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# Synthesis and Properties of 1-Aryl-6-chloro-1,4-dihydro-4-oxothieno [2,3-c]pyridazine-3-carboxylic Acids

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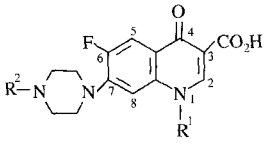
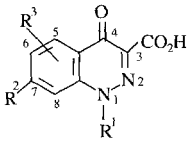
During the past decade, several 4-quinolones (**1**), such as ciprofloxacin **1a** [1] and difloxacin **1b** [2] were recognized as useful antibacterial agents. Almost concurrently, a large number of 4-oxocinnoline-3-carboxylic acids **2** was prepared and bioassayed [3–5]. Some 1-ethyl derivatives, e.g. **2a** [3] showed good antibacterial activities, while the related 1-aryl cinnolones, e.g. **2b** [4] were reported as potentially useful agrochemicals [4, 5].



(1a,b)



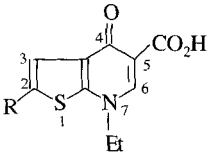
(2a,b)

| 1 | $R^1$ | $R^2$ |
|---|---|---|
| a | cycloprpyl | H |
| b | *p*-$FC_6H_4$ | $CH_3$ |

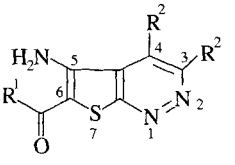
| 2 | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| a | Et |  | 6-F |
| b | *p*-$ClC_6H_4$ | H | 5-F |

A number of 4-oxothieno[2,3-*b*] pyridine-5-carboxylic acids **3** (bioisosteres of quinolones **1**) has been reported to exhibit potency *versus* Gram-negative bacteria [6, 7]. Notable examples are **3a** [6], and **3b** [7].

To the best of our knowledge, 1-substituted 4-oxo-thieno[2,3-*c*] pyridazines (potential bioisostere of cinnolones **2**) have not been described in the literature. Moreover, thieno [2,3-*c*] pyridazines lacking substituents at N1 have received limited attention. Syntheses of model compounds, e.g. **4a** [8] and **4b** [9], *via* substituted pyridazines have been reported.



(3a,b)



(4a,b)

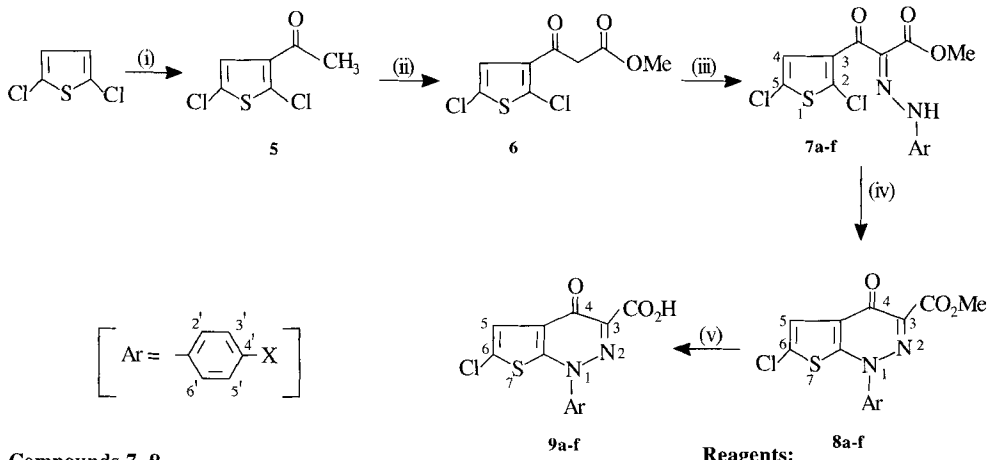
| 3 | R |
|---|---|
| a | Cl |
| b | CH = NOMe |

| 4 | $R^1$ | $R^2$ |
|---|---|---|
| a | OEt | $C_6H_5$ |
| b | OMe | H |

The present work describes the synthesis (*via* compounds **5** → **8**, Scheme 1), and properties of 1-aryl-6-chloro-1,4-dihydro-4-oxothieno[2,3-*c*]pyridazine-3-carboxylic acids **9**. Thus, 3-acetyl-2,5-dichlorothiophene **5** [10] was condensed with dimethyl carbonate in the presence of sodium hydride at 84–86 °C to give the β-keto ester **6** which was coupled with the appropriate arenediazonium chloride to produce the hydrazones **7a–f**. Cyclization of deprotonated **7** (sodium hydride in refluxing tetrahydrofuran (THF)) gave the pyridazines **8a–f**. A similar process has been successfully applied to syntheses of 1-arylcinnolones [5] and 1-arylquinolones [2]. Saponification of the esters **8a–f** produced the acids **9a–f** in excellent purities.

Compounds **6–9** were characterized by elemental analysis (Table 1), by $^1$H NMR spectroscopy (Table 1), and by electron impact mass spectrometry.

In the mass spectra of compounds **7–9** a-cleavage at the ketone function gives rise to the strong peak for the acylium ion at *m/z* 179. Loss of carbon monoxide affords the thienyl cation at *m/z* 151. Fragments corresponding to the azatropylium cations arise from cleavage of the N–N bond. These ions extrude HCN to give the cyclopentadienyl cations. Consecutive ejection of a chlorine atom and methanol from $M^+$ leads to ions $[M-35]^+$ and $[M-67]^+$.



**Compounds 7–9**

| Entry | a | b | c | d | e | f |
|---|---|---|---|---|---|---|
| X | H | F | Cl | Br | $OCH_3$ | $CH_3$ |

**Reagents:**
(i) $AlCl_3/CH_3COCl$, $CS_2$; 23 °C (24 h), [10]
(ii) $(CH_3O)_2CO$; 84–86 °C (3 to 4 h)/$H_2O$ + AcOH
(iii) $ArN_2Cl$/pyridine + $H_2O$ (2 : 1 v/v); o to 4 °C (5 to 10 min)
(iv) NaH/dry THF; 15 °C (40 to 50 min), 60 to 63 °C (2 to 3 h)
(v) 0.1M ethanolic NaOH; 23 °C (1 h)/aq. HCl (1M)

The main fragmentation pathway of the molecular ions of **8a–f** starts with elimination of the ester group *via* a process that gives ions $[M-58]^{+\cdot}$. Expulsion of HCN produces the radical cations $[M-85]^+$ as the base peak in a number of cases. The latter ions undergo successive loss of carbon monoxide and a chlorine atom to furnish the ions $[M-113]^+$ and [M–148]. Alternatively, ions $[M-120]^{+\cdot}$ and [M–148] may be formed first by loss of CO and then of Cl. The ions [M–120] eject CS to give ions [M–192], a process which is common for thiophenes under electron impact [11]. Elimination of the methoxy radical from $M^+$ produces the cations M–31 (8–12%). These processes are substantiated by the detection of the appropriate metastable ions. The aryl cations, $Ar^+$, are observed in all cases.

Compounds **9a–f** lose carbon dioxide to produce ions $[M-44]^{+\cdot}$ which fragment as described for the esters **8a–f**. The thioformyl cation $H-C\equiv\overset{+}{S}$ (*m/z* = 45), previously reported for several substituted thiophenes [11], is also observed in the mass spectra of the thiophenes **6–9**.

The exchangeable N–H and $CO_2H$ protons of **7** and **9** resonate in the range 12.80–13.15 (s, 1*H*) and 14.53–14.73 (s, 1*H*); the $CO_2CH_3$ protons' signals of **8** and **9** appear at 3.83–3.95 (s, 3*H*). Other typical $^1H$ NMR signals of **7–9** are included in Table 1.

The target compounds **9a–f** were tested against *Escherichiacoli* and *Pseudomonus aeruginosa* by using standard techniques [12]. Aqueous stock solutions were prepared with 0.1M sodium hydroxide. None of these compounds showed any activity at concentrations ≤ 50 µg/ml.

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## Experimental

Melting points : uncorrected. $^1H$ NMR spectra : Bruker WM 300 spectrometer; $CDCl_3$ solutions; δ-scale; TMS as internal standard. Electron impact mass spectra : Finnigan MAT 731 spectrometer at 70 eV.

3-Acetyl-2,5-dichlorothiophene **(5)** was prepared by Friedel – Crafts acetylation of 2,5-dichlorothiophene (Fluka) [10].

*Methyl 3-(2,5-dichlorothien-3-yl)-3-oxopropanoate* **(6)**

NaH (suspension in oil, 80%) (2.25g, 75 mmol) was added in portions at 23 °C to a stirred solution of **5** (14.00 g, 72 mmol) in anhydrous dimethyl carbonate (150 ml). After stirring at 84–86 °C for 2 to 3h and cooling to 23 °C, the orange reaction mixture was poured onto ice-cold water (350 ml) containing acetic acid (10 ml). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (3×70 ml). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. The black gummy residue was extracted with hexane (6×50 ml). Evaporation of the solvent afforded a yellowish solid (6.10 g, 67%); *m.p.* 39–41 °C. Crystallization at 0 °C from a filtered (Norite) solution in hexane gave colourless cotton–like crystals (5.30 g, 58%); *m.p.* 46–47 °C. – MS (*m/z*): 252 ($M^{+\cdot}$, 18%), 217 (40), 179 (100), 151 (7), 116 (8), 81 (14). – $^1H$ NMR ($CDCl_3$): δ3.69 (s, 2.22 H, $OCH_3$, keto tautomer), 3.74* (s, 0.78 H, $OCH_3$, enol tautomer), 3.92 (s, 1.48 H, $CH_2$), 5.68* (s, 0.26 H, vinyl-H, enol), 12.42* (s, 0.26 H, OH, enol), 7.17 (s, 0.78 H, ArH), 7.05* (s, 0.26 H, ArH, enol) (*refers to the minor enol tautomer).

### General Procedure for the Synthesis of Methyl 2-(2-Arylhydrazono)-3-(2,5-dichlorothien-3-yl)-3-oxopro-panoates (7a–f)

To a cold (–5 °C) stirrred solution of the aniline (50 mmol) in 6M HCl (40 ml) was added dropwise a solution of $NaNO_2$ (4.40 g, 64 mmol) in $H_2O$ (15 ml). After stirring at 0 to 3 °C for 20 to 30 min the solution of the arenediazonium chloride was poured under vigorous stirring onto a cold solution (–5 to –10 °C) of the β-keto ester **6** (5.10 g, 20 mmol) in pyridine (40 ml) and $H_2O$ (20 ml). Stirring was continued at 0 to 4 °C until a precipitate of **7** was formed (5 to 10 min). The mixture was diluted with cold $H_2O$ (400 ml) and **7** was filtered and washed with cold $H_2O$ and dried.

**Table 1** Physical, Analytical and $^1$H NMR Data of Compounds **6–9**

| No. (%) | Yield (°C) | *m.p.* (Mol. Mass) | Molecular Formula | % Analysis Calcd./Found | | | $^1$H NMR Spectral Data | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | N | S | 2'-H / 6'-H | 3'-H / 5'-H | 4-H |
| **6a** | 56 | 46–47 | $C_8H_6Cl_2O_3S$ | 37.96 | 2.39 | – | 12.67 | | |
| | | (253.10) | | 38.04 | 2.34 | – | 12.49 | | |
| **7a** | 89 | 123–124 | $C_{14}H_{10}Cl_2N_2O_3S$ | 47.07 | 2.82 | 7.84 | 8.98 | 7.17 ($m_c$, 3H) [b] | 7.06 (s) |
| | | (357.22) | | 47.17 | 2.77 | 7.62 | 8.81 | 7.35 ($m_c$, 2H) | |
| **7b** | 58 | 104–105 | $C_{14}H_9Cl_2FN_2O_3S$ | 44.82 | 2.42 | 7.47 | 8.55 | 7.12 (dd, 7.00 (dd, | 6.99 (s) |
| | | (375.21) | | 44.92 | 2.29 | 7.14 | 8.25 | $J$ = 9.0) [c] $J$ = 9.0) [d] | |
| **7c** | 82 | 133–134 | $C_{14}H_9Cl_3N_2O_3S$ | 42.93 | 2.32 | 7.15 | 8.19 | 7.25 (d, 7.07 (d, | 7.09 (s) |
| | | (391.66) | | 42.96 | 2.33 | 6.98 | 7.99 | $J$ = 8.6) $J$ = 8.6) | |
| **7d** | 92 | 145–146 | $C_{14}H_9BrCl_2N_2O_3S$ | 38.56 | 2.08 | 6.42 | 7.35 | 7.38 (d, 7.02 (d, | 7.01 (s) |
| | | (436.12) | | 38.70 | 2.12 | 6.40 | 7.42 | $J$ = 8.9) $J$ = 8.9) | |
| **7e** | 44 | 75–77 | $C_{15}H_{12}Cl_2N_2O_4S$ | 46.53 | 3.12 | 7.23 | 8.28 | 7.08 (d, 6.88 (d, | 7.03 (s) |
| | | (387.24) | | 46.78 | 3.20 | 7.09 | 8.09 | $J$ = 9.0) $J$ = 9.0) | |
| **7f** | 70 | 112–113 | $C_{15}H_{12}Cl_2N_2O_3S$ | 48.53 | 3.26 | 7.55 | 8.64 | 7.11 (d, 7.05 (d, | 6.98 (s) |
| | | (371.24) | | 48.34 | 3.22 | 7.44 | 8.71 | $J$ = 8.0) $J$ = 8.0) | |
| | | | | | | | | | **5-H** |
| **8a** | 55 | 160–161 | $C_{14}H_9ClN_2O_3S$ | 52.42 | 2.83 | 8.73 | 10.00 | 7.50 ($m_c$, 3H) [b] | 7.40 (s) |
| | | (320.75) | | 52.51 | 2.79 | 8.62 | 10.12 | 7.60 ($m_c$, 2H) | |
| **8b** | 52 | 154–156 | $C_{14}H_8ClFN_2O_3S$ | 49.64 | 2.38 | 8.27 | 9.47 | 7.64 (dd, 7.26 (dd, | 7.41 (s) |
| | | (338.74) | | 49.80 | 2.39 | 8.07 | 9.22 | $J$ = 9.0) [e] $J$ = 9.0) [f] | |
| **8c** | 60 | 169–170 | $C_{14}H_8Cl_2N_2O_3S$ | 47.34 | 2.27 | 7.89 | 9.03 | 7.59 (d, 7.55 (d, | 7.40 (s) |
| | | (355.20) | | 47.53 | 2.39 | 7.64 | 8.82 | $J$ = 9.1) $J$ = 9.1) | |
| **8d** | 63 | 192–193 | $C_{14}H_8BrClN_2O_3S$ | 42.07 | 2.02 | 7.01 | 8.02 | 7.71 (d, 7.53 (d, | 7.42 (s) |
| | | (399.66) | | 41.87 | 1.90 | 6.81 | 8.15 | $J$ = 8.6) $J$ = 8.6) | |
| **8e** | 52 | 125–126 | $C_{15}H_{11}ClN_2O_4S$ | 51.36 | 3.16 | 7.99 | 9.14 | 7.52 (d, 7.04 (d, | 7.42 (s) |
| | | (350.78) | | 51.29 | 3.06 | 7.75 | 8.87 | $J$ = 9.0) $J$ = 9.0) | |
| **8f** | 56 | 164–165 | $C_{15}H_{11}ClN_2O_3S$ | 53.82 | 3.31 | 8.37 | 9.58 | 7.47 (d, 7.34 (d, | 7.42 (s) |
| | | (334.78) | | 53.93 | 3.14 | 8.07 | 9.60 | $J$ = 7.4) $J$ = 7.4) | |
| **9a** | 82 | 240–241 | $C_{13}H_7ClN_2O_3S$ | 50.91 | 2.30 | 9.13 | 10.45 | 7.55 ($m_c$, 5H) [g] | 7.27 (s) |
| | | (306.73) | | 50.71 | 2.10 | 8.89 | 10.19 | | |
| **9b** | 80 | 257–258 | $C_{13}H_6ClFN_2O_3S$ | 48.09 | 1.86 | 8.63 | 9.87 | 7.86 (dd, 7.48 (dd, | 7.25 (s) |
| | | (324.72) | | 48.06 | 1.86 | 8.72 | 9.76 | $J$= 9.2) [h] $J$ = 9.2) [i] | |
| **9c** | 84 | 265–266 | $C_{13}H_6Cl_2N_2O_3S$ | 45.77 | 1.77 | 8.21 | 9.40 | 7.63 (d, 7.56 (d, | 7.26 (s) |
| | | (341.17) | | 45.77 | 1.72 | 8.11 | 9.48 | $J$ = 8.5) $J$ = 8.5) | |
| **9d** | 87 | 268–270 | $C_{13}H_6BrClN_2O_3S$ | 40.49 | 1.57 | 7.26 | 8.31 | 7.75 (d, 7.58 (d, | 7.26 (s) |
| | | (385.63) | | 40.60 | 1.46 | 7.32 | 8.21 | $J$ = 8.6) $J$ = 8.6) | |
| **9e** | 78 | 236–237 | $C_{14}H_9ClN_2O_4S$ | 49.93 | 2.69 | 8.32 | 9.52 | 7.59 (d, 7.07 (d, | 7.26 (s) |
| | | (336.75) | | 49.76 | 2.53 | 8.18 | 9.26 | $J$ = 9.0) $J$ = 9.0) | |
| **9f** | 85 | 233–234 | $C_{14}H_9ClN_2O_3S$ | 52.42 | 2.83 | 8.73 | 10.00 | 7.60 (d, 7.37 (d, | 7.27 (s) |
| | | (320.75) | | 52.25 | 2.70 | 8.63 | 9.94 | $J$ = 7.6) $J$ = 7.6) | |

[a] Analysis for Cl: Calcd.: 28.01%. Found: 27.85%. – [b] 4'-H Signal: Overlapped with 3'-H / 5'-H Signals. – [c] $J_{2'\text{-H-F}}$ = 5.1. [d] $J_{3'\text{-H-F}}$ = 8.6. – [e] $J_{2'\text{-H-F}}$ = 5.0. – [f] $J_{3'\text{-H-F}}$ = 10.1. – [g] 4'-H Signal: Overlapped with 2'-,6'-/ 3'-,5'-H Signals. – [h] $J_{2'\text{-H-F}}$ = 5.1. – [i] $J_{3'\text{-H-F}}$ = 9.2.

However, the red oily compound **7e** was isolated by extraction with $Et_2O$ (3×70 ml) and usual workup. On trituration with light petroleum (*b.p.* 40–60 °C) the product solidified slowly.

Compounds **7a–f** were purified by column chromatography (Merck Silica gel 100, particle size 63–200 mm) using $CHCl_3$/hexane (1:1 v/v) as the eluent until most of the dark coloured impurities were removed. The chromatogram was then eluted with $CHCl_3$ to desorb **7**. Crystallization from $CHCl_3$/hexane afforded the pure products.

### General Procedure for the Synthesis of Methyl 1-Aryl-6-chloro-1,4-dihydro-4-oxothieno[2,3-c]pyridazine-3-carboxylates (8a–f)

NaH (suspension in oil, 80%) (0.20 g, 6.7 mmol) was added portionwise with exclusion of moisture to a stirred solution of **7** (6.0 mmol) in dry THF (200 ml). The reaction mixture was stirred at 23 °C for 40 to 50 min, and then heated at 60–63 °C for 2 to 3 h. The solvent was evaporated and the residue was soaked *into* $H_2O$ (50 ml) and filtered. Purification by preparative thick layer chromatography (Merck Silica gel 60 HF–254 glass plates, $CHCl_3/CH_3OH$ (99 : 1 v/v) as solvent) and crystallization from $CHCl_3$/light petroleum furnished analytically pure samples.

### General Procedure for the Synthesis of 1-Aryl-6-chloro-1,4-dihydro-4-oxothieno[2,3-c]pyridazine-3-carboxylic acids (9a–f)

A suspension of **7** (3.5 mmol) in 0.1M NaOH in EtOH solution (80 ml) was stirred at 23 °C for 1h. The solution was acidified with 1M HCl to pH 2. The precipitate was filtered, washed with $H_2O$ (2×10 ml), dried and crystallized from $CHCl_3$/light petroleum.

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