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Melamine Trisulfonic Acid: An Efficient, Heterogeneous and Reusable Catalyst for the Synthesis of 10-Aryl-6,8-dimethyl- 6, 10-dihydro-5-oxa-6,8-diazaanthra [2,3-d][1,3]dioxole- 7,9-diones

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Abstract: Melamine trisulfonic acid was used as an efficient and recyclable catalyst for the one-pot synthesis of 10-aryl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-*d*][1,3]dioxole-7,9-diones by condensation of 3,4-methylene dioxyphenol, aromatic aldehydes and 1,3-dimethylbarbituric acid under solvent-free conditions. Different types of aromatic. aldehydes were used in the reaction and in all cases the products were obtained in good to excellent yields.

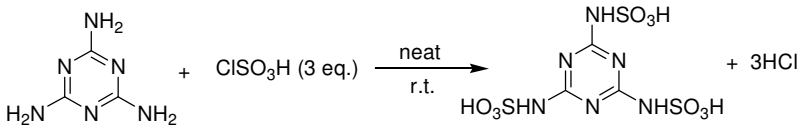
Keywords: Benzo[1,3]dioxoles, 3,4-Methylene dioxyphenol, Melamine trisulfonic acid, Solvent-free

Introduction

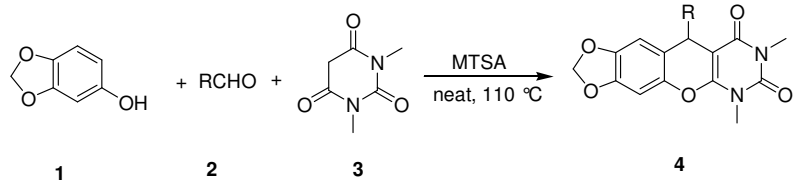
Multi-component, one-pot synthesis has received considerable attention because of their wide range of applications in pharmaceutical chemistry for creation of structural diversity and combinatorial libraries for drug discovery[1]. MCRs are extremely convergent, producing a remarkably high increase of molecular complexity in just one step[2]. The ready availability, potential biological activity and high reactivity of 3,4-methylenedioxyphenol makes it attractive molecule in pharmaceutical chemistry[3]. Consequently, a large number of 3,4-methylenedioxyphenol derivatives have been prepared for biological evaluation[4].

Recently, melamine trisulfonic acid (MTSA) has emerged as a promising solid acid catalyst for acid catalyzed reactions, such as acetylation of alcohols, phenols and amines[5], oxathioacetalyzation of aldehydes[6] and methoxymethylation of alcohols[7]. MTSA as a solidacid catalyst is prepared from the reaction of melamine with neat chlorosulfonic acid at

room temperature (Scheme 1). Compared to conventional acids, MTSA in particular has advantages of low catalyst loading, moisture stability and catalyst recycling. In the present research, we wish to describe a simple and efficient protocol for the rapid preparation of 10-aryl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-*d*][1,3]dioxole-7,9-diones using a catalytic amount of recyclable MTSA under solvent-free conditions (Scheme 2). To the best of our knowledge, there are no reports on three-component coupling of aldehyde, 3,4-methylenedioxyphenol and 1,3-dimethylbarbituric acid to produce a new class of 3,4-methylenedioxyphenol derivatives.



Scheme 1



Scheme 2

Experimental

NMR spectra were determined on Bruker AV-400 instrument 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; Mass spectra were taken on a Macro mass spectrometer (Waters) by electro-spray method (ES); 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.

Preparation of MTSA catalyst

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. 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 30min; meanwhile, the residual HCl was removed by suction. Melamine trisulfonic acid (7.7 g, 85%) was obtained as a white solid.

*General procedure for the preparation of **4***

A mixture of 3,4-methylene dioxyphenol, (1 mmol), aldehyde (1 mmol), 1,3-dimethylbarbituric acid (1 mmol) and MTSA (0.05 mmol) was heated at 110 °C for an appropriate time (TLC). After completion, the reaction mixture was washed with water (15 mL) 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, MTSA was recovered.

10-Phenyl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-d][1,3]dioxole-7,9-dione **(4a)**

White powder, m.p. 245-246 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26-7.16 (m, 5H), 6.68 (s, 1H), 6.52 (s, 1H), 5.95 (d, 1H, J = 0.8 Hz), 5.91 (d, 1H, J = 0.8 Hz), 5.03 (s, 1H), 3.55 (s, 3H),

3.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 161.9, 152.6, 150.7, 147.2, 145.6, 145.1, 143.1, 128.6, 127.8, 127.7, 126.9, 116.8, 108.2, 101.8, 98.0, 90.0, 39.2, 29.0, 28.1; MS (ESI): *m/z* 365 $[M+H]^+$; Anal. calcd for $C_{20}H_{16}N_2O_5$: C 65.93, H 4.43, N 7.69; found: C 65.90, H 4.48, N 7.74.

*10-(4-Chlorophenyl)-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-d][1,3] dioxole-7,9-dione***(4b)**

White powder, m.p. 254-255 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22 (d, 2H, *J* = 6.4 Hz), 7.18 (d, 2H, *J* = 6.8 Hz), 6.67 (s, 1H), 6.47 (s, 1H), 5.97 (d, 1H, *J* = 0.8 Hz), 5.92 (d, 1H, *J* = 0.8 Hz), 5.00 (s, 1H), 3.54 (s, 3H), 3.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 161.8, 152.6, 150.6, 147.4, 145.7, 143.6, 143.0, 132.7, 129.3, 128.8, 128.7, 116.1, 108.0, 101.9, 98.1, 89.6, 38.6, 29.0, 28.1; MS (ESI): *m/z* 399 $[M+H]^+$; Anal. calcd for $C_{20}H_{15}ClN_2O_5$: C 60.23, H 3.79, N 8.89; found: C 60.19, H 3.85, N 8.95..

10-(4-Fluorophenyl)-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-d][1,3] dioxole-7,9-dione **(4c)**

White powder, m.p. 253-254 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22-7.19 (m, 2H), 6.95-6.91 (m, 2H), 6.67 (s, 1H), 6.48 (s, 1H), 5.96 (d, 1H, *J* = 1.2 Hz), 5.92 (d, 1H, *J* = 1.2 Hz), 5.01 (s, 1H), 3.54 (s, 3H), 3.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 161.9, 152.5, 150.6, 147.3, 145.6, 143.0, 140.9, 129.4, 116.5, 115.4, 115.2, 108.1, 101.9, 98.0, 89.8, 38.4, 29.0, 28.1; MS (ESI): *m/z* 383 $[M+H]^+$; Anal. calcd for $C_{20}H_{15}FN_2O_5$: C 62.83, H 3.95, N 7.33; found: C 62.90, H 3.89, N 7.40.

10-(4-Methylphenyl)-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-d][1,3] dioxole-7,9-dione **(4d)**

White powder, m.p. 248-249 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.14 (d, 2H, *J* = 8.0 Hz), 7.07 (d, 2H, *J* = 8.0 Hz), 6.67 (s, 1H), 6.52 (s, 1H), 5.95 (d, 1H, *J* = 0.8 Hz), 5.90 (d, 1H, *J* = 0.8 Hz), 4.99 (s, 1H), 3.54 (s, 3H), 3.28 (s, 3H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 161.9, 152.5, 150.7, 147.1, 145.5, 143.0, 142.3, 136.5, 129.3, 129.2, 127.7, 127.6, 117.0, 108.2, 101.8, 98.0, 90.1, 38.8, 29.0, 28.1, 21.0; MS (ESI): *m/z* 379 $[M+H]^+$; Anal. calcd for $C_{21}H_{18}N_2O_5$: C 66.66, H 4.79, N 7.40; found: C 66.70, H 4.69, N 7.49.

10-(4-Nitrophenyl)-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-d][1,3] dioxole-7,9-dione **(4e)**

White powder, m.p. 259-260 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.12 (d, 2H, *J* = 8.8 Hz), 7.43 (d, 2H, *J* = 8.4 Hz), 6.71 (s, 1H), 6.44 (s, 1H), 5.98 (d, 1H, *J* = 0.8 Hz), 5.95 (d, 1H, *J* = 0.8 Hz), 5.15 (s, 1H), 3.56 (s, 3H), 3.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 161.8, 152.8, 152.1, 150.5, 147.8, 146.8, 145.9, 143.1, 128.9, 123.9, 114.9, 107.9, 102.1, 98.3, 88.8, 39.1, 29.1, 28.1; MS (ESI): *m/z* 410 $[M+H]^+$; Anal. calcd for $C_{20}H_{15}N_3O_7$: C 58.68, H 3.69, N 10.27; found: C 58.60, H 3.72, N 10.20.

10-(3-Nitrophenyl)-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-d][1,3] dioxole-7,9-dione **(4f)**

White powder, m.p. 262-263 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.05-8.03 (m, 1H), 8.00-7.98 (m, 1H), 7.72 (d, 1H, *J* = 7.6 Hz), 6.71 (s, 1H), 6.44 (s, 1H), 5.98 (d, 1H, *J* = 0.8 Hz), 5.94 (d, 1H, *J* = 0.8 Hz), 5.15 (s, 1H), 3.57 (s, 3H), 3.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 161.8, 152.8, 150.5, 148.5, 147.8, 147.1, 145.9, 143.0, 134.5, 129.3, 122.9, 115.0, 107.9, 102.1, 98.4, 88.8, 39.1, 29.1, 28.1; MS (ESI): *m/z* 410 $[M+H]^+$; Anal. calcd for $C_{20}H_{15}N_3O_7$: C 58.68, H 3.69, N 10.27; found: C 58.72, H 3.75, N 10.22.

*10-(3,4-Dichlorophenyl)-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-d] [1,3]dioxole-7,9-dione***(4g)**

White powder, m.p. 247-248 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33 (d, 1H, J = 8.0 Hz), 7.26-7.25 (m, 1H), 7.15 (dd, 1H, J = 2.0, 8.0 Hz), 6.68 (s, 1H), 6.45 (s, 1H), 5.98 (d, 1H, J = 0.8 Hz), 5.94 (d, 1H, J = 0.8 Hz), 4.98 (s, 1H), 3.55 (s, 3H), 3.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 161.8, 152.7, 150.6, 147.6, 145.8, 145.3, 143.0, 132.6, 131.0, 130.4, 129.8, 127.5, 115.4, 107.9, 102.0, 98.2, 89.0, 38.5, 29.1, 28.1; MS (ESI): *m/z* 433 $[M+H]^+$; Anal. calcd for $C_{20}H_{14}Cl_2N_3O_7$: C 55.45, H 3.26, N 6.47; found: C 55.50, H 3.20, N 6.50.

*10-(2,4-Dichlorophenyl)-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-d] [1,3]dioxole-7,9-dione***(4h)**

White powder, m.p. 277-278 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36 (d, 1H, J = 2.0 Hz), 7.14-7.12 (m, 2H), 6.63 (s, 1H), 6.55 (s, 1H), 5.96 (d, 1H, J = 1.6 Hz), 5.92 (d, 1H, J = 1.6 Hz), 5.52 (s, 1H), 3.57 (s, 3H), 3.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 161.7, 153.1, 150.7, 147.4, 145.6, 142.7, 141.0, 133.5, 133.2, 131.2, 129.7, 127.6, 115.1, 107.5, 101.9, 98.0, 88.2, 38.6, 29.1, 28.1; MS (ESI): *m/z* 433 $[M+H]^+$; Anal. calcd for $C_{20}H_{14}Cl_2N_3O_7$: C 55.45, H 3.26, N 6.47; found: C 55.38, H 3.24, N 6.52.

*10-(2-chlorophenyl)-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-d][1,3] dioxole-7,9-dione***(4i)**

White powder, m.p. 233-234 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.34 (d, 1H, J = 7.6 Hz), 7.17-7.12 (m, 3H), 6.63 (s, 1H), 6.61 (s, 1H), 5.95 (d, 1H, J = 0.8 Hz), 5.90 (d, 1H, J = 0.8 Hz), 5.58 (s, 1H), 3.57 (s, 3H), 3.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ:161.7, 153.1, 150.8, 147.3, 145.5, 142.7, 142.3, 132.8, 130.3, 130.0, 128.1, 127.2, 115.7, 107.7, 101.8, 97.9, 88.7, 38.2, 29.1, 28.1; MS (ESI): *m/z* 399 $[M+H]^+$; Anal. calcd for $C_{20}H_{15}ClN_2O_5$: C 60.23, H 3.79, N 8.89; found: C 60.22, H 3.80, N 8.92.

Results and Discussion

To choose optimum conditions, first, the effect of temperature on the rate of the reaction was studied for the preparation of 10-phenyl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra[2,3-*d*] [1,3] dioxole-7,9-dione from the three-component condensation reaction of 3,4-methylenedioxyphenol, benzaldehyde and 1,3- dimethylbarbituric acid in presence of 5 mol% melamine trisulfonic acid under solvent-free conditions (Table 1). At 110 °C, the reaction proceeded smoothly and gave short reaction time and high yield. Therefore, we kept the reaction temperature at 110 °C.

Table 1. Temperature optimization for the synthesis of synthesis of 7-phenyl-6*H*,7*H*-naphtho[1',2': 5,6]pyrano[3,2-*c*]chromen-6-one[a]

Entry	Temperature /°C	Time /h	Yield/ %[b]
1	25	5	0
2	50	3	10
3	60	3	25
4	70	3	36
5	80	2	42
6	90	2	58
7	100	1.5	74
8	110	1.5	86
9	120	1.5	86
10	130	1	85
11	140	1	85

[a]Reaction conditions: 3,4-methylenedioxyphenol (1 mmol); benzaldehyde (1 mmol); 1,3- dimethylbarbituric acid (1 mmol); MTSA (0.05 mmol); neat, [b]Isolated yield

Next, the study set out to determine optimal amount of MTSA, the reaction was carried out by varying amount of the catalyst (Table 2). Maximum yield was obtained with 5 mol% of the catalyst. Further increase in amount of MTSA in the mentioned reaction did not has any significant effect on the product yield.

Table 2. The amounts of catalyst optimization for the synthesis of 7-phenyl-6*H*,7*H*-naphtho[1',2': 5,6]pyrano[3,2-*c*]chromen-6-one[a]

Entry	MTSA /mol%	Time /h	Yield /%[b]
1	0	5	0
2	1	2	42
3	2	2	56
4	3	1.5	68
5	4	1.5	79
6	5	1.5	86
7	6	1.5	86
8	7	1.5	84
9	8	1.5	85

[a]Reaction conditions: 3,4-methylenedioxyphenol (1 mmol); benzaldehyde (1 mmol); 1,3-dimethylbarbituric acid (1 mmol); 110 °C; neat, [b]Isolated yield

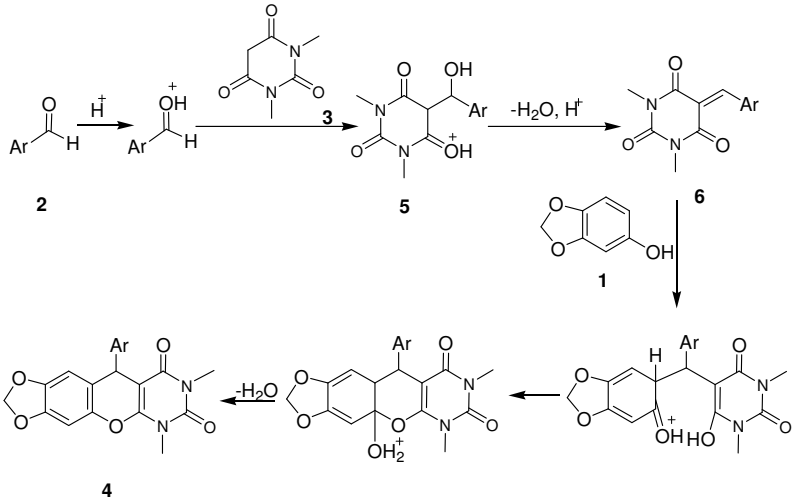
In order to extend the above reaction (Scheme 2) to a library system, various kinds of arylaldehydes **2** (Table 2) were subjected to react with **1** and **3** to give the corresponding 10-aryl-6,8-dimethyl-6,10-dihydro-5-oxa-6,8-diazaanthra [2,3-*d*][1,3]-dioxole- 7,9-diones and representative examples are shown in Table 2. All of 1 gave expected products at high yields, either bearing electron-withdrawing groups (such as halide, nitro) or electron-donating groups (such as alkyl group) under the same reaction condition. To further demonstrate the scope and limitation of the substrates, aliphatic aldehydes, such as phenylacetaldehyde, propionaldehyde, *n*-butyl aldehyde and *n*-heptaldehyde, were used as reactants to react with3,4-methylenedioxyphenol and 1,3- dimethylbarbituric acid. However, the desired products were not found and obtained successfully. All of the structures were characterized by ^{1}H NMR, ^{13}C NMR, MS and elemental analysis

Table 3. Preparation of 10-aryl-6,8-dimethyl-6,10- dihydro-5-oxa-6,8-diazaanthra [2,3-*d*] [1,3]dioxole-7,9-diones[a]

Entry	R	Time/ min	Product	Yield/ %[b]
1	C_6H_5	1.5	**4a**	86
2	4-Cl-C_6H_4	1	**4b**	89
3	4-F-C_6H_4	1	**4c**	85
4	4-Me-C_6H_4	2	**4d**	80
5	4-NO_2-C_6H_4	1	**4e**	95
6	3-NO_2-C_6H_4	1.5	**4f**	88
7	2,4-Cl_2-C_6H_3	2	**4g**	85
8	3,4-Cl_2-C_6H_3	2	**4h**	83
9	2-Cl-C_6H_4	1.5	**4i**	79

[a] Reaction conditions: 3,4-methylenedioxyphenol (1 mmol); aldehyde (1 mmol); 1,3-dimethylbarbituric acid (1 mmol);MTSA (0.05 mmol); 110 °C; neat. [b]Isolated yield

A tentative mechanism for this transformation is proposed in Scheme 3. The reaction likely proceeds *via* initial formation of oxonium species **5,** which then undergo dehydration to give olefin **6**. Subsequent Michael-type addition of 3,4-methylenedioxyphenol **1** to the olefin followed by cyclization and dehydration to afford the corresponding products **4a-4i.**



Scheme 3

Conclusion

In conclusion, an efficient protocol for the one-pot preparation of 10-aryl-6,8-dimethyl-6,10- dihydro-5-oxa-6,8- diazaanthra[2,3-*d*][1,3]dioxole-7,9-diones from the three-component condensation reaction of 3,4-methylene dioxyphenol, aromatic aldehydes and 1,3-dimethylbarbituric acid using a reusable MTSA as catalyst was described. The reactions were carried out under thermal solvent-free conditions with short reaction time and produced the corresponding products in good to excellent yields. Also the catalyst could be successfully recovered and recycled at least for three runs without significant loss in activity.

Acknowledgment

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