Thienopyrimidines. Part III.† Synthesis of Novel Substituted Thieno[2,3-*d*]pyrimidinone Derivatives and their Condensed Products with Molluscicidal and Larvicidal activities

J. Chem. Research (S), 1999, 646–647
J. Chem. Research (M), 1999, 2775–2794

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A range of novel substituted thieno[2,3-*d*]pyrimidinones are synthesized and screened for malluscicidal and larvicidal biological activity.

Many thienopyrimidine derivatives have been reported to possess useful pharmaceutical[1,6] and molluscicidal properties.[8] In the present work, some newer thienopyrimidinones and related derivatives were synthesized to probe their molluscicidal and larvicidal activities. Thus, treatment of the 2-chloromethyl-5-(2-thienyl)thieno[2,3-*d*]-pyrimidin-4(3*H*)-one **2** with ethyl cyanoacetate and ethyl chloroformate afforded 1,8-dioxo-7-(2-thienyl)pyrrolo[1,2-*a*]-thieno[2,3-*d*]pyrimidine-2-carboxylic acid **5** and 3-ethoxycarbonylthieno[2,3-*d*]pyrimidinone **6** respectively. Reaction of product **6** with hydrazine hydrate in ethanol at room temperature gave the hydrazide derivative **7**. When the same reaction was carried out in boiling ethanol, the 2-amino-6-(2-thienyl)thieno[2,3-*d*]imidazo[1,5-*b*]pyrimidine-1,5-dione **9** was obtained. Product **9** was also obtained by heating **7** in ethanol. Presumably, **9** was obtained through Dimroth rearrangement of the intermediate (**8**). 2-Substituted-methylthieno[2,3-*d*]pyrimidinones **10** and **11** were synthesized from the reaction of **2** with cyclic amines and hydrazine hydrate, respectively (Scheme 1). Reaction of 2-hydrazinomethylthieno[2,3-*d*]pyrimidinone **11** with acetylacetone, ethyl acetoacetate and isothiocyanates gave the corresponding 2-pyrazolomethyl **12**, 2-pyrazolonomethyl **13** and thiosemicarbazide **14** derivatives of thienopyrimidinones respectively (Scheme 2).

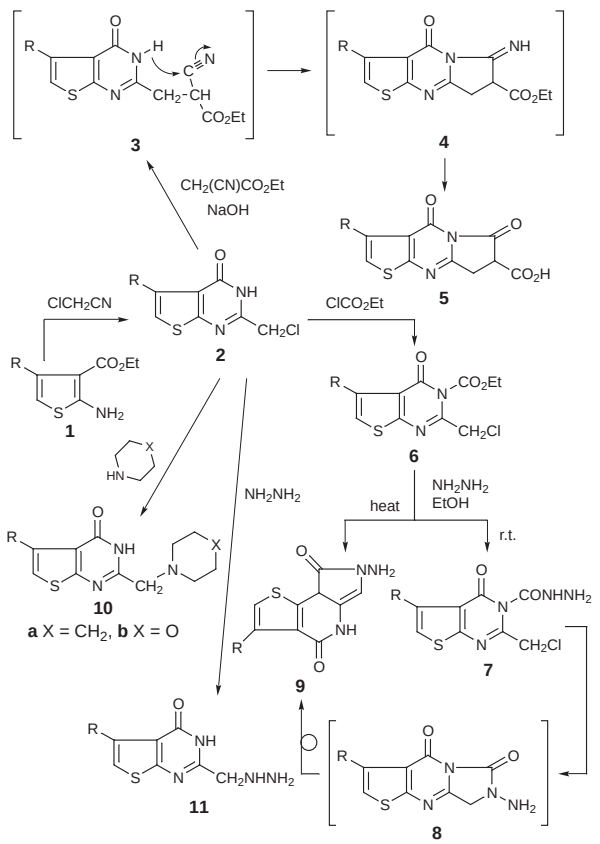
Mass spectra of products **7**, **12**, **13** and **14** showed *m/z* at 248 (100%), which corresponds to splitting of the groups attached to the methylene moiety at position-2.[10,11]

Upon using EI MS raising the temperature by 25 °C min^{-1} before reaching the melting points, the complete fragmentation patterns including M^+, see full text, were at 341 ($M^+ + 1$), 342, 344, 365 and 393, respectively (Table 2, see full text).

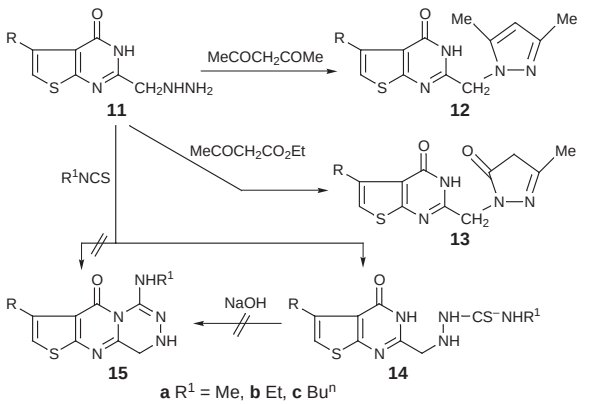
On the other hand, reaction of 2-benzylthieno[2,3-*d*]-pyrimidinone **16** with ethyl chloroformate, chloroacetonitrile and chloroacetone in the presence of potassium carbonate afforded the 3-substituted-2-benzylthieno[2,3-d]pyrimidinones **17** and **19**, respectively. Treatment of products **17** and **19a** with hydrazine hydrate gave the corresponding hydrazide **18** and 3-amino-6-benzyl-10-(2-thienyl)thieno[2′,3′:4,5]pyrimido[1,6-*a*][1,2,4]triazine **20** respectively (Scheme 3).

The IR spectrum of product **19a** showed *ν*(CN) at 2255 cm^{-1} with weak intensity, as rationalized by Kitson and Griffith.[12]

In the present work, when 2-cyanomethylthieno[2,3-*d*]pyrimidinone **21** was allowed to react with ethyl chloroformate under the same reaction conditions, the unexpected 2-di(ethoxycarbonyl)methylthieno[2,3-*d*]-pyrimidinone **22** was obtained, without isolation of the



Scheme 1 R = C_4H_3S



Scheme 2 R = C_4H_3S

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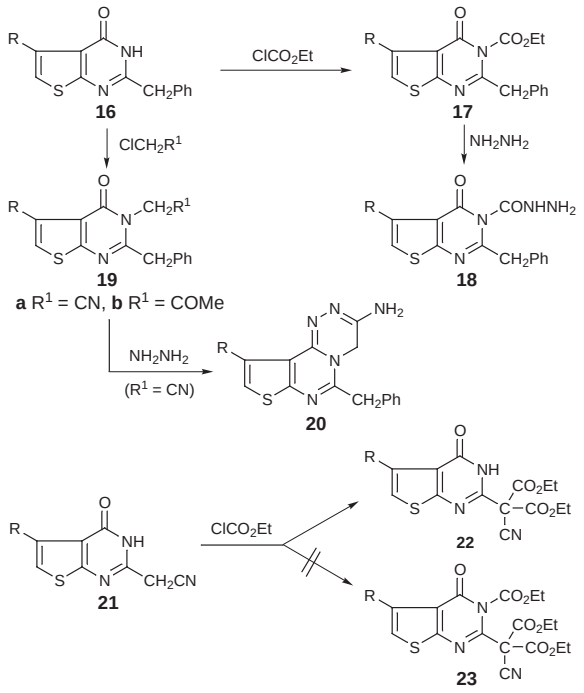
‡ Responsible for biological activity studies.



Scheme 3 R = C_4H_3S

triethoxycarbonyl derivative **23**. This could be attributed to the instability of product **23**, which is readily hydrolyzed and loses the ethoxycarbonyl group at position-3 (Scheme 3).

The IR spectrum of **22** showed a weak intensity ν(CN) band at 2220 cm^{-1} arising from attachment of the ester groups on the carbon atom bearing the nitrile group.[13]

Molluscicidal and larvicidal properties of products **5**, **6**, **10**, **11**, **12**, **13**, **14a**, **19b** and **22** were studied.

The molluscicidal activity of the tested products was screened against *Biomphalaria alexandrina* snails. From the results it was noted that product **6** is highly active with an LC_{90} at 7 ppm. Products **11**, **13**, **14a** and **22** showed higher LC_{90} values of 45, 50, 100 and 95 ppm respectively.[17]

The larvicidal activity was carried out against the free larval stages of *Schistosoma mansoni*; cercariae and miracidia.[19,20]

Cercaricidal activity results showed that products **6**, **11**, **13** and **22** gave about 90% cercarial mortality at 10 ppm while miracidicidal potencies of the tested products showed that the same products were effective over essentially the same period at the same concentration.

Techniques used: IR, ^{1}H NMR, EI mass spectrometry, biological screening.

Table 1: Characterization of the synthesized products

Table 2: Spectral properties of the synthesized products

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Received, 15th June 1999; Accepted, 4th August 1999
Paper E/9/04776J

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