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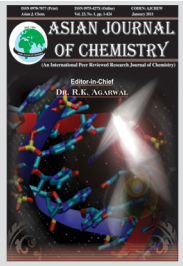

A Facile, Chemoselective and Eco-friendly Solid Phase Synthesis of Enaminones Catalyzed by L-Proline

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A facile and chemoselective method for the synthesis of enaminones by the reaction of aromatic primary amines with various β-ketoesters in the presence of L-proline as activator under solid phase is described. The reactions are promoted by the catalyst in short time (5-6 min) under ambient conditions, without any side products.

Key Words: β-Ketoesters, Aromatic amines, Enaminones, L-Proline, Solid phase.

INTRODUCTION

L-Proline has emerged as an efficient and important catalyst in several transformations such as asymmetric aldol reaction[1], conjugate addition[2] and additions to imines, nitro alkenes[3]. Proline is the only natural amino acid with a secondary amine functionality, which raises the Pk_a value and better nucleophilicity as compared to other amino acids[4]. The reactivity and enantioselectivity of proline-catalyzed reactions are considered as outstanding[4] reactions.

The principles of "solid-phase synthesis" were introduced in 1963 by Merrifield[5]. Since then, the concept of solid phase synthesis has been applied extensively in numerous areas and there has been significant progress in small molecules, especially heterocycles[6], due to several advantages like operational simplicity, easier work-up, better yield and eco-friendly nature. In recent years, chemists have been paying more attention to the applicaton of solvent free methods[7]. Solid-phase organic synthesis (SPOS) is a valuable tool for the generation of structurally diverse compounds for combinatorial libraries[8].

The preparation of enamines is an important transformation due to the wide range of synthetic applications of β-enaminones[9]. Existing methods for the preparation of β-enaminones normally involve the presence of catalysts such as silica gel[10], alumina[11], zinc perchlorate[12], indium tribromide[13], trimethylsilyl triflate[14], cerium ammonium nitrate[15]. Occasionally, these reactions can be performed in the absence of catalysts by use of ionic liquids[16] as the reaction media. In spite of this abundance of methods, they suffer from a number of limitations such as the use of expensive[10,11] or toxic[13,14] catalysts and costly reaction media[16], moderate yields *etc*. For this reason, the development of a general and efficient method for β-enaminones synthesis, that uses a nontoxic and inexpensive catalyst or no solvent at all are still important.

EXPERIMENTAL

Melting points were determined on a Buchi melting-point apparatus and were uncorrected. The progress of the reaction was monitored by thin-layer chromatography (TLC) was performed on silica gel G (Merck) and spots were exposed to iodine vapour or UV light. IR spectra were recorded by using KBr disc on a Perkin-Elmer 240c analyzer. ^{1}H NMR spectra were recorded on Brucker DPX-400 at 400-MHz (chemical shifts in δ, ppm) and mass spectra on an Agilent LC-MS instrument giving only M^+ values in Q + 1 mode.

Preparation of 3 (general procedure): A mixture of compound **1** (1 mmol), compound **2** (1 mmol) and L-proline (1.5 mmol) were ground thoroughly in a mortar using a pestle to a fine powder for 5-6 min. After TLC checking, solid mixture was processed by treating with water. The crude residue was washed with water and dried. The crude solid was recrystallized from a suitable organic solvent to get the pure compound **3(a-j)**.

3a: IR (KBr, ν_{max}, cm^{-1}): 1728 cm^{-1} (s, sharp, -C=O group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 1.30 (t, 3H, $-CH_3$) δ 1.71 (s, 3H, $-CH_3$) δ 4.0 (s, 1H, -NH) δ 4.19 (q, 2H, $-CH_2$) δ 5.24 (s, 1H, vinylic proton) δ 6.46-7.01 (m, 5 H aromatic protons); m/z (M^+ + 1): 206; anal. calcd. (%) for ($C_{12}H_{15}NO_2$) requires C, 70.22; H, 7.36; N, 6.82; found (%) C,70.21; H, 7.36; N, 6.81.

3b: IR (KBr, n_{max}, cm^{-1}): 1735 (s, sharp, -C=O group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ 1.31 (t, 3H, $-CH_3$) δ 4.1

(s, 1H, -NH) δ 4.20 (q, 2H, $-CH_2$) δ 5.26 (s, 1H, vinylic proton) δ 6.45-7.30 (m, 10H aromatic protons); m/z ($M^+ + 1$): 268; anal. calcd. (%) for ($C_{17}H_{17}NO_2$) requires C, 76.38; H, 6.41; N, 5.24; found C, 76.37; H, 6.40; N, 5.22.

3c: IR (KBr, ν_{max}, cm^{-1}): 1725 (s, sharp, -C=O group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 1.25 (t, 3H, $-CH_3$) δ 1.73 (s, 3H, $-CH_3$) δ 3.73 (s, 3H, $-CH_3$) δ 4.2 (s, 1H, -NH) δ 4.25 (q, 2H, $-CH_2$) δ 5.26 (s, 1H, vinylic proton) δ 6.46-7.01 (m, 4H aromatic protons); m/z ($M^+ + 1$): 236; anal. calcd. (%) for ($C_{13}H_{17}NO_3$) requires C, 66.36; H, 7.28; N, 5.95; found (%) C, 66.34; H, 7.29; N, 5.93.

3d: IR (KBr, ν_{max}, cm^{-1}): 1739 (s, sharp, -C=O group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 1.32 (t, 3H, $-CH_3$) δ 3.73 (s, 3H, $-CH_3$) δ 4.08 (s, 1H, -NH) δ 4.20 (q, 2H, $-CH_2$) δ 5.44 (s, 1H, vinylic proton) δ 6.45-7.34 (m, 9H aromatic protons); m/z ($M^+ + 1$): 298; anal. calcd. (%) for ($C_{18}H_{19}NO_3$) requires C, 72.71; H, 6.44; N, 4.71; found (%) C, 72.70; H, 6.42; N, 4.70.

3e: IR (KBr, ν_{max}, cm^{-1}): 1724 (s, sharp, -C=O group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 1.29 (t, 3H, $-CH_3$) δ 1.74 (s, 3H, $-CH_3$) δ 4.15 (s, 1H, -NH) δ 4.24 (q, 2H, $-CH_2$) δ 5.26 (s, 1H, vinylic proton) δ 6.46-7.03 (m, 4H aromatic protons); m/z ($M^+ + 1$): 240; anal. calcd. (%) for ($C_{12}H_{14}NO_2Cl$) requires C, 60.13; H, 5.89; N, 5.84; found (%) C, 60.15; H, 5.9; N, 5.86.

3f: IR (KBr, ν_{max}, cm^{-1}): 1738 (s, sharp, -C=O group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 1.28 (t, 3H, $-CH_3$) δ 4.22 (s, 1H, -NH) δ 4.26 (q, 2H, $-CH_2$) δ 5.26 (s, 1H, vinylic proton) δ 6.40-7.33 (m, 9H aromatic protons); m/z ($M^+ + 1$): 302; anal. calcd. (%) for ($C_{17}H_{16}NO_2Cl$) requires C, 67.66; H, 5.34; N, 4.64; found (%) C, 67.68; H, 5.39; N, 4.66.

3g: IR (KBr, ν_{max}, cm^{-1}): 1724 (s, sharp, -C=O group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 1.26 (t, 3H, $-CH_3$) δ 1.76 (s, 3H, $-CH_3$) δ 4.22 (s, 1H, -NH) δ 4.30 (q, 2H, $-CH_2$) δ 5.26 (s, 1H, vinylic proton) δ 6.46-6.72 (m, 4H aromatic protons); m/z ($M^+ + 1$): 224; anal. calcd. (%) for ($C_{12}H_{14}NO_2F$) requires C, 64.5; H, 6.32; N, 6.27; found (%) C, 64.6; H, 6.31; N, 6.25.

3h: IR (KBr, ν_{max}, cm^{-1}): 1740 (s, sharp, -C=O group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 1.31 (t, 3H, $-CH_3$) δ 4.0 (s, 1H, -NH) δ 4.24 (q, 2H, $-CH_2$) δ 5.43 (s, 1H, vinylic proton) δ 6.44-7.42 (m, 9H aromatic protons); m/z ($M^+ + 1$): 286; anal. calcd. (%) for ($C_{17}H_{16}NO_2F$) requires C, 71.56; H, 5.65; N, 4.91; found (%) C, 71.55; H, 5.63; N, 4.94.

3i: IR (KBr, ν_{max}, cm^{-1}): 1720 (s, sharp, -C=O group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 1.24 (t, 3H, $-CH_3$) δ 1.70 (s, 3H, $-CH_3$) δ 2.35 (s, 3H, $-CH_3$) δ 3.9 (s, 1H, -NH) δ 4.19 (q, 2H, $-CH_2$) δ 5.20 (s, 1H, vinylic proton) δ 6.34-6.81 (m, 4H aromatic protons); m/z ($M^+ + 1$): 220; anal. calcd. (%) for ($C_{13}H_{17}NO_2$) requires C, 71.21; H, 7.81; N, 6.39; found (%) C, 71.22; H, 7.80; N, 6.40.

3j: IR (KBr, ν_{max}, cm^{-1}): 1732 (s, sharp, -C=O group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ 1.33 (t, 3H, $-CH_3$) δ 2.37 (s, 3H, $-CH_3$) δ 4.10 (s, 1H, -NH) δ 4.22 (q, 2H, $-CH_2$) δ 5.43 (s, 1H, vinylic proton) δ 6.34-7.30 (m, 9H aromatic protons); m/z ($M^+ + 1$): 282; anal. calcd. (%) for ($C_{18}H_{19}NO_2$) requires C, 76.84; H, 6.81; N, 4.98; found (%) C,76.82; H, 6.80; N, 4.96.

RESULTS AND DISCUSSION

We have been engaged in the development of new methods for preparing amines. In this context, we desired an expeditious method for the direct conversion of ß-ketoesters and amines to β-enaminones. Here we disclose our latest findings wherein L-proline acts as an effective catalyst under solvent free conditions.

A mixture of β-ketoesters **2(a,b)** (1 mmol), such as ethyl acetoactate, ethyl benzoyloacetate, substituted aromatic amine **1(a-e)** (1 mmol) and L-proline (1.5 mmol) were mixed thoroughly by a simple physical grinding in a mortar using a pestle for 5-6 min under solvent free conditions at room temperature. Immediate TLC examination of the resulting mixture showed the disappearance of the starting material. On processing, the mixture gave a colourless crystalline product different from starting material. Based on the spectral data, the compound was assigned 3-phenylamino-but-2-enoic acid ethyl ester structure (**3a, 3c, 3e, 3g, 3i**) or 3-phenyl-3-phenylamino-acrylic acid ethyl ester structure (**3b, 3d, 3f, 3h, 3j**). The IR spectra in KBr phase of these compounds showed peaks at ≈ 3400 cm^{-1} (NH, broad, strectching) and at 1660 cm^{-1} (sharp, strong, due to α,β-unsaturated carbonyl group). In ^1H NMR a signal for N-attached proton as singlet was formed at δ 8.4 which disappeared on D_2O exchange.

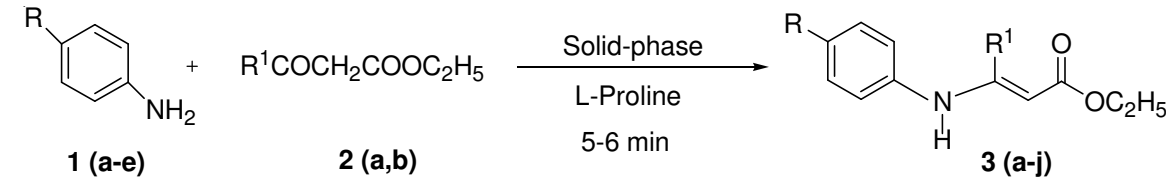
The use of L-proline seems to be essential. This is shown by the fact that the reaction did not proceed in the absence of L-proline, the starting material remained as such on TLC examination even after several hours. The same reaction was examined in different acids like CH_3COOH, dil HCl, H_2SO_4 and different Lewis acids $InCl_3$, $FeCl_3$, $MnCl_2$, out of all these L-proline gives better results in a short duration with high purity and yields.

The effect of the molar ratios of reactants and catalyst has been observed and optimum conditions were determined on the basis of these observations. The ratio of β-ketoester, aromatic substituted amine and L-proline was kept 1 : 1:1.5. Besides the β-ketoester, β-diketone can also be utilized in such reaction. The results are summarized in the Table-1. The transformation proceeded very cleanly, without any traces of side products The regenerated catalyst was removed during workup, which is soluble in water.

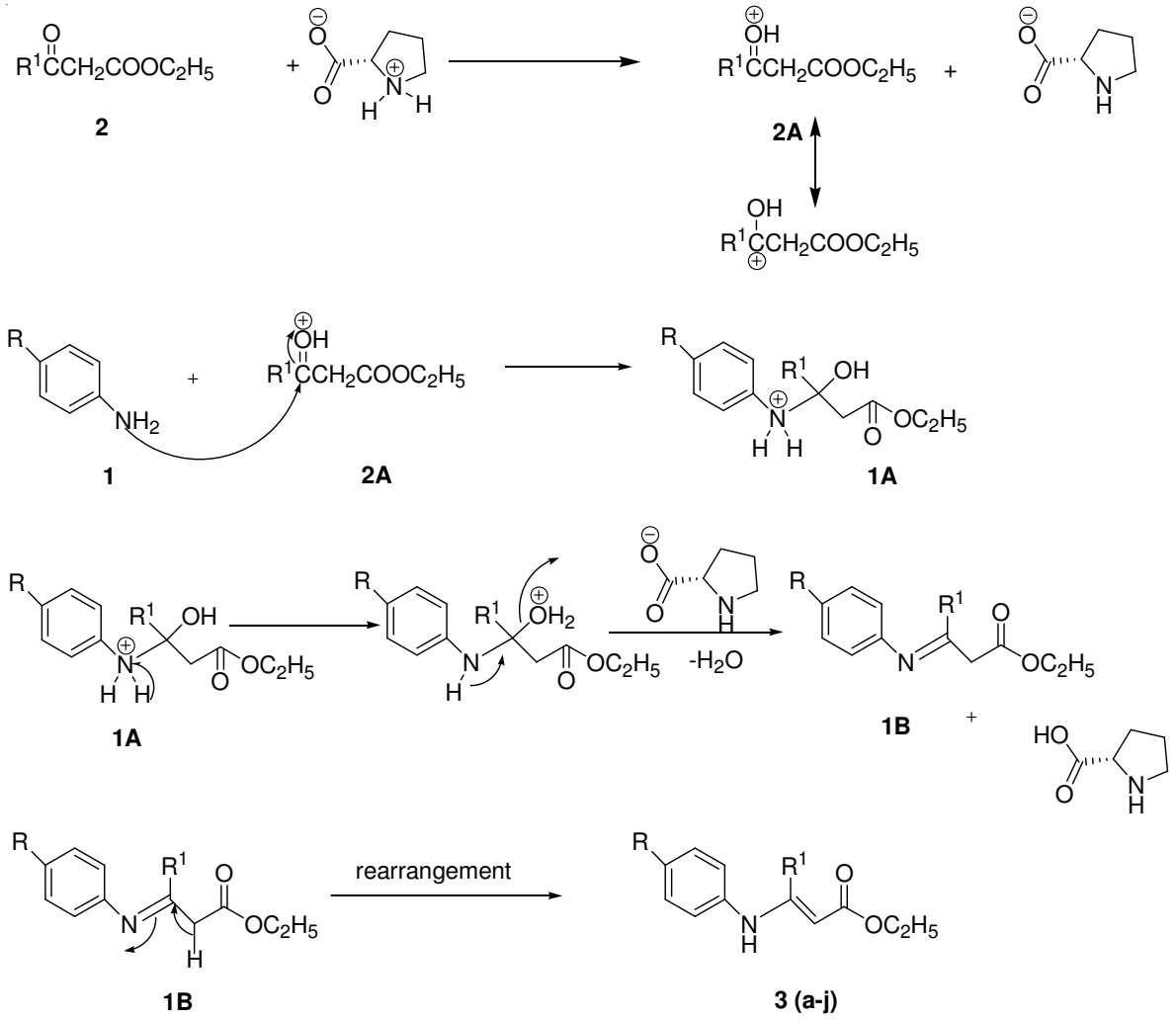
TABLE-1
PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS

Product	R	R^1	m.p. (ºC)	Time (min)	Yield (%)
3a	H	CH_3	41-43	5	85
3b	H	C_6H_5	95-98	5-6	88
3c	OCH_3	CH_3	44-46	4	90
3d	OCH_3	C_6H_5	115-117	5-6	88
3e	Cl	CH_3	40-43	5	86
3f	Cl	C_6H_5	110-112	5-6	91
3g	F	CH_3	42-44	5	87
3h	F	C_6H_5	120-123	5-6	90
3i	CH_3	CH_3	44-47	4-5	84
3j	CH_3	C_6H_5	114-116	5-6	88

It may be mentioned here that Kundu *et al.*[17], carried out the condensation of aromatic amines with β-ketoesters in the



Scheme-I



Scheme-2: Plausible mechanism

presence of L-proline by stirring the reaction mass (liquid mixture) at room temperature without the aid of any solvent for a period of 4-5 h. Then they isolated the products by silica gel chromatography. This seems to be the lone reference as far as the condensation of aromatic amines with β-ketoesters catalyzed by L-proline is concerned. However, out method is different from their method which involves physical mixing of the reactants in a mortar and pestle for a brief period of 5-6 min, giving the products in good yield and high purity, without the aid of any column chromatography.

The probable mechanism of the above condensation, *i.e*., physical grinding, using L-proline as catalyst involves, carbonyl carbon of the β-ketoester protonated by L-proline to yield (2A). The lone pair of electrons on nitrogen attacks the carbonyl carbon to form a condedsed product (IA). Successive deprotonation and dehydration results in the imine (IB) which eventually rearranges to the more conjugated and so better resonance stabilized enamine **3(a-j)**.

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