

Arbeitsvorschriften und Meßwerte • Procedures and Data

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

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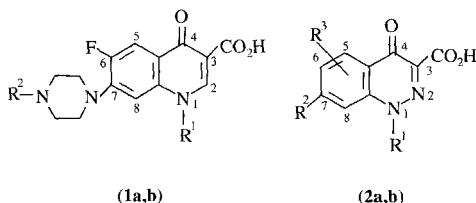
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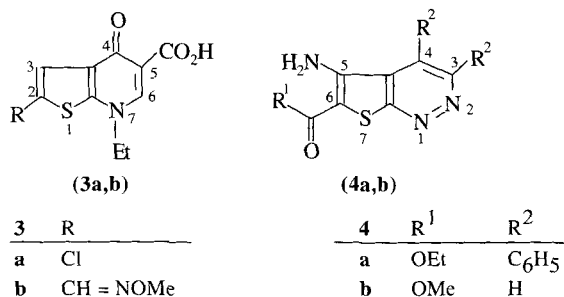
During the past decade, several 4-quinolones (**1**), such as ciprofloxacin **1a** [1] and difloxacin **1b** [2] were recognized as useful antibacterial agents. Almost concurrently, a large number of 4-oxocinnoline-3-carboxylic acids **2** was prepared and bioassayed [3–5]. Some 1-ethyl derivatives, 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].



1	R ¹	R ²	2	R ¹	R ²	R ³
a	cyclopropyl	H	a	Et		6-F
b	<i>p</i> -FC ₆ H ₄	CH ₃	b	<i>p</i> -ClC ₆ H 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].

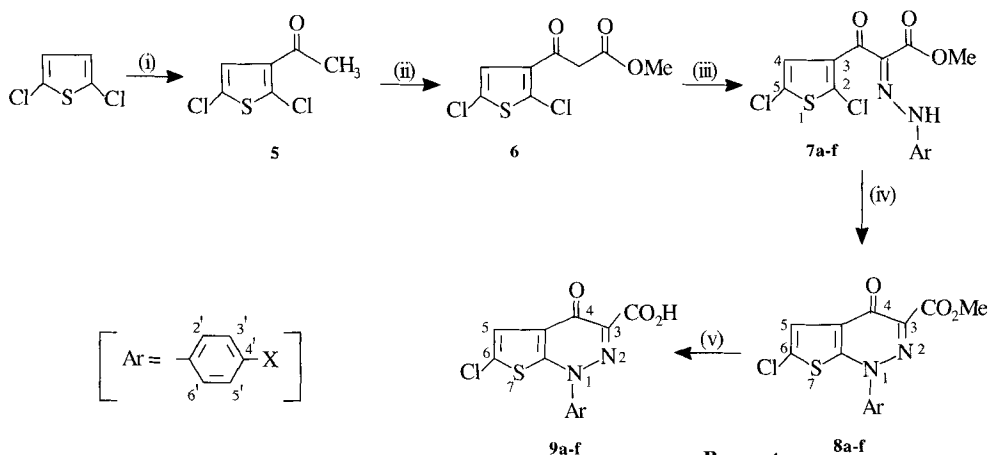
To the best of our knowledge, 1-substituted 4-oxo-thieno[2,3-*c*] pyridazines (potential bioisostere of cinnolones **2**) have not been described in the literature. Moreover, thieno [2,3-*c*] pyridazines lacking substituents at N1 have received limited attention. Syntheses of model compounds, e.g. **4a**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



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 ¹H 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]⁺.

**Reagents:**

- (i) AlCl₃/CH₃COCl, CS₂; 23 °C (24 h), [10]
 (ii) (CH₃O)₂CO; 84–86 °C (3 to 4 h)/H₂O + AcOH
 (iii) ArN₂Cl/pyridine + H₂O (2 : 1 v/v); 0 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]⁺. 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]⁺ 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]⁺ which fragment as described for the esters **8a–f**. The thioformyl cation H–C≡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 CO₂H protons of **7** and **9** resonate in the range 12.80–13.15 (s, 1H) and 14.53–14.73 (s, 1H); the CO₂CH₃ protons' signals of **8** and **9** appear at 3.83–3.95 (s, 3H). Other typical ¹H NMR signals of **7–9** are included in Table 1.

The target compounds **9a–f** were tested against *Escherichiacoli* and *Pseudomonas 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; CDCl₃ 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 Et₂O (3×70 ml). The combined organic phases were dried (MgSO₄) 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⁺, 18%), 217 (40), 179 (100), 151 (7), 116 (8), 81 (14). – ¹H NMR (CDCl₃): δ 3.69 (s, 2.22 H, OCH₃, keto tautomer), 3.74* (s, 0.78 H, OCH₃, enol tautomer), 3.92 (s, 1.48 H, CH₂), 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-Aryl-hydrazono)-3-(2,5-dichlorothien-3-yl)-3-oxopropanoates (**7a–f**)

To a cold (–5 °C) stirred solution of the aniline (50 mmol) in 6M HCl (40 ml) was added dropwise a solution of NaNO₂ (4.40 g, 64 mmol) in H₂O (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 H₂O (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 H₂O (400 ml) and **7** was filtered and washed with cold H₂O and dried.

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

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

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, $\text{CHCl}_3/\text{CH}_3\text{OH}$ (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 1 h. 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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