Physical Sciences

Pak J Sci Ind Res 2001 ***44*** *(2) 63-66*

SYNTHESIS OF 5 H-IMIDAZO [1, 2-a] THIOPYRANO-[4', 3': 4, 5] THIENO[2, 3-d] PYRIMIDIN-5-ONE

A Z M Shaifullah Chowdhury*, M M Rahman Khandker, M M H Bhuiyan and M K Hossain

Department of Chemistry, Chittagong University, Chittagong-4331, Bangladesh

(Received 5 August 1999; accepted 25 March 2000)

The enamino-ester, ethyl, 2-amino-4,7-dihydro-5H-thieno[2,3-c]thiopyrano-3-carboxylate (**5**) was prepared from tetrahydrothiopyran-4-one (**4**). Annelating reagent, 5-methyl-2-methylthioimidazoline (**8**) was prepared starting from 1, 2-diaminopropane (**6**) via 5-methyl-2-imidazolidinethione (**7**). The reaction of enamino-ester (**5**) with the annelating reagent (**8**) in HMPTA leaded to new 1, 2, 3, 6, 7, 9-hexahydro-5H-imidazo[1, 2-a]thiopyrano[4', 3':4, 5]thieno-[2, 3-d]pyrimidin-5-one (**9**) in good yield.

Key words: Tetrahydrothiopyran, Annelating reagent, Fused pyrimidines

Introduction

Fused pyrimidines have become attractive targets for organic synthesis because of their structural diversity and biological importance. Recent development of physiologically highly potent fused pyrimidines with interesting sedative, antimalarial, antibacterial and antiallergic activities(Ram *et al* 1981; Roth and Chang 1982; Albert 1986) prompted us to synthesize these compounds by simple route in satisfactory yields. The barbiturates (medical drugs), valuable soporific and hypnotic drugs and a number of useful antibacterial and antimalarial drugs also contain pyrimidine rings (Achesom 1967). Derivatives of thieno[2,3-d]pyrimidine system are of great interest because of their antibacterial and antimalarial activities(Albert 1986). We are interested in the synthesis of heterocycles containing the thieno-pyrimidine systems which possess the above biological activities (Sauter *et al* 1996; Shaifullah Chowdhury *et al* 1997)

Enamino-esters or enamino-nitriles readily undergo cyclization which allow convenient preparation of variety of condensed pyrimidines(Shaifullah Chowdhury 1997). Thiopseudourea, 2-methylthioimidazoline is a versatile reagent for the preparation of fused pyrimidine .

The synthesis of a new tetracyclic compound, 1, 2, 3, 6, 7, 9-hexahydro-5H-imidazo[1, 2-a]thiopyrano [4', 3':4, 5] thieno [2, 3-d] pyrimidin-5-one is reported here.

Experimental

Melting points were determined on an electrothermal melting point apparatus and were uncorrected. Thin layer chromatography (T.L.C.) was performed on silica gel plates (Woelm, Germany) and spots were detected by heating the plates at 150-200°C. Column chromatography was carried out at room temperature with silica gel (Merck 70, 230-400 mesh), eluted with chloroform-acetone (9:2, vv^{-1}). ^1H and ^{13}C-NMR spectra were recorded on a Bruker AC 200 (200 MHz) at the Institute of Organic Chemistry, Technical University of Vienna, Austria. Tetramethylsilane (TMS) was used as internal standard, and chemical shifts are expressed in ppm (δ units). All evaporations were conducted under reduced pressure at bath temperature below 50°C.

*Author for correspondence

Methyl-B-thiodipropionate (2). A solution of methylacrylate (**1**) (5g, 58.14 mmol) and triton base (0.024g, 58.03 mmol) was placed in a 250 ml three-necked flask, fitted with an efficient reflux condenser, a sintered glass bubbler tube and a thermometer which reached almost to the bottom of the flask. A steady stream of H_2S gas was introduced through a bubbler tube, and temperature was maintained at 70°C. The solution attained room temperature after 45 min. The gas flow was stopped; 10 ml of toluene was added and washed successively twice with 10% HCl and H_2O and finally dried over Na_2SO_4 and filtered. The solvent was evaporated in vacuo and the syrupy mass was distilled under reduced pressure, 151°C 10 mm^{-1} Hg, yield 5.3g (88.77%).

^1H-NMR ($CDCl_3$): δH 3.60 (s, 3H x 2, CH_3), 2.70 (t, 2H x 2, CH_2), 2.50 (t, 2Hx2, CH_2).

4-Oxo-tetrahydrothiopyran-3-carboxylic acid methylester (3). Sodium metal (2.83g, 123.04 mmol) was dissolved in absolute MeOH (40 ml) with stirring, refluxed for 1 hour and the excess MeOH distilled off. NaOMe thus obtained may contain Ca 5% MeOH. Dry diethyl ether (40 ml) was added to NaOMe, stirred and cooled to room temperature and then methyl β-thiodipropionate (**2**) (12.36g, 60 mmol) in small amount of dry diethyl ether was added drop wise. The reaction mixture was refluxed for 8 h, cooled and hydrolyzed with least amount of acetic acid. The ethereal so-

lution was washed with water and the aqueous solution was extracted with ether (5×20 ml). The combined organic layers were washed successively with $NaHCO_3$ and H_2O and finally dried over anhydrous Na_2SO_4. Evaporation of the filtered solution and distillation under reduced pressure (10 mm Hg at 134°C) afforded 4-oxo-tetrahydrothio-pyran-3-carboxylic acid methyl ester (**3**), yield 4g (38.30%).

Tetrahydrothiopyran-4-one (4). A solution of 4-oxo-tetrahydrothiopyran-3-carboxylic acid methyl ester (**3**) in 10% H_2SO_4 (45 ml) was refluxed for 6 h at 100°C. The reaction mixture was cooled and extracted three-times with Et_2OH (3×30 ml). The organic layer was washed with $NaHCO_3$ and H_2O and dried over Na_2SO_4. The evaporation of the solvent under reduced pressure gave tetrahydrothiopyran-4-one (**4**) as yellow crystals, m.p. 58°C, yield 56.73%.

^{1}H-NMR ($CDCl_3$): (δ_H 3.00 (t, 2H x 2, $2CH_2$), 2.70 (t, 2H x 2, CH_2-S-CH_2).

Ethyl 2-amino-4,7-dihydro-5H-thieno[2,3-c] thiopyrano-3-carboxylate (5). A suspension of sulfur (0.64g, 20 mmol), ethyl cyanoacetate (1.32g, 11.68 mmol) and tetrahydrothiopyranone (**4**) (2.32g, 20 mmol) in diethylamine (4 ml) and ethanol (10 ml) was stirred below 50°C for 1 h and then another hour at room temperature. The resultant yellow precipitate was collected by filtration and washed with water and ethanol. The obtained crystals were recrystallized from ethanol to give (**5**), m.p. 86-87°C (Lit Sauter *et al* 1996) 87-89°C, yield 1.61g (70%).

^{1}H-NMR ($CDCl_3$): (δ_H 6.00 (s, 2H, NH_2), 4.30 (q, 2H, -OCH_2), 3.60 (s, 2H, 7-H), 3.00 (t, 2H, 5-H), 2.80 (t, 2H, 4-H), 1.30 (t, 3H, CH_3), ^{13}C-NMR ($CDCl_3$) : (δ_C 165.69 (s, C-2), 161.02 (s, C=O), 132.10 (s, C-3a), 113.41 (s, C-7a), 105.80 (s, C-3), 59.47 (t, -OCH_2), 28.56 (s, C-7), 25.97 (t, C-5), 25.01 (t, C-4), 14.32 (q, CH_3).

5-Methyl-2-imidazolidinethione (7). Carbon disulfide (4.05ml, 67.56 mmol) was added dropwise with occasional shaking for 2 h to a solution of 1, 2-diaminopropane (**6**) (5g, 67.56 mmol) in ethanol (100 ml), refluxed on a water bath for 1 h and then concentrated HCl (15 ml) was added and refluxed for 10 h. The resulting solid product was filtered on cooling, washed with cold acetone (80 ml) and crystallized from ethanol to furnish (**7**), m.p. 98°C, yield 4g (65%).

^{1}H-NMR (DMSO-d): δ_H 8.10 (s, ^{1}H, NH), 7.90 (s, ^{1}H, NH), 4.00-3.80 (m, ^{1}H, 5-H), 3.60 (t, ^{1}H, 4-H), 3.00 (t, ^{1}H, 4-H), 1.10 (d, 3H, CH_3).

5-Methyl-2-methylthioimidazoline (8). A 5-methyl-2-imi-dazolidinethione (**7**) (5g, 43.10 mmol) and methyl iodide (3.28 ml, 0.33 mmol) were dissolved in absolute methanol (20 ml) and refluxed for 2 h. The solvent was removed under reduced pressure and the solid white hydroiodide salt was neutralized with 50% NaOH solution. The solid residue was extracted with chloroform (3×30 ml), the extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated in vacuo to afford (**8**), m.p. 72°C, yield 3g (62.50%).

^{1}H-NMR (DMSO-d): (δ_H 10.10-9.90 (bs, 1H, NH), 4.40-4.30 (m, 1H, 5-H), 3.90 (t, 1H, 4-H), 3.40 (t, 1H, 4-H), 2.60 (s, 3H, SCH_3), 1.20 (d, 3H, CH_2).

^{13}C-NMR (DMSO-d_6): (δ_C 169.02 (s, C-2), 53.90 (d, C-5), 51.78 (t, C-4), 20.31 (q, -SCH_3), 14.17 (q, CH_3).

1, 2, 3, 6, 7, 9-Hexahydro-5H-imidazo-[1,2-a] thiopyrano ['4, '3:4,5] thieno[2,3-d] pyrimidin-5-one (9). A mixture of ethyl 2-amino-4,7-dihydro-5H-thieno [2, 3-c] thiopyrano-3-carboxylate (**5**) (0.48g, 2 mmol) and 5-methyl-2-methylthioimidazoline (**8**) (0.34g, 3 mmol) in hexamethyl phosphoric triamide (HMPTA) (5 ml) was heated to 160°C for 3 h. After cooling to room temperature, crushed-ice (35g) was added and the mixture stirred for 1 h. The precipitate was collected and crystallized from methanol to give 1,2,3,6,7,9-hexahydro-5H-imidazo[1,2-a]thiopyrano ['4, '3:4, 5] thieno [2, 3-d] pyrimidin-5-one (**9**) as red crystals, m.p. 220°C, yield 3g (64%). Anal. calc. for $C_{12}H_{13}ON_3S_2$ (279.39): C, 51.59; H, 4.69; N, 15.04; Found: C, 51.62; H, 4.59; N, 15.01%.

^{1}H-NMR ($CDCl_3$): δ_H 5.25 (s, 1H, NH), 3.80-3.50 (m, 1H, 2-H), 3.00 (s, 2H, 9-H), 2.80 (t, 2H, 7- H), 2.60 (t, 2H, 6-H), 2.40 (ABX, 2H, 3-H), 1.35 (d, 3H, CH_3).

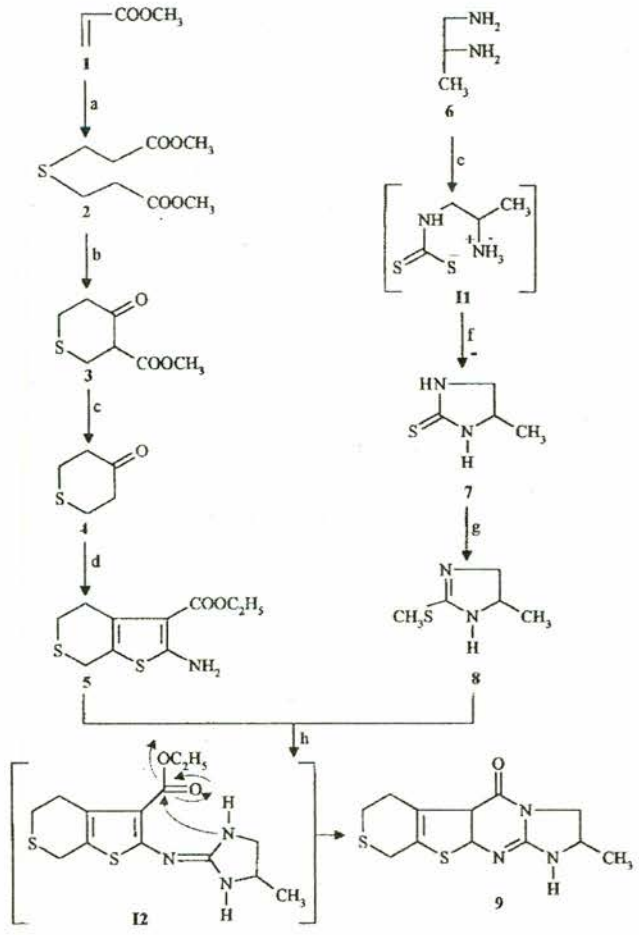
Results and Discussion

Methylacrylate (**1**) was basified and generated with triton base and then subsequently treated with H_2S while temperature was maintained at 60-70°C. Thus after usual work up and vacuum distillation at 153°C (10 mm Hg) thiodipropionate (**2**) was obtained in excellent yield (88.77%). The values of ^{1}H-NMR of 2 were in accordance with literature data (Kozich 1995).

Solid sodium methoxide (less than 5% of MeOH) was prepared very carefully and refluxed with thiodipropionate (**2**) in dry ether. It was hydrolyzed with acetic acid and cyclized to 4-oxo-tetrahydrothiopyran-3-carboxilic acid methyl ester (**3**). Without analysis the compound (**3**) was used for the next step in Scheme 1.

The compound (**3**) was treated with 10% H_2SO_4 to afford tetrahydrothiopyran-4-one (**4**) in excellent yield (87%) as yellow crystals. The structural assignments and conformational studies of 4 were in accordance with literature data (Shaifullah Chowdhury 1997).

The direct one-step base catalyzed condensation of ketone with ethyl cyanoacetate and sulfur described by Gewald



Scheme 1

et al. (1966) served the basis of the synthesis of annelating substrate, the ethyl 2-amino-4, 7-dihydro-5H-thieno [2, 3-c] thiopyrano-3-carboxylate (**5**) from (**4**) as crystals, m.p. 86-87°C [Lit(Sauter *et al* 1996). 87-89°C], yield 70%.

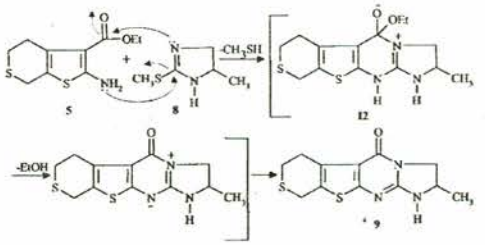
The presence of a two-proton singlet at δ 6.00 in the ^{1}H-NMR spectrum of 5 indicates the presence of a NH_2 group. A three-proton triplet at δ 1.30 and two-proton quartet at δ 4.30 confirm the introduction of CH_2CH_3 group. The spectrum also reveales two two-proton triplets at δ 2.80 and 3.00 for 4- and 5 H protons respectively and a two-proton singlet at δ 3.60 for 7 H protons.

5-Methyl-2-imidazolidinethione (**7**) as crystals, m.p. 98°C, was prepared form 1,2-diaminopropane (**6**) by using Trivedi method (Dave *et al* 1988). The compound was confirmed by its ^{1}H-NMR spectrum. In the ^{1}H-NMR spectrum, singlets at δ 8.10 and 7.90, indicated the presence of two -NH protons. A one proton multiplet was observed at δ 4.00-3.80 for 5 H proton and two triplets at δ 3.60 and 3.00 for two 4 H protons. The presence of methyl group in the structure was confirmed by a three-proton doublet at δ 2.10.

Treatment of 5-methyl-2-imidazolidinethione (**7**) and methyl iodide in absolute methanol under reflux furnished 5-methyl-2-mehylthioimidazoline (**8**). In the ^{1}H-NMR spectrum, a three-proton singlet at δ 2.60 confirms the presence of - SCH_3 group in the structure as well as all other chemical shifts are in agreement with the structure assigned for the compound (**8**). The structure of 5-methyl-2-methylthio-imidazoline (**8**) was also confirmed by ^{13}C-NMR spectrum. The spectrum gave signals at δ 169.02 as singlet indicated for C-2. The chemical shifts were registered at δ 53.90, doublet for C-5, at δ 51.78, triplet for C-4, at δ 20.31, quartet for $-SCH_3$ and at δ 14.17, quartet for CH_3. The spectrum also displayed the presence of five carbon atoms corresponding to its molecular formula ($C_5H_{10}N_2S$).

Annelating reagent thiopseudourea, 5-methyl-2-methyl thio-imidazoline (**8**) with enamino-ester, ethyl 2-amino-4, 7-dihydro-5H-thieno[2, 3-c]thiopyrano-3-carboxylate (**5**) in HMPTA at 160°C furnished a new linear fashioned tetracyclic compound 1, 2, 3, 6, 7, 9-hexahydro-5H-imidazo[1, 2-a] thiopyrano-[4, 3:4, 5] thieno[2, 3-d] pyrimidin-5-one (**9**) in 64% yield, m. p. 220°C.

The mechanism of this reaction probably involved by the initial nucleophilic addition of the amino group of enamino-ester (**5**) to the electron deficient carbon of the imidazoline, 5-methyl-2-methylthioimidazoline (**8**) forms the interme diate (**I2**) by elimination of methyl mercaptane together with simultaneous nucleophilic attack of the nitrogen atom from the imidazol moiety to the sp^2 carbon of the carboxylate, followed by an elimination of ethanol to give compound (**9**).



The proton spectrum exhibited a one-proton singlet at δ 5.25 for NH, a two-proton singlet at δ 3.00 for 9 H and two two-proton triplets at δ 2.80 and 2.60 for 7 and 6 H respectively were observed. The spectrum showed two-proton ABX at δ 2.40 for 3 H protons, one-proton multiplet at δ 3.80-3.50 for 2-H and three-proton doublet at δ 1.35 for CH_3 in the structure. The signals at δ 4.30 and δ 1.30 for -$COOCH_2CH_3$ and at δ 6.0 also for NH_2 were absent in the spectrum of compound (**9**). The microanalytical data of the compound (**9**) for C, H, N were in accordance with the calculated values.

Thus the above method has the advantage of easy availability of starting material, mild reaction conditions and good yields in the reaction steps with fused pyrimidine ring.

References

Ram J V, Pandey H K, Vlietinck A J 1981 Thieno [2, 3-d] pyrimidines as potential chemotherapeutic agents. II. *J Heterocyclic Chem* **18** 1277.

Albert A 1986 *Advance Heterocycles Chemistry*, Academic Press, New York, USA, **39** 117.

Roth B, Cheng C C 1982 *Progress in Medicinal Chemistry,* Elseveir Biomedical Press, New York, USA, **19** 267.

Achesom R M 1967 *An Introduction to the Chemistry of Heterocyclic Compounds,* 2nd, Ed Interscience Publishers, pp 334.

Shaifullah Chowdhury A Z M, Matin M M, Anwar M N 1997 Synthesis and anti-microbial activities of fused pyrimidines: Benzothieno [2, 3-d] imidazo [1, 2-c] pyrimidine. *Chittagong Univ Stud Part II*: Sci. **21**(2) 79-83.

Shaifullah Chowdhury A Z M, Rahimunnesa B 1997 Synthesis of benzothieno[2,3-d]imidazo[1,2-a] pyrimidi-2, 5-(1H,3H)-dione. Chittagong Univ Stud Part II: Sci. **21** (2) 85-90.

Sauter F, Frohlich J, Ahmed E K 1996 New hetero-annelation reactions using N-[bis (methylthio) methylene]amino and related reagents. *Monatsh Chem* **127** 319-324.

Kozich M 1995 Synthesis of some base Heterocycles. Ph D Thesis, Institute of Organic Chemistry, Technical University, Vienna, Austria.

Shaifullah Chowdhury A Z M, Shehab M, Manchur M A Synthessis and antimicrobial activities of fused pyrimidines:Imidazo[1,2-c]thiopyrano['4,'3:4,5] thieno [3, 2-e] pyrimidine. *Chittagong Univ J Sci* (in press).

Gewald K, Schinke E, Bottcher H 1966 2-Amino-thiophene aus methylenktiven nitrilen, carbonyl-verbindungen und schwefel. *Chem Ber* **99** 94.

Dave A M, Bhatt K N, Undavia, Trivedi P B 1988 Studies on synthesis of 2-(substituted-thiazolyl/ benzthiazolyl-amino)-4,5-dihydroimidazoles. *J Indian Chem Soc* LXV April 296.