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Orginal Research Article

Catalyst and solvent-free synthesis of β-enaminone derivatives

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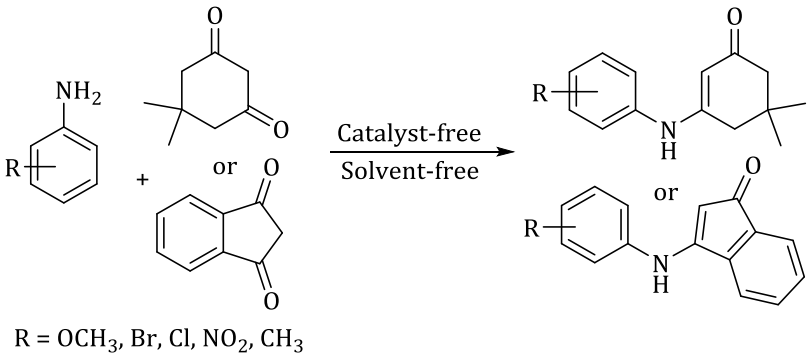
ABSTRACT

In this study, the green procedure for synthesis of the β-enaminones is described. The reaction of aromatic amines with β-dicarbonyl compounds under solvent and catalyst-free conditions at 120 °C affords the β-enaminone and β-enamino esters in high-to-excellent yields, in short reaction time, easy separation, work up and purification without need to column chromatography. Also, some new derivatives of β-enaminones were synthesized using this method. The prominent advantages of this new method is operational simplicity, good yields in short reaction times, easy work-up procedures, catalyst and solvent free condition.

Graphical Abstract



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Introduction

β-Enaminone derivatives are an important owing to apply as synthons for the synthesis of various biologically active compounds, such as anti-epileptic, antibacterial, anti-inflammatory, anticonvulsant, antitumor, and other trapiutic agents [1–8]. Therefore, a great deal of interest in the synthesis of this class of compounds is demanded. The direct condensation of the amines with the β-dicarbonyl compounds has been employed as a useful synthetic procedure toward β-enaminones by several catalysts [9]. However, these reported methods are accompanied by some drawbacks including low yield, long reaction time, low selectivity, no generality, the use of non-available and expensive reagents, tedious work-up procedure, and lack of adaptation with the green chemistry standpoint. Therefore, an efficient, simple, general, green, and cheap protocol for the synthesis of β-enaminones is desired.

In this paper, the authors report a new, clean and highly efficient method for synthesis of the β-enaminones *via* β-enamination of β-dicarbonyl compounds using aryl amines and dicarbonyl compounds without solvent and catalyst as a new and non-toxicprotocol at 120 °C (Scheme 1).

Experimental

Materials and methods

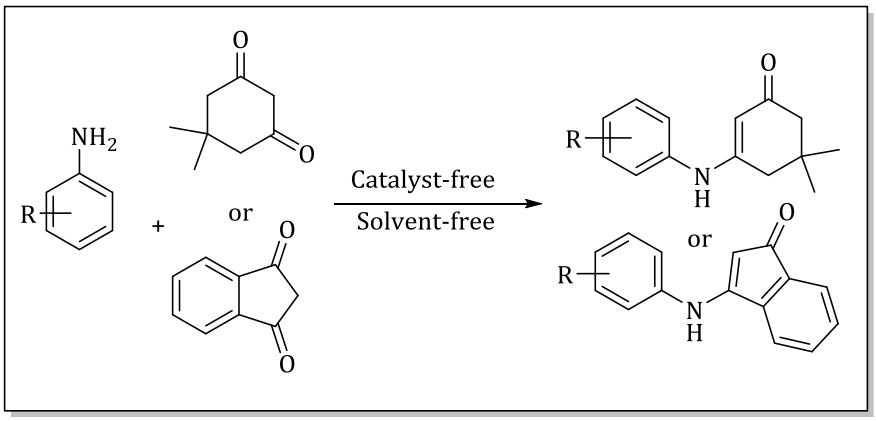
The melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. The IR spectra were recorded by the Perkin Elmer FT-IR spectrometer at the scanning range of 4000-400 cm^{-1}. ^1H NMR spectra were obtained by using the Bruker DRX- 300 MHZ NMR instrument.

General procedure for the synthesis of β-enaminone and β-enamino ester derivatives

The mixture of the amine (1 mmol) and β-dicarbonyl compound (1 mmol) in a round-bottomed flask was stirred in an oil-bath under solvent and catalyst-free condition at 120 °C. After completion of the reaction (Monitored by TLC) at appreciated time in Table 1, EtOH (15 mL) was added and mixed for 15 min. The reaction mixture was cooled to produce the crude product. Then, the mixture was purified by recrystallization from EtOH/H_2O (1:1). This method is large scalable for 100 g of starting material.

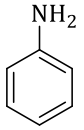
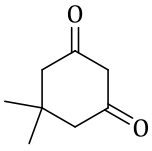
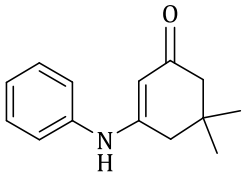
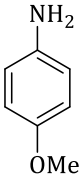
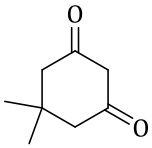
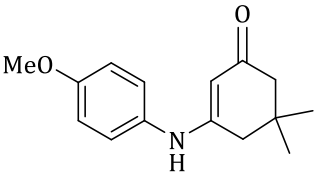
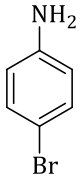
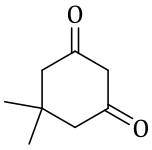
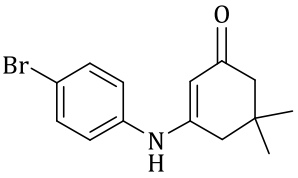
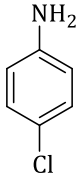
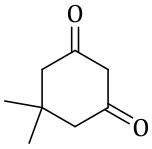
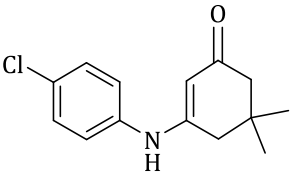
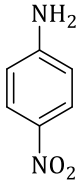
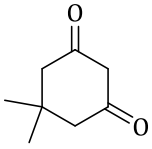
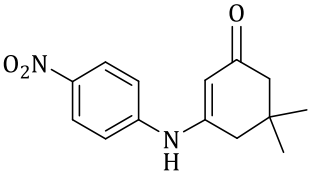
The selected spectral data

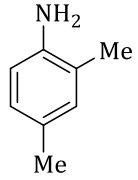
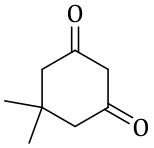
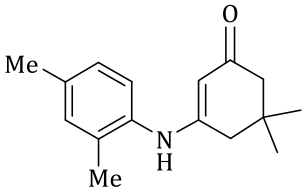
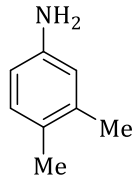
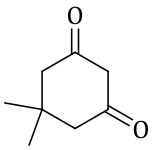
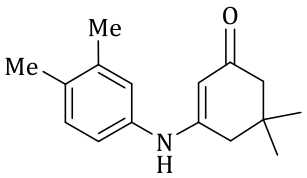
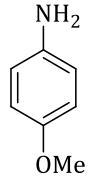
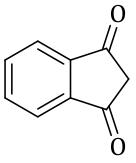
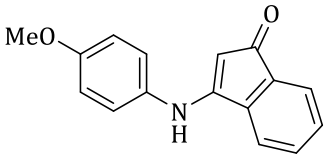
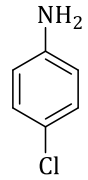
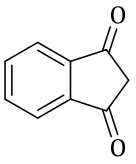
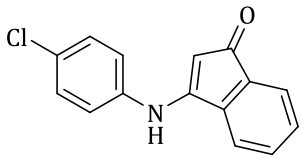
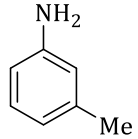
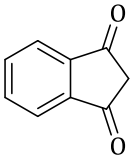
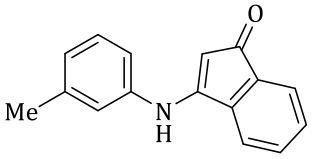
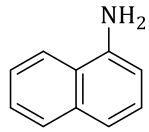
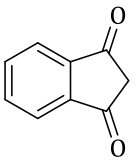
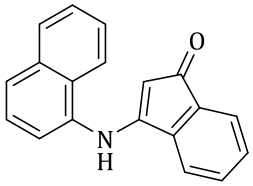
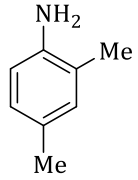
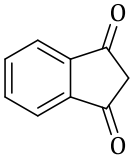
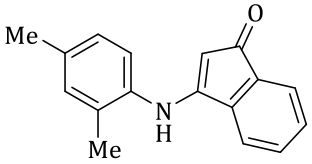
5,5-Dimethyl-3-(phenylamino)cyclohex-2-en-1-one (Entry 1)



Scheme 1. Catalyst and solvent-free synthesis of β-enaminones

Table 1. The catalyst and solvent-free synthesis of the β-enaminone and β-enamino esters using aryl amines and ethyl acetoacetate, dimedone or 2*H*-indene-1,3-dione

Entry	Amine	β-dicarbonyl	Product	Time (h)	Yield (%)	M.p. (°C)	[lit.]
1				2.0	92	182	[10]
2				1.5	94	190	[10]
3				3.0	87	221	[11]
4				3.0	86	195	[12]
5				2.0	89	200	[12]

6				2.5	90	168-170
7				2.5	92	160-162
8				1.5	94	197-200
9				3.0	87	177-185
10				2.0	89	170-175
11				2.5	92	163-167
12				2.5	89	123-127

Brown solid, IR (KBr) (ν_{max}/ cm^{-1}): 3236, 3061, 2959, 1597, 1572, 1525, and 1368. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (s, 6H, 2×CH_3), 2.21 (s, 2H, CH_2), 2.34 (s, 2H, CH_2), 5.57 (s, 1H, CH), 7.13 (s, 1H, NH), 7.26-7.16 (m, 5H, Ar).

3-((4-Methoxyphenyl) amino)-5,5-dimethylcyclohex-2-en-1-one (Entry 2)

Cream solid, IR (KBr) (ν_{max}/ cm^{-1}): 3206, 3011, 2955, 1509, 1570, 1608, and 1036. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (s, 6H, 2×CH_3), 2.12 (s, 2H, CH_2), 2.13 (s, 2H, CH_2), 3.8 (s, 3H, OCH_3), 5.37 (s, 1H, CH), 6.04 (s, 1H, NH), 6.85 (d, 2H, *J* = 9Hz, Ar), 7.07 (d, 2H, *J* = 9 Hz, Ar).

3-((4-Bromophenyl) amino)-5,5-dimethylcyclohex-2-en-1-one (Entry 3)

Yellow solid, IR (KBr) (ν_{max}/ cm^{-1}): 3241, 3042, 2956, 1610, and 1544. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 6H, 2×CH_3), 2.21 (s, 2H, CH_2), 2.32 (s, 2H, CH_2), 5.53 (s, 1H, CH), 6.43 (s, 1H, NH), 7.02 (d, 2H, J = 8.5 Hz, Ar), 7.43 (d, 2H, J = 8.7 Hz, Ar).

3-((4-Chlorophenyl) amino)-5,5-dimethylcyclohex-2-en-1-one (Entry 4)

Yellow solid, IR (KBr) (ν_{max}/ cm^{-1}): 3241, 3044, 2957, 1574, 1545, and 1611. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (s, 6H, 2×CH_3), 2.21 (s, 2H, CH_2), 2.33 (s, 2H, CH_2), 5.49 (s, 1H, CH), 6.79 (s, 1H, NH), 7.08 (d, 2H, *J* = 9 Hz, Ar), 7.26 (d, 3H, *J* = 9 Hz, Ar).

5,5-Dimethyl-3-((4-nitrophenyl) amino)cyclohex-2-en-1-one (Entry 5)

Yellow solid, IR (KBr) (ν_{max}/ cm^{-1}): 3254, 3068, 2954, 1557, 1606, and 1538. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (s, 6H, 2×CH_3), 2.29 (s, 2H, CH_2), 2.38 (s, 2H, CH_2), 5.87 (s, 1H, CH), 6.18 (s, 1H, NH), 7.29-7.26 (m, 2H, Ar), 8.21 (d, 2H, *J* = 9Hz, Ar).

3-((2,4-Dimethylphenyl) amino)-5,5-dimethylcyclohex-2-en-1-one (Entry 6)

Yellow solid, IR (KBr) (ν_{max}/ cm^{-1}): 3255, 2953, 3033, 2868, 1571, 1607, and 1525. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.09 (s, 6H, 2×CH_3), 2.15 (m, 5H, CH_2), 2.33 (m, 5H, CH_2), 4.99 (s, 1H, CH), 5.90 (s, 1H, NH), 7.04-6.99 (m, 3H, Ar).

3-((3,4-Dimethylphenyl) amino)-5,5-dimethylcyclohex-2-en-1-one (Entry 7)

Yellow solid, IR (KBr) (ν_{max}/ cm^{-1}): 3222, 3097, 2961, 1538, 1579, and 1601. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (s, 6H, 2×CH_3), 2.19-2.21 (m, 8H, 2×CH_3, CH_2), 2.31 (s, 2H, CH_2), 5.51 (s, 1H, CH), 6.44 (s, 1H, NH), 7.07-6.85 (m, 3H, Ar).

3-(4-methoxyphenyl) amino)-1H-inden-1-one (Entry 8)

Purple solid, IR (KBr) (ν_{max}/ cm^{-1}): 3227, 3049, 1713, 1656, 1607, and 1350. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.59 (s, 3H, OCH_3), 5.10 (s, 1H ,CH), 6.48 (d, 2H, *J* = 6.69, Ar), 6.620 (d, 2H , *J* = 6.54 , Ar), 7.00 (d, 1H, *J* = 8.96 Hz, Ar), 7.49-7.30 (m, 2H, Ar), 7.805 (d, 1H, Ar), 9.85 (s, 1H, NH).

3-(4-chlorophenyl) amino)-1H-inden-1-one (Entry 9)

Red solid, IR (KBr) (ν_{max}/ cm^{-1}): 3049, 3234, 1657, 1540, and 1491. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.29 (s, 1H, CH), 7.95-7.89 (m, 3H, Ar), 7.82 (d, 2H, Ar, *J* = 7.16 Hz), 7.56 (d, 1H, Ar), 7.33 (d, 2H, *J* = 7.0 Hz, Ar), 9.92 (s, 1H, NH).

3-(3-methylphenyl)amino)-1H-inden-1-one (Entry 10)

Violet solid, IR (KBr) (ν_{max}/ cm^{-1}): 3319, 2922, 1700, 1651, and 1450. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, CH_3), 6.44 (d, 1H, *J* = 8.148 Hz, CH), 6.79 (d, 1H, *J* = 8025 Hz, Ar), 7.45-7.30 (m, 4H, Ar), 7.73 (s, 1H, Ar), 7.92-7.87 (m, 1H, Ar), 9.14-9.12 (m, 1H, Ar) 10.71 (s, 1H, NH).

3-(naphthalen-1-ylamino)-1H-inden-1-one (Entry 11)

Purple solid, IR (KBr) (ν_{max}/ cm^{-1}): 3422, 2923, 1570, 1702, and 1489. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75 (s, 1H, CH), 8.241-7.76 (m, 8H, Ar), 8.43 (d, 1H, *J* = 7.35), 9.16 (s, 1H, Ar), 9.45 (d, 1H, *J* = 6.83 Hz, Ar), 11.10 (s, 1H, NH).

3-(2,4-dimethylphenylamino)-1H-inden-1-one (Entry 12)

Purple solid, IR (KBr) (ν_{max}/ cm^{-1}): 3446, 3235, 1585, 1484, 353.39. ^{1}HNMR (300 MHz, $CDCl_3$): δ 2.03 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 4.52 (s, 1H, CH), 9.128 (d, 1H, *J* = 6.84 Hz, Ar), 7.99-7.39 (m, 6H, Ar), 10.59 (s, 1H, NH).

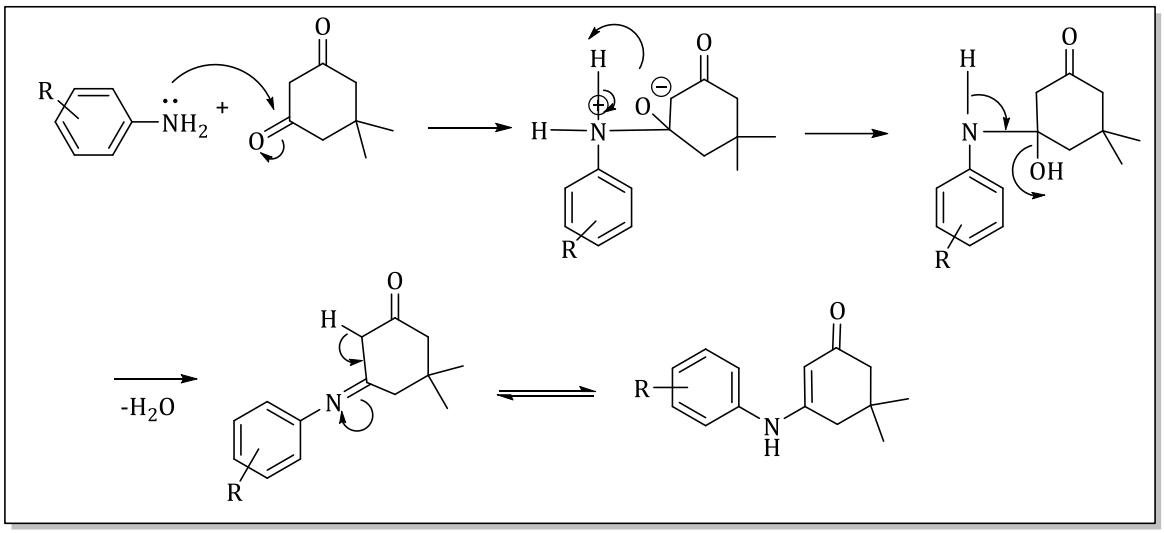
Results and discussion

To achieve the scope of this high green protocol, variety of aryl amines and dicarbonyl compounds were subjected under solvent and catalyst-free condition. Armed in Table 1, dimedone and 2*H*-indene-1,3-dione reacted with the various amines having electron withdrawing and electron releasing groups in short reaction times and high yields.

The proposed mechanism for this reaction is shown in Scheme 2. Nuclephilic attacking of the aryl amine to carbonyl group of the dicarbonyl compounds followed by *H*-abstraction and dehydration to give keto-imine form which taotumerized to the desired product.

Conclusion

In sammery, in this study, an efficient and green procedure was developed for a convenient and mild synthesis of various β-enaminones through the reaction of 1,3-dicarbonyl compounds and amines under solvent and catalyst-free conditions. Operational simplicity, high yields, short reaction times, easy work-up procedures, efficiency, and catalyst and solvent-free condition are advantages of this method for the preparation of β-enaminone derivatives.



Scheme 2. Suggested mechanism for the catalyst and solvent-free synthesis of β-enaminones

Disclosure statement

No potential conflict of interest was reported by the authors.

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