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Rapid Communication

Cerium catalysed Michael addition to α,β-unsaturated oximes: A facile and efficient synthesis of substituted pyridines

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$CeCl_3.7H_2O$-NaI is found to be an effective catalyst for the synthesis of various tetra-substituted pyridine derivatives via Michael addition of β–dicarbonyl compounds to α,β–unsaturated oximes and subsequent ring closure by cyclo-dehydration of these products.

Keywords: Cerium, Michael addition, unsaturated oximes, pyridines

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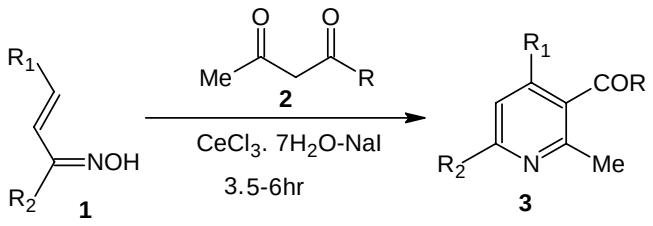
Michael reaction is a very important and useful method of carbon-carbon bond formation in organic chemistry. The classical version of this reaction involves the use of strong Bronsted bases like alkoxides, hydroxides catalysed conjugate addition of β–dicarbonyl compounds to activated olefins[1]. The use of strong bases is the main limiting factor of this reaction, as the highly basic conditions always lead to several types of side products, fragmentation and rearranged by-products[2]. To address this problem a variety of metal salts of transition metals were searched to be useful mild lewis acid[3] catalysts of this reaction. The first in this row being the copper salts[4] and subsequently several others were found to be affective catalysts[5,6]. In recent years cerium chloride heptahydrate have emerged to be very useful catalyst for this reaction. Further studies of this reagent lead to $CeCl_3.7H_2O$-NaI protocol, which is reported to be more efficient than the original cerium chloride heptahydrate catalysis. This system is reported to be more user friendly and catalyses the conjugate addition of β–dicarbonyl compounds to enones[7] even at room temperature to afford Michael adducts in excellent yields. There are several other excellent qualities attached to this reagent system, like it is non-toxic, non-hazardous, can cleave ethers[8] and several other heterobonds successfully[9]. It has been reported to be very efficient dehydrating reagent leading to the formation of carbon-carbon double bonds[10]. These highly attractive properties of this reagent system ($CeCl_3.7H_2O$-NaI) prompted us to investigate the Michael reaction of α,β-unsaturated oxime with ethyl-acetoacetate and acetylacetone respectively which after addition would cyclodehydrate to afford substituted pyridines.

The pyridine structure and its derivatives substituted or in polycyclic systems constitute an important class of nitrogen heterocycles, because of several biological properties available with this nucleus. This scaffold is present in several pharmaceutical[11] and natural products[12]. The therapeutic properties bodes well in pyridine skeleton and this results in its application in pharmaceutical compounds[13] like antihistamines, antiarrythmic antirheumatic, antiseptic etc. As pharmaceuticals it's derivatives found use as anticancer agents and agrochemicals also. Keeping in view of this much valuable skeleton several methods of its synthesis continue to be developed. These includes Vilsmeier-Hack reaction of conjugated oximes involving Beckmann rearrangement of oximes[14], cyclisation of gluteraldehyde which produce pyridine in upto 53% yield only using ammonium salt and malachite green or by copper (II) or iron (III) halides[15]. Also this skeleton was produced from furan precursors by Bryce and co-workers[16]. Other methods including Michael addition-cyclodehydration of enamino ester and alkynone[17], reaction of the methyl acetoacetate and N-benzylenimines in presence of LiI[18], and from amidrazone of unsymmetrical tricarbonyl compound product followed by reation with norbornadiene[19] are also reported. But these methods suffer from several limitations like involvement of more sluggish steps, less efficient in terms of yields and are not user friendly.

In continuation to our earlier studies on metal salts catalyzed Michael reaction[20], we report herein the cerium catalyzed Michael addition of β–dicarbonyl compounds to α,β–unsaturated oximes leading to the synthesis of tetrasubstituted pyridines (**Scheme I**).



R = CH_3, OEt
R_1 = Ph, p-ClC_6H_4, p-$CH_3C_6H_4$, p-$OCH_3C_6H_4$
R_2 = CH_3, Ph

Scheme I

Table I — $CeCl_3.7H_2O$-NaI catalysed synthesis of tetrasubstituted pyridine derivatives **3a-j**[a]

Product[b]	R	R^1	R^2	Reaction time (hr)	Yield[c,d] (%)
3a	OEt	Ph	Me	3.5	86
3b	OEt	Ph	Ph	5.0	69
3c	OEt	*p*-ClC_6H_4	Me	4.0	74
3d	OEt	*p*-CH_3 C_6H_4	Me	4.0	78
3e	OEt	*p*-$OCH_3C_6H_4$	Me	4.0	72
3f	OEt	*p*-$CH_3C_6H_4$	Ph	5.0	66
3g	Me	Ph	Me	6.0	71
3h	Me	*p*-ClC_6H_4	Me	4.5	69
3i	Me	*p*-$CH_3C_6H_4$	Me	4.5	68
3j	Me	*p*-$OCH_3C_6H_4$	Me	4.5	66

[a] Reaction condition: α,β-Unsaturated oxime (1 mmole), β-dicarbonyl compound (1 mmole), $CeCl_3.7H_2O$ (0.1 equiv.) and NaI (0.1 equiv.) heated at 150-160°C under stirring without solvent.
[b] All products were identified by comparison of IR, ^{1}H NMR and ^{13}C NMR with that of authentic samples.
[c] Isolated yield based on single experiment, no optimization is done.
[d] Cleavage of ester function to the extent of 5-10% of the isolated yield cannot be ruled out though it is not observed during these experiments.

α,β–Unsaturated oxime was allowed to react with β–dicarbonyl compound in the presence of $CeCl_3.7H_2O$ at room temperature. The desired reaction did not take place which is in contrast to earlier reports and can be rationalised in terms of poor electron withdrawing effect of C=N-OH in comparison to C=O function. The higher temperature and addition of NaI proved to be fruitful viz. $CeCl_3.7H_2O$-NaI when heated at 160°C under stirring afforded pyridines in good yields. Also the reaction of α,β–unsaturated carbonyl compound, β-dicarbonyl compound and ammonium acetate also gave nearly equivalent results. It is worthy to mention here that when $RuCl_3.3H_2O$ replaces $CeCl_3.7H_2O$-NaI protocol or $SnCl_2.2H_2O$ it also promoted the reaction effectively.

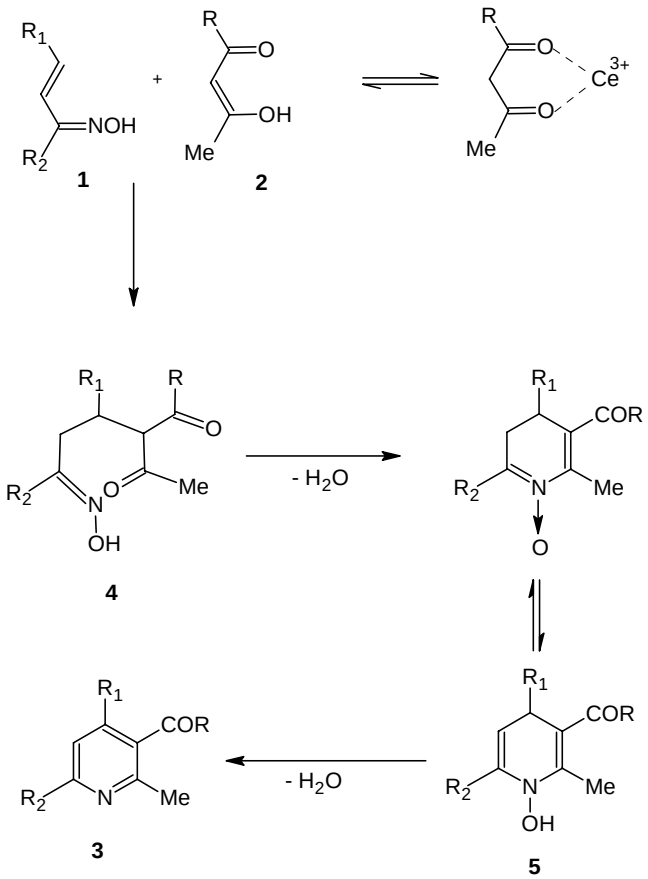
Reaction of α,β–dicarbonyl oxime **1a** with ethyl acetoacteate **2** in the presence of $CeCl_3.7H_2O$-NaI without any solvent at 160°C with stirring for stipulated time period afford tetrasubstituted pyridine[21] **3a** as pale yellow viscous oil in 86% yield. Similarly other substituted α,β–unsaturated oximes and β-dicarbonyl compounds were reacted to produce the corresponding tetrasubstituted pyridines **3b-j** following the same procedure (**Table I**).

The catalyst efficacy is fairly general, 10 mol% of catalyst ($CeCl_3.7H_2O$-NaI) is enough to promote the reaction effectively while the use of 5 mol% of catalyst is equieffective. Higher amount of catalyst (20 mol%) and increase in reaction time did not prove fruitful. The reaction conditions are tolerant to ether group as well as halogens as this procedure gave the corresponding substituted pyridine derivatives without any dehalogenation. All the comounds obtained were fully characterised by spectroscopic analysis (IR, ^{1}H NMR and ^{13}C NMR). At this stage of investigation the detailed mechanism of this reaction is not very clear, certainly a plausible reaction sequence is presented here. It is believed that Michael reaction is facilitated by $CeCl_3.7H_2O$-NaI system effectively and then the adduct **4** undergoes ring closure through cyclodehydration which further loses another water molecule, which can be conceived to be, via hydrogen migration to afford N-OH and then the loss of water molecule (**Scheme II**).

In conclusion we have reported cerium catalysed efficient, economical, environment and user-friendly synthesis of various tetra-substituted pyridine derivatives.

Experimental Section

Melting points were determined by using a Buchi melting point apparatus and are uncorrected. IR spectra were recorded in KBr discs on a Perkin-Elmer 240C analyzer; ^{1}H NMR spectra on a 90 MHz spectrometers (chemical shift in δ) relative to Me_4Si as internal standard. The 100 MHz NMR spectra were recorded with TMS as internal standard. Elemental analyses were performed with TMS as internal standard on a Hitachi 026 CHN analyzer. All solvents were distilled before use.



Scheme II

Typical Experimental Procedure. Ethyl aceto-acetate (0.13 g, 1 mmole), $CeCl_3.7H_2O$ (0.1 equiv) and NaI (0.1 equiv) were added to enone oxime **1a** (0.16 g, 1 mmole) and the reaction mixture was heated with vigorous stirring at 150-160°C and kept at this temperature for 3.5-6 hr (monitored by TLC). After that the unreacted ethyl acetoacetate (if any remains) was removed under reduced pressure. The residue was then taken in diethyl ether (25 mL) and the resulting mixture was extracted with 1 *M* HCI (3 × 20 mL). The combined acidic aqueous extracts were adjusted to *p*H 9 by means of aqueous ammonia and extracted with dichloromethane (2 × 20 mL). The dichloromethane extract was dried over anhydrous sodium sulphate and concentrated on a rotary evaporator to afford the crude tetra-substituted pyridine derivative **3a** in 86% yield, which was then purified by column chromatography on silica gel using chloroform as eluent to give the pure ethyl 2,6-dimethyl-4-phenylpyridine-3-carboxylate **3a** as a light yellow viscous oil. **3a**: IR (KBr): 2967, 2923, 1728, 1575, 1256, 1092, 771, 702 cm^{-1}; ^1H NMR ($CDCI_3$): δ 1.08 (t, *J*=7.0 Hz, 3H, OCH_2CH_3), 2.49 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 4.21 (q, *J*=7.0 Hz, 2H, OCH_2CH_3), 7.18 (s, 1H, pyridine-H), 7.32 (m, 5H, aromatic); ^{13}C NMR ($CDCl_3$): δ 169.4, 159.2, 152.5, 150.9, 143.2, 130.46, 128.9, 127.9, 126.4, 121.6, 61.5 (CH_2), 24.3 (Me), 23.2 (Me), 14.0 (Me); EI MS: *m/z* 255. Calcd for $C_{16}H_{17}NO_2$: C, 75.29; H, 6.67; N, 5.49%. Found: C, 75.47; H, 6.77; N, 5.42%.

Similarly other enone oximes and β-dicarbonyl compounds were reacted to afford various pyridine derivatives (**Table I**). All the compounds obtained were fully characterised by spectroscopic analysis (IR, ^1H NMR, ^{13}C NMR) and finally by comparison with authentic samples.

3c: IR (KBr): 2980, 2941, 1721, 1570, 1541, 1262, 1102 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.21 (t, *J*= 7.0 Hz, 3H, -OCH_2CH_3), 2.52 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 4.27 (q, *J*=7.0 Hz, 2H, -OCH_2CH_3), 7.21 (s, 1H, Pyridine H_5), 7.34 (d, *J*=8.3 Hz, 2H), 7.42 (d, *J*=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 13.7, 17.2, 62.1, 117.2, 121.4, 128.1, 130.2, 139.3 160.3, 163.4, 167.6.

3e: IR (KBr): 2960, 2925, 1722, 1568, 1521, 1245, 1035 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, 3H, -OCH_2CH_3), 2.52 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 4.29 (q, *J* = 7.2 Hz, 2H, -OCH_2CH_3), 6.85 (d, *J* = 8.3 Hz, 2H), 7.20 (s, 1H, Pyridine H_5), 7.34 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 13.9, 15.1, 22.3, 56.3, 59.8, 116.1, 119.8, 126.9, 131.6, 148.6, 159.7,162.7, 167.9.

3g: IR (KBr): 2957, 2922, 1702, 1570, 1531, 1257 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.48 (s, 3H, -$COCH_3$), 2.51 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 7.32-7.41 (m, 5H, aromatic), 7.19 (s, 1H, Pyridine H_5); ^{13}C NMR ($CDCl_3$): δ 14.1, 21.8, 24.2, 119.6, 126.8, 130.1, 140.2, 149.0, 159.2, 163.0, 169.4.

3i: IR (KBr): 2965, 2921, 1696, 1565, 1533, 1266 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.48 (s, 3H, -$COCH_3$), 2.52 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 7.16 (d, *J* = 8.2 Hz, 2H) 7.39 (d, *J* = 8.2 Hz, 2H), 7.51 (s, 1H, Pyridine H_5); ^{13}C NMR ($CDCl_3$): δ 15.1, 22.1, 23.8, 119.1, 127.5, 131.2, 137.7, 148.9, 160.2, 163.3, 198.0.

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References and Notes

1 (a) Bergmann E D, Ginsburg D & Pappo R, *Org React*, 10, **1959,** 179.

(b) Oare D A & Heathcock C H, in *Topics in Stereochemistry*, Vol. 19 edited by E L Eliel & S H Wilen, (Wiley Interscience, New York) **1989**, 227.

(c) Perlmutter P, *Conjugate Addition Reactions in Organic Synthesis,* Tetrahedron Organic Chemistry Series Vol. 9 (Pergamon, Oxford) **1992.**

2 In some cases these base mediated subsequent processes can be utilized for reaction cascades: (a) Rodriguez J, *Synlett*, **1999**, 505.
(b) Varner M A & Grossman R B *Tetrahedron*, 55, **1999**, 13867.
(c) Review: Grossman R B, *Synlett*, **2001**, 13.

3 Kotsuki H, Arimura K, Ohishi T & Maruzasa R, *J Org Chem*, 64, **1999**, 3770.

4 Saegusa T, Ito Y, Tomita S & Kinoshita H, *Bull Chem Soc Jpn*, 45, **1972**, 496.

5 Review: (a) Christoffers J, *Eur J Org Chem*, **1998**, 1259.
(b) Saiki T & Aoyama Y, *Chem Lett*, **1999**, 797.
(c) Kotsuki H, Arimura K, Maruzawa R & Ohshima R *Synlett*, **1999**, 650.
(d) Picquet M, Bruneau C & Dixneuf P H, *Tetrahedron*, 55, **1999**, 3937.
(e) Matsuda I, Makino T, Hasegawa Y & Itoh K, *Tetrahedron Lett*, 41, **2000**, 1409.
(f) Loh T P & Wei L L, *Tetrahedron*, 54, **1998**, 7615.

6 For some recent reports see: (a) Bartoli G, Bartolacci M, Giuliani A, Marcantoni E, Massaccesi M & Torregiani E, *J Org Chem*, 70, **2005,** 169.
(b) Garg S K, Kumar R & Chakraborti A K, *Tetrahedron Lett*, 46, **2005**, 1721.
(c) Ortiz A, Herńandez H, Mendoza G, Quintero L & Bernès S, *Tetrahedron Lett*, 46, **2005**, 2243.
(d) Boy K M & Guernon J M, *Tetrahedron Lett*, 46, **2005**, 2251.
(e) Cave G W V & Raston C L, *Tetrahedron Lett*, 46, **2005**, 2361.
(f) Takenaka K & Uozumi Y, *Org Lett*, 6, **2004**, 1833.

7 Duval D & Geribaldi S, *The Chemistry of Enones*, *Part I*, edited by S Patai & Z Rappoport, (Interscience, New York) **1989**, 335.

8 (a) Bartoli G, Marcantoni E & Sambri L, *Seminars in Organic Synthesis;* XXV Summer School 'A. Corbella' Gargnano (BS), Italian Chemical Society: Rome, **2000**, 117.
(b) Bartoli G, Bellucci M C, Bosco M, Cappa A, Marcantoni E, Sambri L & Torregiani E, *J Org Chem*, 64, **1999,** 5696.

9 (a) Bartoli G, Bosco M, Marcantoni E, Sambri L & Torregiani E, *Synlett*, **1998**, 208.
(b) Bartoli G, Cupone G, Dalpozzo G, De Nino A, Maiuolo L, Procopio A, Sambri L & Tagarelli A, *Tetrahedron Lett*, 43, 2002, 5945.
(c) Chen M Y, Lu K C, Lee A S Y & Lin C C, *Tetrahedron Lett*, 41, **2000**, 2777.
(d) Gopinath R & Patel B K, *Org Lett*, 2, **2000**, 4177.
(e) Ranu B C, Jana U & Majee A, *Tetrahedron Lett*, 40, **1999**, 1985.

10 Bartoli G, Bellucci M C, Marcantoni E, Petrini M, Sambri L & Torregiani E, *Org Lett*, 2, **2000**, 1791.

11 Pyridine scaffold is present in over 7000 drugs; (a) *Pharmaceutical Chemistry*. *Drug Synthesis*, edited by H J Roth & A Kleemann, (Prentice Hall Europe, London, **1988**) Vol. I, p. 407. (b) MDDR: MDL Drug Registry, by MDL Informations System, Inc, San Leandro, California, USA.

12 Hanket T, Brunne R M, Miller H & Reichel F *Angew Chem Int Ed Engl*, 38, **1999**, 643.

13 Nefzi A, Ostresh J M & Houghten R A, *Chem Rev*, 97, **1997**, 449.

14 (a) Thomas A D & Asokan C V, *J Chem Soc, Perkin Trans I*, **2001**, 2583.
(b) Ahmed A S & Boruah R C, *Tetrahedron Lett*, 37, **1996**, 8231.

15 (a) Baumgarten P, *Ber*, 57, **1924**, 1622.
(b) Baumgarten P, *Ber*, 58, **1925**, 2018; British Patent, 1968, 1102261.

16 Chubb R W J, Bryce M R & Tarbit B, *J Chem Soc, Perkin Trans I*, **2001**, 1853.

17 Bagley M C, Brace C, Dale J W, Ohnesorge M, Phillips N G, Xiong X & Bower J, *J Chem Soc, Perkin Trans I*, **2002**, 1663.

18 Geirsson J K F & Johannesdottir J F, *J Org Chem*, 61, **1996**, 7320.

19 Stanforth S P, Tarbit B & Watson M D, *Tetrahedron Lett*, 43, **2002**, 6015.

20 Baruah B, Baruah A, Prajapati D & Sandhu J S, *Tetrahedron Lett*, 38, **1997**, 1449 and references cited therein.