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FUSED PYRIMIDINES: *PART-I:* SYNTHESIS OF IMIDAZO[1,2-a]THIENO[2,3-d]-PYRIMIDIN-5(1*H*)- IMINE AND PYRIMIDO[1,2-a] THIENO[2,3-d] PYRIMIDIN-6-IMINE

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Annelating reagents, 2-(methylthio)-2-imidazoline **(2)** and 1,4,5,6-tetrahydro-2-methylthiopyrimidine **(4)** were prepared from 1,2-diaminoethane and 1,3-diaminopropane *via* 2-imidazolidinethione and 1,4,5,6-tetrahydropyrimidin-2-thione respectively. The substrate, 2-amino-4,-5-dimethylthiophen-3-carbonitrile **(5)** was prepared from butanone. The reaction of substrate **(5)** with the annelating reagents,**(2)** and **(4)**, in HMPT led to 2,3-dihydro-6,7-dimethylimidazo[1,2-a]thieno[2,3-d]pyrimidin-5(1*H*)-imine **(6)** and 1,2,3,4-tetrahydro-7,8-dimethylpyrimido[1,2-a]thieno[2,3-d]pyrimidin-6-imine **(7)** in good yields.

Key words: Annelating reagents, Substrate, HMPT, Fused pyrimidines.

Introduction

The most important and naturally occurring diazines are pyrimidine bases uracil, thymine and cytosine, which are constituents of the nucleic acids (Blackburn and Gait 1996). Following from this, several pyrimidine nucleoside analogues have been developed as antiviral agents, for example idoxuridine is used in the treatment of *Herpes* infections of the eye and AZT (Zidovudine) is the most widely used anti-AIDS drug; 3-TC (Lamivudine) is used to treat both hepatitis B and AIDS, while d4T (Stavudine) is a fourth drug approved for treatment of HIV infection and AIDS. The pyrimidine ring also occurs in the vitamin thiamin (Joule and Mills 2000). Derivatives of thieno[2,3-d]pyrimidine system are of great interest because of their antimalarial (Albert 1986), antibacterial and antifungal (Rahman *et al* 1999 & 2003) activities. (Hetero) Aromatic *o*-aminoesters and *o*-aminonitriles undergo ready cyclization, which allows convenient preparation of a variety of condensed pyrimidines (Taylor 1987). Thiopseudourea is a versatile reagent for the preparation of fused pyrimidines (Sauter *et al* 1997). Along this route and in continuation of our ongoing program (Chowdhury *et al* 2000 a & b and 2001), we report here the synthesis of 2,3-dihydro-6,7-dimethylimidazo[1,2-a] thieno [2,3-d] pyrimidin-5 (1*H*)-imine and 1,2,3,4-tetrahydro-7, 8-dimethylpyrimido[1,2-a] thieno [2,3-d] pyrimidin-6-imine, **(6)** and **(7)**, respectively.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. ^{1}H-and ^{13}C-NMR spectra were recorded on a Bruker AC 200 spectrometer using DMSO-d_6/$CDCl_3$ as solvents and TMS as an internal standard (chemical shifts in δ, ppm). TLC was run on silica gel-G plates and spots were located by iodine vapor. All evaporations were conducted under reduced pressure at bath temperature below 50°C. The starting material **(2)** (Dave *et al* 1988), **(4)** (Gewald *et al* 1966) and **(5)** (Chowdhury 1996) were prepared according to reported in literature.

2,3-Dihydro-6,7-dimethylimidazo[1,2-a] thieno [2,3-d] pyrimidin-5 (1H)-imine ***(6).*** A solution of *o*-aminonitrile **(5)** (0.465 g, 3 mmol) and 2-methylthio-2-imidazoline **(2)** (0.522 g, 4.5 mmol) in hexamethyl phosphoric triamide (HMPT, 6 ml) was heated under reflux at 160°C for 3 h. After cooling to room temperature, crushed ice (35 g) was added and the mixture stirred for additional 1 h. The separated solid was collected by filtration and recrystallized from methanol to give **(6)** as brown crystals, m.p. 177-178°C, yield 0.47 g (70%). *Anal. Calc*. for $C_{10}H_{12}N_4S$ (220.30): C, 54.52; H, 5.49; N, 25.43; Found C, 54.30; H, 5.50; N,25.08%. ^{1}H-NMR ($CDCl_3$): δ 7.40 (s,1H,NH), 6.60 (bs, 1H, NH), 3.90 (t, 2H,3-H), 3.60 (t,2H,2-H),2.46 (s, 6H, $2CH_3$). ^{13}C-NMR (DMSO-d_6) δ 160.44, (s, C-5), 155.02 (s,C-9a), 152.43 (s, C-8a), 129.37 (s,C-7), 124.60 (s, C-5a) 111.96 (s,C-6), 42.54 (t, C-3), 39.65 (t, C-2), 19.25 (q, 7-CH_3), 18.06 (q, 6-CH_3).

1,2,3,4-Tetrahydro-7,8-dimethylpyrimido[1,2-a]thieno[2,3-d]pyrimidin-6-imine **(7).** This compound was prepared from *o*-aminonitrile **(5)** and 1,4,5,6-tetrahydro -2-methylthio pyrimidine **(4)** following the same method used for the preparation of **(6)** to give **(7)** as brown crystals in 64% yield, m.p.>250 °C. *Anal. Calc.* for $C_{11}H_{14}N_4S$ (234.33): C, 56.38; H, 6.02; N, 23.91; Found C, 56.15; H, 6.03; N, 23.58%.

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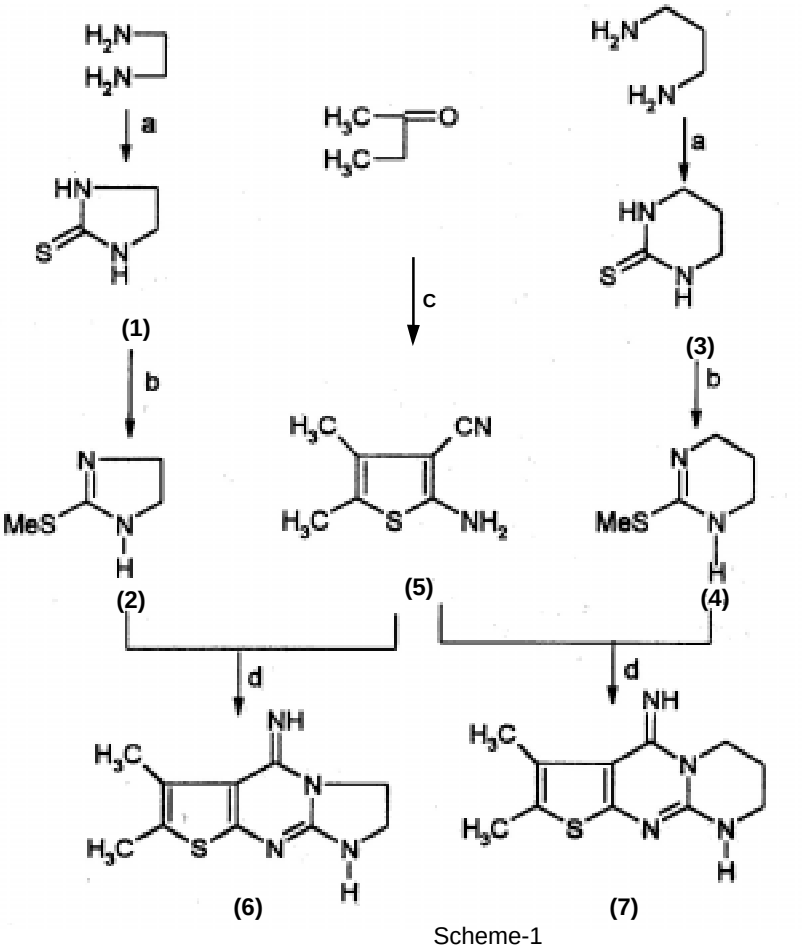


Scheme-1

Reagents: a) CS_2, EtOH; b) Mel, MeOH; c) S, $CNCH_2CN$, Et_2NH, EtOH; d) HMPT, reflux

^{1}H-NMR (CDC1$_3$): δ 7.40 (s,1H, NH), 6.70 (bs, 1H NH), 3.90 (t, 2H, 4-H), 3.20 (t ,2H, 2-H), 1.90 (m, 2H, 3-H), 2.49 (s, 6H, 2CH$_3$). ^{13}C-NMR (DMSO-d$_6$): δ 159.64 (s, C-6), 153.24 (s, C-10a), 148.32 (s, C-9a), 128.02 (s, C-8), 121.54 (s, C-6a), 110.01 (s, C-7), 37.34 (t, C-2 and C-4), 22.34 (t, C-3), 21.02 (q, 8-CH$_3$), 20.08 (q, 7-CH$_3$).

Results and Discussion

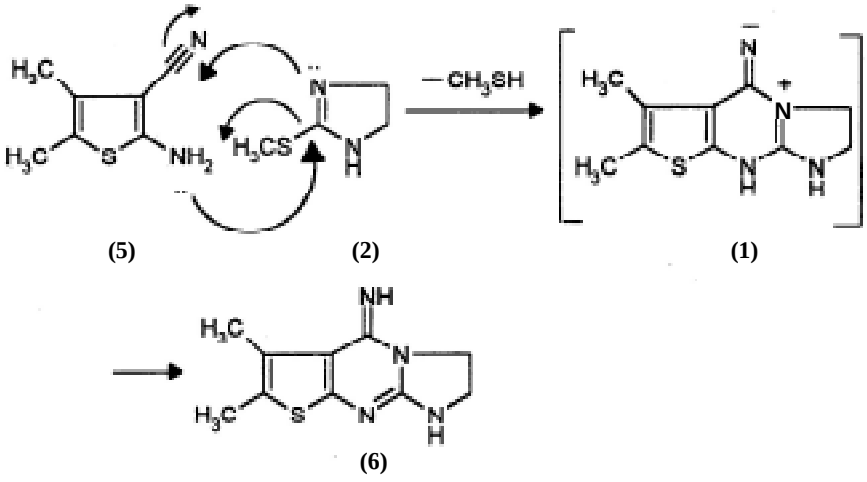
2-(Methylthio)-2-imidazoline **(2)** was prepared *via* two-step procedure from 1,2-diaminoethane and carbon disulfide., followed by the reaction with iodomethane according to the method reported in literature (Dave *et al* 1988). Similarly, another annelating reagent, 1,4,5,6-tetrahydro-2-methylthiopyrimidine (**4**), was prepared from 1,3-diaminopropane and carbon disulfide followed by iodomethane in 64% yield as white crystals, m.p. 153-155˚C as reported (Chowdhury 1996).

The direct one-step base catalyzed condensation of butanone with malononitrile and sulfur described by Gewald *et al* (1966) serves the basis of the synthesis of substrate, 2-amino-4,5-dimethylthiophen-3-carbonitrile **(5)** as yellowish crystals 75% yield, m.p. 140-141 ˚C.

The annelating reagents, **(2)** and **(4)** on reaction with compound **(5)** in HMPT at 160˚C furnished two linear fashioned new tricyclic compounds 2,3-dihydro-6,7-dimethylimidazo[1,2-a] thieno[2,3-d]pyrimidin-5 (1*H*)-imine **(6)** and 1,2,3, 4-tetrahydro and 7,8-dimethylpyrimido[1,2-a]thieno-[2,3-d]pyrimidin-6-imine **(7)** in 70 and 64% yields, respectively (Scheme 1).

The mechanism of this reaction probably involved by the initial nucleophilic addition of the amino group of amino-nitrile **(5)** to the electron deficient carbon of the annelating reagent to form the intermediate **(I)** by the elimination of methyl mercaptan with a simultaneous necleophilic attack of the nitrogen atom of the imidazolo and pyrimido moiety to the *sp* carbon of the nitrile to give the final products.

The ^{1}H-NMR spectrum of **(6)** exhibited two one-proton singlets at δ 7.40 and 6.50 for two NH, two-proton triplets at δ



3.90 and 3.60 for 3-H and 2-H and a six-proton singlet at δ 2.46 for two CH_3 groups. The ^{13}C-NMR spectrum of **(6)** is also consistent with its structure. The ^{1}H-NMR spectrum of **(7)** showed two one-proton singlets at δ 7.40 and 6.70 for two NH groups, two two-proton triplets at δ 3.90 and 3.20 for 4-H and 2-H, a two-proton multiplet at δ 1.90 for 3-H, a six-proton singlet at δ 2.49 for two CH_3 groups. The microanalytical data of the compounmds **(6)** and **(7)** for C, H, N, were in accordance with the calculated values.

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

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