Synthesis of new thiopyridines, thienopyridines, pyridothienopyrimidines and pyranothienopyridines with anticipated biological activity

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(5-Acetyl-4-aryl-3-cyano-6-methylpyridin-2-ylthio)acethydrazides (**4a,b**), 5-acetyl-3-amino-4-aryl-6-methylthieno[2,3-*b*]pyridine-2-carbohydrazides (**5a,b**) and 5-acetyl-3-amino-6-methyl-4-phenylthieno[2,3-*b*]pyridine-2-carboxylic acid (**13**) were synthesised and used as key intermediates in the synthesis of the target compounds.

Keywords: pyridine-2-thiones, pyridines, fused pyrans, fused thiophenes, fused pyridines, fused pyrimidines

As a continuation of our previous work on thieno[2,3-*b*]pyridines,[17-21] we undertook the synthesis of further novel compounds in the series which might show enhanced activities owing to the incorporation of pharmacophores such as the thiopyridine, thienopyridine, pyridothienopyrimidine or pyranothienopyridine moiety into their structures.

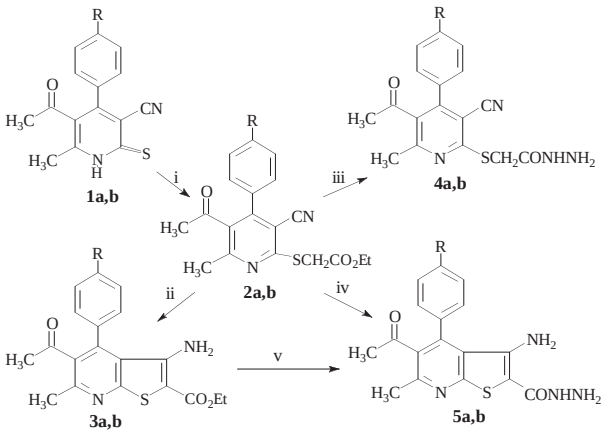
5-Acetyl-4-aryl-3-cyano-6-methylpyridine-2(1*H*)-thiones (**1a,b**)[20,22] were reacted with ethyl chloroacetate to give ethyl 5-acetyl-4-aryl-3-cyano-6-methylpyridin-2-ylthio)acetates (**2a,b**) which, in turn, underwent intramolecular Thorpe-Ziegler cyclization to furnish ethyl 5-acetyl-3-amino-4-aryl-6-methylthieno[2,3-*b*]pyridine-2-carboxylates (**3a,b**). The reaction of esters **2a,b** with an equimolar amount of hydrazine hydrate in refluxing ethanol produced (5-acetyl-4-aryl-3-cyano-6-methylpyridin-2-ylthio)acethydrazides (**4a,b**). When the latter reaction was performed in the presence of an excess of hydrazine hydrate, heating without solvent, the products were identified as 5-acetyl-3-amino-4-aryl-6-methylthieno[2,3-*b*]pyridine-2-carbohydrazides (**5a,b**). The latter compounds were also obtained upon heating of compounds **3a,b** with hydrazine hydrate [22] (Scheme 1).

The acethydrazides **4a,b** and carbohydrazides **5a,b** were used as precursors to other new thiopyridines and thienopyridines as well as to pyridothienopyrimidines. Thus, the reaction of **4a,b** with aromatic aldehydes by refluxing in ethanol gave the corresponding hydrazones **6a–f** which underwent intramolecular Thorpe-Ziegler cyclization upon treatment with sodium ethoxide to give thieno[2,3-*b*]pyridine derivatives **7a–f**. The latter compounds were also synthesized *via* direct condensation of **5a,b** with equimolar amount of aromatic aldehydes in refluxing ethanol (Scheme 2).

Heating compounds **7a–c** with acetic anhydride or compounds 7**d–f** with triethyl orthoformate in the presence of acetic anhydride at reflux temperature led to the formation of pyridothieno-pyrimidinones **8a–c** and **9a–c** respectively (Scheme 3).

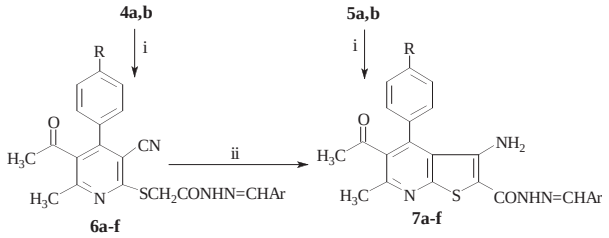
Compound **5a** was reacted with formic acid to give pyridothienopyrimidinone derivative **10**. Also, heating **5a,b** with acetic anhydride at reflux temperature led to the diacetylaminopyridothienopyrimidinones **11a,b**. The dimethylpyrazolyl derivative **12** was prepared from the reaction of **5a** with acetylacetone (Scheme 4).

The *o*-aminoester **3a** was also used as an intermediate in the synthesis of other new thienopyridines, pyridothienopyrimidines and pyranothienopyridines. Thus, saponification of **3a** with an ethanolic sodium hydroxide solution followed by acidification with acetic acid gave the corresponding carboxylic acid **13**. The latter compound underwent ring closure reaction upon treatment with acetic anhydride to afford the oxazinone derivative **14**. In



1-5	R
a	OCH_3
b	Cl

Scheme 1



6, 7	R	Ar
a	OCH_3	C_6H_5
b	OCH_3	4-$CH_3OC_6H_4$
c	OCH_3	4-ClC_6H_4

6, 7	R	Ar
d	Cl	C_6H_5
e	Cl	4-$CH_3OC_6H_4$
f	Cl	4-ClC_6H_4

Scheme 2

contrast, heating of **13** with orthophosphoric acid at 100 °C resulted in decarboxylation followed by hydrolysis of the imino group to afford the thieno[2,3-*b*]pyridinone **15**[19] (Scheme 5).

The oxazinone **14** was transformed into some fused pyrimidinone derivatives upon treatment with certain reagents. Thus, the reaction of **14** with hydrazine hydrate gave 8-acetyl-3-amino-2,7-dimethyl-9-(4'-methoxyphenyl) pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(*3H*)-one (**16**). The latter compound was reacted with aromatic aldehydes or acetic anhydride to give the corresponding pyrimidinone derivatives **8a–c** and **11a** Also, heating of **14** with ammonium acetate in glacial acetic acid led to the formation of pyridothienopyrimidinone **17** which has previously been prepared.[20] Reaction of **17** with ethyl chloroacetate in DMF

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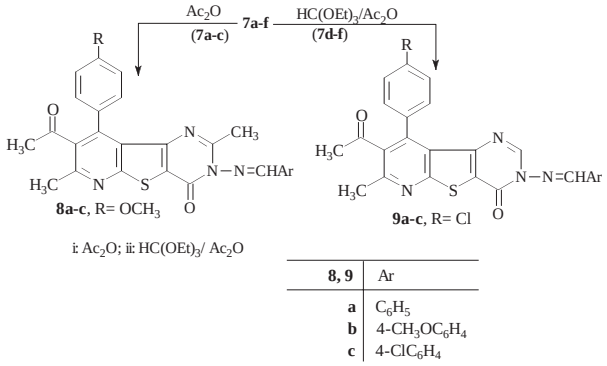
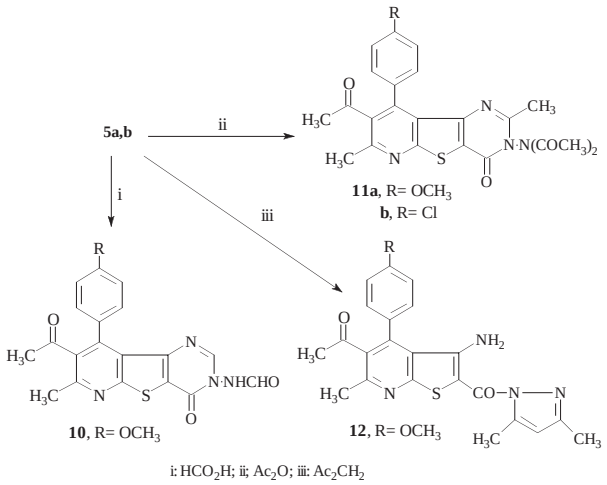
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

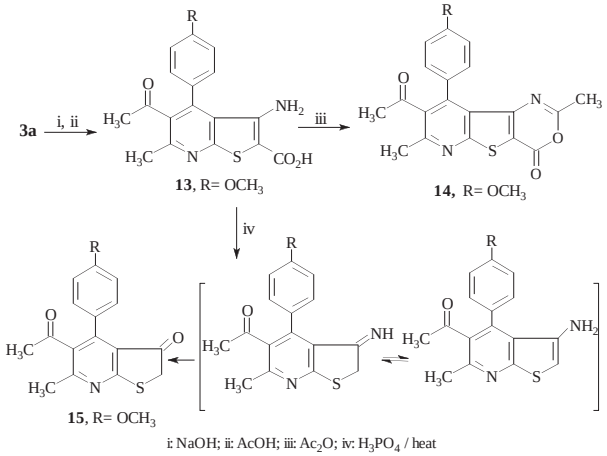


8, 9	Ar
a	C_6H_5
b	4-$CH_3OC_6H_4$
c	4-ClC_6H_4

Scheme 3



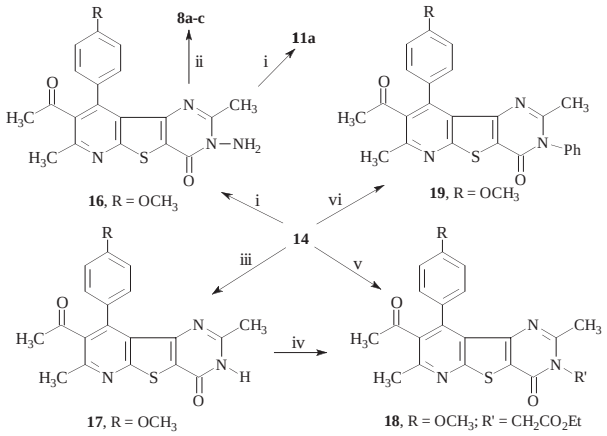
Scheme 4



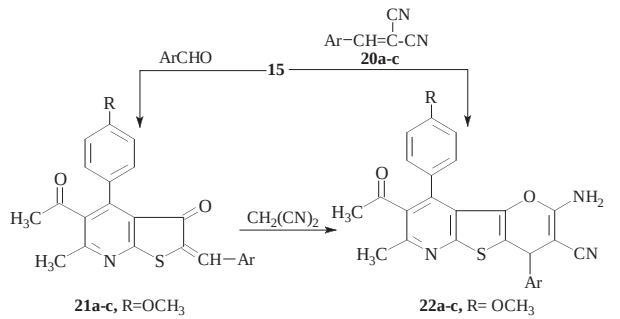
Scheme 5

containing anhydrous K_2CO_3 afforded the N-alkylated derivative **18**. The latter compound was also synthesised *via* direct reaction of **14** with ethyl glycinate hydrochloride. In the same manner, compound **14** was reacted with aniline to afford the pyrimidinone derivative **19** (Scheme 6).

On treatment of the ketone **15** with arylmethylene-malononitriles (**20a–c**) in ethanol containing catalytic amounts of piperidine, a cycloaddition reaction occurred and 4*H*-pyrano[2',3':4,5]thieno[2,3-*b*]pyridine derivatives **22a–c** were obtained. The latter compounds were also obtained *via* condensation of **15** with aromatic aldehydes followed by treating the formed chalcones **21a–c** with malononitrile (Scheme 7).



Scheme 6



21, 22	R'
a	
b	OCH_3
c	Cl

Scheme 7

It is noteworthy that the acetyl group attached to the pyridine ring did not react with any reactive entity such as the amino-compounds, aldehydes or active methylenes during the entire sequence of reactions described in this investigation. This may be the result of steric effects.

Techniques used: IR, 1H NMR.

Schemes: 7

Table 1: Melting points, yields, and analytical data

Table 2: IR and 1H NMR spectral data

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