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Synthesis of Some Functionalized Thiazolo[3,2-b][1,2,4]triazoles

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A facile synthesis of some 6-aminothiazolo[3,2-b][1,2,4]triazole-5-carbonitriles in good yields has been developed through base catalyzed cyclocondensation of 1,2,4-triazole-3-thiones with bromomalononitrile. In case of phenyl derivative, hydrolysis of the cyano group into amide and subsequent cyclocondesation with benzoyl chloride afforded to the novel tricyclic compound 2,6-diphenyl[1,2,4]triazolo-[5',1':2,3][1,3]thiazolo[4,5-d]pyrimidin-8(7*H*)-one.

Key Words: 1,2,4-Triazole-3-thiones, Thiazolo[3,2-b][1,2,4]triazoles, [1,2,4]Triazolo[5',1':2,3][1,3]thiazolo[4,5-d]pyrimidines, Bromomalononitrile.

INTRODUCTION

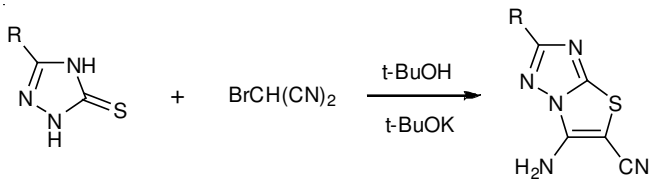
1,2,4-Triazoles and thiazoles are two class of heterocyclic compounds with wide-ranging biological activities. These compounds are reported to possess significant antiviral[1], antibacterial[2], antifungal[3], antiasthmatic[4], antiinflammatory[5], antitumor[6], anticonvulsant[7] and anticancer[8] activities.

The thiazolotriazoles are those compounds which contain in their structure two fused rings of thiazole and triazole. These condensed heterocyclic compounds can exist in both the isomer forms *i.e.*, thiazolo[3,2-b][1,2,4]triazole and thiazolo[2,3-c][1,2,4]triazole. The interest in the synthesis of thiazolo[3,2-b][1,2,4]triazoles emerges from the numerous reports on their diverse biological activities[9-11]. To the best of our knowledge, synthesis of amino and cyano functionalized thiazolo[3,2-b][1,2,4]triazoles has not been reported in the literature.

Prompted by these findings and due to our interest in the synthesis of heterocyclic compounds with potential biological activities[12-28], in this paper we wish to report an efficient approach to the synthesis of new functionalized derivatives of thiazolo[3,2-b][1,2,4]triazoles (**3a-e**) through cyclocondensation of 1,2,4-triazole-3-thiones (**1a-e**) with bromomalononitrile (**2**) (**Scheme-I**).

EXPERIMENTAL

Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. ^{1}H NMR



1a-e **2** **3a-e**

a: R = Me; **b**: R = Ph; **c**: = 4-BrC_6H_4; **d**: R = 3-ClC_6H_4; **e**: = R = 4-ClC_6H_4

Scheme-I: Synthesis of functionalized thiazolo[3,2-b][1,2,4]triazoles

(100 MHz) spectra were recorded on Bruker AC100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV.

General procedure for the synthesis of 6-aminothiazolo-[3,2-b][1,2,4]triazole-5-carbonitriles (3a-e): To a solution of the 1,2,4-triazole-3-thiones (**1a-e**)[29] (5 mmol) and potassium *tert*-butoxide (10 mmol) in *tert*-butanol (20 mL), bromomalononitrile (**2**) (6 mmol) was added. The reaction mixture was heated under reflux for 6-8 h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and neutralized by 1M HCl. The precipitate was filtered off, washed with *n*-hexane and recrystallized from ethanol to give new compounds **3a-e** in good yields.

Synthesis of 6-amino-2-phenylthiazolo[3,2-b][1,2,4]-triazole-5-carboxamide (4): 6-Amino-2-phenylthiazolo[3,2-b][1,2,4]triazole-5-carbonitrile (**3b**) (5 mmol) was dissolved in conc. H_2SO_4 (7 mL). The mixture was stirred for 12 h at room temperature and then neutralized by ammonia solution.

The precipitate was collected and washed with water and methanol respectively, then recrystallized from ethanol to give compound **4** in high yield.

Synthesis of 2,6-diphenyl[1,2,4]triazolo[5',1':2,3][1,3]-thiazolo[4,5-d]pyrimidin-8(7*H*)-one (5): A mixture of 6-amino-2-phenylthiazolo[3,2-b][1,2,4]triazole-5-carboxamide (**4**) (3 mmol) and benzoyl chloride (3.5 mmol) in pyridine (10 mL) was heated under reflux for 10 h. During the procedure, the reaction was monitored by TLC. Upon completion, the solvent was evaporated *in vacuo*. The crude product was collected and recrystallized from ethanol to give compound **5** in good yield.

Spectral data of compounds 3a-e, 4 and 5

6-Amino-2-methylthiazolo[3,2-b][1,2,4]triazole-5-carbonitrile (3a): Yield 74 %; m.p. 332-335 ºC; ^{1}H NMR (100 MHz, DMSO-d_6, δ ppm): 2.40 (s, 3H, CH_3), 8.22 (s br., 2H, NH_2); IR (KBr, ν_{max}, cm^{-1}): 2212 (CN), 3191 and 3275 (NH_2); MS, m/z : 179 (M^+).

6-Amino-2-phenylthiazolo[3,2-b][1,2,4]triazole-5-carbonitrile (3b): Yield 70 %; m.p. 306-308 °C; ^{1}H NMR (100 MHz, DMSO-d_6, δ ppm): 7.50-7.65 (m, 3H, arom-H), 8.00-8.20 (m, 2H, arom-H), 8.38 (s br., 2H, NH_2); IR (KBr, ν_{max}, cm^{-1}): 2202 (CN), 3162 and 3263 (NH_2); MS, m/z : 241 (M^+).

6-Amino-2-(4-bromophenyl)thiazolo[3,2-b][1,2,4]-triazole-5-carbonitrile (3c): Yield 68 %; m.p. 320-323 ºC; ^{1}H NMR (100 MHz, DMSO-d_6, δ ppm): 7.30 (s br., 2H, NH_2), 7.49 (d, 2H, *J* = 7.8 Hz, arom-H), 7.95 (d, 2H, *J* = 7.8 Hz, arom-H); IR (KBr, ν_{max}, cm^{-1}): 2208 (CN), 3302 and 3215 (NH_2); MS, m/z : 321 (M^+ + 2), 319 (M^+).

6-Amino-2-(3-chlorophenyl)thiazolo[3,2-b][1,2,4]-triazole-5-carbonitrile (3d): Yield 79 %; m.p. 318-320 °C; ^{1}H NMR (100 MHz, DMSO-d_6, δ ppm): 7.30-8.20 (m, 4H, arom-H), 8.33 (s br., 2H, NH_2); IR (KBr, ν_{max}, cm^{-1}): 2218 (CN), 3196 and 3283 (NH_2); MS, m/z: 277 (M^+ + 2), 275 (M^+).

6-Amino-2-(4-chlorophenyl)thiazolo[3,2-b][1,2,4]-triazole-5-carbonitrile (3e): Yield 83 %; m.p. 329-330 °C; ^{1}H NMR (100 MHz, DMSO-d_6, δ ppm): 7.58 (d, 2H, *J* = 7.3 Hz, arom-H), 8.03 (d, 2H, *J* = 7.3 Hz, arom-H), 8.39 (s br., 2H, NH_2); IR (KBr, ν_{max}, cm^{-1}): 2214 (CN), 3179 and 3267 (NH_2); MS, m/z: 277 (M^+ + 2), 275 (M^+).

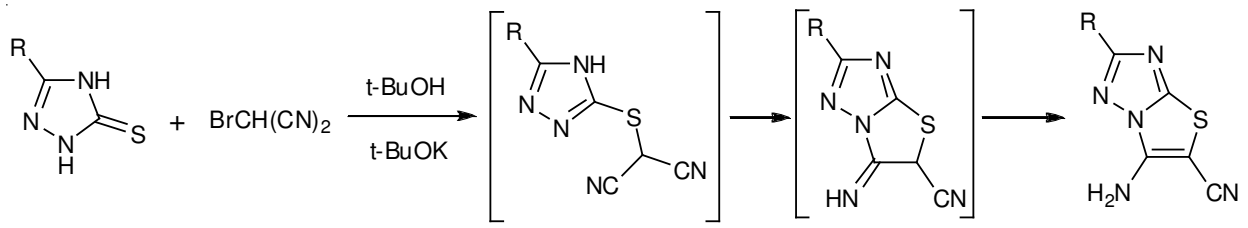
6-Amino-2-phenylthiazolo[3,2-b][1,2,4]triazole-5-carboxamide (4): Yield 89 %; m.p. 336-337 °C; ^{1}H NMR (100 MHz, DMSO-d_6, δ ppm): 7.37 (s br., 2H, NH_2), 7.40-8.25 (m, 7H, arom-H & NH_2); IR (KBr, ν_{max}, cm^{-1}): 1643 (C=O), 3152, 3249, 3304 and 3364 (two NH_2); MS, m/z : 259 (M^+).

2,6-Diphenyl[1,2,4]triazolo[5',1':2,3][1,3]thiazolo[4,5-d]pyrimidin-8(7*H*)-one (5): Yield 75 %; m.p. 395-396 °C; ^{1}H NMR (100 MHz, DMSO-d_6, δ ppm): 7.50-8.20 (m, 10H, arom-H), 11.65 (s, 1H, NH); IR (KBr, ν_{max}, cm^{-1}): 1654 (C=O), 3288 (NH_2); MS, m/z : 345 (M^+).

RESULTS AND DISCUSSION

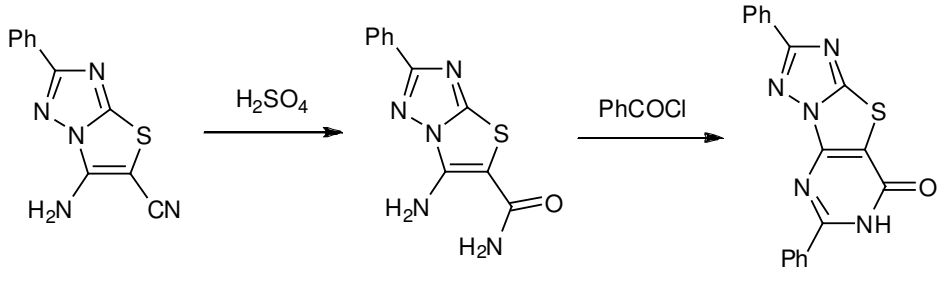
When 1,2,4-triazole-3-thiones (**1a-e**) was allowed to interact with bromomalononitrile (**2**) in refluxing *t*-butanol containing potassium *t*-butoxide, cyclocondensation reaction occurred giving the 6-aminothiazolo[3,2-b][1,2,4]triazole-5-carbonitriles (**3a-e**) (**Scheme-II**). A plausible mechanism for the present reaction may proceed as depicted in **Scheme-II**. The formation of the products **3a-e** was assumed to proceed *via* the intermediates [I] and [II]. However, under these conditions, attempts to isolate the intermediates failed when we carefully monitored the reactions. Based on our previous work[29], we believe that the cyclization of the intermediate [I] occur by nucleophilic attack of the nitrogen in 2-position of triazole at the cyano group.

The compounds **3a-e** with cyano and amino moieties can be used for the synthesis of new fused heterocyclic compounds. For example, in compound **3b**, hydrolysis of the cyano group



1a-e **2** **I** **II** **3a-e**

Scheme-II: Plausible mechanism for the formation of 6-aminothiazolo[3,2-b][1,2,4]triazole-5-carbonitriles



3b **4** **5**

Scheme-III: Synthesis of 6-diphenyl[1,2,4]triazolo[5',1':2,3][1,3]-thiazolo[4,5-d]pyrimidin-8(7*H*)-one

into amide followed by cyclocondensation with benzoyl chloride gave product identified as 2,6-diphenyl[1,2,4]-triazol[5',1':2,3][1,3]thiazolo[4,5-d]pyrimidin-8(7*H*)-one (**5**) (**Scheme-III**).

The structure of new products (**3a-e**, **4** and **5**) were established from their spectral data. For example, the ^{1}H NMR spectrum of **3b** in DMSO-d_6 showed a broad singlet 2H (NH_2) signal at δ 8.38 ppm which was removed on deuteration along with two multiplet at δ 7.50-7.65 ppm and δ 8.00-8.20 ppm due to 5 aromatic protons. The IR spectrum showed a band at 2202 cm^{-1} for CN absorption and two bands at 3162 and 3263 cm^{-1} for NH_2 group. Also, the molecular ion of compound **3b** was observed at m/z 241 (M^+), corresponding to the molecular formula $C_{11}H_7N_5S$.

Conclusion

A facile synthesis of some 6-aminothiazolo[3,2-b][1,2,4]-triazole-5-carbonitriles (**3a-e**) through cyclocondensation of 1,2,4-triazole-3-thiones (**1a-e**) with bromomalononitrile (**2**) is reported. Also, hydrolysis of the cyano group into amide in compound **3b** followed by cyclocondensation with benzoyl chloride gave a novel tricyclic compound, 2,6-diphenyl-[1,2,4]triazolo[5',1':2,3][1,3]- thiazolo[4,5-d]pyrimidin-8(7*H*)-one (**5**).

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