A Novel and Facile One-Pot Synthesis of 3-Aryl-4*H*-benzo[1,4]thiazin-2-amine

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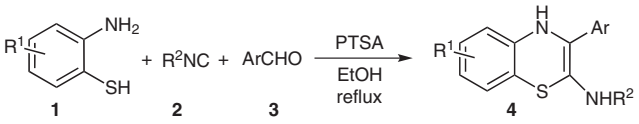
Abstract: A high-yielding and fast method for the synthesis of 3-aryl-4*H*-benzo[1,4]thiazin-2-amine via one-pot, three-component reaction of an aromatic aldehyde, isocyanide, and *o*-amino thiophenol using PTSA as a catalyst is described.

Key words: one-pot synthesis, 3-aryl-4*H*-benzo[1,4]thiazin-2-amine, catalyst

Benzofused heterocycles containing a sulfur moiety possess many biological activities across wide therapeutic fields, including vasodilator,[1] antidiabetic,[2] anticataract,[3] and antiarrhythmic activities.[4] Benzothiazines have been reported as calcium channel blockers,[5] phosphodiesterase inhibitors,[6] 5-HT3 antagonists,[7] anticataract agents,[8] dopamine D_4,[9] Na^+/H^+ exchange inhibitors,[10] coagulation factor Xa inhibitors,[11] and matrix metalloproteinase inhibitors.[12] Therefore, a wide range of studies for the synthetic development of benzothiazine derivatives has been carried out.[13–15] In recent years, multicomponent reactions (MCR) have become important tools in modern preparative synthetic chemistry because these reactions increase the efficiency by combining several operational steps without any isolation of intermediates or change of the conditions[16,17] and MCR have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of druglike heterocyclic compounds.[18–20] In 1921, Passerini[21] pioneered the use of isocyanides and successfully developed a three-component synthesis of α-acyloxycarboxamides by reaction of a carboxylic acid, an aldehyde, and an isonitrile.[22] However, the most important breakthrough came in 1959 when Ugi described a four-component synthesis of α-acylamino amides from an aldehyde, an amine, an acid, and an isocyanide.[23,24] This reaction, named after Ugi (Ugi 4CR or U-4CR) has become a widely investigated transformation during the past decade, in conjunction with technologies such as high-throughput screening and combinatorial chemistry.[25–27]

As part of our program aimed at developing new methods for the preparation of new compounds,[28] we would like to report one-pot synthesis of 3-aryl-4*H*-benzo[1,4]thiazin-2-amines via a three-component reaction of an aromatic aldehyde, an isocyanide, and an *ortho*-amino thiophenol using PTSA as a catalyst (Scheme 1).

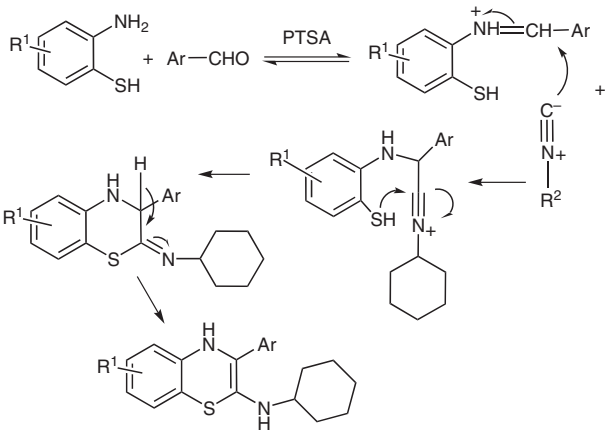


Scheme 1

In a typical procedure, benzaldehyde (1 mmol), malonitrile (1 mmol), and *o*-aminothiophenol (1 mmol) in the presence of a catalytic amount of PTSA in ethanol at reflux afforded the desired 3-phenyl-4*H*-benzo[1,4]thiazin-2-amine (**4a**) in 88% yield (entry 1, Table 1). The reaction then was applied to a variety of aromatic aldehydes with good yields (as shown in Table 1). To the best of our knowledge there are no reports in the literature for the synthesis of these compounds.

All aromatic aldehydes containing electron-withdrawing or electron-donating groups reacted well to give the corresponding products **4** in good to excellent yields under these reaction conditions. We also found that the reaction did not proceed in the cases when aliphatic aldehydes were used. In order to show the generality and scope of this new protocol, we used various *o*-aminothiophenols and isocyanides in the presence of PTSA, and the results obtained are summarized in Table 1.

A plausible mechanism for this reaction is suggested in Scheme 2. The first step, similar to the Ugi reaction, involves reaction of the aromatic aldehyde with the *o*-aminothiophenol followed by isocyanide attack on the resulting intermediate followed by intramolecular trapping by the sulfur nucleophile[29] to give the desired product.



Scheme 2

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Table 1 Synthesis of *N*-Cyclohexyl-3-aryl-4*H*-benzo[1,4]thiazin-2-amines Using Various Aldehydes

Entry	R^1	R^2	Ar	Product	Yield (%)[a]
1	H	*c*-Hex	Ph	**4a**	88
2	H	*c*-Hex	4-ClC_6H_4	**4b**	90
3	H	*c*-Hex	3-$O_2NC_6H_4$	**4c**	89
4	H	*c*-Hex	4-$O_2NC_6H_4$	**4d**	90
5	H	*c*-Hex	4-MeC_6H_4	**4e**	88
6	H	*c*-Hex	4-$MeOC_6H_4$	**4f**	88
7	H	*c*-Hex	4-HOC_6H_4	**4g**	87
8	H	*t*-Bu	Ph	**4h**	89
9	H	*t*-Bu	4-$MeOC_6H_4$	**4i**	88
10	H	*t*-Bu	4-$O_2NC_6H_4$	**4j**	91
11	Me	*c*-Hex	Ph	**4k**	89
12	Cl	*c*-Hex	Ph	**4l**	86

[a] Yields refer to isolated products.

In conclusion, we have described a highly efficient procedure for the preparation of 3-aryl-4*H*-benzo[1,4]thiazin-2-amines by a three-component condensation using PTSA as a catalyst, furnishing the products in good yield without further purification in moderate to good yields.

All products were characterized by mp, IR, ^{1}H NMR, and GC-MS. Melting points were measured by using the capillary tube method with an electrothermal 9200 apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX Avance spectrometer at 500 MHz and 125 MHz, respectively, with $CDCl_3$ as solvent. IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC-MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network mass selective detector. Thin-layer chromatography on commercial aluminum-backed plates of silica gel 60 F_{254} was used to monitor the progress of reactions.

N-Cyclohexyl-3-aryl-4*H*-benzo[1,4]thiazin-2-amines; Typical Procedure

A mixture of the aromatic aldehyde 1 (1 mmol), *o*-aminothiophenol (1 mmol), cyclohexyl isocyanide (1 mmol), and PTSA (0.05 g) in EtOH (5 mL) was refluxed for 5 h and then cooled to r.t. The product was precipitated by addition of 10 mL of H_2O. The precipitate was filtered off and washed with H_2O. The residue was crystallized from EtOH to give the pure product.

N-Cyclohexyl-3-phenyl-4*H*-benzo[1,4]thiazin-2-amine (4a)

Mp 192 °C. IR (KBr): ν_{max} = 3167, 3153 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10–2.10 (m, 10H), 3.56 (m, 1H), 4.32 (s, 1H, NH), 4.65 (s, 1H, NH), 7.42-7.94 (m, 9H, arom.) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.21, 24.67 (2 CH_2), 28.82 (2 CH_2), 47.76, 121.11 (2 CH), 123.33, 123.98, 124.78, 126.95 (2 CH), 127.76, 130.07, 131.12, 136.11, 137.97, 138.81, 140.32 ppm. GC-MS: *m/z* = 322 [M$^+$]. Anal. Calcd (%) for $C_{20}H_{22}N_2S$: C, 74.49; H, 6.88; N, 8.69. Found: C, 73.98; H, 6.35; N, 8.55.

N-Cyclohexyl-3-(4-chlorophenyl)-4*H*-benzo[1,4]thiazin-2-amine (4b)

Mp 202 °C. IR (KBr): ν_{max} = 3185, 3165 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22–2.23 (m, 10 H), 3.42 (m, 1 H), 4.35 (s, 1 H, NH), 4.66 (s, 1 H, NH), 7.44–8.26 (m, 8 H, arom.) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.35, 26.45 (2 CH_2), 33.61 (2 CH_2), 49.18, 121.84 (2 CH), 123.55, 124.13 (2 CH), 127.19, 129.67, 130.39, 131.51, 138.47, 140.26, 142.37, 147.87, 149.99 (CCl) ppm. GC-MS: *m/z* = 356 [M$^+$]. Anal. Calcd (%) for $C_{20}H_{21}N_2SCl$: C, 67.30; H, 5.93; N, 7.85. Found: C, 67.11; H, 5.63; N, 7.91.

N-Cyclohexyl-3-(4-nitrophenyl)-4*H*-benzo[1,4]thiazin-2-amine (4d)

Mp 207 °C. IR (KBr): ν_{max} = 3178, 3150 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16–2.38 (m, 10 H), 3.55 (m, 1 H), 4.39 (s, 1 H, NH), 4.71 (s, 1 H, NH), 7.42–8.39 (m, 8 H, arom.) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.42, 24.33 (2 CH_2), 26.21 (2 CH_2), 48.68, 121.99 (2 CH), 123.72, 125.34 (2 CH), 126.27, 128.08, 131.33, 137.42, 139.57, 141.64, 142.18, 146.97, 150.22 (CNO_2) ppm. GC-MS: *m/z* = 367 [M$^+$]. Anal. Calcd (%) for $C_{20}H_{21}N_3SO_2$: C, 65.37; H, 5.76; N, 11.43. Found: C, 65.22; H, 5.77; N, 11.33.

N-Cyclohexyl-3-(4-methylphenyl)-4*H*-benzo[1,4]thiazin-2-amine (4e)

Mp 205 °C. IR (KBr): ν_{max} = 3169, 3157 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16–2.28 (m, 10 H), 2.44 (s, 3 H), 3.63 (m, 1 H), 4.43 (s, 1 H, NH), 4.72 (s, 1 H, NH), 7.29–8.06 (m, 8 H, arom.) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.13, 24.18 (2 CH_2), 27.17 (2 CH_2), 40.84, 53.51, 124.67 (2 CH), 122.56, 125.40 (2 CH), 127.17, 128.74, 129.25, 137.17, 138.56, 140.69, 141.09, 143.91, 149.93 ppm. GC-MS: *m/z* = 336 [M$^+$]. Anal. Calcd (%) for $C_{21}H_{24}N_2S$: C, 74.96; H, 7.19; N, 8.32. Found: C, 79.84; H, 7.20; N, 8.21.

N-Cyclohexyl-3-(4-hydroxyphenyl)-4*H*-benzo[1,4]thiazin-2-amine (4g)

Mp 188 °C. IR (KBr): ν_{max} = 3163, 3147 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18–2.23 (m, 10 H), 3.36 (m, 1 H), 4.22 (s, 1 H, NH), 4.62 (s, 1 H, NH), 4.93 (s, 1 H, OH), 7.34–8.09 (m, 8 H, arom.) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.43, 24.88 (2 CH_2), 26.72 (2 CH_2), 52.19, 121.13 (2 CH), 123.31, 124.32 (2 CH), 125.29, 130.96, 131.46, 133.51, 137.16, 139.17, 143.01, 148.82, 149.23 ppm. GC-MS: *m/z* = 338 [M$^+$]. Anal. Calcd (%) for $C_{20}H_{22}N_2SO$: C, 70.97; H, 6.56; N, 8.28. Found: C, 70.81; H, 6.35; N, 8.11.

N-*tert*-Butyl-3-phenyl-4*H*-benzo[1,4]thiazin-2-amine (4h)

Mp 232 °C. IR (KBr): ν_{max} = 3158, 3143 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 9 H), 4.14 (s, 1 H, NH), 4.68 (s, 1 H, NH), 7.28–7.99 (m, 9 H, arom.) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.36 (3 CH_3), 40.49, 122.55 (2 CH), 124.64, 124.87, 125.46, 126.86 (2 CH), 128.77, 131.74, 132.89, 136.88, 137.62, 138.93, 141.54 ppm. GC-MS: *m/z* = 296 [M$^+$]. Anal. Calcd (%) for $C_{18}H_{20}N_2S$: C, 72.93; H, 6.80; N, 9.45. Found: C, 72.88; H, 6.62; N, 9.34.

N-Cyclohexyl-6-methyl-3-phenyl-4*H*-benzo[1,4]thiazin-2-amine (4k)

Mp 241 °C. IR (KBr): ν_{max} = 3166, 3158 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.14–2.26 (m, 10 H), 3.09 (s, 3 H), 3.64 (m, 1 H), 4.66 (s, 1 H, NH), 4.98 (s, 1 H, NH), 7.29–7.93 (m, 8 H, arom.) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.11, 24.43 (2 CH_2), 28.88 (2 CH_2), 30.98, 47.98, 121.99 (2 CH), 124.44, 124.76, 125.33, 126.88 (2 CH), 127.19, 130.87, 131.49, 136.55, 137.90, 138.49, 140.98 ppm. GC-MS: *m/z* = 336 [M$^+$]. Anal. Calcd (%) for $C_{21}H_{24}N_2S$: C, 74.96; H, 7.19; N, 8.32. Found: C, 74.85; H, 7.09; N, 8.21.

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