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Melamine Trisulfonic Acid as a New, Efficient and Reusable Catalyst for the Solvent Free Synthesis of Coumarins

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Melamine trisulfonic acid (*MTSA*) is easily prepared by the reaction between melamine and neat chlorosulfonic acid at room temperature. This compound can be used as an efficient and recyclable catalyst for the synthesis of coumarins *via* von Pechmann condensation reaction under solvent-free conditions.

Keywords: Melamine trisulfonic acid, Coumarins, Pechmann reaction, Phenols, Solvent-free reaction conditions

INTRODUCTION

Coumarins and their derivatives are important classes of heterocyclic compounds whose synthesis has been the focus of attention of many organic and medicinal chemists. Such an interest in these compounds can be attributed to their variety of bioactivities such as, inhibition of platelet aggregation [1], antibacterial [2], anticancer [3], inhibitor of steroid 5α-reductase [4] and inhibitor of HIV-1 protease [5]. They are widely used as additives in food, perfumes, agrochemicals, cosmetics, pharmaceuticals [6] and in the preparation of insecticides, optical brightening agents, dispersed fluorescent and tunable dye lasers [7]. Coumarins also act as intermediates for the synthesis of fluorocoumarins, chromenes, coumarones, and 2-acylresorcinols [8]. A variety of methods including Pechmann [9], Knoevenagel [10], Reformatsky [11], Perkin [12] and Wittig [13] reactions and flash vacuum pyrolysis [14] have been used for the synthesis of coumarins of which the Pechmann reaction is the most common procedure.

Generally, the Pechmann reaction is carried out by the condensation of phenols with β-ketonic esters under catalysis of reagents such as H_2SO_4 [9], P_2O_5 [15], $AlCl_3$ [16], CF_3CO_2H [17], $InCl_3$ [18], $Sm(NO_3)_3.6H_2O$ [19], $Bi(NO_3)_3.5H_2O$ [20], silica triflate [21], H_2SO_4-microwave [22], [bmim][H_2SO_4]-microwave [23], $HClO_4$-SiO_2 [24], polyaniline supported acid catalyst [25], $ZrCl_4$ [26], $TiCl_4$ [27], Wells-Dawson hetropolyacid [28], nano-crystalline sulfated zirconia-microwave [29] and benzylsulfonic acid functionallized mesoporous Zr-TMS [30]. The main disadvantages of the processes using these catalysts are, long reaction times, low yields, harsh reaction conditions, non-reusability of the catalyst, use of excess amounts of the reagent, strictly reactive conditions (N_2 atmosphere), special efforts required to prepare the catalyst and tedious work-up procedures. Thus, the search for new reagents and methods is still of growing importance.

EXPERIMENTAL

Preparation of Melamine Trisulfonic Acid *(MTSA)*

A 250 ml suction flask charged with chlorosulfonic acid (5 ml, 75.2 mmol) was equipped with a gas inlet tube for

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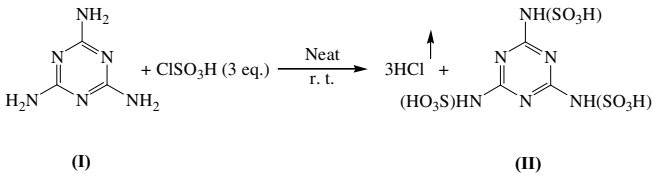
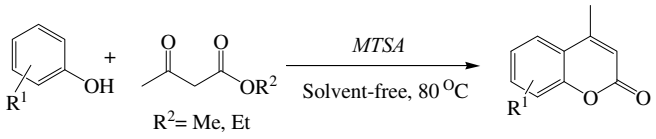
conducting HCl gas over an adsorbing solution *i.e.* water. Melamine (3.16 g, 25.07 mmol) was added in small portions over a period of 30 min at room temperature. HCl gas evolved from the reaction vessel immediately (Scheme 1). After completion of the addition of melamine, the mixture was shaken for 30 min; meanwhile, the residual HCl was exhausted by suction. The mixture was triturated with n-hexane (10 ml) and then filtered. The solid residue was washed with n-hexane (10 ml) and dried under vacuum. Melamine trisulfonic acid (7.9 g, 87%) was obtained as a white solid, which was stored in a capped bottle. M.p.: 142-144 °C; IR: $\overline{\nu}$ = 3133, 2621, 1654, 1509, 1175, 1069 cm^{-1}; Anal. Calcd. for $C_3H_6N_6O_9S_3$ (366.3): C, 9.83%; N, 22.95%; H, 1.64%. Found: C, 9.81%; N, 22.95%; H, 1.64%. The presence of three atoms of sulfur per each molecule of MTSA was confirmed by the titration of MTSA in acetonitrile environment with 1.0 M Bu_4NOH (MeOH), according to the previously reported method [31].



Scheme 1



Scheme 2

General Procedure

A mixture of the phenol (1 mmol), ethyl acetoacetate or methyl acetoacetate (1 mmol) and *MTSA* (0.05 mmol, 0.02 g) was heated in an oil bath (80 °C) under stirring. The progress of the reaction was monitored by TLC. After completion, the mixture was allowed to cool, ethyl acetate (5 ml) was added and the catalyst was recovered by filtration, washed with ethyl acetate (5 ml), dried and reused according to the procedure mentioned above. Evaporation of the solvent from the filtrate and recrystallization of the solid residue from hot ethanol afforded the requested coumarins in high yields.

RESULTS AND DISCUSSION

In recent years, introduction of new reagents for the promotion of the organic reactions, became an important part of our research program [21,32-35]. In continuation of these studies, we have found that melamine (I), as a cheap and commercially available reagent, reacts with neat chlorosulfonic acid to give melamine trisulfonic acid (*MTSA*) (II) at room temperature. The reaction is easy and clean, and needs no special work-up procedure (Scheme 1).

The structure of *MTSA*, convinced us to accept that this reagent could potentially act as an efficient catalyst in reactions that need acidic reagents to speed up. In practice this prediction turned out to be correct and the synthesis of coumarins *via* von Pechmann condensation of phenols with β-ketonic esters was efficiently catalyzed in the presence of *MTSA* (Scheme 2).

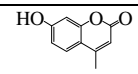
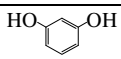
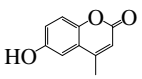
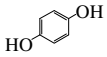
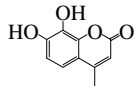
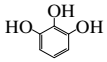
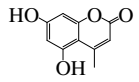
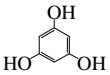
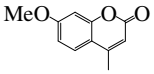
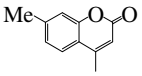
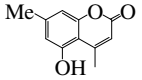
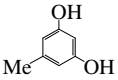
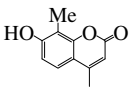
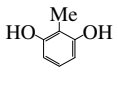
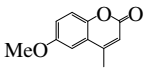
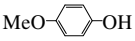
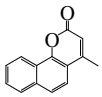
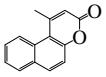
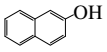
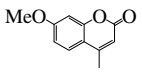
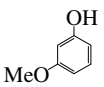
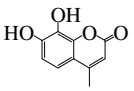
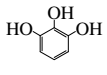
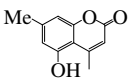
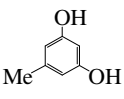
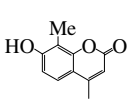
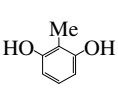
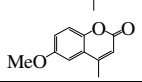
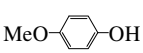
To establish the reaction conditions, a mixture of equimolar quantities of resorcinol and ethyl acetoacetate was treated with MTSA (0.5 mmol, 0.02 g) and heated in an oil bath (80 °C) for 10 min to give the corresponding coumarin in 94% yield, m.p.: 184-186 °C (lit. [19] 185-187 °C) (Table 1, entry 1).

Encouraged by the above results, other phenolic substrates were subjected to the Pechmann reaction using *MTSA*. As shown in Table 1, phenols with electron-donating groups are easily converted to their corresponding coumarins under the same reaction conditions. Short reaction times were observed regardless of the structural varieties in the phenols or β-ketoesters. When the reaction was triggered on phenols with electron-withdrawing groups, starting materials remained intact even after prolonged heating.

It should be noted that the catalyst could be recovered by simple filtration and reused for several times without a considerable change in the reaction times and yields (Table 2).

In order to show the efficiency of the proposed method, Table 3 compares some of the results with some of those reported in the literature [18,23,24,28].

Table 1. Synthesis of Coumarins Catalyzed by *MTSA*[a, b]

Entry	Phenol	Product	R^2	Time (min)	Yield (%)	M.P. (°C)	
						Found	Reported [Ref.]
Et			1	10	94	184-186	185-187 [19]
Et			2	28	85	245-247	246-247 [36]
Et			3	7	93	242-244	241-245 [29]
Et			4	5	91	280-281	281-283 [19]
Et			5	10	95	159-161	160-162 [19]
Et			6	65	65	131-133	132 [29]
Et			7	5	95	258-259	257-258 [19]
Et			8	8	93	138-140	138-139 [19]
Et			9	26	92	169-170	169-170 [36]
Et			10	22	88	156-157	154-156 [19]
Et			11	95	86	180-182	181-182 [36]
Et			12	10	93	159-161	160-162 [19]
Et			13	5	95	242-244	241-245 [29]
Et			14	7	92	258-259	257-258 [19]
Et			15	8	90	138-140	138-139 [19]
Et			16	20	90	165-167	169-170 [36]

[a]Products were identified spectroscopically . [b]Isolated yields.

Table 2. Synthesis of Coumarins Catalyzed by Recycled *MTSA*

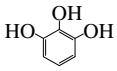
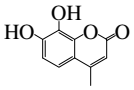
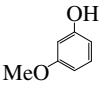
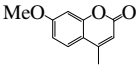
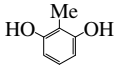
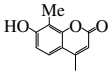
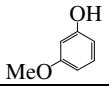
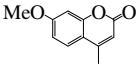
Entry	Phenol	Product	R	Time (min)	Yield (%)
1			Et	9	90
2			Et	12	95
3			Et	8	92
4			Me	10	90

Table 3. Comparison of Some of the Results Obtained by the Promotion of the Pechman Reaction in the Presence of *MTSA* (1) with Some of those Reported by $InCl_3$ (2) [18], [bmim][HSO_4] (3) [23], $HClO_4$-SiO_2 (4) [24], and Wells-Dawson Heteropolyacid (5) [28]

Entry	Phenol	Time (min)/Yield (%)				
		(1)	(2)	(3)	(4)	(5)
1		10/94	30/98	12 (h)/62	35/95	42/87
2		7/93	30/92	20 (h)/65	60/97	48/97
3		22/88	90/88	6 (h)/75	65/89	48/75

CONCLUSIONS

In conclusion, we have developed an efficient method for the solvent-free synthesis of coumarins *via* Pechmann reaction using melamine trisulfonic acid, as a newly prepared reagent. Moreover, high yields of the products, relatively short reaction times, ease of preparation, easy work-up procedure, low toxicity and reusability of the catalyst are the other advantages of our method which make it a useful and attractive addition to the currently available methods. We are exploring further applications of MTSA to other types of organic reactions in our laboratory.

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