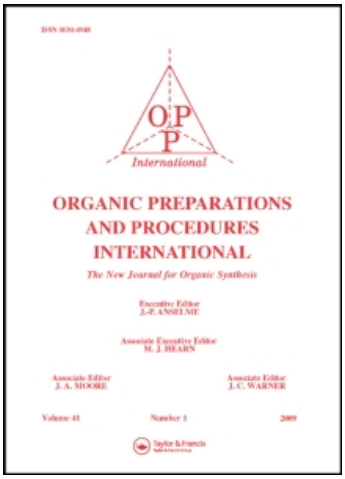

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REGIOSELECTIVE SYNTHESIS OF *E*-OXIMES CATALYZED BY FERRIC CHLORIDE UNDER SOLVENT-FREE CONDITIONS

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REGIOSELECTIVE SYNTHESIS OF *E*-OXIMES CATALYZED BY FERRIC CHLORIDE UNDER SOLVENT-FREE CONDITIONS

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(06/08/05)

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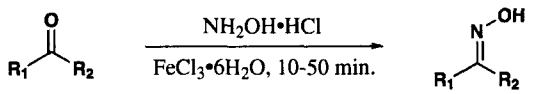
Oximes are useful for the isolation, purification and characterization of carbonyl compounds.[1,2] They undergo a number of transformations such as the Beckmann and the Neber rearrangement, halogenation, nitration, deoxygenation, or reaction with organometallic reagents.[3] The Beckmann rearrangement of cyclohexanone oxime to ε-caprolactam has been used as a powerful method for its manufacture industrially.[4] Oximes are typically prepared by the reaction of a carbonyl compound with hydroxylamine hydrochloride and a base such as pyridine.[5] Except in the case of symmetrical ketones, two isomeric oximes are generated, *Z* and *E*, which have different physical and biological activities.[6] Chemical methods for the synthesis of oximes usually give a mixture of the two geometrical isomers which must be separated by chromatography or recrystallization. However, the reagents that have been used for the oximation of ketones or the Beckmann rearrangement can also catalyze the interconversion of these geometrical isomers.[7] The rate of equilibrition of a mixture of *Z* and *E* isomers and the position of the equilibrium is temperature dependent;[7a] therefore, temperature control is critical. Although the reaction of carbonyl compounds with hydroxylamine hydrochloride is accelerated by phase-transfer catalyst,[8] microwave irradiation,[9] or solvent-free conditions,[10] the selectivity is not affected. A few methods are available of the synthesis of *Z* and *E* isomer of aldoximes.[7d, 11,12] In many cases, *E* isomers were obtained from the *Z* forms by either the hydrochloride salt method[13] or by column chromatography.[14] Recently, it has been shown that antibodies[7d] and molecular sieve 3Å[15] can catalyze the stereoselective oxime formation. Thus, there is considerable interest in finding more selective methods of oximes synthesis. We now report a very simple and efficient procedure for the selective preparation of *E*-oximes from ketones and hydroxylamine hydrochloride using the $FeCl_3 \cdot 6H_2O$ in solventless conditions (*Scheme*).



Various ketones were ground with hydroxylamine hydrochloride in the presence of $FeCl_3 \cdot 6H_2O$ in solvent-free media. In this approach, the corresponding *E*-ketoximes were

obtained in quantitative yield in 10 minutes (*Table*). In the case of aryl substituted aliphatic ketones, the amount of $FeCl_3 \cdot 6H_2O$ was increased to 0.5 equimolar and the reactions were performed at ambient temperature for 15-30 minutes. Acetophenone and its derivatives which

Table 1. Conversion of Ketones into *E*-Ketoximes in the Presence of $FeCl_3 \cdot 6H_2O$

Entry	R_1	R_2	$FeCl_3 \cdot 6H_2O$ to Substrate (mole ratio)	Temp. (°C)	Time (min)	Yield[a,b] (%)	bp/ Torr or mp (°C) Found	*Lit.*
1	Et	Me	0.2	25	10	93	152-5/760	152-3/760[17]
2	n-Pro	Me	0.2	25	10	91	164-6/760	167/760[17]
3	n-Bu	Me	0.2	25	10	94	180-3/760	185/760[18]
4	i-Bu	Me	0.2	25	10	88	78-80/760	77-8/760[17]
5	$C_6H_5CH_2CH_2$	Me	0.5	50	15	95	83-5	85[19]
6	$C_6H_5CH_2$	Me	0.5	50	20	90	68-9	68-70[18]
7	C_6H_5	Et	2	50	50	93	53-4	53-5[17]
8	C_6H_5	Me	2	50	50	91	56-8	59-61[15]
9	*p*-MeC_6H_4	Me	2	50	50	94	85-6	85-7[15]
10	*p*-ClC_6H_4	Me	2	50	50	89	93-4	93-5[15]
11	*p*-$NO_2C_6H_4$	Me	2	50	45	92	170-2	172-4[7d]

a) Isolated yield. b) All the compounds give satisfactory spectral analysis (IR and ^1H NMR).

Table 2. ^1H NMR Data of Products

Cmpd	^1H NMR Data (δ, 100 MHz, $CDCl_3$, 25°C)
1	1.1 (t, 3 H, J = 7.5 Hz, CH_3), 1.9 (s, 3 H, CH_3), 2.0-2.5 (m, 2H, CH_2), 8.3 (broad, = NOH)
2	0.9 (t, 3 H, J = 7.5 Hz, CH_3), 1.2-1.6 (m, 2 H, CH_2), 1.9 (s, 3 H, CH_3), 2.0-2.4 (m, 2H, CH_2), 8.7 (broad, = NOH)
3	0.9 (t, 3 H, J = 7.5 Hz, CH_3), 1.0-1.6 (m, 4 H, CH_2CH_2), 1.9 (s, 3 H, CH_3), 1.9-2.3 (m, 2H, CH_2), 8.0 (broad, = NOH)
4	0.9 (d, 6 H, J = 7 Hz, CH_3), 2.0 (s, 3 H, CH_3), 1.9-2.6 (m, 3H, $CHCH_2$), 8.3 (broad, = NOH)
5	1.9 (s, 3 H, CH_3), 2.5 (m, 2 H, CH_2), 2.8 (m, 2H, CH_2), 7.0-7.4 (m, 5 H, ArH), 7.7 (broad, = NOH).
6	1.8 (s, 3 H, CH_3), 3.5 (s, 2 H, CH_2), 7.0-7.3 (m, 5 H, ArH), 9.1 (broad, = NOH)
7	1.0 (t, 3 H, J = 7.5 Hz, CH_3), 2.6 (q, 2 H, J = 7.5 Hz, CH_2), 7.0-7.3 (m, 5 H, ArH), 9.6 (broad, = NOH).
8	2.3 (s, 3 H, CH_3), 7.0-7.6 (m, 5 H, ArH), 10.0 (broad, = NOH)
9	2.4 (s, 3 H, CH_3), 2.5 (s, 3 H, CH_3), 7.3 (d, 2H, J = 8 Hz, ArH), 7.5 (d, 2H, J = 8 Hz, ArH), 9.4 (broad, = NOH).
10	2.3 (s, 3 H, CH_3), 7.1-7.6 (m, 5H, ArH), 8.3 (broad, = NOH)
11	2.5 (s, 3 H, CH_3), 8.0 (d, 2H, J = 9.5 Hz, ArH), 8.0 (d, 2H, J = 9.5 Hz, ArH), 10.2 (broad, = NOH).

failed in above conditions reacted only in the presence of two equivalents $FeCl_3 \cdot 6H_2O$ at ambient temperature for 45-50 minutes. However, symmetrical ketones such as 3-pentanone, cyclopentanone and cyclohexanone give the corresponding oximes as the only products in high yields under these conditions.

The purity of the products was determined by ^1H NMR and IR spectra, which showed the exclusive formation of the corresponding *E*-ketoximes whose structure was confirmed by melting points comparison. In all the IR spectra, the OH and C=N groups of ketoximes were observed around 3250 and 1640-1670 cm^{-1}, respectively and in ^1H-NMR spectra the OH group appeared around δ 7.7-10.2 as a broad singlets. The chemical shift values of methyl and methylene groups that are *syn* to the hydroxyl group are always higher than those of the corresponding *anti* group.[20] Our data did not show the presence of the *Z*-isomers in the crude products, except for 5% of *Z*-isomer in the cases of *entries 5 and 6* in the *Table*. Also, we only detected and isolated the *E*-ketoximes according to TLC examinations and melting point comparison. We suggest that it is due to the fact that the *Z-E* equilibrium is very rapid and highly shifted towards the *E*-ketoxime as the thermodynamic product. The regioselectivity may be rationalized by the different steric hindrance around the oxime double bond of the plausible intermediates as formed by interaction of hydroxyl group and $FeCl_3$. Recently, excess of anhydrous ferric chloride was used as a reagent for the Beckmann rearrangement of ketoximes under solvent-free conditions in 80-90°C.[16] We suggested that the Lewis acid strength of the hydrated ferric chloride is diminished such that only the oximes are obtained chemoselectively and rearrangement does not occur.

In conclusion, the reported procedure is a novel method for the facile preparation of ketoximes in solvent-free media. In addition, this simple and readily available reagent affords various ketoximes in good to excellent yields (85-95%), and high stereoselectivity in shorter reaction time (10-50 min).

EXPERIMENTAL SECTION

All materials and solvents were obtained from Merck Co. (Germany) and Fluka (Switzerland). All mps were recorded in open capillary measurements and are uncorrected. IR spectra were determined on a Shimadzu IR 470 spectrophotometer. ^1H NMR spectra were obtained on Bruker-80 and 100 MHz instruments using TMS as an internal standard.

Preparation of *E*-Ketoximes. General Procedure.- A mixture of the ketone (1 mmol), hydroxylamine hydrochloride (0.14 g, 2 mmol) and $FeCl_3 \cdot 6H_2O$ (0.054-0.54 g, 0.2-2 mmol) was grounded thoroughly in a mortar for 10 minutes. Usually, an immediate color change was observed. The completion of the reaction was monitored by TLC examination (CH_2Cl_2/CH_3OH 9:1). After the completion of the reaction, water (15 mL) was added to the mixture. The resulting solution was extracted with CH_2Cl_2 (2 x 10 mL). The extracts were combined and washed with saturated sodium hydrogen bicarbonate (10 mL). The organic layer was dried and evaporated

under vacuum to give the ketoximes in high purity (based on TLC, ^{1}H NMR, IR and mps). The structures of the products were confirmed by the melting points[7d,15,17-19] and ^{1}H NMR[15,17,20] comparisons.

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TWO-STEP PROTIC SOLVENT-CATALYZED REACTION OF PHENYLETHYLAMINE WITH METHYL ACRYLATE

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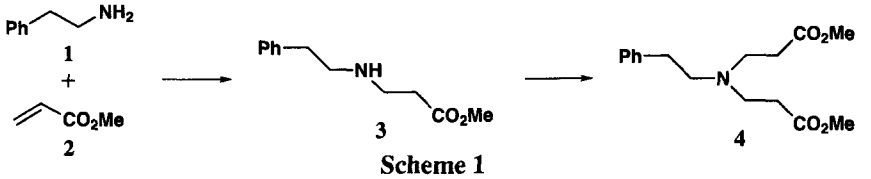
The reaction of phenylethylamine (**1**) with methyl acrylate (**2**), performed in two steps, led to *N*-(β-carbomethoxyethyl)phenethylamine (**3**) and *N,N-bis*-(β-carbomethoxyethyl)phenethylamine (**4**). Compounds **3** and **4** are useful for the preparation of important and valuable compounds, *e. g.* 1-(2-phenethyl)piperidine-4-one and its derivatives, utilized in the synthesis of analgesics such as *fentanyl,*[1-8] *carfentanyl,*[9] *3-methylfentanyl,*[10-13] and lactam analogues of *fentanyl.*[14]



Scheme 1