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ORIGINAL PAPER

Reusable melamine trisulfonic acid-catalyzed three-component synthesis of 7-alkyl-6*H*,7*H*-naphtho[1′,2′:5,6]pyrano-[3,2-*c*]chromen-6-ones

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Abstract An efficient synthesis of 7-alkyl-6*H*,7*H*-naphtho-[1′,2′:5,6]pyrano[3,2-*c*]chromen-6-ones by three-component condensation reaction of *β*-naphthol, aromatic aldehydes, and 4-hydroxycoumarin under solvent-free conditions in good to excellent yields and short reaction times using reusable melamine trisulfonic acid as solid acid catalyst has been investigated.

Keywords Naphtho[1′,2′:5,6]pyrano[3,2-*c*]chromen-6-one · Melamine trisulfonic acid · Acidity · Catalysis · Solvent-free

Introduction

Chromenes constitute a major class of naturally occurring compounds [1–7], and interest in their chemistry continues unabated because of their wide range of biological and therapeutic properties such as antioxidant [8, 9], antibacterial [10, 11], antirhinovirus [12], cytotoxic [13], anticancer [14, 15], antimicrobial [16, 17], and antihypertensive activity [18]. Considering the above reports, development of new and simple synthetic methods for efficient preparation of new chromenes is therefore an interesting challenge.

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 [19], oxathioacetalyzation of aldehydes [20], and methoxymethylation of alcohols [21]. This catalyst is safe, easy to handle, and environmentally benign, and presents fewer disposal problems. Melamine trisulfonic acid as a solid acid catalyst is prepared from reaction of melamine with neat chlorosulfonic acid at room temperature.

Herein, we describe a simple and efficient protocol for rapid preparation of 7-alkyl-6*H*,7*H*-naphtho[1′,2′:5,6]pyrano[3,2-*c*]chromen-6-ones using a catalytic amount of recyclable melamine trisulfonic acid under solvent-free conditions (Scheme 1). To the best of our knowledge, there is only one previous account describing this quinoidal system [22].

Results and discussion

To choose optimum conditions, first, the effect of temperature on the rate of the reaction was studied for the preparation of 7-phenyl-6*H*,7*H*-naphtho[1′,2′:5,6]pyrano[3,2-*c*]chromen-6-one by three-component condensation reaction of *β*-naphthol, benzaldehyde, and 4-hydroxycoumarin in presence of 2 mol% melamine trisulfonic acid under solvent-free conditions (Table 1). At 120 °C, the reaction proceeded smoothly and gave short reaction time and high yield. Therefore, we kept the reaction temperature at 120 °C.

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

Using these optimized reaction conditions, the scope and efficiency of these procedures were explored for synthesis of

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Scheme 1

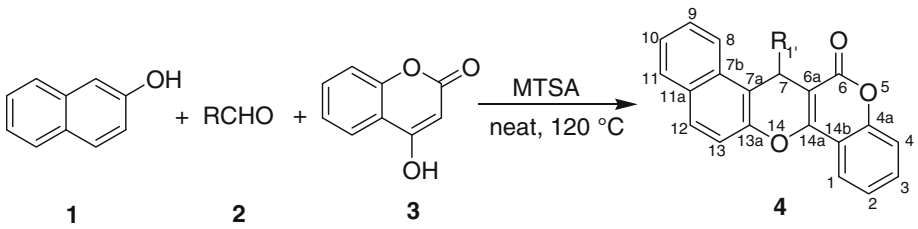


Table 1 Temperature optimization for the synthesis of 7-phenyl-6*H*,7*H*-naphtho[1′,2′:5,6]pyrano[3,2-*c*]chromen-6-one

Entry	Temperature (°C)	Time (h)	Yield (%)[a]
1	25	8	0
2	50	5	34
3	60	3	38
4	70	3	42
5	80	3	56
6	90	1.5	63
7	100	1.5	72
8	110	1	82
9	120	1	89
10	130	1	88
11	140	1	88

Reaction conditions: *β*-naphthol (1 mmol), benzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), MTSA (0.02 mmol); neat

[a] Isolated yields

Table 2 Optimization of the catalyst amount for the synthesis of 7-phenyl-6*H*,7*H*-naphtho[1′,2′:5,6]pyrano[3,2-*c*]chromen-6-one

Entry	MTSA (mol%)	Time (h)	Yield (%)[a]
1	0	8	0
2	0.5	2	45
3	1	1.5	61
4	1.5	1.5	79
5	2	1	89
6	2.5	1	89
7	3	1	88
8	3.5	1	89

Reaction conditions: *β*-naphthol (1 mmol), benzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol); 120 °C; neat

[a] Isolated yields

a wide variety of 7-alkyl-6*H*,7*H*-naphtho[1′,2′:5,6]pyrano-[3,2-*c*]chromen-6-ones. The results are summarized in Table 3. As shown in Table 3, the direct three-component reaction worked well with a variety of aryl aldehydes including those bearing electron-withdrawing and electron-donating groups such as Me, Cl, F, and NO_2, and the desired compounds were obtained in high to excellent yields. When this reaction was carried out with aliphatic aldehydes such as butanal or pentanal, thin-layer chromatography (TLC) and

Table 3 Preparation of 7-alkyl-6*H*,7*H*-naphtho[1′,2′:5,6]pyrano-[3,2-*c*]chromen-6-ones

Entry	*R*	Time (h)	Product	Yield (%)[a]
1	C_6H_5	1	**4a**	89 (85, 82, 76)[b]
2	4-Cl-C_6H_4	1	**4b**	88
3	4-F-C_6H_4	1	**4c**	84
4	4-Me-C_6H_4	0.5	**4d**	91
5	4-NO_2-C_6H_4	1	**4e**	89
6	3-NO_2-C_6H_4	1.5	**4f**	83
7	2,4-Cl_2-C_6H_3	1.5	**4g**	82
8	3,4-Cl_2-C_6H_3	1.5	**4h**	81

Reaction conditions: *β*-naphthol (1 mmol), aldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), MTSA (0.02 mmol); 120 °C; neat

[a] Isolated yields

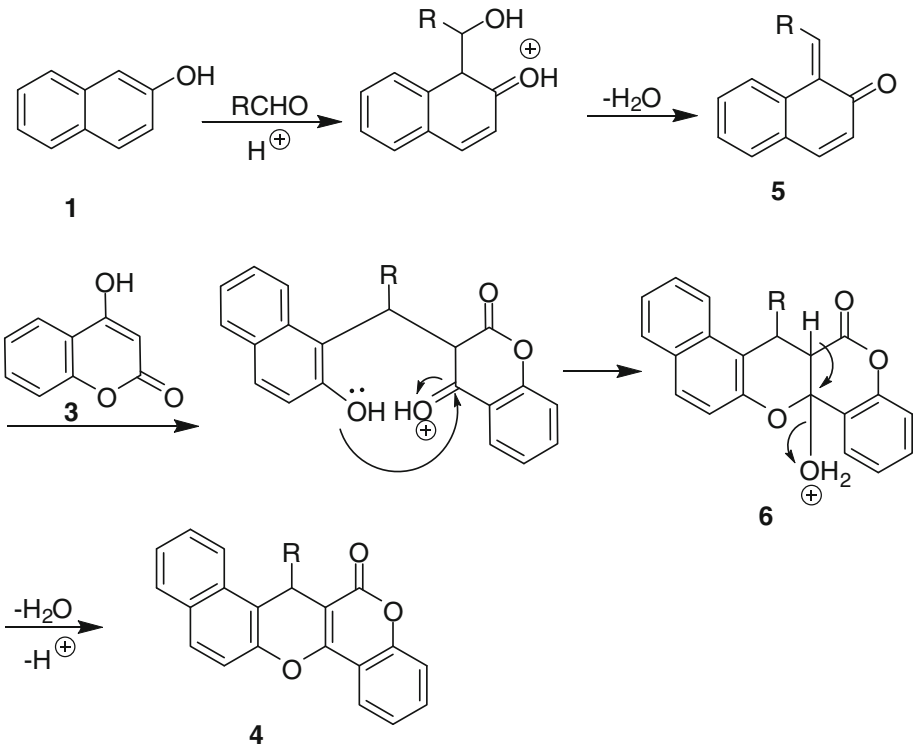
[b] Yields after three times of catalyst recovery

^{1}H nuclear magnetic resonance (NMR) spectra of the reaction mixture showed a combination of starting materials and numerous products, and the yield of the expected product was very poor. This methodology offers significant improvements with regard to the scope of this transformation, simplicity in operation, and green aspects by avoiding expensive or corrosive catalysts. All of the products **4** exhibited a singlet in their ^{1}H spectra at $\delta = 5.71$–6.11 ppm for H-7, and a distinguishing peak at $\delta = 34.3$–36.4 ppm for C-7 in their ^{13}C NMR spectra. The resonances of carbonyl groups in the ^{13}C NMR spectrum of **4** appeared at $\delta = 172.9$–176.8 ppm. To assign the observed signals to individual protons and carbons, we performed two-dimensional (2D) NMR studies [^{1}H–^{1}H correlation spectroscopy (COSY), heteronuclear multiple-bond correlation (HMBC), heteronuclear single quantum correlation (HSQC)] for compound **4e** (see "Experimental" part).

The reusability of the catalyst was tested in the synthesis of 7-phenyl-6*H*,7*H*-naphtho[1′,2′:5,6]pyrano[3,2-*c*]chromen-6-ones. The catalyst was recovered after each run, washed with CH_2Cl_2, dried in an oven at 100 °C for 30 min prior to use, and tested for its activity in the subsequent run with no fresh catalyst added. The catalyst was tested for three runs. It was seen that the catalyst displayed very good reusability (Table 3, entry 1).

The suggested mechanism of the MTSA-catalyzed transformations is shown in Scheme 2. The reaction likely

Scheme 2



proceeds via initial formation of *ortho*-quinone methide **5**. The oxonium species **6** is then formed on reaction with 4-hydroxycoumarin, which then undergoes dehydration to afford the desired product **4**. In *β*-naphthol the electron density at the benzylic C-1 position (which is in conjugation with the aromatic ring) is higher than that at the C-3 position. Thus, regioselective formation of the *ortho*-quinone methide from this compound involving the C-1 and C-2 positions is favored. In simple phenolic compounds and 1-naphthol (which are weaker nucleophiles compared with *β*-naphthol) the electron density at the *ortho*-position of the hydroxyl group is not sufficient for the reaction of these compounds with the aldehydes, leading to the formation of the corresponding *ortho*-quinone methides.

To emphasize the effect of the catalyst, the model reaction of *β*-naphthol, benzaldehyde, and 4-hydroxycoumarin was investigated using various catalysts. All the reactions were run under the same conditions, and similar amounts of catalysts (2 mol%) were used. As shown in Table 4, satisfactory results were obtained only with MTSA.

In summary, an efficient protocol for one-pot preparation of 7-alkyl-6*H*,7*H*-naphtho[1′,2′:5,6]pyrano[3,2-*c*]chromen-6-ones by three-component condensation reaction of *β*-naphthol, aromatic aldehydes, and 4-hydroxycoumarin using reusable MTSA as catalyst is 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.

Table 4 Comparison of the effect of catalysts in the synthesis of 7-phenyl-6*H*,7*H*-naphtho[1′,2′:5,6]pyrano[3,2-*c*]chromen-6-one

Entry	Catalyst	Yield (%)[a]
1	H_2SO_4	25
2	$NaHSO_3$	40
3	$NaHSO_4$	72
4	$AlCl_3$	58
5	I_2	69
6	MTSA	89

Reaction conditions: *β*-naphthol (1 mmol), benzaldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), catalyst (0.02 mol); 120 °C; neat

[a] Isolated yields

Experimental

NMR spectra were determined on a Fourier-transform (FT)-NMR Avance 400 spectrometer in $CDCl_3$ or dimethyl sulfoxide (DMSO)-d_6 and are expressed in δ values relative to tetramethylsilane; coupling constants (J) are measured in Hz. Mass spectra were recorded on a Finnigan LCQ Advantage mass spectrometer. Elemental analyses were recorded on a Vario-III elemental analyzer. Melting points were determined on a XT-4 binocular microscope.

Commercially available reagents were used throughout without further purification unless otherwise stated.

Preparation of MTSA catalyst

A 250-cm^3 suction flask charged with 5 cm^3 chlorosulfonic acid (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 3). After completion of the addition of melamine, the mixture was shaken for 30 min; 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 β-naphthol (1 mmol), aldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), and MTSA (0.02 mmol) was heated at 120 °C for an appropriate time (TLC). After completion, the reaction mixture was washed with 15 cm^3 water and the 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.

7-Phenyl-6H,7H-naphtho[1′,2′:5,6]pyrano[3,2-c]-chromen-6-one (**4a**)
White powder; m.p.: 281–282 °C (Ref. [22]: 275 °C).

7-(4-Chlorophenyl)-6H,7H-naphtho[1′,2′:5,6]pyrano-[3,2-c]chromen-6-one (**4b**, $C_{26}H_{15}ClO_3$)
White powder; m.p.: 267–268 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.20 (d, 1H, J = 7.6 Hz, ArH), 7.97 (d, 1H, J = 8.0 Hz, ArH), 7.91–7.86 (m, 2H, ArH), 7.69–7.40 (m, 8H, ArH), 7.18 (d, 2H, J = 8.4 Hz, ArH), 6.11 (s, 1H, CH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 174.6, 160.7, 154.8, 152.5, 147.0, 142.9, 133.3, 131.9, 130.8, 130.7, 130.4, 129.1, 128.8, 127.9, 125.9, 125.2, 123.9, 132.2, 117.7, 117.0, 116.2, 114.1, 104.5, 35.8 ppm; MS (ESI): m/z = 411 ([M + H]$^+$).

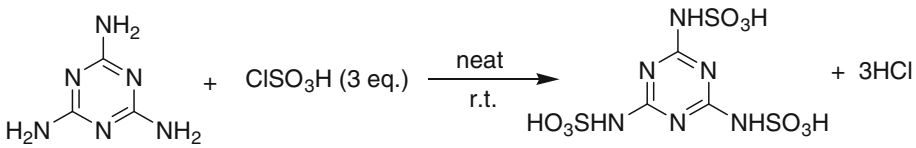
7-(4-Fluorophenyl)-6H,7H-naphtho[1′,2′:5,6]pyrano-[3,2-c]chromen-6-one (**4c**, $C_{26}H_{15}FO_3$)
White powder; m.p.: 253–254 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.20 (d, 1H, J = 7.6 Hz, ArH), 7.98 (d, 1H, J = 8.0 Hz, ArH), 7.87 (t, 2H, J = 9.6 Hz, ArH), 7.67 (t, 1H, J = 8.0 Hz, ArH), 7.50–7.39 (m, 7H, ArH), 6.90 (t, 2H, J = 8.4 Hz, ArH), 6.11 (s, 1H, CH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 173.5, 165.6, 156.2, 153.0, 147.4, 139.5, 133.5, 131.8, 130.9, 130.0, 129.9, 129.7, 128.6, 127.5, 126.0, 125.5, 125.3, 123.9, 123.3, 117.4, 117.3, 116.5, 115.3, 115.1, 100.0, 35.5 ppm; MS (ESI): m/z = 395 ([M + H]$^+$).

7-(4-Methylphenyl)-6H,7H-naphtho[1′,2′:5,6]pyrano-[3,2-c]chromen-6-one (**4d**, $C_{27}H_{18}O_3$)
White powder; m.p.: 230–231 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 8.17–8.14 (m, 1H, ArH), 8.06–8.01 (m, 2H, ArH), 7.90 (d, 1H, J = 7.6 Hz, ArH), 7.72–7.68 (m, 2H, ArH), 7.54–7.45 (m, 4H, ArH), 7.26 (d, 2H, J = 8.0 Hz, ArH), 7.01 (d, 2H, J = 8.0 Hz, ArH), 5.71 (s, 1H, CH), 2.14 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 172.9, 160.7, 154.5, 152.4, 147.0, 141.1, 136.4, 133.1, 131.8, 130.8, 130.1, 129.4, 129.1, 128.8, 127.8, 125.8, 125.1, 123.9, 123.1, 117.6, 117.0, 116.8, 114.1, 105.1, 35.9, 20.9 ppm; MS (ESI): m/z = 391 ([M + H]$^+$).

7-(4-Nitrophenyl)-6H,7H-naphtho[1′,2′:5,6]pyrano-[3,2-c]chromen-6-one (**4e**, $C_{26}H_{15}NO_5$)
White powder; m.p.: 257–258 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.17 (d, 1H, J = 8.0 Hz, H-1), 8.05 (d, 2H, J = 8.8 Hz, H-3′, 5′), 7.91–7.84 (m, 3H, H-3, 8, 11), 7.68–7.62 (m, 3H, H-9, 2′, 6′), 7.50–7.38 (m, 5H, H-2, 4, 10, 12, 13), 6.19 (s, 1H, H-7) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.8 (C-6), 160.2 (C-14a), 153.0 (C-4a), 150.8 (C-1′), 147.5 (C-7b), 146.7 (C-4′), 133.7 (C-9), 131.9 (C-13a), 130.8 (C-11a), 130.4 (C-8), 129.4 (C-2′, 6′), 128.8 (C-3), 127.8 (C-2), 126.0 (C-1), 125.8(C-13), 125.6 (C-4), 123.8 (C-3′, 5′), 123.5 (C-11), 123.2 (C-14b), 117.5 (C-10), 116.6 (C-12), 116.0 (C-7a), 98.9 (C-6a), 36.3 (C-7) ppm; MS (ESI): m/z = 422 ([M + H]$^+$).

7-(3-Nitrophenyl)-6H,7H-naphtho[1′,2′:5,6]pyrano-[3,2-c]chromen-6-one (**4f**, $C_{26}H_{15}NO_5$)
White powder; m.p.: 249–250 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.17–8.12 (m, 2H, ArH), 8.01–7.85 (m, 5H, ArH), 7.63–7.58 (m, 2H, ArH), 7.52–7.35 (m, 5H, ArH), 5.97 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 176.2, 161.4, 155.4, 152.7, 148.5, 147.3, 145.1, 135.0, 132.5, 131.9, 130.6, 130.4, 129.3, 128.8, 127.7, 125.6, 124.4, 123.4, 123.1, 122.9, 122.2, 117.1, 116.8, 115.0, 114.1, 103.8, 36.3 ppm; MS (ESI): m/z = 422 ([M + H]$^+$).

Scheme 3



7-(2,4-Dichlorophenyl)-6H,7H-naphtho[1′,2′:5,6]-pyrano[3,2-c]chromen-6-one (**4g**, $C_{26}H_{14}Cl_2O_3$)
White powder; m.p.: 267–268 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): $\delta = 8.18$ (d, 1H, $J = 7.2$ Hz, ArH), 8.04 (d, 2H, $J = 8.0$ Hz, ArH), 7.97 (d, 1H, $J = 7.2$ Hz, ArH), 7.73–7.67 (m, 2H, ArH), 7.52–7.48 (m, 6H, ArH), 7.26 (m, 1H, ArH), 6.02 (s, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 175.5$, 161.6, 155.0, 152.6, 147.3, 143.2, 132.0, 131.8, 131.0, 129.5, 128.8, 128.6, 128.5, 128.4, 127.4, 126.9, 125.3, 124.2, 123.6, 122.7, 116.9, 116.7, 116.6, 114.5, 105.2, 36.4 ppm; MS (ESI): $m/z = 445$ ($[M + H]^+$).

7-(3,4-Dichlorophenyl)-6H,7H-naphtho[1′,2′:5,6]-pyrano[3,2-c]chromen-6-one (**4h**, $C_{26}H_{14}Cl_2O_3$)
White powder; m.p.: 256–257 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 8.20$ (dd, 1H, $J = 1.2$, 7.6 Hz, ArH), 7.93–7.86 (m, 3H, ArH), 7.70–7.66 (m, 1H, ArH), 7.55–7.36 (m, 7H, ArH), 7.29 (m, 1H, ArH), 6.07 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.5$, 161.5, 155.3, 152.7, 147.3, 143.2, 132.6, 132.4, 131.8, 131.1, 130.8, 130.4, 130.3, 130.1, 128.7, 128.2, 127.7, 125.6, 124.3, 123.3, 122.8, 116.9, 116.8, 115.3, 114.2, 104.1, 35.8 ppm; MS (ESI): $m/z = 445$ ($[M + H]^+$).

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