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Reaction of *R*-pulegone with P–H phosphonium salts

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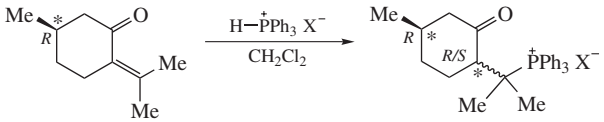
The reaction of the *R*-pulegone with P–H-phosphonium salts gives the corresponding 8-phosphonio-*p*-menthan-3-one salts with high regio- and stereoselectivity. The structure of salts was determined by NMR and IR spectroscopy, mass spectrometry and X-ray diffraction analysis.

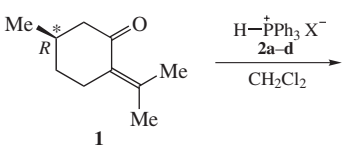


X = Cl, Br, CF_3COO, CF_3SO_3

Keywords: phosphonium salt, *R*-pulegone, *p*-menthane, α,β-enones, terpenes, terpenoids, triphenylphosphine, addition reaction.

Phosphorylated derivatives of cyclic monoterpenoids are used as ligands in metal complex catalysis,[1] organic synthesis[2] and the preparation of physiologically active compounds.[3] Phosphonium salts can manifest antitumor[4] and antibacterial[5] activity. Incorporation of a phosphonium moiety into molecules of physiologically active compounds is used for their targeted delivery to mitochondria.[6] Modification of biologically active natural compounds with phosphonium moieties sometimes increases the level of biological activity. For example, quaternary phosphonium salts obtained on the basis of rosmarinic acid exhibit a significantly higher antimicrobial activity than the acid itself;[7] phosphonium derivatives of naphthoquinones demonstrate a moderate antimicrobial and antitumor activity;[8] phosphonium derivatives of lupane triterpenoids exhibit a tenfold higher antitumor activity;[9] and triphenylphosphonium conjugates of the isosteviol diterpenoid manifest a cardioprotective effect.[10] However, only a few syntheses of monoterpenoid phosphonium derivatives are documented.[11] Here we report a convenient synthesis of phosphonium salts based on *R*-pulegone **1**, a cyclic α,β-enone of *p*-menthane series. The very *R*-pulegone is known to exhibit antimicrobial,[12] fungicidal[13] and insecticidal[14] activities.

The reaction of pulegone **1** with P–H phosphonium salts **2a–d** (triphenylphosphonium chloride, bromide, triflate, and trifluoroacetate) in dichloromethane under mild conditions gives quaternary γ-oxo phosphonium salts **3a–d** in 89–95% yields (Scheme 1).†



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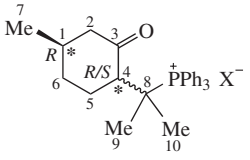

3a–d

a X = Cl
b X = Br
c X = CF_3CO_2
d X = CF_3SO_3

Scheme 1

Phosphonium salts **3a–d** are formed as an epimeric mixture with a considerable predominance of one diastereomeric form. In their ^{31}P NMR spectra, signals in the region of δ_P 40–42 are observed, with the signal at lower field corresponding to the prevailing d_1 diastereomer (Figure S1, Online Supplementary Materials). The ratio of diastereomers d_1 and d_2 depends significantly on the nature of the counterion in the starting phosphonium salt **2** and amounts to (2.8–6.4) : 1. The highest selectivity, *i.e.* the greatest predominance of one diastereomeric form, is typical of reactions involving triphenylphosphonium chloride **2a** and trifluoroacetate **2c** when the $d_1 : d_2$ diastereomer ratios are 6.4 : 1 and 6.3 : 1, respectively. Along with the nature of the counterion, temperature has a significant effect on the stereochemical result of the reaction. It was found in the reaction of *R*-pulegone with triphenylphosphonium triflate **2d**, as an

† *Compounds* **3a**,**b** *(general procedure).* Gaseous hydrogen chloride or bromide was bubbled through a solution of triphenylphosphine (1 g, 3.95 mmol) in hexane (15 ml) at room temperature. The sediment was filtered and dissolved in CH_2Cl_2 (5 ml). Pulegone **1** (0.65 ml, 3.95 mmol) was slowly added at room temperature, and this was stirred for 1 h. Phosphonium salts **3a,b** were precipitated upon addition of hexane or light petroleum (15 ml). The precipitate was filtered and dried *in vacuo* at 60 °C.

Compound **3c**. Trifluoroacetic acid (1.43 ml, 18.73 mmol) was slowly added to a solution of triphenylphosphine (0.98 g, 3.75 mmol) in CH_2Cl_2 (10 ml). A solution of pulegone **1** (0.61 ml, 3.75 mmol) in CH_2Cl_2 (5 ml) was slowly added at room temperature, and this was stirred for 1 h. Phosphonium salt **3c** was precipitated by addition of hexane or light petroleum (15 ml).

Compound **3d**. Triphenylphosphine (1.06 g, 4.05 mmol) was added in portions to a solution of trifluoromethanesulfonic acid (0.61 g, 4.05 mmol) in CH_2Cl_2 (10 ml) on cooling with ice water. A solution of pulegone **1** (0.66 ml, 4.05 mmol) in CH_2Cl_2 (5 ml) was added at room temperature, and the mixture was stirred for 1 h. Phosphonium salt **3d** was precipitated by addition of hexane or light petroleum (15 ml). The sediment was filtered and dried *in vacuo* at 60 °C.

For details and spectral data of compounds obtained, see Online Supplementary Materials.

example, that the reaction proceeds more diastereoselectively at a lower temperature. In fact, the ratio of diastereomers **3d** is 6.2 : 1.0 at –5 °C, against 2.8 : 1.0 at room temperature.

The structure of phosphonium salts **3a–d** was confirmed by IR, ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and mass spectrometry data. In their IR spectra, the absorption band corresponding to the stretching vibrations of the carbonyl group appears at shorter wavelengths ($\nu_{C=O}$ 1711 cm^{-1}) than in the IR spectrum of pulegone ($\nu_{C=O}$ 1683 cm^{-1}), which indicates the absence of α,β-enone moiety. In the ^{1}H, ^{13}C and ^{31}P NMR spectra, two diastereomers (d_1 and d_2) of phosphonium salts **3a–d** correspond to signals with significantly different intensities, which made it possible to characterize both diastereomers reliably and completely. The completeness of the reaction can be judged by the disappearance of the signal with δ_P 2–5 ppm in the ^{31}P NMR spectrum corresponding to P–H phosphonium salts **2** and appearance of signals in the δ_P 40–42 range corresponding to isomeric aliphatic γ-oxo phosphonium salts **3**. The δ ranges of 1.39–1.44 and 1.76–1.80 in their ^{1}H NMR spectra contain two doublets related to the protons for two methyl groups $C^{9}H_3$ and $C^{10}H_3$; the values of the $^{3}J_{PH}$ coupling constants in the multiplets that amount to 20.7 and 18.0 Hz agree with the geminal arrangement of these groups and the phosphorus atom (the P^{+}–$C^{8}Me_2$ moiety). The ^{13}C-{^{1}H} NMR spectrum of salts **3a–d** in the δ_C range of 38–42 contains a doublet of the quaternary carbon C^8 directly bound to the phosphorus atom, and the value of the $^{1}J_{PC}$ constant (42 Hz) confirms the phosphonium nature of the latter. It is also confirmed by the values of the chemical shift (δ_C 118–122) and the $^{1}J_{PC}$ constant (80.0 Hz) in the multiplet of the signal of the phenyl *ipso*-carbon bound to phosphorus.

The structure of compound **3a** was confirmed by single crystal XRD.‡ Figure 1 demonstrates the geometry of the ion pair in a crystal (solvate with an HCl molecule) obtained by crystallization from light petroleum. The conformation of the cyclohexane ring is a chair: the $C^{1'}$ and $C^{4'}$ atoms are deviated from the $C^{2'}C^{3'}C^{5'}C^{6'}$ plane [planar to within 0.016(6) Å] by 0.718(5) and 0.885(5) Å, respectively. The substituents O^2 and C^2 are located in the *gauche*-conformation with respect to the $C^{1'}$–$C^{2'}$ bond [the torsion angle C^2–$C^{1'}$–$C^{2'}$–C^2 is 6.6(7)°]. The substituents $C^{7'}$ and C^2 occupy equatorial positions in the cyclohexane ring [they are deflected from the $C^{2'}C^{3'}C^{5'}C^{6'}$ plane by 0.885(5) and –0.544(6) Å] and are in *trans*-configuration.

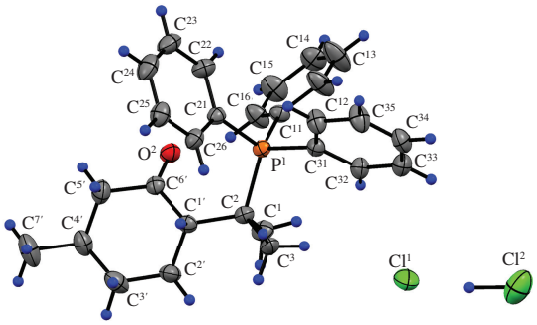

Figure 1 ORTEP diagram and accepted numbering scheme for **3a**·HCl showing 30% probability according to XRD. Atom numbering herein differs from terpenoid and systematic.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.11.003.

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‡ *Crystal data for* **3a**·HCl. $C_{28}H_{33}Cl_2OP$ (M_r = 487.41), orthorhombic, space group $P2_12_12_1$ (No. 19), a = 7.842(3), b = 17.147(6) and c = 19.413(7) Å, V = 2610.2(16) Å^3, Z = 4, Z' = 1, d_{calc} = 1.240 g cm^{-3}, μ(MoKα) = 0.328 mm^{-1}, F(000) = 1032; $T_{max/min}$ = 0.9420 and 0.8016, 19160 reflections were collected (1.585° ⩽ θ ⩽ 25.246°; index ranges: –9 ⩽ h ⩽ 9, –20 ⩽ k ⩽ 20, –23 ⩽ l ⩽ 23), 4731 of which were unique, R_{int} = 0.0702, R_σ = 0.0617; completeness to θ_{max} 100%. The refinement of 296 parameters with 1 restraint converged to R_1 = 0.0482, wR_2 = 0.0922 for 3264 reflections with $I > 2\sigma(I)$ and R_1 = 0.0793, wR_2 = 0.1056 for all data with S = 1.044 and residual electron density, $\rho_{max/min}$ = 0.233 and –0.268 e Å^{-3}. The Flack parameter was equal to –0.08(6).

The X-ray diffraction study was carried out on a Bruker SMART APEX II CCD automatic three-circle diffractometer at 293(2) K: graphite monochromator, λ(MoKα) = 0.71073 Å, ω-scanning. Data acquisition and indexing as well as determination and refinement of unit cell parameters were carried out using the APEX 3 software package (v2018.7-2, Bruker AXS). Absorption correction was based on the crystal shape according to point symmetry group 222. Additional spherical correction of absorption and determination of systematic errors were carried out using the SADABS-2016/2 program.[15] The structure was solved by direct methods using the SHELXT-2018/2 program[16] and refined by the full-matrix least squares method *vs*. F^2 using the SHELXL-018/3 program.[17] Non-hydrogen atoms were refined in anisotropic approximation. The position of the H^2 hydrogen atom was determined using difference Fourier maps, and this atom was refined isotropically; the Cl^2–H^2 distance was limited to 1.3 Å. The hydrogen atoms of the methyl group were found by refinement upon rotation of the group with idealized bond angles. The rest of the hydrogen atoms were placed in geometrically calculated positions and included in the refinement in the riding model. The absolute configuration was determined based on the Flack parameter.[18] The calculations were mainly carried out using the WinGX-2018.3 software package.[19]

CCDC 1981378 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* https://www.ccdc.cam.ac.uk.

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