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EFFICIENT ACETYLATION OF ALCOHOLS, PHENOLS, AND AMINES CATALYZED BY MELAMINE TRISULFONIC ACID (MTSA)

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Melamine trisulfonic acid (MTSA) was easily prepared by the reaction of melamine with neat chlorosulfonic acid at room temperature. This reagent can be used as an efficient catalyst for the acetylation of alcohols, phenols, and amines with Ac₂O under mild and completely heterogeneous reaction conditions.

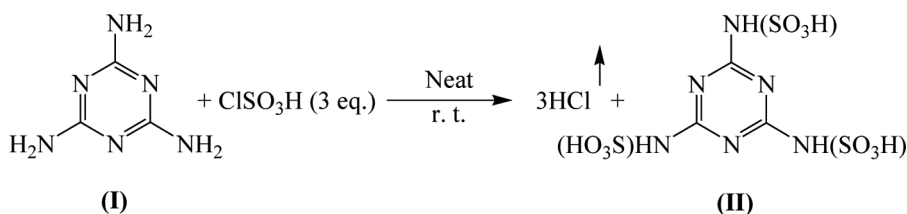
Keywords: Acetylation; alcohols; amines; melamine; melamine trisulfonic acid

Acetic anhydride is one of the most important reagents widely used for the protection of the alcoholic hydroxyl groups during multistep synthesis. A number of reagents have been reported for the promotion of the acetylation of alcohols with Ac₂O, including *p*-toluenesulfonic acid,^[1] fluoros distannoxane,^[2] heteropolyoxometallates,^[3] bismuth(III) salts,^[4] NaHSO₄·SiO₂,^[5] alumina-supported MoO₃,^[6] 12-tungstophosphoric acid,^[7] manganese(III) bis(2-hydroxyanil)acetylacetonato complex,^[8] gadolinium triflate,^[9] bis(cyclopentadienyl) zirconium dichloride,^[10] 3-nitrobenzenboronic acid,^[11] polymer-supported gadolinium triflate,^[12] niobium(V) chloride,^[13] cerium(III) triflate,^[14] H₁₄[NaP₅W₃₀O₁₁₀],^[15] Al(OTf)₃,^[16] N,N-dibromo-4-methylbenzenesulphonimide,^[17] TiCl₃(OTf),^[18] silica sulfuric acid,^[19] Al(HSO₄)₃,^[20] and Zr(HSO₄)₄.^[21] However, some of the reported methods suffer from one or more of the following disadvantages: high temperature, formation of undesirable or toxic by-products, tedious workup procedure, long reaction times, poor yields of the products, thermal instability of the reagents, and use of hazardous, highly flammable, or expensive reagents. Thus, the search for new reagents and methods is still of practical importance.

During the course of our studies on the development of new methods for the functional group transformations,^[19–24] we found that melamine (I) reacts with neat chlorosulfonic acid to give melamine trisulfonic acid (MTSA) (II) at room

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Scheme 1. Preparation of MTSA.

temperature (Scheme 1). The reaction is easy and, because of the fast evolution of HCl gas from the reaction vessel, needs no special workup procedure.

On the basis of the structure of MTSA, we anticipated that this reagent could act as an efficient catalyst in reactions that need the use of acidic reagents to speed them up. Therefore, we were interested in using MTSA for the promotion of acetylation of alcohols with Ac_2O (Scheme 2, Table 1).

As shown in Table 1, different types of alcohols, including benzylic, primary, secondary, and tertiary alcohols, are converted to their corresponding acetates when efficiently catalyzed in the presence of MTSA (Table 1, entries 1–30). All reactions were performed under mild and completely heterogeneous reaction conditions with excellent yields. Our investigation clarified that phenols and amines are also converted to their acetylated forms under the same reaction conditions in good to high yields (Scheme 3, Table 1, entries 31–47).

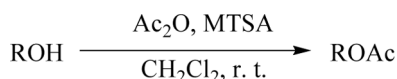
It is very important to note that by using this method, by-products resulting from the dimerization of diarylcarbinols, dehydration of tertiary alcohols, change in the configuration of optically active alcohols, and Firese rearrangement of phenols were not observed.

Investigation in the reusability of the catalyst showed that MTSA is reusable two times (Table 1, entries 2 and 4).

Although the actual role of MTSA is not clear, the mechanism shown in Scheme 4 is the most probable one.

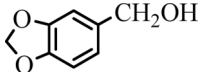
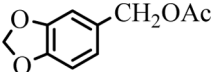
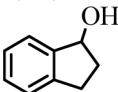
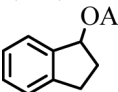
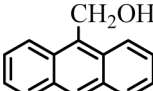
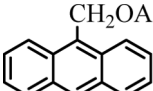
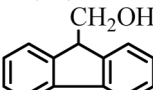
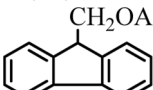
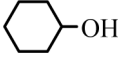
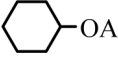
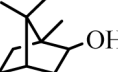
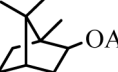
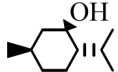
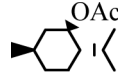
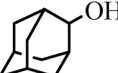
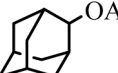
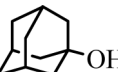
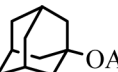
To illustrate the efficiency of the proposed method, Table 2 compares some of the results with some of those reported in the literature.^[4,8,10–12]

In conclusion, the acetylation of alcohols, phenols, and amines with Ac_2O is efficiently catalyzed in the presence of MTSA, as a newly prepared melamine-based reagent. Good yields of the products, relatively short reaction times, ease of the preparation, stability of the reagent, heterogeneous nature of the reaction conditions, and easy workup are among the other advantages of this new method that make this procedure a useful and attractive addition to the available methods. We are exploring further applications of MTSA for the other types of functional group transformations in our laboratory.



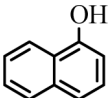
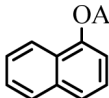
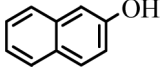
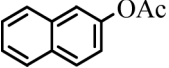
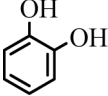
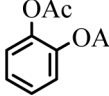


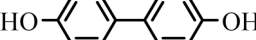
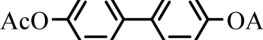
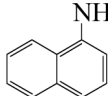
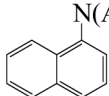
Scheme 2. Acetylation of alcohols catalyzed by MTSA.

Table 1. Acetylation of alcohols, phenols, and amines catalyzed by MTSA^a

Entry	Substrate	Product	Time (min)	Yield (%) ^b
1	C ₆ H ₅ CH ₂ OH	C ₆ H ₅ CH ₂ OAc	14	95
2	4-ClC ₆ H ₄ CH ₂ OH	4-ClC ₆ H ₄ CH ₂ OAc	8 (10 ^c)	90 (90 ^c)
3	2-ClC ₆ H ₄ CH ₂ OH	2-ClC ₆ H ₄ CH ₂ OAc	9	92
4	2-BrC ₆ H ₄ CH ₂ OH	2-BrC ₆ H ₄ CH ₂ OAc	11 (12 ^c)	90 (87 ^c)
5	3-NO ₂ C ₆ H ₄ CH ₂ OH	3-NO ₂ C ₆ H ₄ CH ₂ OAc	17	90
6	4-NO ₂ C ₆ H ₄ CH ₂ OH	4-NO ₂ C ₆ H ₄ CH ₂ OAc	12	94
7	2-MeOC ₆ H ₄ CH ₂ OH	2-MeOC ₆ H ₄ CH ₂ OAc	4	89
8	3-MeOC ₆ H ₄ CH ₂ OH	3-MeOC ₆ H ₄ CH ₂ OAc	10	85
9	4-MeOC ₆ H ₄ CH ₂ OH	4-MeOC ₆ H ₄ CH ₂ OAc	3	90
10			6	92
11	2-MeC ₆ H ₄ CH ₂ OH	2-MeC ₆ H ₄ CH ₂ OAc	15	90
12	4-Me ₃ CC ₆ H ₄ CH ₂ OH	4-Me ₃ CC ₆ H ₄ CH ₂ OAc	12	87
13	C ₆ H ₅ CH(OH)Me	C ₆ H ₅ CH(OAc)Me	12	90
14			6	85
15			10	85
16	Ph ₂ CHOH	Ph ₂ CH(OAc)	9	90
17	C ₆ H ₅ CH(OH)CH ₂ OH	C ₆ H ₅ CH(OAc)CH ₂ (OAc)	45	90 ^d
18	C ₆ H ₅ CH ₂ CH ₂ OH	C ₆ H ₅ CH ₂ CH ₂ OAc	20	92
19	C ₆ H ₅ CH ₂ CH ₂ CH ₂ OH	C ₆ H ₅ CH ₂ CH ₂ CH ₂ OAc	22	95
20	C ₆ H ₅ CH(Me)CH ₂ OH	C ₆ H ₅ CH(Me)CH ₂ OAc	16	90
21			9	90
22	MeCH ₂ CH ₂ CH ₂ OH	MeCH ₂ CH ₂ CH ₂ OAc	22	85
23	MeCH(Me)CH ₂ CH ₂ OH	MeCH(Me)CH ₂ CH ₂ OAc	34	90
24	C ₆ H ₅ CH ₂ CH(OH)Me	C ₆ H ₅ CH ₂ CH(OAc)Me	20	85
25			35	92
26			60	82
27			70	90
28			95	90
29			100	85
30	Ph ₃ COH	Ph ₃ COAc	100	80
31	4-ClC ₆ H ₄ OH	4-ClC ₆ H ₄ OAc	52	90

(Continued)

Table 1. Continued

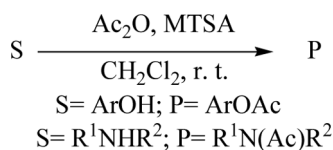
Entry	Substrate	Product	Time (min)	Yield (%) ^b
32	2,4-Cl ₂ C ₆ H ₃ OH	2,4-Cl ₂ C ₆ H ₃ OAc	95	92
33	2-PhC ₆ H ₄ OH	2-PhC ₆ H ₄ OAc	30	90
34	2,4-(NO ₂) ₂ C ₆ H ₃ OH	2,4-(NO ₂) ₂ C ₆ H ₃ OAc	145	87
35			14	85
36			19	90
37	4-MeOC ₆ H ₄ OH	4-MeOC ₆ H ₄ OAc	6	92
38	4-(PhCH ₂)C ₆ H ₄ OH	4-(PhCH ₂)C ₆ H ₄ OAc	8	85
39			20	90 ^d
40			16	95 ^d
41			15	85 ^d
42	C ₆ H ₅ NH ₂	C ₆ H ₅ NHAc	5	92
43	4-MeC ₆ H ₄ NH ₂	4-MeC ₆ H ₄ NHAc	3	92
44	2-MeC ₆ H ₄ NH ₂	2-MeC ₆ H ₄ NHAc	3	90
45	3-CF ₃ C ₆ H ₄ NH ₂	3-CF ₃ C ₆ H ₄ NHAc	19	95
46			25	92
47	PhNHCH ₃	PhN(Ac)CH ₃	13	90

^aProducts were identified spectroscopically.^bIsolated yields.^cResults obtained using recycled catalyst.^dGC yields.

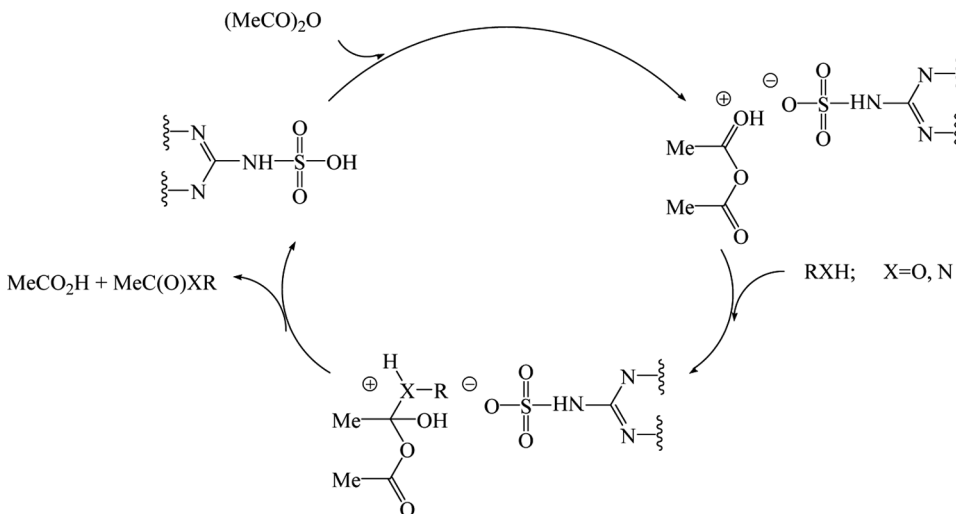
EXPERIMENTAL

Preparation of MTSA

A 250-mL suction flask charged with chlorosulfonic acid (5 mL, 75.2 mmol) was equipped with a gas inlet tube for conducting HCl gas over an adsorbing solution (i.e., water). Melamine (3.16 g, 25.07 mmol) was added in small portions over



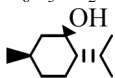
Scheme 3. Acetylation of phenols and amines catalyzed by MTSA.



Scheme 4. Mechanism of the acetylation of alcohols, phenols, and amines.

a period of 30 min at room temperature. HCl gas evolved from 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. Mp: 142–144 °C; IR: $\bar{\nu}$ = 3133, 2621, 1654, 1509, 1175, 1069 cm^{-1} . Anal. calcd. for $\text{C}_3\text{H}_6\text{N}_6\text{O}_9\text{S}_3$ (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 is confirmed by the titration of MTSA in acetonitrile environment with 1.0 M Bu_4NOH (MeOH), according to the previously reported method.^[25]

Table 2. Comparison of some of the results obtained by acetylation of alcohols and phenols in the presence of MTSA (1), with some of those reported by BiCl_3 (2),^[4] manganese(III) bis(2-hydroxyanil) acetylacetonato complex (3),^[8] bis(cyclopentadienyl)zirconium dichloride (4),^[10] 3-nitrobenzeneboronic acid (5),^[11] and polymer-supported gadolinium triflate (6)^[12]

Entry	Substrate	Time (h)/yield (%)					
		1	2	3	4	5	6
1	$\text{C}_6\text{H}_5\text{CH}_2\text{OH}$	0.23/95	0.58/98	5/97	10/93	10/90	1.5/99
2	4- $\text{NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{OH}$	0.2/94	0.5/95	8/86	—	12/94	1/97
3	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{OH}$	0.3/92	1/98	5/95	14/90	—	5/96
4		1.1/90	0.3/94	—	15/86	14/97	24/18
5	β -Naphthol	0.32/90	1.5/95	—	10/89	—	—
6	Ph_3COH	1.7/80	2/0	—	—	—	—

General Procedure

A mixture of the substrate (1 mmol), acetic anhydride (1 mmol), and MTSA (0.3 mmol, 0.11 g) in CH_2Cl_2 (3 mL) was stirred at room temperature. After completion of the reaction (monitored by thin-layer chromatography, TLC), the mixture was filtered. The filtrate was washed with CH_2Cl_2 (5 mL). The organic layer was washed with 5% solution of NaHCO_3 , then with water, and dried over MgSO_4 . Evaporation of the solvent followed by column chromatography on silica gel afforded the pure acetate.

ACKNOWLEDGMENT

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