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ACTA CHEMICA IASI, **24_2**, 112-121 (2016)

DOI: 10.1515/achi-2016-0010

CONVENIENT APPROACH FOR THE ONE-POT, THREE-COMPONENT SYNTHESIS OF 1-(BENZOTHIAZOLYLAMINO)METHYL-2-NAPHTHOL USING CITRIC ACID AS A GREEN CATALYST

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Abstract: A straightforward, one-pot multicomponent synthesis of 1-(benzothiazolylamino)methyl-2-naphthol derivatives was achieved by condensation of 2-naphthol, aldehydes, and 2- aminobenzothiazole catalyzed by a small amount of citric acid, which acts as a benign enviermentally catalyst. Mild conditions with excellent yields and a simple isolation procedure are noteworthy advantages of this method.

***Keywords*:** One-pot; 1-(benzothiazolylamino)methyl-2-naphthol; Multicomponent; Citric acid; Mild conditions.

Introduction

Multicomponent condensation techniques have a broad domain of applicability in the series of synthetic organic chemistry and they form an particularly marvelous synthetic performance because they create simple

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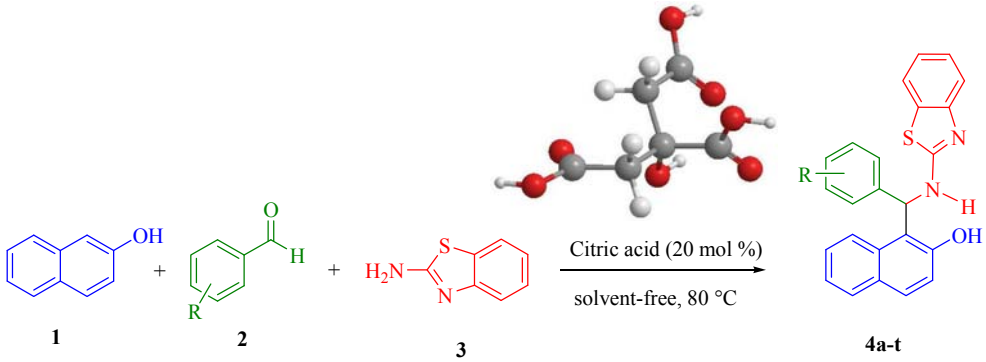
and quick routes to achievement of an aggregate of organic scaffolds with various substitution models.[1-6] In this regard, the multicomponent reactions (MCRs) have been defined as a versatile instrument in gamut of synthetic research that lead to greater efficiency, chemoselectivity issues, molecular diversity, and, specially, high degree of atom economy. The MCR generates worthy complex structure by assembling at least three adducts in a one-pot fashion. All these benefits can be delivered the MCR the ideal substitution against sequential multi-step synthesis.[7-9] On the other hand, this strategy make up a known significant class of drug discovery, which have received much attention in area of medicinal and pharmaceutical chemistry, because, MCRs increase the efficiency of reactions through combining the number of operative steps together with avoiding the separation of intermediates.[10,11]

2-AminoBenzothiazoles as inimitable frames are presented a broad spectrum of pharmacological and biological properties.[12] Simplicity in electron transfer in the firefly luciferine cycle is reason of their different acts,[13] through antitumor,[14] and antidiabetic activity[15] to Alzheimer disease tracer,[16] and anticancer agent in pharmaceutical chemistry.[17] Also, benzothiazoles are commercially momentous as reactive dyes,[18] hair dyes,[19] agrochemical fungicides, acaricides, herbicides, insecticides, plant desiccants, and defolicants.[20]

Citric acid is a very beneficial and impressive preservative, obtained from naturally occurring organic acids. It exists in many varied fruits and vegetables, but is especially concentrated in lemons and limes. Citric acid is widely used in the food, beverage, cosmetic, and pharmaceutical industries. It has been identified as safe by all main national and international food regulatory agencies, and it also serves as an environmentally benign cleaning agent and acts as an antioxidant.

Because of the above-mentioned properties of 2-aminobenzothiazole and citric acid and in continuation of our successive endeavors for the expansion of heterocyclic compounds using multicomponent reactions,[21,22] herein we report a facile method for synthesis of 1-(benzothiazolylamino)methyl-2-naphthols compounds *via* a multicomponent reaction using 2-naphthol, 2-aminobenzothiazole and aryl aldehydes in the presence of citric acid under solvent-free conditions (Scheme 1).



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

Results and Discussion

Our primary target was to develop an effective one-pot manner for the synthesis of 1-(benzothiazolylamino)methyl-2-naphthols derivatives through the reaction of 2-naphthol, 2-aminobenzothiazole and aldehydes by employing citric acid. It was found that 5 mol % of citric acid was suitable for this transformation in solvent free condition (Table 1). To find out the optimized amount of citric acid, the conversion was screened by change in the quantity of catalyst. The most yield was acquired when 20 mol % of catalyst was applied. In the aforesaid reaction, further increment in the amount of citric acid did not have any eligible consequence on the product

yield. The results are summarized in Table 1. As seen in (Table 1, entry 3), the shortest time and highest yield were obtained at 80 °C.

Table 1. Effect of amount of catalysts and temperature for the synthesis of **4r**.

Entry	Catalyst (mol %)	Temperature (°C)	Time (min)	Isolated Yield (%) [a]
1	Citric acid (10)	80	14	80
2	Citric acid (15)	80	10	85
3	**Citric acid (20)**	**80**	**7**	**92**
4	Citric acid (30)	80	8	87
5	Citric acid (20)	50	60	10
6	Citric acid (20)	60	20	35
7	Citric acid (20)	100	8	55

[a] Reaction condition: 2-naphthol (1.0 mmol), 2-aminobenzothiazole (1.0 mmol) and benzaldehyde (1.0 mmol) unless otherwise noted.

To appraise the universality of this transformation, many examples have exhibited in existing study for the synthesis of 1-(benzothiazolylamino)methyl-2-naphthols (**4**) (Table 2). Using 20 mol % citric acid at 80 °C, reaction of 2-naphthol, diverse aryl aldehydes, and 2-aminobenzothiazole were screened. To our delight, a broad scope of corresponding desired compounds (**4a-t**) generated in good to excellent yield at improved reaction times (3-14 min). As shown in Table 2, a variety of aryl aldehydes including bearing electron-withdrawing and electron-donating groups on the aromatic rings to afford favorable compounds in good yields. However, the lower yield of product containing electron-withdrawing substituents on aryl aldehydes implied electronic influence is important (Table 2).

A priori, one can suggest that formation of the 1-(benzothiazolylamino)methyl-2-naphthol derivatives could proceed in two

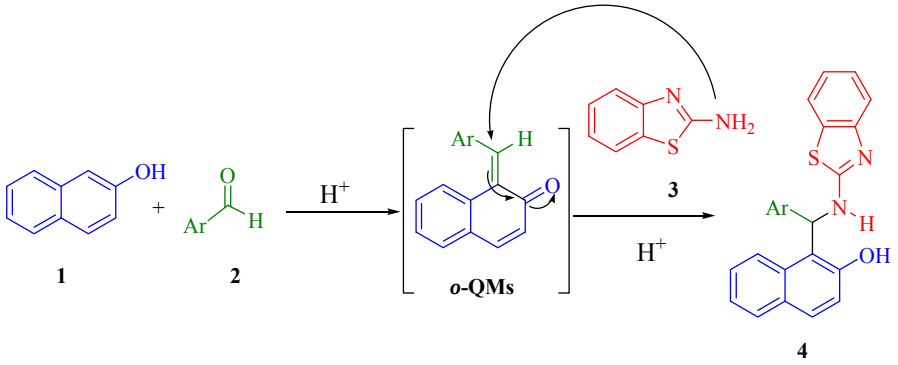
different ways. In the first scenario, the formation of *o*-QMs starts from the reaction of active aldehydes by acid catalyst with 2-naphthol. [23-26]

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

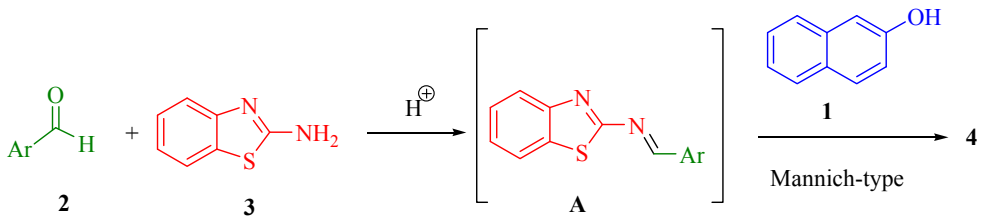
Entry	R	Time (min)	Yield (%)	Product	M.p. (lit. m.p.) (°C)
1	4-NO_2	13	60	**4a**	188–190 (189–191) (23)
2	4-Cl	3	92	**4b**	208–210(209–210) (24)
3	3-NO_2	4	58	**4c**	190–192(191-194) (25)
4	2,4-Cl_2	5	89	**4d**	204–206(206–207) (23)
5	3-MeO	4	93	**4e**	185–187(184–186) (23)
6	4-Me	7	96	**4f**	183–185(182–183) (24)
7	2-Cl	4	91	**4g**	187–189(189–190) (23)
8	2,4-$(MeO)_2$	8	94	**4h**	162-164(161-163) (25)
9	4-OMe	7	96	**4i**	173-175(175-176) (24)
10	2-NO_2	14	62	**4j**	212–214(215–216) (23)
11	2,6-Cl_2	6	90	**4k**	194–196(193–195) (26)
12	3-Br	4	94	**4l**	200–202(202–204) (25)
13	4- Br	4	94	**4m**	200–202(200–202) (26)
14	4-F	9	87	**4n**	175–177(176–178) (25)
15	5-Br,2-HO	5	95	**4o**	181-183(183–185) (26)
16	Thienyl	12	89	**4p**	190–192(191–193) (26)
17	2,3-$(MeO)_2$	8	97	**4q**	200–202(201–203) (26)
18	H	7	92	**4r**	202-204(202–203) (23)
19	2,5-$(MeO)_2$	9	94	**4s**	208-210(209-211) (26)
20	5- MeO,2-HO	4	97	**4t**	201-204(200-202) (26)

The *in situ* generated *o*-QMs, condensation with 2-aminobenzothiazole to create the desired target molecules (Scheme 2). An

alternative pathway comes from direct attack of 2-naphthol at iminium intermediate, Mannich-type reaction (Scheme 3).



Scheme 2. Tentative mechanism based on the formation of *o*-QMs.



Scheme 3. Tentative mechanism based on the Mannish-type reaction.

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

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 Bruker DRX-400 Avance

instruments with DMSO as a solvent. All reagents and solvents were purchased from Fluka and Merck were used without further purification.

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

To a mixture of benzaldehyde (1.0 mmol), 2-naphthol (1.0 mmol) and 2-aminobenzothiazole (1.0 mmol) was added citric acid (20 mol %, 0.038 g) and was heated to 80 ºC for the proper time (Table 1). The progress of the reaction was monitored by TLC. After completion of the reaction, the contents including citric acid (solvable in water) washed with H_2O (3 × 10 mL) and filtered catalyst. Then, the residue was recrystallized from EtOH.

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

Yield: 94 %; m.p. 208-210 °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: (97 %); m.p. 201-204 °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.

Conclusions

In summary, a facile protocol was demonstrated for the synthesis of a library of 1-(benzothiazolylamino)methyl-2-naphthols under solvent-free conditions. The most prominent points for this methodology are use of mild reaction conditions, great atom economy, shorter reaction times, and higher yields. Moreover, the favorable compounds were refined simply with avoiding from resort chromatography.

Acknowledgements

Financial support from the Research Council of the University of Sistan and Baluchestan is gratefully acknowledged.

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