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Note

Simple synthetic protocols for tertiary alkyl and allyl thiols

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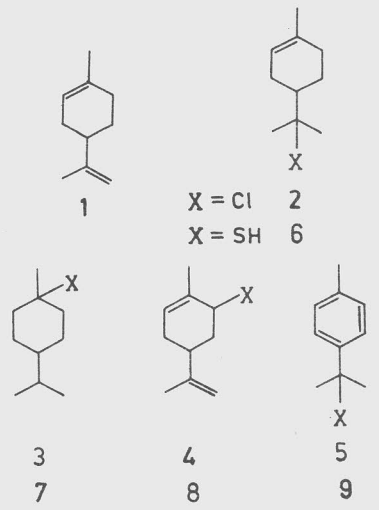
Convenient preparative methods for tertiary alkyl and allyl thiols are described. Accordingly, thiolesters and thiocyanates, obtained from the reaction of S_N1-active halides and appropriate zinc salts, on hydrolysis and LAH reduction respectively, afford the corresponding thiols in near quantitative yields. Besides the well known *p*-menth-1-ene-8-thiol, *p*-menthane-1-thiol, *p*-mentha-1, 8-diene-6-thiol and 2-(2-phenyl)propane thiol have been thus prepared.

Organosulphur compounds are an important class of flavourants present in foods, beverages and natural isolates[1,2]. Some of these have been established as flavour-impact principles, majority being thiols and sulphides[3]. These volatiles have high-flavour impact values and are usually present in very low concentrations. For example, *p*-menth-1-ene-8-thiol **6**, a tertiary thiol and a minor component of grapefruit juice, is the most powerful flavourant with a threshold value of $<10^{-4}$ ppb in water[4]. Tertiary thiols, generally are known to have flavour threshold values 300-3000 times lower than those of primary and secondary thiols[3].

Thiols can be prepared from a wide array of starting materials like olefins, alkyl halides, alcohols and their derivatives, amines, disulphides, sulfonic acids and their derivatives[5]. Allylic terpenic thiols are obtained in good yields from the corresponding terpenic alcohols or olefins via xanthogenate[6] and *N*-sulphinyl benzenesulphonamide[7] respectively. Direct addition of hydrogen sulphide to olefinic bonds in terpenic hydrocarbons in the presence of catalysts like aluminium trihalides affords terpene thiols in low yields[8,9]. But cyclic sulphides are formed as by-products in the process. Synthesis of **6** from reaction of limonene



1 with hydrogen sulphide has been reported[10]. It has been also synthesised *via* the corresponding episulphide by two alternative but similar methods[11a,b]. Yet another approach for the synthesis of **6** would be via the halide **2**. Earlier, we demonstrated that S_N1-active halides (*t*-alkyl, allylic and benzylic) on reaction with various zinc salts afford excellent yields of substitution products[12,13] This route has been explored for the synthesis of tertiary benzylic and monoterpene thiols, which are sensitive and not easily accessible.

S_N1 Active halides on reaction with zinc thiocyanate[16] or thiolacetate[17] in aprotic solvents give the substitution products in good yields. While zinc thiocyanate is made by contacting zinc chloride and potassium thiocyanate, zinc thiolacetate is prepared by reacting either zinc chloride or zinc sulphide with thiolacetic acid. Accordingly, thiocyanate derivative of **2** is obtained along with its isothiocyanate isomer, a minor product and it could be easily isolated in pure form. Similarly, *p*-menth-1-enyl-8-thiolaceate is obtained from **2** but its separation from the minor isomeric thiolacetates is rather difficult. So, the preparative method now developed for **6** involves LAH reduction of its thiocyanate precursor. On the other hand, *p*-1-menthanyl thiolacetate, obtainable in excellent yield from the saturated tertiary halide **3**, was hydrolysed to give *p*-menthane-1-thiol **7** quantitatively. Interestingly, reaction of the allylic halide **4**

with zinc thiocyanate afforded exclusively the corresponding isothiocyanate and therefore access to thiol **8** was possible only via its thiolacetate. Reaction of the tertiary benzylic halide **5**, a very sensitive compound prone to rapid dehydrohalogenation and polymerisation, with zinc thiolacetate gave good yields of the thiolacetate whose hydrolysis afforded the thiol **9**.

While two alternative synthetic protocols for the preparation of sensitive thiols are described here, the actual method of choice depends on the nature of the substrate as well as on the yields of the intermediate thiolacetate or thiocyanate derivatives. The advantage of these routes lies in the facile preparation of sensitive thiols from their relatively stable precursors. Thiols **7, 8** and **9** are new and they possess the characteristic aroma of their alcoholic analogues with typical sulphurous top note. Although none of them is as powerful as **6**, they have potential applications as flavourants.

Experimental Section

GC-MS Analyses were carried out employing 25 m×0.25 mm (i.d.) fused silica capillary column carbowax-20M (0.33 μm film thickness) under the following conditions: carrier gas, helium, flow rate, 1 ml/min ; temp. progr. 70° (2 min)-8°/min-200°C; Inj. port 150°C; Det. 70 eV. ^{1}H NMR spectra were recorded on a 90 MHz instrument in CCl_4 with TMS as the internal standard. BPs, expressed as °C/Torr, are uncorrected. Specific rotations were recorded using an automatic digital polarimeter at 589 nm and 20°C. 8-Chloro-*p*-menth-1-ene **2** and 1-chloro-*p*-menthane **3** were prepared by adding HCl to *R*-(+)-limonene and dihydrolimonene respectively[12]. *trans*-(+)-6-Chloro-*p*-mentha-1, 8-diene **4** was prepared from the reaction of (+)-*p*-mentha-1, 8-diene-6-ol (*cis* carveol) with PPh_3 and CCl_4[14]. 2-Chloro-2-phenylpropane **5** was obtained from hydrohalogenation of 2-phenylpropene (α-methylstyrene)[15].

***p*-Menth-1-ene-8-thiol 6**. Anhydrous $ZnCl_2$ (4.89 g, 36 mmol) was added to a suspension of anhyd. KSCN (6.98 g, 72 mmol) in CH_2Cl_2 (50 mL) and the mixture stirred under reflux for 2 h. After cooling, C_5H_5N (4.74 g, 60 mmol) and **2** 10.30 g, 60 mmol) were added and the mixture stirred under reflux. At the end of the reaction (8 h, TLC), 2 *N* HCl (100 mL) was added to the reaction mixture. The organic layer was separated, washed successively with water and with sat. aq. $NaHCO_3$, dried over anhyd. Na_2SO_4 and the solvent distilled off. The residue (9.6 g) was chromatographed on silica gel (100-200 mesh, 100 g) to afford *p*-menth-1-enyl-8-thiocyanate, b.p. 116°/2 (5.26 g: 45%). It was taken in dry diethyl ether (50 mL) and $LiAlH_4$ (0.48 g, 12.5 mmol) was gradually added while stirring. At the end of the reaction (1 h, TLC), 0.1 *N* aq. oxalic acid (2 mL) was added and the product filtered at the pump. The grey precipitate was washed with ether (15 mL). The combined ethereal layers on distillation afforded **6**, b.p. 83°/0.5 (4.11 g: 90 %). ^{1}H NMR : 1.35 (s, 3H), 1.42 (s, 3H), 1.66 (s, 3H), 1.80-2.22 (m, 8H), 5.40 (br, 1H). MS (m/z): 170(2.5), 136(36), 121(42), 119(19), 107(12.5), 105(10), 93(100), 92(27), 91(52), 81(10), 79(33), 77(37), 68(38), 67(31), 65(13), 53(16), 51(11), 43(10), 41(29).

***p*-Menthane-1- thiol 7.** CH_3COSH (3.04 g, 40 mmol) and ZnS (1.95 g, 20 mmol) were stirred together for 2 h in CH_2Cl_2 (30 mL) at 25°C. **3** (3.50 g, 20 mmol) was added and the reaction mixture refluxed under stirring. At the end of the reaction (24 h, GC), the salts were filtered off and the filtrate washed successively with 2 *N* HCl and water, dried and concentrated. The crude product (3.8 g) was chromatographed on silica gel (40 g) to get 1-*p*-menthanyl thiolacetate, b.p. 90°/0.8 (2.96 g: 70%). It was taken in dry CH_3OH (30 mL) and sodium methoxide (2 mL, 5 % in CH_3OH) was added. At the end of the reaction (0.5 h, GC), the solvent was evaporated, and the residue extracted with ether (2×25 mL). The ethereal layer was dried and distilled under reduced pressure to afford **7**, b.p. 80°/1.5 (2.10 g: 87 %). ^{1}H NMR: 0.86 (d, 6H), 1.33 (s, 3H), 1.00-1.86 (m, 11H). MS (m/z): 172(10.5), 139(23), 138(35), 123(10.5), 97(10.5), 96(14.5), 95(52), 83(100), 81(33), 69(39), 67(14.5), 55(29), 43(10), 41(12).

***p*-Mentha-1,8-diene-6-thiol 8**. To $Zn(SCOCH_3)_2$ (4.30 g, 20 mmol) in CH_2Cl_2 (25 mL), **4** (3.41 g, 20 mmol, $[\alpha]_D^{20}$ + 225°) was added and the mixture stirred under reflux for 2 h. To the product, 2 *N* HCl (50 mL) was added and the organic layer washed free of acid, dried and evaporated. The residue on fractionation under reduced pressure yielded *p*-mentha-1, 8-dienyl-6-thiolacetate, b.p. 110°/0.8 (3.15 g: 75%), $[\alpha]_D^{20}$ +

0.15^0. It was taken in dry CH_3OH (30 mL) and sodium methoxide (2 mL, 5 %) was added. After 30 min, the product was worked-up as described earlier and distilled to afford **8**, b.p. 68°/0.5 (2.26 g: 90 %). ^{1}H NMR: 1.80 (s, 3H), 1.83 (s, 3H), 3.40 (br, 1H), 4.76 (s, 2H), 5.50 (br, 1H), 1.90-2.70 (m, 6H). MS (m/z): 168(0.4), 134(49), 132(25), 119(81), 117(37), 105(27), 93(27), 92(38), 91(100), 76(36), 41(24).

2-(2-Phenyl)propane thiol 9. CH_3COSH (3.04 g, 40 mmol) and ZnS (1.95 g, 20 mmol) were stirred together for 2 h in CH_2Cl_2 (30 mL) at 25°C. Compound **5** (3.08 g, 20 mmol) was added slowly at 10°C and then the reaction mixture brought to total reflux. At the end of the reaction (10 h, NMR), product was worked up as described above to yield 2-(2-phenyl)propyl thiolacetate, b.p. 96°/1 (2.79 g: 72%). It was taken in dry CH_3OH (30 mL) and sodium methoxide (2 mL, 5%) was added. The product, after the usual work-up, followed by distillation under reduced pressure, afforded **9**, b.p. 58°/0.8 (2.06 g: 95 %). ^{1}H NMR: 1.73 (s, 6H), 1.93 (s, 1H), 7.36 (m, 5H); MS(m/z): 152(1), 119(25), 118(100), 117(92), 115(35), 103(76), 102(14), 78(58), 77(56), 65(22), 63(34), 51(18), 50(44), 41(16).

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