

**MICROWAVE-INDUCED BISMUTH NITRATE-CATALYZED EXPEDITIOUS ENAMINATION OF  $\beta$ -DICARBONYL COMPOUNDS UNDER SOLVENT-FREE CONDITIONS**

**Debasish Bandyopadhyay, and Bimal K. Banik\***

*Department of Chemistry, The University of Texas-Pan American, 1201 West University Drive, Edinburg, Texas 78539; Phone: 956-665-8741; Fax: 956-665-5006, E-mail: banik@utpa.edu*

**Abstract:** Bismuth nitrate-catalyzed, automated microwave-assisted expeditious synthesis of  $\beta$ -enaminones and  $\beta$ -enaminoesters has been carried out in an efficient manner under solvent-free condition. The reaction is general for primary, secondary (cyclic, heterocyclic and acyclic), benzylic as well as aromatic amines.

**Keywords:** Enamination,  $\beta$ -dicarbonyl compounds, microwave irradiation, bismuth nitrate pentahydrate, catalysis, ecofriendly.

**Introduction:** Enamination of  $\beta$ -dicarbonyl compounds to form  $\beta$ -enaminones and  $\beta$ -enaminoesters is a significant and widely used transformation in organic chemistry<sup>1</sup>. The products can be used as an important scaffold for the synthesis of several bioactive compounds which includes anticancer<sup>2</sup>, antibacterial<sup>3</sup>, anti-inflammatory<sup>4</sup> and anticonvulsant<sup>5</sup> agents. They are valuable intermediates for the synthesis of biologically active amino acids<sup>6</sup>, alkaloids<sup>7</sup>, aminols<sup>8</sup> as well as peptides<sup>9</sup>. Consequently, many methods<sup>10</sup> for the synthesis of  $\beta$ -enaminones and  $\beta$ -enaminoesters have been developed using different catalysts, solvents and conditions. Recently, bismuth salts have emerged as efficient Lewis acids due to their relatively low toxicity, ready availability at a low cost and tolerance of trace amounts of water. Therefore, we have investigated bismuth salts to address some of the limitations posed by known methods. Herein, in continuation of our research on bismuth salts-catalyzed<sup>11</sup> reactions, we disclose a novel one-pot synthesis of structurally diverse  $\beta$ -enaminones and  $\beta$ -enaminoesters by reacting amines with  $\beta$ -dicarbonyl compounds in the presence of catalytic amount (~5 mol%) of bismuth nitrate pentahydrate under solvent-free condition (Scheme 1).

**Scheme 1**

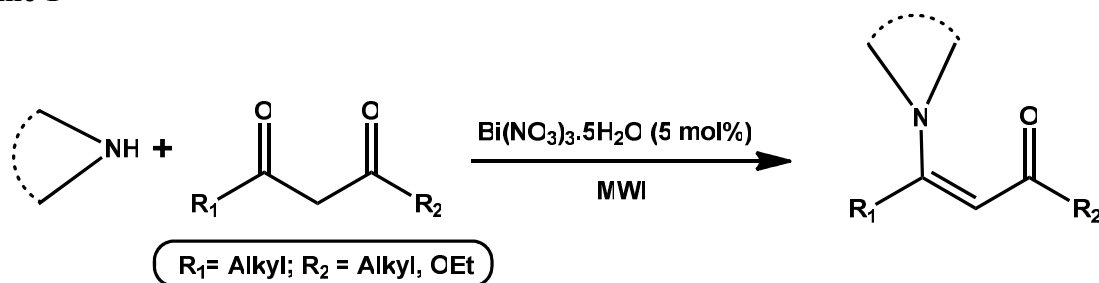
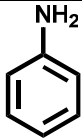

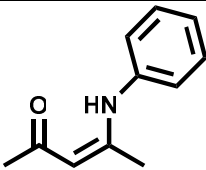
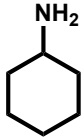

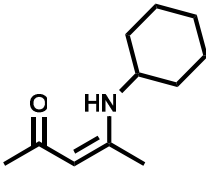
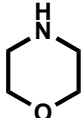
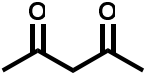
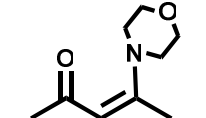
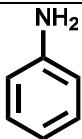
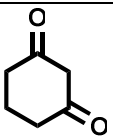
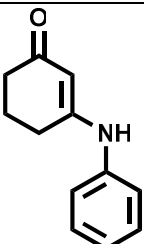
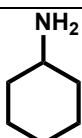
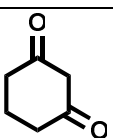
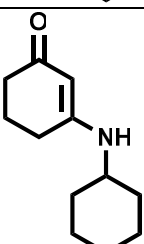
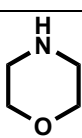
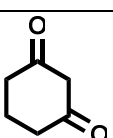
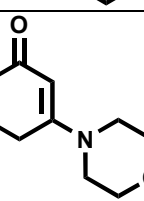

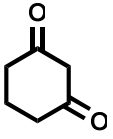
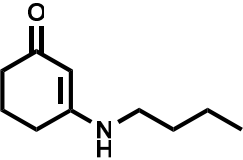
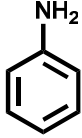
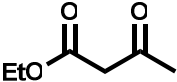
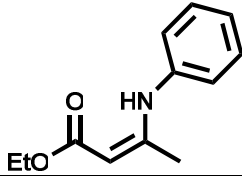

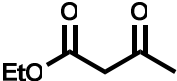
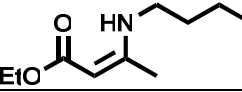
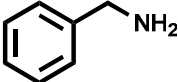
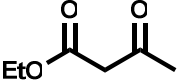
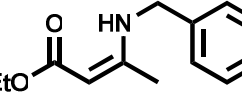
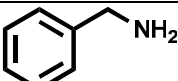
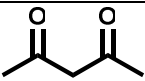
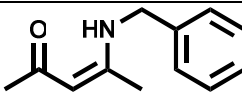


Table 1.

Entry	Amine	$\beta$ -dicarbonyl compound	Product	Time (min)	Yield (%) <sup>a</sup>
1				3	99
2				2	98
3				2	92
4				5	89
5				3	98
6				3	94
7				1	96

8				2	93
9				1	98
10				5	90
11				5	94

<sup>a</sup>Isolated yield

**Results and Discussion:** Currently, there has been an increasing demand for efficient synthetic processes and solvent-free reactions due to environmental concerns. Reaction of  $\beta$ -dicarbonyl compounds with amines results in the formation of  $\beta$ -enaminones or  $\beta$ -enaminoesters (Scheme 1). A number of bismuth salts (5 mol%) have been screened using the reaction of acetylacetone and aniline (1:1 molar ratio) as a probe. Bismuth nitrate has been found to be the best one. challenging and timely. The present methodology has been tested with several primary, secondary (cyclic, heterocyclic and acyclic), benzylic as well as aromatic amines with  $\beta$ -dicarbonyl compounds; the results which have been very encouraging (**Table 1**).

In a typical experiment, equimolar amounts of acetylacetone and aniline were irradiated by CEM automated microwave instrument in the presence of bismuth nitrate pentahydrate (5 mol%) to obtain the corresponding 4-(phenylamino)pent-3-ene-2-one in 99% yield (entry 1) and the reaction was completed within 3 minutes. Encouraged by this result, the acetylacetone was treated with cyclohexyl amine (entry 2), morpholine (entry 3) and benzyl amine (entry 11) to afford the corresponding products in excellent yields (Table 1). In a similar manner, 1,3-cyclohexanedione was reacted with various amines like aniline (entry 4), alicyclic (entry 5), heterocyclic (entry 6) and *n*-butyl amine (entry 7) to get the desired products in very good yields. In the case of  $\beta$ -ketoester (ethyl acetoacetate) and various amines, the reactions take place very smoothly to afford the desired products in very good yields (entries 8, 9 and 10). To confirm the role of catalyst, a blank reaction was carried out at similar reaction conditions with aniline and acetylacetone in absence of catalyst. Only 50% completion was found even after irradiating for a long reaction time (1h). It clearly shows the role of catalyst bismuth nitrate pentahydrate for activation of the carbonyl group. All the reactions were completed within 1-5 minutes to give the desired products in excellent yields (89- 99%), with high regio and chemoselectivity, without forming any side products. In all the cases the catalyst was used in 5 mol% only. In general the nucleophilic addition of amines to carbonyl compounds shows some steric effects on the rate of reaction. In the case of aliphatic amines the rate of reaction is little faster when compared with other amines. In a similar manner, the aromatic amines were a little slower than other amines under similar reaction conditions. All the products were identified by their <sup>1</sup>H-NMR, IR and elemental analysis data.

## Experimental:

Melting points were determined in a Fisher Scientific electrochemical Mel-Temp manual melting point apparatus (Model 1001) equipped with a 400°C thermometer. FT-IR spectra were registered on a Bruker IFS 55 Equinox FTIR spectrophotometer as KBr discs. <sup>1</sup>H-NMR (300 MHz) and <sup>13</sup>C-NMR (75.4 MHz) spectra were obtained at room temperature with JEOL Eclipse-300 equipment using TMS as internal standard and CDCl<sub>3</sub> as solvent. Analytical grade chemicals (Sigma-Aldrich) were used throughout the project. Deionized water was used for the preparation of all aqueous solutions.

*Representative experimental procedure for the enamination reaction (Table 1, entry 1):* Aniline (1 mmol) was added to acetylacetone (1 mmol) in presence of bismuth nitrate pentahydrate (5 mol%) and the mixture was irradiated under CEM automated microwave at 50°C and 300μ for 3 minutes. The reaction was monitored by TLC every one minute interval. After completion of the reaction, it was extracted with diethyl ether (2 x 5 mL), washed with brine solution (10 mL) and dried over Na<sub>2</sub>(SO<sub>4</sub>). The solvent was removed under reduced pressure and the crude mass was crystallized from ethyl acetate/hexane mixture to afford pure compound (99%). This procedure was followed for all the reactions listed in **Table 1**. All the products are known compounds and were easily identified by comparison of their spectroscopic data with those reported. This procedure was also effective for gram-scale reactions.

## Conclusion:

In summary, a simple and efficient method was achieved for the preparation of β-enaminones and β-enaminoesters, employing a green methodology. We demonstrated that Bi(NO<sub>3</sub>)<sub>3</sub>·5H<sub>2</sub>O is a remarkably efficient catalyst for the synthesis of β-enaminones and β-enaminoesters from β-dicarbonyl compounds and amines using CEM automated microwave irradiation. The present method is associated with several advantages such as the simplicity of the reaction conditions, shorter reaction times, excellent yields of products, simple workup procedure, and low cost of catalyst. The use of solvent-free reaction condition employed in the present protocol constitutes an attractive contribution among the existing methodologies.

**Acknowledgements:** We gratefully acknowledge the funding support from National Cancer Institute (NIH/NCI-P20, Grant# 5P20CA138022-02).

## References:

1. Z. Rappoport, Ed., *The Chemistry of Enamines*, Part 1; John Wiley & Sons: New York, (1994).
2. D.L. Boger, T. Ishizaki, J.R.J. Wysocki, S.A. Munk, P.A. Kitos, O. Suntornwat, *J. Am. Chem. Soc.*, **111**, 6461 (1989).
3. Y.F. Wang, T. Izawa, S. Kobayashi, M. Ohno, *J. Am. Chem. Soc.*, **104**, 6465 (1982).
4. J.P. Michael, C.B. Koning, G.D. Hosken, T.V. Stanbury, *Tetrahedron*, **57**, 9635 (2001).
5. N.D. Eddington, D.S. Cox, M. Khurana, N.N. Salama, J.P. Stables, S.J. Harrison, A. Negussie, R.S. Taylor, U.Q. Tran, J.A. Moore, J.C. Barrow, K.R. Scott, *Eur. J. Med. Chem.*, **38**, 49 (2003).
6. K. Tomioka, K. Ando, Y. Takemasa, K. Koga, *J. Am. Chem. Soc.*, **106**, 2718 (1984); (b) W.D. Lubell, M. Kitamura, R. Noyori, *Tetrahedron: Asymmetry*, **2**, 543 (1991).
7. (a) K. Paulvannan, J.R. Stille, *J. Org. Chem.* **59**, 1613 (1994); (b) N.S. Barta, A. Brode, J.R. Sille, *J. Am. Chem. Soc.*, **116**, 6201 (1994). (c) J. Blot, A. Bardou, C. Bellec, M.-C. Fargeau-Bellassoued, J.P. Ce'le'rier, G. Lhommet, D. Gardette, J.-C. Gramain, *Tetrahedron Lett.*, **38**, 8511 (1997).
8. (a) C. Cimarrelli, S. Giuli, G. Palmieri, *Eur. J. Org. Chem.*, **4**, 1017 (2006); (b) G. Bartoli, C. Cimarrelli, E. Marcantoni, G. Palmieri, M. Petrini, *J. Org. Chem.*, **59**, 5328 (1994).
9. L.G. Beholz, R. Benovsky, D.L. Ward, N.S. Bata, J.R. Stille, *J. Org. Chem.*, **62**, 1033 (1997).
10. (a) R. Lenin, R.M. Raju, *ARKIVOC*, **13**, 204 (2007); (b) J. Lin, L.-F. Zhang, *Monatsh. Chem.*, **138**, 77 (2007); (c) C.K.Z. Andrade, A.F.S. Barreto, W.A. Silva, *ARKIVOC*, **12**, 226 (2008); (d) H.A. Oskooie, M.M. Heravi, N.M. Javadi, K. Bakhtiari, F.F. Bamoharram, *Synth. Commun.*, **38**, 2864 (2008); (e) B. Das, B.S. Kanth, A. Majhi, K.R. Reddy, *Heteroatom Chem.*, **19**, 630 (2008); (f) F. Epifano, S. Genoveseb, M. Curini, *Tetrahedron Lett.*, **48**, 2717 (2007) and the references cited therein.
11. A. Banik, S. Batta, D. Bandyopadhyay, B.K. Banik, *Molecules*, **15**, 8205 (2010); (b) L. Iglesias, C. Aguilar, D. Bandyopadhyay, B.K. Banik, *Synth. Commun.*, **40**, 3678 (2010); (c) S. Rivera, D. Bandyopadhyay, B.K. Banik, *Tetrahedron Lett.*, **50**, 5445 (2009) and the references cited therein.