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Solvent-Free Synthesis of β-Enamino Compounds Promoted by Ferric(III) Ammonium Nitrate

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A variety of β-enamino esters and β-enaminones can be synthesized by the reaction of 1,3-dicarbonyl compounds and various primary amines in the presence of catalytic amount of ferric(III) ammonium nitrate at room temperature. This method is simple, requires short reaction times, high yield and the reaction proceeds under solvent-free conditions.

Key Words: Amines, Ferric(III) ammonium nitrate, Solvent-free, β-Enamino ester, β-Enaminones, 1,3-Dicarbonyl compounds.

INTRODUCTION

β-Enamino esters and β-enamino ketones are the attractive synthones for the construction of bio-active heterocycles such as pyrazoles, oxazoles, quinolines, dibenzodiazepins, pyridinones, tetrahydrobenzoxazines, tetronic acids and tetrahydrophenanthridines[1-6]. They have been used for the preparation of different important antibacterial[7], antiinflammatory[8], anticonvulsant[9] and antitumour agents[10]. They are also important precursors for the synthesis of 3-amino sugar derivatives[11], azo compounds[12], β-amino ketones[13], hexahydroazulenes[14] and indolizidine alkaloids[15]. Thus it is very important to search for a convenient and efficient method for synthesis of this type of compounds. The most commonly used method for the preparation of these compounds is the direct condensation of 1,3-dicarbonyl compounds and various amines, in which the azeotropic removal of water is usually require under reflux using a Dean Stark trap in aromatic solvent[16]. Some improved procedures were reported for this transformation of with catalysts, protonic acids such as H_2SO_4[17], HCl[18], *p*-TSA[19], acetic acid[20], lewis acids such as zirconium(IV) chloride[21], erbium triflate[22], $Bi(OTf)_3$[23], $NaAuCl_4$[24], $LaCl_3$[25], $BF_3 \cdot OEt_2$[26], $Zn(ClO_4)_2 \cdot 6H_2O$[27], $CeCl_3 \cdot 7H_2O$[28], $InBr_3$[29], $Sc(OTf)_3$[30] and heterogeneous catalysts like silica gel[31], silica chloride[32], natural clays[33]. In addition, microwave irradiation[34], I_2[35], $(EtNH_3)NO_3$[36], $Zn(OAc)_2 \cdot 6H_2O$[37], $CoCl_2$[38] and water[39] also have been employed to promote this condensation. The above mentioned methods have certain limitations such as costly catalysts[40], drastic reaction conditions[16], need excess of catalyst[41] and also require extended reactions times[31], *etc*. Hence the development of new reagents with great efficiency,

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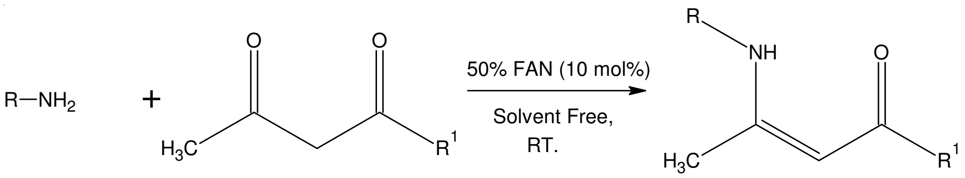
time saving and more convenient and eco-friendly approaches is of interest. Many catalysts are derived from heavy or rare metals and they have several drawbacks for large-scale applications. In contrast, iron is one the most abundant metals on earth and consequently one of the most inexpensive and environmental friendly[42]. Iron catalysts play an important role in the oxidation of the aldehydes[43], addition reactions[44], cross-coupling reactions[45], cycloadditions[46] and reduction of aryl halides[47]. In the present study, we developed a simple, convenient, solvent-free, time saving and high yielding method. Ferric(III) ammonium nitrate (FAN) is a cheap and commercially available compound. Herein, we report efficient method for the synthesis of β-enamino compounds from 1,3-dicarbonyl compounds and various primary amines catalyzed by ferric(III) ammonium nitrate (**Scheme-I**).



1 **2** **3**

R = $CH_3(CH_2)_3$, Ph, $PhCH_2$, $PhCH_2CH_2$, *p*-Me-C_6H_4, *p*-OMe-C_6H_4, *o*-OMe-C_6H_4, *p*-Br-C_6H_5.
R¹ = OEt, Me; FAN = Ferric(III) ammonium nitrate, RT = Room temperature.

Scheme-I

EXPERIMENTAL

All the chemicals used in the present study are analytical grade and obtained from local suppliers. Melting points were recorded on a Kumar capillary melting point apparatus and are uncorrected. The IR spectra were recorded on a Nicolet FT-IR AVATAR 320 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 298 K on a Jeol FT (90 MHz) spectrometer, using $CDCl_3$ as solvent and TMS as an internal reference.

General procedure: A mixture of primary amine **1** (1 mmol) and 1,3-dicarbonyl compound **2** (1 mmol) was stirred at room temperature in the presence of 50 % of ferric(III) ammonium nitrate solution (10 mol %) for an appropriate time (Table-1) progress of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was poured into cold water and the product was extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude products were purified with column chromatography by using silica gel.

Spectral data for selected compounds

Ethyl-3-(butylamino)but-2-enoate (3a)[25]: Oil IR (neat, cm^{-1}): 3498, 1615, 1595. ^{1}H NMR δ 0.91 (t, 3H), 1.32 (m, 2H), 1.43 (t, 3H, *J* = 7.0 Hz), 1.86 (m, 2H), 1.90 (s, 3H), 2.02 (m, 2H,), 4.12 (q, 2H, *J* = 7.0 Hz), 4.53 (s, 1H), 11.26 (br, s, 1H, NH). ^{13}C NMR δ 13.6, 17.9, 19.6, 27.8, 32.6, 39.8, 44.1, 95.6, 162.1, 188.6.

Ethyl-3-(benzylamino)but-2-enoate (3c)[25]: Oil. IR (neat, cm^{-1}): 3305, 1645, 1610; ^{1}H NMR δ 1.31 (t, 3H, *J* = 7.0 Hz), 1.93 (s, 3H), 4.14 (q, 2H, *J* = 7.0 Hz), 4.45 (S, 2H), 4.54 (s, 1H), 7.25-7.45 (m, 5H) 12.31 (br, s, 1H, NH). ^{13}C NMR δ 15.6, 26.2, 31.5, 39.6, 91.7, 122.4, 126.3, 127.1, 136.1, 162.6, 189.2.

Ethyl-3-[(4-methylphenyl)amino]but-2-enoate (3e)[38]: Oil. IR (neat, cm^{-1}): 3254, 1654, 1608. ^{1}H NMR δ 1.30, (t, 3H, *J* = 7.2 Hz), 1.81 (s, 3H), 2.41 (s, 3H), 4.34 (q, 2H, *J* = 7.2 Hz), 4.57 (s, 1H), 6.98 (d, 2H, *J* = 8.3 Hz), 7.13 (d, 2H, *J* = 8.3 Hz), 12.58 (br, s, 1H, NH). ^{13}C NMR δ 17.1, 26.8, 30.9, 32.1, 95.6, 121.1, 124.2, 126.1, 135.2, 162.6, 185.9,

4-[(4-Methylphenyl)amino]pent-3-en-2-one (3m)[34]: Solid, m.p. 59-60 ºC (Lit.[34] m.p. 58.60 ºC): IR (neat, cm^{-1}): 3379, 1606, 1562. ^{1}H NMR δ 1.97 (s, 3H), 2.10 (s, 3H), 2.41 (s, 3H), 5.18 (s, 1H), 6.60-7.44 (br, s, 4H), 12.41 (br, s, 1H, NH). ^{13}C NMR δ 19.72, 20.83, 29.10, 97.29, 124.90, 129.69, 135.50, 136.17, 160.65, 195.89.

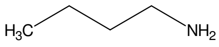
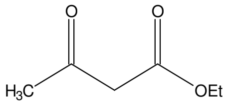
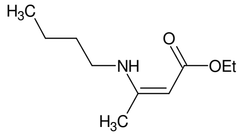
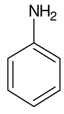
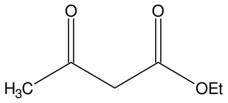
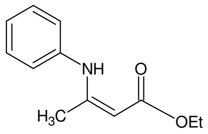
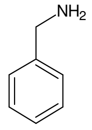
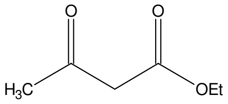
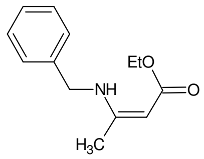
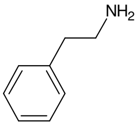
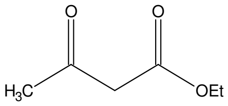
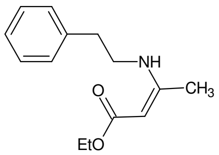
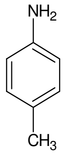
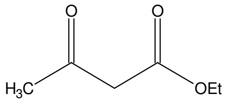
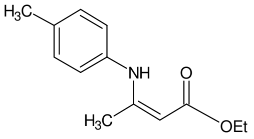
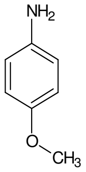
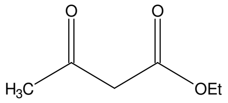
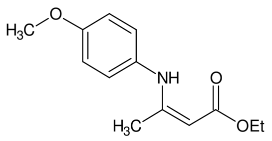
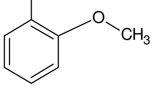
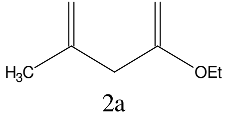
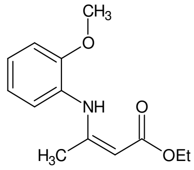
4-[(4-Methoxyphenyl)amino]pent-3-en-2-one (3n)[34]: Oil. IR (neat, cm^{-1}): 3767, 1625, 1571. ^{1}H NMR δ 1.91 (s, 3H), 2.22 (s, 3H), 3.80 (s, 3H), 5.27 (s, 1H), 6.72 (d, 2H, *J* = 9.1 Hz), 7.39 (d, 2H, *J* = 9.1 Hz), 12.01 (br, s, 1H, NH). ^{13}C NMR δ 18.9, 28.5, 49.3, 98.6, 110.7, 126.6, 132.1, 157.8, 162.4, 194.2.

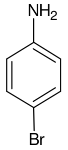
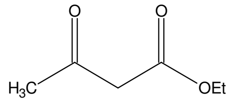
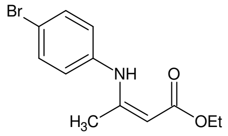
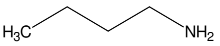
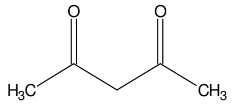
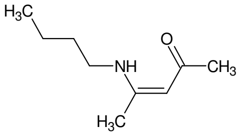
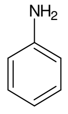
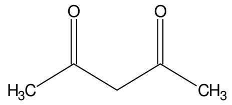
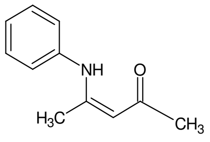
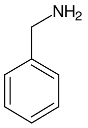
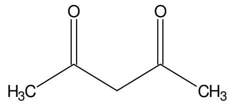
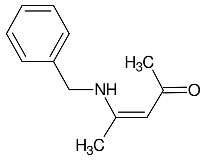
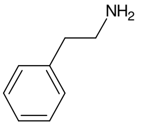
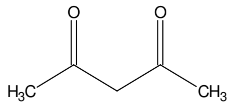
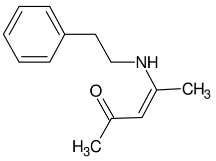
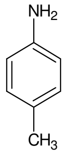
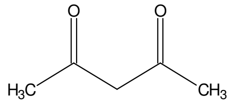
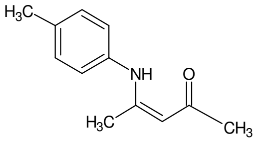
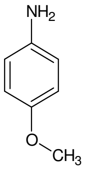
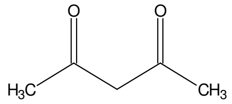
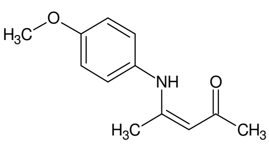
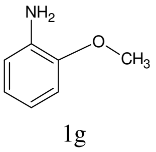
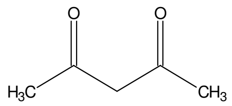
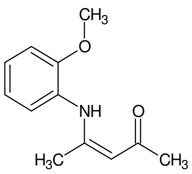
4-[(4-Bromophenyl)amino]pent-3-en-2-one (3p)[34]: Solid, m.p. 52-53 ºC (Lit.[34] m.p. 49-51 ºC): IR (neat, cm^{-1}): 3396, 1615, 1568. ^{1}H NMR δ 1.92 (s, 3H), 2.15 (s, 3H), 5.22 (s, 1H), 7.02 (d, 2H), 7.39 (d, 2H), 12.51 (br, s, 1H, NH). ^{13}C NMR δ 20.1, 29.4, 99.6, 119.6, 127.1, 132.0, 138.1, 161.1, 198.6.

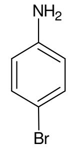
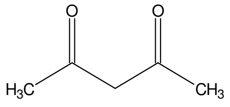
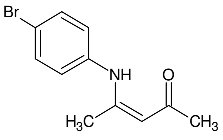
RESULTS AND DISCUSSION

Our preliminary studies were focused on the reaction conditions for the synthesis of β-enamino esters and β-enamino ketones. A variety of primary amines and 1,3-dicarbonyl compounds were subjected to the enamination reaction at room temperature, without any solvent and in presence catalytic amount (10 mol %) of 50 % ferric(III) ammonium nitrate (FAN) to furnish corresponding β-enamino esters and β-enamino ketones in satisfactory yields (69-92 %). All the results were presented in the Table-1. The completion of the reaction was monitored by TLC (EtOH:hexane; 4:6). All the reactions were completed within 20 min except *p*-bromo aniline with ethyl-3-oxobutanoate (entry 8) and pentane-2,4-dione (entry 16). The aryl amines having no substituents or electron-donating group substituents on the phenyl ring were more reactive (entries 2, 6, 10 and 14). An electron-withdrawing group had a strong deactivating effect, thus longer reaction times were required and the corresponding products were obtained in lower yields (entries 8 and 16). In case of *ortho*-substituted aryl amines were reacted little slower than other aryl amines (entries 7 and 15). As expected, a streic factor was pronounced when the group is at the *ortho*-position. The -NH- group was confirmed by ^{1}H NMR spectra, appeared in the region of 11.1-12.9 ppm.

TABLE-1
SYNTHESIS OF β-ENAMINO COMPOUNDS USING FERRIC(III) AMMONIUM NITRATE UNDER SOLVENT FREE CONDITIONS

Entry	Amines	1,3-Dicarbonyl compounds	Product	Time (min)	Yield (%)[a]
1	 1a	 2a	 3a	8	90
2	 1b	 2a	 3b	10	92
3	 1c	 2a	 3c	8	92
4	 1d	 2a	 3d	8	92
5	 1e	 2a	 3e	10	90
6	 1f	 2a	 3f	8	92
7	 1g	 2a	 3g	20	82

8	 1h	 2a	 3h	5 h	69
9	 1a	 2b	 3i	10	90
10	 1b	 2b	 3j	10	90
11	 1c	 2b	 3k	12	92
12	 1d	 2b	 3l	15	92
13	 1e	 2b	 3m	15	90
14	 1f	 2b	 3n	10	90
15	 1g	 2b	 3o	20	85

16	 1h	 2b	 3p	5 h	72

[a]Yield's refer to pure isolated products.

Conclusion

In conculsion, we have developed a new and efficient procedure for the preparation of β-enamino esters and β-enamino ketones catalyzed by FAN. The significant advantages offered by this methodology are operational simplicity, mild reaction conditions, short reaction times, excellent yield of products, no excess of catalyst, no solvent is employed.

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