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A mild, efficient and environmentally friendly method for the regio- and chemoselective synthesis of enaminones using Bi(TFA)$_3$ as a reusable catalyst in aqueous media

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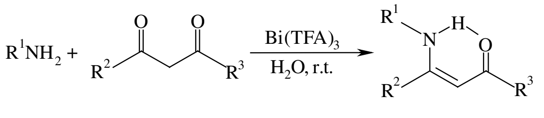
Abstract—Bismuth(III) trifluoroacetate has been found to be an extremely efficient catalyst for the preparation of β-enaminones in water. In addition, by employing this catalyst, high regio- and chemoselective enamination of carbonyl compounds was achieved.

Enamination of β-dicarbonyl compounds forming β-enaminones, is an important and widely used transformation in organic chemistry.[1] Such compounds are important precursors for the synthesis of a variety of heterocycles[2] and pharmaceutical compounds.[3] Due to the importance of these compounds as intermediates in organic synthesis, a simple and high yielding one-pot approach for this transformation is highly desirable. Despite their wide range of pharmacological activity[3] and synthetic applications, the synthesis of β-enaminones has received little attention. The most well-known route to β-enaminones involves the direct condensation of β-dicarbonyl compounds with amines at reflux in an aromatic solvent with azetropic removal of water.[4] Several improved procedures have been reported including the reaction of amines and 1,3-dicarbonyl compounds supported on silica with microwave irradiation,[5] clay K$_{10}$/ultra-sound[6] or NaAuCl$_4$.[7] Recently, these compounds have been prepared by direct condensation of β-dicarbonyl compounds and primary amines in water as solvent.[8] However, these methods suffer from drawbacks such as long reaction times, unsatisfactory yields, low selectivity or the use of toxic solvents that limit these methods to small-scale synthesis. Lewis acid catalyzed organic reactions in water, because they allow environmentally friendly processes under mild conditions, are currently one of the most challenging topics in organic synthesis.[9] Many recent papers describing the use of bismuth compounds in organic transformations pointed out that their use is ecologically friendly.[10] In addition, bismuth derivatives have been widely used in medicine.[11] They have attracted much attention because they are easy to handle, are low in cost and are relatively insensitive to air and moisture.[12] In the course of our research on Bi(III) salts we found that bismuth(III) trifluoroacetate is relatively nontoxic, readily available at low cost and fairly stable to water, unlike common Lewis acids (e.g., AlCl$_3$), which decompose readily in aqueous media.[13]

We herein report a green, mild and efficient method for the regio- and chemoselective enamination of β-dicarbonyl compounds in water, in good to excellent yields, catalyzed with Bi(TFA)$_3$ (Scheme 1).

The experimental procedure for this reaction is remarkably simple and does not require the use of organic solvents or inert atmospheres. A catalytic quantity of Bi(TFA)$_3$ (5 mol%) and the required amine were added to a stirred solution of the 1,3-dicarbonyl compound in water, and the mixture stirred at room temperature. The generality of this process was illustrated by the wide range of aromatic and aliphatic



Scheme 1.

Keywords: Amines; β-Dicarbonyl compounds; Enamination; Chemoselective; Catalyst; Bismuth compounds.

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Table 1. Enamination of β-dicarbonyl compounds in water catalyzed by $Bi(TFA)_3$

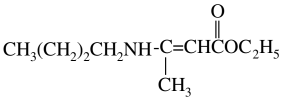
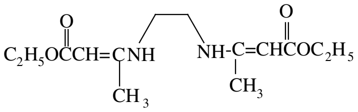
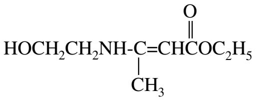
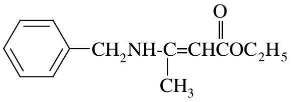
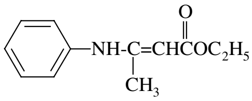
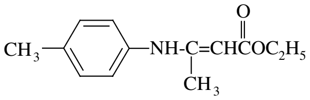
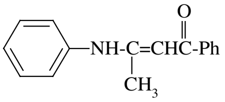
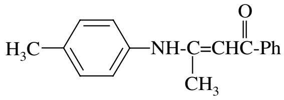
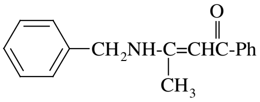
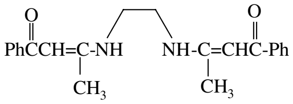
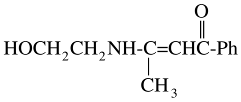
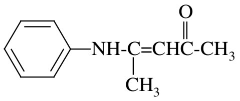
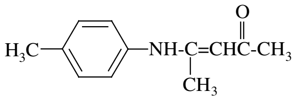
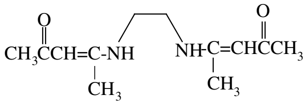
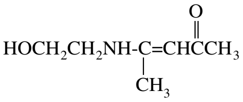
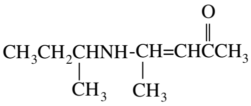
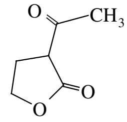
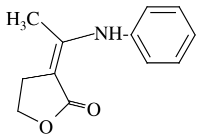
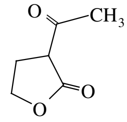
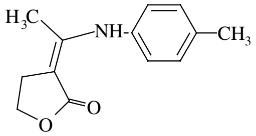
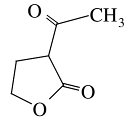
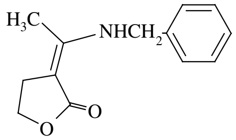
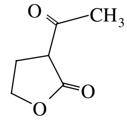
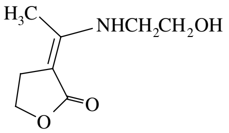
Entry	R^1	R^2	R^3	Time (min)	Product[a]	Yield (%)[b]
1	$CH_3(CH_2)_2CH_2$[c]	CH_3	OC_2H_5	5	 $CH_3(CH_2)_2CH_2NH\text{-}\underset{\displaystyle CH_3}{\underset{\vert}{C}}{=}CH\overset{\displaystyle O}{\overset{\Vert}{C}}OC_2H_5$	98
2	$H_2NCH_2CH_2$	CH_3[c]	OC_2H_5	7		95
3	$HOCH_2CH_2$	CH_3	OC_2H_5	10	 $HOCH_2CH_2NH\text{-}\underset{\displaystyle CH_3}{\underset{\vert}{C}}{=}CH\overset{\displaystyle O}{\overset{\Vert}{C}}OC_2H_5$	93
4	$C_6H_5CH_2$	CH_3	OC_2H_5	5		97
5	C_6H_5	CH_3	OC_2H_5	10		86
6	$4\text{-}CH_3C_6H_4$	CH_3	OC_2H_5	45		84
7	C_6H_5	CH_3	Ph	60		63
8	$4\text{-}CH_3C_6H_4$	CH_3	Ph	45		66
9	$C_6H_5CH_2$	CH_3	Ph	50		70
10	$H_2NCH_2CH_2$	CH_3[c]	Ph	45		76
11	$HOCH_2CH_2$	CH_3	Ph	30	 $HOCH_2CH_2NH\text{-}\underset{\displaystyle CH_3}{\underset{\vert}{C}}{=}CH\overset{\displaystyle O}{\overset{\Vert}{C}}\text{-}Ph$	83
12	C_6H_5[c]	CH_3	CH_3	60		64
13	$4\text{-}CH_3C_6H_4$[c]	CH_3	CH_3	150		68
14	$H_2NCH_2CH_2$	CH_3[c]	CH_3	60		83
15	$HOCH_2CH_2$[c]	CH_3	CH_3	60	 $HOCH_2CH_2NH\text{-}\underset{\displaystyle CH_3}{\underset{\vert}{C}}{=}CH\overset{\displaystyle O}{\overset{\Vert}{C}}CH_3$	77
16	$CH_3CH_2CHCH_2$[c]	CH_3	CH_3	180	 $CH_3CH_2\underset{\displaystyle CH_3}{\underset{\vert}{CH}}NH\text{-}\underset{\displaystyle CH_3}{\underset{\vert}{CH}}{=}CH\overset{\displaystyle O}{\overset{\Vert}{C}}CH_3$	63

Table 1 (*continued*)

Entry	R^1	R^2	R^3	Time (min)	Product[a]	Yield (%)[b]
17	C_6H_5			150		82
18	4-$CH_3C_6H_4$			50		79
19	$C_6H_5CH_2$			180		84
20	$HOCH_2CH_2$			10 h		93

[a] All products were identified by comparison of their physical and spectral data with those of authentic samples.

[b] Isolated yields.

[c] 2 mmol.

primary amines and β-dicarbonyl compounds examined. The results are shown in Table 1.

The reactions proceeded smoothly at room temperature and the products were obtained in excellent yields and chemoselectivity. Both activated and weakly activated anilines formed enaminones in nearly quantitative yields. Although Stefani et al. stated that the synthesis of these compounds was limited to amines soluble in water,[8] we have now shown that in the presence of $Bi(TFA)_3$ water insoluble amines were also converted efficiently to the corresponding enaminones in good to high yields. However, anilines with strongly electron-withdrawing groups such as 4-nitroaniline did not yield any product under the present reaction conditions.

Aliphatic amines also reacted efficiently to produce the corresponding enaminones. In the case of 1,2-diaminoethane, 2 equiv of β-dicarbonyl compounds were used giving products with two enaminone groups (entries 2, 10 and 14).

This method was successfully applied to enamination of β-diketones (entries 7–16), linear (entries 1–6) and cyclic β-ketoesters (entries 17–20). In all cases, amine attack took place only at the methyl ketone carbonyl for diketones and ketoesters. The use of $Bi(TFA)_3$ as a heterogeneous catalyst showed rate enhancements, high yields and short reaction times. The other advantage of the use of this Lewis acid for this transformation, is the recyclability of the catalyst. Since $Bi(TFA)_3$ is only slightly soluble in water, it could be separated by simple filtration, washed with CH_2Cl_2 and dried at 80 °C under reduced pressure and reused in three runs without any loss of activity.

In conclusion, the present procedure demonstrates a new, regio- and chemoselective method for the enamination of β-dicarbonyl compounds with aromatic and aliphatic amines under mild conditions in aqueous media where the catalyst could be recovered readily and reused, in good to excellent yields. Furthermore, the low toxicity of the catalyst and media, make this procedure environmentally acceptable. Moreover, the low cost of $Bi(TFA)_3$, fast reaction rates and highly catalytic nature of this Lewis acid as a water stable catalyst, make the present method a practical protocol for the enamination reaction.

General procedure. A mixture of the β-dicarbonyl compound (1 mmol), the amine (1 mmol) and $Bi(TFA)_3$ (0.05 mmol) in water (5 mL) was stirred at room temperature for the appropriate time (Table 1). After completion of the reaction as indicated by GLC or TLC, $Bi(TFA)_3$ was removed by filtration, washed with CH_2Cl_2 (3×10 mL) and dried over $MgSO_4$. Evaporation of the solvent followed by chromatography on a silica-gel plate or silica-gel column gave the pure enaminones in 63–98% yields.[14]

Acknowledgements

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14. Analytical data for products **10**, **13**, **17**, **20**. Compound **10** mp 177–179 °C; $\nu_{\max}$(KBr) 3360, 3120, 1525, 1512, 1080, 800, 748, 705 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 11.6 (s, 2H, NH), 8.17–7.1 (m, 10H, Ph), 5.7 (s, 2H, =CH–), 3.82–3.3 (m, 4H, –CH_2), 2.1 (s, 6H, CH_3); δ_C (50 MHz, $CDCl_3$) 188.7, 165.4, 140.5, 131.1, 128.7, 127.4, 93.4, 44.2, 19.7. Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.63; H, 6.94; N, 9.16. Found: C, 75.24; H, 6.8; N, 8.4. Compound **13** mp 58–59 °C; $\nu_{\max}$(KBr) 3340, 3012, 2952, 2900, 2860, 1606, 1595, 1558, 1268, 1015, 803 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 12.41 (s, 1H, NH), 7.23–6.9 (m, 4H, Ar), 5.16 (s, 1H, =CH–), 2.31 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 1.92 (s, 3H, CH_3); δ_C (50 MHz, $CDCl_3$) 195.8, 171.0, 160.7, 136.4, 135.0, 129.9, 124.9, 60.5, 29.3, 20.7. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 75.8; H, 7.9; N, 7.1. Compound **17** mp 90–92 °C; $\nu_{\max}$(KBr) 3250, 3030, 2900, 1674, 1634, 1247, 1019, 920 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 10.1 (br, 1H, NH), 7–7.41 (m, 5H, Ar), 4.42–4.3 (t, $J = 8.2$ Hz, 2H, OCH_2), 3.07–2.89 (t, $J = 8.1$ Hz, 2H, =C–CH_2–), 2.1 (s, 3H, CH_3); δ_C (50 MHz, $CDCl_3$) 174.3, 153.9, 147.8, 139.6, 129.6, 125.3, 124.6, 89.7, 65.8, 26.9. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.5; H, 6.5; N, 7.0. Compound **20** mp 110–111 °C; $\nu_{\max}$(KBr) 3240, 2923, 1668, 1584, 1250, 1012, 955, 763 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.32 (br, 1H, NH), 4.33–4.22 (t, $J = 8.7$ Hz, 2H), 3.8–3.69 (t, $J = 5.8$ Hz, 2H), 3.47–3.36 (q, $J = 5.1$, 5.2 Hz, 2H), 3.18 (br, 1H, OH), 2.9–2.8 (t, $J = 7.3$ Hz, 2H), 2.1 (s, 3H, CH_3); δ_C (50 MHz, $CDCl_3$) 174.8, 158.4, 156.9, 85.2, 65.8, 62.1 45.7, 26.9. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.0; H, 7.7; N, 8.3.