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Convenient approach for the one-pot, three-component synthesis of 1-(benzothiazolylamino)methyl-2-naphthol using fumaric acid as a green catalyst

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One-pot, efficient three-component condensation of aldehydes, 2-naphthol, and 2-aminobenzothiazole in the presence of fumaric acid as an effective catalyst for the synthesis of 1-(benzothiazolylamino)methyl-2-naphthol derivatives under thermal and solvent-free conditions is described. The present approach of this methodology offers several advantages such as mild conditions, high yields, clean reaction profiles, operational simplicity, and environmentally benign and simple work-up procedures.

Keywords: Green protocol, 1-(Benzothiazolylamino)methyl-2-naphthol, Multi-component reaction, Fumaric acid, Solvent-free conditions.

INTRODUCTION

Multicomponent condensation reactions have a wide range of applicability in the field of synthetic organic chemistry. They constitute an especially attractive synthetic strategy because they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns. Being one-pot reactions, they are easier to carry out than multistep syntheses, and the products are formed in a single step. Diversity can be achieved simply by varying the components [1]. In the past few years, combinatorial methods using multicomponent reactions have been closely examined as fast and convenient solutions for the synthesis of diverse classes of compounds [2]. Recently, this strategy became important in drug discovery in the context of synthesis of biologically active compounds. This method increases the efficiency of the reactions and decreases the number of laboratory operations along with solvents and chemicals used. It also reduces reaction time and increases the yield of products in comparison with normal multistep methods [3].

2-Aminobenzothiazoles are unique scaffolds that are widely used in medicinal and biological chemistry [4]. Their diverse functions range from electron transfer facilitation in the firefly luciferin cycle [5], through antitumor [6], and antidiabetic activity [7] to Alzheimer's disease tracer (8) and anticancer agent in pharmaceutical chemistry [9]. Also, benzothiazoles are commercially important as reactive dyes [10], hair dyes [11], agrochemical fungicides, insecticides, acaricides, herbicides, plant desiccants and defoliants [12].

Fumaric acid ($C_4H_4O_4$) is an organic acid widely found in nature, and is a component of organic biosynthesis in humans. Chemically, it is an unsaturated dicarboxylic acid. It exists as white or nearly white crystals, odorless, with a very tart taste. Fumaric acid is generally nontoxic and nonirritant. Fumaric acid has been used in food and beverage products since the 1940s. Food research shows that fumaric acid can improve quality and reduce the costs of many food and beverage products. It is non-hygroscopic (absorbs no moisture). In the cosmetic industry, it is used as a bath salt cleaning agent for dentures. It is also used in animal feeds. Fumaric acid is used in oral pharmaceutical formulations and clinically in the treatment of psoriasis.

Because of the above-mentioned properties of 2-aminobenzothiazole and fumaric acid and as a part of our ongoing program on multi-component reactions [13,14], herein we present an eco-friendly, simple and efficient method for the synthesis of 1-(benzothiazolylamino)methyl-2-naphthol compounds *via* a one-pot three-component reaction using 2-naphthol, 2-aminobenzothiazole and aromatic aldehydes in the presence of fumaric acid under solvent-free conditions (Scheme 1).

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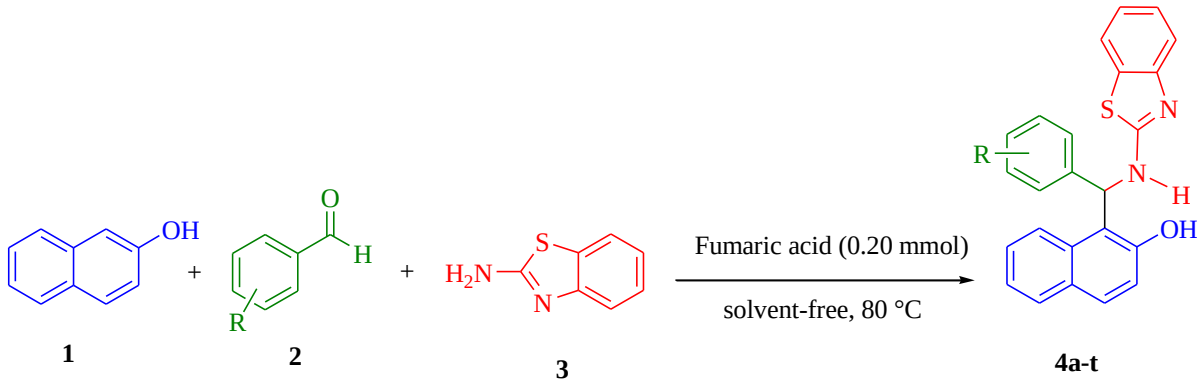

1 **2** **3** **4a-t**

Scheme 1. Fumaric acid catalyzed synthesis of 1-(benzothiazolylamino)methyl-2-naphthols **4a-t**.

EXPERIMENTAL

General

Melting points and IR spectra were measured on an Electrothermal 9100 apparatus and a JASCO FT/ IR- 460 plus spectrometer, respectively. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DRX-400 Avance instrument with DMSO as a solvent. All reagents and solvents were purchased from Fluka and Merck and were used without further purification.

*Typical procedure for the synthesis of 1-amidoalkyl -2-naphthols (**4a-t**)*

Fumaric acid (0.20 mmol, 0.023 g) was added into a mixture of benzaldehyde (1.0 mmol), 2-naphthol (1.0 mmol) and 2-aminobenzothiazole (1.0 mmol), then the reaction mixture was stirred at 80 ºC for the appropriate time (Table 1). After completion of the reaction (monitored by TLC), the reaction mixture was washed with H_2O (3 × 10 mL). As the catalyst is soluble in water, it was removed from the reaction mixture. Then, the residue was recrystallized from EtOH.

*1-((Benzo[d]thiazol-2-ylamino)(2,5-dimethoxyphenyl)methyl)naphthalen-2-ol (**4s**)*

Yield: 90 %; m.p. 209-211 °C; IR (KBr, cm^{-1}): 3368 (N-H), 3060 (O-H), 1628 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.50 and 3.64 (2s, 6H, $2OCH_3$), 6.76 (d, 1H, *J*=8.4 Hz, H_{Ar}), 6.84 (d, 1H, *J*=8.8 Hz, H_{Ar}), 6.98 (d, 1H, *J*=7.2 Hz, H_{Ar}), 7.15-7.45(m, 7H, H_{Ar},$1H_{benzylic}$), 7.63 (d, 1H, *J*=7.6 Hz, H_{Ar}), 7.71 (d, 1H, *J*=8.8 Hz, H_{Ar}), 7.77 (d, 1H, *J*=8Hz, H_{Ar}), 8.26 (d, 1H, *J*=8.4 Hz, H_{Ar}), 8.61 (brs, 1H, NH), 9.92 (S, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.56, 55.69, 56.44, 111.64, 112.41, 116.22, 118.46, 118.72, 119.06, 121.22, 121.26, 122.66, 123.89, 125.82, 126.39, 128.70, 128.80, 129.51, 131.07, 131.70, 133.06, 151.37, 152.74, 153.24, 153.81, 166.14.

*1-((Benzo[d]thiazol-2-ylamino)(2-hydroxy-3-methoxyphenyl)methyl)naphthalen-2-ol (**4t**)*

Yield: (92%); m.p. 200-202 °C ; IR (KBr, cm^{-1}): 3366 (N-H), 3141 (O-H), 1632 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.74 (S, 3H, OCH_3), 6.67 (t, 1H, *J*=7.6 Hz, H_{Ar}), 6.82 (d, 1H, *J*=7.6 Hz, H_{Ar}), 6.96 (t, 1H, *J*=7.6 Hz, H_{Ar}), 7.01 (d, 1H, *J*=7.2 Hz, H_{Ar}), 7.14-7.40 (m, 6H, H_{Ar},$1H_{benzylic}$), 7.61 (d, 1H, *J*=7.2 Hz, H_{Ar}), 7.71 (d, 1H, *J*=8 Hz, H_{Ar}), 7.76 (d, 1H, *J*=8 Hz, H_{Ar}), 8.18 (d, 1H, J=8.4 Hz, H_{Ar}), 8.64 and 8.79 (brs, 2H, NH and OH), 9.95 (brs, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.90, 56.12, 56.27, 110.81, 118.29, 118.53, 118.86, 119.16, 121.13, 121.24, 122.66, 123.43, 125.81, 126.42, 128.82, 129.30, 130.96, 132.17, 133.22, 144.29, 147.79, 151.68, 152.69, 153.66, 166.27.

RESULTS AND DISCUSSION

Our initial aim was to develop an efficient one-pot procedure for the synthesis of 1-(benzothiazolylamino)methyl-2-naphthol derivatives through the reaction of 2-naphthol, 2-aminobenzothiazole and aldehydes in the presence of fumaric acid. To find out the optimum amount of fumaric acid, the reaction was carried out by varying the quantity of catalyst. The maximum yield was obtained when 0.20 mmol of catalyst was used (Table 1). Further increase in the amount of fumaric acid did not have any significant effect on the product yield. The results are summarized in Table 1. As shown in Table 1, the shortest time and best yield were achieved at 80 °C.

In order to evaluate the generality of the process, several examples illustrating the present method for the synthesis of 1-(benzothiazolylamino)methyl-2-naphthols (**4**) were studied (Table 2). The reactions of 2-naphthol with various aromatic aldehydes and 2-aminobenzothiazole were carried out in the presence of 0.20 mmol fumaric acid at 80°C. In all reactions, good to excellent yields were obtained at

short reaction times (4–15 min). Using these optimized reaction conditions, the generality of the reaction was examined using several types of aldehydes. As shown in Table 2, the direct three-component reaction worked well with a variety of aryl aldehydes including those bearing electron-withdrawing and electron-donating groups, and the desired compounds were obtained in good yields. However, the yield of product was lower in comparison with aryl aldehydes containing electron-withdrawing substituents (Table 2).

The products were identified by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of **4s** exhibited a multiplet at δ = 7.15-7.45 for the 7 aromatic hydrogens and benzylic hydrogen and two singlets at δ = 8.61 and δ = 9.92 for the NH and OH groups, respectively.

Table 1. Optimization of catalyst for the synthesis of 1-(benzothiazolylamino)methyl-2-naphthols.[a]

Entry	Catalyst (mmol)	Temperature (°C)	Time (min)	Isolated Yield (%)
1	Fumaric acid (0.10)	80	15	78
2	Fumaric acid (0.15)	80	14	84
3	**Fumaric acid (0.20)**	**80**	**12**	**93**
4	Fumaric acid (0.30)	80	9	87
5	Fumaric acid (0.20)	50	60	10
6	Fumaric acid (0.20)	60	20	35
7	Fumaric acid (0.20)	100	10	52

[a] Reaction conditions: 2-naphthol (1.0 mmol), 2-aminobenzothiazole (1.0 mmol) and benzaldehyde (1.0 mmol) in the presence of catalyst at different temperatures.

Table 2. Synthesis of 1-(benzothiazolylamino)methyl-2-naphthol derivatives

Entry	R	Time (min)	Yield (%)[a]	Product	M.p. (lit. m.p.) (°C)[Ref.]
1	4-NO_2	15	52	**4a**	188–190 (189–191)[15]
2	4-Cl	4	89	**4b**	208–210(209–210)[16]
3	3-NO_2	5	50	**4c**	190–192(191-194)[17]
4	2,4-Cl_2	5	82	**4d**	204–206(206–207)[15]
5	3-MeO	5	89	**4e**	185–187(184–186)[17]
6	4-Me	10	92	**4f**	183–185(182–183)[16]
7	2-Cl	4	88	**4g**	187–189(189–190)[15]
8	2,4-$(MeO)_2$	9	89	**4h**	162-164(161-163)[17]
9	4-OMe	7	92	**4i**	173-175(175-176)[16]
10	2-NO_2	15	58	**4j**	212–214(215–216)[15]
11	2,6-Cl_2	7	86	**4k**	194–196(193–195)[20]
12	3-Br	4	90	**4l**	200–202(202–204)[17]
13	4- Br	4	90	**4m**	200–202(200–202)[20]
14	4-F	11	82	**4n**	175–177(176–178)[17]
15	5-Br,2-HO	7	90	**4o**	181-183(183–185)[20]
16	Thienyl	8	90	**4p**	190–192(191–193)[20]
17	2,3-$(MeO)_2$	10	93	**4q**	200–202(201–203)[20]
18	H	8	89	**4r**	202-204(202–203)[15]
19	2,5-$(MeO)_2$	10	90	**4s**	209-211[b]
20	5- MeO,2-HO	6	92	**4t**	200-202[b]

[b] New compounds synthesized in this work. All known products reported previously in the literature were characterized by comparison of m.p., IR and NMR spectra with those of authentic samples.

CONCLUSION

In summary, an efficient method for the synthesis of 1-(benzothiazolylamino)methyl-2-naphthol derivatives is described. The reactions were carried out under solvent-free conditions with short reaction times and gave the corresponding products in good yields. The present methodology offers several advantages such as good yields, simple procedure, shorter reaction times, clean reaction conditions. Moreover, the products were purified without chromatography.

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УДОБЕН ПОДХОД ЗА ЕДНОСТАДИЙНА ТРИ-КОМПОНЕНТНА СИНТЕЗА НА 1-(БЕНЗОТИАЗОЛАМИНО) МЕТИЛ-2-НАФТОЛ С ФУМАРОВА КИСЕЛИНА КАТО ЗЕЛЕН КАТАЛИЗАТОР

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(Резюме)

Описана е едностадийна три-компонентна кондензация на алдехиди, 2-нафтол и 2-аминобензотиазол за синтезата на 1-(бензотиазоламино) метил-2-нафтолови производни с фумарова киселина като ефективен катализатор при висока температура и в отсъствието на разтворител. Този подход предлага няколко предимства: меки условия, високи добиви, чист реакционен профил, оперативна простота, екологично съвместима и проста процедура.