Notes

Convenient Synthesis of Novel *N*-Substituted-5-aminothiazole Derivatives

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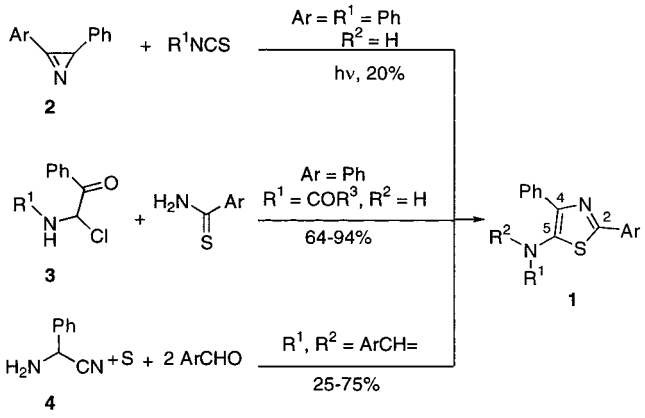
Introduction

Many thiazoles are important pharmaceuticals,[1a−d] dyes, and photographic chemicals.[2] Simple 2,4-diarylthiazoles, readily synthesized by Hantzsch reactions,[3] include 2,4-bis(3-indolyl)thiazoles, which are potent cytotoxic agents.[4] Less is known about efficient syntheses of 2,4-diarylthiazoles functionalized at the 5 position. Literature syntheses of 2,4-diaryl-5-aminothiazoles (**1**) (Scheme 1) include: (i) the photoconversion of unstable azirene 2 into **1** (where Ar = R^1 = Ph, R^2 = H) in a 20% yield;[5] (ii) the condensation of unstable *ω*-chloro-*ω*-acylamidoacetophenones (**3**) with benzothioamide to generate **1** (where Ar = Ph, R^1 = COR^3, R^2 = H) in 64−94% yields,[6] which is limited by the need to access of **3**, via condensation of phenylglyoxal with acid amides and thionyl chloride; (iii) a general method of synthesizing 5-(arylidenamino)-2-aryl-4-phenylthiazoles in 25−75% yields, as presented by Gewald et al.[7] In these syntheses, phenyl was the only 4-substituent and yields were low for the thiazoles bearing electron-withdrawing groups in the 2 position (25%).

Existing synthetic routes for 5-aminothiazoles[8a−f] appear not to have been used for 2,4-diaryl-5-aminothiazoles. In our group, readily available[9] *N*-arylmethylene-[(benzotriazol-1-yl)arylmethyl]amines were used in 1,3-dipolar cyclizations with alkenes or alkynes to prepare pyrroles and dihydropyrroles.[10] We now report the convenient synthesis of *N*-substituted-2,4-diaryl-5-aminothiazoles from such 1,3-dipolar synthons.

Scheme 1



Results and Discussion

N-Arylmethylene[(benzotriazol-1-yl)arylmethyl]-amines 6a−c,**e** (Scheme 2) were previously reported to be obtained in high yields by stirring a mixture of benzotriazole, the appropriate arylaldehyde, and ethanolic ammonia at room temperature (route b).[9] Compound 6e was prepared cleanly in 90% yield using the published procedure. However, in the present study, application of this procedure gave products **6a**−**d** mixed with varying amounts of trimers **5a**−**d**. In a general two-step synthesis (route a), intermediate trimers **5a**−**d** were readily obtained in 75−90% yields by stirring the corresponding aldehydes and excess (10-fold) aqueous NH_3 solution (or methanolic NH_3 solution) at 20 °C for ca. 10 h.[11a−c] Subsequent refluxing of **5a**−**d** with benzotriazole in toluene or 1,4-dioxane then gave **6a**−**d** in 80−92% yields. This procedure was particularly suitable for compound **6c** with an electron-withdrawing group: **6c** was obtained in 90% yield. Novel compound **6d** functionalized with a thiophene moiety was prepared in 80% yield. Purification on silica gel is not suitable for compounds **6a**−**e** due to the acid-sensitive imine functionality. However, if the imine is solid, recrystallization or removal of excess benzotriazole by washing with saturated Na_2CO_3 solution after reactions provided the pure imines **6a**−**e**.

Treatment of **6a**−**e** with 1 equiv of *n*-BuLi in dry THF at −78 °C resulted in a dark solution within seconds, typical of carbanions stabilized by a benzotriazole group.[12a,b] Presumably the resonance-stabilized lithiated

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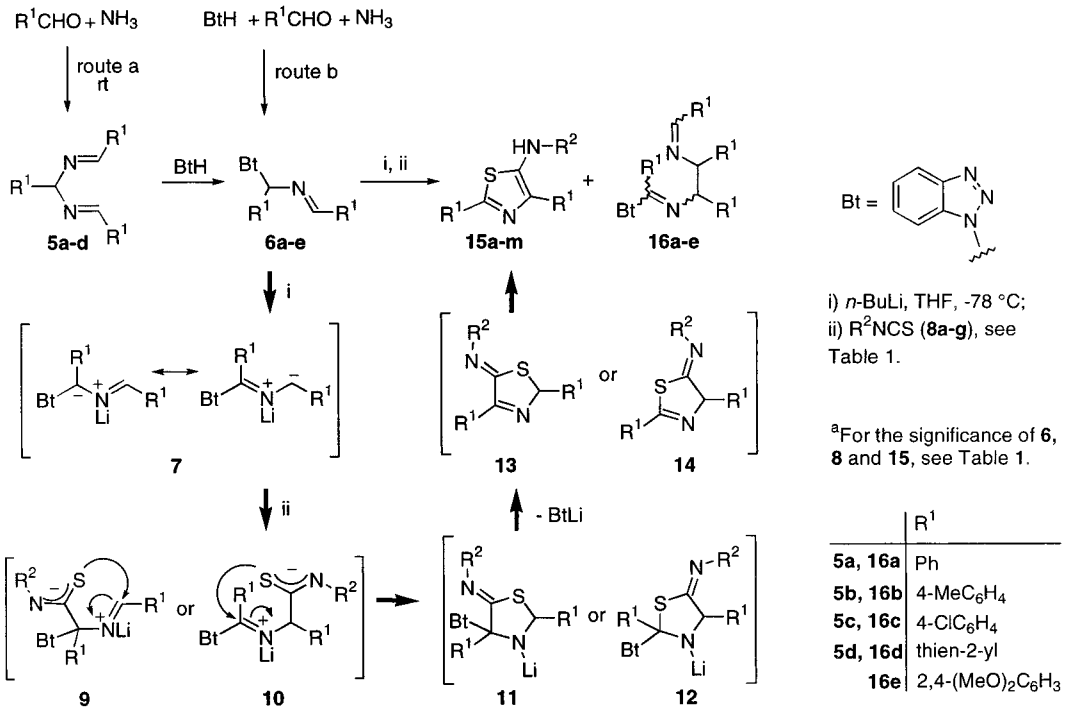
Scheme 2[a]



	R^1
5a, 16a	Ph
5b, 16b	4-MeC_6H_4
5c, 16c	4-ClC_6H_4
5d, 16d	thien-2-yl
16e	2,4-$(MeO)_2C_6H_3$

Table 1. Synthesis of Thiazole Derivatives 15a−m

SM[a]	R^1	R^2	product	yield (%)
6a, 8a	Ph	Ph	**15a**	81
6a, 8b	Ph	3-FC_6H_4	**15b**	65
6a, 8c	Ph	4-FC_6H_4	**15c**	60
6a, 8d	Ph	4-ClC_6H_4	**15d**	56
6a, 8e	Ph	2-ClC_6H_4	**15e**	35
6a, 8f	Ph	4-MeC_6H_4	**15f**	44
6a, 8g	Ph	4-$MeOC_6H_4$	**15g**	55
6b, 8a	4-MeC_6H_4	Ph	**15h**	60
6c, 8a	4-ClC_6H_4	Ph	**15i**	61
6c, 8d	4-ClC_6H_4	4-ClC_6H_4	**15j**	80
6e, 8a	2,4-$(MeO)_2C_6H_3$	Ph	**15k**	55
6e, 8d	2,4-$(MeO)_2C_6H_3$	4-ClC_6H_4	**15l**	70
6d, 8a	thien-2-yl	Ph	**15m**	47

[a] Starting Material: **6a−d**, $R^1CH(Bt)N{\simeq}CHR^1$; **8a−g,** R^2NCS.

azomethine ylide **7** (Scheme 2) was formed. After 5−10 min, the appropriate isothiocyanate (R^2NCS, 1.1 equiv) was added dropwise while stirring at −78 °C. The color of the solution changed to dark red ca. 5 min after the complete addition of the electrophile. Any lack of regioselectivity in providing a mixture of intermediates **9** and **10** is immaterial since isomers **9** and **10** both cyclize and then aromatize to the same thiazole **15**. Consistent with the hypothesis of azomethine ylide **7** is the observation of precipitates only 15 min after the addition of isothiocyanate at −78 °C. The precipitates were tentatively identified by the ^1H NMR spectra as possibly complexes of the benzotriazole lithium salt with THF. The reaction was monitored by TLC and found to produce mainly the desired **15a−m**. Only thiazoles were isolated as final products which reflects the nucleophilicity of sulfur: no imidazoles were formed by cyclization of intermediates **9** and **10** from nitrogen anion to the ylides.

Products **15a−g** (Table 1) were obtained in 35−81% yields as stable solids (except 15g which is an oil) starting from imine **6a**. Product **15a** was easily obtained in high yield with no substituent on *N*-phenyl ring. Products **15b−d** were isolated in reasonable yields of 56−65% after flash chromatography starting from electron-deficient phenyl isothiocyanates **8b−d**. A lower yield (35%) was observed for **15e** starting with 2-chlorophenyl isothiocyanate (**8e**) compared with **15d** starting with 4-chlorophenyl isothiocyanate (**8d**, 56%), possibly due to the steric hindrance of the *ortho*-chloro atom substituted. For the electron-rich isothiocyanates (**8f**,**g**, R^2 = *p*-Me, *p*-MeO), the precipitates took longer to form than in reactions with electron-deficient isothiocyanates, but **15f**,**g** were obtained as expected (44%, 55% yield). The ^1H NMR spectra of **15a−g** all show signals from phenyl rings directly attached to the thiazole ring appearing between 7.2 and 8.0 ppm. Proton signals from the *N*-phenyl rings occur between 6.7 and 7.3 ppm. The NH-proton signals typically show around 5.5 ppm (for **15a−d**,**f**,**g**), except that for **15e** which is shifted downfield to 6.1 ppm, perhaps by a steric effect.

During the one-pot reaction starting from 6a, self-condensation of **6a** gave **16a** as a side product (<10%), as suggested by the two doublets [4.79 (d, J = 6.6 Hz, 1H), 5.09 (d, J = 6.3 Hz, 1H)] from the ^1H NMR spectrum of the crude sample (Scheme 2). Self-condensation reaction of **6a** indeed gave **16a**, in 50% yield as a single isomer (which isomerized during flash column chromatography on silica gel). The ^1H NMR spectra of isomers, each characterized by CHN analysis, show the same pattern of double doublet peaks (see Supporting Information).

The reaction of **6b** with phenyl isothiocyanate (**8a**) gave the expected thiazole **15h** (60%) as yellow needles. A self-condensation product of **6b** was observed as a minor side reaction (<10%).

When there was an electron-withdrawing group such as a chlorine atom in **6c**, the reaction went smoothly with both phenyl (**8a**) and 4-chlorophenyl isothiocyanate (**8d**). The fact that the self-condensation products were hardly observed from the ^1H NMR spectra of crude mixtures is consistent with the relatively stable ylide **7** compared with the ylide formed from **6a**.

Products with strong electron-donating moieties, like methoxy groups in **15k**,**l**, were obtained in 55% and 70% yields, respectively. There are significant changes in the ^{1}H NMR spectra for the phenyl rings directly attached to the thiazole ring. The protons on these phenyl rings show signals in a broader range 6.9−8.3 ppm. The peak for the proton attached to the nitrogen shifts downfield to 6.4−6.5 ppm. In the ^{1}H NMR spectra of crude mixtures, there were no peaks at 4.00−6.00 ppm for the suggested self-condensation product; possibly, these peaks were also shifted downfield because of the strong electron-donating moieties in the molecule.

1*H*-1,2,3-Benzotriazol-1-yl(2-thienyl)-*N*-[(*E*)-2-thienylmethylidene]methanamine (**6d**) was successfully deprotonated and further reacted with phenyl isothiocyanate **8a** to result in the final product **15m** in 47% yield. During workup, brine solution was used instead, as aqueous 2 M NaOH solution seemed to decompose **15m** significantly. A minor self-condensation product observed from the ^{1}H NMR spectrum of the crude product was represented by two doublet-doublet peaks at 5.28 and 5.53 ppm.

In conclusion, this paper describes a practical and facile way to make 2,4-diaryl-*N*-substituted-5-aminothiazoles in moderate to good yields. Compared to literature procedures, this method has the advantages of easily available stable starting materials and simple reaction procedures.

Experimental Section

General Procedure for the Synthesis of Compounds 5a−d. Aldehydes (0.1 mol) were added to aqueous NH_3 (1 mol, 30%) or methanolic NH_3 (for **5d**, 38 mL) solution and stirred vigorously for 10 h (or until precipitates formed) at room temperature. The crude products were filtered out, washed with water and recrystallized from ethanol to give products **5a**−**d**.

Phenyl-*N*,*N*-bis[(*E*)-phenylmethylidene]methanediamine (5a): white solid; mp 99.0−99.9 °C (lit.[13] mp 102 °C).

General Procedure for the Synthesis of Compounds 6a−d. Compounds **5a**−**d** (20 mmol) and benzotriazole (37 mmol, 1.5 equiv) were dissolved in 1,4-dioxane (for **6a**) or toluene (for **6b**−**d**) (100 mL), and the solution was refluxed for 12 h. The reaction mixture was cooled to room temperature, and the solvent was removed. The crude mixture was recrystallized from ethyl acetate/hexane, to give pure product **6a**,**d**. Otherwise, the crude mixture was dissolved in ether and washed with saturated aqueous Na_2CO_3 solution to remove excess BtH. The organic layer was dried over $MgSO_4$. Upon removal of the $MgSO_4$ and solvent, oily products **6b**,**c** were obtained and can be used further without any purification.

1*H*-1,2,3-Benzotriazol-1-yl(2-thienyl)-*N*-[(*E*)-2-thienylmethylidene]methan- amine (6d): brown powder; mp 101.0−102.2 °C; ^{1}H NMR δ 6.90−7.10 (m, 1H), 7.05−7.10 (m, 2H), 7.30−7.39 (m, 4H), 7.50−7.52 (m, 2H), 7.75 (s, 1H), 8.04−8.07 (m, 1H), 8.37 (s, 1H); ^{13}C NMR δ 79.6, 112.1, 119.8, 124.1, 126.2, 126.6, 127.2, 127.5, 127.8, 131.3, 131.5, 133.3, 140.7, 140.8, 146.7, 156.9. Anal. Calcd for $C_{16}H_{12}N_4S_2$: C, 59.23; H, 3.73; N, 17.27. Found: C, 59.26; H, 3.72; N, 17.17.

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General Procedure for the Synthesis of Compounds 15a−m. *n*-BuLi (1.6 M in hexane, 2.5 mL, 4 mmol) was added to a solution of the corresponding *N*-arylmethylene[(benzotriazole-1-yl)arylmethyl]amines **6** (4 mmol) in THF (50 mL) at −78 °C under argon. After 5 min of stirring, isothiocyanate (4.1 mmol) was added. If precipitates were observed after around 15 min and TLC showed the desired product, the reaction mixture was quenched at −78 °C by the addition of 2 M NaOH solution (30 mL). Otherwise the reaction mixture was allowed to warm to room temperature overnight, before being washed with 2 M NaOH or brine solution (30 mL). After separation, the aqueous layer was extracted by Et_2O (2 × 20 mL). The combined organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The products were purified by flash chromatography with the combination of pentane and ethyl ether as eluent to give the product.

***N*-Phenyl-2,4-diphenyl-1,3-thiazol-5-amine (15a):** yellow microcrystals (yield 81%); mp 125.0−125.7 °C (lit.[5] mp 122.5−124.0 °C); ^{1}H NMR δ 5.48 (br s, 1H), 6.84−6.91 (m, 3H), 7.19−7.39 (m, 8H), 7.92−7.94 (m, 4H); ^{13}C NMR δ 114.8, 120.4, 126.1, 127.7, 127.8, 128.6, 128.8, 129.5, 129.7, 133.9, 134.0, 135.6, 145.3, 146.7, 160.6. Anal. Calcd for $C_{21}H_{16}N_2S$: C, 76.80; H, 4.91; N, 8.53. Found: C, 77.09; H, 5.03; N, 8.61.

***N*-[2,4-Bis(4-methylphenyl)-1,3-thiazol-5-yl]-*N*-phenylamine (15h):** yellow needles (yield 60%); mp 143.2−143.3 °C;^{1}H NMR δ 2.34 (s, 3H), 2.37 (s, 3H), 5.45 (s, 1H), 6.86−6.90 (m, 3H), 7.17−7.27(m, 6H), 7.81−7.85 (m, 4H); ^{13}C NMR δ 21.3, 21.4, 114.6, 120.2, 126.0, 127.7, 129.2, 129.5, 131.3, 131.4, 134.4, 137.6, 139.9, 145.5, 147.0, 161.1. Anal. Calcd for $C_{23}H_{20}N_2S$: C, 77.49; H, 5.65; N, 7.86. Found: C, 77.43; H, 5.71; N, 7.84.

2,4-Bis(4-chlorophenyl)-*N*-phenyl-1,3-thiazol-5-amine (15i): yellow microcrystals (yield 61%); mp 44.5−45.5 °C; ^{1}H NMR δ 5.50 (s, 1H), 6.86−6.96 (m, 3H), 7.24−7.29 (m, 2H), 7.32−7.41 (m, 4H), 7.83−7.93 (m, 4H); ^{13}C NMR δ 114.9, 120.9, 127.3, 128.8, 129.0, 129.1, 129.6, 132.3, 133.7, 135.9, 136.3, 144.9, 145.8, 159.6. Anal. Calcd for $C_{21}H_{14}Cl_2N_2S$: C, 63.48; H, 3.55; N, 7.05. Found: C, 63.31; H, 3.65; N, 6.84.

2,4-Bis(2,4-dimethoxyphenyl)-*N*-phenyl-1,3-thiazol-5-amine (15k): yellow microcrystals (yield 55%); mp 141.7−144.3 °C; ^{1}H NMR δ 3.81 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 3.92 (s, 3H), 6.48−6.64 (m, 5H), 6.80 (t, J = 7.2 Hz, 1H), 6.98 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 7.5 Hz, 2H), 7.63 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 9.0 Hz, 1H); ^{13}C NMR δ 55.3, 55.4, 55.5, 56.1, 98.2, 99.3, 105.5, 105.9, 114.7, 116.3, 117.1, 119.6, 128.8, 129.1, 132.3, 136.6, 139.2, 145.2, 152.4, 156.9, 157.0, 160.7, 161.3. Anal. Calcd for $C_{25}H_{24}N_2O_4S$: C, 66.94; H, 5.39; N, 6.25. Found: C, 66.56; H, 5.21; N, 6.16.

***N*-Phenyl-2,4-bis(2-thienyl)-1,3-thiazol-5-amine (15m):** yellow microcrystals (yield 47%); mp 141.1−143.1 °C; ^{1}H NMR δ 5.39 (s, 1H), 6.83−6.88 (m, 2H), 6.91 (d, J = 7.5 Hz, 1H), 7.01−7.06 (m, 2H), 7.22−7.27 (m, 3H), 7.37−7.42 (m, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.60 (d, J = 3.6 Hz, 1H); ^{13}C NMR δ 114.7, 120.6, 125.7, 125.8, 126.4, 127.3, 127.8, 129.5, 132.3, 136.1, 137.7, 143.0, 144.9, 156.0. Anal. Calcd for $C_{17}H_{12}N_2S_3$: C, 59.97; H, 3.55; N, 8.23. Found: C, 59.94; H, 3.64; N, 8.12.

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Supporting Information Available: Text providing ^{1}H and ^{13}C NMR spectral data and elemental analyses for compounds **5b**−**d**, **6a**−**c**,**e**, **15b**−**g**,**j**,**l,** and **16a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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