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Research Article

(+)-CSA Catalyzed Multicomponent Synthesis of 1-[(1,3-Thiazol-2-ylamino)methyl]-2-naphthols and Their Ring-Closure Reaction under Ultrasonic Irradiation

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New 1-[(1,3-thiazol-2-ylamino)methyl]-2-naphthols were obtained by condensation of 2-aminothiazole, aromatic aldehydes, and 2-naphthol in the presence of (+)-camphor-10-sulfonic acid ((+)-CSA) as an effective catalyst under ultrasound-promoted solvent-free conditions. The 1-[(1,3-thiazol-2-ylamino)methyl]-2-naphthol derivatives were converted in ring-closure reaction with formaldehyde to the corresponding naphthoxazine derivatives.

Dedicated to the memory of Professor Yiannis Elemes

1. Introduction

Multicomponent reactions have increasing importance in synthetic organic chemistry because they allow the building of several new bonds in a single step [1–4]. Some of the significant advantages of multicomponent reactions over conventional reactions are a high degree of atomic economy, structural diversity, easier progress of reactions, decreased reaction times, low power consumption, and lack of waste products [5, 6].

The Mannich reaction is one of the most important carbon-carbon bond forming reactions in organic chemistry. This reaction is used as a key step in the synthesis of many synthetically and biologically important nitrogen-containing compounds [7–11]. A large number of studies on Mannich-type reactions have been reported under many varied processes in the literature [12–16]. The Mannich reaction has also been performed to achieve stereoselective synthesis of aminonaphthol derivatives in the last decades. These stereoselective compounds have exhibited fairly good enantioselectivity in asymmetric reactions [17–20]. There are some reports on the use of heteroarylamines in Mannich-type reactions and synthesis of 2-amino-1,3-thiazoles in the literature [21–26].

CSA has been demonstrated to be an efficient, nontoxic, ecofriendly, economical, and water soluble catalyst for several reactions such as synthesis of β-amino carbonyl compounds [27], Friedel-Crafts reactions [28, 29], Meyer-Schuster reactions [30], Friedlander annulations [31], synthesis of α-hydroxy and α-amino phosphonates [32], synthesis of 1,3,4-oxadiazoles [33], synthesis of pseudoglycosides [34], synthesis of coumarins [35], synthesis of spirocyclic compounds [36], and rearrangement of 1,2-dialkynylallyl alcohols [37], and it is widely used in the optical resolution of amines [38].

The development of efficient and environmentally friendly chemical processes has an increasing popularity in organic chemistry. In this context, ultrasound-assisted organic reactions have become an important research area in recent years [39–43]. Ultrasound irradiation is able to activate many organic reactions due to cavitational collapse [44, 45]. Compared with traditional methods, a broad range of organic syntheses can be successfully performed in higher

yields and selectivity, shorter reaction times, and milder reaction conditions under ultrasonic irradiation [46–48].

1,3-Oxazine derivatives have shown many biological properties such as analgesic, anticonvulsant, antitubular, antibacterial, antifungal, and anticancer activity [49–56]. Also, in the last decades, these compounds have been used in the treatment of AIDS and Parkinson's disease [57, 58]. Furthermore, 1,3-oxazine derivatives can also be used as an intermediate in the synthesis of N-substituted aminoalcohols [59]. Therefore, several methods for the synthesis of 1,3-oxazine derivatives have been reported [60–66].

Here, we report on the preparation of 1-[(1,3-thiazol-2-ylamino)methyl]-2-naphthols catalyzed by (+)-CSA ((+)-camphor-10-sulfonic acid) under ultrasonic irradiation and solvent-free conditions and then ring-closure reaction of these compounds with formaldehyde under ultrasonic irradiation in THF solvent with short reaction times and good yields.

2. Experimental

2.1. Materials and Methods. NMR spectra were determined on a Bruker Avance III-500 MHz NMR. Chemical shifts are given in ppm downfield from Me_4Si in DMSO-d_6 or $CDCl_3$ solution. Coupling constants are given in Hz. The FTIR spectra were recorded on a Perkin-Elmer FTIR spectrometer (ATR) and absorption frequencies are reported in cm^{-1}. MS spectra were recorded on a Thermo Elemental X Series ICP-MS. Elemental analyses were measured with Flash EA 1112 Series apparatus and were in good agreement (±0.2%) with the calculated values. Ultrasonication was performed in a Bandelin Sonorex Ultrasonic Bath (Super RK) with a frequency of 35 kHz and a power of 230 W. The internal dimensions of the ultrasonic cleaner tank were 240 × 140 × 100 mm with liquid holding capacity of 3 L. The reactor was a 100 mL Pyrex round-bottom flask. The reaction flasks were suspended in the center of the bath, and the addition or removal of water controlled the temperature of the water bath. Melting points were measured on a Gallenkamp melting-point apparatus. Silica gel 60 (Merck) was used for column separation. TLC was conducted on standard conversion aluminum sheets precoated with a 0.2 mm layer of silica gel. All reagents were commercially available. Anhydrous (+)-CSA was purchased from commercial suppliers.

*2.2. General Procedure for the Synthesis of 1-[(1,3-Thiazol-2-ylamino)methyl]-2-naphthols (**1a–n**) under Ultrasonic Irradiation.* A mixture of (+)-CSA (11.6 mg, 0.05 mmol), 2-aminothiazole (1.00 mmol), aromatic aldehyde (1.00 mmol), and 2-naphthol (1.00 mmol) was irradiated with ultrasound of low power (with a frequency of 35 kHz and a nominal power of 230 W) at 50°C for the period of time indicated in Table 3 and Scheme 3. The reaction flask was located at the maximum energy area in the cleaner and the surface of the reactants was placed slightly lower than the level of the water. The addition or removal of water controlled the temperature of the water bath. After completion of the reaction, as indicated by TLC monitoring, the resultant solid was crystallized from acetone to give products **1a–n**.

*1-[Phenyl(1,3-thiazol-2-ylamino)methyl]-2-naphthol (**1a**).* White powder; m.p. 197–199°C (Lit. [23] 196–198°C); FTIR (ATR, cm^{-1}): 3363, 3131, 3055, 3024, 2971, 1629, 1553, 1514, 1439, 1338, 1264, 1248, 1157, 1055, 1029, 949, 736. ^{1}H NMR δ_H (DMSO-d_6, 500 MHz): 6.50 (d, J = 6.00 Hz, 1H), 7.10–8.36 (m, 13H), 9.36 (d, J = 1.50 Hz, 1H), 12.22 (br s, 1H). ^{13}C NMR δ_C (DMSO-d_6, 125 MHz): 56.28, 107.32, 120.21, 123.51, 123.78, 123.97, 124.73, 127.29, 127.71, 129.07, 129.65, 130.55, 136.00, 139.80, 143.96, 150.32, 155.37, 171.06. MS m/z (ESI): 333 (M^+ + 1), 233, 215, 101, 71, 57. Anal. Calc. for $C_{20}H_{16}N_2OS$: C, 72.26; H, 4.85; N, 8.43. Found: C, 72.13; H, 4.81; N, 8.40.

*1-[4-Methylphenyl(1,3-thiazol-2-ylamino)methyl]-2-naphthol (**1b**; Supporting Information Page 2 in Supplementary Material available online at http://dx.doi.org/10.1155/2016/9315614).* White powder; m.p. 163–165°C; FTIR (ATR, cm^{-1}): 3357, 3131, 3055, 3020, 2939, 1628, 1541, 1513, 1436, 1325, 1262, 1246, 1155, 1051, 1020, 953, 869, 805, 782, 738. ^{1}H NMR δ_H (DMSO-d_6, 500 MHz): 2.21 (s, 3H), 6.59 (br s 1H), 6.98–7.32 (m, 9H), 7.74 (d, J = 8.00 Hz, 1H), 7.78 (d, J = 8.50 Hz, 1H), 7.89 (br s 1H), 8.34 (br s 1H), 10.15 (br s, 1H). ^{13}C NMR δ_C (DMSO-d_6, 125 MHz): 20.52, 53.43, 106.62, 112.90, 118.48, 119.26, 122.30, 126.08, 128.43, 128.54, 128.62, 129.19, 132.12, 132.75, 135.06, 138.19, 139.55, 153.02, 168.92. MS m/z (ESI): 347 (M^+ + 1), 247, 232, 214, 189, 101, 71, 57. Anal. Calc. for $C_{21}H_{18}N_2OS$: C, 72.80; H, 5.24; N, 8.09. Found: C, 72.76; H, 5.21; N, 8.05.

*1-[4-Bromophenyl(1,3-thiazol-2-ylamino)methyl]-2-naphthol (**1c**; Supporting Information Page 3).* White powder; m.p. 173–175°C; FTIR (ATR, cm^{-1}): 3377, 3113, 3060, 3020, 2966, 1630, 1548, 1509, 1435, 1338, 1264, 1245, 1158, 1054, 1009, 946, 842, 805, 775, 741. ^{1}H NMR δ_H (DMSO-d_6, 500 MHz): 6.63 (d, J = 3.50 Hz, 1H), 7.00 (d, J = 3.50 Hz, 1H), 7.04 (d, J = 7.00 Hz, 1H), 7.16 (d, J = 8.00 Hz, 2H), 7.22 (d, J = 8.50 Hz, 1H), 7.26 (d, J = 7.50 Hz, 1H), 7.35 (d, J = 5.50 Hz, 1H), 7.44 (d, J = 8.50 Hz, 2H), 7.77 (d, J = 8.00 Hz, 1H), 7.80 (d, J = 8.00 Hz, 1H), 7.84 (br s, 1H), 8.38 (d, J = 4.50 Hz, 1H), 10.20 (br s, 1H). ^{13}C NMR δ_C (DMSO-d_6, 125 MHz): 53.00, 106.99, 118.36, 118.65, 119.03, 122.42, 126.28, 127.38, 128.38, 128.53, 129.53, 130.81, 132.00, 133.49, 138.21, 142.41, 153.03, 168.68. MS m/z (ESI): 412 (M^+ + 1), 312, 232, 214, 189, 101, 71, 57. Anal. Calc. for $C_{20}H_{15}BrN_2OS$: C, 58.40; H, 3.68; N, 6.81. Found: C, 58.25; H, 3.63; N, 6.78.

*1-[4-Isopropylphenyl(1,3-thiazol-2-ylamino)methyl]-2-naphthol (**1d**; Supporting Information Page 4).* White powder; m.p. 159–161°C; FTIR (ATR, cm^{-1}): 3344, 3118, 3060, 3020, 2957, 1625, 1531, 1505, 1435, 1326, 1272, 1255, 1155, 1046, 1019, 954, 860, 817, 782, 744. ^{1}H NMR (DMSO-d_6, 500 MHz): 1.14 (d, J = 4.00 Hz, 6H), 2.79–2.81 (m, 1H), 6.60 (d, J = 3.50 Hz, 1H), 6.98–7.35 (m, 9H), 7.76 (dd, J_1 = 17.50 Hz, J_2 = 7.50 Hz, 2H), 7.97 (d, J = 2.00 Hz, 1H), 8.34 (br s, 1H), 10.13 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): 23.82, 23.90, 32.95, 53.57, 106.60, 114.52, 118.48, 119.21, 122.32, 125.89, 126.20, 128.46, 128.57, 129.16, 132.20, 133.24, 138.24, 139.90, 146.15, 153.00, 168.88. MS m/z (ESI): 375 (M^+ + 1), 275, 233, 215, 189, 157, 101, 71, 57. Anal. Calc. for $C_{23}H_{22}N_2OS$: C, 73.76; H, 5.92; N, 7.48. Found: C, 73.72; H, 5.87; N, 7.45.

*1-[2,4-Dimethylphenyl(1,3-thiazol-2-ylamino)methyl]-2-naphthol (**1e**; Supporting Information Page 5)*. White powder; m.p. 171–173°C; FTIR (ATR, cm^{-1}): 3343, 3125, 3062, 3000, 2956, 2916, 1625, 1604, 1578, 1528, 1504, 1435, 1365, 1330, 1269, 1242, 1156, 1083, 1043, 946, 842, 816, 745. ^{1}H NMR (DMSO-d_6, 500 MHz): 2.12 (s, 3H), 2.20 (s, 3H), 6.53 (d, J = 3.50 Hz, 1H), 6.87–6.90 (m, 2H), 6.93 (d, J = 3.50 Hz, 2H), 7.17–7.23 (m, 3H), 7.31 (t, J = 7.50 Hz, 1H), 7.73 (d, J = 9.00 Hz, 1H), 7.77 (d, J = 7.50 Hz, 1H), 8.02 (d, J = 9.00 Hz, 1H), 8.30 (br s, 1H), 10.08 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): 18.97, 20.42, 52.95, 106.20, 117.69, 118.42, 122.21, 125.75, 127.34, 128.46, 128.52, 129.17, 131.14, 132.67, 135.58, 136.04, 136.70, 138.35, 153.32, 168.27. MS *m/z* (ESI): 361 (M^+ + 1), 318, 274, 260, 246, 101, 71, 57. Anal. Calc. for $C_{22}H_{20}N_2OS$: C, 73.30; H, 5.59; N, 7.77. Found: C, 73.25; H, 5.60; N, 7.74.

*1-[(2,4-Dichlorophenyl)(1,3-thiazol-2-ylamino)methyl]-2-naphthol (**1f**; Supporting Information Page 6)*. White powder; m.p. 164–166°C; FTIR (ATR, cm^{-1}): 3336, 3122, 3072, 3027, 2974, 1624, 1578, 1534, 1515, 1505, 1465, 1434, 1370, 1319, 1268, 1183, 1156, 1082, 1052, 1042, 948, 883, 813, 748. ^{1}H NMR (DMSO-d_6, 500 MHz): 6.60 (d, J = 3.50 Hz, 1H), 6.98 (d, J = 3.50 Hz, 1H), 7.01 (d, J = 7.00 Hz, 1H), 7.12 (d, J = 8.50 Hz, 1H), 7.25 (t, J = 7.50 Hz, 1H), 7.39–7.41 (m, 2H), 7.47 (d, J = 2.00 Hz, 1H), 7.66 (d, J = 8.50 Hz, 1H), 7.75 (d, J = 8.00 Hz, 1H), 7.79 (d, J = 9.00 Hz, 1H), 8.01 (d, J = 6.50 Hz, 1H), 8.43 (br s, 1H), 9.94 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): 52.57, 106.81, 116.22, 118.52, 122.31, 122.73, 126.34, 128.26, 128.47, 129.74, 131.28, 131.58, 132.70, 133.09, 138.37, 139.27, 153.69, 167.68. MS *m/z* (ESI): 402 (M^+ + 1), 317, 302, 256, 157, 101, 71, 57. Anal. Calc. for $C_{20}H_{14}Cl_2N_2OS$: C, 59.86; H, 3.52; N, 6.98. Found: C, 59.84; H, 3.50; N, 6.96.

*1-[(2,4-Difluorophenyl)(1,3-thiazol-2-ylamino)methyl]-2-naphthol (**1g**)*. White powder; m.p. 165–167°C; FTIR (ATR, cm^{-1}): 3313, 3126, 3069, 3055, 3024, 2970, 1620, 1607, 1548, 1515, 1500, 1434, 1371, 1347, 1261, 1235, 1159, 1139, 1083, 1053, 966, 850, 815, 744. ^{1}H NMR (DMSO-d_6, 500 MHz): 6.61 (d, J = 3.50 Hz, 1H), 6.98–7.27 (m, 6H), 7.40 (d, J = 6.00 Hz, 1H), 7.61 (d, J = 5.50 Hz, 1H), 7.64–8.06 (m, 3H), 8.38 (br s, 1H), 10.08 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): 48.90, 103.43, 106.88, 110.50, 117.23, 118.42, 122.31, 122.88, 125.75, 126.26, 128.29, 128.53, 129.52, 130.20, 132.15, 138.28, 153.25, 167.98. MS *m/z* (ESI): 369 (M^+ + 1), 284, 269, 256, 156, 138, 101, 71, 57. Anal. Calc. for $C_{20}H_{14}F_2N_2OS$: C, 65.20; H, 3.83; N, 7.60. Found: C, 65.18; H, 3.80; N, 7.58.

*1-[(3-Phenoxyphenyl)(1,3-thiazol-2-ylamino)methyl]-2-naphthol (**1h**)*. White powder; m.p. 162–164°C; FTIR (ATR, cm^{-1}): 3356, 3122, 3060, 3006, 2939, 1623, 1579, 1531, 1480, 1437, 1317, 1257, 1243, 1221, 1155, 1064, 1045, 971, 866, 740. ^{1}H NMR (DMSO-d_6, 500 MHz): 6.62 (br s, 1H), 6.78 (d, J = 6.00 Hz, 1H), 6.89 (d, J = 6.00 Hz, 2H), 7.00 (d, J = 9.50 Hz, 3H), 7.08 (d, J = 9.50 Hz, 2H), 7.24–7.31 (m, 6H), 7.75–7.79 (m, 2H), 7.86 (br s, 1H), 8.39 (br s, 1H), 10.20 (br s, 1H) ^{13}C NMR (DMSO-d_6, 125 MHz): 53.20, 106.91, 116.32, 116.89, 117.95, 118.39, 118.89, 121.53, 122.40, 123.06, 126.14, 128.51, 128.60, 129.45, 129.62, 129.86, 132.05, 133.44, 138.18, 145.38, 153.03, 155.97, 156.67, 168.72. MS *m/z* (ESI): 425 (M^+ + 1), 406, 362, 325, 318, 274, 261, 256, 202, 101, 71, 57. Anal. Calc. for $C_{26}H_{20}N_2O_2S$: C, 73.56; H, 4.17; N, 8.28. Found: C, 73.53; H, 4.15; N, 8.25.

*1-[(4-Benzyloxyphenyl)(1,3-thiazol-2-ylamino)methyl]-2-naphthol (**1i**)*. White powder; m.p. 153–155°C; FTIR (ATR, cm^{-1}): 3385, 3126, 3057, 3021, 2947, 2862, 1628, 1609, 1579, 1554, 1510, 1459, 1441, 1338, 1266, 1251, 1240, 1175, 1157, 1120, 1054, 1038, 1027, 951, 874, 810, 743. ^{1}H NMR (DMSO-d_6, 500 MHz): 5.01 (s, 2H), 6.59 (d, J = 3.50 Hz, 1H), 6.89 (d, J = 8.50 Hz, 2H), 6.98 (d, J = 3.50 Hz, 2H), 7.14 (d, J = 8.00 Hz, 2H), 7.21 (d, J = 9.00 Hz, 1H), 7.24 (d, J = 7.50 Hz, 1H), 7.30 (d, J = 7.00 Hz, 1H), 7.34–7.37 (m, 3H), 7.41 (d, J = 7.00 Hz, 2H), 7.74 (d, J = 9.00 Hz, 1H), 7.78 (d, J = 8.00 Hz, 1H), 7.90 (br s, 1H), 8.33 (br s, 1H), 10.15 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): 53.25, 69.09, 114.27, 114.91, 118.45, 119.16, 121.18, 122.31, 124.76, 125.05, 127.32, 127.62, 127.74, 128.36, 128.45, 129.17, 134.59, 137.119, 138.23, 138.67, 139.50, 150.55, 152.99, 156.77, 168.86. MS *m/z* (ESI): 439 (M^+ + 1), 420, 377, 361, 339, 326, 316, 299, 256, 247, 154, 101, 71, 57. Anal. Calc. for $C_{27}H_{22}N_2O_2S$: C, 73.95; H, 5.06; N, 6.39. Found: C, 73.93; H, 5.05; N, 6.36.

*1-[(3-Nitrophenyl)(1,3-thiazol-2-ylamino)methyl]-2-naphthol (**1j**)*. White powder; m.p. 183–185°C, (Lit. [23] 181–183°C); FTIR (ATR, cm^{-1}): 3387, 3124, 3054, 3020, 2927, 2852, 1628, 1606, 1574, 1537, 1458, 1440, 1336, 1263, 1250, 1237, 1155, 1120, 1056, 1041, 1025, 954, 876, 810, 745. ^{1}H NMR (DMSO-d_6, 500 MHz): 6.62 (d, J = 3.50 Hz, 1H), 6.88–7.78 (m, 9H), 7.87 (br s, 1H), 8.00–8.46 (m, 3H), 10.23 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): 53.12, 108.07, 118.30, 118.52, 119.76, 121.15, 122.43, 123.05, 126.40, 128.35, 128.55, 129.55, 130.81, 132.12, 133.10, 138.23, 138.36, 144.00, 152.98, 168.56. MS *m/z* (ESI): 378 (M^+ + 1), 360, 332, 270, 201, 101, 71, 57. Anal. Calc. for $C_{20}H_{15}N_3O_3S$: C, 63.65; H, 4.01; N, 11.13. Found: C, 63.53; H, 4.03; N, 11.15.

*1-[(1,3-Thiazol-2-ylamino)(thiophen-2-yl)methyl]-2-naphthol (**1k**; Supporting Information Page 7)*. White powder; m.p. 155-156°C; FTIR (ATR, cm^{-1}): 3326, 3126, 3091, 3061, 2980, 2908, 2869, 1629, 1550, 1514, 1436, 1372, 1340, 1266, 1247, 1160, 1075, 1051, 945, 870, 809, 744. ^{1}H NMR (DMSO-d_6, 500 MHz): 6.63 (d, J = 3.00 Hz, 1H), 6.77 (br s, 1H), 6.89 (d, J = 3.00 Hz, 1H), 7.02 (d, J = 3.00 Hz, 1H), 7.21–7.27 (m, 3H), 7.32 (d, J = 4.50 Hz, 1H), 7,37 (br s, 1H), 7.77 (d, J = 9.00 Hz, 1H), 7.80 (d, J = 8.00 Hz, 1H), 8.01 (br s, 1H), 8.50 (br s, 1H), 10.27 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): 50.81, 107.06, 118.40, 118.51, 122.42, 124.03, 124.44, 126.11, 126.53, 128.50, 129.58, 131.99, 138.22, 147.01, 153.02, 168.33. MS *m/z* (ESI): 339 (M^+ + 1), 318, 273, 256, 239, 221, 202, 101, 71, 57. Anal. Calc. for $C_{18}H_{14}N_2OS_2$: C, 63.88; H, 4.17; N, 8.28. Found: C, 63.85; H, 4.15; N, 8.26.

*1-[(1,3-Thiazol-2-ylamino)(thiophen-3-yl)methyl]-2-naphthol (**1l**)*. White powder; m.p. 154–156°C; FTIR (ATR, cm^{-1}): 3328, 3122, 3055, 2975, 1624, 1549, 1513, 1434, 1362, 1338, 1248, 1156, 1142, 1053, 949, 837, 804, 741. ^{1}H NMR (DMSO-d_6, 500 MHz): 6.60 (d, J = 3.50 Hz, 1H), 6.86 (d, J = 2.50 Hz, 1H), 6.97–7.00 (m, 2H), 7.20–7.26 (m, 3H), 7.35–7.39 (m, 2H), 7.73–7.78 (m, 2H), 8.01 (d, J = 3.50 Hz, 1H), 8.48 (br s,

1H), 10.23 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): 51.29, 106.68, 118.55, 118.81, 120.51, 122.33, 125.87, 127.04, 128.45, 128.58, 129.23, 132.03, 138.13, 143.53, 152.92, 168.62. MS *m/z* (ESI): 339 (M^+ + 1), 318, 273, 256, 239, 221, 202, 101, 71, 57. Anal. Calc. for $C_{18}H_{14}N_2OS_2$: C, 63.88; H, 4.17; N, 8.28. Found: C, 63.86; H, 4.14; N, 8.26.

*1-[5-Methylfuran-2-yl(1,3-thiazol-2-ylamino)methyl]-2-naphthol (**1m**; Supporting Information Page 8).* White powder; m.p. 164–166°C; FTIR (ATR, cm^{-1}): 3368, 3129, 3062, 3054, 3014, 2973, 2950, 1632, 1560, 1542, 1509, 1447, 1373, 1338, 1261, 1240, 1215, 1175, 1154, 1103, 1053, 1020, 953, 863, 817, 785, 752. ^{1}H NMR (DMSO-d_6, 500 MHz): 2.14 (s, 3H), 5.96 (d, J = 3.00 Hz, 1H), 5.99 (d, J = 3.00 Hz, 1H), 6.58 (d, J = 3.50 Hz, 1H), 6.97–6.98 (m, 2H), 7.18–7.25 (m, 2H), 7.38 (br s, 1H), 7.73–7.78 (m, 2H), 8.12 (d, J = 8.00 Hz, 2H), 8.43 (br s, 1H), 10.18 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): 13.32, 49.14, 106.34, 106.67, 107.28, 116.67, 118.48, 122.33, 123.61, 125.97, 128.39, 128.48, 129.40, 132.35, 138.17, 150.35, 152.65, 153.31, 168.25. MS *m/z* (ESI): 337 (M^+ + 1), 318, 274, 256, 237, 219, 195, 101, 57. Anal. Calc. for $C_{19}H_{16}N_2O_2S$: C, 67.84; H, 4.79; N, 8.33. Found: C, 67.86; H, 4.77; N, 8.30.

*1-[5-Bromofuran-2-yl(1,3-thiazol-2-ylamino)methyl]-2-naphthol (**1n**; Supporting Information Page 9).* White powder; m.p. 158–160°C; FTIR (ATR, cm^{-1}): 3366, 3129, 3066, 3024, 2991, 2980, 2915, 1632, 1580, 1542, 1508, 1448, 1373, 1337, 1271, 1258, 1198, 1154, 1122, 1105, 1052, 1009, 921, 862, 816, 787, 751. ^{1}H NMR (DMSO-d_6, 500 MHz): 6.20 (d, J = 3.00 Hz, 1H), 6.46 (d, J = 3.50 Hz, 1H), 6.62 (d, J = 3.50 Hz, 1H), 7.01 (d, J = 3.50 Hz, 1H), 7.04 (d, J = 6.50 Hz, 1H), 7.21 (d, J = 9.00 Hz, 1H), 7.27 (t, J = 7.50 Hz, 1H), 7.40 (t, J = 7.50 Hz, 1H), 7.77 (d, J = 9.00 Hz, 1H), 7.80 (d, J = 8.00 Hz, 1H), 8.08 (d, J = 8.50 Hz, 1H), 8.47 (d, J = 5.00 Hz, 1H), 10.24 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): 48.83, 106.99, 109.35, 112.28, 115.64, 118.31, 119.25, 122.41, 123.15, 126.20, 128.36, 128.45, 129.72, 132.18, 138.11, 153.38, 156.95, 168.01. MS *m/z* (ESI): 402 (M^+ + 1), 384, 340, 302, 284, 259, 255, 138, 101, 71, 57. Anal. Calc. for $C_{18}H_{13}BrN_2O_2S$: C, 53.88; H, 3.27; N, 6.98. Found: C, 53.85; H, 3.25; N, 6.96.

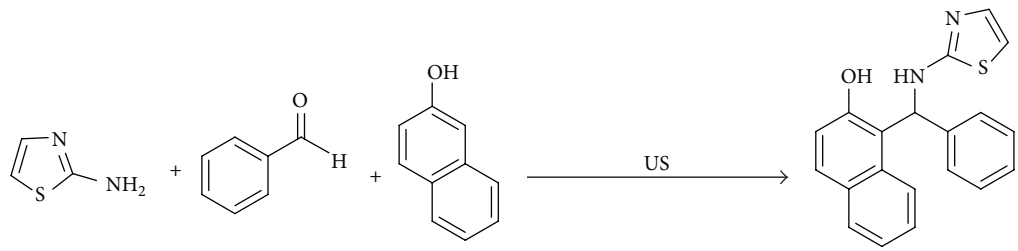
*2.3. General Procedure for the Synthesis of the Naphthoxazines (**2a–f**) under Ultrasonic Irradiation.* 1-[(1,3-Thiazol-2-ylamino)methyl]-2-naphthols **1a**, **1c**, **1d**, **1k**, **1m**, and **1n** (1 mmol) were dissolved in THF (3 mL) and 35% aqueous formaldehyde (1.2 mmol) was added. The solution was irradiated with ultrasound of low power (with a frequency of 35 kHz and a nominal power of 230 W) at 50°C for 3 hours. The reaction flask was located at the maximum energy area in the cleaner and the surface of the reactants was placed slightly lower than the level of the water. The addition or removal of water controlled the temperature of the water bath. Solvent was removed and the residue was dried under reduced pressure. The crude oil was purified by column chromatography eluting with EtOAc/hexane.

*1-Phenyl-2-(thiazol-2-yl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine(**2a**; Supporting Information Page 10).* White powder; m.p. 125-126°C; FTIR (ATR, cm^{-1}): 3126, 3106, 3077, 3057, 3025, 2944, 2922, 2898, 2850, 1623, 1599, 1508, 1483, 1466, 1404, 1382, 1312, 1233, 1201, 1125, 1089, 1058, 1000, 969, 915, 816, 745. ^{1}H NMR ($CDCl_3$, 500 MHz): 5.11 (d, J = 11.00 Hz, 1H), 5.64 (d, J = 11.00 Hz, 1H), 6.67 (d, J = 3.50 Hz, 1H), 6.87 (s, 1H), 7.13 (d, J = 9.00 Hz, 1H), 7.25 (d, J = 3.50 Hz, 1H), 7.29–7.33 (m, 5H), 7.36–7.38 (m, 2H), 7.44 (d, J = 9.00 Hz, 1H), 7.73 (d, J = 9.00 Hz, 1H), 7.76 (d, J = 9.00 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): 59.53, 73.69, 109.44, 112.86, 118.81, 123.05, 123.79, 126.92, 128.10, 128.55, 128.64, 128.96, 129.21, 129.72, 131.89, 139.63, 140.90, 151.69. MS *m/z* (ESI): 345 (M^+ + 1), 260, 232, 215, 175, 102, 71, 57. Anal. Calc. for $C_{21}H_{16}N_2OS$: C, 73.23; H, 4.68; N, 8.13. Found: C, 73.20; H, 4.66; N, 8.10.

*1-(4-Bromophenyl)-2-(thiazol-2-yl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (**2b**; Supporting Information Page 11).* White powder; m.p. 101–103°C; FTIR (ATR, cm^{-1}): 3119, 3062, 2952, 2925, 2853, 1625, 1588, 1508, 1484, 1466, 1434, 1401, 1311, 1268, 1230, 1176, 1131, 1057, 1000, 968, 917, 877, 812, 773, 745. ^{1}H NMR ($CDCl_3$, 500 MHz): 4.99 (d, J = 11.00 Hz, 1H), 5.52 (dd, J_1 = 11.00 Hz, J_2 = 2.00 Hz, 1H), 6.62 (d, J = 3.50 Hz, 1H), 6.79 (s, 1H), 7.05 (d, J = 9.00 Hz, 1H), 7.17 (d, J = 8.50 Hz, 1H), 7.22–7.33 (m, 4H), 7.36 (d, J = 8.50 Hz, 2H), 7.56–7.70 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): 58.69, 73.81, 109.67, 118.80, 122.84, 123.51, 123.94, 127.08, 128.64, 129.24, 129.95, 130.69, 131.65, 131.78, 132.46, 139.56, 139.91, 151.68. MS *m/z* (ESI): 424 (M^+ + 1), 339, 316, 311, 293, 254, 236, 102, 71, 57. Anal. Calc. for $C_{21}H_{15}BrN_2OS$: C, 59.58; H, 3.57; N, 6.62. Found: C, 59.55; H, 3.55; N, 6.60.

*1-(4-Isopropylphenyl)-2-(thiazol-2-yl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (**2c**; Supporting Information Page 12).* White powder; m.p. 115–117°C; FTIR (ATR, cm^{-1}): 3113, 3091, 3059, 3012, 2961, 2921, 2893, 2869, 1624, 1597, 1505, 1485, 1466, 1432, 1404, 1381, 1311, 1271, 1230, 1177, 1126, 1089, 1050, 1001, 973, 918, 857, 812, 773, 746. ^{1}H NMR ($CDCl_3$, 500 MHz): 1.22 (d, J = 3.50 Hz, 6H), 2.84–2.92 (m, 1H), 5.13 (d, J = 11.00 Hz, 1H), 5.65 (d, J = 11.00 Hz, 1H), 6.66 (d, J = 7.00 Hz, 1H), 6.82 (s, 1H), 7.12 (d, J = 9.00 Hz, 1H), 7.16 (d, J = 8.00 Hz, 1H), 7.25 (d, J = 3.50 Hz, 1H), 7.27 (d, J = 8.00 Hz, 2H), 7.31 (d, J = 8.00 Hz, 1H), 7.34 (d, J = 7.00 Hz, 1H), 7.48 (d, J = 8.00 Hz, 1H), 7.72 (d, J = 9.00 Hz, 1H), 7.76 (d, J = 8.00 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): 23.90, 23.93, 33.77, 59.46, 73.64, 109.33, 113.16, 118.81, 123.13, 123.73, 126.67, 126.87, 128.51, 128.84, 129.18, 129.60, 131.93, 138.24, 139.62, 148.73, 151.62. MS *m/z* (ESI): 387 (M^+ + 1), 318, 302, 274, 256, 237, 218, 202, 102, 71, 57. Anal. Calc. for $C_{24}H_{22}N_2OS$: C, 74.58; H, 5.74; N, 7.25. Found: C, 74.56; H, 5.76; N, 7.23.

*2-(Thiazol-2-yl)-1-(thiophen-2-yl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (**2d**).* White powder; m.p. 117-118°C; FTIR (ATR, cm^{-1}): 3107, 3091, 3072, 3057, 2961, 2922, 2898, 2850, 1623, 1598, 1505, 1485, 1467, 1405, 1376, 1361, 1312, 1230, 1169, 1116, 1087, 1058, 1003, 967, 816, 748, 706. ^{1}H NMR ($CDCl_3$, 500 MHz): 5.33 (d, J = 11.00 Hz, 1H), 5.68 (dd, J_1 = 11.00 Hz, J_2 = 2.00 Hz, 1H), 6.69 (d, J = 3.50 Hz, 1H), 6.82 (d, J = 3.50 Hz, 1H), 6.87 (dd, J_1 = 9.00 Hz, J_2 = 3.50 Hz, 1H), 7.02 (s, 1H), 7.10 (d, J = 9.00 Hz, 1H), 7.25 (d, J = 3.50 Hz, 1H), 7.30 (dd, J_1 = 8.50 Hz, J_2 = 1.50 Hz, 1H), 7.32–7.40 (m, 2H), 7.63 (d, J = 8.50 Hz, 1H), 7.72 (d, J = 9.00 Hz, 1H), 7.75 (d, J



Scheme 1: One-pot three-component Mannich reaction.

= 7.50 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): 55.09, 73.83, 109.71, 118.75, 122.84, 123.88, 126.25, 126.71, 127.02, 128.41, 128.55, 129.25, 129.97, 131.67, 139.62, 144.46, 151.11. MS *m/z* (ESI): 351 (M^+ + 1), 323, 268, 266, 238, 220, 182, 101, 71, 57. Anal. Calc. for $C_{19}H_{14}N_2OS_2$: C, 65.12; H, 4.03; N, 7.99. Found: C, 65.15; H, 4.05; N, 7.97.

*1-(5-Methylfuran-2-yl)-2-(thiazol-2-yl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (**2e**; Supporting Information Page 13)*. White powder; m.p. 126–128°C; FTIR (ATR, cm^{-1}): 3111, 3072, 3057, 3025, 2930, 2913, 2893, 2855, 1623, 1599, 1508, 1466, 1432, 1402, 1375, 1314, 1230, 1129, 1057, 998, 969, 913, 809, 747, 700. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.43 (s, 3H), 5.36 (d, J = 11.00 Hz, 1H), 5.68 (dd, J_1 = 11.00 Hz, J_2 = 1.50 Hz, 1H), 6.51 (dd, J_1 = 3.50 Hz, J_2 = 1.00 Hz, 1H), 6.57 (dd, J_1 = 3.50 Hz, J_2 = 1.00 Hz, 1H), 6.67 (d, J = 3.50 Hz, 1H), 6,90 (s, 1H), 7.09 (d, J = 8.50 Hz, 1H), 7.24 (d, J = 3.50 Hz, 1H), 7.30–7.41 (m, 2H), 7.67 (d, J = 8.50 Hz, 1H), 7.71 (d, J = 9.00 Hz, 1H), 7.74 (d, J = 7.50 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): 15.45, 55.35, 73.72, 109.57, 118.74, 122.90, 123.83, 124.77, 126.96, 128.38, 128.51, 129.21, 129.86, 131.71, 139.61, 140.89, 141.75, 151.11. MS *m/z* (ESI): 349 (M^+ + 1), 306, 264, 236, 218, 180, 101, 71, 57. Anal. Calc. for $C_{20}H_{16}N_2O_2S$: C, 68.94; H, 4.63; N, 8.04. Found: C, 68.96; H, 4.65; N, 8.02.

*1-(5-Bromofuran-2-yl)-2-(thiazol-2-yl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (**2f**)*. White powder; m.p. 105–107°C; FTIR (ATR, cm^{-1}): 3120, 3065, 2997, 2928, 1625, 1600, 1507, 1467, 1434, 1352, 1314, 1230, 1202, 1164, 1122, 1058, 1000, 976, 950, 908, 811, 782, 728. ^{1}H NMR ($CDCl_3$, 500 MHz): 5.20 (d, J = 11.00 Hz, 1H), 5.58 (dd, J_1 = 11.00 Hz, J_2 = 1.50 Hz, 1H), 5.89 (d, J = 3.00 Hz, 1H), 6.10 (d, J = 3.00 Hz, 1H), 6.57 (d, J = 3.50 Hz, 1H), 6.75 (s, 1H), 6.97 (d, J = 9.00 Hz, 1H), 7.12 (d, J = 3.50 Hz, 1H), 7.20–7.31 (m, 2H), 7.46 (d, J = 8.50 Hz, 1H), 7.60 (d, J = 9.00 Hz, 1H), 7.63 (d, J = 8.50 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): 53.61, 74.13, 110.14, 112.26, 114.00, 118.77, 122.28, 122.77, 123.01, 124.01, 127.16, 128.65, 129.28, 130.21, 131.52, 139.48, 151.67. MS *m/z* (ESI): 414 (M^+ + 1), 329, 306, 301, 283, 236, 102, 71, 57. Anal. Calc. for $C_{19}H_{13}BrN_2O_2S$: C, 55.22; H, 3.17; N, 6.78. Found: C, 55.20; H, 3.15; N, 6.80.

3. Results and Discussion

Li and Mao reported that the reaction of 2-aminothiazole, 2-naphthol, and benzaldehyde under solvent-free conditions at 120°C gave the desired product in 6 h (Lit. [23]). We decided to perform this reaction under ultrasonic irradiation to get a shorter reaction time, milder reaction conditions, and higher yield.

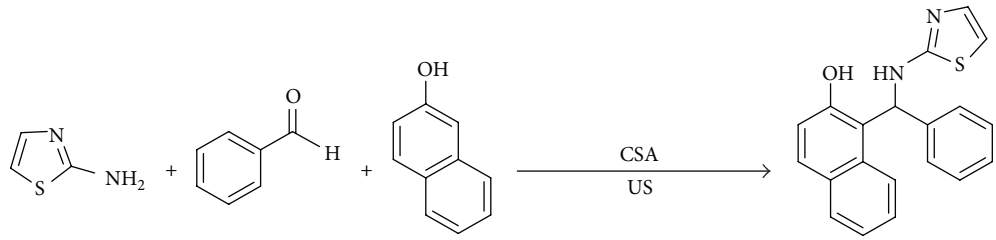
Table 1: Screening of catalysts for the three-component reaction of 2-aminothiazole, benzaldehyde, and 2-naphthol.

Catalyst (mol%)	Solvent	Temperature (°C)	Time (min)	Yield (%)[a]
—	—	25	120	65
—	—	50	120	74
VB1 (10)	—	50	60	66
$Sc(OTf)_3$ (10)	—	50	60	70
$Bi(OTf)_3$ (10)	—	50	60	67
$Yb(OTf)_3$ (10)	—	50	60	73
(+)-CSA (10)	—	50	60	87
—	IL1	50	60	32
—	IL2	50	60	34
—	IL3	50	60	40

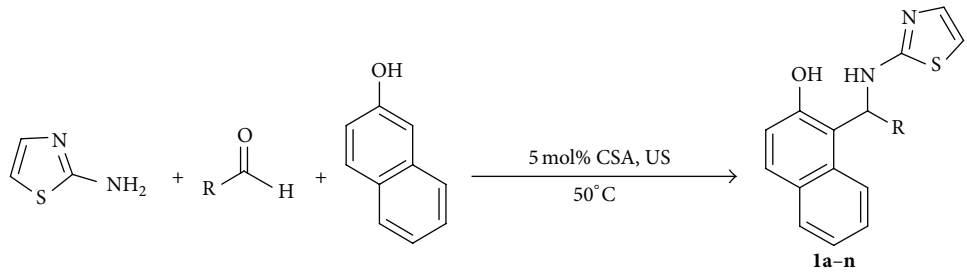
[a]Isolated yield.
IL1: 1-benzyl-3-methylimidazoliumchloride.
IL2: 1-ethyl-2,3-dimethylimidazoliumtetrafluoroborate.
IL3: 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate.

Initially, the three-component Mannich reaction of benzaldehyde (1.00 mmol), 2-naphthol (1.00 mmol), and 2-aminothiazole (1.00 mmol) was examined under ultrasonic irradiation without a catalyst at room temperature (Scheme 1). The reaction was completed in 120 minutes with a yield of 65%. When the temperature was increased from room temperature to 50°C, the yield of product increased. In recent years, the field of greener catalysts such as reusable lanthanide triflates, organocatalysts, biodegradable reagents, and ionic liquids has an increasing importance in synthetic organic chemistry [67–70]. In order to observe the effect of several greener catalysts and ionic liquids such as $Bi(OTf)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, VB1 (thiamine hydrochloride), (+)-CSA (camphor-10-sulfonic acid), 1-benzyl-3-methylimidazoliumchloride (IL1), 1-ethyl-2,3-dimethylimidazoliumtetrafluoroborate (IL2), and 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate (IL3), they were examined under ultrasound irradiation (Table 1) at 50°C. As a result, (+)-CSA was found to be the most effective catalyst at 50°C for this reaction.

Next, in order to observe the effect of the amount of (+)-CSA on the reaction, we also performed the experiments



Scheme 2



1a–n

Scheme 3: (+)-CSA catalyzed one-pot three-component Mannich reaction under US conditions.

Table 2: Optimization of catalyst loading in the Mannich-type reaction of 2-aminothiazole with benzaldehyde and 2-naphthol using (+)-CSA (see Scheme 2).

CSA (mol%)	Temperature (°C)	Time (min)	Yield (%)[a]
10	25	60	81
10	50	30	87
15	50	30	84
20	50	30	79
5	50	30	90

[a]Isolated yield.

Table 3: (+)-CSA catalyzed one-pot three-component Mannich reaction of 2-naphthol with 2-aminothiazole and aromatic aldehydes (see Scheme 3).

Product	R	Time (min)	Yield (%)[a]
1a	Phenyl	30	90
1b	4-Methylphenyl	30	76
1c	4-Bromophenyl	45	70
1d	4-Isopropylphenyl	30	87
1e	2,4-Dimethylphenyl	30	74
1f	2,4-Dichlorophenyl	45	72
1g	2,4-Difluorophenyl	45	75
1h	3-Phenoxyphenyl	30	83
1i	4-Benzyloxyphenyl	30	86
1j	3-Nitrophenyl	30	68
1k	Thiophen-2-yl	30	75
1l	Thiophen-3-yl	30	70
1m	5-Methylfuran-2-yl	30	88
1n	5-Bromofuran-2-yl	30	81

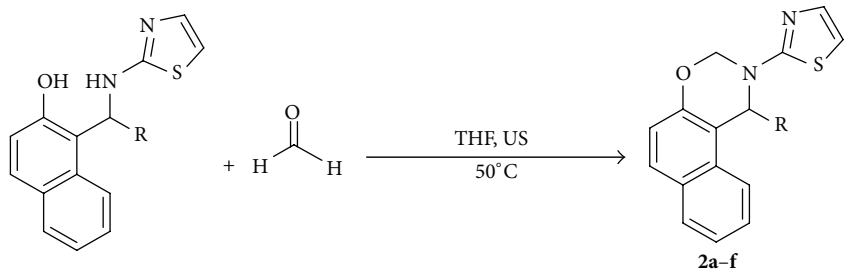
[a]Isolated yield.

using different amounts of catalyst (Table 2 and Scheme 2). The best result was obtained by carrying out the reaction using 5 mol% of (+)-CSA at 50°C under solvent-free conditions (Table 2 and Scheme 2).

With these optimal reaction conditions, we then examined a variety of aromatic and heteroaromatic aldehydes in ultrasound-promoted catalytic Mannich-type reactions. As shown in Table 3 and Scheme 3, the one-pot three-component reactions work well with a variety of aromatic and heteroaromatic aldehydes, and the desired compounds were obtained in good yields. However, the aryl aldehydes which contain electron-withdrawing groups gave the desired products in lower yields. On the other hand, reactions with pyridine-2-carbaldehyde and pyridine-4-carbaldehyde did not give the desired product.

The structures of the newly generated compounds have been confirmed by Fourier transform-infrared (FTIR), mass, and NMR techniques. The characteristic absorption bands of OH and NH bands were observed at 3326–3385 cm^{-1} in the FTIR spectra of the 1-[(1,3-thiazol-2-ylamino)methyl]-2-naphthol derivatives. In the ^1H NMR spectra, NH proton signals were observed at 8.29–9.36 ppm. The CH protons which are next to Ar groups were observed at 5.96–7.01 ppm, and the OH protons appeared in the range 10.08–12.23 ppm. The mass spectra of all new compounds showed the expected molecular ion peak.

1,3-Oxazine derivatives were prepared by the ring-closure reactions of 1-[(1,3-thiazol-2-ylamino)methyl]-2-naphthols **1a**, **1c**, **1d**, **1k**, **1m**, and **1n** with formaldehyde under ultrasound irradiation at 50°C (Table 4 and Scheme 4) in THF solvent.



Scheme 4: Synthesis of naphthoxazines under US conditions.

Table 4: Synthesis of naphthoxazines (**2a–f**) (see Scheme 4).

Product	R	Time (min)	Yield (%)[a]
2a	Phenyl	120	53
2b	4-Bromophenyl	120	36
2c	4-Isopropylphenyl	120	69
2d	Thiophen-2-yl	120	64
2e	5-Methylfuran-2-yl	120	65
2f	5-Bromofuran-2-yl	120	57

[a]Isolated yield.

The ring-closure reaction of **1a** (1.00 mmol) with formaldehyde (1.20 mmol) without a catalyst under conventional conditions at room temperature gave the desired product in 15 h with 40% yield. The best result was obtained by carrying out the reaction at 50°C under ultrasonic irradiation.

In the ^{1}H NMR spectra of 1,3-oxazine derivatives the CH_2 protons which are between N and O atoms appeared in the ranges 4.98–5.37 and 5.51–5.70 ppm. The CH protons which are near the Ar group were observed at 6.75–7.02 ppm.

4. Conclusions

In conclusion, we have described a greener, efficient, and practical method for the synthesis of 1-[(1,3-thiazol-2-ylamino)methyl]-2-naphthols via a three-component one-pot Mannich-type reaction of 2-aminothiazole, aromatic aldehydes, and 2-naphthol using commercially available, less expensive (+)-camphor-(10)-sulfonic acid ((+)-CSA) as a metal-free catalyst under solvent-free ultrasound irradiation. The ring-closure reactions of the 1-[(1,3-thiazol-2-ylamino)methyl]-2-naphthols with formaldehyde gave 1,3-oxazine derivatives in moderate to good yields. The advantages of this synthesis are use of ultrasonic irradiation as energy source, nontoxic and economically viable catalyst, short reaction times, and simplified workup procedure.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

Acknowledgments

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