EFFICIENT SYNTHESIS OF β-ENAMINONES AND β-ENAMINO ESTERS USING TRIS(HYDROGENSULFATO)BORON OR TRICHLOROACETIC ACID AS CATALYSTS

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New and efficient methods have been developed for the synthesis of β-enaminones and β-enamino esters in the presence of a catalytic amount of tris(hydrogensulfato)boron or trichloroacetic acid as highly efficient catalysts at 120 °C under solvent-free conditions. Both methods are simple, and provide desired products in good yields and short reaction times.

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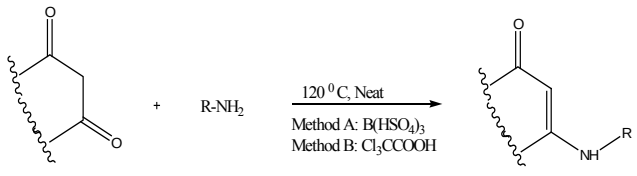
Introduction

Enaminones and enamino esters are useful intermediates for synthesis of biologically significant heterocyclic compounds, nitrogen containing compounds, and naturally occurring alkaloids.[1-4] They even served as synthons for γ-aminoalcohol, β-aminoacids which are a class of very stable compounds useful in asymmetric catalysis as a chelating agent.[5]

The most well-known and exploited route for the synthesis of β-enaminones involves the direct condensation of 1,3-dicarbonyl compounds with amines in refluxing aromatic hydrocarbons with azeotropic removal of water.[6] Some improved procedures have been subsequently reported for this transformation using different catalysts.[7-14] Although, these approaches are satisfactory for synthesis of enaminones, the harsh reaction conditions, expensive reagents, use of toxic organic solvents and long reaction times limit the use of these methods.

Due to extending our interest in the development of practical, safe, and environmentally friendly procedures for several important organic transformations,[15-19] we now describe a simple and efficient protocol for the synthesis of β-enaminones through the reaction of 1,3-dicarbonyl compounds and amines using catalytic amounts of tris(hydrogensulfato)boron or trichloroacetic acid as catalysts under solvent-free conditions (Scheme 1).



Scheme 1. Synthesis of β-enaminones and β-enamino esters

Experimental

General procedure for the synthesis of β-enaminones

To a mixture of amines (1 mmol), 1,3-diketone (1 mmol) and $B(HSO_4)_3$(10 mol%) or trichloroacetic acid (20 mol%) was added and the mixture was stirred and heated in an oil bath at 120 °C for appropriate time. Completion of the reaction was indicated by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. Chloroform (10 mL) was added and the catalyst was recovered by filtration. The solvent was evaporated and the product was isolated in almost pure form. Further purification was carried out by recrystallization from ethanol.

Selected spectral data

Product Table 1, entry 1:^{1}HNMR (250 MHz, $CDCl_3$) δ: 1.08 (s, 6H, CH_3), 2.20 (s, 2H, CH_2), 2.34 (s, 2H, CH_2), 5.56 (s, 1H, CH), 7.15 (s, 1H, NH), 7.26-7.34 (m, 5H, ArH) ppm; IR (KBr): 3237, 3062, 2958,1597, 1571, 1525, 1495, 1446, 1369, 1150, 1124 cm^{-1}.

Product Table1, entry 2: ^{1}HNMR (250 MHz, $CDCl_3$) δ: 1.10 (s, 6H, CH_3), 2.22 (s, 2H, CH_2), 2.33 (s, 2H, CH_2), 5.52 (s,1H, CH), 6.34 (s, 1H, NH), 7.08 (d, 2H, J= 8.75 Hz, ArH), 7.28 (d, 2H, J=12.5 Hz, ArH) ppm; IR (KBr): 3241, 2956, 1727, 1596, 1567, 1489, 1364, 1258, 1084, 818 cm^{-1}.

Product Table1, entry 3:^{1}HNMR (250 MHz, $CDCl_3$) δ: 1.06 (s, 6H, 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, ArH), 7.43 (d, 2H, J =8.75 Hz,ArH) ppm; IR (KBr): 3241, 3173, 3096, 3042, 2955, 1610, 1571, 1524, 1487, 1462, 1401, 1368, 1262, 1147, 1071, 719 cm^{-1}.

Product Table1, entry 4: ^{1}HNMR (250 MHz, $CDCl_3$) δ: 1.13 (s, 6H, CH_3), 2.27 (s, 2H, CH_2), 2.39 (s, 2H, CH_2), 5.66 (s, 1H, CH), 6.66 (s,1H, NH), 7.51-7.57 (m, 2H, ArH), 7.99-8.01 (m, 2H, ArH) ppm; ^{13}CNMR (62.5 MHz, $CDCl_3$) δ: 28.22, 32.88, 43.29, 49.94, 99.54, 118.95, 129.72, 139.59,

148.81, 160.46, 198.07 ppm; IR (KBr): 3270, 3195, 3099, 2927, 1580, 1537, 1480, 1434, 13550,1265, 1150 cm^{-1}.

Product Table1, entry 12:^{1}HNMR (250 MHz, $CDCl_3$) δ: 1.21-1.26 (m, 6H, CH_3), 1.09 (s, 6H, CH_3), 3.34-3.36 (m,4H, $2CH_2$), 4.03-4.11 (q, J= 21.25 Hz, $2CH_2$), 4.47 (s, 2H, CH), 8.64 (s, 2H, NH) ppm; 13CNMR (62.5 MHz, CDCl3) δ: 14.59, 19.27, 43,78, 58.47, 83.49, 161.33, 170.61 ppm; IR (KBr) : 3296, 2985, 1649, 1605, 1510, 1457, 1438, 1390, 1339, 1289, 1259, 1224, 1167, 1091, 1066, 1081 cm^{-1}.

Results and Discussion

Initially the reaction of dimedone with aniline in the presence of tris(hydrogensulfato)boron was used as a model reaction and this reaction was optimized using different conditions. It was found that best conditions were solvent-free at 120 °C using 10 mol% tris(hydrogensulfato) boron and a molar ratio of dimedone/aniline of 1:1.

Tris(hydrogensulfato)boron [$B(HSO_4)_3$] was easily prepared by addition of chlorosulfonic acid to boric acid under N_2 atmosphere at room temperature. This reaction was easy and clean, because HCl gas was evolved from the reaction vessel immediately. This catalyst is safe and easy to handle.[20] It has been utilized as a catalyst by our group for the synthesis of α,α′-benzylidene bis(4-hydroxycoumarin) derivatives[17] and 2,3-dihydroquinazolin-4(1H)-ones.[18]

To study the scope of the reaction, a series of 1,3-dicarbonyl compounds with various anilines under catalytic amounts of tris(hydrogensulfato)boron were applied. The reaction proceeded well with aromatic amines. As shown in Table 1, by this method (Method A), reaction of various aryl amines carrying either electron-donating or electron-withdrawing substituents were successfully reacted with dimedone to produce their corresponding β-enaminones in high yields with short reaction times.

Under the optimized reaction conditions, the reactions of acetyl acetone with aryl amines were examined and very good yields of products were obtained (Table 1, entries 7-8).

The condensation of amines with ethyl acetoacetate was also successfully carried out under the same conditions and the corresponding β-enamino esters were obtained in high yields and short reaction times (Table 1, entries 9-12).

These results encouraged us to exploit the generality and scope of this reaction by using other catalyst such as trichloroacetic acid. Trichloroacetic acid (TCAA) is a readily available and inexpensive reagent and can conveniently be handled and removed from the reaction mixture.[16]

Trichloroacetic acid (TCAA) is an efficient catalyst which has been successfully utilized by our group in some reactions, for example, synthesis of 1,4-dihydropyranopyrazoles,[16] tetrahydrobenzoxanthen-11-ones and dibenzoxanthenes.[19] Thus, the remarkable catalytic activities together with its operational simplicity make it the most suitable catalyst for the synthesis of β-enaminones and β-enamino esters. After systematic screening, TCAA was found to be the catalyst of choice. Similarly, the mole ratio of TCAA was studied and found 20 mol% of TCAA to be optimum. The reaction was carried out with amine (1 mmol) and 1,3-dicarbonyl compounds (1 mmol) in the presence of TCAA (20 mol%) and heated at 120 °C under solvent-free conditions resulted to the formation of the corresponding β-enaminones and β-enamino esters (Scheme 1). The results are compiled in Table 1 (Method B). This protocol is remarkably simple and requires non-hazardous reagents or inert atmosphere.

All products were identified by ^{1}H-NMR, ^{13}C NMR and IR spectroscopic methods and the results were confirmed by comparison with those available in the literature.

Table 1 Synthesis of β-enaminones and β-enamino esters

Entry	R	1,3-diketone	Method A[a]		Method B[b]		m.p. (°C)[ref.]
			Time (min)	Yield (%)	Time (min)	Yield (%)	
1	C_6H_5	Dimedone	7	85	7	75	183-184[21]
2	4-ClC_6H_4	Dimedone	8	80	8	80	191-194[22]
3	4-BrC_6H_4	Dimedone	7	83	7	83	159-163[21]
4	3-$NO_2C_6H_4$	Dimedone	8	80	8	80	165-170
5	4-$NO_2C_6H_4$	Dimedone	7	82	7	82	191-193[22]
6	2-$COOHC_6H_4$	Dimedone	7	85	7	85	187-189[23]
7	$H_2N(CH_2)_2$	Acetylacetone	7	85	7	85	110-113[24]
8	n-butyl	Acetylacetone	7	85	7	85	Oil[8]
9	n-butyl	Ethyl acetoacetate	7	85	7	85	Oil[8]
10	Ph-CH_2	Ethyl acetoacetat	10	85	10	85	Oil[24]
11	4-ClC_6H_4	Ethyl acetoacetate	7	83	7	83	Oil[8]
12	$H_2N(CH_2)_2$	Ethyl acetoacetate	8	85	8	85	121-124[24]

[a]Method A: tris(hydrogensulfato) boron; [b] Method B: Trichloroacetic acid

Conclusion

In conclusion, we have developed efficient procedures for a convenient and mild synthesis of various β-enaminones through the reaction of 1,3-dicarbonyl compounds and amines using catalytic amounts of tris(hydrogensulfato) boron or trichloroacetic acid as catalysts under solvent-free conditions. Prominent among the advantages of these new methods are operational simplicity, good yields in short reaction times and easy work-up procedures employed.

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