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Mannich-type three component condensation of α-substituted caran-4-one oximes with formaldehyde and secondary amines

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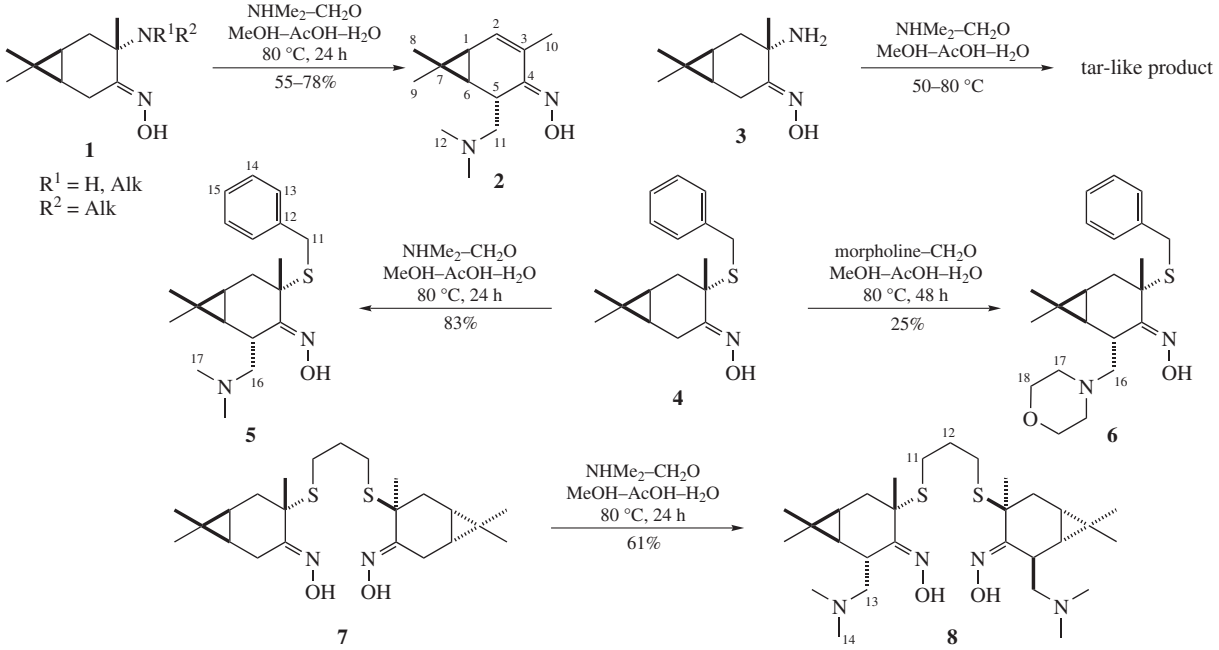
Under the conditions of the Mannich reaction, 3-substituted oximes of caran-4-one undergo aminomethylation at the α-carbon atom to oxime. The reaction takes place successfully only in a mixture of methanol and acetic acid to produce α-aminomethyl derivatives in 25–83% yields. The secondary or tertiary amino group at the α′-position is eliminated under the reaction conditions to form derivatives of α,β-unsaturated oxime, while sulfur-containing substituents remain unchanged.

The Mannich reaction of carbonyl compounds is a well-known synthetic method for the preparation of a variety of nitrogen-containing organic molecules.[1] The aza derivatives of carbonyl compounds (like imines[2] and enamines[3]) are also known as substrates for the Mannich-type condensation to yield β-amino-substituted derivatives.[4] *N*-Hydroxyimino derivatives (oximes) are poorly studied (if at all) as the C–H active component in the Mannich-type reaction. Chiral α-substituted oximes derived from natural terpenes are of great importance for coordination chemistry as polyheteroatomic ligands having an open-chain or cyclic topology of the set of donor atoms,[5–8] and Mannich-type condensation could be a prospective approach to the design of new polydentante ligands. Here we report on the first successful stereoselective introduction of an additional donor moiety into chiral α-substituted oximes by a three-component Mannich-type reaction.

Usual conditions of the Mannich reaction [formalin–secondary amine–alcohol (as a solvent) with a catalytic amount of acetic or hydrochloric acid] are useless for modification of oximes: the reaction either does not take place or results in complex mixtures or even in a tar-like product. However, if a mixture of methanol and acetic acid (*ca.* 3:1 to 2:1 by volume) is used as the solvent, the reaction smoothly leads to aminomethylation of the carbon atom at α-position to the oxime moiety. If the starting molecule contains a secondary or tertiary amino group at the α′-position, the aminomethylation is accompanied by the elimination of the amino group and the formation of an α,β-unsaturated oxime moiety (Scheme 1, transformation **1** → **2**). A primary amino group at the α-position to oxime (compound **3**) seems to react with formaldehyde to produce a tar-like mixture. Sulfur-containing groups are stable under the reaction conditions and remain untouched during aminomethylation (Scheme 1).†

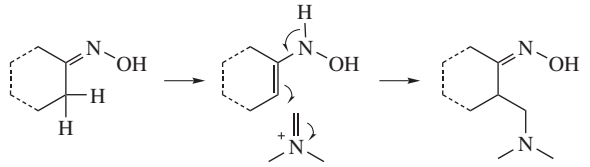
Analysis of high-field 2D ^{1}H–^{1}H and ^{13}C–^{1}H correlation NMR spectra of products **2**,† **5**,‡ **6**§ and **8**¶ and a comparison of the data with the spectra of the starting compounds showed that all the new derivatives: (1) are C(5)-aminoalkylation products formed as a single stereoisomer with the same configuration of the asymmetric carbon atom C(5) ($^{3}J_{H(5)–H(6)}$ 0–1 Hz), (2) like the



Scheme 1 The numbering scheme is given for NMR interpretation only.

initial compounds have the same (*E*)-configuration of the hydroxyimino moiety. The configuration of derivative **5** was proved by X-ray crystallography (Figure 1).††

The Mannich reaction of carbonyl compounds is believed to proceed *via* the electrophilic addition of an imminium salt to a



Scheme 2

† *Typical synthetic procedure.* Starting oxime **1**, **4** or **7** (7 mmol) was dissolved in a mixture of methanol (12 ml), glacial acetic acid (5 ml), aqueous 30% dimethylamine (1 ml) and freshly prepared 40% formalin (2.5 ml), and the mixture was kept at reflux (80 °C) for 24 h. After the starting compound was used up (TLC), the reaction mixture was cooled to room temperature and neutralized with aqueous ammonia to pH 10 (white precipitate appears) and treated with $CHCl_3$ (50 ml). The organic layer was separated, and the aqueous phase was extracted with $CHCl_3$ (3×50 ml). The combined organic extracts were washed with brine (30 ml) and dried over anhydrous Na_2SO_4. The removal of the solvent under reduced pressure gave the crude product (white solid), whose crystallization provided pure derivatives of **2**, **5** or **8** in 55–83% yields. For the preparation of derivative **6**, aqueous 30% dimethylamine was replaced with morpholine (1.2 g) and the reaction lasted 48 h.

(1S,5S,6S)-5-[(Dimethylamino)methyl]car-2-en-4-one (E)*-oxime* **2**: yield 78%, yellowish crystals, mp 160–161 °C (from MeCN); $[\alpha]_{578}^{21}$ +28 (*c* 1.18, $CHCl_3$). IR (*c* 0.75% in KBr, ν_{max}/cm^{-1}): 3417, 1449. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.76 (s, 3H, H-8), 1.10 (s, 3H, H-9), 1.20 (dd, 1H, H-1, *J* 8.1, 5.8 Hz), 1.29 (d, 1H, H-6, *J* 8.1 Hz), 1.81 (d, 3H, H-10, *J* 1.2 Hz), 2.24 (dd, 1H, H_a-11, *J* 11.9, 9.1 Hz), 2.28 (s, 6H, H-12), 2.32 (dd, 1H, H_b-11, *J* 11.9, 4.7 Hz), 3.55 (dd, 1H, H-5, *J* 9.1, 4.7 Hz), 6.08 (dq, 1H, H-2, *J* 6.8, 1.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 13.85 [C(8)], 18.26 [C(10)], 23.08 [C(1)], 24.40 [C(7)], 25.77 [C(6)], 28.13 [C(9)], 28.49 [C(5)], 45.63 [C(12)], 63.26 [C(11)], 126.92 [C(3)], 131.09 [C(2)], 158.17 [C(4)].

‡ *(1S,3S,5S,6S)-3-Benzylthio-5-(dimethylamino)methylcaran-4-one* (E)*-oxime* **5**: yield 83%, yellowish crystals, mp 143–145 °C (from EtOAc); $[\alpha]_{578}^{21}$ +18 (*c* 1.14, $CHCl_3$). IR (*c* 2% in $CHCl_3$, ν_{max}/cm^{-1}): 3596, 1602. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.78 (s, 3H, H-8), 0.78 (m, 1H, H-1), 0.78 (m, 1H, H-6), 1.06 (s, 3H, H-9), 1.47 (s, 3H, H-10), 1.55 (dd, 1H, $H_{pro\text{-}S}$-2, *J* 15.7, 4.3 Hz), 2.21 (dd, 1H, $H_{pro\text{-}R}$-2, *J* 15.7, 9.3 Hz), 2.33 (s, 6H, H-17), 2.79 (dd, 1H, H_a-16, *J* 12.2, 6.1 Hz), 2.83 (dd, 1H, H_b-16, *J* 12.2, 6.1 Hz), 3.18 (dd, 1H, H-5, *J* 6.1, 6.1 Hz), 3.58 (AB system, 2H, $H_{a,b}$-11, J_{AB} 12.0 Hz, $\Delta\delta_{AB}$ 145.0 Hz), 7.17–7.27 (m, 5H, H_{Ar}), 10.6 (br. s, 1H, OH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.23 [C(8)], 17.08 [C(1)], 18.82 [C(7)], 24.27 [C(6)], 25.84 [C(10)], 27.67 [C(9)], 30.43 [C(5)], 32.99 [C(11)], 34.67 [C(2)], 45.39 [C(17)], 49.32 [C(3)], 66.64 [C(16)], 126.84 [C(15)], 128.40 [C(14)], 128.80 [C(13)], 137.54 [C(12)], 162.77 [C(4)]. MS, *m/z* (%): 346.2061 (2, [M$^+$], calc. for $C_{20}H_{30}N_2OS$: 346.2073), 224 (2), 92 (1), 91 (9), 79 (1), 77 (1), 65 (3), 59 (3), 58 (100), 44 (1), 42 (2), 41 (1), 39 (1). Found (%): C, 69.4; H, 8.6; N, 8.3; S, 9.6. Calc. for $C_{20}H_{30}N_2OS$ (%): C, 69.32, H, 8.73, N, 8.08, S, 9.25.

§ *(1S,3S,5S,6S)-3-Benzylthio-5-(*N*-morpholino)methylcaran-4-one* (E)*-oxime* **6**: yield 25%, colourless crystals, mp 107–109 °C (from EtOAc), $[\alpha]_{578}^{21}$ +62 (*c* 1.87, $CHCl_3$). IR (*c* 2% in $CHCl_3$, ν_{max}/cm^{-1}): 3582, 1602. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.76 (s, 3H, H-8), 0.80 (m, 1H, H-1), 0.90 (dd, 1H, H-6, *J* 9.3, 1.3 Hz), 1.02 (s, 3H, H-9), 1.45 (s, 3H, H-10), 1.54 (dd, 1H, $H_{pro\text{-}S}$-2, *J* 15.5, 5.4 Hz), 2.21 (dd, 1H, $H_{pro\text{-}R}$-2, *J* 15.5, 9.6 Hz), 2.59 (m, 4H, H-17), 2.85 (AB-part of ABX system, 2H, H-16, $\Delta\delta_{AB}$ 4.5 Hz, J_{AB} 13.5 Hz, J_{AX} 9.0 Hz, J_{BX} 5.0 Hz), 3.22 (ddd, 1H, H-5, *J* 7.8, 6.0, 1.3 Hz), 3.38 (d, 1H, H_a-11, *J* 12.2 Hz), 3.69 (d, 1H, H_b-11, *J* 12.2 Hz), 3.72 (m, 4H, H-18), 7.15–7.30 (m, 5H, H_{Ar}). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.25 [C(8)], 17.10 [C(1)], 18.78 [C(7)], 24.07 [C(6)], 25.70 [C(10)], 27.61 [C(9)], 29.08 [C(5)], 33.02 [C(11)], 34.77 [C(2)], 49.19 [C(3)], 53.57 [C(17)], 64.68 [C(18)], 66.70 [C(16)], 126.91 [C(15)], 128.45 [C(14)], 128.82 [C(13)], 137.50 [C(12)], 162.81 [C(4)]. MS, *m/z* (%): 388.2197 (1, [M$^+$], calc. for $C_{22}H_{32}N_2O_2S$: 388.2179), 266 (1), 101 (5), 100 (100), 98 (1), 91 (8), 77 (1), 70 (1), 65 (1), 56 (4), 42 (1), 41(1).

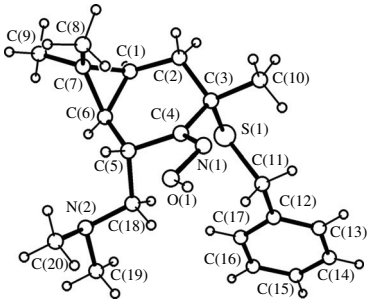


Figure 1 Crystal structure of compound **5**. Selected bond lengths (Å): S(1)–C(3) 1.856(3), S(1)–C(11) 1.814(4), C(3)–C(4) 1.512(4), N(1)–C(4) 1.279(4), N(1)–O(1) 1.410(3).

C=C bond of the enol formed from the carbonyl compound. The mechanism of the oxime transformation found seems to be the same: the protonation of the oxime nitrogen followed by the removal of a proton from the α-carbon should result in *N*-hydroxy enanime as the key intermediate (Scheme 2).

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¶ *1,3-Bis[(1S,3S,6S,5S)-5-(dimethylamino)methyl-4*(E)*-hydroxyimino-caran-3-ylthio]propane* **8**: yield 61%, colourless crystals, mp 138–143 °C (from $CHCl_3$), $[\alpha]_{578}^{21}$ –21.8 (*c* 1.49, $CHCl_3$). IR (*c* 2% $CHCl_3$, ν_{max}/cm^{-1}): 3584. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.75 (m, 2H, H-1), 0.76 (s, 6H, H-8), 0.78 (m, 2H, H-6), 1.02 (s, 6H, H-9), 1.36 (s, 6H, H-10), 1.50 (m, 2H, $H_{pro\text{-}S}$-2), 1.76 (dddd, 2H, H-12, *J* 7.5, 7.5, 7.5, 7.5 Hz), 2.15 (m, 2H, $H_{pro\text{-}R}$-2), 2.23 (ddd, 2H, H_a-11, *J* 12.0, 7.4, 7.4 Hz), 2.43 (s, 12H, H-14), 2.47 (ddd, 2H, H_b-11, *J* 12.0, 7.4, 7.4 Hz), 2.72 (dd, 2H, H_a-13, *J* 12.0, 7.4 Hz), 2.78 (dd, 2H, H_b-13, *J* 12.0, 5.5 Hz), 3.15 (dd, 2H, H-5, *J* 7.4, 5.5 Hz), 9.0 (br. s, 2H, OH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 15.22 [C(8)], 17.19 [C(1)], 18.73 [C(7)], 24.51 [C(5)], 25.82 [C(10)], 27.69 [C(9)], 27.73 [C(2)], 29.36 [C(12)], 29.77 [C(6)], 34.68 [C(11)], 45.21 [C(14)], 48.54 [C(3)], 65.97 [C(13)], 162.41 [C(4)]. MS, *m/z* (%): 552.3520 (1, [M$^+$], calc. for $C_{29}H_{52}N_4O_2S_2$: 552.3526), 134 (3), 106 (3), 91 (4), 79 (4), 77 (3), 59 (3), 58 (100), 44 (3), 42 (4), 41 (5), 40 (3), 39 (3).

†† *X-ray crystallographic data for compound* **5**. $C_{20}H_{30}N_2OS$, M_r = 346.52, monoclinic, space group $P2_1$, a = 15.802(1), b = 6.7026(7) and c = 19.382(2) Å, β = 95.283(7)°, V = 2044.1(3) Å^3, Z = 4, d_{calc} = 1.126 g cm^{-3}, μ(MoKα) = 0.167 mm^{-1}, T = 296 K, wR_2 = 0.1117, S = 1.028 for all 4390 *hkl*, R_{int} = 0.0145, R = 0.0410 for observed 3575 $I > 2\sigma(I)$, absolute structure parameter (Flack) –0.02(9). The data were measured on a Bruker P4 diffractometer [MoKα radiation, $\theta/2\theta$ scans ($2\theta < 50°$)]. A correction for absorption was made by an empirical method based on ψ scans (transmission of 0.66–0.96). The structure was solved by direct methods using the SHELXS-97 program and refined in the full-matrix anisotropic (isotropic for H atoms) approximation using the SHELXL-97 program. The H atom positions were located geometrically.

CCDC 713036 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2009.