential oils, such as eugenol, methyleugenol, isoeugenol,[1,2] sesamol and thymol,[3] have been found to have either insecticidal or antifeedant activities.[4,5] They are also environmentally safe. However, because of their low solubility in water, it may be necessary to dissolve them in organic solvents which can be harmful to the environment. A possible solution to avoid this problem of water solubility is the introduction of the hydrophilic and electrophilic sulfonyl group by sulfonation.

The sulfonation reaction is often accomplished with concentrated sulfuric acid, but it can also be done with fuming sulfuric acid, SO_3, $ClSO_3H$. These sulfur compounds, which are potentially very harmful and difficult to handle, are problems in the use of sulfonation. In addition to this, the occurrence of oxidation side reactions makes difficult the isolation of the desired product.

A viable alternative to conventional methods is to use trimetylsilylchlorosulfonate as a sulfonating agent. Trimethylsilylchlorosulfonate which can be easily prepared by treatment of trimethylchlorosilane with chlorosulfonic acid,[6,7] is now a commercial product. It has the advantage of being soluble in most organic solvents. A wide range of organic products have been sulfonated by this agent in various conditions. We decided to modify the original procedure[8-10] by diluting trimethylsilylchlorosulfonate in methylene chloride and by operating at room temperature.

The compounds that were successfully sulfonated are listed in Table 1.

The products were identified by their ^1H NMR spectra. The assignments were supported by ^{13}C NMR, IR, and HRMS data. These are given in the experimental section.

In one case, the expected sulfonic acid as well as the corresponding sultone was obtained. This sultone has been described elsewhere, as minor product, in the sulfonation of methyl eugenol using sulfuric acid.[11] The mechanism of formation of the sultone is described in Scheme 1.

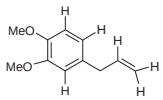
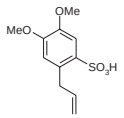
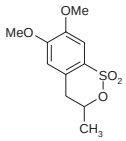
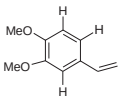
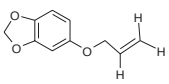
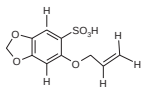
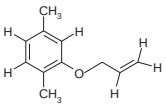
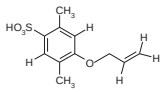
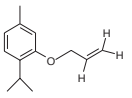
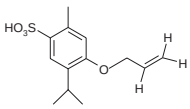
In order to confirm the above mechanism we chlorinated and brominated the acid. We obtained respectively the chlorosultone and the bromosultone, as represented in Scheme 2.

The sulfonation of the methylisoeugenol was carried out but it yielded to a complex mixture in which the identification of the sulfonated product has not been possible. This result could be explained by a possible polymerisation of the double bond.

One of the sulfonic acids was identified by its sulfonamide and the Claisen rearrangement product.

In conclusion, in the few examples given, the mono sulfonated derivative was obtained in good yields with high para or ortho selectivity and without involving the reactive double bound. The sulfonic acids which were obtained, were totally soluble in both water and organic solvents such as, methylene chloride and chloroform. Those results corroborate others works which showed that trimethylsilylchlorosulfonate affords a mild and selective method for the sulfonation of reactive aromatic prenyl ethers and may provide an alternative to the classical ones.

Table 1 The sulfonation of methyl and prenyl ethers of naturally occurring phenols with trimetylsilylchlorosulfonate as sulfonating agent

Substrate	Product	Yield[a]/%
Methyleugenol 		67.14
		17.71
Methylisoeugenol 	Complex mixture	none
O – allyl sesamol 		84
O – allyl 2,5xylenol 		82.6
O –allyl thymol 		86

[a]The yield of isolated product.

Experimental

General sulfonation method: The phenyl ether (25 mmol) was dissolved in methylene chloride (10 ml).

Trimethylsilyl chlorosulfonate (4.71 g, 25 mmol) was added dropwise, and the mixture was stirred overnight at room temperature.

A sample of the reaction mixture was taken and submitted to a $BaCl_2$ test.

Once it was negative (reaction time did not exceed 48 h), the mixture was hydrolysed with cold water (20 ml) and placed in a separating funnel.

The water extract was evaporated at reduced pressure to yield the sulfonic acid.

* Correspondence. E-mail: philippe.petit@univ-ag.fr

Alternatively the sulfonate was obtained by treating the reaction mixture with a saturated solution of sodium carbonate.

In the methyleugenol case, the sultone was obtained from the organic phase which was dried over magnesium sulfate and evaporated at reduced pressure.

Methylation procedure: Potassium carbonate (10 mmol) and methyl iodide (65 mmol) were added sequentially to a solution of the phenol (6.5 mmol) in acetone. The resulting solution was stirred at rt for 48 h, after which time the solvent was evaporated under reduced pressure. The remaining K_2CO_3 was dissolved in water and the aqueous phase extracted with ether (3×15 ml).

Methyleugenol sulfonic acid was identified as its sultone: White solid, m.p.: 212°C. ^{1}H NMR ($CDCl_3$/ CD_3OD; δ ppm): 3.19 (d, 2H), 3.71 (s, 6H), 5.03 (m, 2H), 5.94 (m, 1H), 6.73 (s, 1H), 7.42 (s, 1H).

Sultone: White solid, m.p.: 150°C. IR (ν cm^{-1}): 1327 (m), 1260 (m), 1182 (m), 1158 (s, SO_2OR), 1060 (m), 881 (s), 787 (m). ^{1}H NMR ($CDCl_3$; δ ppm) : 1.59 (d, 3H, *J* = 6.0 Hz), 2.89 (dd, 1H, *J* = 16.9 Hz, *J* = 3 Hz), 3.07 (dd, 1H, *J* = 16.9 Hz, *J* = 11.6 Hz), 3.90 (s, 6H), 5.23 (m, 1H, *J* = 11.6 Hz, *J* = 6.0 Hz, *J* = 3 Hz), 6.64 (s, 1H), 7.24 (s, 1H).

^{13}C NMR ($CDCl_3$; δ ppm): 21.08, 35.45, 56.14, 56.25, 79.39, 106.57, 110.35, 126.32, 127.35, 148.67, 152.32.

Chlorination procedure: Methyl eugenol sulfonic acid (2.58 g, 10 mmol) was dissolved in methanol (5 ml). Hydrochloric acid (35%; 2.10 ml) was added, followed by dropwise addition of 2.27 ml of hydrogen peroxide (30%; 20 mmol) with cooling.

The reaction mixture was then stirred overnight at room temperature.

The reaction mixture was extracted with methylene chloride, dried over anhydrous $CaCl_2$ and evaporated at reduced pressure to yield of chlorosultone (2.13 g).

The bromosultone was obtained by treatment of the sulfonate with brominated water (Br_2/H_2O).

Chlorosultone: Yield: 73 %. White crystals, m.p.: 174 °C. IR (ν cm^{-1}): 1329 (m), 1259 (m), 1155 (s), 1155 (s, SO_2OR), 911 (s), 784 (m). ^{1}H NMR ($CDCl_3$; δ ppm) : 3.17 (dd, 1H, *J* = 3.3 Hz, *J* = 16.9 Hz), 3.28 (dd, 1H, *J* = 10.7 Hz, *J* = 16.9 Hz), 3.82 (dd, 1H, *J* = 6.3 Hz, *J* = 11.7 Hz), 3.87 (dd, 1H, *J* = 7.9 Hz, *J* = 11.7 Hz), 3.91 (s, 6H), 5.21 (m, 1H), 6.69 (s, 1H), 7.22 (s, 1H). ^{13}C NMR: 31.11, 44.41, 56.19, 56.27, 80, 106.45, 110.67, 126.30, 126.30, 148.77, 152.58.

EI-MS Mcal. for $C_{11}H_{13}SO_5Cl$ 292.0167, M found : 292.0800.

Bromosultone: Yield: 80 %. White crystals, m.p.: 178 °C. IR (ν cm^{-1}): 1352 (m), 1259 (m), 1185 (s), 1157 (s, SO_2OR), 901 (s), 779 (m). ^{1}H NMR (Acetone D_6; δ ppm): 7.23, 7.01, 5.25, 3.90, 3.86, 3.24 ^{13}C NMR (Acetone D_6; δ ppm): 32.43, 33.31, 56.24, 56.37, 81.42, 107.04, 112.15, 126.86, 127.82, 149.69, 153.63. HRMS $C_{11}H_{13}SO_5Br$ (M+.calc +23) 360.9641, M+.found 360.9

Allylation procedure: A solution of the phenol, (26 mmol), anhyd. K_2CO_3 (4.40 g, 32 mmol and of allyl bromide (2.52 ml) in acetone (40 ml) when refluxed for 23 h, to yield the desired alllyl ether.

O-allyl-sesamol: Clear oil. ^{1}H NMR ($CDCl_3$; δ ppm) : 4.45 (d, 1H, *J* = 5.3 Hz), 5.28 (dd, 1H, *J* = 1.5 Hz, *J* = 10.5 Hz), 5.44 (dd, 1H, *J* = 1.5 Hz, *J* = 17.3), 5.91 (s, 2H), 6.00 (ddd, 1H, *J* = 5.3 Hz, *J* = 10.5 Hz, *J* = 17.3 Hz), 6.71 (d, 1H, *J* = 8.5 Hz), 6.53 (d, 1H, *J* = 2.5 Hz), 6.35 (dd, 1H, *J* = 8.5 Hz, *J* = 2.5 Hz). ^{13}C NMR ($CDCl_3$; δ ppm) : 69.56, 98.13, 100.99, 105.78, 107.75, 117.39, 133.3, 141.58, 148.10, 153.97.

Sulfonic acid: Clear oil. IR (ν cm^{-1}): 1502 (m), 1483 (m), 1423 (m), 1267 (w), 1182 (s, SO_2OR), 1149 (m), 1034 (s, SO_2OR), 1011 (m), 914 (m), 865 (m). ^{1}H NMR ($CDCl_3$; δ ppm) : 4.6 (d, 1H, *J* = 5.3 Hz), 5.28 (dd, 1H, *J* = 1.5 Hz, *J* = 10.5 Hz), 5.41 (dd, 1H, *J* = 1.5 Hz, *J* = 17.3), 5.93 (s, 2H), 6.02 (ddd, 1H, *J* = 5.3 Hz, *J* = 10.5 Hz, *J* = 17.3 Hz), 7.32 (s, 1H), 6.52 (s, 1H). ^{13}C NMR ($CDCl_3$/ CD_3OD; δ ppm): 70.69, 96.92, 101.83, 108.70, 117.75, 123.44, 132.85, 140.46, 150.74, and 152.18. HRMS calcd. for $C_{10}H_{10}O_6S$: 258.01981 ; found : 258.01958.

O- allyl-2,5,-xylenol: Clear oil. ^{1}H NMR ($CDCl_3$; δ ppm) : 2.30 (s, 3H), 2.40 (s, 3H), 4.6 (dt, 1H, *J* = 5.0 Hz, *J* = 1.6 Hz), 5.32 (ddd, 1H, *J* = 10.5 Hz, *J* = 3.4 Hz, *J* = 1.5Hz), 5.46 (ddd, 1H, *J* = 17.6 Hz, *J* = 3.4 Hz, *J* = 1.7 Hz), 6.17 (m, 1H), 6.71 (s, 1H), 6.75 (d, 1H, *J* = 7.5 Hz). 7.10 (d, 1H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$; δ ppm): 15.82, 21.36, 68.57, 112.27, 116.71, 120.95, 123.71, 130.38, 133.70, 136.40, 156.57.

Sulfonic acid: White needles, m.p.: 92 °C. IR (ν cm^{-1}): 1260 (m), 1195 (m), 1175 (m), 1059 (s), 1013 (m), 973 (m). ^{1}H NMR ($CDCl_3$; δ ppm) : 2.00 (s, 3H), 2.39 (s, 3H), 4.39 (d, 2H, *J* = 4.7 Hz), 5.22 (d, 1H, *J* = 10.6 Hz), 5.37 (d, 1H, *J* = 17.4 Hz), 5.96 (ddd, 1H, *J* = 17.2 Hz, *J* = 10.6 Hz, *J* = 5.0 Hz), 6.46 (s, 1H), 7.52 (s, 1H). ^{13}C NMR ($CDCl_3$/CD_3OD; δ ppm): 15.38, 20.07, 68.50, 114.06, 117.02, 123.71, 129.85, 130.40, 132.91, 135.80, 158.55. HRMS calcd. for $C_{11}H_{14}O_4S$: 242.0612; found: 242.0585

O-allyl thymol: Clear oil. ^{1}H NMR ($CDCl_3$; δ ppm) : 1.39 (d, 6H, *J* = 6.6 Hz), 2.47 (s, 3H), 3.24 (m, 1H), 4.68 (d, 2H, *J* = 4.2 Hz), 5.42 (d, 1H, *J* = 10.6 Hz), 5.6 (d, 1H, *J* = 17.3 Hz), 6.23 (m, 1H), 6.82 (s, 1H), 6.92 (d, 1H, *J* = 7.7 Hz). 7.27 (d, 1H, *J* = 7.7 Hz). ^{13}C NMR ($CDCl_3$; δ ppm) : 21.28, 22.71, 26.57, 68.63, 112.55, 116.53, 121.26, 125.85, 133.69, 134.19, 136.14, 155.62.

Sulfonic acid: Blue oil. IR (ν cm^{-1}): 1249 (m), 1047(s, SO_2), 1152 (m), 908 (m), 733 (m, S–O). ^{1}H NMR ($CDCl_3$; δ ppm) : 1.15 (d, 6H, *J* = 6.9 Hz), 2.49 (s, 3H), 3.24 (m, 1H), 4.51 (d, 2H, *J* = 4.7Hz), 5.28 (d, 1H, *J* = 10.6 Hz), 5.42 (d, 1H, *J* = 17.1 Hz), 6.02 (m, 1H), 6.60 (s, 1H), 7.70 (s, 1H), 9.17 (SO_3H). ^{13}C NMR ($CDCl_3$; δ ppm): 20.04, 22.13, 26.75, 68.61, 114.56, 117.01, 125.92, 131.15, 132.87, 134.08, 135.69, 157.86.

O-allyl thymol sulfonamide: Procedure: Sulfonic acid 2.4 g (~ 10 mmol) was dissolved in methylene chloride (10 ml). PCl_5 was added until the reaction mixture no longer reacted.

After refluxed for 30 min solvent the solution was evaporated. Toluene was added and the mixture was washed with cold water. The organic phase was dried over magnesium sulfate and evaporated at reduced pressure.

NH_3 aq was added until it didn't react. 2.3 g of sulfonamide were isolated. Excess aquesus ammonia was added to give the sulfonamide (2.3g).

White solid, mp: 108°C. IR (ν cm^{-1}) : 3374 (w, NH_2), 3273 (w), 2357 (w), 2339, 1300 (s, SO_2N), 1251 (s), 1148 (s, SO_2N), 1037 (s), 917 (m).^{1}H NMR ($CDCl_3$; δ ppm) : 1.15 (d, 6H, *J* = 6.9 Hz), 2.49 (s, 3H), 3.24 (m, 1H), 4.51 (d, 2H, *J* = 4.7Hz), 5.28 (d, 1H, *J* = 10.6 Hz), 5.42 (d, 1H, *J* = 17.1 Hz), , 6.02 (m, 1H), 6.60 (s, 1H), 7.70 (s, 1H), HRMS calcd. for $C_{13}H_{19}O_3SN$: 292.0983 ; found : 292.0994.

Claisen rearrangement of the sulfonamide: Procedure: The sulfonamide (2g, 10 mmol) obtained as described above was dissolved in N, N-dimethylaniline (2 ml) and heated to 190°C for 2h. The cooled reaction mixture was extracted with methylene chloride and washed with HCl (1N), followed by a saturated solution of NaCl and 10 ml H_2O.

Further as a purification yielded the desired Claisen rearrangement product.

White solid, m.p.: 62 °C. IR (ν cm^{-1}) : 3420 (w, NH_2) , 3291 (w), 1297 (m), 1184 (m), 1143 (s), 1132 (s, SO_2N), 905 (m).^{1}H NMR ($CDCl_3$; δ ppm) : 1.24 (d, 6H, *J* = 6.9 Hz), 2.60 (s, 3H), 3.16 (m, 1H), 3.51 (d, 2H, *J* = 5.7 Hz), 5.06 (d, 1H, *J* = 17.2, 1.55 Hz), 5.16 (d, 1H, *J* = 10.2,1.50 Hz), 5.94 (m, 1H), 7.85 (s, 1H), 4.72 (s, 2H) NH_2.^{13}C NMR ($CDCl_3$; δ ppm) : 16.1, 22.36, 27.12, 30.89,(116.69) 116.69, 125.49, 125.57, 131.71, 132.26, 134.24, 155.13. HRMS calcd. for $C_{13}H_{19}O_3SN$: 292.0983 ; found : 292.0994.

We thank Dr C.Poupat and Dr A.Ahond de l'Institut des Substances Naturelles from CNRS de Gif-Sur-Yvette (France) and C.Absalon Director of the Cesamo Mass Analysis Department (France).

Received 23 January 2004; accepted 10 February 2004
Paper 04/2315

References

1 E. Guenter, *The essential oils*, vol. 4. Van Nostrand Co., Inc., New York 1950.
2 Huang *et al*. *J Stored Products Res*., 1997, **33**, 289.
3 P.J. Rice and J.R. Coats, *J. of Econ. Entomol*., 1994, **87**, 1172.
4 K. Yano and H. Kamimura, *Biosci., Biotechnol. Biochemi*., 1993, **57**, 129.
5 Y. Huang H. Shuit-Hung and H.C. Lee, *J. Stored Products Res.*, 2002, **38**, 403.
6 M. Schmidt and H. Schmidbaur, *Angew. Chem.*, 1958, **70**, 631.
7 N. Duffaut, R. Calas and J. Dunoguès, *Bull. Soc. Chim. Fr.*, 1963, 512.
8 P. Bourgeois and N. Duffaut, *C.R. Acad. Sci.* , 1968, **C226**, 810.
9 R. Calas and P. Bourgeois, *J.Organometal. Chem*., 1970, **22**, 89.
10 P. Bourgeois and N. Duffaut, *Bull. Soc. Chim. Fr.*, 1980, 195.
11 M. Ya.Zarubin and S.M. Krutov, *J. Org. Chem. USSR*, 1977, **13**, 2286.