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Synthesis and Reactions of Some 2-Aminobenzothiazoles

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Abstract

N-(2-Benzothiazolyl)- and *N*-(6-methoxy-2-benzothiazolyl)cyanoacetamides **4, 5** resulted in the reaction of 2-aminobenzothiazole **1** or its 6-methoxy derivative **2** with 1-cyanoacetyl-3,5-dimethylpyrazole **3**. Both cyanoacetylamides **4** and **5** have been transformed into the corresponding 2-oxo-2*H*-pyrimido[2,1-b]-benzothiazole-3-carbonitrile **8** and its 8-methoxy derivative **9** by reaction with triethyl orthoformate, followed by cyclization.

Keywords: *N*-(2-benzothiazolyl)cyanoacetamides, 2-oxo-2*H*-pyrimido[2,1-b]benzothiazole-3-carbonitriles

Introduction

The availability of precursors and significant biological properties of the members known so far motivated our entry into the family of substituted benzothiazoles.

In our previous work, we found, that *N*-(2-benzothiazolyl)cyanoacetamide **4** and its 6-methoxy derivative **5** served as starting materials for polysubstituted 1-(2-benzothiazoyl)-2-pyridones [1, 2]. The present communication deals with the utilization of the above mentioned cyanoacetamides **4** and **5** in the synthesis of some fused heterocycles.

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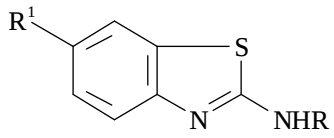
Results and Disscussion

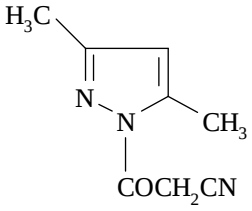
The treatment of 2-aminobenzothiazole **1** or its 6-methoxy derivative **2** with 1-cyanoacetyl-3,5-dimethylpyrazole **3** as cyanoacetylation agent [3, 4], resulted in the formation of the corresponding cyanoacetamides **4** and **5**. The reactions were carried out in boiling toluene, and gave 91 and 75% yields respectively [1, 2].

2-Oxo-2*H*-pyrimido[2,1-b]benzothiazole-3-carbonitrile **8** was prepared in very good yield (79%) in a one-pot reaction of cyanoacetamide **4** with triethyl orthoformate in hot nitrobenzene, followed by cyclization and splitting off of ethanol. Similarly, compound **5** gave 8-methoxy derivative **9** in 77% yield (Scheme 1). The cyanoacetamide **7**, prepared from the amine **6**, failed to react under similar conditions.

The neighbouring carbonyl and nitrile groups in compounds **8** and **9** should lend themselves to further annelation to tetracycles [5].



1: R = H, R^1 = H
2: R = H, R^1 = OCH_3
4: R = $COCH_2CN$, R^1 = H
5: R = $COCH_2CN$, R^1 = OCH_3



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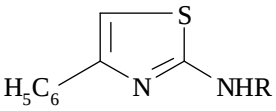
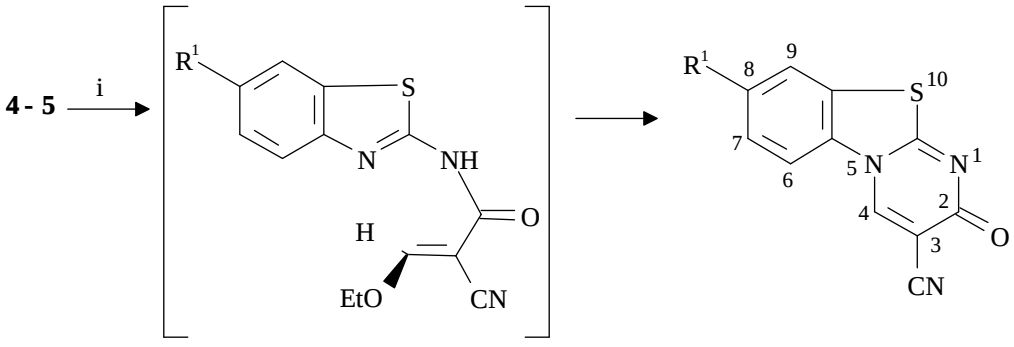


6: R = H
7: R = $COCH_2CN$

The infrared, ^{1}H-, ^{13}C-NMR and mass spectra of the prepared compounds were studied in order to confirm the proposed structures. Thus characteristic signals of the benzothiazole ring protons were observed in ^{1}H-NMR spectra of nitriles **8** and **9** at δ 7.21–8.10. As expected, the signal of *H*-4 of the fused pyrimidine ring was shifted downfield to δ 9.83 and 9.74 respectively. Also ^{13}C-NMR spectral data confirmed unequivocally the structures of target heterocycles.

The EI mass spectra of pyrimidobenzothiazoles **8** and **9** display relativily intense molecular ion peaks. The main directions of their fragmentation is the expulsion of neutral carbon monooxide and elimination of the species HC≡C-CN (Scheme 2).



Reagents and conditions:
(i) excess $HC(OEt)_3$, nitrobenzene, 190 °C.

Scheme 1. *Synthesis of fused heterocycles* ***8***, ***9***.

8: R^1 = H (79%)
9: R^1 = OCH_3 (77%)

Experimental Section

Infrared spectra of KBr discs were recorded with an FTIR PU 9800 (Philips) spectrometer. Proton and ^{13}C-NMR spectra were taken with the Varian VXR-300 spectrometer (300 MHz for ^{1}H and 60 MHz for ^{13}C) in DMSO-d_6. Chemical shifts were related to that of the solvent. The ^{13}C-NMR spectra were assigned using the SINEPT and HETCOR techniques and a set of CHEM3WIND programs. Mass spectra (EI) were measured with an MS 902 S (A. E. I. Manchester) spectrometer, equipped with direct inlet, electron energy of 70 eV, trap current 100 mA, ion source temperature 220–240 °C.

2-Aminobenzothiazole **1**, 2-amino-6-methoxybenzothiazole **2**, 1-cyanoacetyl-3,5-dimethylpyrazole **3** and 2-amino-4-phenylthiazole **6** were prepared according to know procedures [6, 7, 3, 8].

2-Oxo-2H-pyrimido[2, 1-b]benzothiazole-3-carbonitrile ***8***

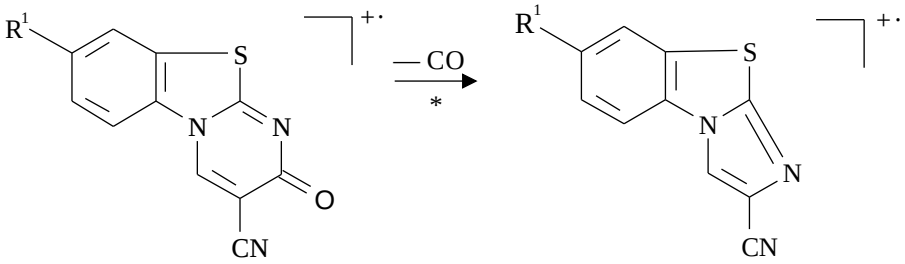
A mixture of cyanoacetamide **4** (2.17 g, 10 mmol) and triethyl orthoformate (3.71 g, 25 mmol) in nitrobenzene (10 ml) was kept at 190–200 °C for 3 h with occasionally shaking. For 0.5 h the solid was gradually separated from the original solution. After cooling, the precipitated *title compound* **8** (1.8 g, 79%) was filtered off with suction, washed with diethyl ether (5 ml) and recrystallized from acetic acid as a yellow solid.

mp 312—316 °C

IR (KBr) 2230 (C≡N), 1655 (C=O) cm^{-1}.

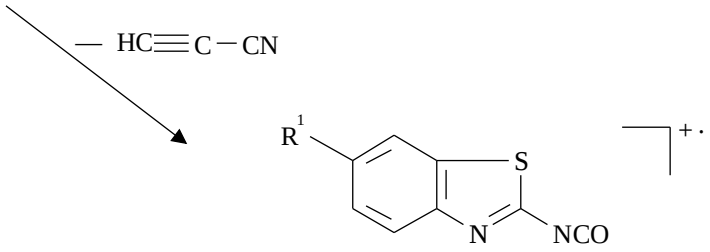
^{1}H-NMR (300 MHz; DMSO-d_6) 7.54 (1 H, t, $J_{8,9}$ = $J_{8,7}$ 7.6 Hz, 8-H), 7.64 (1 H, t, $J_{7,6}$ = $J_{7,8}$ 7.8 Hz, 7-H), 8.04 (1 H, d, $J_{9,8}$ 7.7 Hz, 9-H), 8.10 (1 H, d, $J_{6,7}$ 8.3 Hz, 6-H), 9.83 (1 H, s, 4-H).

^{13}C-NMR (60 MHz; DMSO-d_6) 97.2 (C, C-3), 113.3 (CH, C-6), 114.8 (CN, 3-CN), 123.3 (C, C-9a), 124.0 (CH,



8: R^1 = H, $M^{+\cdot}$, *m/z* 227 (62%)
9: R^1 = OCH_3, $M^{+\cdot}$, *m/z* 257 (100 %)

8: *m/z* 199 (100 %)
9: *m/z* 229 (80 %)



8: *m/z* 176 (41 %)
9: *m/z* 206 (43 %)

Scheme 2. *The main direction of fragmentation of derivatives **8**, **9**.*

C-8), 127.2 (CH, C-7), 127.6 (CH, C-9), 134.3 (C, C-5a), 143.9 (CH, C-4), 162.9 (C, C-10a), 164.9 (CO, C-2).

MS (EI) *m/z* 227 ($M^{+\bullet}$, 62), 200 (15), 199 (100), 176 (41), 148 (28), 90 (14), 69 (17), 63 (15), 45 (13), 39 (12).

Anal. Cald for $C_{11}H_5N_3OS$: C, 58.14; H, 2.22; N, 18.49; S, 14.11.Found: C, 57.51; H, 2.20; N, 18.17; S, 14.15.

*8-Methoxy-2-oxo-2H-pyrimido[2,1-b]benzothiazole-3-carbonitrile **9***

The *title compound* **9** (2.0 g, 77%) was prepared as **8** from the cyanoacetamide **5** (2.47 g, 10 mmol), triethyl orthoformate (3.71 g. 25 mmol) and nitrobenzene (10 ml) and a pale yellow solid was obtained after recrystallization from acetic acid.

mp 311–314 °C

IR (KBr) 2230 (C≡N), 1631 (C=O) cm^{-1}.

^{1}H-NMR (300 MHz; DMS*O*-d_6) 3.83 (3 H, s, OCH_3), 7.21 (1 H, dd, $J_{7,6}$ 9.1 and $J_{7,9}$ 2.5 Hz, 7-H), 7.66 (1 H, d, $J_{9,7}$ 2.5 Hz, 9-H), 8.00 (1 H, d, $J_{6,7}$ 9.1 Hz, 6-H), 9.74 (1 H, s, 4-H).

^{13}C-NMR (60 MHz; DMS*O*-d_6) 56.0 (CH_3, 8-OMe), 96.8 (C, C-3), 108.1 (CH, C-7), 114.3 (CH, C-9), 114.8 (CH, C-6), 114.9 (CN, 3-CN), 124.7 (C, C-9a), 128.1 (C, C-5a), 143.7 (CH, C-4), 158.3 (C, C-8), 162.7 (C, C-10a), 164.6 (CO, C-2).

MS (EI) *m/z* 258 (14), 257 ($M^{+\bullet}$, 100), 230 (10), 229 (80), 214 (33), 206 (43), 191 (70), 163 (13), 135 (21), 63 (17).

Anal. Cald for $C_{12}H_7N_3O_2S$: C, 56.02; H, 2.74; N, 16.33; S, 12.46. Found: C, 56.04; H, 2.74; N, 16.38; S, 12.77.

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