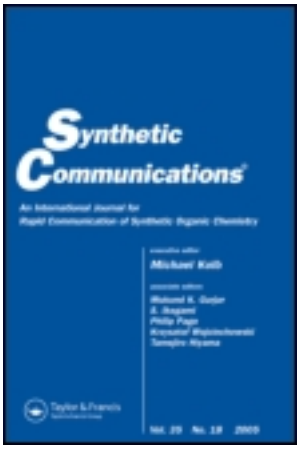

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Molecular Iodine-Catalyzed Mild and Effective Synthesis of β-Enaminones at Room Temperature

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MOLECULAR IODINE–CATALYZED MILD AND EFFECTIVE SYNTHESIS OF β-ENAMINONES AT ROOM TEMPERATURE

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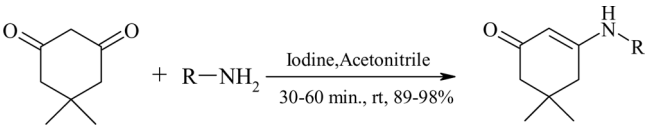
GRAPHICAL ABSTRACT



Abstract *Molecular iodine has been found to be an efficient and ecofriendly catalyst for the synthesis of β-enaminones from dimedone and amines at room temperature in the presence of acetonitrile within 60 min. The experimental procedure is simple, includes shorter reaction times, and results in excellent yields of the products.*

Keywords Acetonitrile; amines; dimedone; β-enaminones; molecular iodine

INTRODUCTION

β-Enaminones are very useful synthons and are used successfully in the syntheses of bioactive heterocyclic compounds such as 1,4-dihydropyridines,[1] 4-arylacridinediones,[2] and many therapeutic agents like antibacterial,[3a] anticonvulsant,[3b] anti-inflammatory,[3c] and antitumor agents.[3d] β-Enaminone also finds application as intermediates in the syntheses of several amino acids,[4a] aminols,[4b] peptides,[4c] and alkaloids.[4d]

The classical synthesis of β-enaminones involves direct condensation of β-dicarbonyl compounds with amines under reflux in an aromatic solvent with azeotropic removal of water.[5] The other reported methods include condensation of β-dicarbonyl compounds with amines in the presence of catalytic HCl,[6] *para*-tolune sulfonic acid (*p*-TSA),[7] AcOH,[8] $HClO_4$-SiO_2,[9] montmorillonite K10,[10] silica gel,[11] ceric ammonium nitrate (CAN),[12] $CoCl_2 \cdot 6H_2O$,[13] $NaAuCl_4$,[14] and $ZrCl_4$.[15] Each of the reported protocols has its own merits and demerits. Recently, microwave irradiation has been explored for this conversion in the presence of water[16] or without any catalyst and solvent.[17] Subsequently, a

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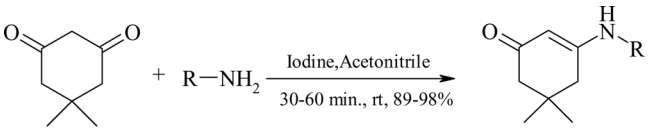


1 2 3

Scheme 1. Synthesis of β-enaminones from dimedone and amines.

solid-state synthesis involving $KHSO_4 \cdot SiO_2$ has also appeared.[18] However, in these methods, the condensation of aromatic amines takes longer and requires higher temperatures for the conversion. Hence, there is still a chance to develop a simpler and greener method for the condensation of amines and β-dicarbonyl compounds.

From our laboratory, we have reported the successful use of molecular iodine as a catalyst for the syntheses of various biologically important organic molecules and in different organic transformations, such as synthesis of dibenzo[*a,j*]xanthenes by a one-pot condensation of 2-naphthol with aldehydes,[19a] synthesis of β-acetamido-β-aryl-propiophenones,[19b] α,α′-bis(arylmethylidene) cycloalkanones,[19c] and *N,N*′-disubstitutedureas/thioureas,[19d] the regioselective synthesis of β-iodoethers,[19e] and a rapid chemoselective synthesis of azines.[19f] In continuation of our work on the development of efficient and ecofriendly methods for the synthesis of various organic molecules under different reaction conditions, synthesis of a series of β-enaminones from dimedone in the presence of iodine is being reported herein (Scheme 1).

RESULTS AND DISCUSSION

Initially, we carried out an uncatalysed reaction between aniline (5 mmol) and dimedone (5 mmol) in acetonitrile, as this condensation is expected to give the best results in polar solvents at room temperature, but no significant yield was obtained. Reactions in solvents such as tetrahydrofuran (THF), CH_2Cl_2, dimethylformamide (DMF), and EtOAc as well as solvent-free reaction were also tried but gave only lower yields of the desired product after prolonged reaction times. We executed the same reaction in acetonitrile in the presence of molecular iodine to obtain β-enaminone in 98% yield. To standardize the amount of catalyst used in this reaction, we carried out reactions of dimedone (5 mmol) with aniline (5 mmol) in acetonitrile with different amount of iodine, and the results are summarized in Table 1.

To check the scope of this reaction, a variety of substituted amines were treated with dimedone in the presence of catalytic amount of iodine. Quantitative conversions were obtained within 1 h of reaction, and the results are presented in Table 2.

Anilines containing electron-donating groups such as $–CH_3$ and $–OCH_3$ (entries **3b**–**3f**) and electron-withdrawing substituents such as $–NO_2$ and –Cl (entries **3i**–**3l**) afforded the corresponding β-enaminone in excellent yield. It is noteworthy that substituents such as –COOH (entry **3m**) were tolerated, and benzyl amine (entry **3h**) was also shown to be efficient. The structures of all the products were confirmed by mass spectral analysis and were found to be comparable with authentic samples.

Table 1. Optimization of amount of iodine for the synthesis of β-enaminones

Entry	Amount of iodine (mmol)	Time (min)	Yield (%)[a]
1	0	120	Trace
2	5	60	20
3	2.5	60	50
4	1.0	60	65
5	0.5	60	72
6	0.1	30	97

[a]Isolated yields.
[b]Reaction conditions: dimedone (5 mmol), aniline (5 mmol), and catalyst as shown in the table.

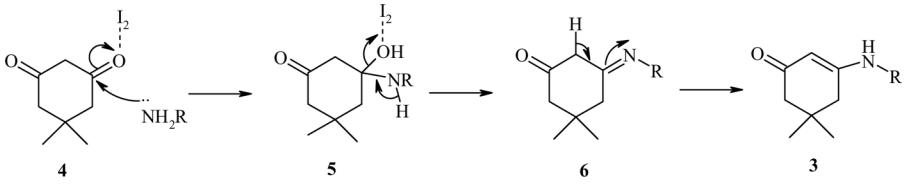
Table 2. β-Amination of dimedone with amines (**2**) using catalytic iodine[a]

Product (**3**)	**2**	Time (min)	Yield[b] (%)
3a	$C_6H_5NH_2$	30	98
3b	$4\text{-}CH_3C_6H_4NH_2$	40	96
3c	$2\text{-}CH_3C_6H_4NH_2$	40	95
3d	$2\text{-}CH_3OC_6H_4NH_2$	45	93
3e	$3\text{-}CH_3C_6H_4NH_2$	50	95
3f	$4\text{-}CH_3OC_6H_4NH_2$	35	97
3g	$C_{10}H_7NH_2$	60	90
3h	$C_6H_5CH_2NH_2$	40	97
3i	$4\text{-}NO_2C_6H_4NH_2$	55	89
3j	$4\text{-}ClC_6H_4NH_2$	50	95
3k	$3\text{-}ClC_6H_4NH_2$	50	93
3l	$2\text{-}ClC_6H_4NH_2$	45	90
3m	$2\text{-}HOOCC_6H_4NH_2$	60	93

[a]All reactions were performed using amine (5 mmol), dimedone (5 mmol), and iodine (0.1 mmol).
[b]Isolated yield. All the compounds are known and physical properties agree with the reported values. Mass spectral data of all the products matches with the reported data.

Mechanism

A plausible mechanism for the formation of β-enaminone has been envisaged. The condensation of dimedone with amine is expected to proceed through an addition–elimination mechanism. It is assumed that dimedone first gets activated in the presence of iodine; subsequently, the lone pair of electrons on nitrogen of the amine adds onto the carbonyl moiety to furnish an intermediate **5**, which may



Scheme 2. Plausible mechanism for the formation of β-enaminone.

lose a molecule of water to give an imine **6**. This imine may get tautomerized to give β-enaminone as shown in Scheme 2.

EXPERIMENTAL

All amines and β-dicarbonyl compound were commercial products and were used without further purification. Yields refer to yield of the isolated products. Melting points were measured on a Raaga, Chennai apparatus; gas chromatography (GC)–mass spectra were recorded on a Shimadzu GC-MS QP 5050A instrument.

General Experimental Procedure for the Synthesis of β-Enaminones

A mixture of amine (5 mmol), dimedone (5 mmol), and iodine (0.1 mmol) was taken in a round-bottomed flask in 5 ml of acetonitrile and stirred at room temperature (for a stipulated time as indicated in Table 1). After completion of the reaction as monitored by thin-layer chromatography (TLC), EtOAc (3 mL) was added, and the mixture washed with hot water (5 mL) followed by diluted HCl (5 mL) and dried over $MgSO_4$. The solvent was then removed under vacuum to get the product. An analytical grade sample was obtained by recrystallization from aqueous alcohol. Yields of all the products prepared by this procedure are presented in Table 1.

CONCLUSION

In conclusion, a rapid, efficient, and cost-effective procedure has been developed for the synthesis of β-enaminones. The procedure follows green chemistry norms because no heating or additional equipment is required. The simplicity, together with the use of inexpensive, nontoxic, easy-to-handle, and environmentally benign catalyst iodine, at 25 °C is a remarkable feature of the procedure.

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