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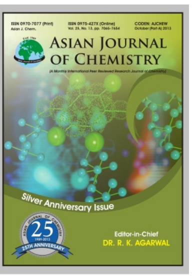

A Mild and Efficient Method for Synthesis of β-Enaminones using Melamine-Formaldehyde Resin Supported H^+ Under Solvent Free Conditions

RAMIN REZAEI* and MOZHDEH SHAKERI

Department of Chemistry, Firoozabad Branch, Islamic Azad University, P.O. Box 74715-117 Firoozabad, Iran

*Corresponding author: Fax: +98 712 6224402; Tel: +98 917 3138690; E-mail: rezaieramin@yahoo.com

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A green and efficient practical approach is developed for the synthesis of β-enaminones using melamine-formaldehyde resin supported H^+ (MFRH) as a mild and inexpensive catalyst in solvent-free media. The present method was performed by combining low cost and readily available amines, 1,3-dicarbonyls and melamine-formaldehyde resin supported H^+ (MFRH) as a catalyst. This method is applicable to both cyclic and acyclic ketones with aromatic and aliphatic amines, and provides several advantages such as environmental friendliness, low cost, good yields and simple workup procedure.

Key Words: β-Enaminones, Amines, 1,3-Dicarbonyls, Melamin formaldehyde, Solvent-free.

INTRODUCTION

β-Enaminones whose chemistry is being continuously developed at an unparallel rapid pace, represents a core skeleton in a large number of natural products[1] and pharmacophores[2]. Experience has shown that compounds with the β-enaminones scaffold often show biological and medical activities[3]. They are also the useful intermediates for the preparation of several amino acids[4], aminols[4c], peptides[5] and alkaloids[6]. The biological activity of β-enaminones and their significances in organic synthesis has attracted continuous interest in developing new methods for their synthesis. The conventional route for the synthesis of enaminones is condensation between 1,3-dicarbonyls and amines. Various catalysts have been used to affect the synthesis of β-enaminones: these include the use of β-cyclodextrin[7], ytterbium triflate[8], $HClO_4{\cdot}SiO_2$[9], silica chloride[10], B_2O_3/Al_2O_3[11], $NaHSO_4/SiO_2$[12], dilute HCl[13], $[(PPh_3)AuCl]/AgOTf$[14], bismuth(III) trifluoroacetate[15], molecular iodine[16], Amberlyst-15®[17], zeolite (ZSM-5)[18], $CoCl_2{\cdot}6H_2O$[19], silica sulphuric acid[20] and ferric(III) ammonium nitrate[21]. Some of these synthetic approaches suffer from harsh reaction conditions, long reaction time, use of costly catalysts and volatile organic solvents and low to moderate yields. Therefore, the expansion of convenient, environmental friendliness and clean approaches is of great interest to chemists and academicians. In addition, in recent years the green context has become a noted issue[22]. The reactions under catalyst- or solvent-free conditions are considerably safe, non-toxic and environmentally friendly. To the best of our knowledge, however, no melamine-formaldehyde resin supported H^+ promoted condensation of 1,3-dicarbonyls and amines has been reported to date. Melamine-formaldehyde resin (MF) is one of the most widely used in polywood and particleboard adhesives and for the preparation and bonding of low- and high-pressure paper laminates and overlays[23]. These facts, prompts us to explore the feasibility of the use of (MFRH) as the mild catalyst to construct the β-enaminone skeleton from the condensation of 1,3-dicarbonyls and amines under solvent-free condition. In this communication, we reported the development of a green and efficient procedure for the synthesis of β-enaminone.

EXPERIMENTAL

Chemicals were either purchased from Fluka, Merck and Aldrich Chemical Companies. Most of the products were purified by recrystallization and were identified by comparison of their mp, IR and NMR spectra with those reported for authentic samples. Progress of the reactions was monitored by TLC using silica gel polygrams SIL G/UV_{254} plates. FT-IR spectra were recorded on a BurkerPenssor 27 Spectrometer. NMR spectra were recorded on a Bruker AVANCE DRX 500 Instrument in $CDCl_3$ or DMSO-d_6 using TMS as internal standard. Chemical shifts were reported in ppm (δ) and coupling constants (*J*), in Hz. Melting points were determined in open capillaries on Mettler FP51 melting point apparatus and are not corrected.

Preparation of melamine-formaldehyde resin supported H^+ (MFRH): Melamine-formaldehyde resin (purchased from

Fars Chemical Company; http://www.farschemical.com) (10 g) was added to 100 mL H_2SO_4 (60 %) at 0 ºC and was stirred for 72 h. The mixture was filtered and washed with acetone (200 mL). The resin was kept at 80 ºC for 10 h in oven to furnish MFRH as a free flowing powder. The amount of H^+ of the new successful heterogeneous MFRH catalyst synthesized by this simple procedure was characterized using back-titration method.

General procedure for the synthesis of β-enaminones 3a-j: To a magnetically stirred mixture of the β-dicarbonyl compounds (1 mmol) and amines (1 mmol), MFRH (0.1 g, 3.90 mol %) was added and the reaction mixture was stirred at 80 ºC for the appropriate time. The reaction was monitored by TLC on silica-gel plates (GF_{254}). After completion of the reaction, warm ethylacetate (10 mL) was added and filtered and the remaining was washed with warm ethyl acetate (10 mL) in order to separate catalyst. Then, EtOAc was evaporated under vacuum and crude product was recrystallized from *n*-hexane/EtOAc.

Spectral data of the product

Compound 3a: Cream crystal, m.p. 197-200 ºC, yield: 83 (%). IR (KBr, ν_{max}, cm^{-1}): 3242(m), 2956(m), 1610(s), 1573(s), 1525(s), 724(w). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.10 (6H, s), 2.22 (2H, s), 2.32 (2H, s), 5.52 (1H, s), 6.23 (1H, s), 7.07-7.10 (2H, d, J = 7.5 Hz), 7.28-7.31 (2H, d, J = 7.5 Hz).

Compound 3b: Cream crystal, m.p. 184-185 ºC, yield: 90 (%). IR (KBr, ν_{max}, cm^{-1}): 3237(s), 2958(m), 1598(s), 1572(s), 1495(s). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.07 (6H, s), 2.19 (2H, s), 2.34 (2H, s), 5.55 (1H, s), 6.92 (1H, s), 7.11-7.29 (5H, m).

Compound 3c: Cream crystal, m.p. 221-222 ºC, yield 87 (%). IR (KBr, ν_{max}, cm^{-1}): 3241(m), 2956(m), 1609(s), 1571(s), 1525(s), 1072(m). ^{1}H NMR ($CDCl_3$) δ (ppm): 1.08 (6H, s), 2.20 (2H, s), 2.32 (2H, s), 5.51 (1H, s), 6.55 (1H, s), 6.99-7.03 (2H, d, J = 10 Hz), 7.40-7.43 (2H, d, J = 10 Hz).

Compound 3d: Cream crystal, m.p. 171-172 ºC, yield: 88 (%). IR (KBr, ν_{max}, cm^{-1}): 3253(s), 2951(m), 1600(s), 1573(s), 1529(s). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.05 (6H, s), 2.12 (5H, d, J = 4.5 Hz), 2.29(5H, d, J = 5.0 Hz), 4.92 (1H, s), 6.36 (1H, s), 6.94-7.00 (3H, m). ^{13}C NMR ($CDCl_3$) δ (ppm): 17.6, 21.0, 28.3, 32.9, 43.0, 50.3, 97.7, 127.0, 127.4, 131.6, 133.5, 134.3, 137.1, 162.6, 197.3.

Compound 3e: Cream crystal, m.p. 102-105 ºC, yield: 84 (%). IR (KBr, ν_{max}, cm^{-1}): 3173(w), 2959(m), 1580(s), 1526(s), 1368(m). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.09 (6H, s), 2.16 (2H, s), 2.31 (2H, s), 2.38 (3H, s), 4.90 (1H, s), 6.55 (1H, s), 7.25-7.75 (3H, m). ^{13}C NMR ($CDCl_3$), δ (ppm): 14.0, 28.2, 33.0, 42.9, 50.3, 98.9, 122.9, 127.1, 129.7, 131.7, 138.4, 151.3, 161.5, 197.7.

Compound 3f: Yellow crystal, m.p. 165-170 ºC, yield: 79 (%). IR (KBr, ν_{max}, cm^{-1}): 3261(m), 2959(w), 1613(s), 1578(s), 1537(s), 1482(m), 1354(m). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.10 (6H, s), 2.24 (2H, s), 2.40 (2H, s), 5.60 (1H, s), 7.10 (1H, s), 7.51-7.96 (4H, m). ^{13}C NMR ($CDCl_3$), δ (ppm): 28.3, 32.9, 43.5, 50.4, 100.1, 117.9, 119.7, 129.0, 130.2, 139.8, 148.9, 158.9, 198.2.

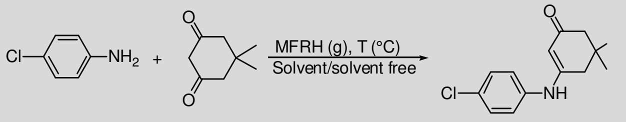
Compound 3i: Yellow crystal, m.p. 133-135 ºC, yield: 75 (%). IR (KBr, ν_{max}, cm^{-1}): 3263(m), 2950(w), 1675(s), 1602(m), 1551(s), 1529(s), 1351(s). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.62 (3H, s), 2.24 (3H, s), 7.48-8.35 (6H, m). ^{13}C NMR ($CDCl_3$), δ (ppm): 24.6, 114.4, 118.9, 125.4, 129.9, 139.0, 148.5, 168.6.

Compound 3j: White crystal, m.p. 104-108 ºC, yield: 90 (%). IR (KBr, ν_{max}, cm^{-1}): 3428(br), 2922(m), 1610(s), 1578(s). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.83 (6H, s), 1.85 (6H, s), 3.35-3.44 (4H, q), 4.92 (2H, s), 10.61 (2H, s).

RESULTS AND DISCUSSION

First of all we carried out a study of the proper conditions to carry out the condensation reaction between the 5,5-dimethylcyclohexane-1,3-dione (dimedone) and 4-chloroaniline (Table-1).

TABLE-1
OPTIMIZATION OF THE REACTION
CONDITIONS FOR THE SYNTHESIS OF **3a-j**[a]



1a **2** **3a-j**

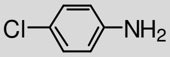
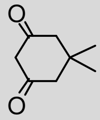
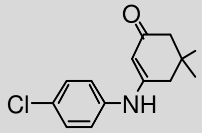
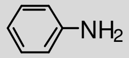
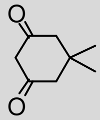
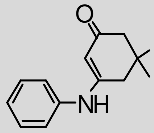
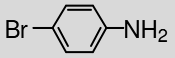
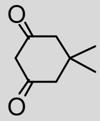
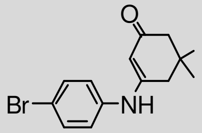
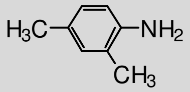
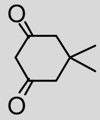
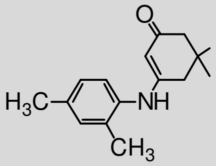
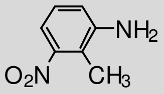
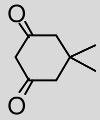
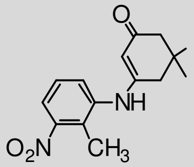
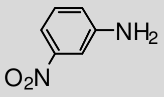
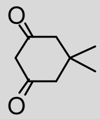
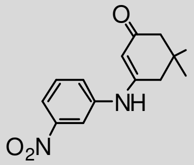
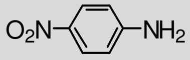
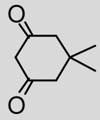
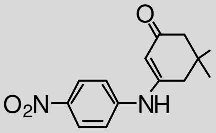
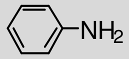
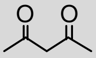
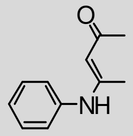
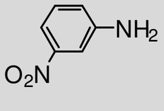
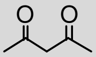
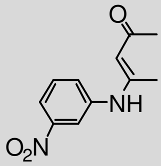
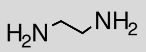
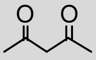
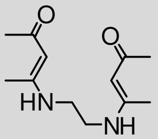
Entry	Solvent	T (ºC)	Amount of catalyst (g)	Time (min)	Yield (%)[b]
1	EtOH	Reflux	0.1	30	85
2	CH_3CN	Reflux	0.1	30	61
3	THF	Reflux	0.1	30	56
4	Toluene	Reflux	0.1	30	37
5	None	r.t.	0.1	120	–
6	None	50	0.1	5	40
7	None	80	0.1	4	90
8	None	100	0.1	4	88
9	None	80	0.08	4	85
10	None	80	0.06	4	74
11	None	80	0.12	4	90
12	None	80	0.14	4	89

[a]Reaction conditions: **1a** (1 mmol), 2 (1 mmol) and catalyst as shown in the table. [b]Isolated yields.

First, we studied the effect of solvents and temperature on the progress of the reaction. Among all the solvents tested, refluxing ethanol proved to be the most efficient (Table-1, entries 1-4). However, as Table-1 indicates, the best results were obtained when the reaction was carried out under solvent-free condition at 80 ºC (Table-1, entry 7). The amount of catalyst (MFRH) has some influence on the reaction yield. The use of 0.1 g of MFRH is sufficient to push the reaction forward (Table-1, entry 7) and an excess has a negative effect on the overall yield (Table-1, entries 11 and 12). When the amount of MFRH was reduced to 0.08 or 0.06 g, the same effect was observed (Table-1, entries 9 and 10). With an optimized condition in hand, the scope of the process with regard of the substituents of the anilines and 1,3-dicarbonyls was studied. The results of the reactions of substituted anilines (**1a-j**) with dimedone **2a** and acetylacetone **2b** to deliver β-enaminones **3a-j** are summarized in Table-2.

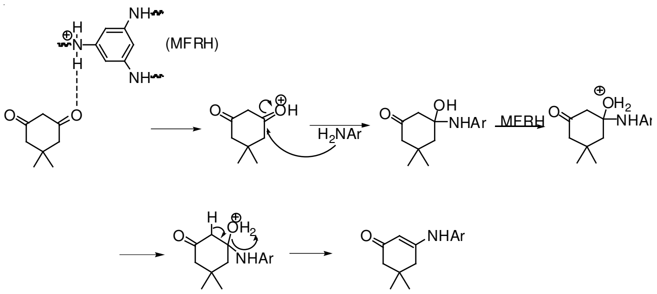
As depicted in Table-2, the reaction tolerates electron-neutral, electron poor and electron-rich substituents in anilines. The yields of these reactions figure in the range of 75-90 % and the reaction time varied from 3 to 20 min. The structures

TABLE-2
REACTION OF ANILINES WITH 1,3-DICARBONYLSIN THEPRESENCE OF 0.1 g MELAMINE-FORMALDEHYDE RESIN SUPPORTED H$^+$ (MFRH) IN SOLVENT-FREE CONDITION[a]

Entry	Amine		β-Dicarbonyl		Product		Time (min)	Yield[b] (%)
1		**1a**		**2a**		**3a**	4	90
2		**1b**		**2a**		**3b**	3	90
3		**1c**		**2a**		**3c**	7	87
4		**1d**		**2a**		**3d**	6	88
5		**1e**		**2a**		**3e**	8	84
6		**1f**		**2a**		**3f**	5	79
7		**1g**		**2a**		**3g**	4	86
8		**1h**		**2b**		**3h**	20	75
9		**1i**		**2b**		**3i**	15	75
10		**1j**		**2b**		**3j**	12	90

[a]Reaction conditions: amine (1 mmol), 1,3-dicarbonyl (1 mmol) and MFRH (0.1 g) under solvent-free condition. [b]Isolated yields after column chromatography or recrystallization.

of the products were established on the basis of spectroscopic evidence. 4-Chloroaniline (**1a**) which had a weak electron-withdrawing chloro group, afforded a comparable yield to that of the corresponding unsubstituted aniline (**1b**) (Table-2, entry 1 *versus* entry 2). Aniline (**3c**) bearing a *p*-Br on the phenyl ring delivered a slightly lower yield than that of the counterpart with a *p*-Cl (Table-2, entry 3 *versus* 1). Introduction of two methyl group at the *ortho* and *para*-position of phenyl ring of aniline caused a somewhat lower yield (Table-2, entry 4) due to the steric factor. In the case of strongly electron-poor aniline such as **1f**, the reactivity in the condensation reaction dropped (Table-2, entry 6). In comparison with dimedone, acetylacetone furnished a relatively lower yield and longer reaction time (Table-2, entry 8 *versus* 2). Aliphatic diamines such as 1,2-ethylene diamine can be used in this reaction smoothly and the yield was good (Table-2, entry 10). A proposed reaction mechanism is depicted in **Scheme-I**.



Scheme-I: Proposed mechanism for the melamine-formaldehyde resin supported H^+ (MFRH) catalyzed synthesis of β-enaminones.

Conclusion

A simple and an efficient synthesis method is developed for β-enaminones using melamine-formaldehyde resin supported H^+ (MFRH) catalyst under solvent-free conditions. This method offers some advantages in terms of simplicity of performance, low reaction times, good to excellent yields, solvent-free condition and it follows along the line of green chemistry.

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