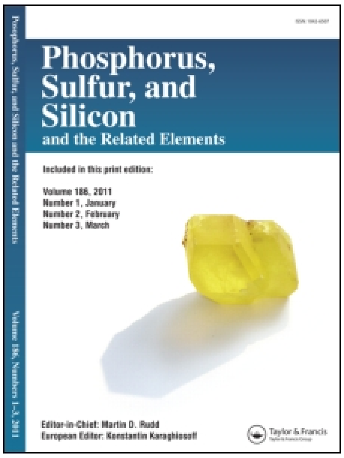

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Novel Synthesis of Pyrido[2,1-B]Benzothiazoles and 1,3-Benzothiazole Derivatives

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NOVEL SYNTHESIS OF PYRIDO[2,1-B]BENZOTHIAZOLES AND 1,3-BENZOTHIAZOLE DERIVATIVES

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A variety of new pyrido[2,1-b]benzothiazole and benzothiazoles, have been prepared via the reaction of 2-substituted methylthiazole with α,β-unsaturated nitriles and activated methylene compounds. The structures of the reaction products were established based on the elemental analyses and spectral data (IR, ^{1}H-, ^{13}C-NMR, MS).

Keywords: Pyrido[2,1-*b*]benzothiazoles; α,β-Unsaturated nitriles; 2-mercaptoaniline; Thioglycolic acid; Malononitrile; Ethyl acetoacetate

Continuing our interest in the development of efficient and simple procedures for the synthesis of fused heterocyclic nitrogen compounds, [1-3] we have previously reported several new approaches for the synthesis of condensed heterocycles utilizing 2-substituted methylazolyl derivatives as starting materials. [4-6] In conjunction with this work, we report here in a novel synthesis of pyrido[2,1-*b*]benzothiazoles and thiazole derivatives utilizing the benzothiazol-2-ylacetonitrile **4** as starting material. Compound **4** was prepared by the reaction of 2-mercaptoaniline (**1**) and malononitrile (**2**) in an EtOH/AcOH mixture at room temperature. Compound **4** reacted with thioglycolic acid in refluxing ethanol containing a catalytic amount of piperidine in a 1:1 molar ratio to give a condensation product by water elimination. The mass spectral data for this product revealed a molecular formula $C_{11}H_8N_2S_2O$ (m/z = 248). Three tautomeric structures **6a-c** were considered. The structure of **6a** was readily ruled out

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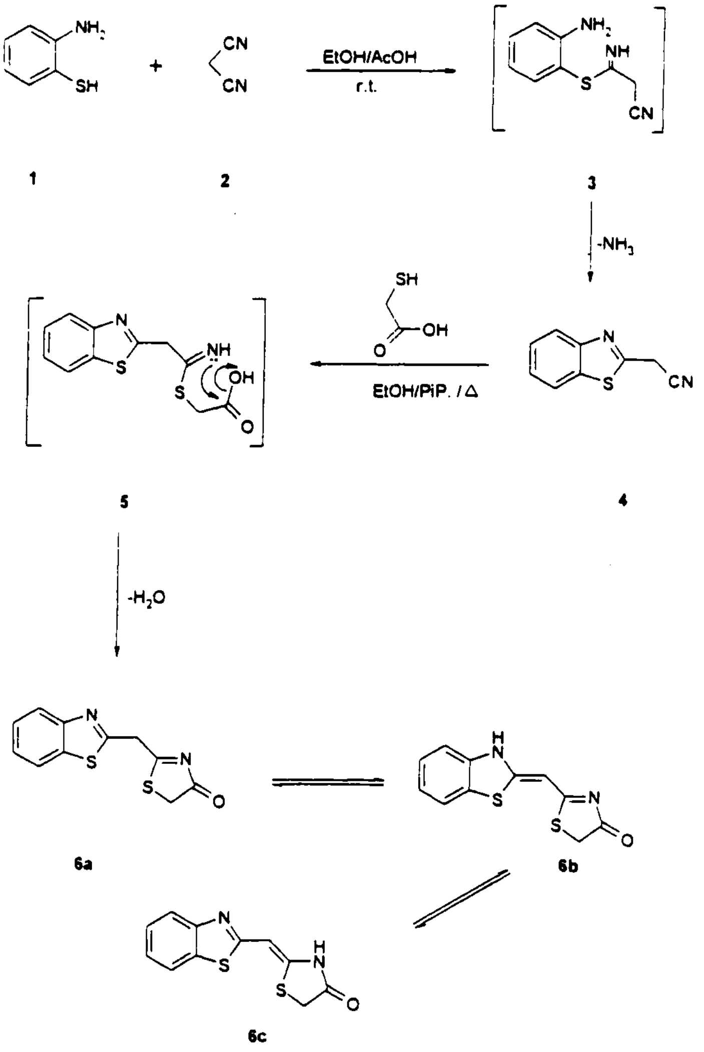
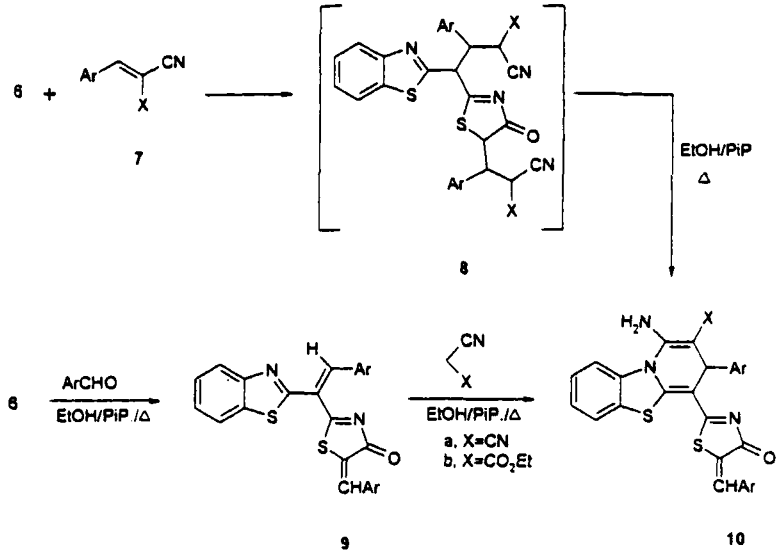
based on the ^1H NMR spectrum that revealed one proton signal at $\delta = 6.37$. This signal can only interpreted in terms of the 2-(1,3-benzothiazol-2-yl)-methylidene-2-thiazolin-4-one (**6c**) or possible tautomer **6b**. The formation of **6** by reaction of **4** with thioglycolic acid is assumed to proceed via the intermediacy of **5** formed by addition of thioglycolic acid to the cyano group in **4**. Compound **6** bearing latent functional substituents were found to be useful for synthesizing fused ring derivatives. Thus, **6** readily reacted with aldehydes in refluxing ethanol containing a catalytic amount of piperidine in a 1:2 molar ratio to give the corresponding diarylidene derivatives **7a-d**. Compound **6** reacted with arylmethylidenemalononitriles **8a-d** and ethyl arylmethylidenecyanoacetates **8e-f** to yield products for which structure **10** was assigned. Although one may argue that the reaction of **6** with **8** may involve benzothiazole or thiazole ring nitrogen, involvement of benzothiazole ring nitrogen leading to **10** was assumed based on its greater nucleophilicity than the other nitrogen center. Compounds **10** could also be prepared by reaction of thiazoles **7** with malononitrile or ethyl cyanoacetate. Formation of **10** from **6** and **8** may be assumed to proceed via the 1:2 Michael adduct intermediates **9** which cyclize with the loss of malononitrile or ethyl cyanoacetate to give the final product **10**. Mass spectral data for compound **10a** revealed a molecular formula $C_{28}H_{18}N_4S_2O$ (m/z = 490). ^1H NMR spectroscopy confirmed this structure for the product. Thus, ^1H NMR spectroscopy revealed the presence of a singlet at $\delta = 4.83$, assigned to the 1,4-dihydropyridine H-4 proton, a broad band at $\delta = 6.53$, assigned to the amino group, and a multiplet at $\delta = 7.24$–8.10, assigned to aromatic protons. The ^{13}C NMR spectrum revealed a signal at $\delta = 62.4$, assigned to the parafinic carbon at position 3, all the other carbon values being in agreement with the proposed structure and also are consistent with an analogues known compound.[5] Compound **4** reacted with ethyl acetoacetate to give 1-oxo-1H-pyrido[2,1-b]-[1,3]benzothiazole-3 -methyl-4-carbonitrile (**12**). The structure of **12** was established by mass spectrometry, IR, and ^1H NMR data. Thus, the mass spectrum of compound **12** showed a molecular ion corresponding to the formula $C_{13}H_8N_2SO$ ($M^+ = 240$). The IR spectra showed a CN absorption at 2205 cm^{-1}, and its ^1H NMR spectra revealed a band at $\delta = 2.51$ assigned to a methyl group and a band at $\delta = 9.02$, assigned to a pyridone H-3 proton.

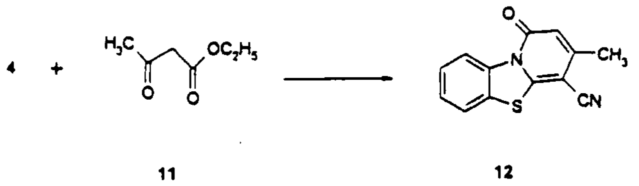
These results indicate that the reaction of 2-cyanobenzothiazole **4** with thioglycolic acid can be utilized as an expedient route for the synthesis of a



bithiazolyl derivative, which can be utilized as an excellent starting material for the synthesis of thiazolinylpyrido[2,1-b]benzothiazoles, via a Michael addition and cyclization. Such compounds appear promising for further chemical transformations and for biological evaluations.



9	Ar	**10**	Ar	X	Ar	X
	a, C_6H_5		a, C_6H_5	CN	e, C_6H_4	CO_2Et
	b, 2-Cl-C_6H_4		b, 2-Cl-C_6H_4	CN	f, 2-Cl-C_6H_4	CO_2Et
	c, 4-H_3C-C_6H_4		c, 4-H_3C-C_6H_4	CN	g, 4-H_3C-C_6H_4	CO_2Et
	d, 4-H_3OC-C_6H_4		d, 4-H_3CO-C_6H_4	CN	h, 4-H_3CO-C_6H_4	CO_2Et



EXPERIMENTAL

All melting points are uncorrected. IR spectra were obtained (KBr discs) on a pye Unicam Spectra-1000 or on a Shimadzu IR instrument. ^1H NMR spectra were measured on a Varian 400 MHz spectrometer for solutions in

$(CD_3)_2SO$ using $SiMe_4$ as internal standard. Analytical data were obtained from the Microanalytical Data Center at Cairo University. Compound **4** was prepared following literature procedures[7].

Benzothiazol-2-yl acetonitrile (4)

A solution of 2-aminothiophenol (0.1 mol) in ethanol (50 ml), malononitrile (0.1 mol) and acetic acid (0.1 mol) was stirring over night. The precipitate was filtered off and recrystallized from ethanol.

4: pale yellow, mp 103°C, 1.4 g (80 %).

2-(1,3-Benzothiazol-2-yl)-methylidene-2-thiazolin-4-one (6)

A solution of **4** (0.01 mol) in ethanol (20 ml), thioglycolic acid (0.01 mol) and piperidine (3 drops) was refluxed for 3 hours and then cooled to room temperature. The precipitate was filtered off and recrystallized from ethanol.

6: 1.7 g (70%) mp 160 °C. IR (KBr) cm^{-1} 1707 (C=O). ^1H NMR (DMSO-*d*6) δ 3.93 (s, 2H, CH_2), 6.37 (s, 1H, CH), 7.3–8.0 (m, 4H, C_6H_4) $C_{11}H_8N_2S_2O$ (M^+= 248); Calcd: C, 53.2; H, 3.2; N, 11.3. Found: C, 53.3; H, 3.0; N, 11.0 %.

2-(β-Benzothiazolestyryl)-5-arylidene-2-thiazolin-4-ones (7a-d)

General procedure

A solution of **6** (0.01 mol) in ethanol (20 ml), an aldehyde (0.02 mol) and piperidine (3 drops) was refluxed for 3 hours. The solution was left to cool to room temperature. The precipitate was filtered offand recrystallized from an appropriate solvent.

7a: 3.0 g (73%), mp 280 °C. IR (KBr) cm^{-1} 1681 (C=O). ^1H NMR (DMSO-d_6) δ 7.25–8.09 (m, 14H, $2C_6H_5$, C_6H_4). $C_{25}H_{16}N_2S_2O$ (M^+ = 424); Calcd: C, 70.7; H, 3.7; N, 6.6. Found: C 70.6; H, 4.0; N, 7.0 %.

7b: 3.5 g (72%) mp 290 °C IR (KBr) cm^{-1} 1704 (C=O) $C_{25}H_{14}N_2S_2OCl_2$ Calcd: C, 60.9; H, 2.8; N, 5.7, Found: C, 61.1; H, 2.7; N, 5.3%.

7c: 3.8 g (85%), mp 180 °C. IR (KBr) cm^{-1} 1680 (C=O) $C_{27}H_{20}N_2S_2O$. Calcd: C, 71.6; H, 4.4; N, 6.2. Found: C, 71.9; H, 4.6; N, 6.3%.

7d: 4.3 g (90%), mp 230 °C. IR (KBr) cm^{-1} 1698 (C=O). ^1H NMR (DMSO-d_6) δ: 3.27 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 6.59–8.02 (m, 14H, $3C_6H_4$, 2CH). $C_{27}H_{20}N_2S_2O_3$, Calcd: C, 66.9; H, 4.1; N, 5.7. Found: C, 66.7; H, 4.1; N, 5.4 %.

1-Amino-3-aryl-3H-pyrido[2,1-b]benzothiazol-4-(5-arylidene-4-oxo-2-thiazolin)-2-carbonitrile (10a-d) and Ethyl 1-amino-3-aryl-3H-pyrido[2,1-b]benzothiazol-4-(5-arylidene-4-oxo-2-thiazolin)-2-carboxylates (10e-h)

Method (a) General Procedure

A solution of **6** (0.01 mol) in ethanol (20 ml), along with arylmethylidene mlononitriles **8a-d** or ethyl arylmethylidenecyanoacetate **8e-h** (0.01 mol) and piperidine (3 drops) was refluxed for 5 hours. The reaction mixture was left to cool to room temperature. The precipitate was filtered off and recrystallized from an appropriate solvent.

Method (b) General Procedure

A solution of **7** (0.01 mol) in ethanol (20 ml), malononitrile or ethyl cyanoacetate (0.01 mol), and piperidine (3 drops) was refluxed for 3 hours. The reaction mixture was left to cool to room temperature. The formed solid product was filtered off and recrystallized from the appropriate solvent.

10a: 3.9 g (80%), mp 260 °C. IR (KBr) cm^{-1} 3373, 3313, 3221 (NH_2), 2192 (CN), 1706 (C=O). ^1H NMR (DMSO-d_6) δ: 4.83 (s, 1H. pyridine H-4), 6.53 (s, br, 2H, NH_2), 7.24–8.10 (m, 15H, $2C_6H_5$, C_6H_4, CH). $C_{28}H_{18}N_4S_2O$ (M^+ = 490). Calcd: C, 68.5; H, 3.7; N, 11.4. Found: C, 68.9; H, 3.3; N, 11.0 %.

10b: 3.9 g (71%), mp 220 °C. IR (KBr) cm^{-1} 3562, 3276 (NH_2), 2190 (CN), 1708 (C=O). ^1H NMR (DMSO-d_6) δ 5.30 (s, 1H, pyridine H-4), 6.48 (s, br, 2H,NH_2), 7.23–8.04 (m, 13H, $3C_6H_4$, CH). $C_{28}H_{16}N_4S_2OCl_2$ (M^+ =559), Calcd: C, 60.1; H, 2.9; N, 10.0. Found: C, 60.0; H, 3.0; N, 9.6%.

10c: 3.8 g (73%), mp 230 °C. IR (KBr) cm^{-1} 3368 (NH_2), 2196 (CN), 1704 (C=O). $C_{30}H_{22}N_4S_2O$ (M^+ = 518), Calcd: C, 69.5; H, 4.2; N, 10.8. Found: C, 69.9; H, 4.6; N, 11.0%.

10d: 3.5 g (65%), mp 270 °C. IR (KBr) cm^{-1} 3211 (NH_2), 2187 (CN), 1704(C=O). ^{1}H NMR (DMSO-$\underline{d}_6$) δ 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.58 (s, br, 2H, NH_2), 7.16–8.02 (m, 13H, 3 C_6H_4, CH). $C_{30}H_{22}N_4S_2O_3$, Calcd: C, 65.5; H, 4.0; N, 10.2. Found: C, 65.1; H, 3.9; N, 9.7 %.

10e: 3.7 g (70%), mp 270 °C. IR (KBr) cm^{-1} 3651, 3393, 3257 (NH_2), 1702 (CO), 1730 (CO). ^{1}H NMR (DMSO-$\underline{d}_6$) δ: 1.28 (t, 3H, ester CH_3), 4.12 (q, 2H, ester CH_2), 4.98 (s,1H, pyridine H-4), 7.26 (s, br, 2H, NH_2), 7.39–8.65 (m, 15H, 2C_6H_5, C_6H_4, CH). $C_{30}H_{23}N_3S_2O_3$ ($M^+ = 537$), Calcd: C, 67.0; H, 4.2; N, 7.8. Found: C, 66.7; H, 4.1; N, 7.7%.

10f: 4.6 g (77%), mp 210 °C IR (KBr) cm^{-1} 3379, 3239 (NH_2), 1705 (C=O), 1735 (CO). ^{1}H NMR (DMSO-$\underline{d}_6$) δ: 1.18 (t, *J*=7.5 Hz, 3H, ester CH_3), 4.11 (q, *J*=7.0 Hz, 2H, ester CH_2), 5.36 (s, 1H, pyridine H-4), 7.29–9.8 (m, 15H, 3C_6H_4, NH_2, CH). $C_{30}H_{21}N_3S_2O_3Cl_2$ (M^+ = 606), Calcd: C, 59.4; H, 3.4; N, 6.9. Found: C, 59.5; H, 3.7; N, 6.7%.

10g: 3.6 g (64%), mp 220 °C. IR (KBr) cm^{-1} 3386 (NH_2), 1701 (C=O), 1740 (CO). ^{1}H NMR (DMSO-$\underline{d}_6$) δ 1.29 (t, *J*=7.0 Hz, 3H, ester CH_3), 2.42 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 4.12 (q, *J*=7.0 Hz, 2H, ester CH_2), 4.96 (s, 1H, pyridine H-4), 7.29–8.64 (m, 13H, 3C_6H_4, CH), 7.07 (s, br, 2H, NH_2). $C_{32}H_{27}N_3S_2O_3$ (M^+ = 565), Calcd: C, 67.9; H, 4.8; N, 7.4. Found: C,67.7; H, 4.9; N, 7.0%.

10h: 4.4 g (75%), mp 220 °C. IR (KBr) cm^{-1} 3383 (NH_2), 1709 (C=O), 1735 (CO). ^{1}H NMR (DMSO-$\underline{d}_6$) δ 1.34 (t, *J*= 7.0 Hz, 3H, CH_3), 3.83 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.37 (q, *J*=6.5 Hz, 2H, CH_2), 5.0 (s, 1H, pyridine H-4), 6.57 (s, 2H, NH_2), 7.15–8.32 (m, 13H, 3C_6H_4, CH). ^{13}C NMR (DMSO-$\underline{d}_6$) δ 14.3 (CH_3), 55.7 (OCH_3), 56.0 (OCH_2), 62.4 (C-3), 122.1–133.8 (aromatic carbons), 142.2 (C-4), 154.6 (C-2), 158.4 (C-1), 160.8 (C-5), 163.9 (CO), 167.3 (ester CO); $C_{32}H_{27}N_3S_2O_5$, Calcd: C, 64.3; H, 4.5; N, 7.0. Found: C, 64.1; H,4.9; N, 6.9%.

1-Oxo-1H-pyrido[2,1-b] benzothiazol-3-methyl-4-carbonitriles(12)

A solution of **4** (0.01 mol) in ethanol (20 ml), ethyl acetoacetate (0.01 mol), and piperidine (3 drops) was refluxed for three hours. The reaction mixture was left to cool to room temperature. The precipitated solid was filtered off and recrystallized from ethanol.

12: 1.9 g (80%), mp 250 °C. IR (KBr) cm^{-1} 2205 (C≡N),1673 (C=O). ^{1}H NMR (DMSO-$\underline{d}_6$) δ 2.51 (s, 3H, CH_3), 6.4 (m, 1H, aromatic proton), 7.56–7.65 (m, 2H, aromatic protons), 8.13 (m, 1H, aromatic protons), 9.02 (s, 1H, pyridine H-3). $C_{13}H_8N_2SO$ ($M^+ = 240$), Calcd: C, 65.0; H, 3.3; N, 11.6. Found: C, 65.3; H, 3.5; N, 11.7%.

References

1. G. E. H. Elgemeie and B. A. Hussain, *Tetrahedron*, **50**, 199 (1994).
2. G. E. H. Elgemeie and N. M. Fathy, *Tetrahedron*, **51**, 3345 (1995).
3. G. E. H. Elgemeie, A. H. Elghandour, A. M. Elzanate and S. A. Ahmed, *J. Chem. Soc. Perkin Trans. 1*, 3285 (1997).
4. M. A. Azzem, G. E. H. Elgemeie, N. A. Neguib, H. M. Fahmy and Z. M. Elmassry, *J. Chem. Soc. Perkin Trans 2*, 545 (1990).
5. G. E. H. Elgemeie and F. M. Abdel Aal, *Heterocycles*, **24**, 349 (1986).
6. G. E. H. Elgemeie and N. M. Fathy, *Sulfur Lett.*, *7*, 189 (1988).
7. K. Saito, S. Kampe and Y. Nanano, *Synthesis*, 210 (1983).