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NOTE

Synthesis of some New Thienylpyrimidine and Condensed Pyrimidines

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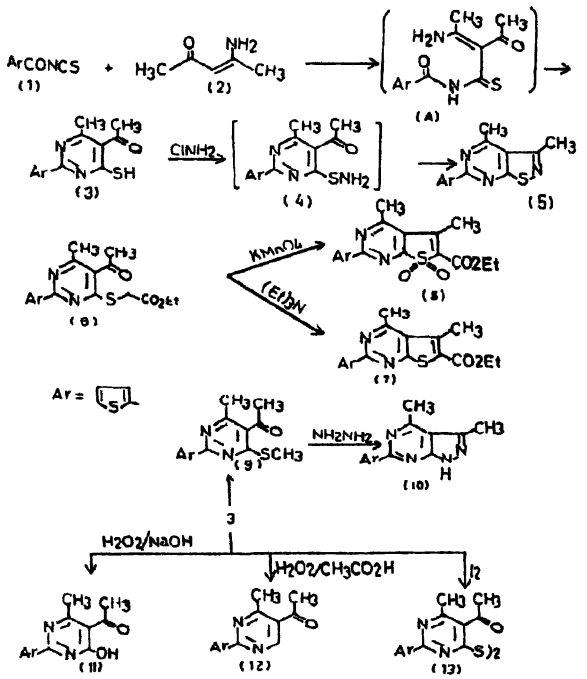
We have been interested in the synthesis and biological evaluation of pyrimidine systems[1]. This together with the fact that pyrimidine ring possesses remarkable biological properties[2], prompted additional work in this area. The present communication describes the synthesis of substituted isothiazolopyrimidine and thienopyrimidine[3].



Scheme 1

Aroyl isothiocyanates are versatile reagents for the synthesis of pyrimidine derivatives[4]. Thus, the reaction of thienoyl isosthiocyanate (1) with 2-aminopent-2-en-4-one (2) gave 5-acetyl-6-methyl-4-mercapto-2-thienylpyrimidine (3), presumably via the non-isolable intermediate (A) (Scheme 1). The reaction of the pyrimidine (3) with aqueous chloramine[5] resulted in aminative cyclisation, affording isothiazolo[5,4-*d*]pyrimidine (5) in an essentially one-pot procedure. This isothiazole cyclisation probably proceeded via the non-isolable sulphenamide[5] intermediate (4) which cyclised directly to 5. The pyrimidine (3) was allowed to react with ethyl bromoacetate in aqueous sodium carbonate to yield 4-carbethoxymethylthiopyrimidine (6). Heating an ethanolic solution of 6 in presence of triethylamine afforded thieno[2,3-*d*]pyrimidine-6-carboxylate (7). Compound 7 was also obtained directly from 3 by heating with ethyl bromoacetate and triethylamine. Oxidation of 6 with potassium permanganate in sulphuric acid provided the thieno[2,3-*d*]pyrimidine-7,7-dioxide (8). Methylation of compound 3 with methyl iodide in an alkaline medium yielded 4-methylthiopyrimidine (9). Reaction of 9 with hydrazine hydrate provided pyrazolo-[3,4-*d*]pyrimidine (10). Reaction of 3 with hydrogen peroxide in the presence of NaOH provided the oxo derivative (11), while in the presence of acetic acid desulphurisation took place leading to the formation of the pyrimidine (12)[6]. Oxidation of 3 with iodine in acetic acid gave the disulphide (13).

Experimental

All m.ps. are uncorrected. Ir spectra (KBr) were determined on an Unicam Sp 200G spectrophotometer and ^1H nmr spectra ($CDCl_3$) on a Varian A 60 (EM 360 L) spectrometer. Microanalysis was carried out at the Microanalytical Unit, Cairo University. All compounds gave satisfactory C, H and N analyses.

4-Mercapto-6-methyl-2-thienyl-5-acetylpyrimidine (3): A mixture of thienoyl isothiocyanate (1) [prepared from ammonium thiocyanate (0.12 mol) and thienoyl chloride (0.01 mol)[7]] and 2 (0.1 mol) in dioxane (20 ml) was refluxed for 2 h. The solid separated after cooling was crystallised from ethanol as yellow crystals (60%), m.p. 250–51°; δ 2.5 (3H, s, CH_3), 3.0 (3H, s, CH_3), 6.8–7.7 (3H, m, thiophene-H's), 9.2 (1H, s, NH).

3,4-Dimethyl-6-thienylisothiazolo[5,4-d]pyrimidine (5): An aqueous chloramine solution[5] (125 ml) was added dropwise over a period of 20 min to a stirred solution of the pyrimidine (3; 0.025 mol) in aqueous NaOH (33%; 90 ml) at room temperature. The separated solid was washed with water and crystallised from ethanol as colourless crystals (50%), m.p. 260°; δ 2.4 (3H, s, CH_3), 2.9 (3H, s, CH_3), 7.1–7.9 (3H, m, thiophene-H's).

4-Carbethoxymethylthio-6-methyl-2-thienyl-5-acetyl-5-acetylpyrimidine (6) : A mixture of 3 (0.01 mol) and ethyl bromoacetate (0.01 mol) in aqueous sodium carbonate (10%; 10 ml) was stirred for 0.5 h. The resulting solid was crystallised from methanol as colourless crystals (65%), m.p. 60–62°; υ_{max} 1 670, 1 660 cm^{-1} (CO).

Ethyl 4,5-dimethyl-2-thienylthieno[2,3-d]pyrimidine-6-carboxylate (7) : (a) A mixture of 6 (0.01 mol) and triethylamine (3 drops) in ethanol (10 ml) was refluxed for

0.5 h. The solid obtained on cooling was crystallised from ethanol to give colourless crystals (50%). (b) A mixture of 3 (0.01 mol), ethyl bromoacetate (0.01 mol) and triethylamine (3 drops) in ethanol (10 ml) was refluxed for 0.5 h. The solid obtained on cooling was crystallised from ethanol as colourless crystals (60%), 150–52°; υ_{max} 1 665 cm^{-1}(CO).

*Ethyl 4,5-dimethyl-2-thienylthieno[2,3-*d*]pyrimidine-7,7-dioxide-6-carboxylate* (**8**) : A solution of **6** (0.01 mol) in chloroform (10 ml) and sulphuric acid (2 ml) was cooled to 0° and then potassium permanganate (0.1 mol) was added slowly in portions. The solution was set aside at room temperature, made alkaline, decolourised with acetone and extracted with chloroform. After evaporation to dryness the residue was crystallised from ethanol as colourless crystals (40%), m.p. 180–81°; δ 1.5 (3H, t, CH_2CH_3), 2.7 (3H, s, CH_3), 3.0 (3H, s, CH_3), 4.3 (2H, q, CH_2CH_3), 6.8–7.8 (3H, m, thiophene-H's).

4-Methylthio-6-methyl-2-thienyl-5-acetylpyrimidine (**9**) : A mixture of **3** (0.01 mol), methyl iodide (0.015 mol), water (25 ml) and NaOH (0.01 mol) was stirred for 2 h. The solid that separated was crystallised from aqueous methanol as colourless crystals (70%), m.p. 55–56°; υ_{max} 1 670 cm^{-1} (CO).

*4,5-Dimethyl-2-thienylpyrazolo[3,4-*d*]pyrimidine* (**10**) : A mixture of **9** (0.01 mol), hydrazine hydrate (0.02 mol) and ethanol (20 ml) was refluxed for 2 h. After cooling, the resulting precipitate was crystallised from ethanol as yellow crystals (60%), m.p. 270–71°; δ 2.4 (3H, s, CH_3), 2.9(3H, s, CH_3), 6.9–7.8 (3H, m, thiophene-H's), 8.7(1H, s, NH).

*6-Methyl-2-thienyl-5-acetyl-(3*H*)-pyrimidin-4-one* (**11**) : A mixture of **3** (0.01 mol), hydrogen peroxide (30 ml; 30%) and NaOH (20 ml) was shaken for 5 min. After cooling with ice-water and scratching, the resulting solid was crystallised from ethanol as colourless crystals (40%), m.p. 265°; υ_{max} 3 400–3 100 (OH), 1 665 cm^{-1}(CO).

6-Methyl-2-thienyl-5-acetylpyrinidine (**12**) : A mixture of **3** (0.01 mol), hydrogen peroxide (30 ml; 30%) and acetic acid (20 ml) was shaken for 5 min. The solution was then boiled 3 min. After cooling with ice-water and scratching, the resulting solid was crystallised from acetic acid as yellow crystals (50%), m.p. 220°; υ_{max} 1 670 cm^{-1} (CO); δ 2.5 (3H, s, CH_3), 2.9 (3H, s, CH_3), 6.8–7.8 (4H, m, thiophene-H's + pyrimidine-H).

(6-Methyl-2-thienyl-5-acetylpyrimidin-4-yl)disulphide (**13**) : To a solution of **3** (0.01 mol) in acetic acid was added iodine (0.01 mol) with stirring. The resulting solid was crystallised as yellow crystals (50%),m.p. 195°; υ_{max} 1 670 cm^{-1} (CO).

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