

Preparative Synthesis of Cyclohexanone Oxime Esters

E. A. Dikumar and N. A. Zhukovskaya

Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus,
ul. Surganova 13, Minsk, 220072 Belarus
e-mail: evgen_58@mail.ru

Received November 20, 2007

Abstract—Preparative procedures have been developed for the synthesis of cyclohexanone oxime esters by acylation of cyclohexanone oxime with carboxylic acid anhydrides in the presence of perchloric acid or with carboxylic acid chlorides in the presence of pyridine.

DOI: 10.1134/S1070428008090248

We previously reported on the synthesis of menthone oxime esters that attract interest as grassy and fruity aromatizers for perfumery and food industry [1]. The goal of the present work was to develop preparative procedures for the synthesis of cyclohexanone oxime esters. Cyclohexanone oxime (**I**) is an accessible and relatively inexpensive reagent which is widely used in industry for separation and concentration of chemical elements [2]. We anticipated that esters derived from cyclohexanone oxime (**I**) could possess a pleasant odor. Comparison of the odors of esters derived from cyclohexanone and menthone (2-isopropyl-5-methylcyclohexanone) oximes [1] should make it possible to estimate the contribution of substituents in the cyclohexane ring to variation of their odor.

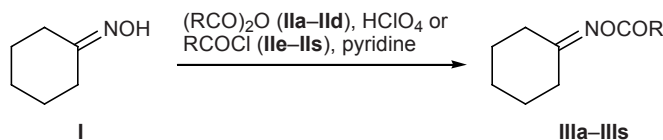
Cyclohexanone oxime esters were synthesized by reaction of cyclohexanone oxime (**I**) with aliphatic carboxylic acid anhydrides **IIa–IId** in hexane in the presence of a catalytic amount of 57% HClO₄ or with aliphatic and aromatic acid chlorides **IIe–IIs** in hexane in the presence of pyridine (Scheme 1). The reactions were carried out by mixing equimolar amounts of the reactants, followed by keeping the mixture for 24–48 h at 20–23°C. Neither strong external cooling nor pro-

longed stirring was necessary. The corresponding cyclohexanone oxime esters **IIIa–IIIs** were isolated in 87–92% yield.

Compounds **IIIa–IIIs** are colorless liquids or crystalline substances. They were isolated sufficiently pure (they contained no impurities of initial compounds, hexane, or pyridine), so that they can be used directly in perfume and food industry [3]. According to the ¹H NMR data, the purity of oxime esters **IIIa–IIIs** was 97–98%. Compounds **IIIa–IIIs** can be stored for a long time at a temperature below 5°C with protection from light and atmospheric oxygen.

The IR, UV, and ¹H NMR spectra of cyclohexanone oxime esters **IIIa–IIIs** were consistent with their structure. The IR spectra of **IIIa–IIIs** contained absorption bands in the regions 3000–2800 (C–H_{aliph}), 1765–1740 (C=O), 1642–1638 (C=N), 1470–1450 (CH₂), and 1200–1050 cm⁻¹ (C–O); esters **IIIn–IIIq** derived from aromatic carboxylic acids displayed in the IR spectra absorption bands at 3100–3000 and 900–680 (C–H_{arom}) and 1600–1320 cm⁻¹ (C–C_{arom}); in the IR spectrum of **IIIq** the C=C stretching vibration band was located at 1631 cm⁻¹. The electronic spectra of cyclohexanone oxime esters **IIIa–IIIm**, **IIIr**, and **IIIs** showed an absorption maximum at λ 208 nm (ε = 8000); compound

Scheme 1.



R = Me (**a**), Et (**b**), Pr (**c**), *i*-Pr (**d**), Bu (**e**), *i*-Bu (**f**), Me(CH₂)₄ (**g**), Me(CH₂)₅ (**h**), Me(CH₂)₆ (**i**), Me(CH₂)₇ (**j**), Me(CH₂)₈ (**k**), Me(CH₂)₁₁ (**l**), *cyclo*-C₆H₁₁ (**m**), Ph (**n**), Ph(CH₂)₂ (**o**), PhCH(Me)CH₂ (**p**), *trans*-PhCH=CH (**q**), MeO (**r**), EtO (**s**).

III_n was characterized by absorption maxima at λ 208 ($\epsilon = 23\,000$), 225 ($\epsilon = 14\,000$), and 260 nm ($\epsilon = 12\,000$); oximes esters **III_o** and **III_p** showed a maximum at λ 209 nm ($\epsilon = 15\,000$); absorption maxima of **III_s** were observed at λ 208 ($\epsilon = 30\,000$), 223 ($\epsilon = 23\,000$), 274 ($\epsilon = 20\,000$), and 290 nm ($\epsilon = 4\,000$).

In the ^1H NMR spectra of **III_a–III_s** protons in the cyclohexane ring resonated in the region δ 1.55–2.85 ppm; protons of the acetyl group in **III_a** gave a singlet at δ 2.12 ppm; signal from the methoxy group of methyl carbonate **III_r** was located at δ 3.85 ppm (s); signals from the EtCOO and EtO groups of **III_b** and **III_s** appeared as triplets at δ 1.15–1.23 ppm (Me) and quartets at δ 2.30–2.42 ppm (CH_2); the Me_2C group in **III_e** gave a doublet at δ 1.22 ppm; and aromatic protons in compounds **III_n–III_q** resonated in the region δ 7.00–8.30 ppm.

Organoleptic evaluation of cyclohexanone oxime (**I**) and its esters **III_a–III_s** was performed by the Degustation Council at the Tereza-Inter Ltd. Control Analytical Laboratory (Moscow). No odor was revealed for pure samples of cyclohexanone oxime (**I**) and its *O*-acetyl derivatives **III_a–III_s**.

EXPERIMENTAL

The IR spectra were recorded from films (neat) or KBr pellets on a Nicolet Protege-460 spectrometer. The UV spectra were measured from 1×10^{-3} M solutions in methanol on a Specord UV-Vis spectrophotometer. The ^1H NMR spectra were obtained from 5% solutions in chloroform-*d* on a Tesla BS-587A instrument at 100 MHz; the chemical shifts were determined relative to tetramethylsilane as internal reference. The molecular weights were determined by cryoscopy in benzene.

Commercial cyclohexanone oxime (**I**) with a purity of 97% was used, mp 89–91°C.

Cyclohexanone oxime esters III_a–III_s (general procedure). *a.* Cyclohexanone oxime (**I**), 0.01 mol, and carboxylic acid anhydride **II_a–II_d**, 0.011 mol, were dissolved in 30 ml of hexane, one drop of 57% perchloric acid was added, and the mixture was stirred by shaking and was left to stand for 24–36 h at 20–23°C. The mixture was then diluted with water and extracted with hexane, the organic phase was separated, washed with water and a 5% solution of sodium hydrogen carbonate, and dried over CaCl_2 , and the solvent was removed under reduced pressure (30–45 mm) at a temperature not exceeding 25–30°C.

Cyclohexanone *O*-acetyloxime (III_a). Yield 87%, $d_{20}^{20} = 0.9870$, $n_D^{20} = 1.4835$. Found, %: C 62.24; H 8.51; N 8.76. *M* 144.7. $\text{C}_8\text{H}_{13}\text{NO}_2$. Calculated, %: C 61.91; H 8.44; N 9.03. *M* 155.2.

Cyclohexanone *O*-propanoyloxime (III_b). Yield 88%, $d_{20}^{20} = 0.9856$, $n_D^{20} = 1.4825$. Found, %: C 64.07; H 9.10; N 8.09. *M* 157.9. $\text{C}_9\text{H}_{15}\text{NO}_2$. Calculated, %: C 63.88; H 8.93; N 8.28. *M* 169.2.

Cyclohexanone *O*-butanoyloxime (III_c). Yield 89%, $d_{20}^{20} = 0.9833$, $n_D^{20} = 1.4800$. Found, %: C 65.83; H 9.52; N 7.41. *M* 171.3. $\text{C}_{10}\text{H}_{17}\text{NO}_2$. Calculated, %: C 65.54; H 9.35; N 7.64. *M* 183.2.

Cyclohexanone *O*-(2-methylpropanoyl)oxime (III_d). Yield 88%, $d_{20}^{20} = 0.9521$, $n_D^{20} = 1.4775$. Found, %: C 65.72; H 9.39; N 7.35. *M* 176.4. $\text{C}_{10}\text{H}_{17}\text{NO}_2$. Calculated, %: C 65.54; H 9.35; N 7.64. *M* 183.2.

b. Anhydrous pyridine, 0.01 mol, was added to a solution of 0.01 mol of cyclohexanone oxime (**I**) in 50 ml of hexane, the mixture was cooled to 15°C, and 0.01 mol of carboxylic acid chloride **II_e–II_s** was added under careful shaking. The mixture was left to stand for 24–36 h at 20–23°C, diluted with water, and extracted with hexane. The organic phase was separated, washed with water and a 5% solution of sodium hydrogen carbonate, and dried over CaCl_2 . The solvent was removed under reduced pressure (30–45 mm) at a temperature not exceeding 25–30°C.

Cyclohexanone *O*-pentanoyloxime (III_e). Yield 91%, $d_{20}^{20} = 0.9688$, $n_D^{20} = 1.4745$. Found, %: C 67.20; H 9.86; N 6.90. *M* 190.0. $\text{C}_{11}\text{H}_{19}\text{NO}_2$. Calculated, %: C 66.97; H 9.71; N 7.10. *M* 197.3.

Cyclohexanone *O*-(3-methylbutanoyl)oxime (III_f). Yield 89%, $d_{20}^{20} = 0.9389$, $n_D^{20} = 1.4765$. Found, %: C 67.14; H 9.84; N 6.85. *M* 188.3. $\text{C}_{11}\text{H}_{19}\text{NO}_2$. Calculated, %: C 66.97; H 9.71; N 7.10. *M* 197.3.

Cyclohexanone *O*-hexanoyloxime (III_g). Yield 89%, $d_{20}^{20} = 0.9556$, $n_D^{20} = 1.4765$. Found, %: C 68.36; H 10.15; N 6.42. *M* 204.5. $\text{C}_{12}\text{H}_{21}\text{NO}_2$. Calculated, %: C 68.21; H 10.02; N 6.63. *M* 211.3.

Cyclohexanone *O*-heptanoyloxime (III_h). Yield 87%, $d_{20}^{20} = 0.9213$, $n_D^{20} = 1.4765$. Found, %: C 69.55; H 10.31; N 5.97. *M* 214.8. $\text{C}_{13}\text{H}_{23}\text{NO}_2$. Calculated, %: C 69.30; H 10.29; N 6.22. *M* 225.3.

Cyclohexanone *O*-octanoyloxime (III_i). Yield 90%, $d_{20}^{20} = 0.9599$, $n_D^{20} = 1.4770$. Found, %: C 70.43; H 10.65; N 5.70. *M* 222.8. $\text{C}_{14}\text{H}_{25}\text{NO}_2$. Calculated, %: C 70.25; H 10.53; N 5.85. *M* 239.4.

Cyclohexanone *O*-nonanoyloxime (III_j). Yield 92%, $d_{20}^{20} = 1.0158$, $n_D^{20} = 1.4750$. Found, %: C 71.38;

H 10.96; N 5.22. M 239.0. $C_{15}H_{27}NO_2$. Calculated, %: C 71.10; H 10.74; N 5.53. M 253.4.

Cyclohexanone *O*-decanoyloxime (IIIk). Yield 89%, mp 24–25°C. Found, %: C 72.03; H 11.05; N 5.02. M 258.4. $C_{16}H_{29}NO_2$. Calculated, %: C 71.87; H 10.93; N 5.24. M 267.4.

Cyclohexanone *O*-tridecanoyloxime (IIIl). Yield 90%, mp 35–36°C. Found, %: C 73.91; H 11.45; N 4.23. M 295.6. $C_{19}H_{35}NO_2$. Calculated, %: C 73.74; H 11.40; N 4.53. M 309.5.

Cyclohexanone *O*-(cyclohexylcarbonyl)oxime (IIIm). Yield 88%, $d_{20}^{20} = 1.0708$, $n_D^{20} = 1.5050$. Found, %: C 70.18; H 9.56; N 6.04. M 217.7. $C_{13}H_{21}NO_2$. Calculated, %: C 69.92; H 9.48; N 6.27. M 223.3.

Cyclohexanone *O*-benzoyloxime (III n). Yield 87%, mp 56–57°C. Found, %: C 72.12; H 7.08; N 6.12. M 208.4. $C_{13}H_{15}NO_2$. Calculated, %: C 71.87; H 6.96; N 6.45. M 217.3.

Cyclohexanone *O*-(3-phenylpropanoyl)oxime (IIIo). Yield 88%, $d_{20}^{20} = 1.1226$, $n_D^{20} = 1.5410$. Found, %: C 73.69; H 7.96; N 5.45. M 229.6. $C_{15}H_{19}NO_2$. Calculated, %: C 73.44; H 7.81; N 5.71. M 245.3.

Cyclohexanone *O*-(3-phenylbutanoyl)oxime (IIIp). Yield 91%, $d_{20}^{20} = 1.1609$, $n_D^{20} = 1.5345$. Found,

%: C 74.45; H 8.24; N 5.08. M 241.8. $C_{16}H_{21}NO_2$. Calculated, %: C 74.10; H 8.16; N 5.40. M 259.3.

Cyclohexanone *O*-[(*E*)-3-phenylprop-2-enoyl]oxime (IIIq). Yield 90%, mp 85–86°C. Found, %: C 74.37; H 7.22; N 5.58. M 231.7. $C_{15}H_{17}NO_2$. Calculated, %: C 74.05; H 7.04; N 5.76. M 243.3.

Cyclohexanone *O*-(methoxycarbonyl)oxime (IIIr). Yield 88%, mp 27–28°C. Found, %: C 56.36; H 7.71; N 7.89. M 160.1. $C_8H_{13}NO_3$. Calculated, %: C 56.13; H 7.66; N 8.18. M 171.2.

Cyclohexanone *O*-(ethoxycarbonyl)oxime (III s). Yield 87%, $d_{20}^{20} = 1.1160$, $n_D^{20} = 1.4735$. Found, %: C 58.54; H 8.39; N 7.31. M 179.4. $C_9H_{15}NO_3$. Calculated, %: C 58.36; H 8.16; N 7.56. M 185.2.

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