1-(Cyanomethyl)benzotriazole as a Convenient Precursor for the Synthesis of 2-Substituted Thiazoles

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Treatment of 1-(cyanomethyl)benzotriazole with hydrogen peroxide followed by a Lawesson reagent afforded (benzotriazol-1-yl)thioacetamide which condensed with α-halo carbonyl compounds (Hantzsch thiazole synthesis) to give the corresponding 2-(benzotriazol-1-ylmethyl)thiazoles. Lithiation of 2-(benzotriazol-1-ylmethyl)-4-phenylthiazole with butyllithium occurred exclusively at the methylene group, and subsequent quenching of the resulting anion with alkyl halides produced the corresponding alkylated products in good yields. Treatment of these intermediates with Grignard reagents in toluene or with electron-rich heterocycles in the presence of zinc bromide resulted in the displacement of benzotriazole to afford the corresponding thiazoles with elaborated 2-substituents.

Introduction

Thiazole nuclei appear frequently in the structures of various natural products and biologically active compounds, notably thiamine (vitamin B), penicillins, antibiotics such as micrococcin,[1] and many metabolic products of fungi and primitive marine animals, including 2-(aminoalkyl)thiazole-4-carboxylic acids.[2] Numerous thiazole derivatives exhibit pharmacological activity;[3] *e.g.*, 4-amino-*N*-(thiazol-2-yl)benzenesulfonamide is a commercial drug.

Many methods have been documented for the preparation of thiazoles. The commonly employed Hantzsch synthesis involves condensation of α-halo carbonyl compounds with thioamides.[2,4-7] Thiazoles have also been prepared from α-amino nitriles[4] or from amino thiols and carbonyl compounds.[8] Other procedures are generally of less importance due to either the limited availability of starting materials and/or lack of overall generality.[4]

Work in our laboratory has demonstrated the use of benzotriazole as a synthetic auxiliary in the synthesis of various types of compounds.[9] The combination of the activating and leaving ability of benzotriazole affords new possibilities for synthetic elaboration (for recent reviews, see refs 10–12). In particular, we have shown that intermediates containing a $-CH_2Bt$ substituent attached to an electron-rich benzenoid or heteroaromatic ring are of potential value for the introduction of elaborated substituents of the type $-CHENu$ or $-CE_2Nu$ because of the possibility of deprotonation and reaction with an electrophile followed by replacement of the Bt group by a nucleophile.[13]

We have now found that 1-(cyanomethyl)benzotriazole ($BtCH_2CN$), readily available from 1-(chloromethyl)-benzotriazole and sodium cyanide,[14] can be used advantageously *via* a modified Hantzsch synthesis to prepare 2,4-di-, 2,5-di-, and 2,4,5-trisubstituted thiazoles. The versatility of this method again arises from a combination of the activating and leaving ability of the benzotriazolyl group which facilitates the introduction of complex substituents at the thiazole 2-position.

Results and Discussion

1-(Cyanomethyl)benzotriazole (**1**) was converted to amide **2a** in 93% yield by treatment with 30% hydrogen peroxide in dimethyl sulfoxide.[15] Treatment of **2a** with a modified Lawesson's reagent[16] afforded (benzotriazol-1-yl)thioacetamide (**2b**) in 83% yield. Heating thioamide **2b** with 2-bromoacetophenone in ethanol at reflux for 4 h provided 2-(benzotriazol-1-ylmethyl)-4-phenylthiazole (**3**) in 81% yield (Scheme 1).

Lithiation of 2-methylthiazole with butyllithium at −100 °C was reported to occur at the 4-, 5-, and methyl-positions in a ratio of 52:3:45,[17] indicating the competing acidity of the three types of hydrogens. When 2-(benzotriazol-1-ylmethyl)-4-phenylthiazole (**3**) was treated with butyllithium at −78 °C for 2 h, lithiation occurred exclusively at the methylene group, a result of the

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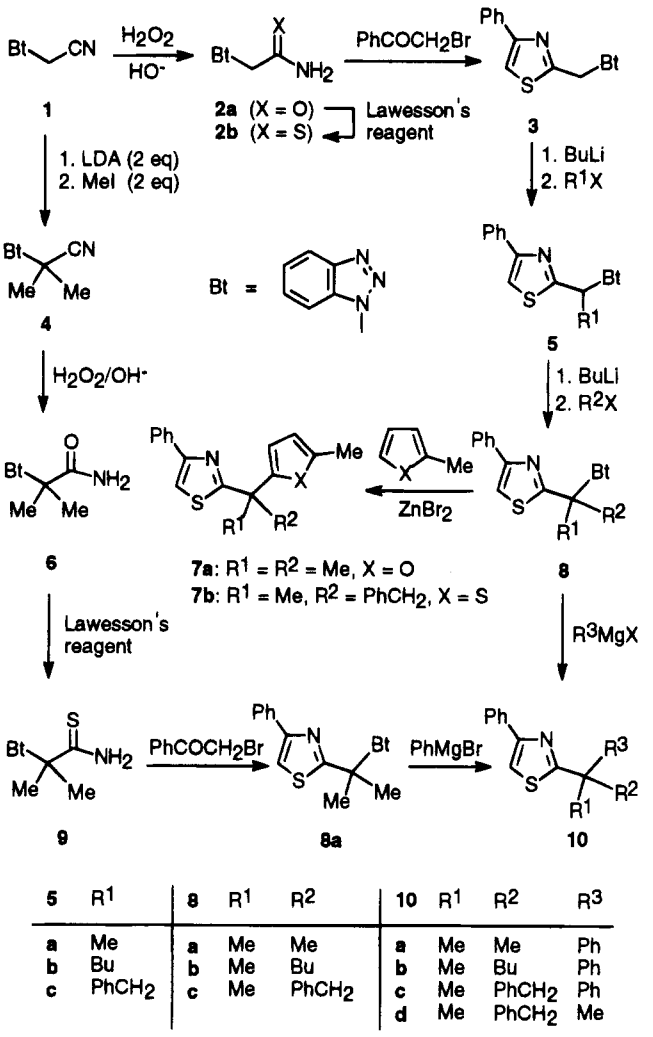
Scheme 1



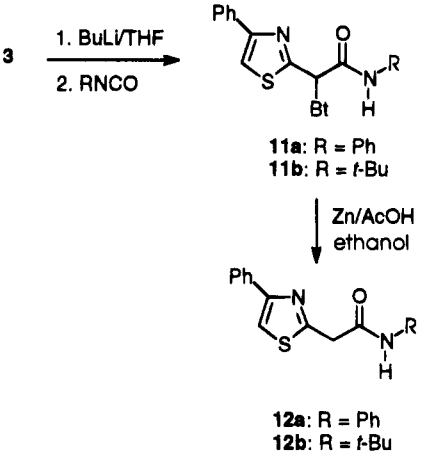
5	R^1	8	R^1	R^2	10	R^1	R^2	R^3
a	Me	a	Me	Me	a	Me	Me	Ph
b	Bu	b	Me	Bu	b	Me	Bu	Ph
c	$PhCH_2$	c	Me	$PhCH_2$	c	Me	$PhCH_2$	Ph
					d	Me	$PhCH_2$	Me

activating effect of the benzotriazolyl group. Quenching the anion of **3** with methyl iodide, butyl bromide, and benzyl bromide afforded the corresponding monoalkylated products **5a**, **5b**, and **5c**, respectively, in yields of 76–83% (Scheme 1). The dominant activating ability of the benzotriazolyl group was evident as further lithiation of **5a** with butyllithium took place completely at the methine group. Subsequent reactions of the anion of **5a** with alkyl halides such as methyl iodide, butyl bromide, and benzyl bromide yielded the corresponding disubstituted adducts **8a**, **8b**, and **8c**. Combination of these two steps allows two identical or different alkyl groups to be introduced into the 2-methylene position.

Treatment of **8a-c** with phenylmagnesium bromide in toluene at reflux for 20 h afforded 2-*tert*-alkylthiazoles **10a-c** in yields of 54–75%. Similarly, reaction of **8c** with methylmagnesium iodide provided compound **10d** in 58% yield. The benzotriazole generated was readily removed by washing the organic extracts with dilute aqueous sodium carbonate during workup. The intermediates **8a-c** and displacement products **10a-d** were characterized by ^1H and ^{13}C NMR spectroscopy and by elemental analysis. The resonances of the tertiary carbons of **8a-c** and **10a-d** were characteristic as they decreased from about 67 ppm (for **8a-c**) to 44–49 ppm (for **10a-d**) in the ^{13}C NMR spectra.

Lewis acid promoted displacements of benzotriazolyl groups by electron-rich heterocycles and aromatics have been previously reported by our group.[13c,18] Following a similar procedure, reaction of **8a** with 2-methylfuran and zinc bromide in refluxing 1,2-dichloroethane provided compound **7a** in 65% yield (Scheme 1). Similarly, compound **7b** was obtained in 82% yield from **8c** and 2-methylthiophene.

Scheme 2



Alkyl substituents can also be introduced before the formation of the thiazole ring. Thus, 1-(cyanomethyl)-benzotriazole (**1**) was treated with LDA (2 equiv) followed by methyl iodide (2 equiv) to give the dimethylated product **4**. Following the same procedures described previously, **4** was converted to thioamide **9** *via* amide **6**. Condensation of **9** with bromoacetophenone afforded thiazole derivative **8a**. The combination of the two synthetic routes described allows a variety of 2-*tert*-alkylthiazoles to be readily accessible. The route **1** to **8** *via* **2**, **3**, and **5** is particularly advantageous in that the parent thiazole **3** is readily prepared in quantity and that two different alkyl groups (R^1, R^2) can be introduced in a clean and controllable manner.

Reactions of the anion of **3** with phenyl and *tert*-butyl isocyanate afforded amides **11a** and **11b**, respectively, which upon treatment with zinc and acetic acid gave the corresponding reduced products **12a** and **12b** in good yields (Scheme 2).

The generality of the present method was further extended as (benzotriazol-1-yl)thioacetamide (**2b**) readily condensed with other aryl and alkyl α-haloalkyl ketones to give the corresponding 2,4,5-trisubstituted thiazoles **14a-c** in 50–66% yields (Scheme 3). Treatment of **14b** with 2 equiv of butyllithium and of methyl iodide formed the dimethylated product **16** in 56% yield. Following the procedures described above, reactions of **16** with 2-methylfuran and zinc bromide or with phenylmagnesium bromide afforded the displacement products **15** and **17**, respectively.

In conclusion, we have developed a general and versatile method for the preparation of 2-*tert*-alkyl and other highly substituted thiazoles. The use of simple and readily available starting materials and the facile introduction of substituents either before or after thiazole ring formation endows the procedure with considerable synthetic potential.

Experimental Section

Melting points were determined on a hot-stage microscope and are uncorrected. ^1H NMR spectra were recorded on a 300 MHz spectrometer with tetramethylsilane (TMS) as the in-

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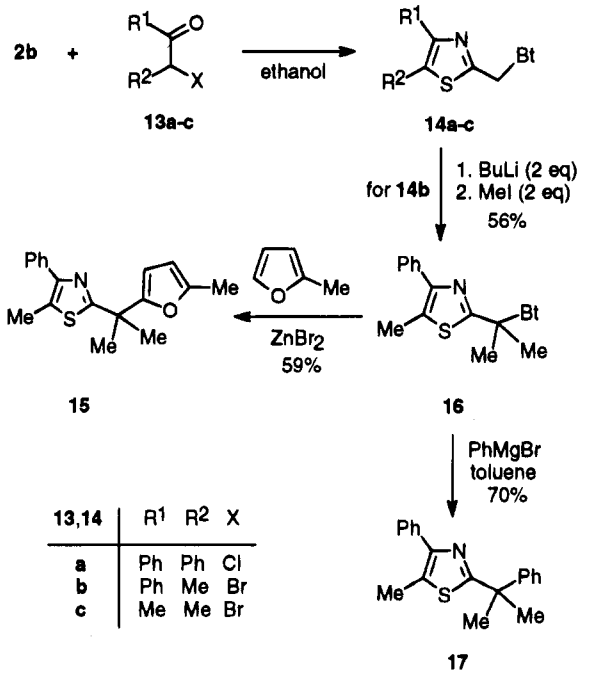
Scheme 3



ternal reference. ^{13}C NMR spectra were recorded at 75 MHz on the same instrument using the solvent peak ($CDCl_3$, δ = 77.0 ppm; DMSO-d_6, δ = 39.5 ppm) as reference. Microanalyses were carried out within the department. High resolution mass measurements were determined on a Finnigan Mat 95. Flash column chromatography was run on EM Science silica gel (230–400 mesh).

The following compounds were prepared according to the literature procedures: 1-(cyanomethyl)benzotriazole (**1**), mp 86–88 °C (lit.[14] mp 85–86 °C), and 2-(benzotriazol-1-yl)-2-cyanopropane (**4**) as an oil.[19]

Preparation of (Benzotriazol-1-yl)acetamide (2a) and 2-(Benzotriazol-1-yl)-2-methylpropylamide (6). Potassium carbonate ($K_2CO_3 \cdot 1.5H_2O$) (1 g) and 30% H_2O_2 (10 mL) were added to a solution of 1-(cyanomethyl)benzotriazole (**1**) or 2-(benzotriazol-1-yl)-2-cyanopropane (**4**) (50 mmol) in DMSO (50 mL) at 0–5 °C. The mixture was allowed to warm to room temperature for 1 h, and water (100 mL) was added. The white solid which precipitated was collected by filtration and recrystallized from ethanol to give the pure product.

(Benzotriazol-1-yl)acetamide (2a): obtained as white needles; mp 188–189 °C; yield 93%; ^1H NMR (DMSO-d_6) δ 8.06 (d, 1 H, J = 8.3 Hz), 7.90 (s, 1 H), 7.78 (d, 1 H, J = 8.0 Hz), 7.62–7.36 (m, 3 H), 5.45 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 167.6, 145.1, 133.8, 127.3, 123.8, 119.0, 110.9, 49.7. Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.45; H, 4.55; N, 32.11.

2-(Benzotriazol-1-yl)-2-methylpropylamide (6): obtained as white needles; mp 192–193 °C; yield 86%; ^1H NMR (DMSO-d_6) δ 8.10 (d, 1 H, J = 8.3 Hz), 7.63–7.51 (m, 4 H), 7.42 (t, 1 H, J = 7.9 Hz), 1.97 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 172.7, 146.1, 132.0, 127.0, 123.7, 119.4, 111.9, 65.1, 25.4. Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.59; H, 5.92; N, 27.60.

Preparation of (Benzotriazol-1-yl)thioacetamide (2b) and 2-(Benzotriazol-1-yl)-2-methylpropylthioamide (9). A mixture of (benzotriazol-1-yl)acetamide (**2a**) or 2-(benzotriazol-1-yl)-2-methylpropylamide (**6**) (20 mmol), Lawesson's reagent (4.49 g, 11 mmol), and THF (100 mL) was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure and the residue extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with 5% $NaHCO_3$ (2 × 30 mL), dried over $MgSO_4$, and evaporated to give the crude product which was recrystallized from ethyl acetate to afford the pure product.

(Benzotriazol-1-yl)thioacetamide (2b): obtained as a white powder; mp 178–179 °C; yield 83%; ^1H NMR (DMSO-d_6) δ 9.99 (s, 1 H), 9.63 (s, 1 H), 8.06 (d, 1 H, J = 8.3 Hz), 7.79 (d, 1 H, J = 8.3 Hz), 7.55 (t, 1 H, J = 7.6 Hz), 7.41 (t, 1 H, J = 7.6 Hz), 5.72 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 199.1, 145.1, 133.7, 127.3, 123.8, 119.0, 111.0, 56.2. Anal. Calcd for $C_8H_8N_4S$: C, 49.98; H, 4.19; N, 29.14. Found: C, 49.63; H, 4.12; N, 29.28.

2-(Benzotriazol-1-yl)-2-methylpropylthioamide (9): obtained as white crystals; mp 179–180 °C; yield 86%; ^1H NMR (DMSO-d_6) δ 10.05 (s, 1 H), 9.05 (s, 1 H), 8.09 (d, 1 H, J = 8.3 Hz), 7.61 (d, 1 H, J = 8.3 Hz), 7.53 (t, 1 H, J = 6.8 Hz), 7.41 (t, 1 H, J = 7.0 Hz), 2.05 (s, 6 H); ^{13}C NMR (DMSO-d_6) δ 206.0, 146.1, 131.8, 127.0, 123.7, 119.4, 111.9, 69.3, 28.1. Anal. Calcd for $C_{10}H_{12}N_4S$: C, 54.52; H, 5.49; N, 25.43. Found: C, 54.37; H, 5.50; N, 25.23.

General Procedure for the Condensation of (Benzotriazol-1-yl)thioacetamide (2b) or 2-(Benzotriazol-1-yl)-2-methylpropylthioamide (9) with α-Haloalkyl Carbonyl Compounds. Preparation of 2-(Benzotriazol-1-yl)alkylthiazoles 3, 8a, and 14a-c. A solution of (benzotriazol-1-yl)-thioacetamide (**2b**) or 2-(benzotriazol-1-yl)-2-methylpropylthioamide (**9**) (10 mmol) and the appropriate α-halo carbonyl compound (11 mmol) in ethanol (30 mL) was stirred at room temperature overnight and then refluxed for 4 h. The solvent was evaporated and the resulting residue extracted with chloroform (3 × 30 mL). The combined organic layers were washed successively with 10% $NaHCO_3$ (20 mL) and water (20 mL), dried over $MgSO_4$, and evaporated to give the crude product.

2-(Benzotriazol-1-ylmethyl)-4-phenylthiazole (3): obtained as a yellow powder in pure state; mp 104–106 °C; yield 81%; ^1H NMR ($CDCl_3$) δ 8.07 (d, 1 H, J = 8.3 Hz), 7.87 (d, 2 H, J = 8.4 Hz), 7.67 (d, 1 H, J = 8.3 Hz), 7.52–7.30 (m, 6 H), 6.18 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 162.9, 155.7, 146.2, 133.8, 132.8, 128.8, 128.4, 127.8, 126.3, 124.2, 120.1, 114.4, 109.9, 49.4. Anal. Calcd for $C_{16}H_{12}N_4S$: C, 65.73; H, 4.14; N, 19.16. Found: C, 65.72; H, 4.10; N, 19.31.

2-(Benzotriazol-1-yl)-2-(4-phenylthiazol-2-yl)propane (8a): obtained as a yellow oil after column chromatography (hexane:chloroform = 1:1); yield 47%; ^1H NMR ($CDCl_3$) δ 8.07–8.03 (m, 1 H), 7.94–7.90 (m, 2 H), 7.46–7.17 (m, 7 H), 2.37 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 172.5, 154.4, 146.8, 133.8, 131.9, 128.6, 128.2, 126.9, 126.1, 123.6, 119.9, 114.0, 111.6, 64.6, 28.9. Anal. Calcd for $C_{18}H_{16}N_4S$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.86; H, 5.25; N, 17.09.

2-(Benzotriazol-1-ylmethyl)-4,5-diphenylthiazole (14a): obtained as a white solid in pure state after briefly washing with diethyl ether; mp 165–166 °C; yield 50%; ^1H NMR ($CDCl_3$) δ 8.97 (d, 1 H, J = 8.4 Hz), 7.74 (d, 1 H, J = 8.4 Hz), 7.54–7.47 (m, 3 H), 7.39 (t, 1 H, J = 7.4 Hz), 7.31–7.21 (m, 8 H), 6.18 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 160.7, 149.9, 146.2, 135.1, 134.2, 132.8, 131.1, 129.4, 128.9, 128.7, 128.4, 128.3, 128.0, 127.9, 124.2, 120.1, 109.9, 49.5. Anal. Calcd for $C_{22}H_{16}N_4S$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.74; H, 4.38; N, 15.32.

2-(Benzotriazol-1-ylmethyl)-5-methyl-4-phenylthiazole (14b): obtained as a white solid after column chromatography (hexane:chloroform = 1:1); mp 106–107 °C; yield 59%; ^1H NMR ($CDCl_3$) δ 8.08 (d, 1 H, J = 8.2 Hz), 7.70–7.61 (m, 3 H), 7.50–7.34 (m, 5 H), 6.11 (s, 2 H), 2.47 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.7, 151.1, 146.2, 134.3, 132.7, 130.4, 128.4, 127.7, 124.1, 120.0, 109.9, 49.5, 12.6. Anal. Calcd for $C_{17}H_{14}N_4S$: C, 66.64; H, 4.61; N, 18.29. Found: C, 66.41; H, 4.57; N, 18.38.

2-(Benzotriazol-1-ylmethyl)-4,5-dimethylthiazole (14c): obtained as a white powder after recrystallization from hexane/ethyl acetate; mp 113–114 °C; yield 66%; ^1H NMR ($CDCl_3$) δ 8.04 (d, 1 H, J = 8.3 Hz), 7.62 (d, 1 H, J = 8.3 Hz), 7.46 (t, 1 H, J = 7.2 Hz), 7.35 (t, 1 H, J = 7.2 Hz), 6.03 (s, 2 H), 2.31 (s, 3 H), 2.25 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.8, 148.2, 146.0, 132.5, 128.5, 127.5, 123.9, 119.7, 109.7, 49.2, 14.4, 11.1. Anal. Calcd for $C_{12}H_{12}N_4S$: C, 58.99; H, 4.95; N, 22.93. Found: C, 58.68; H, 4.90; N, 23.04.

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General Procedure for the Lithiation of 2-(Benzotriazol-1-ylmethyl)-4-phenylthiazole (3), 2-(1-Benzotriazol-1-ylethyl)-4-phenylthiazole (5a), and 2-(Benzotriazol-1-ylmethyl)-5-methyl-4-phenylthiazole (14b) and Subsequent Reactions with Electrophiles. Preparation of Compounds 5a-c, 8a-c, 11a,b, and 16. Butyllithium (5.5 mL, 11 mmol, 2 M in cyclohexane) was added to a solution of **3** (10 mmol) or **5a** (10 mmol) or **14b** (5 mmol) in THF (150 mL) at −78 °C and the solution stirred at this temperature for 2 h. The appropriate electrophile (11 mmol) was added and the mixture stirred at −78 °C for 2 h and then at room temperature overnight. The reaction was quenched with water (50 mL) and the suspension extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water (2 × 50 mL), dried over $MgSO_4$, and evaporated to give the crude product.

2-(1-Benzotriazol-1-ylethyl)-4-phenylthiazole (5a): obtained as a yellow solid; mp 89−90 °C; yield 76%; ^{1}H NMR ($CDCl_3$) δ 8.04 (d, 1 H, J = 8.3 Hz), 7.86 (d, 2 H, J = 6.9 Hz), 7.59 (d, 1 H, J = 8.3 Hz), 7.42−7.24 (m, 6 H), 6.47 (q, 1 H, J = 7.1 Hz), 2.27 (d, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.9, 154.9, 146.1, 133.6, 132.0, 128.5, 128.1, 127.3, 126.0, 123.9, 119.8, 113.8, 110.1, 56.8, 19.9. Anal. Calcd for $C_{17}H_{14}N_4OS$: C, 66.65; H, 4.61; N, 18.30. Found: C, 66.94; H, 4.63; N, 18.26.

2-(1-Benzotriazol-1-ylpentyl)-4-phenylthiazole (5b): obtained as a yellow oil after column chromatography (hexane:AcOEt = 10:1); yield 78%; ^{1}H NMR ($CDCl_3$) δ 8.06 (d, 1 H, J = 8.3 Hz), 7.88 (d, 2 H, J = 8.4 Hz), 7.70 (d, 1 H, J = 8.3 Hz), 7.42−7.24 (m, 6 H), 6.33 (dd, 1 H, J_1 = 9.4 and J_2 = 6.2 Hz), 2.90−2.63 (m, 2 H), 1.44−1.12 (m, 4 H), 0.81 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.2, 154.8, 146.0, 133.6, 132.2, 128.4, 127.9, 127.2, 125.9, 123.8, 119.7, 113.7, 110.0, 61.3, 33.6, 27.9, 21.7, 13.4. Anal. Calcd for $C_{20}H_{20}N_4S$: C, 68.94; H, 5.79; N, 16.08. Found: C, 69.07; H, 5.78; N, 16.08.

2-[1-(Benzotriazol-1-yl)-2-phenylethyl]-4-phenylthiazole (5c): obtained as a brown oil after column chromatography (hexane:AcOEt = 10:1); yield 83%; ^{1}H NMR ($CDCl_3$) δ 8.02 (d, 1 H, J = 8.2 Hz), 7.90 (d, 2 H, J = 8.2 Hz), 7.57 (d, 1 H, J = 8.4 Hz), 7.45−7.28 (m, 6 H), 7.17−7.04 (m, 5 H), 6.53 (dd, 1 H, J_1 = 8.9 and J_2 = 6.7 Hz), 4.12−4.00 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 166.6, 155.3, 146.1, 136.0, 134.0, 132.7, 128.9, 128.8, 128.5, 128.3, 127.5, 127.1, 126.3, 124.0, 120.0, 114.3, 110.0, 63.0, 40.6. Anal. Calcd for $C_{23}H_{18}N_4S$: C, 72.23; H, 4.74; N, 14.65. Found: C, 72.45; H, 4.85; N, 14.63.

2-(Benzotriazol-1-yl)-2-(4-phenylthiazol-2-yl)propane (8a): obtained as a yellow oil after column chromatography (hexane:AcOEt = 10:1); yield 89%. For spectral and elemental analytical data, see above.

2-(Benzotriazol-1-yl)-2-(4-phenylthiazol-2-yl)hexane (8b): obtained as a yellow oil after column chromatography (hexane:AcOEt = 10:1); yield 86%; ^{1}H NMR ($CDCl_3$) δ 8.11−8.06 (m, 1 H), 7.96 (d, 2 H, J = 7.1 Hz), 7.47−7.41 (m, 3 H), 7.39−7.20 (m, 4 H), 3.03−2.94 (m, 1 H), 2.82−2.72 (m, 1 H), 2.40 (s, 3 H), 1.52−1.26 (m, 3 H), 1.14−0.97 (m, 1 H), 0.87 (t, 3 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 172.8, 154.4, 146.8, 134.0, 132.2, 128.7, 128.2, 126.9, 126.2, 123.6, 120.0, 113.9, 111.7, 67.7, 39.8, 26.4, 25.5, 22.5, 13.7. Anal. Calcd for $C_{21}H_{22}N_4S$: C, 69.58; H, 6.12; N, 15.46. Found: C, 69.85; H, 6.19; N, 15.28.

2-(Benzotriazol-1-yl)-2-(4-phenylthiazol-2-yl)-1-phenylpropane (8c): obtained as a yellow powder in pure form; mp 114−115 °C; yield 93%; ^{1}H NMR ($CDCl_3$) δ 8.11−8.05 (m, 1 H), 7.95 (d, 2 H, J = 8.5 Hz), 7.47−7.42 (m, 3 H), 7.37−7.20 (m, 4 H), 7.17−7.04 (m, 3 H), 6.63 (d, 2 H, J = 8.2 Hz), 4.29 (d, 1 H, J = 14.0 Hz), 4.07 (d, 1 H, J = 14.0 Hz), 2.27 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.5, 154.5, 146.8, 134.6, 134.0, 132.4, 130.1, 128.7, 128.3, 128.0, 127.1, 126.3, 123.7, 120.2, 114.2, 111.8, 67.8, 45.1, 27.1. Anal. Calcd for $C_{24}H_{20}N_4S$: C, 72.70; H, 5.08; N, 14.13. Found: C, 72.52; H, 5.05; N, 14.14.

***N*-Phenyl-α-(benzotriazol-1-yl)-4-phenylthiazol-2-acetamide (11a):** obtained as yellow needles after recrystallization; mp 153−155 °C; yield 96%; ^{1}H NMR ($CDCl_3$) δ 10.48 (s, 1 H), 8.08−8.05 (m, 1 H), 7.88−7.83 (m, 2 H), 7.61−7.51 (m, 3 H), 7.47−7.22 (m, 9 H), 7.15−7.08 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 163.1, 161.3, 155.6, 146.2, 137.0, 133.3, 132.7, 129.1, 128.9, 128.7, 128.2, 126.2, 125.1, 124.5, 120.2, 120.1, 115.0, 110.7, 63.7. Anal. Calcd for $C_{23}H_{17}N_5OS$: C, 67.14; H, 4.16; N, 17.02. Found: C, 67.45; H, 4.16; N, 16.98.

***N-tert*-Butyl-α-(benzotriazol-1-yl)-4-phenylthiazol-2-acetamide (11b):** obtained as a white powder after recrystallization from hexane/chloroform; mp 166−168 °C; yield 87%; ^{1}H NMR ($CDCl_3$) δ 8.12 (s, 1 H), 8.08 (d, 1 H, J = 8.3 Hz), 7.85−7.80 (m, 2 H), 7.53−7.30 (m, 7 H), 7.08 (s, 1 H), 1.42 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 163.5, 162.2, 155.3, 146.1, 133.4, 132.6, 128.8, 128.5, 127.9, 126.1, 124.2, 120.1, 114.6, 110.8, 63.8, 52.2, 28.4. Anal. Calcd for $C_{21}H_{21}N_5OS$: C, 64.43; H, 5.41; N, 17.89. Found: C, 64.13; H, 5.42; N, 17.84.

2-(Benzotriazol-1-yl)-2-(5-methyl-4-phenylthiazol-2-yl)propane (16): obtained as yellow crystals after column chromatography (hexane:AcOEt = 10:1); mp 102−104 °C; yield 56%; ^{1}H NMR ($CDCl_3$) δ 8.09−8.03 (m, 1 H), 7.72−7.67 (m, 2 H), 7.47−7.41 (m, 2 H), 7.37−7.25 (m, 4 H), 2.47 (s, 3 H), 2.35 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 168.1, 149.8, 146.8, 134.5, 132.0, 129.9, 128.3, 128.2, 127.5, 126.8, 123.6, 119.8, 111.8, 64.5, 28.7, 12.6. Anal. Calcd for $C_{19}H_{18}N_4S$: C, 68.24; H, 5.42; N, 16.75. Found: C, 68.57; H, 5.53; N, 16.75.

General Procedure for Reaction of Compounds 8a-c or 16 with Grignard Reagents. Preparation of 2-Substituted Thiazoles 10a-d and 17. The appropriate Grignard reagent (10 mmol) was added to a solution of **8a-c** or **16** (2.5 mmol) in toluene (20 mL). The mixture was refluxed for 20 h and quenched with water (50 mL). The resulting mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated Na_2CO_3 (2 × 20 mL) and water (30 mL), dried over $MgSO_4$, and evaporated to give the crude product.

2-Phenyl-2-(4-phenylthiazol-2-yl)propane (10a): obtained as a yellow powder after column chromatography (hexane:$CHCl_3$ = 10:1); mp 61−62 °C; yield 74%; ^{1}H NMR ($CDCl_3$) δ 7.93 (d, 2 H, J = 7.1 Hz), 7.45−7.36 (m, 4 H), 7.34−7.26 (m, 4 H), 7.25−7.18 (m, 1 H), 1.90 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 179.7, 154.4, 147.8, 134.9, 128.6, 128.2, 127.8, 126.5, 126.4, 126.3, 112.4, 44.8, 30.2. Anal. Calcd for $C_{18}H_{17}NS$: C, 77.38; H, 6.13; N, 5.01. Found: C, 77.69; H, 6.30; N, 4.90.

2-Phenyl-2-(4-phenylthiazol-2-yl)hexane (10b): obtained as a yellow oil after column chromatography (hexane); yield 75%; ^{1}H NMR ($CDCl_3$) δ 7.92 (d, 2 H, J = 8.5 Hz), 7.45−7.32 (m, 4 H), 7.31−7.22 (m, 4 H), 7.21−7.12 (m, 1 H), 2.42−2.22 (m, 2 H), 1.84 (s, 3 H), 1.41−1.10 (m, 4 H), 0.86 (t, 3 H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 179.5, 154.2, 146.8, 134.9, 128.6, 128.1, 127.7, 126.7, 126.4, 126.3, 112.3, 48.2, 42.1, 26.8, 26.3, 23.2, 14.0. Anal. Calcd for $C_{21}H_{23}NS$: C, 78.46; H, 7.21; N, 4.36. Found: C, 78.85; H, 7.53; N, 4.27.

1,2-Diphenyl-2-(4-phenylthiazol-2-yl)propane (10c): obtained as a yellow oil after column chromatography (hexane); yield 54%; ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 2 H, J = 8.3 Hz), 7.45−7.16 (m, 9 H), 7.15−7.02 (m, 3 H), 6.88−6.78 (m, 2 H), 3.80 (d, 1 H, J = 13.2 Hz), 3.61 (d, 1 H, J = 13.2 Hz), 1.72 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 179.0, 154.2, 145.8, 137.6, 134.8, 130.7, 128.7, 128.0, 127.8, 127.5, 127.2, 126.7, 126.3, 126.2, 112.5, 49.0, 48.3, 26.0. Anal. Calcd for $C_{24}H_{21}NS$: C, 81.09; H, 5.95; N, 3.94. Found: C, 80.71; H, 6.06; N, 3.81.

2-Benzyl-2-(4-phenylthiazol-2-yl)propane (10d): obtained as a yellow oil after column chromatography (hexane); yield 58%; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 2 H, J = 8.4 Hz), 7.43 (t, 2 H, J = 7.6 Hz), 7.34 (d, 1 H, J = 7.4 Hz), 7.30 (s, 1 H), 7.21−7.15 (m, 3 H), 7.00−6.94 (m, 2 H), 3.13 (s, 2 H), 1.46 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 179.5, 154.8, 138.1, 135.0, 130.4, 128.7, 127.8, 127.7, 126.4, 126.2, 111.5, 49.8, 41.8, 28.2. Anal. Calcd for $C_{19}H_{19}NS$: C, 77.77; H, 6.53; N, 4.77. Found: C, 77.40; H, 6.83; N, 4.43.

2-(5-Methyl-4-phenylthiazol-2-yl)-2-phenylpropane (17): obtained as a yellow oil after column chromatography (hexane:AcOEt = 100:1); yield 70%; ^{1}H NMR ($CDCl_3$) δ 7.69−7.65 (m, 2 H), 7.43−7.35 (m, 4 H), 7.32−7.24 (m, 3 H), 7.21−7.15 (m, 1 H), 2.43 (s, 3 H), 1.84 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 175.3, 149.6, 147.9, 135.4, 128.5, 128.2, 128.1, 127.7, 127.1, 126.4, 126.2, 44.4, 30.0, 12.5. Anal. Calcd for $C_{19}H_{19}NS$: C, 77.77; H, 6.53; N, 4.77. Found: C, 78.00; H, 6.55; N, 4.53.

General Procedure for Reaction of Compounds 8a,c or 16 with 2-Methylfuran or 2-Methylthiophene in the Presence of Zinc Bromide. Preparation of Thiazoles

7a,b and 15. A solution of **8a**, **8c**, or **16** (4 mmol), 2-methylfuran or 2-methylthiophene (20 mmol), and zinc bromide (6 mmol) in 1,2-dichloroethane (50 mL) was refluxed for 24 h. Water (50 mL) was added and the mixture extracted with chloroform (3 × 50 mL). The combined organic layers were washed with saturated Na_2CO_3 (2 × 30 mL) and water (2 × 30 mL), dried over $MgSO_4$, and evaporated to give the crude product.

2-(5-Methylfuran-2-yl)-2-(4-phenylthiazol-2-yl)propane (7a): obtained as a brown oil after column chromatography (hexane:chloroform = 5:1); yield 65%; ^{1}H NMR ($CDCl_3$) δ 7.91–7.87 (m, 2 H), 7.40–7.33 (m, 2 H), 7.30–7.22 (m, 1 H), 7.26 (s, 1 H), 6.07 (d, 1 H, J = 3.1 Hz), 5.91–5.89 (m, 1 H), 2.23 (d, 3 H, J = 0.6 Hz), 1.82 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 177.5, 158.0, 154.4, 151.3, 134.8, 128.5, 127.7, 126.3, 112.4, 106.0, 105.8, 41.9, 28.0, 13.5. Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 72.42; H, 6.16; N, 4.51.

2-(5-Methylthien-2-yl)-1-phenyl-2-(4-phenylthiazol-2-yl)propane (7b): obtained as a light-yellow oil after column chromatography (hexane:AcOEt = 50:1); yield 82%; ^{1}H NMR ($CDCl_3$) δ 7.95–7.91 (m, 2 H), 7.42–7.33 (m, 2 H), 7.30–7.26 (m, 1 H), 7.24 (s, 1 H), 7.15-7.06 (m, 3 H), 6.96–6.88 (m, 2 H), 6.67 (d, 1 H, J = 3.5 Hz), 6.54–6.51 (m, 1 H), 3.76 (d, 1 H, J = 13.2 Hz), 3.49 (d, 1 H, J = 13.2 Hz), 2.38 (d, 3 H, J = 0.9 Hz), 1.73 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.9, 154.5, 148.6, 138.8, 137.3, 134.8, 130.5, 129.4, 128.6, 128.3, 127.8, 127.6, 126.3, 124.4, 112.3, 49.9, 47.5, 26.6, 15.3. Anal. Calcd for $C_{23}H_{21}NS_2$: C, 73.56; H, 5.64; N, 3.73. Found: C, 73.25; H, 5.55; N, 3.83.

2-(5-Methylfuran-2-yl)-2-(5-methyl-4-phenylthiazol-2-yl)propane (15): obtained as a yellow oil after column chromatography (hexane:chloroform = 5:1); yield 59%; ^{1}H NMR ($CDCl_3$) δ 7.66–7.64 (m, 2 H), 7.44–7.38 (m, 2 H), 7.34–7.26 (m, 1 H), 6.08 (d, 1 H, J = 3.0 Hz), 5.92–5.90 (m, 1 H), 2.48 (s, 3 H), 2.27 (d, 3 H, J = 1.0 Hz), 1.79 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 173.3, 158.3, 151.2, 149.8, 135.5, 128.5, 128.2, 127.7, 127.2, 105.9, 105.6, 41.7, 27.8, 13.6, 12.5. Anal. Calcd for $C_{18}H_{19}NOS$: C, 72.69; H, 6.44; N, 4.71. Found: C, 73.08; H, 6.72; N, 4.37.

General Procedure for Reduction of Compounds 11a,b with Zinc and Acetic Acid. Preparation of Thiazoles 12a,b. Zinc metal (2.60 g, 40 mmol) was added to a solution of **11a** or **11b** (2 mmol) in acetic acid (10 mL) and ethanol (20 mL) and the mixture stirred at reflux for 2 days. The solvent was evaporated and chloroform (100 mL) added. The insoluble material was filtered off and the filtrate washed with water (2 × 50 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product.

***N*-Phenyl-4-phenylthiazol-2-acetamide (12a):** obtained as yellow needles after recrystallization from chloroform/hexane; mp 128–129 °C; yield 86%; ^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1 H), 7.91–7.85 (m, 2 H), 7.59–7.54 (m, 2 H), 7.47–7.26 (m, 6 H), 7.12-7.06 (m, 1 H), 4.13 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 165.1, 163.4, 155.1, 137.6, 133.7, 128.9, 128.8, 128.3, 126.1, 124.3, 119.8, 113.1, 40.6. Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.21; H, 4.79; N, 9.54.

***N*-*tert*-Butyl-4-phenylthiazol-2-acetamide (12b):** obtained as light yellow needles after recrystallization from chloroform/hexane; mp 125–127 °C; yield 73%; ^{1}H NMR (DMSO-d_6) δ 7.98–7.92 (m, 4 H), 7.44 (t, 2 H, J = 7.6 Hz), 7.33 (t, 1 H, J = 7.4 Hz), 3.93 (s, 2 H), 1.30 (s, 9 H); ^{13}C NMR (DMSO-d_6) δ 166.9, 164.4, 153.1, 134.2, 128.7, 125.8, 114.6, 50.3, 40.7, 28.4; HRMS: m/z for $C_{15}H_{18}N_2OS$ (M^+ + 1) calcd 275.1218, found 275.1222.

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