Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2011, 3 (5): 198-201
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Studies on synthesis of 2-(1-(1*H*-benzo(d)imidazol-2-yl)ethylthio)-6-methylpyrimidin-4-ol of potential pharmacological interest

S. Kotaiah*, B. Ramadevi, A. Naidu & P. K. Dubey

Department of Chemistry, J. N. T. University Hyderabad College of Engineering, Kukatpally, Hyderabad (A.P.), India

---

ABSTRACT

*Ethyl acetoacetate (**1**) on condensation with thiourea (**2**) in methanolic KOH under reflux for 4-5 hrs, gave the earlier reported 2-mercapto-6-methylpyrimidin-4-ol (**3**). o-Phenylenediamine **(4)** on condensation with DL- lactic acid **(5)** under Phillip's conditions gave 2-(α-hydroxyethyl)benzimidazole **(6)** which on treatment with $SOCl_2$ gave the previously known 2-(α-chloroethyl)-1H-benzimidazole **(7).** Condensation of **3** with **7** in DMF containing K_2CO_3 as a base and tetrabutylammonium bromide (TBAB) as a phase transfer catalyst gave 2-(1-(1H-benzo(d)imidazol-2-yl)ethylthio)-6-methylpyrimidin-4-ol (**8**). Structure of **8** has been established on the basis of its spectral & analytical data.*

Keywords; Ethyl acetoacetate, thiourea, 2-mercapto-6-methylpyrimidin-4-ol, 2-mercapto-6-methylpyrimidin-4-ol, 2-(1-chloroethyl)-H-benzolol)imidazol.

INTRODUCTION

Literature survey shows that a large number of heterocyclic compounds carrying pyrimidine moiety are found to be associated with diverse types of biological activities such as insecticidal[1], antimicrobial[2], antiviral[3] etc. Pyrimidines are of great importance in fundamental metabolism[4-6]. Various analogues of thiopyrimidines such as 2-thiouracil and 2,4-dithiouracil posses useful biological properties besides being fundamental constituents of nucleic acids[7-13]. Benzimidazoles are also known to be a group of biologically active molecules, possessing anti-fungal, anti-viral, anti-helminthic, anti-hypertensive and anti-tumor activities[14-16]. In view of these observations, it has been considered worthwhile to prepare new chemical entities containing pyrimidine and benzimidazole moieties as potential pharmacologically important molecules.

RESULTS AND DISCUSSION

Condensation of ethyl acetoacetate **(1)** with thiourea **(2)** in the presence of methanolic KOH under reflux for 4-5 hrs, gave the earlier reported[17] 2-mercapto-6- methylpyrimidin-4-ol **(3)**. On the other hand, *o*-phenylenediamine **(4)** with lactic acid **(5)** in 4N HCl under reflux conditions gave the known[18] 2-(α- hydroxyethyl)benzimidazole **(6).** The latter on treatment with thionyl chloride in CCl_4 under reflux yielded 2(1- chloroethyl)benzimidazole (**7)** which is also known in literature[19]. The reaction of (**7**) with **3** in DMF in the presence of K_2CO_3 as a base and a trace amount of tetrabutylammonium bromide(TBAB) as phase transfer catalyst at RT gave a product which has been characterized as (2-[1-(1*H*- benzimidazol-2-yl)-ethylsulfanyl]-6-methyl-pyrimidin -4-ol) **(8)** on the basis of its spectral and analytical data. Thus, its IR (KBr) spectrum showed an absorption at ≈ 3100-2700 cm^{-1} as a medium but very broad band assignable jointly to the tautomeric –**NH**- and –**OH** group of benzimidazole and pyrimidine nuclei respectivety. Its ^{1}H-NMR spectrum showed signals at δ (ppm) 3.04(d, 3H ,-CH-C**H$_3$**), δ 3.O7 (s, 3H, -C**H$_3$**), δ 5.01(q,1H, -C**H**-CH_3), δ 5.2 (s, C**H**- of pyrimidine ring), δ 7.20-7.89 (m, 4H, Ar-**H**), δ 12.80 (s,1H,-N**H**-); Its mass spectrum (CI mode), showed the molecular ion peak at (M^++1) at m/z at 287 corresponding to a molecular mass of 286, when recorded in the Q+1 mode.

The above reaction of **3** with **7** resulting in **8** has also been studied in other solvents such as acetone, acetonitrile and methanol. The results are described in Table -1, it is obvious from the table that best results are obtained using DMF as solvent, TBAB as PTC and K_2CO_3 as base.

Experimental Section :

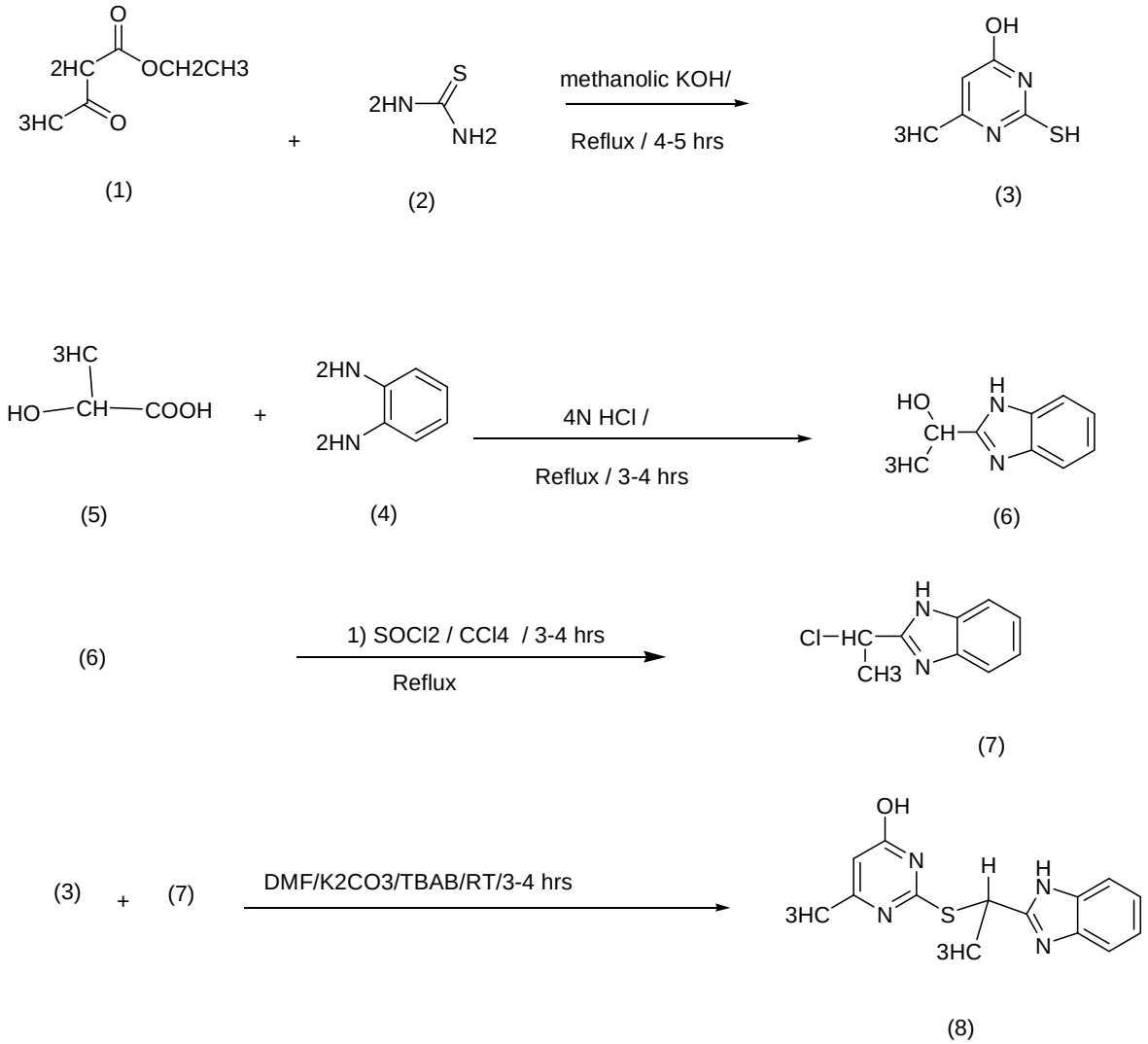
General Conditions: Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was performed on silica gel-G and spotting was done using iodine or UV-light. IR spectra were recorded using Perkin-Elmer 1000 instrument in KBr phase. ^{1}H-NMR spectra were recorded using a varian 400 MHz instrument and Mass spectra on Agilent-LC-MS instrument giving only $M^{+\cdot}$ values using Q+1or Q-1 mode.

Synthesis of 8: A mixture of **3** (0.14 g, 10 mmol), **7** (0.18 g, 10 mmol), K_2CO_3 (5 mmol)**,** TBAB (10mg) and DMF (100 mL) was stirred at RT for 4 hrs. After the completion of reaction , as shown by TLC , the mixture was poured into ice-water (250 ml). The separated solid was filtered, washed with water (2x10 ml) and dried.The crude product was recrystallised from methanol to obtain pure **8,** Yield =0.25 gms (87%).

M.P= 238-240^{0}C .Analytical calcd.for $C_{14}H_{14}N_4OS$: C =58.72%, H=4.93%, N=19.57% ; Found: C= 58.79% , H=4.98% , N= 19.62% ;

Table -1; Reaction of 3 with 7 in different solvents.

S.NO	SOLVENT	BASE	PTC	TIME(hrs)	YIELD(%)
1	Acetone	K_2CO_3	-	6-7	56
2	DMF	K_2CO_3	TBAB	3-4	86
3	Acetonitrile	K_2CO_3	TBAB	4-5	62
4	Methanol	NaOH	-	6-7	58



Acknowledgement

Authors are very thankful to the authorities of Jawaharlal Nehru Technological University Hyderabad for providing laboratory facilities and for constant encouragement.

REFERENCES

[1] M.S. Shingare. *Indian J Chem*, **1983**, 22B, 714.
[2] M. M. Ghorab; S.G. Abdel. Indian *J Heterocycl. Chem*, **1994**, 4, 103.
[3] E. Wagner; L. Becan; E. Nowakowska. *Bioorg. Med. Chem*, **2004** , 12,265.
[4] Z. Wang; T.M. Rana. *Biochemistry*, **1996**, *35*, 6491.
[5] R.P. Martin; J.M. Scheller; A.J.C. Stahl; G. Dirheimer. *Biochem. Biophys. Res. Commun*, **1976**, *70*, 997.
[6] M. Altweg; E. Kubli. *Nucleic Acids Res*, **1980**, *8*, 215.

[7] G. A. Jeffrey; W. Saenger. *Hydrogen Bonding in Biological Structures*; Springer-Verlag: New York, 1991; See also references therein.
[8] H.Charbonneau; J.N. Walsh; J.A. Beavo . *Proc. Natl. Acad. Sci., U.S.A*, **1986**, *83*, 9308.
[9] S. Topiol. *Trends Biochem. Sci*, **1987**, *12*, 419.
[10] C.J. Hunter; D.F. Deen; L.J. Marton. *Internat . J. Cancer*, ***1989***, *44*, 658.
[11] R. Pieters; D.R. Huismans; A.H. Loonen; K. Hahlen; A.J. Veerm. *Jpn. J. Cancer Res*, **1991**, *82*, 1051.
[12] L.M. Beauchamp; B.L. Serling; J.E. Kesley; K.K. Biron; P. Collins; J. Selway; J.C. Lin; H. Schaeffer. *J. Med. Chem*, **1988**, *31*, 144.
[13] R. Pieters; D.R. Huismans; A.H. Loonen; G.J. Peters; K. Hahlen; A. Vander Does-van den Berg; E.R. VanWeiring; A.J.P. Veerman. *Internat. J. Cancer*. **1992**, 51, 213.
[14] J.S. Kim; Gatto; C. Yu; A. Liu; L.F. LaVoice; E.J. *J. Med. Chem*, **1996**,39, 992.
[15] N. Kohei; N. Takeheiko. *J. Med. Chem*, **1993**, 36, 2182-2195.
[16] J. Lu; B. Yang; Y. Bai. *Synth. Commun*, **2002,** 32, 3703-3709.
[17] Anderson; Halverstadt; Miller; Roblin; 87. *Chemical Society*, April, **1947**, 2197
[18] W.R. Roderick; C.W. Nordeen; A.M. Von Esch; R.N. Appell. *J. Med. Chem*, **1979**, 15 , 131.
[19] C.H. Roeder; A.R. Day. *J. 0rg. Chem*, **1956**, 24.