A CONVENIENT APPROACH TO THE SYNTHESIS OF NEW SUBSTITUTED ISOXAZOLO[5,4-D] PYRIMIDIN-4(5H)-ONES

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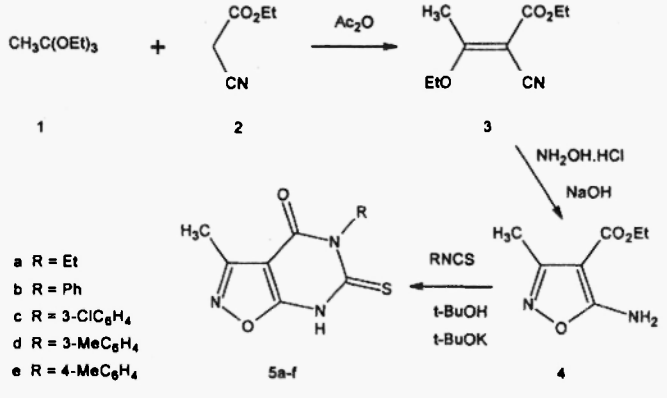
Abstract: Cyclocondensation of 5-amino-3-methyl-4-isoxazole carboxylate with isothiocyanates in the presence of potassium *tert*-butoxide in boiling *tert*-butanol afforded the corresponding isoxazolo [5, 4-d]pyrimidinones.
Keywords: Ethyl cyanoacetate; Isoxazolopyrimidine; Isothiocyanates; Isoxazole; Triethyl orthoacetate.

Introduction

An array of biological activities such as anti-bacterial, anti-fungal, anti-microbial, anti-inflammatory and anti-cancer has been reported to be shown by various isoxazolo[5,4-d]pyrimidinones. [1-8] Members of this family are effective in treatment of epilepsy, angina and immune system disorders.[9-11] It is apparent that some isoxazolo[5,4-d]pyrimidinones are active as enzyme and growth factor TGF inhibitors.[12,13] Prompted by these claims and in continuing our synthetic studies on bioactive heterocyclics,[14-19] we have now synthesized six new isoxazolopyrimidines *via* a convenient and unexplored route.

Results and Discussion

The starting material used in this synthesis was ethyl (E)-2-cyano-3-ethoxy-2-butenoate **3** and it was quantitatively prepared from the reaction of ethyl cyanoacetate **1** with triethyl orthoacetate **2** in acetic anhydride according to a published method. Heterocyclization of compound **3** with hydroxylamine hydrochloride in the presence of sodium hydroxide gave the key intermediate ethyl 5-amino-3-methyl-4-isoxazole carboxylate **4** (Scheme-1).[20] Reaction of this intermediate with several aryl and alkylisothiocyanates in the presence of potassium *tert*-butoxide in *tert*-butanol at reflux temperature furnished the corresponding isoxazolo[5,4-d] pyrimidin-4(5H)-ones **5a-f**.



The structure of new derivatives **5a-f** was confirmed by their spectral and analytical data. For example, the ^{1}H NMR spectrum of **5a** was devoid of the broad NH_2 signal at 6.2 ppm of the precursor but showed a triplet at δ 1.12 ppm, a quartet at δ 4.4 and a broad signal at δ 7.1 assignable to 6 protons for CH_3, CH_2 and NH groups respectively which indicates the formation of this derivative.

In conclusion, we have developed a method for preparing new isoxazolo[5,4-d] pyrimidin-4(5)-ones in good yields.

Experimental Section

The melting points were measured on an Electrothermal type 9100 melting point apparatus. The ^{1}H NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 ev. Elemental analysis was performed on a Thermofinnigan Flash EA microanalyzer.

General procedure for the preparation of 3-methyl-5-substituted-6-thioxo-6,7-dihydroisoxazolo[5,4-d]pyrimidin-4(5H)-ones 5a-f

To a solution of the ethyl 5-amino-3-methyl-4-isoxazole carboxylate **4** (5 mmol) and potassium *tert*-butoxide (5 mmol) in *tert*-butanol (40 mL), aryl or alkylisothiocyanates (10 mmol) was added. The reaction mixture was heated under reflux for 8.0 h. After cooling the reaction mixture, the precipitate was filtered and directly subjected to column chromatography using $CHCl_3$: MeOH (90:10) to afford the title compounds **5a-f** in high yield.

5-Ethyl-3-methyl-6-thioxo-6,7-dihydroisoxazolo[5,4-d]pyrimidin-4(5H)-one (5a)

White solid (0.74g, 70%). mp 240-242 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 1.12 (t, j = 7.0 Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.4 (q, j = 7.0 Hz, 2H, CH_2), 7.1 (broad, 1H, NH); MS, *m/z*, M^+ 211; Anal. Calcd for $C_8H_9N_3O_2S$: C, 45.49; H, 4.29; N, 19.89; S, 15.18. Found: C, 45.17; H, 4.51; N, 19.65; S, 15.33.

3-Methyl-5-phenyl-6-thioxo-6,7-dihydroisoxazolo[5,4-d]pyrimidin-4(5H)-one (5b)

White solid (1.04g, 80%). mp 230-232 °C; ^{1}H NMR (DMSO-d_6) δ(ppm) 2.3 (s, 3H, CH_3), 6.7-7.6 (m, 6H, aromatic ring and NH); MS, *m/z*, M^+ 259; Anal. Calcd for $C_{12}H_9N_3O_2S$: C, 55.59; H, 3.50; N, 16.21; S, 12.37. Found: C, 55.37; H, 3.68; N, 16.39; S, 12.54.

5-(3-Chlorophenyl)-3-methyl-6-thioxo-6,7-dihydroisoxazolo[5,4-d]pyrimidin-4(5H)-one (5c)

Yellow solid (0.82g, 56%). mp 180-183 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 2.2 (s, 3H, CH_3), 7.5 (broad, 1H, NH), 6.7-8.3 (m, 4H, aromatic ring); MS, *m/z*, M^+ 293 (M+2, 295); Anal. Calcd for $C_{12}H_8ClN_3O_2S$: C, 49.07; H, 2.75; N, 14.31; S, 10.92. Found: C, 49.35; H, 2.88; N, 14.53; S, 10.74.

3-Methyl-5-(3-methylphenyl)-6-thioxo-6,7-dihydroisoxazolo[5,4-d]pyrimidin-4(5H)-one (5d)

White solid (0.82g, 60%). mp 260-262 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 2.15 (s, 3H, CH_3), 2.25 (s, 3H, CH_3) 6.7-7.4 (m, 5H, aromatic ring and NH); MS, *m/z*, M^+ 273; Anal. Calcd for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37; S, 11.73. Found: C, 56.87; H, 4.33; N, 15.49; S, 11.55.

3-Methyl-5-(4-methylphenyl)-6-thioxo-6,7-dihydroisoxazolo[5,4-d]pyrimidin-4(5H)-one (5e)

White solid (0.97g, 71%). mp 270-272 °C; ^{1}H NMR (DMSO-d_6) δ(ppm) 2.3 (s, 3H, CH_3), 2.4 (s, 3H, CH_3) 6.7-7.5 (m, 5H, aromatic ring and NH); MS, *m/z*, M^+ 273; Anal. Calcd for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37; S, 11.73. Found: C, 56.94; H, 4.22; N, 15.21; S, 11.86.

3-Methyl-5-(4-nitrophenyl)-6-thioxo-6,7-dihydroisoxazolo[5,4-d]pyrimidin-4(5H)-one (5f)

Yellow solid (0.91g, 60%). mp 250-252 °C; ^{1}H NMR (DMSO-d_6) δ (ppm) 2.25 (s, 3H, CH_3), 7.25 (broad, 1H, NH), 7.3-8.4 (m, 4H, aromatic ring); MS, *m/z*, M^+ 304; Anal. Calcd for $C_{12}H_8N_4O_4S$: C, 47.37; H, 2.65; N, 18.41; S, 10.54. Found: C, 47.55; H, 2.83; N, 18.26; S, 10.41.

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