The sulfonation of safrole with trimethylsilylchlorosulfonate as sulfonating agent

Philippe Petit*, Paul Bourgeois and Micheline Grignon-Dubois

Département de Chimie, Université des Antilles-Guyane, Campus de Fouillole BP 250, 97 157 Pointe- à-Pitre Guadeloupe (F.W.I)

PhyValBio, Bât. A11, Université Bordeaux 1, 351, cours de la Libération, 33405 Talence Cedex, France

The sulfonation of naturally occurring safrole with trimethylsilylchlorosulfonate yielded three new sulfonated products, two sultones and a sulfonic acid the structures of which are discussed.

Keywords: sulfonation, safrole, trimethylsilylchlorosulfonate, sultones, sulfonic acid

In a research program aimed at developing synthetic means for the synthesis of insecticide synergists from naturally occurring phenol ethers, we considered the possibility of introducing the electrophilic and hydrophilic sullfonyl group *via* sulfonation in order to increase their water solubility. Bioactive compounds derived from safrole and containing an SO_2 moiety are described in the literature.[3,4]

We have recently reported the sulfonation of some biologically active phenol ethers, among them methyl eugenol, which was selectively sulfonated at the C-5 position (Table 1).[1]

We decided to explore the reaction with safrole in order to compare its reactivity to methyl eugenol. It is clear from the literature that sulfonated derivatives of phenolic condensation products are of great interest in cosmetics and perfumery, as they can be used as wetting agents, dye bases and perfume bases.[2]

In this paper we report the sulfonation of safrole using $ClSO_3SiMe_3$ as a sulfonating agent.

The sulfonation of safrole yielded a complex mixture from which three products were isolated, as represented in Table 1. Two of them were isolated from the organic phase and one from the aqueous phase (see experimental section).

Compound A was obtained as a white solid, m.p. 158–162°C, and analysed for $C_{10}H_{10}SO_5$.

The IR spectrum exhibited bands at 1260, 1182, 1158, and 1060 cm^{-1} which are characteristic of the SO_2 group.

^1H and ^{13}C NMR data are reported in Tables 2 and 3. ^{13}C NMR and DEPT experiments revealed the presence of one secondary methyl, two sp^3 hybridised methylenes, one sp^3 and two sp^2 methines and four sp^2 quaternary carbons.

The magnitude of the ^3J coupling constants for the 1'-CH2 resonances at 2.86 and 3.06 ppm allowed their attribution to H-1' and H-2' (Fig.1, Table 1).

This structure assignment is in good agreement with data reported in the literature for a similar 6-membered sultone synthesised from methyl eugenol.[5]

A mechanism for the formation of A is depicted in Scheme 1. Safrole is sulfonated as expected in the C-6 position to yield the sulfonic acid which gives the sultone A by cyclisation.

Compound B was obtained as colourless solid, m.p. 115–118 °C, and analysed for $C_{10}H_{10}SO_5$ by HR EIMS.

The IR spectrum exhibited bands at 1342, 1249, 1163 and 1035 cm^{-1} which are characteristic of the SO_2 group.

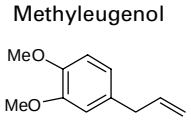
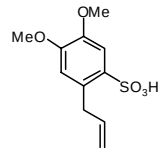
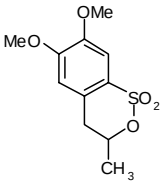
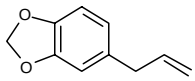
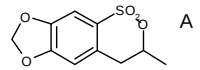
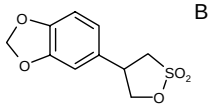
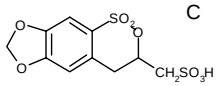
The structure deduced from the NMR spectral analysis (Tables 2 and 3) was confirmed by DEPT experiments and analysis of ^1H-^1H COSY and HMBC correlations.

Analysis of the DEPT spectrum provided evidence that C possessed 10 carbon signals including three quaternary carbons, four methines and three methylenes.

The ^1H-^1H COSY spectrum revealed the connectivities of H-2' to H-1' and H-3', as shown in Fig. 2.

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

Table 1 The sulfonation of safrole with trimethylsilyl-chlorosulfonateas sulfonating agent compared to the sulfonation of methyleugenol

Substrate	Product	%Yield[a]
Methyleugenol 		67.1
		17.7
Safrole 	 A	7
	 B	1.3
	 C	9

[a]The yield of isolated product.

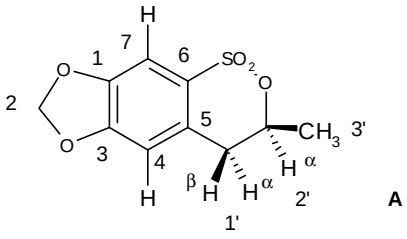


Fig. 1

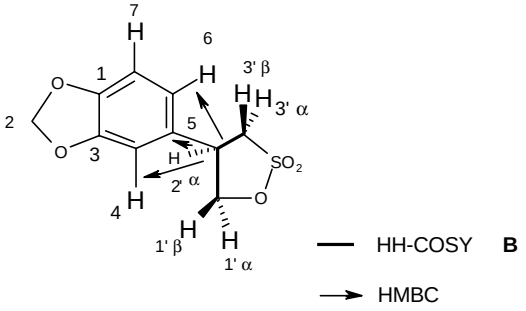


Fig. 2

Table 2 ^{1}H NMR Data [δ ppm (J, Hz)] for A, B ($CDCl_3$) and C (D_2O)

Position	A	B	C
2	6.02 (2H) s	6.00 (2H) s	5.99 (2H) s
4	6.62 s	6.60 d (1.7)	6.75 s
6		6.75 dd (7.9; 1.7)	
7	7.17 s	6.80 d (7.9)	7.17 s
1' α/β	2.86 dd (17.1; 3.1) /3.06 dd (17.1; 11.6)	4.68 dd (9.3; 7.8)/ 4.31 t (9.3)	3.06 dd (17.4; 3.3)/ 3.19 dd (17.4; 11.1)
2' α/β	5.15 m	4.06 dddd (10; 8.6; 9.3; 7.8)	5.37 m
3' α/β	1.56 d (6.41)	3.66 dd (13.2; 8.6)/ 3.27 (13.2; 10)	3.32 dd (15.0; 4.1)/ 3.47 dd (15.0; 7.6)

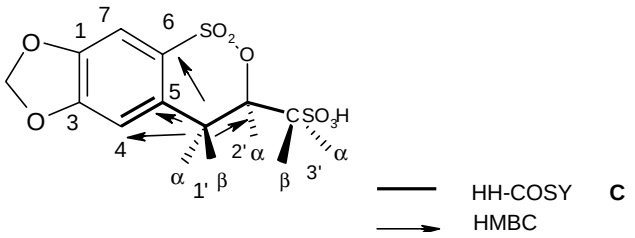


Fig. 3

In the HMBC spectrum (Fig. 2), HMBC correlations of H-2' to C-4, C-5 and C-6, and correlations of C-2' to H-4 and H-6 were observed.

These results allowed the identification of B.

A proposed mechanism for the formation of the sultone B is depicted in Scheme 1.

The key step of the mechanism is the migration of an aromatic bond leading to the formation of an intermediate cyclopropane unit, which allows the formation of B through a rearrangement. Similar mechanisms have been previously proposed in the case of the bromination of safrole.[6-8]

Compound C was obtained as a white amorphous solid, m.p. 210–218 °C, and the molecular formula $C_{10}H_{10}S_2O_8$ was established by LSIMS.

Analysis of ^{1}H and ^{13}C NMR data (Tables 2 and 3) and the DEPT spectrum provided evidence that C possessed 10 carbon signals including four quaternary carbons, three methines and three methylenes.

Noticeable are the ^{1}H–^{1}H COSY connectivities of H-2' to H-1' and H-3' and H-1' to H-4 as well as the HMBC correlations of H-1' to C-5, C-6, C-4 and C-2'.

These results allowed the identification of C. The key step of the mechanism of the formation of C which is depicted in Scheme 1 is the second attack of the double bond in the C-5 position by SO_3 which leads to the formation of a carbocation which allows cyclisation to C.

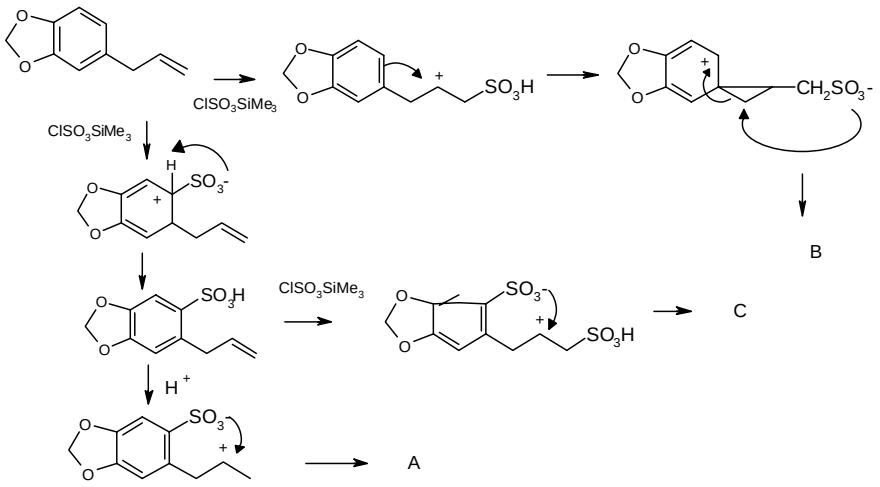
Table 3 ^{13}C NMR Spectral Data (300 MHz) for A, B ($CDCl_3$) and C (D_2O). δ (ppm)

Position	A	B	C
1	147.35	147.65	147.01
2	102.35	101.39	102.72
3	151.25	148.1	151.97
4	104.56	107.13	103.76
5	127.58	129.60	125.09
6	129.40	120.70	130.41
7	108.28	108.74	108.83
1'	39.91	74.09	32.45
2'	79.36	42.25	79.70
3'	21.03	51.16	54.72

Discussion

The low yields and the different products which were obtained from the sulfonation of safrole clearly indicate that the reaction has not been selective. These results could be explained by a competition between reactions at the aromatic ring and the allylic double bond of safrole. In terms of reactivity the aromatic ring of safrole appeared to be less activated than the methyleugenol one, in which the two methoxyls seemed more activated than the methylenedioxy group present in safrole. This higher reactivity of the aromatic ring in methyleugenol avoided the reaction with the allylic double bond which occured for safrole.

In conclusion, these results show that while trimethylsilylchlorosulfonate appeared to be highly selective with



Scheme 1

activated aromatic rings such as methyleugenol, this selectivity was lost in the less activated safrole.

Experimental

Sulfonation method: safrole (4g, 25 mmol) was dissolved in methylene chloride (10 ml). Trimethylsilylchlorosulfonate (4.71 g, 25 mmol) was added dropwise, and the mixture was stirred overnight at room temperature until a negative test with $BaCl_2$ was obtained. The mixture was then hydrolysed with cold water and the two phases were separated in a funnel.

The methylene chloride extract was dried over magnesium sulfate, and evaporated at reduced pressure to yield 1.2 g of a residue.

The residue was subjected to column chromatography on silica gel, eluting with methylene chloride. Two main fractions were obtained. Compound A (425 mg) was obtained from the first fraction while compound B (80 mg) was obtained from the second one.

The water extract was evaporated under *vacuo* to yield 6.2 g of purple oil; 1g of the water residue was purified by PTLC on silica gel, eluting with methylene chloride/methanol 40%. Two fractions were obtained. The first one (35 mg) appeared to be a complex mixture and from the second one compound C (115 mg) was isolated.

Compound A: White solid, m.p. 158–162°C. IR (ν cm^{-1}): 1327 (m), 1260 (m), 1182 (m), 1158 (s, SO_2OR), 1060 (m), 881 (s), 787 (m). ^1H NMR ($CDCl_3$; δ ppm) : 1.56 (d, 3H, *J* = 6.4 Hz), 2.86 (dd, 1H, *J* = 17.1 Hz; *J* = 3.1 Hz), 3.06 (dd, 1H, *J* = 17.1 Hz; *J* = 11.6 Hz), 5.15 (m, 1H), 6.02 (s, 2H), 6.62 (s, 1H), 7.17 (s, 1H).

^{13}C ($CDCl_3$; δ ppm) : 21.03, 39.91, 79.36, 102.35, 104.56, 108.28, 127.58, 129.40, 147.35, 151.25.

HRMS calcd for $C_{10}H_{10}SO_5$: 242.02490 ; found : 242.02487

Compound B: Colourless plates, m.p. 115–118°C. IR (ν cm^{-1}): 1342, 1249 (s), 1163 (s, SO_2OR) and 1035 ^1H NMR ($CDCl_3$; δ ppm) :3.27 (dd, 1H, *J* = 10 Hz, *J* = 13.2 Hz), 3.66 (dd, 1H, *J* = 8.6 Hz, *J* = 13.2 Hz), 4.06 (m, 1H, *J* = 10 Hz, *J* = 8.6 Hz, *J* = 9.3 Hz, *J* = 7.8Hz), 4.31 (t, 1H, *J* = 9.3 Hz), 4.68 (dd, 1H, *J* = 7.8 Hz, *J* = 9.3 Hz), 6.00 (s, 2H), 6.60 (d, 1H, *J*= 1.70 Hz), 6.75 (dd, 1H, *J* = 7.92 Hz, *J* = 1.70 Hz), 6.80(d, 1H, *J* = 7.92 Hz).

^{13}C ($CDCl_3$; δ ppm): 42.25, 51.16, 74.09, 101.39, 107.13, 108.74, 120.70, 129.60, 147.65, and 148.1.

HRMS calcd. for $C_{10}H_{10}SO_5$: 242.02490; found: 242.02487

Compound C: white amorphous solid, m.p. 210–218°C.

^1H NMR (D_2O ; δ ppm): 3.06 (dd, 1H, *J* = 17.4 Hz; *J* = 3.3 Hz), 3.19 (dd , 1H, *J* = 17.4 Hz; *J* = 11.1 Hz); 3.32 (dd , 1H, *J* = 15.0 Hz; *J* = 4.1 Hz) , 3.47 (dd, 1H, *J* = 15.0 Hz; *J* = 7.6 Hz); 5.37 (m, 1H); 5.99 (s, 2H) ; 6.75 (s, 1H) ; 7.17(s, 1H).

^{13}C (D_2O; δ ppm): 32.45, 54.72, 79.70, 102.72, 103.76, 108.83, 125.09, 130.41, 147.01, and 151.97.

LSIMS for $C_{10}H_{10}S_2O_8$: 345 (M+Na) and 367 (M+2Na) compatible with molecular formula.

HRMS calcd for $C_{10}H_{10}S_2O_8$: 322.31440; found: 322.31322

We would like to thank the Cesamo at Université de Bordeaux for HRMS analysis.

Received 25 May 2004; accepted 24 August 2004
Paper 04/2544

References

1 P. Petit, P. Bourgeois**,** *J. Chem. Res.* 2004, 194–195
2 M.T. Harvey, (Harvel Corp.). 1946, US 2412264 19461210 Patent
3 L.M. Limaa and E.J. Barreiro**,** *J. Braz. Chem. Soc.*, 1999, **10**, 421.
4 C.A.M Fraga and E.J. Barreiro, *J. Heterocycl. Chem.*, 1992, **29**, 1667.
5 M.Ya. Zarubin and S.M. Krutov, *J. Org. Chem. USSR*, 1977, **13**, 2286.
6 P.R.R. Costa and A.J. Rabi, *J.Chem.Res,* (S) 1984, 22.
7 P.R.R. Costa and A. J. Rabi, *J.Chem.Res,* (S)1984, 20.
8 I. Jouve-Nobel, J.R. Desmurs and A. Nonn, *Advances in Oganobromine Chemistry*, 1991, **1**, 69.