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Syntheses of α-cyano substituted oximes from terpenic hydrocarbons *via* nitroso chlorides: X-ray structures of 3-cyanocaran-4-one oxime, 2-cyanopinan-3-one oxime and 1-cyano-*p*-menth-8-en-2-one oxime

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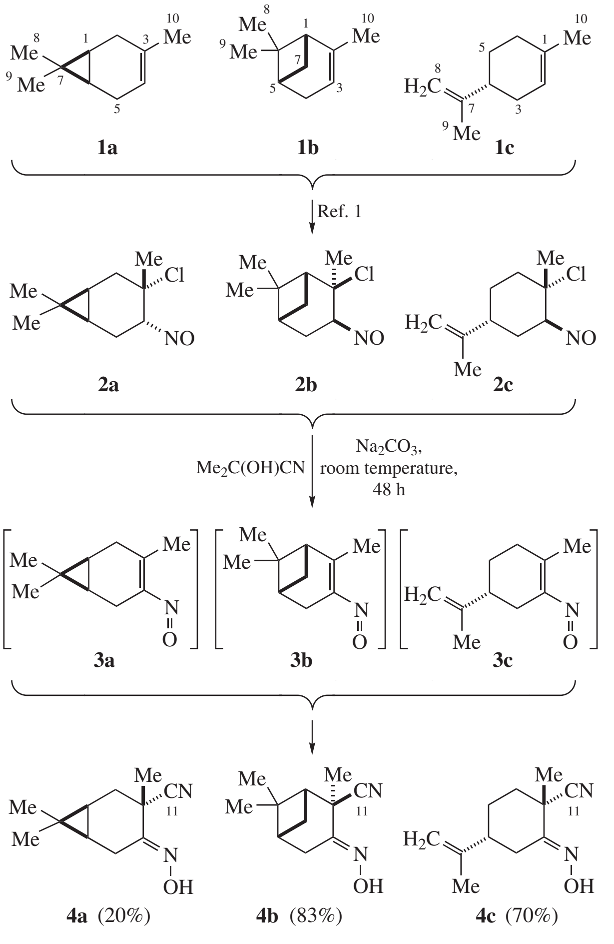
(+)-3-Carene-, (*S*)-(–)-α-pinene- and (*R*)-(+)-limonene-derived α-nitroso chlorides on treatment with an excess of acetone cyanohydrin afford the corresponding α-cyano oximes, whose structure was solved by X-ray crystallography.

Natural terpenes represent a primary source of chirality for organic synthesis.[1] One means of initial functionalization of natural olefins is stereoselective addition of NOCl,[2] which gives terpenoid nitroso chlorides being useful in design of optically active polyheteroatomic terpene derivatives including different types of chiral ligands for coordination chemistry[3] and organic reagents.[4] Terpenoid nitroso chlorides smoothly react with nucleophiles to afford α-substituted derivatives like α-amino oximes[5] or α-sulfanyl oximes.[6] Similar reaction with C-nucleophiles results in carbon–carbon bond formation to provide homo-terpenoid derivatives.[7,8] α-Cyano oximes are used as intermediates in the syntheses of fused diamino pyrimidines,[9] bactericidal structures with isoxazol-5-amine moiety,[10] hexahydrodibenzofurans with a quaternary carbon in the ring juncture,[11,12] substituted indoles[13] and cyano enamides,[14] quinolone antibacterial agents.[15] Several techniques are used to prepare α-cyano oximes and the corresponding *O*-alkyl ethers, including traditional reaction of α-cyano ketones with hydroxylamine[15,16] as well as newly developed approaches: electrochemical reduction of cyano nitro olefins,[17] addition of trimethylsilyl cyanide to conjugated nitroalkenes,[18] and reaction of cyano enamines with hydroxylamine.[10] Now we report a simple method for the preparation of terpenoid α-cyano oximes by treatment of nitroso chlorides with acetone cyanohydrin.

Nitroso chlorides **2a–c**, prepared from natural monoterpene hydrocarbons **1a–c**[†] by known procedure,[2] were treated with an excess of acetone cyanohydrin at room temperature to afford the target α-cyano substituted oximes **4a–c** (Scheme 1) in good yields.[‡] All the cyano derivatives **4a**,[§] **4b**[¶] and **4c**[††] are white well crystallized solids whose structures were solved by X-ray single crystal diffractometry (Figures 1–3),[‡‡] all calculations were carried out using the SHELXTL software.[19] Configurations of the oxime group and tertiary carbon at α-position to the oxime moiety are the same as in the corresponding α-amino substituted derivatives.[20] Configurations of the tertiary carbon in the final products **4a–c** correspond to the typical reaction sequence for nitroso chlorides including dehydrohalogenation followed by addition of nucleophile to the intermediate nitroso olefins **3a–c**, like in the reactions of the terpenoid nitroso chlorides with N-,[8,20] C-[7,8] and S-nucleophiles.[6]



Scheme 1

[†] The following starting compounds were used: (+)-3-carene **1a** with ⩾ 99.5% *ee*, isolated from *Pinus sylvestris* L. turpentine, commercially available (*S*)-(–)-α-pinene **1b** (Fluka AG #80600, 96% *ee*) and (*R*)-(+)-limonene **1c** (Fluka AG #18,316-4, 98% *ee*).

[‡] *Typical procedure*. A suspension of crystalline dimeric nitroso chloride **2b** (2.01 g, 5 mmol), prepared from α-pinene **1b**, and powdered Na$_2$CO$_3$ (2.12 g, 20 mmol) in acetone cyanohydrin (50 ml) was vigorously stirred at room temperature (21–23 °C) for 48 h. The solvent was distilled off *in vacuo*, the residue was treated with benzene (2×30 ml). The combined organic extract was dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to leave the crude product which was crystallized from benzene to yield cyano derivative **4b** (1.0 g). The mother liquor was concentrated under reduced pressure followed by column chromatography (SiO$_2$, benzene–EtOAc, 100:1 → 20:1) to afford additional crop of the cyano derivative (0.6 g) and overall yield of 1.6 g (8.3 mmol, 83%).

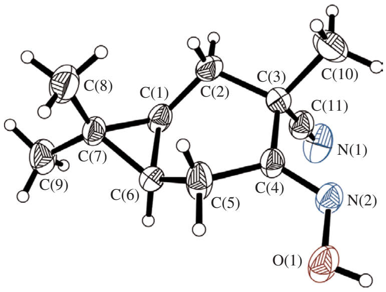


Figure 1 Crystal structure for compound **4a**. Boat conformation of the six-membered ring with bend angles of 51.4 and 46.1° along the C(2)–C(5) line for the two crystallographically independent molecules, like in the ruthenium complex with the similar ligand;[24] the dimers of molecules [supramolecular graph set $R_2^2(6)$] are formed due to the OH···N(OH)= hydrogen bonds without CN participation.

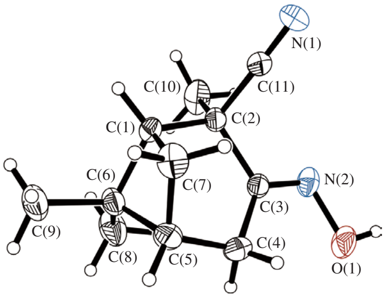


Figure 2 Crystal structure for compound **4b**. The C(1)–C(5) fragment is flat within ±0.019 Å; cyano group interacts with OH, creating chains of molecules [supramolecular graph set $C_1^1(7)$].

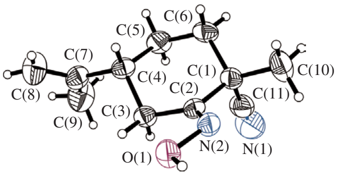


Figure 3 Crystal structure for compound **4c**. Usual chair conformation of the six-membered ring with axial CN group; the dimers of molecules [supramolecular graph set $R_2^2(6)$] are formed due to the OH...N(OH)= hydrogen bonds without CN participation.

α-Cyano substituted oximes had been firstly prepared in the terpene series (treatment of the nitroso chlorides with potassium cyanide) at the beginning of the XX century before the exact structure of natural terpene hydrocarbons was established, the compounds were described under the name ‘α-nitroso cyanide’ for α-pinene[21] and limonene.[22,23] In spite of physical data (melting points and optical rotations) of the compounds described in the old publications differ significantly from those of compounds **4a–c**, careful analysis of chemical data proves the identity of α-cyano substituted oximes **4a–c** and those ‘α-nitroso cyanides’.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.03.003.

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[§] *(1*S*,3*S*,6*R*,*E*)-4-Hydroxyimino-3,7,7-trimethylbicyclo[4.1.0]heptane-3-carbonitrile [(1*S*,3*S*,6*R*)-3-cyanocaran-4-one* E*-oxime]* **4a**. Yield 20%, mp 68.9–69.6 °C (light petroleum), $[\alpha]_D^{28}$ +191 (*c* 0.28, MeOH). Found (%): C, 69.1; H, 8.3; N, 14.5. Calc. for $C_{11}H_{16}N_2O$ (%): C, 68.72; H, 8.39; N, 14.57. HRMS (EI, 70 eV), *m/z*: 192.1256 [M]$^+$ (calc. for $[C_{11}H_{16}N_2O]^+$, *m/z*: 192.1257).

[¶] *(1*R*,2*R*,5*R*,*E*)-3-Hydroxyimino-2,6,6-trimethylbicyclo[3.1.1]heptane-2-carbonitrile [(1*R*,2*R*,5*R*,*E*)-2-cyanopinan-3-one* E*-oxime]* **4b**. Yield 83%, mp 150.4–151.0 °C (benzene); $[\alpha]_D^{28}$ –80 (*c* 0.64, MeOH) [lit.,[21] mp 171 °C (EtOH) for racemic compound]. Found (%): C, 68.9; H, 8.2; N, 14.6. Calc. for $C_{11}H_{16}N_2O$ (%): C, 68.72; H, 8.39; N, 14.57. HRMS (EI, 70 eV), *m/z*: 192.1259 [M]$^+$ (calc. for $[C_{11}H_{16}N_2O]^+$, *m/z*: 192.1257).

[††] *(1*S*,4*R*,*E*)-2-Hydroxyimino-1-methyl-4-(prop-1-en-2-yl)cyclohexane-1-carbonitrile [(1*S*,4*R*)-1-cyano-*p*-menth-7-en-2-one* E*-oxime]* **4c**. Yield 80%, mp 56.2–58.4 °C (light petroleum); $[\alpha]_D^{28}$ +132 (*c* 0.66, MeOH) [lit.,[22] mp 90–91 °C (light petroleum) and $[\alpha]_D$ +165 (in benzene), lit.,[23] $[\alpha]_D$ +152.7 (in $CHCl_3$), lit.,[23] mp 81 °C for racemic ‘α-nitroso cyanide’]. Found (%): C, 68.0; H, 8.1; N, 13.9. Calc. for $C_{11}H_{16}N_2O$ (%): C, 68.72; H, 8.39; N, 14.57. HRMS (EI, 70 eV), *m/z*: 192.1259 [M]$^+$ (calc. for $[C_{11}H_{16}N_2O]^+$, *m/z*: 192.1257).

For full mass, IR, ^{1}H and ^{13}C NMR spectra, see Online Supplementary Materials.

[‡‡] X-ray diffraction experiments were carried out with a Bruker Kappa Apex II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å, φ, ω-scans) at 296 K. The structures were solved by direct method and refined by the full-matrix least-squares against all F^2 in anisotropic approximation for non hydrogen atoms. Hydrogen atoms of OH groups were found in difference Fourier synthesis and refined in the isotropic approximation. All the rest H atoms were refined isotropically in a riding model.

Crystal data for **4a**: crystals of $C_{11}H_{16}N_2O$ (M = 192.26) are monoclinic, space group $P2_1$, a = 9.5005(4), b = 11.4976(4) and c = 10.2862(4) Å, β = 97.423(2)°, V = 1114.18(7) Å^3, d_{calc} = 1.146 g cm^{-3}, Z = 4, μ = = 0.075 mm^{-1}, $\theta_{\max}$ = 27.1°, 21423 reflections were measured, from which 4867 were independent, 4235 reflections with $I > 2\sigma(I)$. The refinement converged to R_1 = 0.0453, wR_2 = 0.1363, GOF = 1.061.

Crystal data for **4b**: crystals of $C_{11}H_{16}N_2O$ (M = 192.26) are orthorhombic, space group $P2_12_12_1$, a = 7.1736(3), b = 11.5193(4) and c = = 13.3821(6) Å, V = 1105.83(8) Å^3, d_{calc} = 1.155 g cm^{-3}, Z = 4, μ = = 0.075 mm^{-1}, $\theta_{\max}$ = 26.4°, 12412 reflections were measured, from which 2247 were independent, 1971 reflections with $I > 2\sigma(I)$. The refinement converged to R_1 = 0.0432, wR_2 = 0.1244, GOF = 1.064.

Crystal data for **4c**: crystals of $C_{11}H_{16}N_2O$ (M = 192.26) are triclinic, space group $P1$, a = 7.0251(6), b = 7.6226(7) and c = 11.287(1) Å, α = = 74.615(3)°, β = 89.894(4)°, γ = 82.606(4)°, V = 577.56(9) Å^3, d_{calc} = = 1.106 g cm^{-3}, Z = 2, μ = 0.072 mm^{-1}, $\theta_{\max}$ = 26.3°, 8635 reflections were measured, from which 3922 were independent, 2901 reflections with $I > 2\sigma(I)$. The refinement converged to R_1 = 0.0476, wR_2 = 0.1554, GOF = 1.025. The propenyl group of second independent molecule is disordered over two positions with 0.70(2) : 0.30(2) ratio.

CCDC 1045399–1045401 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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