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Simple, Efficient and Green Synthesis of Oximes under Ultrasound Irradiation

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ABSTRACT

The condensation of aldehydes and ketones with hydroxylamine hydrochloride gives oximes in 81–95 % yields in water and EtOH under ultrasound irradiation. Compared to conventional methods, the main advantages of the present procedure are milder reaction conditions, shorter reaction times and higher yields.

KEYWORDS

Condensation, oxime, ultrasonication, aldehydes, ketones.

1. Introduction

The chemical applications of ultrasound, 'Sonochemistry', have become an exciting new field of research during the past decade and increasingly used in organic synthesis in recent years. This is because a large number of organic reactions can be carried out in higher yields, shorter reaction times and milder conditions under ultrasonic irradiation.[1]

Ultrasonication can accelerate many reactions as well as condensation of aldehydes and ketones with hydroxylamine hydrochloride. This may be due to the fact that the power of ultrasound (20–100 kHz, >10 W/cm^2) uses the energy to create cavitations, which involve the formation, growth, and implosive collapse of microscopic bubbles in a liquid. These bubbles are generated when the 'negative' pressure during the rarefaction phase of the sound wave is sufficiently large to disrupt the liquid. The implosive collapse of the bubbles can locally produce extreme temperatures and pressures (5000 °C, 20 MPa) for very short times, because of compression of the gas phase inside the cavity. These hotspots can lead to irreversible changes such as the formation of excited states, bond breakage, and the generation of radicals.[2]

Oximes are important in organic synthesis not only for protection, characterization and purification of carbonyl compounds, but also for various functional group transformations such as into nitriles,[3] nitro compounds,[4] nitrones,[5] amines,[6] *gem*-dichloroalkanes,[7] and isoxazolines.[8] It has also been revealed that reactions which involve oxime derivatives of acylgermanes lead to much greater enhancement in cyclization rate constants. Some oxime derivatives present a fungitoxic and herbicide effect,[9–11] or act as growth regulators for plants.[12] Therefore, the wide range of applications of oximes has led to new procedures for their preparation. The standard method for the preparation of oximes is treating an alcoholic solution of a carbonyl compound with hydroxylamine hydrochloride and pyridine at 60 °C.[13] Oximes have also been synthesized from nitriles,[14] phosphinium compounds[15] and via microwave irradiation.[16] In addition to selective preparation of E and Z isomers of oximes,[17] and efficient preparation of aldoximes in water,[18] there is a report on using sonication for the synthesis of oximes in the presence of Na_2SO_4.[19] However each of these methods has its own drawbacks and/or disadvantages.

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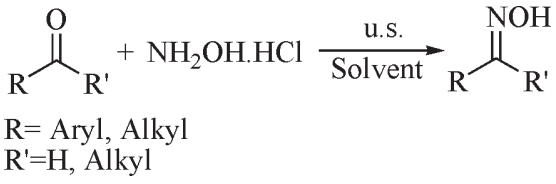
To eliminate the unnecessary steps and/or use of chlorinated solvents outlined in the last report we have developed a very simple, efficient and easy to perform procedure for the preparation of oximes. In this simple procedure, a mixture of a carbonyl compound and hydroxylamine hydrochloride was exposed to sonication for 2 min. Adjusting the pH at ~10 by drop-wise addition of 10% solution of K_2CO_3 under sonication led to the precipitation of the corresponding oximes in excellent yields without further purification. The only cases which needed extraction with diethyl ether were entries 1 and 3 of Table 1 due to solubility problems. In the case of aldoximes, both the melting point and chemical shift of CH group indicated the formation of nearly pure E forms (see Table 1 and experimental section). Comparison of the required times for ketones (entries 13 and 14) shows that this procedure works well for unhindered ketones. In the case of acetophenone (entry 14) we found practically no difference between traditional and sonication procedures: the required times are nearly the same.

2. Results and Discussion

The condensation of primary amines with RR'C=O compounds was first reported by Schiff in 1864 and since then a great number of such reactions were performed and reviewed[23]. When hydroxylamine is employed, the condensation gives oximes, along with water as a by product. The experimental conditions depend mostly on the nature of the parent materials and basicity of the reaction medium; usually, reactions proceed smoothly at pH close to neutral.

Literature survey shows that there are few reports on oximation of aldehydes by ultrasonication, one of which being a report by Li *et al.*[19] in which they have made use of anhydrous Na_2SO_4 in the course of reaction; though the role of this compound remains unclear. According to their report, the reaction times were much higher in the absence of Na_2SO_4. However, as



R= Aryl, Alkyl
R'=H, Alkyl

Scheme 1

Table 1 Conversion of aldehydes and ketones to their oximes.

Entry	Solvent [a]	Reactant	t/min [b]	t/min [e]	t/min [f]	Mp/°C [c]	Yield/%
1	H_2O	C_6H_5CHO	Immediately	5	10	31–33 (35)	91
2	H_2O, 1 mL EtOHd, H^+	4-$CH_3OC_6H_4HO$	Immediately	180	180	59–62 (65)	95
3	H_2O, 2 mL EtOHd	3-HOC_6H_4CHO	–	Immediately	83–86 (87–88)	94	
4	H_2O	2-HOC_6H_4CHO	Immediately	–	54–58 (57–59)	91	
5	H_2O, 3 mL EtOH [d], H^+	4-$(CH_3)_2NC_6H_4CHO$	2	20	30	143–147 (144)	94
6	H_2O, 2 mL EtOH	2-ClC_6H_4CHO	2	20	140	74–78 (75–76)	92
7	H_2O	3-$O_2NC_6H_4CHO$	<1	15	20	122–124 (121–3)	91
8	H_2O	2,4-$Cl_2C_6H_3CHO$	3	5	15	135–139 (136–7)	94
9	H_2O	4-ClC_6H_4CHO	3	10	30	110–114 (110)	89
10	H_2O, 1 mL EtOH [d]	4-$O_2NC_6H_4CHO$	<1	15	110	128–133 (133)	93
11	H_2O, 1 mL EtOH [d]	4-$CH_3C_6H_4CHO$	3	–	75–79 (79–80)	92	
12	H_2O, 3 mL EtOH [d]	$C_6H_5CH{=}CHCHO$	3	–	69.5–72 (69–70)	92	
13	H_2O	Cyclohexanone	<1	10	20	89–91 (89–90)	81
14	H_2O, 5 mL EtOH [d]	$C_6H_5COCH_3$	240	120	120	61–63 (59.5–60.5)	83

[a] Two additional drops of concentrated HCl.
[b] Times for the reaction to complete (after addition of K_2CO_3 solution).
[c] Numbers in brackets refer to the reported melting points (ref. 21).
[d] 96% Ethanol.
[e,f] Ref. 19 in the presence and absence of Na_2SO_4, respectively.

Table 1 shows, the advantages of the present procedure over the one reported by these authors are much shorter reaction times and the elimination of Na_2SO_4. Furthermore, as the oximes are precipitated by the addition of K_2CO_3, there is also no need to use CH_2Cl_2 for their extraction which, according to Li *et al.*[19], must be followed by column chromatography.

As is mentioned in Table 1, in the case of entries 2 and 5, it is necessary to add two drops of concentrated HCl to the reaction media to make it more acidic; the reaction times are approximately 14 minutes without additional HCl drops. It is presumably due to the resonance effect of lone pair electrons of methoxy and amino groups.

In short, we have developed a green (with respect to the reports using toxic solvents such as tetrahydofuran,[24] dichlorimethane[25] and benzene[26]), rapid and efficient procedure for the preparation of aldoximes and unhindered ketoximes. As compared to the other reported methods,[16,17,19] this procedure is very fast (immediately or 1–3 minutes) except for acetophenone. The reactions are easy to perform, water or water-ethanol is taken as solvent and the products are formed in good to excellent yields.

3. Experimental

Melting point apparatus Stuart model SMP3 was used for measuring melting points. IR and ^{1}H NMR spectra were recorded on a PerkinElmer series II spectrum GX and JEOL FX90Q, respectively. Sonication was performed with an Elma Ultrasonic Cleaner Model T660/H at a frequency of 35 kHz and nominal power 360 W.

All chemicals and solvents were purchased from Aldrich, Merck and Fluka, and were used as received. Melting points and spectral data of all products are fully consistent with those of the reported ones.[17,18,20–22]

3.1. General Procedure

In a 50 mL beaker equipped with a mechanical stirrer and containing 10 mL of the appropriate solvent (either water or water-ethanol mixture), 1 mmol of the carbonyl compound was dissolved. The beaker was immersed in the water of the sonicator bath, the temperature of which was approximately 60 °C. To the above solution was added 1.5 mmol $NH_2OH.HCl$ in 1–2 mL of water. The whole mixture was then sonicated for 2 min during which, the pH was adjusted at approximately 10 by the drop-wise addition of a 10 % solution of K_2CO_3 in water. Sonication was continued and the reaction was monitored by TLC (the time mentioned in Table 1 is the time required for completion of the reaction). The precipitate was filtered, washed with water and air-dried without further purification.

3.2. Spectral Data

Note: All reported melting points in brackets are those cited in ref. 21.

E-Benzaldoxime: mp: 31–33 °C (Lit. 35 °C)
IR, liquid film (cm^{-1}): 3446, 1956, 1894, 1632, 1495, 1448, 1303, 1211, 1075, 956, 870, 756,692
^{1}H NMR: ($CDCl_3$): δ 7.35–7.62 (m, 5H, aromatic), 8.28 (s, 1H, CH), 10.23 (s, 1H, OH)

E-4-Methoxybenzaldoxime: mp: 59–62 °C (Lit. 65 °C)
IR, KBr (cm^{-1}): 3315, 1607, 1574, 1514, 1455, 1305, 1252, 1170, 1027, 961, 872, 826, 592.
^{1}H NMR: ($CDCl_3$): δ 3.82 (s, 3H, CH_3), 6.86–7.58(dd, 4H, aromatic), 8.13(s, 1H, CH), 8.63 (s, 1H,OH)

E-3-Hydroxybenzaldoxime: mp: 83–86 °C (Lit. 87–88 °C)
IR, KBr (cm^{-1}): 3330, 1631, 1593, 1454, 1317, 1261, 1172, 972, 784, 685, 642
^{1}H NMR: ($CDCl_3$): δ 6.811–7.26 (m, 5H, aromatic), 8.09 (s, 2H)

E-2-Hydroxybenzaldoxime: mp: 54–58 °C (Lit. 57–59 °C)
IR, KBr (cm^{-1}): 3378, 1619, 1577, 1496, 1412, 1289, 1258, 992, 900, 648
^{1}H NMR: ($CDCl_3$): δ 6.85–7.41(m, 4H, aromatic), 7.80 (s, 1H, OH), 8.24 (s, 1H, CH), 9.99 (s,1H, OH)

E-4-*N*,*N*-Dimethylaminobenzaldoxime: mp: 143–147 °C (Lit. 144 °C)
IR, KBr (cm^{-1}): 3244, 1609, 1527, 1363, 1186, 1128, 957, 869, 812, 736, 572
^{1}H NMR: ($CDCl_3$): δ 3.00 (s, 6H, CH_3), 6.063–7.51 (dd, 4H, aromatic), 8.07 (s, 1H, CH), 8.55 (s, 1H, OH)

E-2-Chlorobenzaldoxime: mp: 74–78 °C (Lit. 75–76 °C)
IR, KBr (cm^{-1}): 3281, 1592, 1481, 1441, 1311, 1209, 1052, 972, 753, 711, 630
^1H NMR: ($CDCl_3$): δ 7.24–7.88 (m, 4H, aromatic), 8.54 (s, OH, assigned by D_2O), 8.57 (s, 1H, CH)

E-3-Nitrobenzaldoxime: mp: 122–124 °C (Lit. 121–123 °C)
IR, KBr (cm^{-1}): 3300, 1619, 1536, 1467, 1351, 980, 734, 670
^1H NMR: ($CDCl_3$): δ 7.26 (s, 1H), 7.75 (t, 1H), 7.86(d, 1H), 8.21 (d, 1H), 8.44 (s, 1H)

E-2,4-Dichlorobenzaldoxime: mp: 135–139 °C (Lit. 136– 137 °C)
IR, KBr (cm^{-1}): 3297, 1584, 1484, 1387, 1319, 1108, 1052, 976, 877, 817, 669, 560
^1H NMR: ($CDCl_3$): δ 7.19–7.82(m, 3H, aromatic), 8.12 (s, 1H, OH), 8.50(s, 1H, CH)

E-4-Chlorobenzaldoxime: mp: 110–114 °C (Lit. 110 °C)
IR, KBr (cm^{-1}): 3299, 1596, 1494, 1399, 1318, 1088, 972, 874, 824, 693
^1H NMR: ($CDCl_3$): δ 7.21–7.58 (dd, 4H, aromatic), 8.12 (s, 1H, CH), 8.28 (s, OH)

E-4-Nitrobenzaldoxime: mp: 128–133 °C (Lit. 133 °C)
IR, KBr (cm^{-1}): 3303,1605, 1536, 1349, 1321, 1108, 970, 943, 847, 749, 688
^1H NMR: ($CDCl_3$): δ 7.99 (s, OH), 7.69–8.29 (dd, 4H), 8.20 (s, 1H, CH)

E-4-Methylbenzaldoxime: mp: 75–79 °C (Lit. 79–80 °C)
IR, KBr (cm^{-1}): 3270, 1608, 1513, 1437, 1289, 959, 873 ,815, 721
^1H NMR: ($CDCl_3$): δ 2.36 (s, 3H, CH_3), 7.13–7.51 (dd, 4H), 8.12 (s, 1H, CH), 8.46 (s, 1H)

E,E-Cinnamaldoxime: mp: 69.5–72 °C (Lit. 69–70 °C)
IR, KBr (cm^{-1}): 3354, 1630, 1460, 1445, 1339, 1151, 1074 ,980, 956, 747, 691, 569
^1H NMR: ($CDCl_3$): δ 6.84 (d, 1H), 7.26–7.49 (m, 5H), 7.95 (t, 1H), 8.56 (s, OH)

Cyclohexanone oxime: mp: 89–91 °C (Lit. 89–90 °C)
IR, KBr (cm^{-1}): 3184, 3112, 2939, 1665, 1482, 1449, 1252, 1225, 1106, 993, 962, 900, 794
^1H NMR: ($CDCl_3$): δ 1.59–2.49 (10H), 9.54 (s, 1H, OH)

E-Acetophenone oxime: mp: 61–63 °C (Lit. 59.5–60.5 °C)
IR, KBr (cm^{-1}): 3260, 1639, 1573, 1497, 1446, 1370, 1005, 925 760, 693
^1H NMR: ($CDCl_3$): δ 2.36 (s, 3H), 7.38–7.74 (m, 5H, aromatic), 9.47 (s, 1H, OH)

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