Synthesis of Indolizine-6,9-diones Annelated to a Thiophene Ring

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Indolizine-6,9-diones fused to a thiophene ring have been prepared by Friedel–Crafts cyclization of (±)-5-oxo-1-(thienylmethyl)prolines. The ketones were converted into oximes, either as *syn–anti* mixtures or as single isomers. The selectivity of the reaction is discussed.

Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

Within the scope of a research programme on cyclised derivatives of both pyrrole and thiophene we have studied the cyclization of the *N*-(thienylmethyl)-5-oxoprolines into new indolizinediones fused to a thiophene ring. The conversion of these products into the corresponding oximes was also studied.

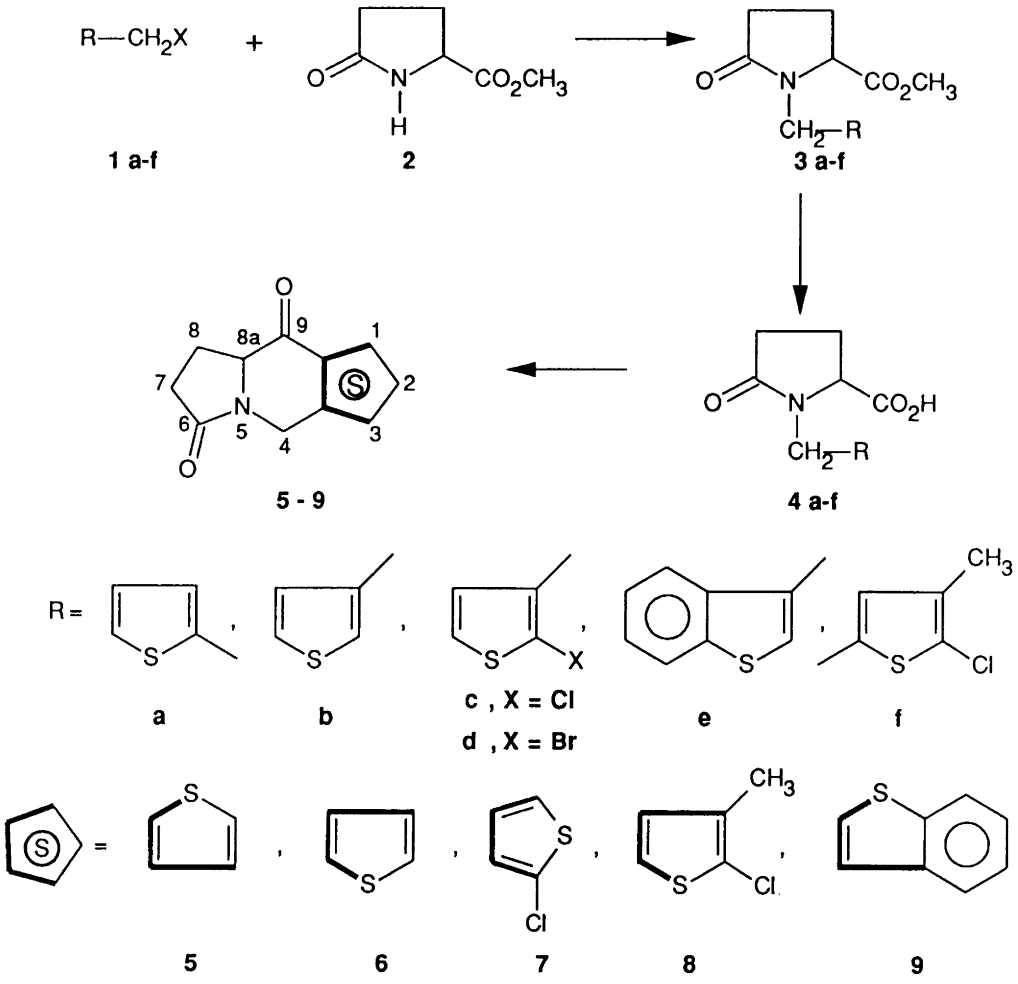
Previous investigations have been performed in the benzene series.[1–3] The results observed prompted us to synthesize thieno-[2,3-*f*]-, -[3,2-*f*]- and -[3,4-*f*]-indolizine-6,9-dione in order to study the influence of the thiophene ring on the corresponding oxime formation (Scheme 1).

The required *N*-thienylmethyl-5-oxoproline esters **3a–f** were prepared in good yields (50–60%) from the halogenomethylthiophenes **1a–d**, **f** or halogenomethylbenzo[*b*]thiophene **1e** with the sodium salt (±)-5-oxoproline methyl ester **2** (see Scheme 1). Saponification of the esters **3a–f** led to the corresponding acids **4a–f** (75–90% yield).

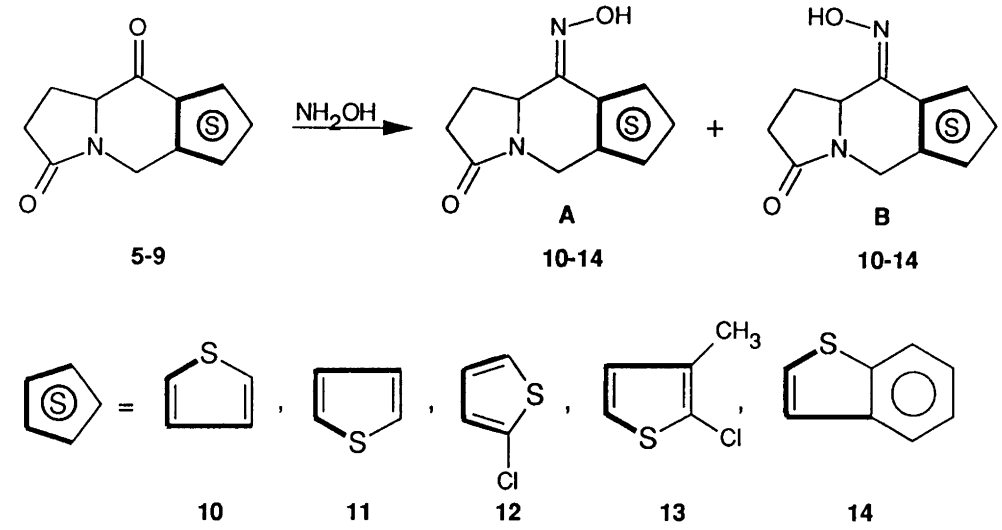
Rigo[1] and Martin[2] have shown that the best method of cyclization to ketones is the Friedel–Crafts intramolecular cyclization in the case of *N*-benzyl-5-oxoproline. It was also mentioned that with *N*-(2-thienylmethyl)-5-oxoproline, cyclization could be realized only when the acid chloride of **4a** was used with tin tetrachloride as a catalyst and then in only poor yield (13%). Because of the difficulty encountered in this reaction, an effort was made to find a convenient process to the ketone **6**. *N*-(2-Thienylmethyl)-5-oxoproline **4a** was treated with thionyl chloride in dichloromethane and the resulting acid chloride, under Friedel–Crafts cyclization conditions using aluminium trichloride of high quality as a catalyst, gave the expected ketone **6** in a very good yield (73%) (Scheme 1). Using the same process the acid **4b** gave the cyclic ketone **5** because the α-position of thiophene is more reactive than the β-position. When the α-position is blocked with a halogen (acid **4c** and **4d**) cyclization can occur at the β-position. In fact, the chloro acid **4c** furnished the ketone **7**, whereas the bromine acid **4d** gave an inseparable mixture of three compounds, ketone **5** and the brominated analogue of ketone **7** (ratio 2:1) and an unknown product (determination by an NMR spectral procedure). The lability of the bromide is responsible for that cyclization; we had already observed this during the cyclization of the bromo acid to dithienothiepinones[4] with polyphosphoric acid. As expected, ketones **8** and **9** are synthesized from the acids **4f** and **4e** in good yields (43% and 70%, respectively). As previously reported[1,2] chloro substitution decreased the yields, ketones **7** and **8** were obtained in 50% and 43% yield, respectively.

All of these intermediates and final compounds were characterized by IR and NMR spectroscopy and microanalysis. Details are reported in the Experimental section, but there are a number of interesting features of the ketones. The C-4 protons in ketones **5** to **9** appear as an AB system with chemical shifts of 4.93–5.30 ppm for the equatorial (eq) proton and 4.13–4.48 ppm for the axial (ax) proton and a coupling constant of $J = 17$ Hz (see Table 2). The non-equivalence of the C-4_{ax} and C-4_{eq} protons observed is in accordance with the observations made with quinolizines.[5–7] Another significant feature of the NMR spectra of ketone **7** is the position of the C-1 proton at a very low field, 8.38 ppm.

Previous work on pyrrolo[1,2-*b*]isoquinolinedione[2,3] showed that these ketones, when treated with hydroxylamine, were converted into a single (*Z*) oxime similar to an oxime of type B (Scheme 2). It was interesting therefore to study the selectivity of this reaction. The above ketones **5–9** under the same conditions led to a mixture of oximes **A** and **B** or the single oxime **B**. The results are summarized in Table 1. Ketone **5** gave a mixture of oxime **10A** (94%) and oxime **10B** (6%). This result can be explained by intramolecular hydrogen bonding between the hydrogen of the oxime group and the sulfur atom of the thiophene ring. This bond would favour the oxime **A**. For the same reason ketone **9** gave the oxime **14A** (81%)



Scheme 1.



Scheme 2.

Table 1.

Oxime	Isomer **A** (%)[a]	Isomer **B** (%)[a]	Yield (%)[b]
10	94	6	87
11	40	60	88
12	80	20	77
13	0	100	50
14	81	19	88

[a] Determined by ^{1}H NMR spectroscopy on the crude product.
[b] Crude product.

as the major product and the oxime **14B** (19%) as the minor product. Analogous considerations have been proposed for the thiophene-2-carbaldehyde oxime.[8] Ketone **7** gave the corresponding oxime **12A** as the major product (80%). This result is supported in the NMR spectra by the position of the C-1 proton at a very low field 8.58 ppm (see Table 3).

Ketone **6** gave a mixture of the oximes **11A** (40%) and **11B** (60%), because the oxime has an s-*trans* conformation with the double bond of the thiophene ring, and the C-1 proton is less acidic than the C-1 proton of the oxime **12A**. This structure has similarities to the benzenoic isomer studied elsewhere.[2]

A single oxime isomer is obtained when the initial ketone is substituted at C-1 with a methyl group. This group prevents the formation of a chelate with the oxime group, so that the ketone **8** gave only the oxime **13B** (100%).

Isomers from the mixtures of oximes **A** and **B** were isolated by fractional crystallization (see the Experimental).

For all the oximes (see Tables 3 and 4) the two protons attached to C-4 are not equivalent in the NMR spectrum. The position of the axial proton H-4_{ax} is at higher magnetic field (3.82–4.10 ppm) than the equatorial proton H-4_{eq} (4.93–5.26 ppm) as in the corresponding ketones.

The reactivity of these ketones and the corresponding oximes is under investigation. The results will be published soon.

Table 2. ^{1}H NMR chemical shifts of ketones **8–12** δ (DMSO-d_6).

					J/Hz	
Ketone	H-7 and H-8	H-8a	H-4	H-arom	4_{ax}, 4_{eq}	Thiophene
5	2.11–2.55 m	4.48–4.56 m	4.26 d (ax) 5.14 d (eq)	7.28 d (H-3) 8.15 d (H-2)	17.82	4.99
6	2.12–2.52 m	4.42–4.58 m	4.46 d (ax) 5.30 d (eq)	7.56 d (H-1) 7.35 d (H-2)	17.97	5.25
7	2.11–2.52 m	4.41–4.54 m	4.13 d (ax) 4.96 d (eq)	8.38 s (H-1)	16.62	—
8[a]	2.12–2.50 m	4.42–4.48 m	4.36 d (ax) 5.23 d (eq)	—	18.11	—
9	2.15–2.52 m	4.63–4.73 m	4.48 d (ax) 5.42 d (eq)	7.51–7.68 m (2H) 8.08–8.17 m (2H)	18.30	—

[a] 2.32 (s, CH_3).

Table 3. ^{1}H NMR chemical shifts of oximes **A** δ (DMSO-d_6).

						J/Hz	
Compound	H-7 and H-8	H-8a	H-4	H-arom	OH	4_{ax}, 4_{eq}	Thiophene
10	2.25–2.50 m	4.53–4.63 m	4.96 d (eq) 4.17 d (ax)	7.12 d (H-3) 7.79 d (H-2)	11.91 s	17.43	5.21
11	2.20–2.50 m	4.45–4.55 m	5.06 d (eq) 4.32 d (ax)	7.51 d (H-2) 7.96 d (H-1)	11.44 s	17.62	5.27
12	2.22–2.50 m	4.45–4.58 m	4.83 d (eq) 3.99 d (ax)	8.58 s	11.93 s	16.77	—
14	2.26–2.50 m	4.62–4.75 m	5.19 d (eq) 4.38 d (ax)	7.42–7.56 m (2H) 7.85–8.06 m (2H)	12.18 s	17.90	—

Table 4. ^{1}H NMR chemical shifts of oximes **B** δ (DMSO-d_6).

Compound	H-7 and H-8	H-8a	H-4	H-arom	OH	J/Hz 4_{ax}, 4_{eq}	J/Hz Thiophene
10	1.92–2.20 m (1 H) 2.22–2.50 m (2 H) 2.75–2.95 m (1 H)	4.76 dd[a]	4.99 d (eq) 3.91 d (ax)	7.06 d (H-3) 7.53 d (H-2)	11.34 s	16.70	5.11
11	1.85–2.05 m (1 H) 2.15–2.50 m (2 H) 2.76–2.96 m (1 H)	4.75 dd[a]	5.12 d (eq) 4.06 d (ax)	7.54 d (H-2) 7.25 d (H-1)	11.25 s	16.67	5.22
12	1.75–1.94 m (1 H) 2.12–2.50 m (2 H) 2.70–2.88 m (1 H)	4.78 dd[a]	4.93 d (eq) 3.82 d (ax)	7.74 s	11.55 s	15.87	—
13[b]	1.76–1.98 m (1 H) 2.10–2.50 m (2 H) 2.72–2.92 m (2 H)	4.82 dd[a]	5.04 d (eq) 3.98 d (ax)	—	11.44 s	16.62	—
14	1.92–2.20 m (1 H) 2.26–2.50 m (2 H) 2.76–2.26 m (1 H)	4.86 dd[a]	5.26 d (eq) 4.10 d (ax)	7.42–7.56 m (2H) 7.85–8.06 m (2H)	11.74 s	17.24	—

[a] $J_1 = 7.5$ Hz, $J_2 = 8.7$ Hz. [b] 2.28 s (CH_3).

Table 5. *N*-Thienylmethyl-5-oxoprolines **3a–f**.

Compound	Yield (%)	B.p./°C (mmHg)	$\nu_{C=O}$/cm^{-1} Ester	$\nu_{C=O}$/cm^{-1} Amide	Analysis
3a	51	146–150 (0.05)	1742	1698	$C_{11}H_{13}NO_3S$: C, H, N
3b	51	150–154 (0.05)	1742	1682	$C_{11}H_{13}NO_3S$: C, H, N
3c	62	146–150 (0.03)	1746	1695	$C_{11}H_{12}ClNO_3S$: C, H, N
3d	52	158–160 (0.03)	1745	1695	$C_{11}H_{12}BrNO_3S$: C, H, N
3e	55	180–185 (0.03)	1747	1699	$C_{15}H_{15}NO_3S$: C, H, N
3f	52	152–154 (0.03)	1749	1704	$C_{12}H_{14}ClNO_3S$: C, H, N

Table 6. Carboxylic acids **4a–f**.

Compound	Yield (%)	M.p./°C (solvent)	$\nu_{C=O}$/cm^{-1} (KBr) Acid	$\nu_{C=O}$/cm^{-1} (KBr) Amide	Analysis
4a	78	109–110 (benzene)	1739	1644	$C_{10}H_{11}NO_3S$: C, H, N
4b	91	103–106 (benzene)	1732	1644	$C_{10}H_{11}NO_3S$: C, H, N
4c	76	172–173 (ethanol–water)	1726	1644	$C_{10}H_{10}ClNO_3S$: C, H, N
4d	79	170–170 (ethanol)	1726	1644	$C_{10}H_{10}BrNO_3S$: C, H, N
4e	74	210–211 (ethanol)	1734	1654	$C_{14}H_{13}NO_3S$: C, H, N
4f	74	104–105 (benzene–hexane)	1734	1649	$C_{11}H_{12}ClNO_3S$: C, H, N

Table 7. Thieno[*f*]indolizine-6,9-diones **5–9**.

Compound	Yield (%)	M.p./°C (solvent)	$\nu_{C=O}$/cm^{-1} (KBr)[a]	Analysis
5	61	136–138 (ethanol)	1689	$C_{10}H_9NO_2S$: C, H, N
6	72	130–132 (ethanol)	1684	$C_{10}H_9NO_2S$: C, H, N
7	50	188–190 (ethanol)	1689	$C_{10}H_8ClNO_2S$: C, H, N
8	43	148–150 (ethanol–water)	1684	$C_{11}H_{10}ClNO_2S$: C, H, N
9	70	204–205 (*n*-propanol)	1684	$C_{14}H_{11}NO_2S$: C, H, N

[a] Amide and ketone.

Table 8. Oximes **10–14**.

Compound	Yield (%)	M.p./°C (solvent)	$\nu_{C=O\ amide}/cm^{-1}$ (KBr)	Analysis
10A	63	240–241 (ethanol)	1652	$C_{10}H_{10}N_2O_2S$: C, H, N
11A, 11B	64	187–190 (ethanol)	1656	$C_{10}H_{10}N_2O_2S$: C, H, N
12A	47	210–212 (ethanol)	1689	$C_{10}H_9ClN_2O_2S$: C, H, N
13B	43	263–264 (ethanol)	1674	$C_{11}H_{11}ClN_2O_2S$: C, H, N
14A, 14B	59	270–272 (dioxane)	1664	$C_{14}H_{12}N_2O_2S$: C, H, N

Experimental

Melting points are uncorrected. IR spectra were recorded with a Beckman IR 20 spectrometer. ^1H NMR spectra were measured with a Bruker AC200 (200 MHz) spectrometer using tetramethylsilane as the internal standard. Microanalyses were performed by the microanalysis laboratory of INSA of Rouen, F 76130 Mt-St-Aignan.

(±)-5-Oxoproline methyl ester was prepared according to the literature.[9] The require halogenomethylthiophenes and halogenomethylbenzothiophenes were synthesized as previously described.[4, 10, 11]

General procedure for N-*alkylation of (±)-5-oxoproline methyl ester.* Sodium hydride (4.8 g of a 60% mineral emulsion, 0.12 mol NaH) was washed with anhydrous benzene and suspended in benzene (100 ml). The stirred suspension was treated under nitrogen over 1 h with a solution of 5-oxoproline methyl ester (**2**) (14.3 g, 0.1 mol) in 50 ml of benzene. The solution was stirred at room temperature for 2 h and allowed to stir at 45–50°C for 12 h. Halogenomethylthiophene **1a–f** (0.12 mol) was then added and the mixture was refluxed for 8 h. The precipitate was filtered off through Celite and the residue was washed with dichloromethane. The combined organic layers were concentrated to give an orange oil. Distillation under reduced pressure afforded the esters **3a–c**. Analytical data are summarized in Table 5.

General procedure for the synthesis of N-*Thienylmethyl-5-oxoprolines* (**4a–f**). A stirred mixture of 1-thienylmethyl-5-oxoproline methyl ester **3a–f**. (0.1 mol) and 1 M sodium hydroxide (150 ml) was heated on a steam bath for 90 min. The cooled solution was washed with ether (3 × 50 ml) and acidified with concentrated HCl. The crystalline precipitate was filtered off, washed with cold water and recrystallized from a suitable solvent (see Table 6). It was sometimes necessary to extract the acidic solution with dichloromethane to obtain the expected product.

General procedure for the synthesis of N *ketones* **5–9**. A stirred solution of acid **4a–f** (0.01 mol) and dichloromethane (30 ml) was treated rapidly with thionyl chloride (1.3 g, 0.011 mol). After being refluxed overnight the chilled solution was treated in portions over 2 h with high-purity aluminium trichloride (4 g, 0.031 mol) with stirring and external cooling (−5 to 0°C). The mixture was stirred with cooling for 1 h and for 1.5 h at room temperature. The mixture was chilled with ice–water and the reaction was quenched by cautious addition of ice chips and then diluted with water. Dichloromethane was added and the mixture was agitated thoroughly until all the solid dissolved. The phases were separated and the aqueous phase was extracted with dichloromethane (50 ml). The combined organic phase was washed with water and saturated brine, dried ($MgSO_4$), filtered and concentrated to an oil, which crystallized to give the crude ketones **5–9**. These ketones were purified by crystallization from a suitable solvent (see Table 7). The chloro ketones **7** and **8** were purified by column chromatography on silica gel using dichloromethane as the eluant.

General procedure for the synthesis of the oximes of ketones **5–9**. A stirred suspension of the ketones **5–9** (5.0 mmol) and 95% ethanol (8 ml) was treated with solution of hydroxylamine hydrochloride (0.69 g, 10 mmol), sodium acetate (0.82 g, 10 mmol) and water (9 ml) and was refluxed for 5 h. Ice–water cooling afforded a crystalline precipitate, which was collected, washed with 50% aqueous ethanol and recrystallized from a suitable solvent (see Table 8).

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