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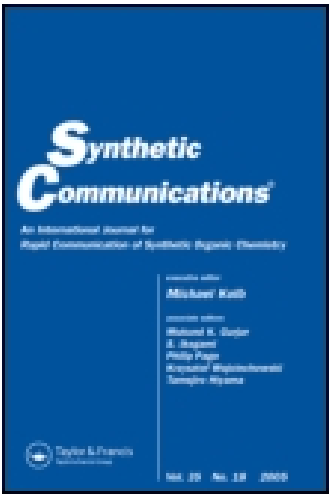

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Zinc Benzenesulfonate-Promoted Eco-Friendly and Efficient Synthesis of 1-Amidoalkyl-2-naphthols

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ZINC BENZENESULFONATE–PROMOTED ECO-FRIENDLY AND EFFICIENT SYNTHESIS OF 1-AMIDOALKYL-2-NAPHTHOLS

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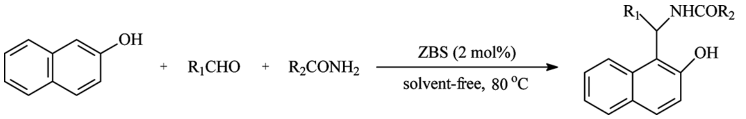
GRAPHICAL ABSTRACT



Abstract *A three-component, one-pot condensation of 2-naphthol, aldehydes, and amides catalyzed by zinc benzenesulfonate gives 1-amidoalkyl-2-naphthols in good yields at 80 °C under solvent-free conditions. The catalytic activities of zinc benzenesulfoante and 12 other metal benzenesulfonates were compared. After the reaction, zinc benzenesulfoante can be recycled several times without distinct loss of catalytic activity.*

Keywords 1-Amidoalkyl-2-naphthols; metal benzenesulfonates; multicomponent reaction; solvent-free conditions

INTRODUCTION

Amidoalkyl naphthol derivatives have attracted considerable interest because of their pharmaceutical and agricultural activities. For example, 1-aminomethyl-2-naphthols have been reported to show cardiovascular activity.[1] The hypotensive and bradycardiac effects of these compounds in normotensive rats as well as their in vitro inotropic and aortic contraction effects in the isolated left atria and aorta of rat have been evaluated. 1-Naphthaleneacetic acid and 2-naphthoxyacetic acid have been reported to act as plant-growth regulators.[2,3] Because of the importance of the title compounds, clean synthetic methods for them have gained considerable attention.

A recent publication reported 1-amidoalkyl-2-naphthols could be synthesized by a three-component condensation of 2-naphthol, aldehydes, and amides in the presence of 10 mol% *para*-toluenesulfonic acid (*p*-TSA) through the tandem process of

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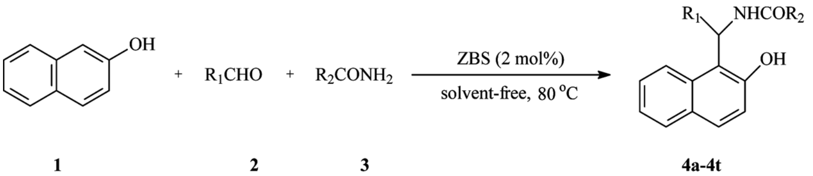

Scheme 1. ZBS-promoted synthesis of 1-amidoalkyl-2-naphthols.

ortho-quinone methide (*o*-QM).[4] Although the use of *p*-TSA satisfies the reaction, the method suffers from several drawbacks in terms of green chemistry such as high temperature (125 °C) and unrecovered catalyst. Therefore, some modified procedures using various homogeneous or heterogeneous catalysts including H_2NSO_3H,[5] oxalic acid,[6] $Fe(HSO_4)_3$,[7] $Sr(OTf)_2$,[8] I_2,[9] $K_5CoW_{12}O_{40}\cdot 3H_2O$,[10] $Yb(OTf)_3$ in ionic liquid,[11] montmorillonite K10,[12] TMSCl/NaI,[13] and Al_2O_3-$HClO_4$ [14] have also been reported. Though most of these methods achieved good to excellent yields, they suffer from at least one of the following disadvantages: long reaction time, toxic and corrosive solvent, higher reaction temperature (>100 °C), and the use of additional microwave or ultrasonic irradiation. Hence, there is great interest in developing green and efficient methods for the synthesis of 1-amidoalkyl-2-naphthols.

Recently, metal sulfonates have attracted attention because of their distinct advantages such as low toxicity, low cost, and relative insensitivity to air and moisture. In our recent study on their catalytic activity, we found they could act as mild and efficient Lewis acid catalysts for one-pot multicomponent reactions (MCRs) such as the Biginelli reaction[15] and Mannich reaction.[16] In a continuation of our investigations on their application, we found they could catalyze one-pot synthesis of 1-amidoalkyl-2-naphthols derivatives **4** by three-component condensation of 2-naphthol **1**, various aldehydes **2**, and different amides **3** in the presence of zinc benzenesulfonate (ZBS) under thermal solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

First, we compared the catalytic activity of 13 metal benzenesulfonates (2 mol%) for the amidoalkylation using 2-naphthol, benzaldehyde, and benzamide as a model reaction (Table 1). These reactions were carried out at 80 °C under solvent-free conditions. After screening several trials, it is interesting to note that transition-metal benzenesulfonates are able to catalyze the reaction to high extent with 66–92% yields. Especially for entries 2–6, the yields of the products were almost the same (89–92%). Among the examined transition metal, rare earth metal, and Al and Mg benzenesulfonates, ZBS gave great yields and it is inexpensive, so ZBS was selected as the most promising catalyst (Table 1, entry 2).

Next, we investigated the effect of reaction temperature on the synthesis of 1-amidoalkyl-2-naphthols using the reaction of 2-naphthol, benzaldehyde, and benzamide in the presence of ZBS as a model. It was found that the reaction carried out at a lower temperature (60 °C) needs longer reaction time. When it was carried out at 100 °C, a decreased yield (87%) was obtained in a short reaction period (0.2 h). Therefore, the optimal reaction temperature is 80 °C.

Table 1. Screening of metal benzenesulfonates for the condensation of 2-naphthol, benzaldehyde, and benzamide

Entry	$M(C_6H_5SO_3)_x \cdot aH_2O$	Time (h)	Yield (%)
1	–	8	0^a
2	$Zn(C_6H_5SO_3)_2 \cdot 6H_2O$	0.25	92
3	$Fe(C_6H_5SO_3)_2 \cdot 6H_2O$	0.5	92
4	$Cu(C_6H_5SO_3)_2 \cdot 6H_2O$	0.25	91
5	$Y(C_6H_5SO_3)_3 \cdot 2H_2O$	0.25	90
6	$Co(C_6H_5SO_3)_2 \cdot 6H_2O$	0.7	89
7	$Ni(C_6H_5SO_3)_2 \cdot 6H_2O$	1	66
8	$La(C_6H_5SO_3)_3 \cdot 2H_2O$	0.25	87
9	$Sm(C_6H_5SO_3)_3 \cdot 2H_2O$	0.25	84
10	$Nd(C_6H_5SO_3)_3 \cdot 2H_2O$	0.25	82
11	$Eu(C_6H_5SO_3)_3 \cdot 2H_2O$	0.25	80
12	$Ce(C_6H_5SO_3)_3 \cdot 2H_2O$	1	54
13	$Al(C_6H_5SO_3)_3 \cdot 7H_2O$	0.25	86
14	$Mg(C_6H_5SO_3)_2 \cdot 2H_2O$	6	62

[a] Yield refers to catalyst-free conditions.

Thus, to explore the reaction scope of ZBS-catalyzed amidoalkylation, reactions of 2-naphthol, aromatic aldehydes, aliphatic aldehydes and different amides (benzamide, urea and acetamide) in the presence of ZBS were carried out at 80 °C. The results are summarized in Table 2. As can be seen, the nature of

Table 2. The one-pot, three component condensation of 2-naphthol, aldehydes, and amines in the presence of ZBS

						Mp	
Entry	R^1	R^2	Time (h)	Product	Yield (%)	Observed	Reported
1	C_6H_5	C_6H_5	0.25	**4a**	$92–84^a$	235–237	233–235[14]
2	$2\text{-}NO_2C_6H_4$	C_6H_5	1	**4b**	91	260–263	266–267[17]
3	$3\text{-}NO_2C_6H_4$	C_6H_5	1	**4c**	87	234–236	233–235[18]
4	$4\text{-}NO_2C_6H_4$	C_6H_5	1	**4d**	89	239–241	239–241[6]
5	$2\text{-}ClC_6H_4$	C_6H_5	1	**4e**	86	266–268	–
6	$4\text{-}ClC_6H_4$	C_6H_5	3	**4f**	84	186–189	187–188[8]
7	$2.4\text{–}Cl_2C_6H_3$	C_6H_5	1	**4g**	83	235–238	–
8	$4\text{-}CH_3C_6H_4$	C_6H_5	2	**4h**	87	211–213	209–211[18]
9	$4\text{-}CH_3OC_6H_4$	C_6H_5	5	**4i**	66	207–209	206–208[17]
10	$4\text{-}(CH_3)_2NC_6H_4$	C_6H_5	3	**4j**	54	218–221	220–221[17]
11	CH_3CH_2	C_6H_5	6.5	**4k**	60	244–246	244–245[8]
12	$CH_3CH_2CH_2$	C_6H_5	0.5	**4l**	75	240–242	–
13	C_6H_5	NH_2	1	**4m**	83	179–181	172–174[5]
14	$3\text{-}NO_2C_6H_4$	NH_2	1	**4n**	87	197–198	192–193[18]
15	$2\text{-}ClC_6H_4$	NH_2	1	**4o**	58	152–155	150–153[19]
16	C_6H_5	CH_3	6.5	**4p**	51	242–244	241–243[10]
17	$3\text{-}NO_2C_6H_4$	CH_3	6	**4q**	74	254–255	255–256[8]
18	$2\text{-}ClC_6H_4$	CH_3	3	**4r**	30	208–209	206–207[17]
19	$4\text{-}CH_3C_6H_4$	CH_3	11	**4s**	15	217–219	222–223[7]
20	CH_3CH_2	CH_3	12	**4t**	24	177–179	173–175[20]

[a] Yields refer to four runs with ZBS.

substituents on the aromatic ring showed significant effects on the conversation. The reactions of aldehydes with electron-withdrawing groups afforded better yields of products than those with electron-donating groups. The scope of different amines was also examined. When benzamide was used as an amine component, both aromatic aldehydes and aliphatic aldehydes worked well, affording moderate to good yields of corresponding products (Table 2, entries 1–12). The condensation yields with acetamide were lower than those with benzamide and urea (Table 2, entries 16–20). In addition to urea, the amidoalkylation of thiourea with 2-napthol and benzaldehyde was also investigated, and no corresponding products were isolated.

Further, the reusability of ZBS was investigated. 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, and then ZBS was recovered and reused for next run. No significant decrease in activity was observed even up to four runs (Table 2, entry 1), which demonstrated that ZBS was water tolerant and efficient for this condensation.

CONCLUSION

In conclusion, a new protocol for synthesizing 1-amidoalkyl-2-naphthols derivatives has been developed. The present protocol enjoys mild reaction conditions, short reaction time, and simple workup. Moreover, the catalyst can be recovered conveniently and reused for at least four reaction cycles without distinct loss of activity. Currently, studies on the extension of this protocol are ongoing in our laboratory.

EXPERIMENTAL

Melting points were determined using a RY-1 micromelting-point apparatus. Infrared (IR) spectra were recorded on a Scimitar 2000 series Fourier transform instrument of Varian. ^{1}H NMR spectra were recorded on a Bruker AV-500 spectrometer in dimethylsulfuric (DMSO-d_6) using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were performed on Bruker AV-500 spectrometer at 125 MHz in DMSO-d_6 using TMS as an internal standard. Elemental analyses were carried out on a EA 2400II elemental analyzer (Perkin-Elmer) and agreed favorably with the calculated values.

Synthesis of 1-Amidoalkyl-2-naphthols Derivatives

ZBS (0.2 mmol) was added to a mixture of 2-naphthol (10 mmol), An aldehyde (10 mmol), and an amide (11 mol). The reaction mixture was magnetically stirred on a preheated water bath at 80 °C. After completion of the reaction (monitored by thin-layer chromatography, TLC), the reaction mixture was cooled to rt and 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 mp, IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis with those reported for the authentic samples. Spectral data for some new compounds are as follows.

N-((2-Chlorophenyl)(2-hydroxynaphthalen-1-yl)methyl)benzamide (4e). White solid. Mp: 266–268 °C. IR (KBr): *v* 3426, 3067, 1633, 1573, 1538, 1346, 1075, 822, 752, 711 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 9.93 (s, 1H, OH), 9.01 (d, 1H, $J = 6.2$ Hz, NH), 8.08 (d, 1H, $J = 8.6$ Hz, ArH), 7.89 (d, 2H, $J = 7.3$ Hz, ArH), 7.82 (d, 1H, $J = 7.7$ Hz, ArH), 7.78 (d, 1H, $J = 8.8$ Hz, ArH), 7.52 (t, 1H, $J = 7.3$ Hz, ArH), 7.44–7.40 (m, 5H, ArH), 7.36 (d, 1H, $J = 5.0$ Hz, CH), 7.30–7.22 (m, 3H, ArH), 7.19 (d, 1H, $J = 8.8$ Hz, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.4, 153.7, 138.8, 134.2, 132.9, 132.7, 131.1, 130.1, 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. Anal. calcd. for $C_{24}H_{18}NO_2Cl$: C, 74.32; H, 4.68; N, 3.61. Found: C, 74.41; H, 4.60; N, 3.55%.

N-((2,4-Dichlorophenyl)(2-hydroxynaphthalen-1-yl)methyl)benzamide (4g). White solid. Mp: 235–238 °C. IR (KBr): *v* 3423, 3069, 1633, 1574, 1536, 1344, 1074, 819, 748, 709 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 9.98 (s, 1H, OH), 9.17 (d, 1H, $J = 6.3$ Hz, NH), 8.05 (d, 1H, $J = 8.6$ Hz, ArH), 7.89 (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), 7.57 (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), 7.30–7.27 (m, 2H, ArH), 7.18 (d, 1H, $J = 8.8$ Hz, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.5, 153.8, 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. Anal. calcd. for $C_{24}H_{17}NO_2Cl_2$: C, 68.26; H, 4.06; N, 3.32. Found: C, 68.34; H, 4.01; N, 3.34%.

N-(1-(2-Hydroxynaphthalen-1-yl)butyl)benzamide (4l). White solid. Mp: 240–242 °C. IR (KBr): *v* 3415, 3221, 3204, 1632, 1575, 1528, 1342, 1074, 815, 747, 715 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 10.08 (s, 1H, OH), 8.60 (d, 1H, $J = 6.3$ Hz, NH), 8.22 (d, 1H, $J = 7.7$ 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, $J = 7.0$ Hz, CH), 2.19–2.11 (m, 1H, CH_2), 1.92–1.85 (m, 1H, CH_2), 1.51–1.41 (m, 1H, CH_2), 1.33–1.23 (m, 1H, CH_2), 0.93 (t, 3H, $J = 7.3$ Hz, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.2, 152.8, 134.7, 132.1, 131.0, 128.5, 128.4, 128.3, 128.2, 126.9, 126.2, 122.3, 119.8, 118.6, 118.5, 46.6, 36.0, 19.6, 13.8. Anal. calcd. for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.88; H, 6.59; N, 4.42%.

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