Selective Synthesis of *E* and *Z* Isomers of Oximes

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Abstract: The highly stereoselective conversion of aldehydes and ketones to their corresponding oximes with hydroxylamin hydrochloride are catalyzed by $CuSO_4$ and K_2CO_3.This method occurs under mild reaction conditions with high yields.

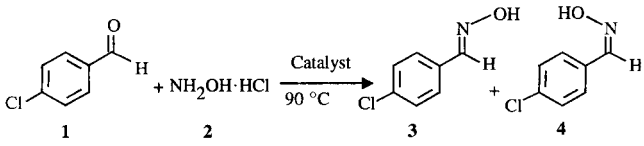
Key words: *E* and *Z* Isomers, oxime, hydroxylamine hydrochloride, $CuSO_4$, K_2CO_3

The addition of hydroxylamine hydrochloride to carbonyls to yield oximes is not only one of the best understood examples of a nonenzymatic addition-elimination reaction[1] but also an important reaction in organic synthesis.[2] Except in the case of symmetrical ketones, both isomeric oximes (*Z* and *E*) are usually produced which have different physical properties and biological activities[3] and should be separated by chromatography or recrystallization techniques.

Very few methods are available for the synthesis of *E* and *Z* isomer of oximes.[4,5] In many cases, *E* isomers were obtained from the *Z* forms by either the hydrochloride method[6] or purified by column chromatography.[7] The reagents which have been used for oximation of aldehydes and ketones, also catalyze the interconvertion of *Z* and *E* isomers. The rate of equilibration of a mixture of *Z* and *E* isomers and the position of the equilibrium is temperature dependent,[8] therefore, temperature control of the experiment is critical.

Having the above facts in mind, we wish to report a convenient method for controlling the stereochemistry of the reaction of hydroxylamine hydrochloride with aldehydes or ketones in solid state.

In order to find a simple and suitable catalyst for controlling the stereochemistry of oximes, the reaction of 4-chlorobenzaldehyde (**1**) with hydroxylamine hydrochloride (**2**) was chosen as a model and its behavior was studied under a variety of conditions via TLC and ^{1}H NMR spectroscopy (Scheme 1, Table 1).



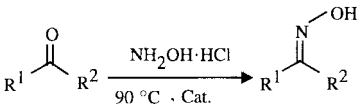
Scheme 1

Table 1 Reaction of **(1)** with **(2)** in the presence of different catalysts.

Entry	Catalyst	Time (min)	Ratio of product [a] (3) : (4)	Yields based on NMR & TLC(%)
1	SiO_2	30	1 : 1	100
2	MgO	30	1 : 4	100
3	Al_2O_3	30	1 : 2	100
4	CaO[18]	5	1 : 4	100
5	$CuCO_3$	30	1 : 4	100
6	Na_2SO_4	30	1 : 4	100
7	K_2CO_3	60	0 : 1	100
8	$CuSO_4$	60	1 : 0	100

a) Ratio of products was determined by ^{1}H NMR.

As shown in Table 1 (Entries 1-6), a mixture of *Z* and *E* isomer of 4-chlorobenzaldoxime was obtained by the use of various types of catalysts. In the comparison, the reaction proceeded rapidly to give exclusively the corresponding *Z*/*E* isomer of 4-chlorobenzaldoxime (**3**,**4**) in excellent yields when K_2CO_3 / $CuSO_4$ were employed (Table 1, Entries 7,8). Similarly, as shown in Scheme 2 and in Tables 2 and 3, the reactions of hydroxylamine hydrochloride with different aldehydes and ketones, including those with electron-withdrawing and donating substituents in the presence of these new catalysts, gave oximes in high yields and stereoselectivity.



Ca t. = Cu SO_4 , K_2CO_3

Scheme 2

As shown in Table 2, various types of aromatic aldehydes with electron donating and withdrawing groups were cleanly and rapidly condensed with hydroxylamine hydrochloride at 90 °C, giving the corresponding *E*-isomer of oximes (OH *anti* to aryl) in excellent yields in the presence of $CuSO_4$ (Entries 1-12). However, aromatic ketones such as benzophenone and others did not afford the corresponding oximes under these conditions. In order to show the chemoselectivity of the presented reagent toward the condensation of different carbonyl groups, a mixture of benzophenone and benzaldehyde was treated with hydroxylamine hydrochloride in the presence of $CuSO_4$ at

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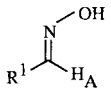
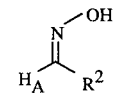
Table 2 Convertion of aldehydes and ketones to *E*-isomer oximes using $CuSO_4$.



Entry	R^1	R^2	Time (min.)	Mp.(lit.)	^{1}H Chemical shifts of H_A	Yields (%)[a]
1	*p*-ClC_6H_4	H	60	110 (110[9,12])	7.97	80
2	*p*-HOC_6H_4	H	30	112 (112[13])	7.81	70
3	*p*-$O_2NC_6H_4$	H	30	120 (131[12])	7.48	90
4	*p*-MeC_6H_4	H	30	110 (110[10])	7.27	90
5	*p*-$MeOC_6H_4$	H	30	63-64 (65[9,12])	6.97	70
6	*m*-ClC_6H_4	H	30	80 (71-72[12])	7.75	95
7	*m*-$O_2NC_6H_4$	H	15	120 (124[12])	7.64	95
8	*m*-MeC_6H_4	H	30	58 (60[12])	7.41	90
9	*m*-$MeOC_6H_4$	H	30	40 (40[12])	7.19	90
10	*m*-HOC_6H_4	H	30	70(88[10])	7.12	70
11	Ph	H	60	32 (30[9], 35[12])	7.40	90
12		H	120	110 (113[10])	7.32	85
13	Ph	Me	360			no reaction
14		Me	360			no reaction
15		Me	360			no reaction
16	*p*-ClC_6H_4	Ph	360			no reaction

a) ^{1}H NMR yields.

Table 3 Convertion of aldehydes and ketones to *Z*-isomer oximes using K_2CO_3.



Entry	R^1	R^2	Time (min.)	Mp.(lit.)	^{1}H Chemical shifts of H_A	Yields[a] (%)
1	H	*p*-MeC_6H_4	60	72 (80[10])	8.49	90
2	H	*m*-MeC_6H_4	60	56 (60[10])	8.13	90
4	H	*p*-HOC_6H_4	60	94 (72[10])	8.07	85
5	H	*m*-HOC_6H_4	120	90 (90[10])	8.09	90
6	H	*o*-HOC_6H_4	15	63 (63[10])	8.22	90
7	H	*p*-$O_2NC_6H_4$	120	100 (129[16])	8.21	80
8	H	*p*-ClC_6H_4	120	146 (145[9])	8.12	85
9	H	*m*-ClC_6H_4	120	100 (118[14])	8.11	85
10	H	*o*-ClC_6H_4	300	103 (100[17])	8.57	90
11	H	*p*-$MeOC_6H_4$	60	132 (133[9,12])	8.00	90
12	H	*m*-$MeOC_6H_4$	15	110 (112[10])	8.10	85
13	H	Ph	60	120 (128[9])	8.17	90
14	H	2,6-di-ClC_6H_3	300	132 (150[7])	8.40	90
15	H		15	130 (133[10])	7.73	80
16	Me		15	114(114[10])	.....	90
17	Me		60	142(132[15],130[11])	.....	85
18	Ph	Me	300	140 (144[10])	.....	80

a) ^{1}H NMR yields.

90 °C for 30 min. The *E*-benzaldoxime was obtained in 85% yield and benzophenone was recovered unchanged.

Table 3 also shows that various types of aromatic aldehydes and ketones with electron-donating and electron-withdrawing groups were cleanly and rapidly condensed with hydroxylamine hydrochloride at 90 °C, giving their corresponding *Z* oximes (OH *cis* to aryl) in high yields in the presence of K_2CO_3 (Entries 1-18).

The advantages of the presented methods may be summarized as: use of commercial and available catalysts, mild reaction conditions, and high stereoselectivities good yields of the desired products.

General Procedure for preparation of *E* isomer of aldoximes in the presence of $CuSO_4$:

Hydroxylamine hydrochloride (0.6 g, 8.6 mmol) was added to a stirred mixture of $CuSO_4$ (1 g) and aldehydes (1 mmol) at 90 °C in an oil bath. The progress of reaction was monitored by TLC. After complete disappearance of the starting material, the reaction mixture was cooled, and washed with cold diethyl ether and filtered to remove $CuSO_4$. Then the mixture was poured into ice-water and extract with cold diethyl ether (2×25 mL).The organic solution was dried over Na_2SO_4 and evaporated over ice to give the crude *E* oximes. The process of work-up was carried out at 0 °C, otherwise, the *Z* isomer was obtained.

General procedure for preparation of *Z* isomer of aldoximes and ketoximes in the presence of K_2CO_3:

Hydroxylamine hydrochloride (0.6 g 8.6 mmol) was added to a stirred mixture of K_2CO_3 (1 g) and aldehydes or ketones (1 mmol) in an oil bath at 90 °C for the periods of time reported in Table 3. Then, the reaction mixture was washed with CH_2Cl_2 (2×10 mL) and water (2×50 mL). The organic layer was dried over Na_2SO_4 and evaporated to give the crude *Z* isomer of oxime. The products were identified by comparison of their physical data with those prepared in accordance with the literature procedures.

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