Asian Journal of Chemistry Vol. 19, No. 5 (2007), 3483-3486

Synthesis of 1,2,3,5-Tetrahydropyrimido-[1,2-c]benzimidazoles

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1,2,3,5-Tetrahydropyrimidol[1,2-c]benzimidazoles **6a-e** have been synthesized by the condensation of 2-methylamino-1-(2,3-dihydro-1H-benzimidazole-2-yliden)-2-thioxoethyl-cyanide **4** with aromatic aldehydes **5a-e** in refluxing N,N'-diethylaniline and *p*-toluene sulphonic acid as catalyst.

Key Words: Tetrahydropyrimido[1,2-c]benzimidazoles derivatives, Synthesis.

INTRODUCTION

Several methods of synthesis of pyrimido[1,2-c]benzimidazole ring systems[1,2] have been attracted much attention due to their variety of biological activiites such as antibacterial[3,4], fungicidal[5,6], anti-inflammatory, antirheumatic, antiallergic[7-9] and DNA gyrase inhibitory[10-12] activities. However, the ring system 1,2,3,5-tetrahydropyrimido[1,2-c]benzimidazole itself has not so far been reported in literature. In this paper, the title compounds is synthesized from 2-methylamino-1-(2,3-dihydro-1*H*-benzimidazole-2-yliden)-2-thioxoethylcyanide (**3**) with aromatic aldehydes **4a-e**.

EXPERIMENTAL

Melting points were determined in capillary tubes in sulphuric acid-bath and are uncorrected. IR spectra were recorded on Perkin-Elmer 1605 instrument. ^{1}H NMR spectra were recorded on Varian Gemini 200 MHz spectrometer using TMS as internal standard and mass spectra on VG micro mass 7070 H (70 eV) instrument.

2-Methylamino-1-(2,3-dihydro-1*H*-benzimidazole-2-yliden)-2-thioxoethylcyanide (3): An equimolar proportion of 1*H*-benzimidazole-2-acetonitrile[13] **1** (1.57 g 0.01 mol) and methylisothiocyanate **2** (0.73 g, 0.01 mol) were dissolved separately in pyridine (10 mL) and mixed throughly at room temperature. It was heated to reflux for 3 h and monitored the progress of the reaction by TLC. The solvent was removed under reduced pressure and poured on to crushed ice. The solution was neutralized with dilute hydrochloric acid to yield a solid, which was filtered, washed

with water and dried. The solid on crystallization from methanol yielded 3. Yileld : 82.4%, m.p. 225ºC; IR (KBr, cm^{-1}) 3164 ν($N_{1,3}$-H, H_3C-NH-), 2176 ν(C≡N), 1622 ν(C=N tautomeric), 1236 ν(C=S). ^{1}H NMR ($CdCl_3$): δ 3.2 (d, 3H, N-CH_3, J=8.0 Hz), δ 7.2-7.4 (m, 5H, Ar-H, -HN-CH_3, D_2O exchangeable), δ 13.1 (br, 2H, N_1-H and N_3-H D_2O exchangeable).

2-Methyl-1-(aryl)-3-thioxo-1,2,3,5-tetrahydrobenzimidazo[1,2-c]pyrimidine-4-yl cyanides (5a-e): An equimolar propotion of 2-methylamino-1-(2,3-dihydro-1*H*-benzimidazol-2-yliden)-2-thioxoethylcyanide (**3**) (0.01 mol) and appropriate aromatic aldehyde **4a-e** (0.01 mol) was heated to reflux in N,N'-diethylaniline (10 mL) with catalytic amount of *p*-toluene sulphonic acid (PTSA) for 2 h. The reaction mixture in each case was checked by TLC and after cooling to room temperature brown coloured solid separated out from the solvent medium. The solid compound in each case was filtered, washed with water and dried. Purification of the solids by crystallization in methanol gave light brown crystalline 2-methyl-1-(aryl)-3-thioxo-1,2,3,5-tetrahydrobenzimidazo[1,2-c]pyrimidine-4-yl cyanides (**5a-e**) in 68-82 % yield.

2-Methyl-1-(2-chlorophenyl)-3-thioxo-1,2,3,5-tetrahydrobenzimidazo[1,2-c]pyrimidine-4yl cyanide (5a): Yield 78 %, m.p. 218ºC. IR (KBr, cm^{-1}) ν(N-H), 2196 ν(C≡N), 1177 ν(C=S). ^{1}H NMR (DMSO-d_6); δ 2.8 (s, 3H, N-CH_3, 7.0 (d, 1H, C_6-H, J=10 Hz), δ 7.6 (m, 7H, C_1-H and Ar-H), δ 8.4 (1H, C_9-H, J=10 Hz) δ 13.95 (br, 1H, N-H, D_2O exchangeable).

2-Methyl-1-(4-dimethylaminophenyl)-3-thioxo-1,2,3,5-tetrahydrobenzimidazo[1,2-c]pyrimidine-4yl cyanide (5b): Yield 68%, m.p. 196ºC. IR (KBr, cm^{-1}) ν(N-H), 2190 ν(C≡N), 1178 ν(C=S). ^{1}H NMR (DMSO-d_6); δ 2.8 (s, 3H, NCH_3) δ 3.0 (s, 6H, $N(CH_3)_2$), δ 7.1 (d, 1H, C_6-H, J=10 Hz), δ 7.6 (m, 7H, C_1-H and Ar-H), δ 8.5 (1H, C_9-H, J=10 Hz) δ 14.0 (br, 1H, N-H, D_2O exchangeable).

2-Methyl-1-(4-chlorophenyl)-3-thioxo-1,2,3,5-tetrahydrobenzimidazo[1,2-c]pyrimidine-4yl cyanide (5c): Yield 82 %, m.p. 215ºC. IR (KBr, cm^{-1}) ν(N-H), 2194 ν(C≡N), 1179 ν(C=S). ^{1}H NMR (DMSO-d_6); δ 2.8 (s, 3H, NCH_3), δ 7.0 (d, 1H, C_6-H, J=10 Hz), δ 7.5 (m, 7H, C_1-H and Ar-H), δ 8.4 (1H, C_9-H, J=10 Hz) δ 14.0 (s, 1H, N-H, D_2O exchangeable).

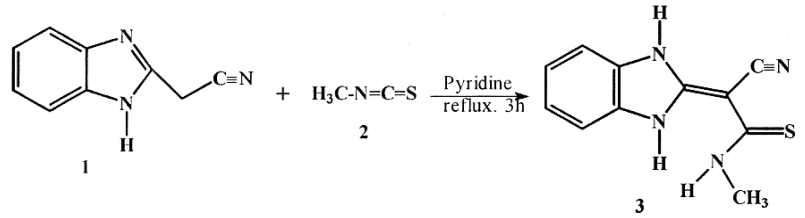
2-Methyl-1-(3-nitrophenyl)-3-thioxo-1,2,3,5-tetrahydrobenzimidazo[1,2-c]pyrimidine-4yl cyanide 5d: Yield 74 %, m.p. 225ºC. IR (KBr, cm^{-1}) 3377 ν(N-H), 2192 ν(C≡N), 1625 ν(C=N tautomeric), 1175 ν(C=S). ^{1}H NMR (DMSO-d_6); δ 2.8 (s, 3H, N-CH_3), δ 7.1 (d, 1H, C_6-H, J=10 Hz), δ 7.4 (m, 7H, C_1-H and Ar-H), δ 8.5 (1H, C_9-H, J=10 Hz) δ 14.0 (s, 1H, N-H, D_2O exchangeable).

2-Methyl-1-(4-nitrophenyl)-3-thioxo-1,2,3,5-tetrahydrobenzimidazo[1,2-c]pyrimidine-4yl cyanide (5e): Yield 75 %, m.p. 218ºC. IR (KBr, cm^{-1}) 3375 ν(N-H), 2194 ν(C≡N), 1176 ν(C=S). ^{1}H NMR (DMSO-

d_6); δ 2.8 (s, 3H, N-CH_3), δ 7.1 (d, 1H, C_6-H, J=10 Hz), δ 7.5 (m, 7H, C_1-H_4 and Ar-H), δ 8.5 (1H, C_9-H, J=10 Hz) δ 14.0 (br, 1H, N-H, D_2O exchangeable).

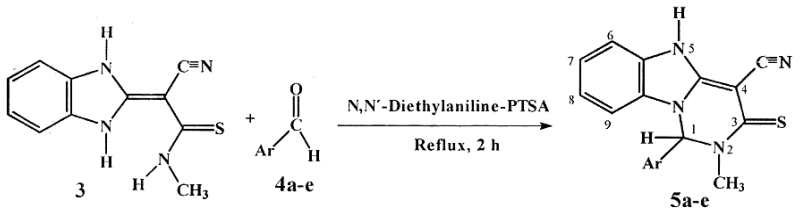
RESULTS AND DISCUSSION

The required starting compound 2-methylamino-1-(2,3-dihydro-1*H*-benzimidazole-2-thioxoethylcyanide **3** was prepared from 1*H*-benzimidazole-2-acetonitrile[13] **1** with methylisothiocynate **2** in refluxing pyridine (**Scheme-I**).



Scheme-I

Condensation of 1,3-diamine 3 with 2-chlorobenzaldehyde (**4a**) in N,N'-diethylaniline containing catalytic amoung of *p*-toluene sulphonic acid at reflux temperature for 2 h, yielded a brown coloured compound 2-methyl-1(2-chlorophenyl)-3-thioxo-1,2,3,5-tetrahydrobenzimidazole[1,2-c] pyrimidine-4-yl cyanide (**5a**). The structure of **5a** has been established based on the spectral data and also eliminated the other possible isomeric strucutre **6a**. Its mass spectrum recorded molecular ion peak at m/z 352 indicating the formation of 1:1 condensation product with the dimination of H_2O molecular. IR spectrum of **5a** showed the absorptions at 3398 cm^{-1} ν(br, imidiazole N-H), 2196 cm^{-1} ν(C≡N) 1177 cm^{-1} ν(C=S). ^1H NMR spectrum (DMSO-d_6) displayed the signals at δ 2.8 (s, 3H, NCH_3), δ 7.0 (d, 1H, C_6-H, J=10 Hz), δ 7.6 (m, 7H, C_1-H, Ar-H) δ 8.4 (d, 1H, C_9-H, J=10 Hz), δ 13.95 (br, 1H, imidazole N-H, N-H, D_2O exchangeable). Mass spectrum of 5a recorded the peaks at m/z 352 (M^+, 20) 316 (21), 176 (6.8) 154 (82) 136 (75) (**Scheme-II**).



Scheme-II

The reaction 3 has been carried out with four other aromatic aldehydes **4a-e** under identical condition lead to the respective 2-methyl-1-(aryl)-3-thioxo-1,2,3,5-tetrahydro benzimidazo[1,2-c]pyrimidine-4-yl cyanides (**5a-e**) in good yielded (74.82 %). The structures of **5a-e** have been ascertained by analogy and based on spectral data.

CHARACTERIZATION TABLE FOR THE COMPOUNDS **5a-e**

Compound	R	m.p. (ºC)	Yield (%)
5a	2-Chlorophenyl	218	78
5b	4-dimethylaminophenyl	196	68
5c	4-chlorophenyl	215	82
5d	3-Nitrophenyl	225	74
5e	4-Nitrophenyl	218	75

ACKNOWLEDGEMENTS

The authors are thankful to the Principal PGCS, Saifabad, Osmania University, for providing laboratory facilities. One of the author (VNSRB) is thankful to CSIR (New Delhi) for the award of Senior Research Fellowship.

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(*Received*: 20 February 2006; *Accepted*: 19 February 2007) AJC-5434