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An Efficient Procedure for Synthesis of Oximes by Grinding

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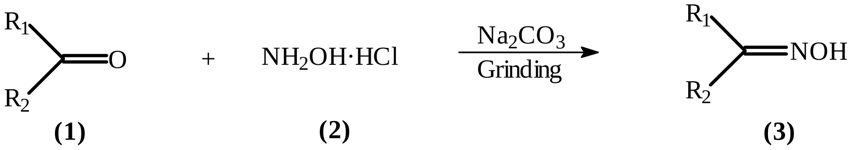
Grinding is a convenient and easily controlled method for synthesis of organic compounds. Condensation of aldehydes with hydroxylamine hydrochlorides leading to oximes has been achieved with high yield by grinding. The advantage of the present method seems to be simple, efficient and environmental friendly.

Key Words: Synthesis, Oximes, Grinding.

INTRODUCTION

Oximes are highly crystalline and the oximation is a very efficient method for characterization and purification of carbonyl compounds. These compounds not only represent a convenient series of carbonyl compounds but also may be used as intermediates for the preparation of amides by the Beckmann rearragement, nitrones[1], hydroximinoyl chlorides[2], nitrile oxide[2] and chiral α-sulfinyl oximes[3]. Furthermore, oximes served for the protection of carbonyl groups as exemplified in the syntheses of erythromycin derivatives and perhydrohistrionicotoxin[4]. Some oximes are highly active tyrosinase inhibitors for skin lightening or antibrowning, because they may be able to complex the two copper atoms in the active site of tyrosinase[5]. Anti-oximes of aldehydes (*e.g.*, benzaldoxime and 4-fluorobenzaldoxime) have proved to be effective inhibitors of aldose reductase rivaling pharmacological agents currently used to inhibit this enzyme *in vivo*[6].

The usual method for the preparation of oximes involves treatment of carbonyl compounds with hydroxylamine hydrochlorides in MeOH[7] or EtOH[8,9] needs higher reaction temperature[5,8,10] and longer reaction time[5,7,8,10]. To the best of our knowledge, there are no literature examples of oximation of aldehyde by grinding. Herein we reported a simple procedure for the preparation of oximes catalyzed by Na_2CO_3 under grinding at room temperature (**Scheme-I**).



Scheme-I

Grinding method is used more and more frequently in organic synthesis in recent three decades. In comparison with the traditional methods, this method is more convenient and easily controlled. Many organic reactions can be carried out in higher yields, shorter time or milder conditions by grinding method. It can even set off some reactions, which can not be carried out under traditional conditions[11].

The solid state organic reactions have attracted great interest in recent years[12,13]. In most cases, the solid-state organic reactions occur more efficiently than solution reactions. Without solvent, the reaction microenvironment and the interaction pattern of reactants are different from those in solution; the molecules are expected to precede the reaction regularly in a certain direction due to the ordered or constrained media. This reaction manner is similar to the chemical reaction occurring in organism. As a result, many useful and fascinating reactions were uncovered and solid state reaction became an important synthetic tool in organic chemistry[14].

EXPERIMENTAL

Melting points were uncorrected. Liquid aldehydes were distillated before use. ^1H NMR spectra were measured on Bruker Avance 400 (400 MHz) spectrometer using TMS as internal reference and $CDCl_3$ as solvent. Elemental analyses were carried out using Heraeus analyzer.

General procedure: A mixture of 3-chlorobenzaldehyde (**1c**, 2 mmol, 0.282 g), hydroxylamine hydrochloride (2 mmol, 0.139 g) and anhydrous sodium carbonate (3 mmol, 0.318 g) was ground thoroughly in a mortar at room temperature for 2 min. After completion of the reaction, 10 mL H_2O was added to the mortar and the solid was filtered, affording the 3-chlorobenzaldoxime (**3c**).

For the low melting point oxime **3a**, the solution was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous $CaCl_2$ for 12 h and filtered. Ethyl acetate was evaporated under reduced pressure to give the product. The authenticity of the products was established by comparing their melting points with the data in the literature and ^1H NMR spectra.

RESULTS AND DISCUSSION

The reaction was optimized using 3-ClC_6H_4CHO (2 mmol) as the substrate. Different parameters such as the molar ratio of 3-ClC_6H_4CHO/$NH_2OH·HCl$/Na_2CO_3 and reaction time were studied (Table-1). When the molar ratio of 3-ClC_6H_4CHO/$NH_2OH·HCl$/Na_2CO_3 was 1:4:0.5, the yield of oxime was 91 %. Increasing the molar rate to 1:4:1. There was no change in the yield of oxime. When the molar ratio increased to 1:4:1.5, the yield increase to 96 %. Further increasing the molar ratio, the yield did not increased. Further, we changed the molar rate to 1:1:1.5, the yield was 95%. When increased the amount of $NH_2OH·HCl$ to 1:2:1.5, 1:5:1.5, the yield of the oxime was 90 and 91 %, respectively. It seemed that the excess of $NH_2OH·HCl$ had no pronounced effect to the reaction.

In the absence of Na_2CO_3, the mixture was ground for 10 min and kept for a night, the yield of the corresponding oxime was 12 %. While in the presence of Na_2CO_3, the yield of the oxime was 95 %. It indicated that Na_2CO_3 was necessary to the reaction.

On the basis of these results, the optimized reaction conditions we chose were: aldehyde (2 mmol), $NH_2OH·HCl$ (2 mmol) and Na_2CO_3 (3 mmol). Using this reaction system, we performed a series of experiments for oximation of aldehydes by grinding. The results were summarized in Table-2.

TABLE-1
EFFECT OF THE REACTION CONDITIONS ON OXIMATION UNDER GRINDING

Entry	Molar ratio of 3-ClC_6H_4CHO/$NH_2OH·HCl$/Na_2CO_3	Grinding time (min)	Yield (%)
a	1:4:0.5	3	91
b	1:4:1	2	91
c	1:4:1.5	2	96
d	1:4:2	2	96
e	1:4:3	2	96
f	1:1:1.5	3	95
g	1:2:1.5	3	90
h	1:5:1.5	2	91

3a: Anal. Calcd. (Found) % for C_7H_7NO: C 69.40 (69.63), H 5.82 (5.80), N 11.56 (11.43).

3b: Anal. Calcd. (Found) % for $C_7H_6NOCl_2$: C 54.04 (54.25), H 3.88 (3.99), N 9.00 (8.79).

3c: ^1H NMR (400 MHz, $CDCl_3$): d 7.32-7.48 (3H, m, Ph-H), 7.62 (1H, s, CH), 7.68 (1H, s, Ph-H), 8.12 (1H, s, OH). Anal. Calcd. (Found) % for $C_7H_6NOCl_2$: C 54.04 (54.16), H 3.88 (4.03), N 9.00 (8.88).

TABLE-2
CONDENSATION OF AROMATIC ALDEHYDES WITH HYDROXYLAMINE HYDROCHLORIDE UNDER GRINDING

Entry	Substrate	Yield (%)	m.p. (ºC)(L.)	E/Z[b]
a	C_6H_5CHO	80	oil product (35)[15]	81/19
b	2-ClC_6H_4CHO	85	73-76 (72-77)[a]	
c	3-ClC_6H_4CHO	95	69-72	92/8
d	4-ClC_6H_4CHO	85	109-113 (105-107)[15]	85/15
e	2,4-$Cl_2C_6H_3CHO$	93	141-143 (134-136)[a]	
f	3-BrC_6H_4CHO	98	68-70 (73-76)	91/9
g	4-BrC_6H_4CHO	92	112-115 (111-113)[15]	86/14
h	4-$NO_2C_6H_4CHO$	90	132-137 (128-130)[15]	
i	4-$(CH_3)_2NC_6H_4CHO$	95	152-157 (138-140)[15]	
j	2-$CH_3OC_6H_4CHO$	74	94-96 (88-90)[15]	
k	4-$CH_3OC_6H_4CHO$	93	59-64 (63-65)[15]	95/5

[a] The melting points reported from www.acros.com

[b] Separated by column chromatography. The authenticity of the stereoisomeric form was established by comparing their melting points with the data in reference no. 16.

3d: Anal. Calcd. (Found) % for $C_7H_6NOCl_2$: C 54.04 (53.90), H 3.88 (4.14), N 9.00 (9.24).

3e: Anal. Calcd. (Found) % for $C_7H_5NOCl_2$: C 44.24 (44.49), H 2.65 (2.78), N 7.37 (7.46).

3h: Anal. Calcd. (Found) % for $C_7H_6N_2O_3$: C 50.60 (50.80), H 3.64 (3.89), N 16.86 (16.65).

3i: ^{1}H NMR (400MHz, $CDCl_3$): δ 3.02 (6H, s, CH_3), 6.71 (2H, d, Ph-H), 7.37 (1H, s, CH), 7.47 (2H, d, Ph-H), 8.07 (1H, s, OH). Anal. Calcd. (Found) % for $C_9H_{12}N_2O$: C 65.83 (65.92), H 7.36 (7.21), N 17.06 (17.04).

3j: Anal. Calcd. (Found) % for $C_8H_9NO_2$: C 63.56 (63.59), H 6.00 (5.97), N 9.26 (9.16).

3k: Anal. Calcd. (Found) % for $C_8H_9NO_2$: C 63.56 (63.74), H 6.00 (5.80), N 9.26 (9.26).

As shown in Table-2, some aldehydes *via* condensation can give oximes in good yields in free solvent under grinding. For example, when 4-$CH_3OC_6H_4CHO$ (**1k**) was as the substrate, the mixture was ground in the air at room temperature for 2 min, gave the corresponding oxime in 93 % (**3k**) yield. Ley *et al.*[5] have reported that the mixture was stirred in water at 80ºC for 2 h to give the oximes in 78 and 88 % yield, respectively. According to Huang report[10], the oxime can be obtained when the reaction was stirred at 120ºC for 25-90 min. Similar yield of oxime was also achieved by Nong[9] under microwave in 50 min. However, in the present method, the oximation reaction was carried out in the air at room temperature for 2 min. The yield of oximes was similar or higher than that reported formerly[10,15]. It indicated that grinding was a simple and efficient method for the oximation reaction. Furthermore, for most grinding reaction the mixture should be kept for a period of time after grinding, to make the reaction completed. But in our experiment, it was not necessity.

It is noted that aldehydes bearing two different groups, are capable of yielding two stereoisomeric oximes (E/Z) and the E-isomer is the predominate form. In some cases, mixtures of such isomers can be separated by column chromatography on silica (Table-2).

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