# Synthesis of some new pyridothienopyrimidines and related [1,2,4]triazolopyridothienopyrimidines

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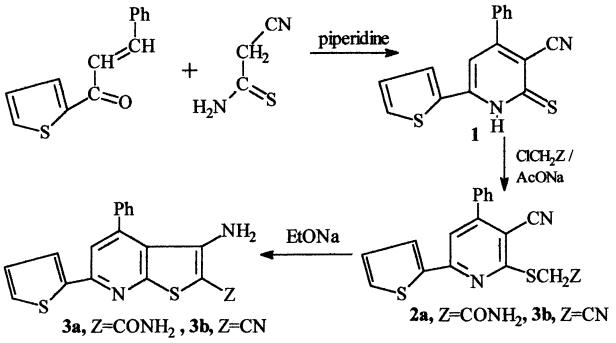
*J. Chem. Research (S),* 2003, 58-59
*J. Chem. Research (M),* 2003, 0236–0247

4-Chloro-9-phenyl-7-(2-thienyl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**5**) and 3-amino-3,4-dihydro-4-imino-9-phenyl-7-(2-thienyl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine (**19**) were prepared and employed as precursors for synthesizing the fused-ring compounds of the title.

**Keywords**: fused pyrimidines, thiophenes, pyridines, 1,2,4-triazoles, Dimroth rearangement

As a continuation of our program directed towards the synthesis of new condensed thieno[2,3-*b*]pyridines with anticipated biological activities,[14-16] we undertook the synthesis of the title compounds which might show good biological activities.

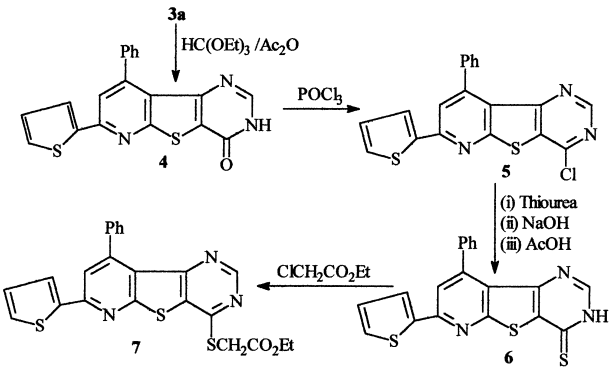
The starting compound, 3-cyano-4-phenyl-6-(2-thienyl)-pyridine-2(1*H*)-thione (**1**) was synthesised from the reaction of 3-phenyl-1-(2-thienyl)prop-2-en-1-one with cyanothioacetamide, in the presence of piperidine as a basic catalyst. The reaction of **1** with chloroacetamide or chloroacetonitrile in the presence of sodium acetate gave 2-substituted methylthiopyridines **2a** and **2b** respectively. Upon treatment of compounds **2a,b** with sodium ethoxide in ethanol, they underwent intramolecular Thorpe-Ziegler cyclisation to furnish 2-functionalised 3-amino-4-phenyl-6-(2-thienyl)thieno[2,3-*b*]-pyridines **3a,b,** which were used as key intermediates in this investigation (Scheme 1).




**Scheme 1**

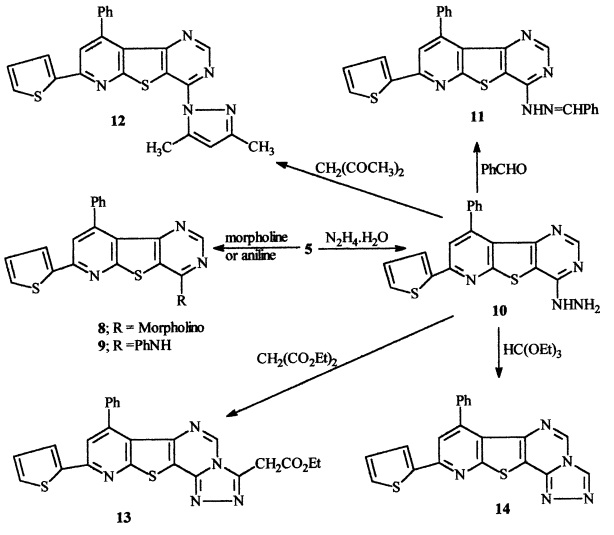
The cyclocondensation of compound **3a** with triethyl orthoformate in the presence of acetic anhydride furnished 9-phenyl-7-(2-thienyl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-4(3*H*)-one (**4**) in excellent yield. Conversion of **4** into the corresponding 4-chloropyrimidine derivative **5** was achieved by boiling with an excess of phosphorus oxychloride. The reaction of **5** with thiourea, followed by treatment of the resulting adduct with sodium hydroxide solution and then acidification with acetic acid gave 9-phenyl-7-(2-thienyl)pyrido-[3′,2′:4,5]thieno[3,2-*d*]pyrimidine-4(3*H*)-thione (**6**). When **6** was allowed to react with ethyl chloroacetate in the presence of sodium acetate, the corresponding ester **7** was obtained (Scheme 2).

The chloropyrimidine **5** underwent other nucleophilic displacements upon treatment with morpholine, aniline and/or hydrazine hydrate to afford 4-substituted 9-phenyl-7-(2-thienyl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines (**8, 9** and **10** respectively). The hydrazino compound **10** served as a convenient point of departure to other pyridothienopyrimidine




**Scheme 2**

derivatives. Thus, its condensation with benzaldehyde gave the hydrazone derivative **11**. Also, compound **10** underwent a cyclocondensation reaction upon treatment with acetylacetone to furnish the dimethylpyrazole derivative **12**. When **10** was heated with neat diethyl malonate, the triazolopyridothieno-pyrimidine derivative **13** was obtained in high yield. Also, the cyclocondensation of **10** with triethyl orthoformate, in the presence of acetic anhydride, led to the formation of 7-phenyl-9-(2-thienyl)-[1,2,4]triazolo[4″,3″-*c*]pyrido[3′,2′:4,5]-thieno[2,3-*c*]pyrimidine (**14**) (Scheme 3).




**Scheme 3**

On heating of hydrazino compound **10** with formic acid at reflux temperature for long time, the product was identified as the *s*-triazolo derivative **15** rather than the expected isomer **14**. In the same manner, the reaction of **10** with acetic acid led to

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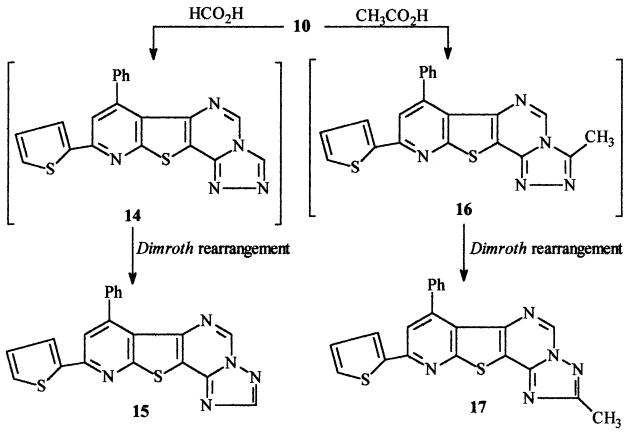
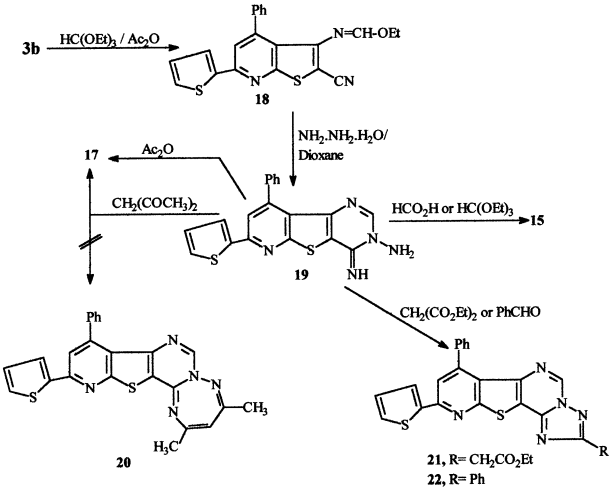
the formation of methyl-*s*-triazolo derivative **17** rather than the other one **16.** From thermodynamic point of view,[17] the compounds **15** and **17** seem to be more stable than the corresponding isomers **14** and **16**. The mechanism of the latter reactions may be involve firstly the usual formation of compounds **14** and **16** which underwent Dimroth rearrangement to give the most stable isomers **15** and **17** under the applied reaction condition.[17] This proposed mechanism was supported by the fact that the conversion of **14** into **15** was achieved upon heating with formic acid (Scheme 4).




**Scheme 4**

The structures of compounds **15** and **17** were also confirmed *via* an independent method of preparation as described below. Thus, the condensation of 3-amino-4-phenyl-6-(2-thienyl) thieno[2,3-*b*]pyridine-2-carbonitrile (**3b**) with triethyl orthoformate led to the formation of methanimidate derivative **18** which upon treatment with hydrazine hydrate furnished 3-amino-3,4-dihydro-4-imino-9-phenyl-7-(2-thienyl) pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidine(**19**). Heating of **19** with an excess amount of formic acid or triethyl orthoformate furnished the *s*-triazolopyridothienopyrimidine derivative **15**. The reaction of **19** with acetylacetone under neat conditions did not give the expected triazepine derivative **20**; instead, the methyl-s-triazolopyridothienopyrimidine **17** was isolated.[15]

Compound **17** was also prepared from the reaction of **19** with acetic anhydride. When compound **19** was allowed to react with diethyl malonate under neat conditions, ethyl 7-phenyl-9-(2-thienyl)-[1,2,4]triazolo[2″,3″-*c*]pyrido[3′,2′:4,5]thieno [2,3-*e*]pyrimidine-2-acetate (**21**) was isolated in high yield. Treatment of **19** with benzaldehyde in refluxing ethanol containing a catalytic amount of acetic acid, led to the formation of the phenyl-[1,2,4]triazolopyridothienopyrimidine **22** (Scheme 5).




**Scheme 5**

*Received 1 August 2002; accepted 9 January 2003*
*Paper 02/1499*

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