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One-Pot Synthesis of Benzo[4,5]imidazo[1,2-a]pyrimidine Derivatives Using Melamine Trisulfonic Acid as Catalyst

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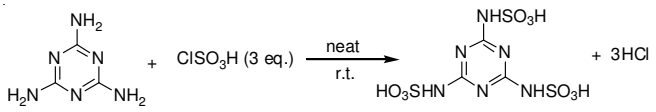
Melamine trisulfonic acid catalyzes efficiently the one-pot condensation of 2-aminobenzimidazole, aldehyde and β-dicarbonyl compounds under solvent-free conditions to afford the corresponding benzo[4,5]imidazo[1,2-a]pyrimidine derivatives in single step. This new approach consistently has the advantage of excellent yields (86-95 %) and short reaction times of 4-6 h. The catalyst can be recovered and recycle.

Key Words: Naphtho[1',2':5,6]pyrano[3,2-c]chromen-6-one, 4-Hydroxycoumarin, Alum, Solvent-free.

INTRODUCTION

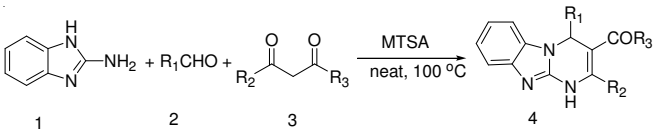
Benzo[4,5]imidazo[1,2-a]pyrimidines are important biologically active heterocyclic compounds, which possess such as antineoplastic[1], protein kinase inhibitor[2], T cell activation[3], TIE-2 and/or VEGFR2 inhibitory activities[4]. The most common methods for the preparation of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives are the one-pot three-component condensation reactions of β-dicarbonyl compounds, aldehyde and 2-aminobenzimidazole in the presence of sulfamic acid[5] and 1,1,3,3,N,N,N',N'-tetramethylguanidinium trifluoroacetate (TMGT)[6], other methods involve the reaction of β-ketoester with aldehyde followed by condensation with 2-aminobenzimidazole to give the target products[7]. However, most of these procedures have signicant drawbacks such as long reaction times, low yields, harsh reaction conditions, difficult work-up and use of environmentally toxic reagents or media. Thus, there is still need of a simple and general for one-pot synthesis of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives under mild conditions.

Recently, melamine trisulfonic acid has emerged as a promising solid acid catalyst for acid catalyzed reactions, such as acetylation of alcohols, phenols and amines[8], oxothioacetylyzation of aldehydes[9] and methoxymethylation of alcohols[10]. This catalyst is safe, easy to handle, environmentally benign and presents fewer disposal problems. Melamine trisulfonic acid (MTSA) as a solid acid catalyst is prepared from the reaction of melamine with neat chlorosulfonic acid at room temperature (**Scheme-I**).



Scheme-I

We now report a simple and efficient route to synthesis of 2-methyl-4-aryl-1,4-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylic acid ethyl esters using melamine trisulfonic acid (MTSA) as an efficient and reusable catalyst under solvent-free conditions (**Scheme-II**).



Scheme-II

EXPERIMENTAL

NMR spectra were determined on Bruker AV-300 spectrometer at room temperature using TMS as internal standard., coupling constants (*J*) were measured in Hz. Elemental analysis were performed by a Vario-III elemental analyzer. Melting points were determined on a XT-4 binocular microscope and were uncorrected. Commercially available reagents were used throughout without further purification unless otherwise stated. Products **4** are known compounds and their physical data, NMR spectra and elemental analysis were essentially identical with those of the authentic sample.

General experimental procedure: To a mixture of 2-aminobenzimidazole (1 mmol) with aldehyde (1 mmol) and β-dicarbonyl compounds (1 mmol), melamine trisulfonic acid (5 mol %) was added. The mixture was stirred at 100 ºC for an appropriate time. After completion, the reaction mixture was washed with water (15 mL) and residue recrystallized from EtOH to afford the pure product **4**.

2-Methyl-4-phenyl-1,4-dihydro-benzo[4,5]imidazo [1,2-a]pyrimidine-3-carboxylic acid ethyl ester (4a): ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 10.42 (s, 1H, NH), 7.32 (t, *J* = 7.6 Hz, 3H, ArH), 7.24 (t, *J* = 7.8 Hz, 3H, ArH), 7.18-7.12 (m, 1H, ArH), 6.99 (t, *J* = 7.8 Hz, 1H, ArH), 6.92 (t, *J* = 7.5 Hz, 1H, ArH), 6.32 (s, 1H, CH), 4.06 (q, *J* = 7.0 Hz, 2H, CH_2), 2.34 (s, 3H, CH_3), 1.20 (t, *J* = 7.0 Hz, 3H, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3266, 3098, 3012, 2920, 2840, 1720, 1599, 1560, 1360, 1280, 1077, 861, 802, 701; Anal. calcd. for $C_{20}H_{19}N_3O_2$: C 72.05, H 5.74, N 12.60; found: C 72.25, H 5.58, N 12.44.

RESULTS AND DISCUSSION

We started to study this condensation reaction by examining the amount of catalyst for the reaction involving 2-aminobenzimidazole (1 mmol), benzaldehyde (1 mmol) and ethyl 3-oxobutanoate (1 mmol) to afford the product 2-methyl-4-phenyl-1,4-dihydro-benzo[4,5]imidazo[1,2-a]pyrimidine-3-carboxylic acid ethyl ester under solvent-free conditions at 100 ºC. The best result was obtained with 5 mol % melamine trisulfonic acid. Higher amounts of catalyst did not improve the result to any greater extent (Table-1).

TABLE-1
OPTIMIZATION ONE-POT SYNTHESIS OF BENZO[4,5]IMIDAZO[1,2-*A*] PYRIMIDINE DERIVATIVES

Entry	MTSA (mol %)	Time (h)	Yield (%)
1	0	8	0
2	1	6	52
3	2	5	69
4	3	5	75
5	4	4	84
6	5	4	90
7	6	4	90
8	7	4	88
9	8	4	88
10	9	3	89

A range of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives was synthesized by the one-spot condensation of 2-aminobenzimidazole **1**, aldehyde **2** and β-dicarbonyl compounds **3**. The reaction proceeded at 100 ºC within 6 h in excellent yields after the addition of the acid cataylst melamine trisulfonic acid (Table-2). After completion, the reaction mixture was washed with water and residue recrystallized from EtOH to afford the pure product **4**. Aqueous washings were collected and evaporated under reduced pressure. After removal of the water, melamine trisulfonic acid was recovered. The efficiency of the recovered catalyst was verified with the reaction of 2-aminobenzimidazole, benzaldehyde and ethyl 3-oxobutanoate. The recovered catalyst has been charged to the reaction mixture for 3 runs without any observable loss of its catalytic activity (entry **1**).

In order to show the merit of the presented protocol, we have compared some of the results obtained by the other catalysts such as H_2SO_4, $NaHSO_4$, NH_2SO_3H, $AlCl_3$ and I_2 for the reaction of 2-aminobenzimidazole, benzaldehyde and ethyl 3-oxobutanoate (Table-3). It revealed that MTSA is an equally efficient, cost-effective and environmentally benign catalyst useful in the synthesis of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives.

TABLE-3
COMPARISON OF THE EFFECT OF CATALYSTS IN SYNTHESIS OF **4A**

Entry	Catalysis	Time (h)	Yield (%)
1	$NaHSO_4$	6	72
2	NH_2SO_3H	5	83
3	$AlCl_3$	6	60
4	I_2	8	42
5	MTSA	4	90

[a]2-Aminobenzimidazole: benzaldehyde: ethyl 3-oxobutanoate = 1: 1: 1; reactions executed at 100 ºC for 4-8 h

Conclusion

In conclusion, we have developed a simple and highly efficient practical method for one-pot synthesis of benzo-[4,5]imidazo[1,2-a]pyrimidine derivatives using melamine trisulfonic acid under solvent-free conditions. The notable features of this procedure are mild reaction conditions, simple experimental procdure and excellent yields (86-95 %), which make it a useful and attractive process for the synthesis of benzo[4,5]-imidazo[1,2-a]pyrimidine derivatives. It is believed that this methodology will be a valuable addition to the existing methods in the field of synthesis of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives.

TABLE-2
PREPARATION OF BENZO[4,5]IMIDAZO[1,2-A]PYRIMIDINES CATALYZED BY MTSA

Entry	R_1	R_2	R_3	Product	Time (h)	Yield (%)	m.p. (ºC) (lit.)
1	C_6H_5	Me	OEt	**4a**	4	90 (90,89)[b]	289-291 (294-296)[5]
2	4-MeO-C_6H_4	Me	OEt	**4b**	5	93	266-268 (272-273)[5]
3	4-Cl-C_6H_4	Me	OEt	**4c**	4	88	> 300 (> 300)[5]
4	3-NO_3-C_6H_4	Me	OEt	**4d**	5	85	288-290 (294-296)[5]
5	C_6H_5	Me	Me	**4e**	4	90	> 300 (> 300)[5]
6	4-MeO-C_6H_4	Me	Me	**4f**	5	88	275-277 (279-281)[5]
7	4-Cl-C_6H_4	Me	Me	**4g**	5	95	> 300 (> 300)[5]
8	2-Cl-C_6H_4	Me	Me	**4h**	5	92	> 300 (> 300)[5]
9	4-MeO-C_6H_4	Ph	OEt	**4i**	5	86	122-123 (117-120)[6]
10	4-NO_3-C_6H_4	Ph	OEt	**4j**	6	88	246 dec (248 dec)[6]

[a]All the products were characterized from their spectral (IR, ^{1}H NMR) and element analysis; [b]Isolated yields after recycling of catalyst

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