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A Simple Synthesis of Oximes

Ivan Damljanović, Mirjana Vukićević, and **Rastko D. Vukićević**[*]

Department of Chemistry, Faculty of Science, University of Kragujevac,
R. Domanovića 12, 34000 Kragujevac, Serbia and Montenegro

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Summary. The conversion of alicyclic and aliphatic carbonyl compounds as well as aromatic aldehydes into the corresponding oximes (up to quantitative yields) was achieved by simply grinding these reactants, hydroxylamine hydrochloride and sodium hydroxide without solvent. However, this procedure was unsuccessful in the case of aromatic ketones. In this case it was necessary to add silica gel as a catalyst.

Keywords. Solid-phase synthesis; Hydroxyimination; Aldehydes; Ketones; Oximes.

Introduction

Numerous functional group transformations of oximes make them very important in synthetic organic chemistry. Among other synthesis applications, these compounds were successfully transformed into amides [1], amines [2], hydroxylamines [3], hydroxylamine *O*-ethers [4], nitroalkanes [5], 1,3-oxazoles, -thiazoles, and -diazoles [6], *etc*. Therefore, synthetic organic chemists are interested in a facilitation of oxime synthesis. Although alternative methods exist [7] reaction of carbonyl compounds with hydroxylamine hydrochloride remains still the most important route. The classical method involves refluxing of an alcoholic solution of these reactants in the presence of sodium acetate or hydroxide [8].

Many improvements of this methodology have been described. Thus, treatment of ketones with hydroxylamine hydrochloride in the presence of an ion-exchange resin (Amberlyst A-21) as the catalyst in ethanol gave oximes in high yields at room temperature and with a simple work-up procedure [9]. Recently, it has been reported that silica gel in the presence of a base [10], or without any base, but coupled with microwave irradiation [11], could be a useful catalyst for this condensation. Similarly to that, irradiation of carbonyl compounds and hydroxylamine hydrochloride impregnated on wet basic Al_2O_3, or grinding them with molecular sieves

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[*] Corresponding author. E-mail: vuk@kg.ac.yu

gave the corresponding oximes [12]. High yields of hydroxyiminocycloalkanes could be also achieved by treatment of the corresponding ketones with hydroxylamine or its salts in ionic liquids and in the presence of additives, such as sodium acetate [13].

Recently, we required considerable amounts of several oximes of aliphatic and alicyclic ketones as starting materials in a more comprehensive synthesis project and carried out extensive re-examination of this reaction. Herein, we report on our findings, which resulted in a quick, simple, and extremely efficient method of oxime synthesis without a solvent, in most cases also without a catalyst, heating, or microwave irradiation.

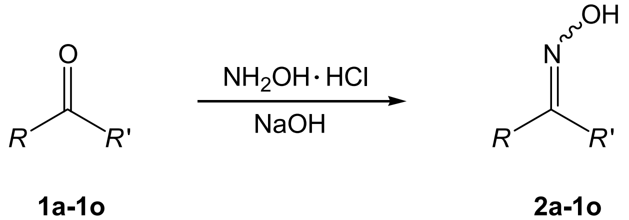
Results and Discussion

First of all, we found that cyclic ketones, such as cyclopentanone (**1a**), cyclohexanone (**1b**), 4-*tert*-butylcyclohexanone (**1c**), and cycloheptanone (**1d**) could be transformed into the corresponding oximes by simple grinding (30–40 min) at room temperature (in a mortar with a pestle) with 1.2 equivalents of hydroxylamine hydrochloride and sodium hydroxide without any catalyst and solvent. Also, there was no need to heat the reaction mixture or to expose it to microwave irradiation. Oximes of very high purity were isolated in excellent yields (85–100%) working in 1, 10, and 50 mmol scales (Scheme 1 and Table 1).

Very similar results were obtained with aliphatic unsaturated carbonyls **1e**–**1h** as well as aromatic aldehydes **1i**–**1l**. These were converted into mixtures of the corresponding (*E*)- and (*Z*)-oximes in 75–98% yields.

In contrast to that, aromatic ketones like acetophenone (**1m**), 2-hydroxyacetophenone (**1n**), and benzophenone (**1o**) did not undergo this reaction even after several hours grinding, so that the corresponding substrates were recovered unchanged. However, if a small amount of silica gel (0.4, 2.0, and 8.0 g for 1, 10, and 50 mmol scales) was added these ketones also could be transformed into their oximes in good yields (up to 98%).

In order to evaluate the preparative value of the present methodology we carried out this reaction with 0.5 mol of cyclohexanone. Hydroxyiminocyclohexane was obtained in high yield, but because of gentle heat production the procedure was slightly modified: to the grinded mixture of cyclohexanone and hydroxylamine hydrochloride sodium hydroxide was added in portions (2–3 g) during one hour.

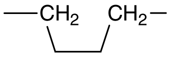
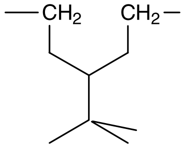
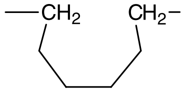
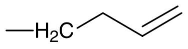
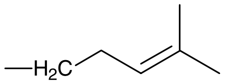
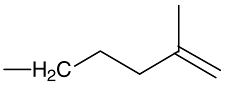
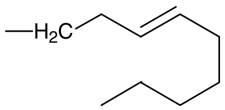


1a-1o **2a-1o**

R, *R*' = cycloalkyl; *R*, *R*' = alkyl; *R* = H, *R*' = alkyl or aryl

Scheme 1

Table 1. Synthesis of oximes from the corresponding carbonyls[a]

Substrate	*R*	*R′*	Time/min	Silica gel	Products	Yield/%[b]
1a			30	None	**2a**	95–100
1b[c]			30	None	**2b**	95–100
1c			40	None	**2c**	89–96
1d			40	None	**2d**	85–90
1e	–CH_3		30	None	**2e**	85–91
1f	–CH_3		40	None	**2f**	85–91
1g	–CH_3		40	None	**2g**	75–80
1h	–H		40	None	**2h**	95–97
1i	–H	–C_6H_5	120	None	**2i**	87–93
1j	–H	–C_6H_4OH-4	60	None	**2j**	87–91
1k	–H	–$C_6H_4OCH_3$-4	60	None	**2k**	91–95
1l[d]	–H	–$C_6H_4N(CH_3)_2$-4	30	None	**2l**	93–98
1m	–CH_3	–C_6H_5	60	Yes[e]	**1m**	72–75
1n	–CH_3	–C_6H_4OH-4	60	Yes[e]	**1n**	93–98
1o	–C_6H_5	–C_6H_5	60	Yes[e]	**1o**	92–97

[a] Reactions were carried out in 1, 10, and 50 mmol scales in a molar ratio of reactants substrate/$NH_2OH{\cdot}HCl$/NaOH = 1/1.2/1.2, if it is not noted differently; [b] isolated yields based on the starting substrate; [c] the reaction was carried out also in a 0.5 mol scale (see text); [d] molar ratio of reactants substrate/$NH_2OH{\cdot}HCl$/NaOH = 1/3/3; after noted grinding time the reaction mixture was allowed to react over night; [e] 0.4, 2.0, and 8.0 g for 1, 10, and 50 mmol scales

In conclusion, these results point to an extremely simple, suitable, and efficient method for the conversion of carbonyl compounds to the corresponding oximes.

Experimental

All chemicals used were commercially available and were used as received. IR spectra were measured with a Perkin-Elmer 457 grating FT instrument. NMR spectra were recorded on a Varian Gemini 200 spectrometer using $CDCl_3$ as the solvent. Chemical shifts are expressed in ppm using *TMS* as an internal standard.

General Procedure

In a typical procedure for 1, 10, and 50 mmol range, the reactants in the molar ratio carbonyl compound/$NH_2OH{\cdot}HCl$/NaOH = 1/1.2/1.2 were grinded in a mortar with a pestle at room temperature for 10 min. Then the mixture was ground from time to time for the time indicated in Table 1. The reaction mixture was then washed with H_2O to remove inorganic salts and the residue dried on air. The corresponding oximes were pure enough for spectral characterization (IR, ^1H and ^{13}C NMR), but purification by recrystallization was necessary for melting points determinations. In the case of liquid products the reaction mixture was carefully extracted with ether or CH_2Cl_2, the organic phase washed with H_2O, dried (Na_2SO_4), and the solvent evaporated. Yields are given in Table 1.

In the 0.5 mol range hydroxyimination of cyclohexanone, 49 g of this ketone and 41.7 g $NH_2OH{\cdot}HCl$ were ground and 24 g of NaOH were added subsequently in ten portions (1 h), grinding the mixture continuously. The solid obtained was washed with H_2O and dried on air giving 56.5 g (97%) of hydroxyiminocyclohexane.

Almost all derived oximes are known compounds and their spectral data, as well as melting points of solids, were in agreement with those known. Herein we give spectral data only for **2g** and **2h**, which could not be found in literature.

(E)- and (Z)-2-Hydroxyimino-6-methyl-6-heptene (**2g**, $C_8H_{15}NO$)

Educt **1g** (1.26 g) afforded 1.13 g (80%) **2g** as a colorless liquid. IR (film): $\bar{\nu} = 3234$, 3076, 1651, 1446, 1374, 1255, 1151, 1074, 953, 886, 741 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 9.22$ (br. s, OH), 4.70 (m, CH_2-7), 2.37 and 2.19 (2 m, altogether 2H at C2 of both isomers in a 3:1 ratio), 2.02 (t, $J = 7.7$ Hz, CH_2-5), 1.89 and 1.87 (2s, altogether 3H at C1 of both isomers in a 3:1 ratio), 1.51–1.72 (m, CH_2-4 + CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 13.4$, 19.9, 22.3, 23.4, 24.1, 28.3, 35.3, 37.1, 37.6110.2, 110.3, 145.1, 159.4, 159.6 ppm.

(1E,5E)- and (1Z,5E)-1-Hydroxyimino-5-decene (**2h**, $C_{10}H_{19}NO$)

Educt **1h** (0.154 g) afforded 0.162 g (96%) **2h** as a colorless liquid. IR (film): $\bar{\nu} = 3253$, 2956, 2924, 2855, 1665, 1444, 1378, 1339, 1139, 1073, 967, 930, 726 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.67$ (br. s, OH), 7.42 and 6.72 (2t, $J = 5.8$ and 5.2 Hz, altogether CH-1 of both isomers in a 1:1.07 molar ratio), 5.45 (m, 2H olefinic), 2.44 and 2.21 (2 m, altogether 4H at C2 and one of the allylic position of both isomers), 1.97 (m, 2H at the other allylic position), 1.28 (m, 6H at C7, C8, and C9), 0.88 (t, $J = 6.7$ Hz, CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 14.0$, 22.5, 24.7, 28.8, 29.1, 29.2, 29.5, 31.3, 32.5, 127.9, 128.1, 132.0, 132.1, 151.7, 152.3 ppm.

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References

[1] Frutos RP, Spero DM (1998) Tetrahedron Lett **39**: 2475
[2] a) Sasatani S, Miyazak T, Maruoka K, Yamamoto H (1983) Tetrahedron Lett **24**: 4711; b) Negi S, Matsukura M, Mizuno M, Miyake K (1996) Synthesis 991
[3] Das MK, Bhaumik A (1997) Indian J Chem Sect B **36**: 1020
[4] Miyabe H, Ushiro C, Naito T (1997) Chem Commun 1789
[5] Bose DS, Vanajatha G (1998) Synth Commun **28**: 4531
[6] Bougrin K, Loupy A, Souaoui M (1998) Tetrahedron **54**: 8055
[7] See, for example: a) Hanson JR (1974) Synthesis 1; b) Barton DHR, Fernandez I, Richard CS, Zard S (1987) Tetrahedron **43**: 551; c) Albanese D, Landini D, Penso M (1990) Synthesis 333;

d) Kizil M, Murphy JA (1997) Tetrahedron **53**: 16847; e) Hwu JR, Tseng WN, Patel HV, Wong FF, Horng DN, Liaw BR, Lin LC (1999) J Org Chem **64**: 2211

[8] a) Beckman E (1890) Chem Ber **23**: 1680; b) Beckman E (1909) Liebigs Ann Chem **365**: 200

[9] Ballini R, Barboni L, Filippone P (1997) Chem Lett 475

[10] Hajipour AR, Mohammadpoor-Baltrok I, Nikbaghat K, Imanzadeh G (1999) Synth Comm **29**: 1697

[11] Hajipour AR, Mallakpour SE, Imanzadeh GJ (1999) Chem Research (S) 228

[12] Kad GL, Bhandari M, Kaur J, Rathee R, Singh J (2001) Green Chemistry **3**: 275

[13] Ren RX, Ou W (2001) Tetrahedron Lett **42**: 8445