Synthesis of Thieno[2′,3′:4,5]pyrimido[2,1-*c*][1,2,4]triazoles and Pyrazolylthieno[2,3-*d*][4,5-*d*′]dipyrimidines

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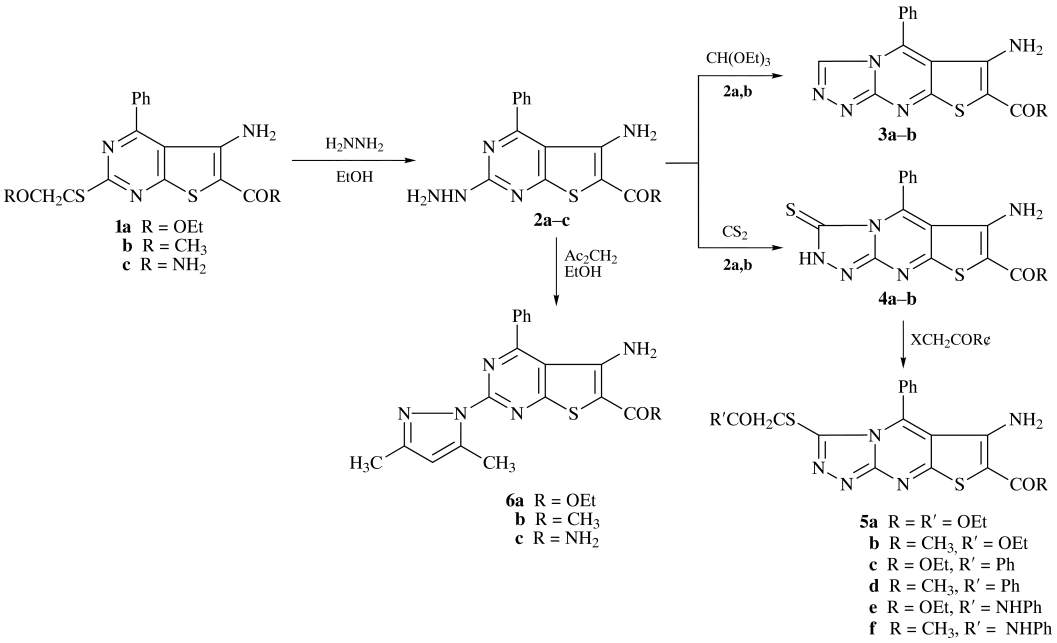
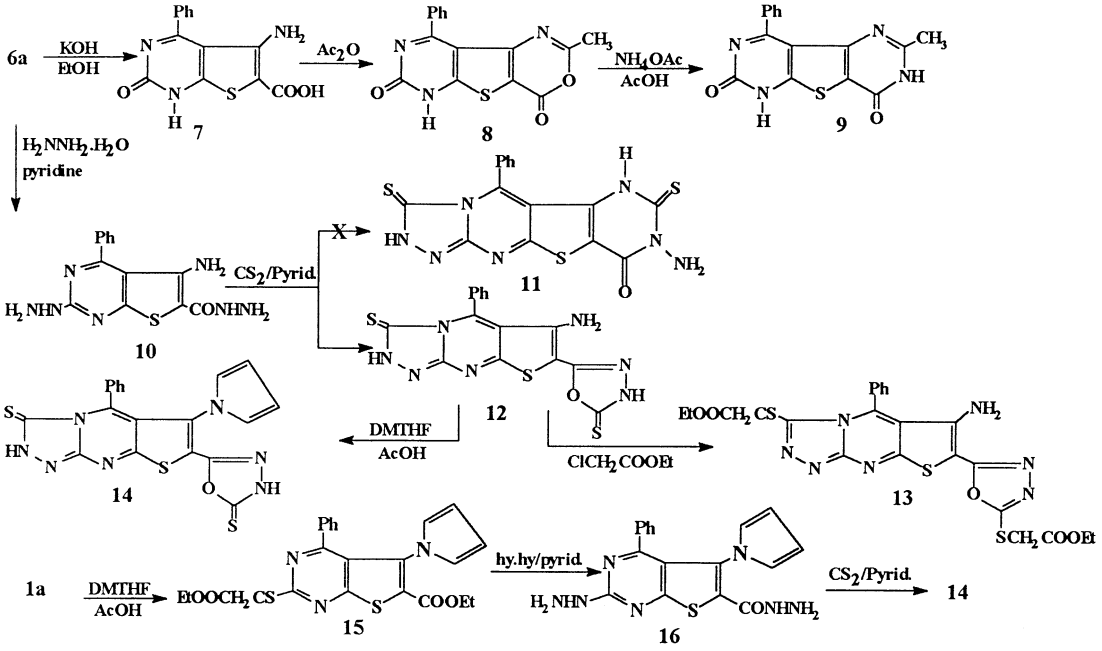
6-Substituted 5-amino-2-hydrazino-4-phenylthieno[2,3-*d*]pyrimidines (**2a**–**c**) were synthesized and used as key intermediates for the synthesis of new thienopyrimidotriazoles and pyrazolylthienodipyrimidines.

In pharmacological studies thieno[2,3-*d*]pyrimidines and thienodipyrimidines have been shown to possess a variety of pharmacological activities including antituberculous,[1] herpes virus inhibitory[2] and anti-anaphylactic activity.[3] Within this context and also, as part of our research programme dealing with the synthesis of heterocyclic systems, particularly those containing a thiophene moiety[6–8] we were interested in the synthesis of polyfused heterocycles containing these ring systems. The synthesis of the desired compounds began with 5-amino-4-phenyl-6-substituted-2-(substituted-thio)thieno[2,3-*d*]pyrimidines (**1a**–**c**), which we have synthesized previously from the reaction of 5-cyano-6-phenylpyrimidine-2,4(1*H*,3*H*)-dithione and α-halo compounds.[9] Treatment of **1a**–**c** with hydrazine hydrate in ethanol afforded the corresponding 2-hydrazino derivatives as a result of extrusion of the $-SCH_2COR$ group. The hydrazino derivatives **2a,b** were reacted with triethyl orthoformate in ethanol containing a few drops of acetic acid and with carbon disulfide in pyridine to give the thienopyrimidotriazoles **3** and **4** respectively. Triazolothione derivatives **4a,b** were easily S-alkylated with α-halo compounds to give compounds **5a**–**f** (Scheme 1). In addition, the hydrazino derivatives **2a**–**c** were condensed with acetylacetone to afford the dimethylpyrazolyl derivatives **6a**–**c**. Alkaline hydrolysis of **6a** with alcoholic potassium hydroxide afforded a compound whose ^{1}H NMR spectrum revealed no signals for a dimethylpyrazolyl moiety, this compound was identified as 5-amino-6-carboxy-4-phenylthieno[2,3-*d*]pyrimidin-2(1*H*)-one (**7**) which has been synthesized previously[9] from the hydrolysis of **1a** by alcoholic potassium hydroxide. Compound **7** was boiled under reflux in acetic anhydride to give the oxazinone **8**, which in turn reacted with ammonium acetate in acetic acid to afford the thienodipyrimidine (Scheme 2).[9] In addition, when the ester derivative **6a** was boiled under reflux with hydrazine hydrate in pyridine to synthesize the corresponding carbohydrazide, the pyrazolyl moiety was substituted by a hydrazino group to give 5-amino-2-hydrazino-4-phenylthieno[2,3-*d*]pyrimidine-6-carbohydrazide **10**. Compound **10** reacted with carbon disulfide in pyridine to yield 7-(oxadiazolyl)thienopyrimidotriazole **12**, which was easily S-alkylated with 2 equiv. of ethyl chloroacetate to give the dithioester derivative **13**. The structure of **12** as an oxadiazole derivative rather than the *N*-aminopyrimidine derivative **11** was established through the synthesis of the pyrrolyl derivative **14** from the reaction of **12** with 2,5-dimethoxytetrahydrofuran in acetic acid. This compound was also obtained from the reaction of **1a** with DMTHF to give compound **15**, which when treated with hydrazine hydrate in ethanol gave the carbohydrazide derivative **16**. Finally, the reaction of **16** with CS_2 in pyridine afforded a compound that was identical with **14** in mp, mixed mp, elemental analyses and spectral data.

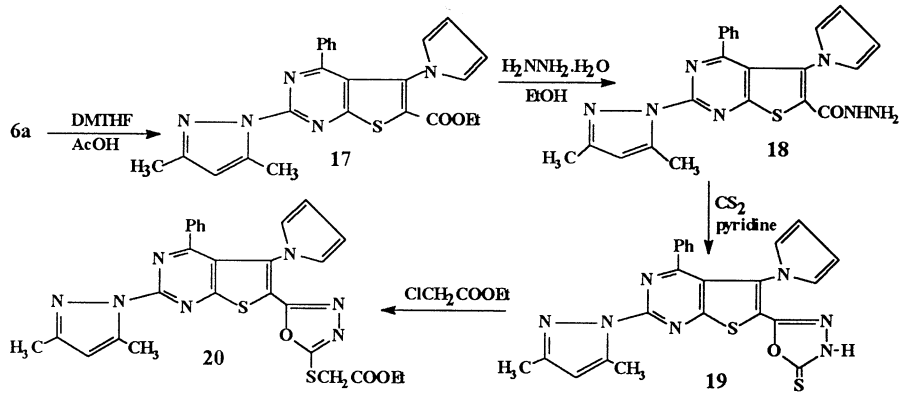
On the other hand, compound **6a** was condensed with DMTHF in acetic acid to give the corresponding 5-pyrrolyl derivative **17**, which in turn could easily be reacted with hydrazine hydrate in ethanol to afford the carbohydrazide derivative **18** (Scheme 3). The ^{1}H NMR spectrum of **18** reveals the presence of signals for the dimethylpyrazolyl moiety. The carbohydrazide **18** was reacted with carbon disulfide in pyridine to afford the oxadiazolethione **19**, which was easily S-alkylated with ethyl chloroacetate in ethanol containing anhydrous sodium acetate to give the



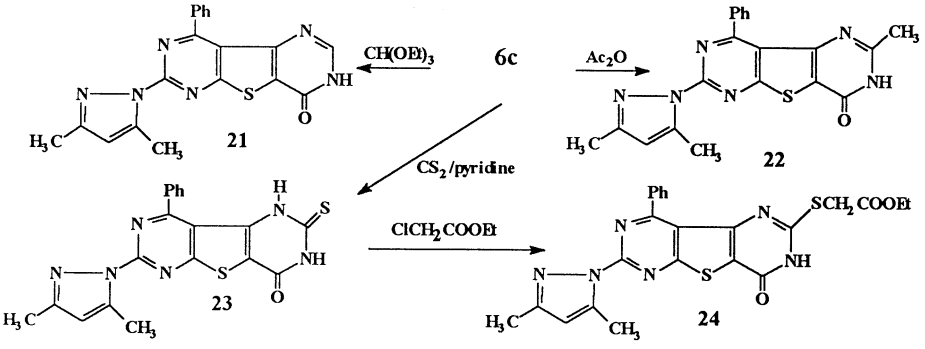
Scheme 1



Scheme 2



Scheme 3



Scheme 4

thioester derivative **20**. 5-Aminocarboxamide **6c** was condensed with triethyl orthoformate in ethanol in the presence of a few drops of acetic acid and with acetic anhydride to give thienodipyrimidines **21** and **22** respectively (Scheme 4). Finally, **6c** was reacted with carbon disulfide in pyridine to give the pyrimidinethione **23** which was S-alkylated with ethyl chloroacetate to afford the thioester derivative **24**.

Techniques used: IR, ^{1}H NMR, elemental analysis; Refs: 9
Schemes: 4; Tables: 1

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