CONVENIENT ONE-POT SYNTHESIS OF 5-(SUBSTITUTED AMINO)-1,2,3,4-THIATRIAZOLES

Alan R. KATRITZKY[1,*], Geeta MEHER[2] and Tamari NARINDOSHVILI[3]

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200, U.S.A.; e-mail: [1] katritzky@chem.ufl.edu, [2] gmeher@ufl.edu, [3] memindia@yahoo.ca

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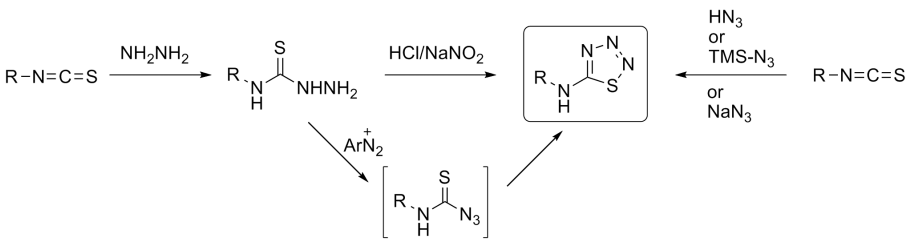
This manuscript is submitted to honor Alfred Bader for his many services to chemistry and to humanity.

5-(Substituted amino)-1,2,3,4-thiatriazoles **15a**–**15i** were conveniently synthesized in 73–97% yields in a one-pot procedure from bis(1*H*-benzotriazol-1-yl)methanethione and amines.

Keywords: Sulfur heterocycles; Benzotriazoles; Aminothiatriazoles; One-pot synthesis; Bis(1*H*-benzotriazol-1-yl)methanethione.

Aminothiatriazoles[1] have diverse potential medical applications including antihypertensive[2], antibacterial[3], antitubercular[4], antiviral[5], fungicidal[6], anticancer[7], and central nervous system stimulant activity[8]. The Freund (1896) synthesis of aminothiatriazoles by reacting thiosemicarbazides with nitrous acid[9] has found wide application[1c,3,10]; a related aza transfer procedure with diazonium salts has also been reported (Scheme 1)[11]. Later synthetic routes involve reaction of hydrazoic acid[12], trimethylsilyl azide[13], or



SCHEME 1
Literature methods for synthesis of 5-(substituted amino)-1,2,3,4-thiatriazoles

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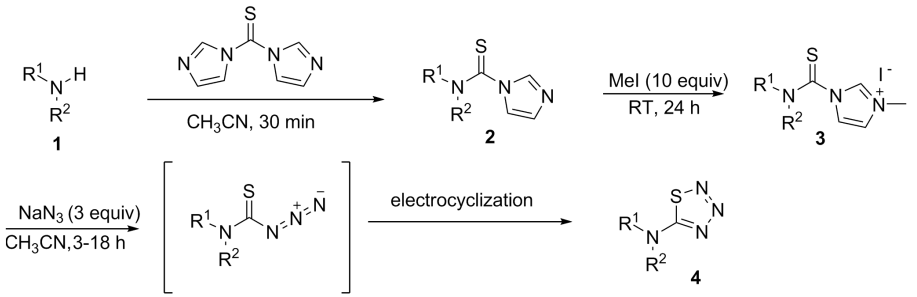
sodium azide[14], with isothiocyanates that proceed through 1,3-dipolar cycloadditions and electrocyclizations (Scheme 1)[15]. However, all these methods suffer from low yields (47–62%) and/or utilize hazardous reagents (isothiocyanates, hydrazine and HCl).

Recently Batey et al. reacted thiocarbamoylimidazolium salts **3** with azide followed by electrocyclization, to give aminothiatriazoles **4** in 50–96% yield (Scheme 2)[16].



SCHEME 2
Literature method for synthesis of 5-(substituted amino)-1,2,3,4-thiatriazoles

In earlier work from our group, 1,1′-carbonylbisbenzotriazole (**5**)[17], di(1*H*-benzotriazol-1-yl)methanimine (**6**)[18], and bis(1*H*-benzotriazole-1-yl)-methanethione (**7**)[19] (Fig. 1) have provided convenient syntheses of substituted ureas from **5** [17], of di- and trisubstituted thioureas from **7** [20], of tri- and tetrasubstituted guanidines from **6** [18], and of 1,2,3-trisubstituted guanidines from **7** [21]. Batey and coworkers have synthesized ureas[22], and thioureas[23] from the corresponding imidazoyl reagents **8**, **10** (Fig. 1) but in each case an extra step of conversion in situ into quaternary derivatives **11** and **3** is involved and the yields reported are comparable to those obtained

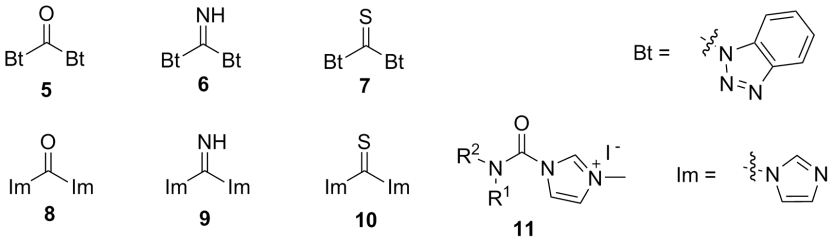


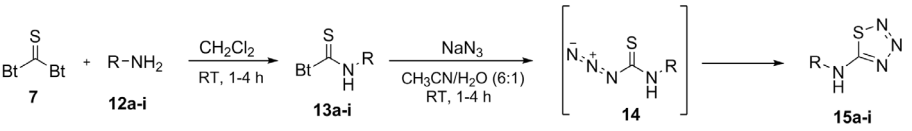
FIG. 1
Structure of bis(1*H*-benzotriazol-1-yl) and diimidazol-1-yl reagents

from **5** and **7** in one less step. However, for the synthesis of substituted guanidines comparable yields in the same number of steps are reported for reagents **6** [18] and **9** [24].

In ongoing research on the utility of bisbenzotriazole functionalized-reagents we now report a one-pot synthesis of 5-(substituted amino)-1,2,3,4-thiatriazoles **15** from **7** (Scheme 4).

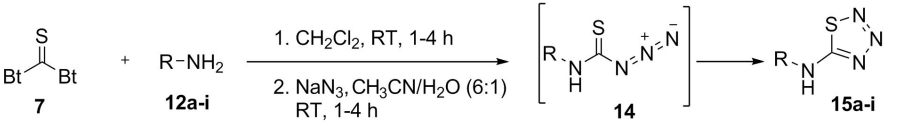
RESULTS AND DISCUSSION

Benzotriazolecarbothioamides **13a**–**13i** are easily prepared[20,21] from bis(1*H*-benzotriazol-1-yl)methanethione (**7**) and primary amines **12a**–**12i** in anhydrous CH_2Cl_2 at 20 °C for 1–4 h (Scheme 3). Subsequent treatment of **13a**–**13i** with NaN_3 in aqueous CH_3CN at room temperature yielded 5-(substituted amino)-1,2,3,4-thiatriazoles **15a**–**15i** in overall yields of 63–94%.



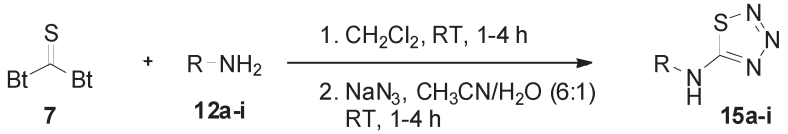
SCHEME 3
Two-step synthesis of 5-(substituted amino)-1,2,3,4-thiatriazoles from bis(1*H*-benzotriazol-1-yl)methanethione (**7**)

Success of this two-step reaction scheme led us to try a one-pot synthesis of **15a**–**15i**, since the by-product in both steps is 1*H*-benzotriazole. In the one-pot reactions, after completion of the first step, CH_2Cl_2 was removed under reduced pressure and the residue (a crude mixture of **13** and by-product, 1*H*-benzotriazole), was treated with NaN_3 in aqueous CH_3CN solution for 1–4 h to obtain 5-(substituted amino)-1,2,3,4-thiatriazoles **15a**–**15i** in yields of 73–97% (Scheme 4, Table I).



SCHEME 4
One-pot synthesis of 5-(substituted amino)-1,2,3,4-thiatriazoles from bis(1*H*-benzotriazol-1-yl)methanethione (**7**)

TABLE I
One-pot synthesis of 5-(substituted amino)-1,2,3,4-thiatriazoles **15a**–**15i**



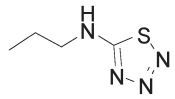
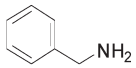
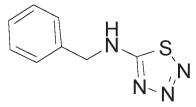
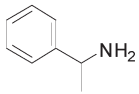
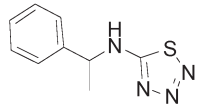
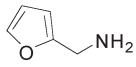
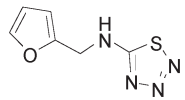
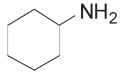
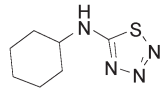
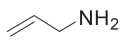
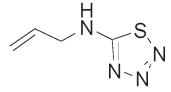
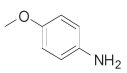
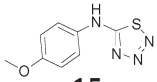
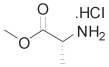
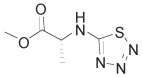
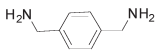
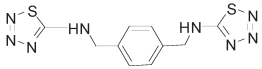
Entry	Amine	Product	Time h	Yield %[a]	Yield %[b]	Yield (lit.)
1	 **12a**	 **15a**	7	92	88	65
2	 **12b**	 **15b**	5	96	94	77
3	 **12c**	 **15c**	5	97	78	–
4	 **12d**	 **15d**	3	93	83	–
5	 **12e**	 **15e**	5	93	87	84
6	 **12f**	 **15f**	5	85	73	62

TABLE I
(*Continued*)

Entry	Amine	Product	Time h	Yield %[a]	Yield %[b]	Yield (lit.)
7	 **12g**	 **15g**	4	81	63	81
8	 **12h**	 **15h**	7	74	65	–
9	 **12i**	 **15i**	8	73	–	–

[a] Isolated yields after one-pot reaction. [b] Isolated overall yields after two-step reaction scheme. [c] Literature references for known compounds are indicated in Experimental.

1*H*-Benzotriazole, the only by-product of the conversion, was removed by simply washing the organic layer with saturated aqueous Na_2CO_3. All products **15a**–**15i** were isolated after one-pot reaction without chromatographic purification. In case of **15h**, the first step of coupling **7** with methyl D-alaninate hydrochloride (**12h**) was achieved in CH_3CN/H_2O instead of CH_2Cl_2. After completion of first step, NaN_3 dissolved in H_2O was directly added to the reaction mixture, without evaporation of CH_3CN. In the case of **15i**, after evaporating the reaction mixture, EtOAc was added as usual for work-up. Since the product was insoluble, it was directly filtered off to give **15i** in pure form.

This represents a general method for the synthesis of 5-(monosubstituted amino)-1,2,3,4-thiatriazoles since a variety of substrates such as aliphatic, aromatic and allylic amines and α-amino acid esters may be utilized (Table I). Amines **12a**–**12e** undergo one-pot reaction to the corresponding aminothiatriazoles **15a**–**15e** in excellent yields (92–97%). Similarly, the allylamine **12f** has been used to prepare **15f** in 85% yield. Interestingly, aromatic amine **12g** can also be converted to the corresponding aminothiatriazole **15g** in 65% yield. In the case of amino acid, methyl D-alaninate hydrochloride (**12h**) gave the product **15h** in 74% yield. The bis(aminothiatriazole) **15i** was also prepared in 73% yield from **12i**. Yields obtained from one-pot procedure were higher than in two-step reaction scheme.

CONCLUSION

In conclusion, a novel and convenient one-pot synthetic route to 5-(monosubstituted amino)-1,2,3,4-thiatriazoles has been developed without the necessity of column purification.

EXPERIMENTAL

Melting points were determined on a capillary point apparatus equipped with a digital thermometer. NMR spectra (δ, ppm; *J*, Hz) were recorded in $CDCl_3$ with TMS for ^1H (300 MHz) and ^{13}C (75 MHz) as the internal reference. All the amines were purchased from Fluka or Aldrich and were used without any further purification. Elemental analysis was preformed on CarloErba-1106 instrument.

One-Pot Procedure for Synthesis of 5-(Substituted amino)-1,2,3,4-thiatriazoles **15a**–**15g**. General Procedure

In the first step, bis(1*H*-benzotriazol-1-yl)methanethione (**7**; 0.280 g, 1 mmol) was added to corresponding amine **12a**–**12g** (1 mmol) dissolved in CH_2Cl_2 (5 ml). The reaction mixture was stirred for 1–3 h at room temperature. Progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was evaporated to remove CH_2Cl_2 and the residue was used in next step. Sodium azide (0.162 g, 2.5 mmol) dissolved in CH_3CN/H_2O (12 ml/2 ml) was added to the mixture of crude product and benzotriazole from step 1. The reaction mixture was stirred at room temperature for 1–4 h. When TLC (15% EtOAc/hexane) indicated complete reaction, CH_3CN was evaporated under vacuum and EtOAc (100 ml) was added. The solution was washed with saturated aqueous Na_2CO_3 (3 × 50 ml) followed by brine (50 ml) and dried over anhydrous Na_2SO_4. Evaporation under vacuum yielded the corresponding 5-(monosubstituted amino)-1,2,3,4-thiatriazoles which were recrystallized from CH_2Cl_2/hexanes.

N-Propyl-1,2,3,4-thiatriazol-5-amine (**15a**). Colorless microcrystals, 0.132 g (92%), m.p. 59–60 °C (lit.[10e] gives m.p. 58–59 °C). ^1H NMR: 1.05 t, 3 H, ^3J = 7.4 (CH_3); 1.80 sextet, 2 H, ^3J = 7.3 (CH_2); 3.27–3.42 m, 2 H (NHC**H**$_2$); 7.18 brs, 1 H (NH). ^{13}C NMR: 11.3, 22.0, 52.0, 179.6.

N-Benzyl-1,2,3,4-thiatriazol-5-amine (**15b**). Colorless microcrystals, 0.170 g (96%), m.p. 78–80 °C (lit.[11] gives m.p. 78–80 °C). ^1H NMR: 4.60 d, 2 H, ^3J = 5.4 (CH_2); 7.30–7.45 m, 6 H (Ar-H, NH). ^{13}C NMR: 52.5, 127.9, 128.5, 129.0, 134.7, 179.1. For $C_8H_8N_4S$ calculated: 49.98% C, 4.19% H, 29.14% N; found: 50.18% C, 4.13% H, 29.00% N.

N-(1-Phenylethyl)-1,2,3,4-thiatriazol-5-amine (**15c**). Colorless microcrystals, 0.186 g (97%), m.p. 120–121 °C. ^1H NMR: 1.79 d, 3 H, ^3J = 6.9 (CH_3); 4.45 quintet, 1 H, ^3J = 6.5 (CH); 7.28–7.46 m, 5 H (Ar-H); 8.32–8.74 m, 1 H (NH). ^{13}C NMR: 23.8, 59.7, 126.7, 128.5, 129.1, 140.0, 178.5. For $C_9H_{10}N_4S$ calculated: 52.41% C, 4.89% H, 27.16% N; found: 52.35% C, 4.86% H, 26.91% N.

N-(Furan-2-ylmethyl)-1,2,3,4-thiatriazol-5-amine (**15d**). Colorless microcrystals, 0.170 g (93%), m.p. 68–69 °C. ^1H NMR: 4.59 d, 2 H, ^3J = 4.4 (CH_2); 6.25–6.40 m, 1 H (Ar-H); 6.42 d, 1 H, *J* = 2.6 (Ar-H); 7.25–7.45 m, 1 H (Ar-H); 7.80–8.00 m, 1 H (NH). ^{13}C NMR: 44.8, 109.9, 110.5, 143.3, 148.0, 178.5. For $C_6H_6N_4OS$ calculated: 39.55% C, 3.32% H, 30.75% N; found: 39.69% C, 3.12% H, 30.48% N.

N-Cyclohexyl-1,2,3,4-thiatriazol-5-amine (**15e**). Colorless microcrystals, 0.171 g (93%), m.p. 118 °C (lit.[11] gives m.p. 113–115 °C). ^{1}H NMR: 1.20–1.72 m, 6 H (3 CH_2); 1.74–1.92 m, 2 H (CH_2); 2.04–2.20 m, 2 H (CH_2); 3.12–3.30 m, 1 H (CH); 6.88–7.30 m, 1 H (NH). ^{13}C NMR: 24.4, 25.1, 31.9, 59.8, 178.9. For $C_7H_{12}N_4S$ calculated: 45.63% C, 6.56% H, 30.41% N; found: 45.99% C, 6.41% H, 30.54% N.

N-Allyl-1,2,3,4-thiatriazol-5-amine (**15f**). Colorless microcrystals, 0.120 g (85%), m.p. 62–64 °C (lit.[10c] gives m.p. 53–53.5 °C). ^{1}H NMR: 4.03 t, 2 H, ^3J = 5.7 (CH_2); 5.31–5.45 m, 2 H (CH_2); 5.82–5.98 m, 1 H (CH); 7.10–7.40 m, 1 H (NH). ^{13}C NMR: 51.3, 119.5, 130.8, 179.2.

N-(4-Methoxyphenyl)-1,2,3,4-thiatriazol-5-amine (**15g**). Colorless microcrystals, 0.168 g (81%), m.p. 142 °C (lit.[3] gives m.p. 140 °C). ^{1}H NMR: 3.85 s, 3 H (CH_3); 7.01 dd, 2 H, J = 8.9, 2.1 (Ar-H); 7.23–7.40 m, 2 H (Ar-H); 10.31 br s, 1 H (NH). ^{13}C NMR: 55.6, 115.3, 120.7, 132.8, 157.5, 176.5.

One-Pot Procedure for Synthesis of 5-(Substituted amino)-1,2,3,4-thiatriazole **15h**

Bis(1*H*-benzotriazol-1-yl)methanethione (**7**; 0.280 g, 1 mmol) was added to a solution of methyl D-alaninate hydrochloride (**12h**; 0.140 g, 1 mmol) in CH_3CN/H_2O (6 ml/1 ml) in presence of Et_3N (1.1 mmol). The reaction mixture was stirred at room temperature for 4 h. Progress of the reaction was monitored by TLC. After completion of the reaction, a solution of sodium azide (2.5 mmol) in H_2O (2 ml) was added directly to reaction mixture. The reaction mixture was stirred at room temperature for 3 h. When TLC (15% EtOAc/hexane) indicated complete reaction, CH_3CN was evaporated under vacuum and EtOAc (100 ml) was added. The solution was washed with saturated Na_2CO_3 (3 × 50 ml) followed by brine (50 ml) and dried over anhydrous Na_2SO_4. Evaporation under vacuum yielded the corresponding aminothiatriazole **15h** which was recrystallized from $CHCl_3$/hexanes.

Methyl N-(1,2,3,4-thiatriazol-5-yl)-D-alaninate (**15h**). Colorless microcrystals, 0.140 g (74%), m.p. 88–91 °C, $[\alpha]_D^{23}$ –3.31 (*c* 1.0, $CHCl_3$). ^{1}H NMR: 1.65 d, 3 H, J = 7.1 (CH_3); 3.83 s, 3 H (OCH_3); 4.22–4.62 m, 1 H (CH); 7.32 s, 1 H (NH). ^{13}C NMR: 17.8, 53.0, 55.3, 172.6, 176.7. For $C_5H_8N_4O_2S$ calculated: 31.91% C, 4.28% H, 29.77% N; found: 32.32% C, 4.14% H, 29.39% N.

One-Pot Procedure for Synthesis of 5-(Substituted amino)-1,2,3,4-thiatriazole **15i**

In the first step, bis(1*H*-benzotriazol-1-yl)methanethione (**7**; 0.560 g, 2 mmol) was added to corresponding amine **12i** (0.136 g, 1 mmol) dissolved in CH_2Cl_2 (35 ml). The reaction mixture was stirred at room temperature for 3 h. Progress of the reaction was monitored by TLC (20% EtOAc/hexane). After completion of the reaction, the reaction mixture was evaporated to remove CH_2Cl_2 and the residue was used in second step. Sodium azide (0.324 g, 5 mmol) dissolved in CH_3CN/H_2O (60 ml/10 ml) was added to the mixture of crude product and benzotriazole from the first step. The reaction mixture was stirred at room temperature for 5 h. When TLC (40% EtOAc/hexane) indicated complete reaction, CH_3CN was evaporated under vacuum and EtOAc (100 ml) was added. The product was insoluble in EtOAc. It was directly filtered off and dried to give the title compound. The solid obtained was further stirred in MeOH for 1 h to remove traces of 1*H*-benzotriazole.

N,N′-(1,4-Phenylenemethylene)bis(1,2,3,4-thiatriazol-5-amine) (**15i**). Colorless microcrystals, 0.223 g (73%), m.p. 141 °C. ^{1}H NMR: 4.59 s, 4 H (2 CH_2); 7.36 s, 4 H (Ar-H); 9.38 br s, 2 H

(2 NH). ^{13}C NMR: 49.3, 127.9, 136.6, 177.2. HRMS: for $C_{10}H_{10}N_8S_2$ [M + Na]$^+$ calculated 329.0362, found 329.0355.

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