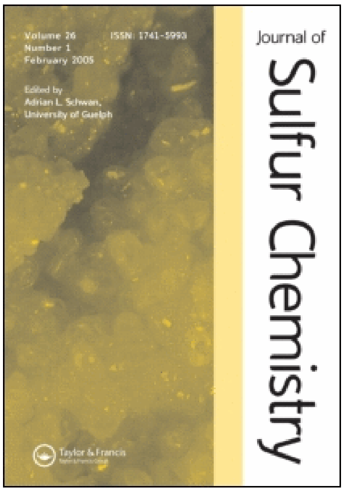

Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

Microwave-assisted solid-phase chemistry for rapid efficient generation and trapping of sulfenic acids

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To cite this Article Menichetti, Stefano , Aversa, Maria Chiara , Bonaccorsi, Paola , Lamanna, Giuseppe and Moraru, Alina(2006) 'Microwave-assisted solid-phase chemistry for rapid efficient generation and trapping of sulfenic acids', Journal of Sulfur Chemistry, 27: 5, 393 — 400

To link to this Article: DOI: 10.1080/17415990600908714

URL: http://dx.doi.org/10.1080/17415990600908714

Journal of Sulfur Chemistry
Vol. 27, No. 5, October 2006, 393–400

RESEARCH ARTICLE

Microwave-assisted solid-phase chemistry for rapid efficient generation and trapping of sulfenic acids

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(Received 22 May 2006; in final form 13 July 2006)

An easy two step procedure starting from commercially available REM resin allowed the preparation of suitable solid-supported precursors of sulfenic acids. Their microwave-assisted generation and trapping resulted superior to the conventional solution-phase procedure and thermal heating in terms of simplicity, eco-compatibility, and final yields.

Keywords: Green chemistry; Microwaves; Solid-phase; Sulfenic acids; Sulfoxides

1. Introduction

It has been widely demonstrated that the *syn*-addition of a sulfenic acid to a carbon-carbon triple bond of alkynes and enynes represents a valuable synthetic tool for the stereocontrolled preparation of alkene and diene sulfoxides (scheme 1) [1–3]. Usually, the generation of sulfenic acid is obtained by thermolysis of a suitable sulfoxide precursor carried out in the presence of the trapping alkyne. This methodology is dependent on the sulfoxide release, in the reaction medium, of an electron-poor olefin together with the required sulfenic acid (scheme 1) [4, 5].

In recent years, the use of solid-supported reagents, including sulfide-based linkers [6], and catalysts have become very popular as a way to simplify the synthetic procedures. The predictable decrease of the reaction rate upon moving to heterogeneous conditions has been frequently overcome by the use of microwave-assisted solid-phase chemistry, which has recently emerged as a successful combined strategy [7].

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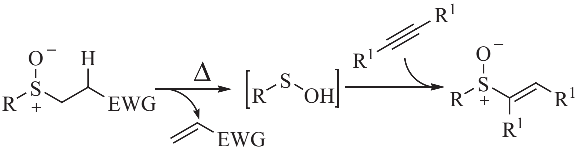
Journal of Sulfur Chemistry
ISSN 1741-5993 print/ISSN 1741-6000 online © 2006 Taylor & Francis
http://www.tandf.co.uk/journals
DOI: 10.1080/17415990600908714

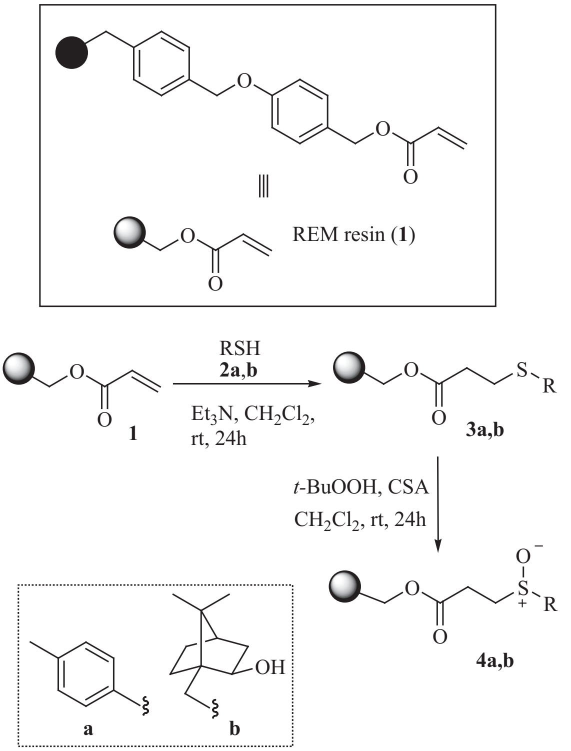


SCHEME 1

In this paper we describe the preparation of solid-supported sulfoxides, suitable to generate sulfenic acids from the solid-phase under classical heating or microwave irradiation.

2. Results and discussion

Commercially available REM resin (Wang acrylate) **1** was reacted with thiols **2a**,**b** in CH_2Cl_2 at room temperature for 24 h in the presence of Et_3N, chosen among several different strategies [8], to afford the 1,4-nucleophilic addition leading to solid-supported sulfides **3a,b** (scheme 2). The exhaustive reaction of the α,β-unsaturated carbonyl moiety in **1** was achieved by washing and drying the resin after the first treatment with the thiol, and reacting it again under the previously reported conditions, before going to the next step of the synthetic procedure. Several attempts to convert supported sulfides **3a,b** into sulfoxides **4a,b** resulted in the choice of performing the oxidation with *tert*-butyl hydroperoxide [9, 10] (*t*-BuOOH, 1 equiv) and camphorsulfonic acid (CSA, 0.2 equiv) in CH_2Cl_2 at room temperature for 24 h. This second

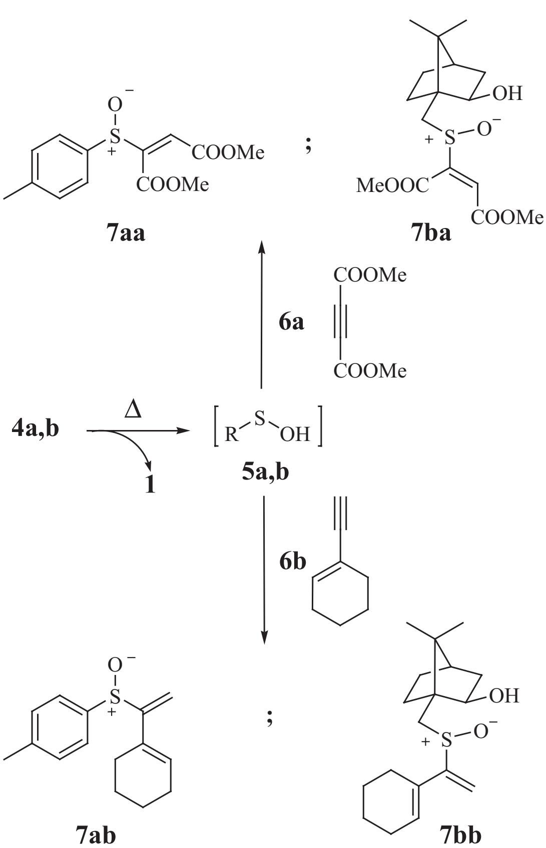


SCHEME 2

step of the reaction path was not repeated in order to avoid overoxidation of sulfoxides **4a,b** to the corresponding sulfones (scheme 2).

The two step sequence was monitored by FT-IR and ^{1}H NMR of the resins having as models the corresponding derivatives prepared in solution from ethyl acrylate and thiols **2a,b** [11,12]. For example, in the IR spectrum of REM resin **1** the C=O stretching appears at 1720 cm^{-1}, while a corresponding strong band at 1731 cm^{-1} characterizes the IR spectrum of sulfide **3a**. The oxidation does not modify the C=O stretching, still appearing at 1731 cm^{-1}, but the progress of the reaction can be monitored by following the appearance of the S=O stretching band (1042 cm^{-1} for sulfoxide **4a**, see Experimental). ^{1}H NMR parameters of resins **3** and **4** were also consistent with the proposed structures. Supported sulfoxides **4a,b** were thermolyzed to verify their ability to release the corresponding sulfenic acids **5a,b** (scheme 3). In a first experiment, the sulfoxide resin **4a** was swelled in toluene (typically 100 mg of 0.55 mmol/g resin [13] in 2 mL of toluene) at rt for 30 min, then heated in an oil bath at 110 °C in the presence of 10 equiv of dimethyl acetylenedicarboxylate (**6a**).

After 4 h the resin was filtered, washed with CH_2Cl_2 and MeOH, and the organic phase evaporated. ^{1}H NMR analysis of the crude material showed the presence of expected vinyl sulfoxide **7aa** which, to our satisfaction, was isolated in nearly quantitative yield [13] by a quick and easy flash chromatography [14] (scheme 3). This result indicates that both the reactions depicted in scheme 2 occurred quantitatively and that the resin-bounded sulfoxide **4a** is a perfect precursor of the sulfenic acid **5a**. Heating of **4a** causes the formation of the



SCHEME 3

sulfenic acid **5a**, efficiently trapped by alkyne **6a**, with simultaneous restoration of REM resin **1**, which is very easily recovered by filtration. To verify the generality of the process we produced either arenesulfenic acid **5a** or alkanesulfenic acid **5b** in the presence of alkyne **6a** or enyne **6b**. In all cases the expected vinyl sulfoxides **7** were isolated in very good yield after flash chromatography (scheme 3, table 1).

The trapping of enantiopure sulfenic acid **5b** afforded diastereoisomeric mixtures of derivative **7ba** and **7bb** [15–18] which were separated by chromatography. In both cases the diastereoisomeric ratios, 3:2 and 2:1 respectively, were consistent with that furnished by solution-phase chemistry [15]. Table 1 shows our optimized results in term of yields of **7** with respect to (a) the formation of undesired disulfides and thiosulfonates, typical by-products coming from sulfenic acid self-condensation [19], and (b) the heating time required for complete release of sulfenic acids **5a,b** from **4a,b**. The effective complete release of **5a,b** was verified either by checking in the FT-IR the disappearance of the C=O stretching at $1731\ \mathrm{cm}^{-1}$ for **4a,b**, in favour of that of the resin **1** at $1720\ \mathrm{cm}^{-1}$, or by re-heating resins **4a**,**b** under the conditions reported in table 1 to verify no further formation of derivatives **7**.

A reasonable excess of alkyne **6a** (3–5 equiv, table 1) was adequate to ensure very good isolated yield of sulfoxides **7aa** and **7ba**. On the contrary, all attempts at performing the trapping reaction in toluene by enyne **6b** gave poor results in terms of yield and purity of sulfoxides **7ab** and **7bb**. This difficulty was overcome by carrying out the reactions in neat **6b** used in the smallest amount required for a perfect swelling and wetting of the resin (typically 100 mg of resins **4a**,**b** in 0.5 mL of **6b**). Under these conditions the generation of sulfenic acids **5a,b**, from the solid-supported sulfoxides **4a,b**, and their trapping with alkynes (table 1) resulted more convenient in terms of simplicity and isolated yields in comparison with the corresponding procedure carried out in solution-phase [15].

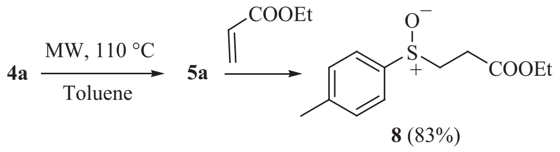
As expected, a slight augmentation of the heating time was necessary to ensure the complete decomposition of the polymer-bound sulfoxides. In this light we tested the releasing and trapping of sulfenic acids **5a,b** under microwave irradiation. The use of this modification permitted the complete generation of the sulfenic acids **5a**,**b** from the solid-supported sulfoxides **4a**,**b** within few minutes. The yields as well as the diastereoisomeric ratios, when proper, of sulfoxides **7** parallel those obtained by classical heating (even *vs* odd entries table 1).

Finally, we decided to verify the possibility of trapping sulfenic acid **5a**, obtained by microwave irradiation of resin **4a**, with alkenes [20, 21]. The generation of **5a** in the presence of cyclohexene or dihydropyran afforded exclusively products of **5a** self-condensation such as diphenyl disulfide and the corresponding thiosulfonate [19]. On the other hand generating **5a** in the presence of an excess of ethyl acrylate allowed the isolation of sulfoxide **8** [11] as single regioisomer in 83% (scheme 4).

Table 1. Optimized conditions for the preparation of sulfoxides **7**.

Entry	Supported sulfoxide	Sulfoxide/alkyne	T °C (mode)	Reaction time	Product (Yield)
1	**4a**[a]	**4a**/**6a** = 1/3	110 (oil bath)	4 h	**7aa** (98%)
2	**4a**[a]	**4a**/**6a** = 1/3	110 (MW)	3 min	**7aa** (>98%)
3	**4b**[a]	**4b**/**6a** = 1/5	110 (oil bath)	6 h	**7ba** (93%)[c]
4	**4b**[a]	**4b**/**6a** = 1/5	110 (MW)	15 min	**7ba** (77%)[c]
5	**4a**[b]	**4a**/**6b**[b]	110 (oil bath)	4 h	**7ab** (91%)
6	**4a**[b]	**4a**/**6b**[b]	110 (MW)	5 min	**7ab** (90%)
7	**4b**[b]	**4b**/**6b**[b]	110 (oil bath)	6 h	**7bb** (86%)[d]
8	**4b**[b]	**4b**/**6b**[b]	110 (MW)	15 min	**7bb** (98%)[d]

[a] Typically 100 mg of supported-sulfoxide **4a** in 2 mL of toluene; [b] Alkyne **6b** was used as solvent: 100 mg of sulfoxide **4b** in 0.5 mL of **6b**; [c] Obtained as a 3:2 mixture of diastereoisomers isolated by flash chromatography; [d] Obtained as a 2:1 mixture of diastereoisomers isolated by flash chromatography.



SCHEME 4

3. Conclusion

In conclusion we have shown that the microwave-assisted solid-phase chemistry allows the generation of sulfenic acids and their trapping by unsaturated moieties, under milder reaction conditions with better overall yields and more care to the ecocompatibility of the whole process, with respect to the conventional solution-phase procedures previously reported in the literature [1–3]. In particular the reaction shown in scheme 4 foreshadows new horizons of useful synthetic applications.

4. Experimental

The reactions were monitored by TLC on commercially available precoated plates (silica gel 60 F 254) and the products were visualized with acidic vanillin solution. Silica gel 60, 230–400 mesh, was used for column chromatography. Petrol refers to light petroleum, bp 40–60 °C. ^{1}H and ^{13}C NMR spectra were recorded at 400 (or 200) and 100 MHz, respectively, in $CDCl_3$ solutions. Residual $CHCl_3$ and the $CHCl_3$ resonance were used as reference at 7.26 ppm and 77.00 ppm, respectively. Optical rotations were measured in $CHCl_3$ solutions unless otherwise stated. FTIR spectra were recorded in KBr pellets or in $CHCl_3$ solutions. Mass spectra were measured with a Shimadzu QP5050. Microwave irradiation was achieved by a CEM Discover instrument operating at 150 W. (1*S*)-10-Mercaptoisoborneol (**2b**) was easily prepared in enantiopure form from commercial (1*S*)-(+)-10-camphorsulfonic acid [22]. REM resin **1** (loading = 0.6 mmol/g) is commercially available. Solid-phase synthesis, FT-IR and ^{1}H NMR spectra on the resins were performed as previously reported [23].

4.1 *Sulfide 3a*

Commercial REM resin **1** (1.05 g, 0.63 mmol) was swelled in CH_2Cl_2 (6 mL) under mechanical stirring for 30 min. To the suspension thiol **2a** (0.16 g, 1.26 mmol) and Et_3N (0.13 g, 1.26 mmol) were added in sequence and stirring was continued for 24 h at rt. The resin was filtered, washed sequentially with CH_2Cl_2, DMF, MeOH, diethyl ether and again CH_2Cl_2 and the shrunken beads dried in vacuum over KOH. The same procedure was repeated another time to obtain 1.13 g of resin **3a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (2H, m), 7.10–7.00 (2H, m), 3.15–3.05 (2H, m), 2.65–2.55 (2H, m), 2.28 (3H, bs). IR (KBr) cm^{-1} 1731 (C=O), 1233 (C−O).

4.2 *Sulfoxide 4a*

Sulfide pending resin **3a** (1.10 g, 0.62 mmol) was swelled in CH_2Cl_2 (5 mL) under mechanical stirring. After 30 min, CSA (0.03 g, 0.12 mmol) and *t*-BuOOH (0.12 mL of a 5 M solution in decane, 0.62 mmol) were added and stirring continued for 24 h at rt. The resin was filtered and washed sequentially with CH_2Cl_2, MeOH, diethyl ether, petroleum ether and again CH_2Cl_2. The shrunken beads were dried in vacuum to obtain 1.11 g of sulfoxide resin **4a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.50 (2H, m), 7.40–7.30 (2H, m), 3.30–3.10 (2H, m), 2.75–2.50 (2H, m), 2.37 (3H, bs). IR (KBr) cm^{-1} 1731 (C=O), 1042 (S=O).

4.3 *Sulfide 3b*

Commercial REM resin **1** (1.16 g, 0.70 mmol) was swelled in CH_2Cl_2 (6 mL) under mechanical stirring for 30 min. To the suspension thiol **2b** (0.26 g, 1.38 mmol) and Et_3N (0.14 g, 1.40 mmol) were added in sequence and stirring was continued for 24 h at rt. The resin was filtered, washed sequentially with CH_2Cl_2, DMF, MeOH, diethyl ether and again CH_2Cl_2 and the shrunken beads dried in vacuum over KOH. The same procedure was repeated another time to obtain 1.29 g of resin **3b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (1H, bs, OH), 3.85–3.75 (1H, m), 2.85–2.70 (2H, m), 2.70–2.50 (2H, m), 1.85–1.60 (3H, m), 1.30–0.90 (2H, m), 1.04 (3H, bs), 0.80 (3H, bs). IR (KBr) cm^{-1} 3512 (O−H), 1731 (C=O), 1239 (C−O).

4.4 *Sulfoxide 4b*

Sulfide pending resin **3b** (0.72 g, 0.40 mmol) was swelled in CH_2Cl_2 (4 mL) under mechanical stirring. After 30 min, CSA (0.02 g, 0.08 mmol) and *t*-BuOOH (0.08 mL of a 5 M solution in decane, 0.40 mmol) were added and stirring continued for 24 h at rt. The resin was filtered and washed sequentially with CH_2Cl_2, MeOH, diethyl ether, petroleum ether and again CH_2Cl_2. The shrunken beads were dried in vacuum to obtain 0.74 g of sulfoxide resin **4b**. ^{1}H NMR (400 MHz, $CDCl_3$, when not indicated signals refer to both diastereoisomers, $d^1 + d^2$) δ 5.07 (2H, bs, OH), 4.05–3.90 (1H, m, d1), 3.90–3.75 (1H, m, d^2), 3.30–2.70 (4H, m), 2.70–2.50 (3H, m), 1.85–1.55 (7H, m), 1.55–1.30 (2H, m), 1.20–0.90 (2H, m), 1.07 (3H, bs, d^1), 1.03 (3H, bs, d^2), 0.79 (6H, bs). IR (KBr) cm^{-1} 3411 (O−H), 1731 (C=O), 1004 (S=O).

4.5 *Vinyl sulfoxide 7aa*

Supported sulfoxide **4a** (0.10 g, 0.05 mmol) was swelled in toluene (2 mL) under mechanical stirring for 30 min, then alkyne **6a** (0.02 g, 0.15 mmol) was added and the mixture was heated at 110 °C with microwave irradiation (150 W) for 3 min. The resin was filtered and washed with several portions of CH_2Cl_2 and MeOH. After evaporation of organic phase, the crude material was purified by flash chromatography (eluent: CH_2Cl_2/EtOAc 40:1) to give compound **7aa** as an oil (>98% yield); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53 (2H, d_{app}, $J = 8.0$ Hz), 7.29 (2H, d_{app}, $J = 8.4$ Hz), 6.98 (1H, s), 3.81 (3H, s), 3.64 (3H, s), 2.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 161.6, 150.9, 143.0, 137.3, 129.9, 125.8, 125.7, 52.7, 52.6, 21.5. MS m/z (%) 282 ($M^{\bullet +}$, 17), 234 (32), 175 (59), 139 (100), 91 (45), 53 (52). IR ($CHCl_3$) cm^{-1} 3009, 2954, 2927, 1731 (C=O), 1636 (C=C), 1256 (C−O), 1058 (S=O). Anal. Calcd for $C_{13}H_{14}O_5S$: C, 55.31; H, 5.00. Found: C, 55.02; H, 4.95.

4.6 *Sulfinyl diene 7ab*

Supported sulfoxide **4a** (0.10 g, 0.05 mmol) was swelled in enyne **6b** (0.5 mL) under mechanical stirring for 30 min, then the mixture was heated at 110 °C with microwave irradiation (150 W) for 5 min. The resin was filtered and washed with several portions of CH_2Cl_2 and MeOH. After evaporation of organic phase, the crude material was purified by flash chromatography (eluent: CH_2Cl_2/EtOAc 20:1) to give compound **7ab** [24] as a yellow oil (90% yield);

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47 (2H, d_{app}, $J = 8.4$ Hz), 7.19 (2H, d_{app}, $J = 8.4$ Hz), 6.00 (1H, s), 5.99–5.92 (1H, m), 5.63 (1H, s), 2.34 (3H, s), 2.21–1.78 (4H, m), 1.66–1.40 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 141.3, 140.6, 131.3, 129.4, 128.7, 125.5, 111.8, 27.7, 25.4, 22.3, 21.7, 21.5. MS m/z (%) 246 ($M^{\bullet+}$, 100), 182 (27), 123 (91), 91 (20), 79 (36). IR ($CHCl_3$) cm^{-1} 3031, 2932, 2859, 1593 (C=C), 1042 (S=O). Anal. Calcd for $C_{15}H_{18}OS$: C, 73.13; H, 7.36. Found: C, 73.49; H, 7.52.

4.7 *Vinyl sulfoxides 7ba*

Supported sulfoxide **4b** (0.10 g, 0.05 mmol) was swelled in toluene (2 mL) under mechanical stirring for 30 min, then alkyne **6a** (0.04 g, 0.25 mmol) was added and the mixture was heated at 110 °C with microwave irradiation (150 W) for 15 min. The resin was filtered and washed with several portions of CH_2Cl_2 and MeOH. After evaporation of organic phase ^{1}H NMR analysis of the crude showed the presence of expected vinyl sulfoxides **7ba** as a 3:2 mixture of two diastereomers which were isolated by flash chromatography using a 4:1 mixture of petroleum ether/EtOAc as eluent, combined yield 77%. *First diastereomer eluted* (oil) $[\alpha]_D^{23} + 28.2$ (c = 0.75, $CHCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (1H, s), 4.10 (1H, dd, $J = 8.2, 4.2$ Hz), 3.89 (3H, s), 3.86 (3H, s), 3.52 (1H, bs, OH), 3.16 (1H, d, $J = 13.2$ Hz), 2.89 (1H, d, $J = 13.2$ Hz), 1.85–1.75 (3H, m), 1.64–1.56 (3H, m), 1.30–1.15 (1H, m), 1.07 (3H, s), 0.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 161.9, 147.9, 129.4, 76.9, 56.4, 53.3, 52.8, 51.7, 48.6, 45.1, 38.6, 30.7, 27.2, 20.5, 19.9. IR ($CHCl_3$) cm^{-1} 3452 (O−H), 1731 (C=O), 1636 (C=C), 1262 (C−O), 1076 (S=O). Anal. Calcd for $C_{16}H_{24}O_6S$: C, 55.80; H, 7.02. Found: C, 55.60; H, 6.99. *Second diastereomer eluted* (oil) $[\alpha]_D^{23} -17.7$ (c = 0.20, $CHCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, s), 4.09 (1H, dd, $J = 7.6, 4.0$ Hz), 3.88 (3H, s), 3.86 (3H, s), 3.57 (1H, d, $J = 14.0$ Hz), 2.93 (1H, bs, OH), 2.61 (1H, d, $J = 14.0$ Hz), 1.84–1.60 (5H, m), 1.43–1.09 (2H, m), 1.08 (3H, s), 0.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 162.3, 148.1, 130.0, 76.5, 55.0, 53.4, 52.8, 52.3, 49.1, 44.7, 39.9, 30.9, 27.6, 20.5, 20.2. IR ($CHCl_3$) cm^{-1} 3452 (O−H), 1731 (C=O), 1636 (C=C), 1262 (C−O), 1076 (S=O). Anal. Calcd for $C_{16}H_{24}O_6S$: C, 55.80; H, 7.02. Found: C, 55.30; H, 7.09.

4.8 *Sulfinyl dienes 7bb*

Supported sulfoxide **4b** (0.10 g, 0.05 mmol) was swelled in enyne **6b** (0.5 mL) under mechanical stirring for 30 min, then the mixture was heated at 110 °C with microwave irradiation (150 W) for 15 min. The resin was filtered and washed with several portions of CH_2Cl_2 and MeOH. After evaporation of organic phase ^{1}H NMR analysis of the crude showed the presence of expected sulfinyl dienes **7bb** [15] as a 2:1 mixture of two diastereomers which were isolated by flash chromatography using a 4:1 mixture of petroleum ether/EtOAc as eluent, combined yield 98%. *First diastereomer eluted* (oil): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.89 (1H, s), 5.88–5.83 (1H, m), 5.71 (1H, s), 4.15 (1H, dd, $J = 7.2$, 3.5 Hz), 2.91 (1H, d, $J = 13.6$ Hz), 2.71 (1H, d, $J = 13.6$ Hz), 2.41–2.06 (5H, m), 1.90–1.48 (10H, m), 1.05 (3H, s), 0.79 (3H, s). *Second diastereomer eluted* (oil): ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.01–5.93 (1H, m), 5.92 (1H, s), 5.73 (1H, s), 4.10 (1H, dd, $J = 7.5$, 3.2 Hz), 3.38 (1H, d, $J = 13.8$ Hz), 2.53 (1H, d, $J = 14.0$ Hz), 2.20–2.00 (5H, m), 1.90–1.50 (10H, m), 1.12 (3H, s), 0.79 (3H, s).

4.9 *Sulfoxide 8*

Supported sulfoxide **4a** (0.10 g, 0.05 mmol) was swelled in toluene (1 mL) and ethyl acrylate (0.5 mL) under mechanical stirring for 30 min, then the mixture was heated at 110 °C with microwave irradiation (150 W) for 12 min. The resin was filtered and washed with several portions of CH_2Cl_2 and MeOH. After evaporation of organic phase, the crude material was purified by flash chromatography (eluent: CH_2Cl_2/EtOAc 9:1) to give compound **8** [11] as an oil (83% yield); ^1H NMR (200 MHz, $CDCl_3$) δ 7.50 (2H, d_{app}, $J = 8.2$ Hz), 7.33 (2H, d_{app}, $J = 8.0$ Hz), 4.11 (2H, q, $J = 7.2$ Hz), 3.28–3.12 (1H, m), 3.02–2.72 (2H, m), 2.60–2.45 (1H, m), 2.41 (3H, s), 1.23 (3H, t, $J = 7.1$ Hz).

Acknowledgements

Work carried out in the framework of the National Projects 'Stereoselezione in sintesi organica. Metodologie ed applicazioni' and 'Cicloaddizioni a basso impatto ambientale per la sintesi di sostanze di interesse biologico' supported by the Ministero dell'Istruzione, dell'Universita'e della Ricerca (MIUR), and by the Universities of Florence and Messina. The 'Ente Cassa di Risparmio di Firenze' is also acknowledged for acquisition of a 400 MHz NMR.

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