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Regioselective synthesis of 2-[(*E*)-(benzo[*d*]thiazol-2(3*H*)-ylidene)(cyano)methyl]thiazoles

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Abstract

Cyclocondensation of 2-[bis(methylthio)methylene]malononitrile and 2-amino-benzenthiol afforded 2-(benzo[*d*]thiazol-2-yl) malononitrile. This compound, on treatment with phosphorus pentasulfide, gave the corresponding thioamide derivative in a regioselective manner. Reaction of this compound with several α-bromocarbonyl compounds gave new 2-[(*E*)-(benzo[*d*]thiazol-2(3*H*)-ylidene)(cyano)methyl]thiazoles.

Keywords: α-bromocarbonyl compounds; benzo[d]thiazole; Hantzsch's synthesis; heterocyclization; phosphorus pentasulfide; regioselective synthesis; thiazole.

Introduction

Heterocycles are widely used in the development of modern pharmaceuticals, this being one of the reasons why continuous efforts are made towards the design of amenable synthetic approaches for the synthesis of new heterocyclic systems. Thiazoles play a prominent role in nature as they are found in numerous biologically active compounds. For example, the thiazolium ring present in vitamin B_1 and its coenzyme complex plays an important role in the decarboxylation of α-keto-acids. A large number of thiazole-based derivatives have emerged as potential pharmaceutical candidates for the treatment of inflammation, cancer, hyperlipidemia, hypertension, and HIV infections (Metzger, 1984; Kumar et al., 1993; Bell et al., 1995; Tsuruni et al., 1995; Miwatashi et al., 2005; Papadopoulou et al., 2005; Wang et al., 2005).

Several methods for the synthesis of thiazole derivatives have been developed (Cook et al., 1949; Dubs and Stuessi, 1976; van Leusen and Wildeman, 1977; Sowinski and Toogood, 1996), the most widely used method being Hantzsch's synthesis utilizing thioamides and α-halocarbonyl compounds as the starting materials (Flaig and Hartmann, 1997). Useful variants include the use of an α-diazoketone in place of the α-halocarbonyl component (Kim et al., 1995), reaction of 2-acylaminoketones with phosphorus pentasulfide and, in an adaptation of the Robinson-Gabriel synthesis, the conversion of 1,3-diketones into their 2-phenyl-iodonium derivatives and reaction of these with thioureas producing 2-amino-5-acyl-thiazoles (Moriarty et al., 1992; Kamproudi et al., 1996).

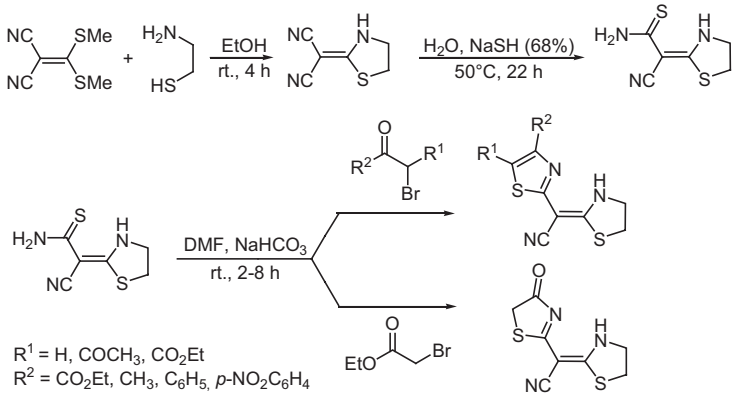
Some heterocycles containing a thiazolecarbonitrile moiety have already been synthesized by employing the Hantzsch's method (Hussain et al., 1988; Dawood, 2001; Abdelhamid and Abdelaziz, 2008), and we previously described the regioselective synthesis of new 2-(*E*)-cyano(thiazolidin-2-ylidene) thiazoles by the reaction of (*E*)-2–cyano-2-(thiazolidin-2-ylidene)ethanethioamide with various α-bromocarbonyl compounds. Corresponding thioamide was prepared as a pure geometric isomer by the reaction of 2-(thiazolidin-2-ylidene) malononitrile with sodium hydrosulfide hydrate, as shown in Scheme 1(Bakavoli et al., 2009).

In connection with our interest in the synthesis of new polyfunctionalized thiazoles as potential precursors for the synthesis of biologically important fused thiazoles, we have studied the reaction of (*E*)-2-(benzo[*d*]thiazol-2(3*H*)-ylidene)-2-cyanoethanethioamide (**2a**) with several α-bromocarbonyl compounds in order to synthesize the new 2-[(*E*)-(benzo[*d*] thiazol-2(3*H*)-ylidene)(cyano)methyl]thiazoles **3a–f** (Scheme 2).

Results and discussion

Products **3a–f** were prepared in a three-step procedure starting from the dinitrile **1** (Scheme 2). The reaction of benzo[*d*] thiazole **1** with phosphorus pentasulfide, in principle, can afford the *E* (**2a**) or *Z* (**2b**) isomer of 2-(benzo[*d*]thiazol-2(3*H*)-ylidene)-2-cyanoethanethioamide. An unequivocal decision between these two geometric isomers was possible on the basis of our previously reported work on 2-(*E*)-cyano(thiazolidin-2-ylidene)thiazoles (Bakavoli et al., 2009). In this context, the *E* isomer is preferred over its *Z* counterpart. Subsequent reaction of isomer **2a** with various α-bromocarbonyl compounds led to the formation of the new thiazole derivatives **3a–f**.

The structural assignments of compounds **2a** and **3a–f** were based on their analytical and spectral data. For example, ^{1}H nuclear mass resonance (NMR) spectrum of dinitrile **1** was devoid of any exchangeable proton signal, which is a good evidence for formation of the thiazole ring in the product. Product **2a** of the reaction of compound **1** with phosphorus pentasulfide showed two broad signals due to NH_2 and NH groups at 8.49 ppm and 12.97 ppm, respectively, indicating the transformation of the product into a thioamide derivative. ^{1}H NMR spectra of products **3a–f** showed multiplet signals at 7.18–8.02 ppm attributed to four aromatic protons of the benzo[*d*]thiazole system, and broad signals due to the NH



Scheme 1 Total synthesis of 2-(*E*)-cyano(thiazolidin-2-ylidene)thiazoles.

group at 12.71–13.18 ppm. The infrared (IR) spectra of **2a** and **3a–f** showed absorption bands at 3,413–3,446 cm^{-1} corresponding to NH groups. All this evidence plus the mass spectral and microanalytical data strongly support the given structures.

Conclusions

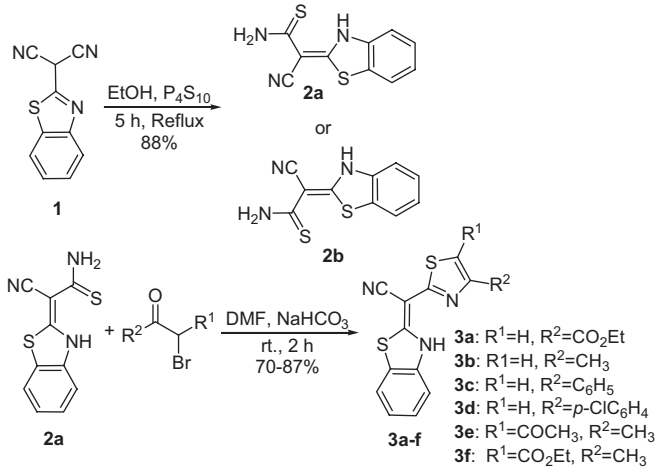
In summary, several new functionalized thiazoles have been synthesized regioselectively by the reaction of a thioamide **2a** with several α-bromocarbonyl compounds. The thioamide itself was synthesized in a regioselective manner by the reaction of functionalized benzo[*d*]thiazole with phosphorus pentasulfide. The geometry of the suggested *E*-regioisomer is consistent with our previous work.

Experimental section

Melting points were recorded on an Electrothermal type 9100 melting point apparatus and are uncorrected. The IR spectra were determined using KBr disks with a 4300 Shimadzu spectrometer and only major absorptions are listed. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer in DMSO-d_6. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS) as internal standard; coupling constants *J* are given in hertz. Low-resolution mass spectra (EI, 70 eV) were measured on a Varian Mat CH-7 instrument. Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyzer. Acetonitrile was distilled from $CaCl_2$.

Compound **1** was obtained according to the published method (Huang and Shi, 1990). All other chemicals used in this study were commercially available.

(*E*)-2-(Benzo[*d*]thiazol-2(3*H*)-ylidene)-2-cyanoethanethioamide (2a) This compound was synthesized according to a procedure reported by Kaboudin and Elhamifar (2006) with slight modification as follows. A solution of P_4S_{10} (4.6 g, 0.02 mol) in absolute ethanol (20 ml) was stirred for 1 h. Dinitrile **1** (2.0 g, 0.01 mol) was added and the resulting mixture was heated under reflux for 5 h. The reaction mixture was cooled to room temperature and the precipitated solid was filtered, washed with water (1×10 ml) and ethanol (2×5 ml), dried in air, and crystallized from CH_3CN to give **2a** (2.05 g, 88%); yellow needles; mp 251–252°C; IR: ν 3,431, 3,295, 2,173, 1,615 cm^{-1}; ^{1}H NMR: δ 7.57 (m, 3H, H-1,2,3), 7.85 (d, *J*=7.2 Hz, 1H, H-4), 8.49 (br., 2H, NH_2), 12.97 (br., 1H, NH); MS *m*/*z* 233 (M^+,



Scheme 2 Total synthesis of 2-[(*E*)-(benzo[*d*]thiazol-2(3*H*)-ylidene)(cyano)methyl]thiazoles **3a–f**.

5), 199 (100). Analysis calculated for $C_{10}H_7N_3S_2$: C, 51.48; H, 3.02; N, 18.01; S, 27.49. Found: C, 51.40; H, 2.99; N, 18.06; S, 27.55.

General procedure for the preparation of products 3a–f

A suspension of thioamide **2a** (0.47 g, 2 mmol), the appropriate α-bromocarbonyl compound (2 mmol) and sodium bicarbonate (0.17 g, 2 mmol) in *N,N*-dimethylformamide (DMF) (4 ml for **3a–d** and 8 ml for **3e,f**) was stirred at room temperature for 2 h. After dilution with water (10 ml), the resultant solid was filtered off, washed with water (1×10 ml) and ethanol (1×10 ml), dried in air, and crystallized from CH_3CN to give compound **3a–f**.

Ethyl 2-[(*E*)-(Benzo[*d*]thiazol-2(3*H*)-ylidene)(cyano) methyl]thiazole-4-carboxylate (3a) This compound was obtained from **2a** and ethyl bromopyruvate; yield 0.46 g (70%); yellow needles; mp 197–199°C; IR: ν 3,433, 2,198, 1,647 cm^{-1}; ^1H NMR: δ 1.32 (t, *J*=6.8 Hz, 3H, CH_3), 4.30 (q, *J*=6.8 Hz, 2H, CH_2), 7.42 (m, 3H, H-1,2,3), 7.89 (d, *J*=7.5 Hz, 1H, H-4), 8.18 (s, 1H, C=C-H), 12.92 (br., 1H, NH); MS *m/z* 329 (M^+, 7), 283 (100). Analysis calculated for $C_{15}H_{11}N_3O_2S_2$: C, 54.69; H, 3.37; N, 12.76; S, 19.47. Found: C, 54.65; H, 3.32; N, 12.81; S, 19.49.

(*E*)-2-[Benzo[*d*]thiazol-2(3*H*)-ylidene]-2-(4-methylthiazol-2-yl)acetonitrile (3b) This compound was obtained from **2a** and bromoacetone; yield 0.39 g (72%); yellow needles; mp 202–203°C; IR: ν 3,446, 2,173 cm^{-1}; ^1H NMR: δ 2.30 (s, 3H, CH_3), 6.75 (s, 1H, C=C–H), 7.27 (m, 2H, Ar–H), 7.80 (m, 2H, Ar–H), 12.71 (br., 1H, NH); MS *m/z* 271 (M^+, 4), 269 (100). Analysis calculated for $C_{13}H_9N_3S_2$: C, 57.54; H, 3.34; N, 15.48; S, 23.63. Found: C, 57.51; H, 3.39; N, 15.54; S, 23.56.

(*E*)-2-[Benzo[*d*]thiazol-2(3*H*)-ylidene]-2-(4-phenylthiazol-2-yl)acetonitrile (3c) This compound was obtained from **2a** and phenacyl bromide; yield 0.54 g (81%); white needles; mp 272–274°C; IR: ν 3,444, 2,192 cm^{-1}; ^1H NMR: δ 7.39 (m, 6H, Ar–H), 8.02 (m, 4H, Ar–H, C=C–H), 12.83 (br., 1H, NH); MS *m/z* 333 (M^+, 24), 331(100). Analysis calculated for $C_{18}H_{11}N_3S_2$: C, 64.84; H, 3.33; N, 12.60; S, 19.23. Found: C, 64.79; H, 3.41; N, 12.52; S, 19.28.

(*E*)-2-[Benzo[*d*]thiazol-2(3*H*)-ylidene]-2-[4-(4-chlorophenyl)thiazol-2-yl]acetonitrile (3d) This compound was obtained from **2a** and *p*-chloro-α-bromoacetophenone; yield 0.61 g (83%); red needles; mp 276–277°C; IR: ν 3,413, 2,175 cm^{-1}; ^1H NMR: δ 7.39 (m, 5H, Ar–H), 7.96 (m, 4H, Ar–H, C=C–H), 12.89 (br., 1H, NH); MS *m/z* 368 (M^+, 18), 153 (100). Analysis calculated for $C_{18}H_{10}ClN_3S_2$; C, 58.77; H, 2.74; N, 11.42; S, 17.43. Found: C, 58.69; H, 2.82; N, 11.39; S, 17.38.

(*E*)-2-(5-Acetyl-4-methylthiazol-2-yl)-2-[benzo[*d*]thiazol-2(3*H*)-ylidene]acetonitrile (3e) This compound was obtained from **2a** and 3-bromo acetylacetone; yield 0.54 g (87%); green needles; mp 264–266°C; IR: ν 3,421, 2,194, 1635 cm^{-1}; ^1H NMR: δ 2.45 (s, 3H, $COCH_3$), 2.61 (s, 3H, CH_3), 7.18 (m, 2H, Ar–H), 7.95 (m, 2H, Ar–H), 13.18 (br., 1H, NH); MS *m/z* 313 (M^+, 9), 107 (100). Analysis calculated for $C_{15}H_{11}N_3OS_2$; C, 57.49; H, 3.54; N, 13.41; S, 20.46. Found: C, 57.43; H, 3.48; N, 13.50; S, 20.51.

Ethyl 2-[(*E*)-(benzo[*d*]thiazol-2(3*H*)-ylidene)(cyano) methyl]-4-methylthiazole-5-carboxylate (3f) This compound was obtained from **2a** and ethyl 2-bromoacetoacetate; yield; 0.58 g (85%); green needles; mp 231–233°C; IR: ν 3,437, 2,183, 1697 cm^{-1}; ^1H NMR: δ 1.26 (t, *J*=7.0 Hz, 3H, CH_2CH_3), 2.58 (s, 3H, CH_3), 4.23 (q, *J*=7.0 Hz, 2H, OCH_2), 7.24 (m, 2H, Ar–H), 7.95 (m, 2H, Ar–H), 12.96 (br., 1H, NH); MS *m/z* 343 (M^+, 10), 271 (100). Analysis calculated for $C_{16}H_{13}N_3O_2S_2$: C, 55.96; H, 3.82; N, 12.24; S, 18.67. Found: C, 56.01; H, 3.78; N, 12.27; S, 18.71.

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