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ORIGINAL PAPER

Solvent-free, one-pot synthesis of amidoalkyl naphthols by a copper *p*-toluenesulfonate catalyzed multicomponent reaction

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Abstract An efficient synthesis of amidoalkyl naphthols using copper *p*-toluenesulfonate (CPTS) as catalyst for the three-component condensation reaction of 2-naphthol, aldehydes, and amides under thermal, solvent-free conditions is described. This new approach has advantages such as short reaction time, high yield, simple work-up, and reusable catalyst.

Keywords Amidoalkyl naphthol
Three-component reaction · Metal sulfonates · One-pot synthesis · Solvent-free

Introduction

Multicomponent reactions (MCRs) have attracted considerable attention in organic synthesis as they can produce the target products in a single operation without isolating the intermediates, thus reducing reaction times and energy consumption. MCRs have merits over conventional linear-type syntheses in several aspects including simple procedures, possible structural variations, and rapid access to complex molecules. Therefore, discovery and development of new MCRs is highly desirable.

Amidoalkyl naphthols are important synthetic building blocks and are used as precursors for the synthesis of 1-aminomethyl-2-naphthol derivatives, which exhibit important cardiovascular activity [1]. The preparation of 1-amidoalkyl-2-naphthols can be carried out by three-component condensation of 2-naphthol, aldehydes, and acetonitrile or different amides in the presence of homogeneous or heterogeneous catalysts such as *p*-toluenesulfonic acid [2], H_2NSO_3H [3], oxalic acid [4], $Fe(HSO_4)_3$ [5], $Sr(OTf)_2$ [6], I_2 [7], $K_5CoW_{12}O_{40}{\cdot}3H_2O$ [8], HPMo [9], $Yb(OTf)_3$ in ionic liquid [10], Indion-130 [11], montmorillonite K10 [12], TMSCl/NaI [13], Al_2O_3–$HClO_4$ [14], $InCl_3$ [15], 2,4,6-trichloro-1,3,5-triazine [16], CuPW and CuPMo [17], $H_3MoO_{40}P$ [18], $H_4SiW_{12}O_{40}$ [19], and P_2O_5 [20]. However, some of the reported methods suffer from disadvantages such as long reaction time, toxic and corrosive solvent, high reaction temperature (>100 °C), and the use of additional microwave or ultrasonic irradiation. Furthermore, the yields of the corresponding amidoalkyl naphthols are not always satisfactory. Because of the importance of these compounds, the introduction of a milder, faster, and more ecofriendly method accompanied with higher yields is needed.

In recent years, metal sulfonates have received considerable attention as inexpensive and recyclable catalysts for numerous organic transformations, affording the corresponding products in excellent yields with high selectivity [21–25]. Their low toxicity, easy preparation, moisture resistance, and air tolerance are other common features that make the use of metal sulfonates an attractive alternative to conventional Lewis acids and triflates. As part of our ongoing work on the application of metal sulfonate catalysts for developing useful synthetic methodologies, we now show that amidoalkyl naphthols can be prepared by using copper *p*-toluenesulfonate (CPTS) as an efficient catalyst via one-pot, three-component condensation of 2-naphthol, various aldehydes, and different amides (Scheme 1).

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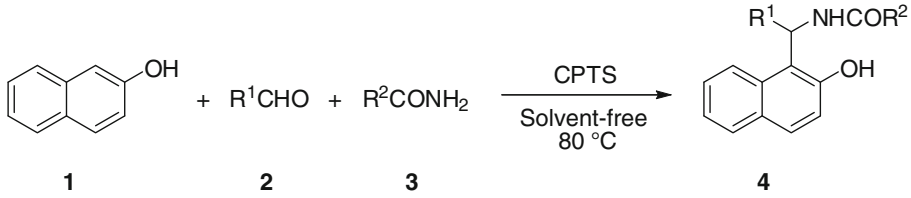
Scheme 1



Results and discussion

First, we compared the catalytic activity of metal *p*-toluenesulfonates with some other catalysts reported in the literature for the three-component condensation reaction of 2-naphthol, benzaldehyde, and benzamide (Table 1). In the absence of catalyst, no product was formed even after 8 h at 80 °C (Table 1, entry 1). After several experiments, CPTS was found to the most efficient catalyst among all the examined metal *p*-toluenesulfonates under these conditions. CPTS gave the highest yield of product in the shortest reaction time (Table 1, entry 2). In order to evaluate the most appropriate reaction temperature, the model reaction was carried out at different temperatures (Table 1, entries 7–10). The reaction rate was increased as the reaction temperature was raised from r.t. to 80 °C, but higher temperature (100 °C) did not increase the yields significantly. Thus, 80 °C was found to be the optimal reaction temperature (Table 1, entry 2). We also studied the model reaction catalyzed by CPTS with different catalyst loading (Table 1, entries 11 and 12). The optimal quantity of catalyst was found to be 2 mol% (Table 1, entry 2). Excess amount of catalyst did not increase the yields. To show the merit of this CPTS-catalyzed method, we compared the results of CPTS with those of reported catalysts such as $Sr(OTf)_2$, $K_5CoW_{12}O_{40}{\cdot}3H_2O$, montmorillonite K10, $Yb(OTf)_3$, HPMo, *p*-TSA, and P_2O_5 in synthesizing *N*-((2-hydroxynaphth-1-yl)phenylmethyl)benzamide (Table 1, entries 13–19). As shown in Table 1, CPTS is a better catalyst with respect to reaction time, reaction temperature, and product yield. Thus, the present protocol with CPTS catalyst is superior to the recently reported catalytic methods.

As shown in Table 2, amidoalkyl naphthols were synthesized in excellent yields by the reaction of 2-naphthol, aromatic or aliphatic aldehydes, and amides using CPTS as catalyst at 80 °C. In all cases, amidoalkyl naphthols were the sole products and no by-product was observed. Aromatic aldehydes carrying electron-withdrawing groups reacted faster than those carrying electron-donating groups. To demonstrate the scope and limitations of the procedure, *ortho*-substituted aromatic aldehydes such as 2-nitrobenzaldehyde and 2-chlorobenzaldehyde were studied. The results show the position of the substituent on the aromatic ring does not show effects on the conversion. Aliphatic

Table 1 Comparison of results of metal *p*-toluenesulfonates with other catalysts reported in the literature

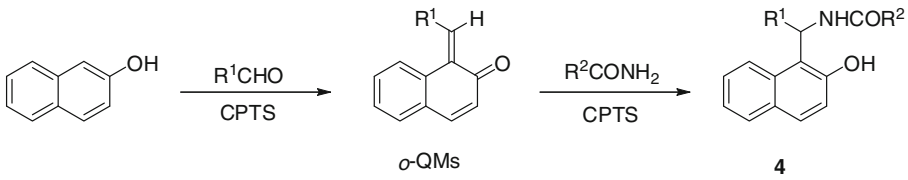
Entry	Catalyst (mol%)	Time (h)	Temp (°C)	Yield (%)	Ref.
1	–	8	80	0	
2	$Cu(p\text{-}CH_3C_6H_4SO_3)_2{\cdot}6H_2O$ (2)	0.3	80	95	
3	$Pb(p\text{-}CH_3C_6H_4SO_3)_2{\cdot}6H_2O$ (2)	0.5	80	85	
4	$Zn(p\text{-}CH_3C_6H_4SO_3)_2{\cdot}5H_2O$ (2)	0.5	80	74	
5	$La(p\text{-}CH_3C_6H_4SO_3)_2{\cdot}2H_2O$ (2)	0.5	80	71	
6	$Sm(p\text{-}CH_3C_6H_4SO_3)_2{\cdot}2H_2O$ (2)	1	80	45	
7	$Cu(p\text{-}CH_3C_6H_4SO_3)_2{\cdot}6H_2O$ (2)	0.3	100	96	
8	$Cu(p\text{-}CH_3C_6H_4SO_3)_2{\cdot}6H_2O$ (2)	0.7	60	62	
9	$Cu(p\text{-}CH_3C_6H_4SO_3)_2{\cdot}6H_2O$ (2)	1	40	17	
10	$Cu(p\text{-}CH_3C_6H_4SO_3)_2{\cdot}6H_2O$ (2)	1	r.t.	0	
11	$Cu(p\text{-}CH_3C_6H_4SO_3)_2{\cdot}6H_2O$ (1)	0.6	80	78	
12	$Cu(p\text{-}CH_3C_6H_4SO_3)_2{\cdot}6H_2O$ (3)	0.15	80	81	
13	$Sr(OTf)_2$ (10)	9	60	93	[6]
14	$K_5CoW_{12}O_{40}{\cdot}3H_2O$ (1)	2	125	80	[8]
15	Montmorillonite K10	1.5	125	78	[12]
16	$Yb(OTf)_3$ (20)	10	80	35	[10]
17	HPMo (1.6)	3.5	65	92	[9]
18	*p*-TSA (10)	6	125	86	[2]
19	P_2O_5 (10)	0.17	60	85	[20]

Table 2 Synthesis of amidoalkyl naphthols in the presence of CPTS

Entry	R^1	R^2	Time (h)	Product	Yield (%)	M.p. (lit. m.p.) (°C)
1	C_6H_5	C_6H_5	0.3	**4a**	95–89[a]	236–239 (233–235 [14])
2	2-$NO_2C_6H_4$	C_6H_5	0.1	**4b**	93	260–263 (266–267 [20])
3	3-$NO_2C_6H_4$	C_6H_5	0.1	**4c**	95	235–237 (233–235 [26])
4	4-$NO_2C_6H_4$	C_6H_5	0.3	**4d**	94	237–239 (239–241 [4])
5	2-ClC_6H_4	C_6H_5	0.15	**4e**	91	266–268
6	4-ClC_6H_4	C_6H_5	0.4	**4f**	96	186–188 (187–188 [6])
7	2,4-$Cl_2C_6H_3$	C_6H_5	0.3	**4g**	92	237–238
8	4-$CH_3C_6H_4$	C_6H_5	0.5	**4h**	93	210–212 (209–211 [26])
9	4-$CH_3OC_6H_4$	C_6H_5	3	**4i**	72	208–210 (206–208 [20])
10	4-$(CH_3)_2NC_6H_4$	C_6H_5	10	**4j**	31	219–221 (220–221 [20])
11	CH_3CH_2	C_6H_5	0.1	**4k**	87	246–247 (244–245 [6])
12	$CH_3CH_2CH_2$	C_6H_5	0.1	**4l**	88	240–242
13	$C_6H_5CH{=}CH$	C_6H_5	9	**4m**	Trace	–
14	C_6H_5	CH_3	1.5	**4n**	94	242–244 (241–243 [8])
15	3-$NO_2C_6H_4$	CH_3	0.5	**4o**	92	255–257 (255–256 [6])
16	2-ClC_6H_4	CH_3	0.7	**4p**	95	207–209 (206–207 [20])
17	4-ClC_6H_4	CH_3	1.3	**4q**	87	234–237 (237–238 [20])
18	4-$CH_3C_6H_4$	CH_3	1.7	**4r**	65	217–220 (222–223 [5])
19	4-$CH_3OC_6H_4$	CH_3	12	**4s**	16	180–182 (183–185 [5])
20	CH_3CH_2	CH_3	5.5	**4t**	60	178–180 (173–175 [27])
21	C_6H_5	NH_2	1	**4u**	86	179–181 (172–174 [3])
22	3-$NO_2C_6H_4$	NH_2	1	**4v**	43	198–200 (192–193 [26])
23	4-ClC_6H_4	NH_2	6	**4w**	Trace	–
24	4-$CH_3C_6H_4$	NH_2	6	**4x**	Trace	–
25	CH_3CH_2	NH_2	9	**4y**	Trace	–

[a] Yield after four recoveries of the catalyst

Scheme 2



aldehydes such as propionaldehyde and butyraldehyde were also examined, and in the case of benzamide the yields of products were as high as those of products from aromatic aldehydes (Table 2, entries 11 and 12). On the other hand, only traces of corresponding product were produced in the reaction with α,β-unsaturated aldehydes such as cinnamaldehyde (Table 2, entry 13). In the case of amide, besides benzamide and acetamide, urea was also employed. The condensation yields with urea were lower than those with benzamide and acetamide.

To investigate the reusability and recycling of CPTS, 2-naphthol, benzaldehyde, and benzamide were used as a model reaction. When the reaction was completed, the reaction mixture was washed with water. The catalyst remaining in the aqueous phase could be recovered by evaporating the filtrate, furnishing CPTS to be reused in the next run. No significant decrease in activity was observed even in up to four runs (Table 2, entry 1), which demonstrated that CPTS was water-tolerant and efficient for this condensation.

A possible mechanism for this transformation is proposed in Scheme 2. As reported in the literature [2], reaction of 2-naphthol with aldehydes in the presence of an acid catalyst is known to give *ortho*-quinone methides (*o*-QMs). The same *o*-QMs, generated in situ, have been reacted with amides via conjugate addition to form 1-amidoalkyl-2-naphthol derivatives **4**.

Experimental

Melting points were determined by using an RY-1 micro-melting point apparatus. Infrared spectra were recorded on a Varian Scimitar 2000 series Fourier transform instrument.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-500 spectrometer in DMSO-d_6 using TMS as an internal standard. Elemental analyses were carried out on an EA 2400II elemental analyzer (Perkin Elmer) and agreed favorably with the calculated values.

General procedure for the synthesis of amidoalkyl naphthols ***4***

A mixture of 2-naphthol (10 mmol), an aldehyde (10 mmol), an amide (11 mmol), and CPTS (0.2 mmol) was added to a 25-cm^3 conical flask. The reaction mixture was magnetically stirred on a preheated water bath at 80 °C. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to r.t., washed with water, and the residue was recrystallized from ethanol. The catalyst remaining in the aqueous phase could be recovered by evaporating the filtrate. The products were characterized by comparing their m.p., IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis with those reported for the authentic samples.

N-((2-Chlorophenyl)(2-hydroxynaphth-1-yl)methyl)-benzamide (**4e**, $C_{24}H_{18}ClNO_2$)
White solid. IR (KBr): $\bar{\nu}$ = 3,426, 3,067, 1,633, 1,573, 1,538, 1,346, 1,075, 823, 753, 711 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.94 (s, 1H, OH), 9.00 (d, 1H, J = 6.2 Hz, NH), 8.08 (d, 1H, J = 8.6 Hz, ArH), 7.88 (d, 2H, J = 7.3 Hz, ArH), 7.82 (d, 1H, J = 7.6 Hz, ArH), 7.78 (d, 1H, J = 8.8 Hz, ArH), 7.51 (t, 1H, J = 7.3 Hz, ArH), 7.44–7.40 (m, 5H, ArH), 7.35 (d, 1H, J = 5.0 Hz, CH), 7.30–7.25 (m, 3H, ArH), 7.19 (d, 1H, J = 8.8 Hz, ArH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.4, 153.7, 138.8, 134.2, 132.9, 132.8, 131.1, 130.2, 129.4, 128.6, 128.5, 128.3, 128.1, 127.4, 126.6, 126.3, 122.8, 122.3, 118.6, 116.8, 48.6 ppm.

N-((2,4-Dichlorophenyl)(2-hydroxynaphth-1-yl)methyl)benzamide (**4g**, $C_{24}H_{17}Cl_2NO_2$)
White solid. IR (KBr):$\bar{\nu}$ = 3,423, 3,069, 1,633, 1,574, 1,537, 1,344, 1,074, 819, 749, 709 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.97 (s, 1H, OH), 9.15 (d, 1H, J = 6.3 Hz, NH), 8.05 (d, 1H, J = 8.6 Hz, ArH), 7.90 (d, 2H, J = 7.2 Hz, ArH), 7.82 (d, 1H, J = 7.6 Hz, ArH), 7.78 (d, 1H, J = 8.8 Hz, ArH), 7.58 (d, 1H, J = 2.1 Hz, ArH), 7.52–7.42 (m, 5H, ArH), 7.37 (dd, 1H, J = 2.1, 6.3 Hz, CH), 7.29–7.27 (m, 2H, ArH), 7.18 (d, 1H, J = 8.8 Hz, ArH) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.5, 153.7, 138.2, 134.1, 133.6, 132.7, 132.1, 131.4, 131.2, 129.6, 128.6, 128.3, 128.1, 127.5, 126.7, 126.5, 122.6, 122.4, 118.6, 116.1, 48.3 ppm.

N-(1-(2-Hydroxynaphth-1-yl)butyl)benzamide (**4l**, $C_{21}H_{21}NO_2$)
White solid. IR (KBr): $\bar{\nu}$ = 3,415, 3,222, 3,204, 1,633, 1,575, 1,528, 1,342, 1,074, 815, 747, 716 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.09 (s, 1H, OH), 8.60 (d, 1H, J = 6.3 Hz, NH), 8.23 (d, 1H, J = 7.6 Hz, ArH), 7.81 (t, 3H, J = 7.2 Hz, ArH), 7.71 (d, 1H, J = 8.8 Hz, ArH), 7.53–7.44 (m, 4H, ArH), 7.31 (t, 1H, J = 7.3 Hz, ArH), 7.20 (d, 1H, J = 8.8 Hz, ArH), 6.04 (q, 1H, J = 7.1 Hz, CH), 2.18–2.11 (m, 1H, CH_2), 1.92–1.85 (m, 1H, CH_2), 1.51–1.42 (m, 1H, CH_2), 1.33–1.23 (m, 1H, CH_2), 0.93 (t, 3H, J = 7.3 Hz, CH_3) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.2, 152.8, 134.7, 132.1, 131.1, 128.5, 128.4, 128.3, 128.2, 126.9, 126.3, 122.3, 119.8, 118.6, 118.5, 46.6, 36.0, 19.6, 13.8 ppm.

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