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Methanesulfonic Acid/SiO_2 as an Efficient Combination for the Synthesis of 2-Substituted Aromatic and Aliphatic Benzothiazoles from Carboxylic Acids

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Abstract: Methanesulfonic acid/SiO_2 (1 mL/0.3 g) was found to be as an expeditious mixture in the synthesis of 2-substituted aromatic and aliphatic benzothiazoles at 140 °C using carboxylic acids. After a simple workup, benzothiazoles were obtained in good yields. Simplicity, use of widely available and diverse carboxylic acids, and easy handling of the reaction conditions are among the benefits of the method.

Keywords: 2-Alkylbenzothiazoles, 2-arylbenzothiazoles, methanesulfonic acid, silica gel

INTRODUCTION

Benzo-fused heterocyclic systems such as benzimidazole, benzoxazole, and benzothiazole derivatives have received special attention in the past few years because of their ever-increasing and undeniable roles in medicinal and organic fields of chemistry. Attempts for expanding synthetic routes to 2-substituted benzothiazoles, especially from the time of introduction of 2-(4-aminophenyl) benzothiazoles as antineoplastic agents in in vitro studies,[1]

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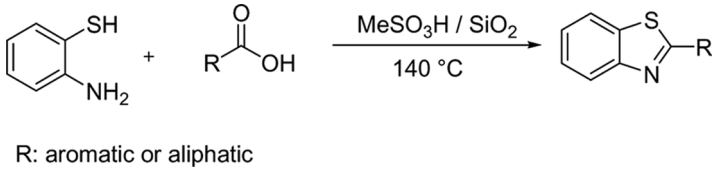
have increased. Ever since, the synthesis of 2-arylbenzothiazole scaffolds has been a greater challenge. In many compounds with antimicrobial,[2] antitumor,[1,3] and antagonistic [like leukotriene D_4 (LTD_4) and orexin receptor antagonists][4,5] activities, the nucleus is shown as a key element.

2-Arylbenzothiazoles are mainly synthesized by the condensation of 2-aminothiophenols with substituted aromatic aldehydes[6] and carboxylic acids or their derivatives in polyphosphoric acid (PPA),[7] polyphosphate ester,[8] or phosphorus pentoxide/methanesulfonic acid (PPMA).[9] Potassium ferricyanide cyclization of thiobenzanilids,[10] ligand-accelerated copper-catalyzed cyclization of *ortho*-halobenzanilides,[11] palladium-catalyzed reaction of aryl halides with 2-aminothiophenol in the presence of carbon monoxide,[12] ceric ammonium nitrate–mediated reaction of thiophenoles and aromatic nitriles,[13] and intramolecular cyclization of thioformanilides using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2 at room temperature[14] are among other reported methods in the literature. Some protocols have been employed for the preparation of 2-arylbenzothiazoles. Nevertheless, most of these methods bear limitations such as (a) high thermal conditions, (b) long reaction times, (c) use of toxic metallic compounds that result in waste streams, (d) cumbersome working procedures, and (e) more than one step in the synthesis process. Thus, establishing new methodologies from two points are important: first, in terms of operational simplicity, economic viability, and reusability, and second, for discovering new application(s) of previously or newly introduced catalytic or noncatalytic reaction conditions. Therefore, ongoing research still continues to expand synthetic routes to the synthesis of this key core.

RESULTS AND DISCUSSION

In continuation of our work to bring in and develop new synthetic methodologies,[15] we report herein a simple, one-pot, easy protocol for the synthesis of 2-substituted benzothiazoles using 2-aminothiophenol and different carboxylic acids in a newly introduced and optimized medium, methanesulfonic acid/silica gel (1 mL/0.3 g), at 140 °C (Scheme 1).



Scheme 1. Introducing the new methanesulfonic acid/silica gel (1 mL/0.3 g) medium in the synthesis of aliphatic and aromatic benzothiazoles from carboxylic acids.

Although neither methanesulfonic acid nor silica gel alone led to the product formation, their combination was efficient for the condensation reaction of 2-aminothiophenol and benzoic acid as a model reaction. The method is simple, isolation of products from the reaction mixture is convenient, and yields are high. The protocol was compatible with both aromatic and aliphatic carboxylic acids as shown in Table 1.

In a typical procedure, 2-aminothiophenol (1 mmol) and a carboxylic acid derivative (1.2 mmol) were mixed in a medium of methanesulfonic acid (1 mL) containing silica gel (0.3 g), and the mixture was kept at 140 °C with stirring for the specified time (Table 1). After workup, the corresponding benzothiazoles were obtained in reasonable yields.

To investigate the general scope of the reaction, we studied the condensation reaction of electronically divergent aromatic and aliphatic carboxylic acids with 2-aminothiophenol. In all cases, the reaction was carried out within 2–12 h. The reaction condition was rather incompatible

Table 1. Condensation reaction of 2-aminothiophnol with different carboxylic acids under optimized reaction conditions, $MeSO_3H/SiO_2$ (1 mL/0.3 g) at 140 °C

Entry	Carboxylic acid	Time (h)	Yields (%)[a]	Melting points		Reference
				Observed	Reported	
1	C_6H_5COOH	2	87	113	112–114	16
2	2-ClC_6H_4COOH	6	81	82	82	17
3	4-$CH_3OC_6H_4COOH$	4	75	122	120–121	16
4	2-HOC_6H_4COOH	4	80	131	127–128	17
5	4-$CH_3C_6H_4COOH$	5	86	85	85	17
6	2-$CH_3C_6H_4COOH$	7	74	54	53–54	17
7	4-HOC_6H_4COOH	3	91	227	227	17
8	3-ClC_6H_4COOH	9	70	95	—	—[c]
9	4-BrC_6H_4COOH	6	83	133	—	—[c]
10	2,6-diFC_6H_3COOH	12	72	73	—	—[c]
11	3-HOC_6H_4COOH	5	86	169	161–163	16
12	$C_6H_5CH_2COOH$	5	89	—[b]	—	—[c]
13	CH_3COOH	4	89	—[b]	—	—[c]
14	CH_3CH_2COOH	2	92	—[b]	—	—[c]
15	$ClCH_2COOH$	2.5	92	—[b]	—	—[c]
16	2-$NO_2C_6H_4COOH$	10	35	138	135–136	17
17	3-$NO_2C_6H_4COOH$	7	11	183	181–12	16
18	4-$NO_2C_6H_4COOH$	10	53	230	230–231	17

[a]Isolated yields.
[b]The products froze solid and then were weighed.
[c]Structural data are cited in the article.

with the nitro containing carboxylic acids as shown in Table 1 (entries 16–18). All products were characterized by infrared (IR), ^{1}H and ^{13}C NMR, and mass spectroscopy. The present method was efficient for both aliphatic and aromatic carboxylic acids possessing either electron-donating or electron-withdrawing substituents.

To sum up, we have developed the novel heterogeneous mixture of methanesulfonic acid and silica gel as an expeditious medium for the condensation reaction of aromatic and aliphatic carboxylic acids with 2-aminothiophenol for the synthesis of 2-substituted benzothiazoles. Yields are high, the process trend is simple, and silica gel is recoverable for the subsequent uses.

EXPERIMENTAL

Instrumentation, Analysis, and Starting Materials

Progress of reactions was monitored by the using silica-gel PolyGrams SILG/UV 254 plates. IR spectra were recorded on the Shimadzu FT-IR 8300 spectra photometer. NMR spectra were recorded on a Bruker DPX 250-MHz instrument, and mass spectra were measured on a Shimadzu GC-MS-QP 1000 EX instrument at 70 or 20 ev. Melting points were determined in open capillary tubes in a Büchi-535 circulating oil melting-point apparatus. Chemical materials were purchased from Fluka, Aldrich, and Merck companies.

General Procedure

For each reaction, 2-aminothiophenol (1 mmol) and a carboxylic acid derivative (1.2 mmol) were blended in a mixture of methanesulfonic acid and silica gel (1 mL/0.3 g) in a Quickfit experimental tube. The tube was heated in an oil bath with a temperature of 140 °C while stirring magnetically. After completion of the reaction, the mixture was cooled, diluted with ethylacetate, and filtered. The filtrate was washed with a 5% sodium bicarbonate solution (3×30 mL) and 30 mL water in the fourth step. The solution was dried over magnesium sulphate; the solvent was evaporated to give the crude product, which was purified by recrystallization or using column chromatography employing n-hexane/ethylacetate (10:1) as eluent.

Unknown compounds or compounds for which incomplete physical data were reported in the literature were characterized by FT-IR, NMR (^{1}H, ^{13}C), mass, and elemental analysis.

Data

2-(3-Chlorophenyl)-1,3-benzothiazole (**8**)

White crystals, mp 95 °C. IR (KBr): 3049 (w), 1562 (w), 1494 (m), 1425 (s), 1234 (m), 762 (s), 729 (s), 675 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ (ppm) 7.18–7.38 (m, 4H), 7.73 (t, 2H, $J = 8.65$ Hz), 7.92–7.95 (m, 2H). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ (ppm) 121.7, 123.4, 125.5, 126.1, 126.5, 127.3, 128.6, 129.2, 130.2, 130.8, 135.1, 153.9, 166.2. Mass (m/z) (%): 247 ($M^+ + 2$, 38.0), 245 (M^+, 100), 210 (17.5), 108 (56.4). Anal. calcd. for $C_{13}H_8ClNS$: C, 63.54; H, 3.28. Found: C, 64.01; H, 3.09.

2-(4-Bromophenyl)-1,3-benzothiazole (**9**)

White crystals, mp: 133 °C. IR (KBr): 1049 (w), 1467 (m), 1427 (m), 1390 (m), 1063 (m), 962 (s), 827 (s), 752 (s). 715 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ (ppm) 7.21–7.45 (m, 4H), 7.63–7.78 (m, 3H), 7.81 (d, 1H, $J = 8.1$ Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ (ppm) 121.6, 123.3, 123.7, 125.4, 126.3, 128.8, 132.2, 132.4, 135.0, 154.0, 166.6. Mass (m/z) (%): 292 ($M^+ + 2$, 31.7), 290 (M^+, 47.3), 211 (15.4). Anal. calcd. for $C_{13}H_8BrNS$: C, 53.81; H, 2.78. Found: C, 53.68; H, 2.84.

2-(2,6-Difluorophenyl)-1,3-benzothiazole (**10**)

White crystals, mp 73 °C. IR (KBr): 3067 (w), 1618 (m), 1581 (m), 1466 (s), 1240 (m), 1009 (s), 957 (s), 762 (s), 723 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ (ppm) 7.03–7.12 (m, 2H), 7.37–7.57 (m, 3H), 7.96 (d, 1H, $J = 8.1$ Hz), 8.19 (d, 1H, $J = 7.89$ Hz) (ppm). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ (ppm) 112.2, 121.3, 123.8, 125.7, 126.3, 131.8, 135.6, 153.0, 158.4, 162.5. Mass (m/z) (%): 247 (M^+, 8.7), 169 (5.2). Anal. calcd. for $C_{13}H_7F_2NS$: C, 63.15; H, 2.85. Found: C, 63.35; H, 2.83.

2-Benzyl-1,3-benzothiazole (**12**)

Pale yellow liquid. IR (neat): 3059 (w), 3030 (w), 2912 (w), 1504 (m), 1427 (m), 1113 (m), 756 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz): δ (ppm) 4.18 (s, 2H), 7.02–7.22 (m, 7H), 7.49 (d, 1H, $J = 7.91$ Hz), 7.82 (d, 1H, $J = 8.1$ Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ (ppm) 40.6, 121.6, 122.8, 124.9, 126.0, 127.6, 128.9, 129.0, 135.7, 137.3, 153.4, 171.1. Mass (m/z) (%): 225 (M^+, 65.7), 91 (31.1). Anal. calcd. for $C_{14}H_{11}NS$: C, 74.63; H, 4.92. Found: C, 75.05; H, 4.69.

2-Methyl-1,3-benzothiazole (**13**)

Pale yellowish liquid. IR (neat): 3059 (w), 2980 (w), 2921 (w), 1527 (m), 1440 (m), 1238 (m), 756 (m) cm $^{-1}$. ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) 2.63 (S, 3H), 7.2 (t, 1H, $J_1 = 7.1$, $J_2 = 1.14$ Hz), 7.26 (t, 1H, $J_1 = 7.1$, $J_2 = 1.18$ Hz), 7.81 (d, 1H, $J = 8.0$ Hz), 7.66 (d, 1H, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ (ppm) 18.9, 120.2, 121.2, 123.6, 124.8, 134.5, 152.2, 165.7. Mass (m/z) (%): 149 (M^+, 14.3), 135 (6.3), 73 (46.3). Anal. calcd. for C_8H_7NS: C, 64.40; H, 4.73. Found: C, 64.12; H, 4.58.

2-Ethyl-1,3-benzothiazole (**14**)

Pale yellowish liquid, IR (neat): 3059 (w), 2970 (w), 2931 (w), 1518 (m), 1431 (m), 1122 (m), 945 (m), 756 (m) cm $^{-1}$. ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) 1.17 (t, 3H, $J_1 = 7.56$, $J_2 = 2.25$ Hz), 2.85 (q, 2H, $J_1 = 7.53$, $J_2 = 2.30$ Hz), 6.99–7.18 (m, 2H), 7.53 (d, 1H, $J = 7.95$ Hz), 7.72 (d, 1H, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ (ppm) 13.7, 27.7, 121.4, 122.4, 124.6, 125.8, 135.0, 153.2, 173.4. Mass (m/z) (%): 163 (M^+, 60.6), 148 (13.8), 134 (3.2), 108 (9.6). Anal. calcd. for C_9H_9NS: C, 66.22; H, 5.56. Found: C, 66.18; H, 5.55.

2-(Chloromethyl)-1,3-benzothiazole (**15**)

Pale yellowish liquid. IR (neat): 3068 (w), 2999 (w), 2941 (w), 1514 (m), 1431 (m), 1263 (m), 1113 (m), 760 (s), 727 (m) cm $^{-1}$. ^{1}H NMR ($CDCl_3$, 250 MHz): δ (ppm) 4.88 (s, 2H), 7.30–7.46 (m, 2H), 7.79 (d, 1H, $J = 7.92$ Hz), 7.98 (d, 1H, $J = 8.0$ Hz). ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ (ppm) 42.1, 121.7, 123.4, 125.4, 127.8, 135.8, 152.8, 166.7. Mass (m/z) (%): 183 (M^+, 49), 148 (100), 108 (31.6). Anal. calcd. for C_8H_6ClNS: C, 52.32; H, 3.29. Found: C, 52.30; H, 3.36.

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