Synthesis of Novel Thieno[2,3-c]pyridazines and Related Heterocycles

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Summary. The reaction of ethyl 2,3-dihydro-5,6-diphenyl-3-thioxopyridazine-4-carboxylate with \( \omega \)-bromoacetophenones, chloro-N-arylacetamides, chloroacetonitrile, ethyl chloroacetate, or chloroacetone furnished the corresponding 4,5-diphenyl-3-hydroxy thieno [2,3-c]pyridazines. 2-Cyano-, 2-ethoxycarbonyl-, and 2-acetyl-4,5-diphenyl-3-hydroxythieno[2,3-c]pyridazines were employed as precursors in the synthesis of some novel furo [2',3':4,5]thieno[2,3-c]pyridazines, pyranono-[2',3',4,5]thieno[2,3-c]pyridazines, and thieno[2,3-c]pyridazines. The antibacterial and antifungal activities of some of the compounds are reported.


Synthese neuer Thieno[2,3-c]pyridazine und verwandter Heterocyclen


Introduction

Pyridazine derivatives and heterocyclic annelated pyridazines continue to attract interest due to a wide spectrum of biological activities [1–6]. In particular, some thienopyridazines have been reported to possess considerable antiasthmatic [7] and fibrinolytic activities [8]. In view of the above facts and in continuation of our program directed towards the synthesis of new polyheterocyclic systems containing a thiophene moiety with potential biological properties [9–12], we synthesized the title compounds and evaluated their antimicrobial properties.

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Results and Discussion

Syntheses

The thiation of ethyl 2,3-dihydro-5,6-diphenyl-4-oxopyridazine-4-carboxylate (1) [13] using P₂S₅ in dry pyridine resulted in the formation of thioxo derivative 2 which was used as a starting material in the synthesis of the target heterocycles. Thus, the reaction of 2 with halocompounds like ω-bromo-acetophenones, chloro-N-arylacetamides, or chloroacetonitrile in refluxing ethanol containing an equimolar quantity of sodium acetate gave the corresponding S-alkylated products 3a–f. Cyclization of 3a–f to the corresponding thienopyridazines 4a–f was achieved by refluxing the educts in ethanol containing an excess of fused sodium acetate or catalytic amounts of sodium ethoxide. Compound 2 was also reacted with ethyl chloroacetate and/or chloroacetone in the presence of fused sodium acetate to give the thienopyridazines 4g, h. (Scheme 1). Reaction of the vicinal hydroxycarbamoyl derivative 4c with ethyl chloroformate afforded the thienopyridazine derivative 6 instead of the expected oxazine-2,4-dione 5 (Scheme 2).

An attempt to synthesize novel heterocyclic systems containing the furo[2',3':4,5]thieno[2,3-c]pyridazine moiety involved reaction of 4f with ethyl chloroacetate in DMF at 100°C for 2 h in the presence of K₂CO₃ to give ethyl-(2-cyano-4,5-diphenylthieno[2,3-c]pyridazin-3-yloxy)-acetate (7); the reaction of 4f

![Chemical diagram]

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Scheme 1