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Water promoted one-pot synthesis of 2′-aminobenzothiazolomethyl naphthols and 5-(2′-aminobenzothiazolomethyl)-6-hydroxyquinolines

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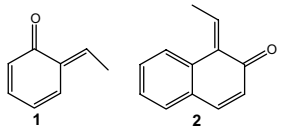
Abstract—A novel one-pot, three-component condensation reaction of an aldehyde, 2-aminobenzothiazole and 2-naphthol or 6-hydroxyquinoline in water to give 2′-aminobenzothiazolomethyl naphthols or 5-(2′-aminobenzothiazolomethyl)-6-hydroxyquinolines in high yields at 90 °C without using any catalyst, is described.

1. Introduction

ortho-Quinone methides (*o*-QMs) such as **1** and **2** are highly reactive intermediates that have been extensively harnessed by Nature. A variety of plants, animals and insects capitalize upon these types of compound as a means of defense. However, despite general knowledge of *o*-QMs for over a century these intermediates still lie outside the synthetic mainstream.[1,2] Very recently, Pettus described[3] the methods by which *o*-QMs **1** are prepared, the benefits and limitations associated with each method as well as current applications in total synthesis. The pseudo three-component condensation reaction of 2-naphthol with aldehydes in the presence of various catalysts to form xanthenes has been studied widely. The reaction proceeds through the in situ formation of *ortho*-quinone methides **2** with 2-naphthol acting as a nucleophile.[4] However, the three-component condensation reactions of 2-naphthol and aldehydes with other nucleophiles is rarely reported in literature.[5]



1 2

During recent years, water has attracted interest as an inexpensive and environmentally benign solvent due to its specific properties. When organic compounds are suspended in water their relative insolubility causes them to associate, diminishing the water-hydrocarbon interfacial area.[6] In other words, the hydrophobic effect of water generates internal pressure and promotes the association of the reactants in the solvent cavity during the activation process and accelerates the reaction. Any factor, which increases the hydrophobic effect will increase the reaction rate.[7] This property of water is very efficient for multi-component reactions (MCRs) in which the entropy of reaction is decreased in the transition state.

Multicomponent condensation reactions are a powerful method for the synthesis of organic compounds, since the products are formed in a single step and diversity can be achieved by simply varying each component.[8]

Due to the biological activity of 2-aminobenzothiazoles and a significant number of compounds containing this moiety[9] and our interest in 2-aminoazole-based MCRs,[10] we report the synthesis of 2′-aminobenzothiazolomethyl naphthols and 5-(2′-aminobenzothiazolomethyl)-6-hydroxyquinolines **6** via the one-pot, three-component condensation reaction of aldehyde **3** and 2-naphthol or 6-hydroxyquinoline **4** in the presence of 2-aminobenzothiazole **5** as a nucleophile in water at 90 °C (Scheme 1).

To achieve suitable conditions for the above transformation, a series of experiments was carried out

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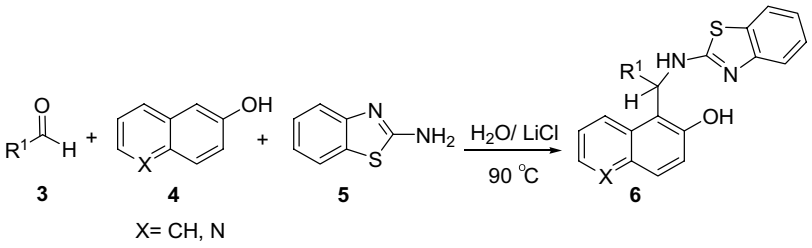


Scheme 1.

Table 1. Solvent effects on the reaction of 2-naphthol and *p*-methylbenzaldehyde with 2-aminobenzothiazole on the synthesis of 2′-benzothiazolomethyl-2-naphthols[a]

Entry	Solvent	Time (h)	Temperature (°C)	Yield (%)
1	CH_2Cl_2	24	Reflux	0
2	$CHCl_3$	24	Reflux	0
3	CH_3COOEt	24	Reflux	0
4	CH_3CN	24	Reflux	0
5	CH_3OH	24	Reflux	0
6	[Bmim]Br	24	90	0
7	[Bmim]PF_6	24	90	0
8	Water	24	90	81
9	Water	6	90	80
10	Water	3	90	52
11	—	24	90	10
12	—	24	120	35

[a] 2-Aminobenzothiazole (1 mmol), 2-naphthol (1 mmol) and *p*-methylbenzaldehyde (1 mmol).

(Table 1). First we investigated the reaction of 2-naphthol and *p*-methylbenzaldehyde with 2-aminobenzothiazole in various solvents, ionic liquids (ILs) and under solvent-free classical heating conditions. The reaction did not proceed in organic solvents and ILs even after 24 h (Table 1, entries 1–7). In the absence of solvent, the reaction was very slow and the yields of product were 10% and 35% at 90 °C and 120 °C after 24 h, respectively (entries 11 and 12). We found that the best solvent for this reaction was water and the reaction yield was 80% after heating for 6 h at 90 °C (entry 9).

Table 2. Salt effects on the reaction of 2-naphthol and *p*-methylbenzaldehyde with 2-aminobenzothiazole on the synthesis of 2′-benzothiazolomethyl-2-naphthols in water after 6 h at 90 °C[a]

Entry	Salt[b]	Yield (%)
1	—	80
2	NaCl	94
3	$NaNO_3$	96
4	Na_2SO_4	92
5	LiCl	96
6	$LiNO_3$	93
7	Li_2SO_4	96

[a] 2-Aminobenzothiazole (1 mmol), 2-naphthol (1 mmol) and *p*-methylbenzaldehyde (1 mmol).
[b] 0.5 g of salt in 3 ml of water.

As the hydrophobic effect of water is increased by ionic solutes,[5] the effects of LiCl, NaCl, $NaNO_3$, Na_2SO_4, $LiNO_3$ and Li_2SO_4 were examined. As expected, we obtained an increase in the yield (12–16%) with 0.5 g of salt in 3 ml of water (Tables 2 and 3).

All the products **6a**–**l** are new compounds, which were identified by IR, ^{1}H NMR and ^{13}C NMR spectral data and mass spectroscopy. The ^{1}H NMR spectrum of **6a** exhibited a multiplet at $\delta = 7.00$–7.79 for the 15 aromatic hydrogens and an aliphatic CH and two singlets at δ 8.79 and δ 10.15 for the NH and OH groups, respectively. The ^{1}H decoupled ^{13}C NMR spectrum of **6a** confirmed the suggested structure and the mass spectrum shows the expected molecular ion peak. The ^{1}H and

Table 3. One-pot synthesis of 2′-aminobenzothiazolomethyl-2-naphthols or 5-(2′-aminobenzothiazolomethyl)-6-hydroxyquinolines via the condensation reaction of 2-aminobenzothiazole, a 2-naphthol or 6-hydroxyquinoline and an aldehyde at 90 °C

Product	X	R^1	Yield (%)/time (h)[a]	Yield (%)/time (h)[b]	Mp (°C)
6a	CH	C_6H_5–	75 (6)	94 (5)	204–205
6b	CH	4CH_3–C_6H_4–	80 (6)	96, (96, 96, 95)[c] (6)	182–183
6c	CH	4CH_3O–C_6H_4–	67 (7.5)	91 (6)	175–176
6d	CH	4Cl–C_6H_4–	78 (8)	92 (6)	209–210
6e	CH	3NO_2–C_6H_4–	70 (8)	91 (6)	198–199
6f	N	C_6H_5–	79 (5)	93 (5)	211–212
6g	N	4CH_3–C_6H_4–	81 (6)	95 (6)	195–196
6h	N	4CH_3O–C_6H_4–	69 (7.5)	88 (7)	172–173
6i	N	4Cl–C_6H_4–	76 (6)	91 (6)	209–210
6j	N	4Br–C_6H_4–	73 (7)	92 (7)	162–163
6k	N	3CH_3O–C_6H_4–	68 (8)	91 (7)	169–170
6l	N	3NO_2–C_6H_4–	74 (7)	93 (7)	184–185

[a] In the absence of salt.
[b] In the presence of LiCl.
[c] Filtered water used three times.

^{13}C NMR spectra of **6b–l** were similar to those of **6a**, except for the R^1 and X groups, which exhibited characteristic signals with appropriate chemical shifts.

To explore the scope and limitations of this reaction, we have extended it to various *meta* and *para*-substituted benzaldehydes in the presence of 2-aminobenzothiazole, 2-aminobenzimidazole, 2-aminothiazole and 3-amino-1,2,4-triazole. As indicated in Table 3, the reaction proceeded efficiently between electron-withdrawing or electron-releasing *meta* and *para*-substituted benzaldehydes and 2-aminobenzothiazole. However, in the case of 2-aminobenzimidazole, 2-aminothiazole or 3-amino-1,2,4-triazole the reaction did not proceed or the yield of the reaction was very low.

Next, we extended this reaction to phenols, *p*-nitrophenol **7** on reaction under similar conditions afforded the product **8** in 43% yield (Scheme 2). However, phenol and *p*-methoxyphenol gave only traces of the expected product under similar conditions after 24 h.

We have not established an exact mechanism for the formation of 2′-aminobenzothiazolomethyl-2-naphthols, however, a reasonable possibility is shown in Scheme 3.

In conclusion, we have reported an efficient and environmentally friendly approach for the synthesis of 2′-aminobenzothiazolomethyl-2-naphthols or 5-(2′-aminobenzothiazolomethyl)-6-hydroxyquinolines via condensation of an aldehyde, 2-naphthol or 6-hydroxyquinoline and 2-aminobenzothiazole using water as the solvent. To the best our knowledge, this is the first report on the synthesis of compounds of type **6** in water and this new procedure opens an important alternative to the use of volatile organic solvents.

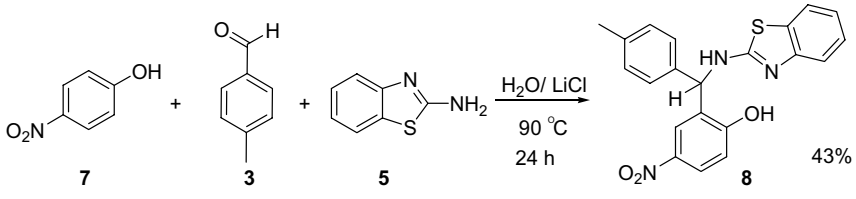
2. Experimental

General procedure for the preparation of 2′-aminobenzothiazolo-arylmethyl-2-naphthols or 5-(2′-amino benzothiazolomethyl)-6-hydroxyquinolines: A mixture of 2-naphthol or 6-hydroxyquinoline (1 mmol), aldehyde (1 mmol) and 2-aminobenzothiazole (1 mmol), in the presence of LiCl (0.5 g, 71 mmol) or in the absence of LiCl, in water (3 ml) was stirred for the time shown in Table 3. The progress of reaction was monitored by TLC. On completion, the reaction mixture was filtered and the precipitate washed with H_2O. The crude products were purified by recrystallization from acetone in 67–96% yields.

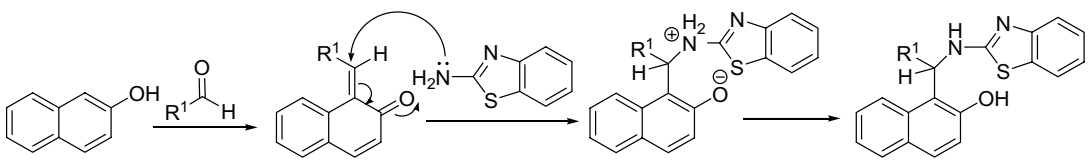
Compound (**6a**): 2′-*Aminobenzothiazolo-phenylmethyl*-2-*naphthol*: White powder; mp 204–205 °C; IR (KBr) (ν_{max}, cm^{-1}): 3381, 1599, 1542, 1515, 1449; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 7.00–7.79 (16H, m, 15H$_{arom}$ and *CH*NH), 8.79 (1H, s, NH), 10.15 (1H, s, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 53.55, 118.57, 118.86, 119.16, 121.35, 121.37, 122.88, 124.31, 125.91, 126.53, 128.55, 129.00, 129.05, 130.03, 131.25, 132.63, 132.70, 142.96, 152.60, 153.67, 166.78; MS (EI, 70 eV) (*m*/*z*): 382 (M$^+$, 10), 239 (100), 202 (20), 144 (50). Anal. Calcd for $C_{24}H_{18}N_2OS$: C, 75.36; H, 4.75; N, 7.32; S, 8.38%. Found: C, 75.15; H, 4.83; N, 7.27; S, 8.47%.

Compound (**6b**): 2′-*Aminobenzothiazolo*-(4-*methylphenyl*)*methyl*-2-*naphthol*: White powder; mp 182–183 °C; IR (KBr) (ν_{max}, cm^{-1}): 3308, 1624, 1536, 1450; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.23 (3H, s, CH_3), 7.01–7.81 (15H, m, 14H$_{arom}$ and *CH*NH), 8.80 (1H, s, NH), 10.14 (1H, s, OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 21.03, 53.53, 118.56, 118.94, 119.32, 121.34, 121.44, 122.86, 124.45, 125.91, 126.51, 126.63, 129.00, 129.16, 129.95, 131.24, 132.65, 135.65, 139.89, 152.64, 153.65, 166.81; MS (EI, 70 eV) (*m*/*z*): 396 (M$^+$, 25), 251 (90), 231 (100), 202 (30), 150 (75). Anal. Calcd for $C_{25}H_{20}N_2OS$: C, 75.72; H, 5.09; N, 7.07; S, 8.09%. Found: C, 75.96; H, 4.89; N, 6.98; S, 8.16%.

Compound (**8**): 2′-*Aminobenzothiazolo*-(4-*methylphenyl*)*methyl*-4-*nitrophenol*: Yellow powder; mp 189–190 °C; IR (KBr) (ν_{max}, cm^{-1}): 3418, 1621, 1541, 1511, 1446; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.26 (3H, s, CH_3), 6.50–8.94 (13H, m, 11H$_{arom}$, NH and *CH*NH), 11.03 (1H, br s, OH); ^{13}C NMR (75 MHz, DMSO-d_6):



Scheme 2.



Scheme 3.

δ_C 21.09, 55.31, 116.12, 118.78, 121.47, 121.70, 123.65, 125.28, 126.01, 127.69, 129.48, 130.50, 130.93, 136.98, 138.41, 139.94, 152.54, 161.78, 165.58; MS (EI, 70 eV) (*m*/*z*): 391 (M^+, 2), 283 (25), 251 (25), 150 (100), 96 (50). Anal. Calcd for $C_{21}H_{17}N_3O_3S$: C, 64.42; H, 4.39; N, 10.74; S, 8.19%. Found: C, 64.18; H, 4.51; N, 10.93; S, 8.29%.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.042.

References and notes

1. Wan, P.; Backer, B.; Diao, L.; Fischer, M.; Shi, Y.; Yang, C. *Cancer J. Chem.* **1996**, *74*, 465–475.
2. Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651–692.
3. Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367–5405.
4. (a) Rajitha, B.; Kumar, B. S.; Reddy, Y. T.; Reddy, P. N.; Sreenivasulu, N. *Tetrahedron Lett.* **2005**, *46*, 8691–8693; (b) Khosropour, A. R.; Khodaei, M. M.; Moghannian, H. *Synlett* **2005**, 955–958; (c) Ko, S.; Yao, C.-F. *Tetrahedron Lett.* **2006**, *47*, 8827–8829; (d) Sarma, R. J.; Baruah, J. B. *Dyes Pigments* **2005**, *64*, 91–92; (e) Van Allan, J. A.; Giannini, D. D.; Whitesides, T. H. *J. Org. Chem.* **1982**, *47*, 820–823; (f) Sen, R. N.; Sarkar, N. N. *J. Am. Chem. Soc.* **1925**, *47*, 1079–1091; (g) Buehler, C. A.; Cooper, D. E.; Scrudder, E. O. *J. Org. Chem.* **1943**, *8*, 316–319; (h) Khoramabadi-Zad, A.; Kazemi, Z.; Amiri-Rudbari, H. *J. Korean Chem. Soc.* **2002**, *46*, 541–544; (i) Kumar, P. S.; Kumar, B. S.; Rajitha, B.; Reddy, P. N.; Sreenivasulu, N.; Reddy, Y. T. *ARKIVOC* **2006**, *xii*, 46–50.
5. (a) Cimarelli, C.; Palmieri, G.; Volpini, E. *Tetrahedron: Asymmetry* **2002**, *13*, 2417–2426; (b) Lu, J.; Xu, X.; Wang, C.; He, J.; Hu, Y.; Hu, H. *Tetrahedron Lett.* **2002**, *43*, 8367–8369; (c) Szatmári, I.; Lázár, L.; Fülöp, F. *Tetrahedron Lett.* **2006**, *47*, 3881–3883; (d) Saidi, M. R.; Azizi, N. *Tetrahedron: Asymmetry* **2003**, *14*, 389–392; (e) Khosropour, A. R.; Khodaei, M. M.; Moghannian, H. *Synlett* **2005**, 916–920; (f) Das, B.; Laxminarayana, K.; Ravikanth, B.; Rao, B. R. *J. Mol. Catal. A: Chem.* **2006**, *261*, 180.
6. (a) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997; (b) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional, 1998; (c) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023–2035; (d) Chan, T. H.; Li, C.-J.; Lee, M. C.; Wei, Z. Y. *Cancer J. Chem.* **1994**, *72*, 1181–1192; (e) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741–760; (f) Lubineau, A.; Augé, J. In *Modern Solvents in Organic Synthesis, Topics in Current Chemistry*; Knochel, P., Ed.; Springer: Berlin Heidelberg, 1999; Vol. 206, pp 1–39; (g) Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* **2001**, *42*, 781–784.
7. (a) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159–164; (b) Kleiner, C. M.; Schreiner, P. R. *Chem. Commun.* **2006**, 4315–4317; (c) Pirrung, M. C.; Sarma, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 444–445; (d) Lubineau, A. *J. Org. Chem.* **1986**, *51*, 2142–2144; (e) Von Hippel, P. H.; Schleich, T. *Acc. Chem. Res.* **1969**, *2*, 257–265.
8. (a) Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, *6*, 314–320; (b) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210; (c) *Multicomponent Reactions*; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, 2005.
9. (a) Paget, C. J.; Chamberlin, J. W.; Wikel, J. H. *British Patent*, 1,568,542, 1982; (*Chem. Abstr.* **1981**, *91*, 30754); (b) Paget, C. J.; Kisner, K.; Stone, R. L.; Delong, D. C. *J. Med. Chem.* **1969**, *12*, 1010–1015; (c) *The Strategy in Chemotherapy*; Tamm, J., Cowan, S. T., Rowatt, E., Eds.; Cambridge University Press: Cambridge, 1958.
10. (a) Shaabani, A.; Rahmati, A.; Naderi, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5553–5557; (b) Shaabani, A.; Safaei, H. R.; Bijanzadeh, H. R. *Synth. Commun.* **2001**, *31*, 2639–2644; (c) Shaabani, A.; Farhangi, E.; Rahmati, A. *Comb. Chem. High Throughput Screening* **2006**, *9*, 771–776.