

Synthesis of heterocycles

III. A convenient route to substituted thieno [3,2-c] pyridines*

N. F. EWEISS AND A. A. HOSNI (MRS)

Department of Chemistry, University of Kuwait

ABSTRACT

A simple route, with a reasonably high yield, for the preparation of 4-arylthieno [3,2-c] pyridine-6-carboxylic acids and 4-arylthieno [3,2-c] pyridines is reported.

INTRODUCTION

Interest in the chemistry of the six possible thienopyridine systems has been increasing since the 1970s. There are two main explanations for this. First, there is the obvious theoretical interest in the behaviour of systems that contain a π -excessive and a π -deficient ring fused together. Second, the search for pharmacologically active substances and plant growth regulators has led to the synthesis of analogues of various quinolines and isoquinolines in which the benzene ring is replaced by a thiophene nucleus.

The hitherto reported successful syntheses of thieno [3,2-c] pyridines and/or its derivatives involve either the application of the Bischler–Napieralski synthesis, or its Herz modification, of isoquinoline to this thiophene system (Descamps & Binon 1962; Dressler & Joullié 1970), the application of the Pictet–Spengler synthesis to the thienopyridine series (Gronowitz & Sandberg 1970), or through a ring-closure synthesis involving pyrylium salts (Dulenko *et al.* 1972) or isocyanates (Gittos 1974). All these routes utilise rather vigorous conditions and give average yields of 50–60%. We wish to report here on a convenient route for the synthesis of some mono- and disubstituted thieno [3,2-c] pyridines with a 75% average yield.

RESULTS AND DISCUSSION

A series of N-aroyleglycines (Ia–f) reacted smoothly with thiophene-2-aldehyde in sodium acetate–acetic anhydride mixture to give high yields (Table 1) of the 2-aryl-4-(2-thenylidene)-2-oxazolin-5-ones (IIa–f) (Scheme 1). The i.r. spectra of compounds (II) showed a C=N stretching frequency at 1650 cm^{-1} and a carbonyl stretching frequency at around 1790 cm^{-1} , characteristic of the five-membered oxazolinone rings (Bellamy 1960). Their u.v. spectra were similar to the absorption

* Part II, Eweiss N.F. and Osman, A. 1980. *J. Heterocycl. Chem.* **17**: 1713–8.

Table 1. Physical and analytical data

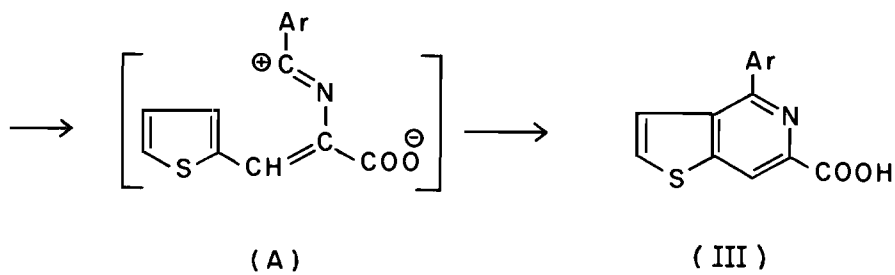
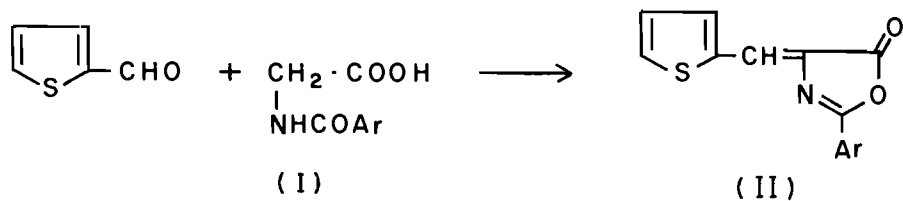
Compound	m.p. (°C)	Yield (%)	Mol. formula (mol. wt)	%C	%H	%N	%S
				found/calculate			
IIa	178-9	78	C ₁₄ H ₉ NO ₂ S (255.3)	65.80 65.86	4.69 4.74	5.40 5.49	12.54 12.56
IIb	187	91	C ₁₅ H ₁₁ NO ₂ S (269.3)	66.85 66.89	4.13 4.12	5.14 5.20	11.49 11.91
IIc	202	84	C ₁₅ H ₁₁ NO ₃ S (285.3)	63.06 63.14	3.87 3.88	4.84 4.91	11.11 11.24
II d	174	86	C ₁₄ H ₈ ClNO ₂ S (289.7)	57.86 58.03	2.81 2.78	4.80 4.83	10.81 ¹ 11.07
IIe	205	74	C ₁₄ H ₈ BrNO ₂ S (334.2)	50.27 50.31	2.34 2.41	4.15 4.19	9.68 ² 9.59
II f	207	76	C ₁₄ H ₈ N ₂ O ₄ S (300.3)	55.79 55.99	2.59 2.68	9.30 9.33	10.56 10.68
IIIa	188 ³	73	C ₁₄ H ₉ NO ₂ S (255.3)	65.88 65.86	4.66 4.74	5.41 5.49	12.62 12.56
IIIb	196 ³	80	C ₁₅ H ₁₁ NO ₂ S (269.3)	66.87 66.89	4.12 4.12	5.17 5.20	11.91 11.91
IIIc	217 ³	71	C ₁₅ H ₁₁ NO ₃ S (285.3)	63.13 63.14	3.86 3.88	4.87 4.91	11.17 11.24
III d	200 ⁴	76	C ₁₄ H ₈ ClNO ₂ S (289.7)	57.95 58.03	2.71 2.78	4.73 4.83	10.94 ⁵ 11.07
IIIe	215 ⁴	83	C ₁₄ H ₈ BrNO ₂ S (334.2)	50.25 50.31	2.33 2.41	4.11 4.19	9.57 ⁶ 9.59
III f	228 ⁴	69	C ₁₄ H ₈ N ₂ O ₄ S (300.3)	55.82 55.99	2.60 2.68	9.27 9.33	10.61 10.68
IVa	61-2 ⁷	88	C ₁₃ H ₉ NS (211.3)	73.93 73.89	4.17 4.29	6.64 6.63	15.00 15.14
IVc	98-9 ⁸	84	C ₁₄ H ₁₁ NOS (241.3)	68.63 69.68	4.44 4.59	5.83 5.80	14.03 13.26

Notes: ¹ Cl, found: 12.10, calcd: 12.23%. ² Br, found: 24.05, calcd: 23.97%. ³ Crystallised from ethanol. ⁴ Crystallised from methanol-water. ⁵ Cl, found: 12.23, calcd: 12.23%. ⁶ Br, found: 23.88, calcd: 23.97%. ⁷ Lit.m.p. 60°C, Descamps & Binon (1962). ⁸ Lit.m.p. 98°C, Descamps & Binon (1962).

spectra of azlactones reported by Schueler and Wang (1950) and ¹H-n.m.r. spectra were in accordance with the structures assigned (Table 2).

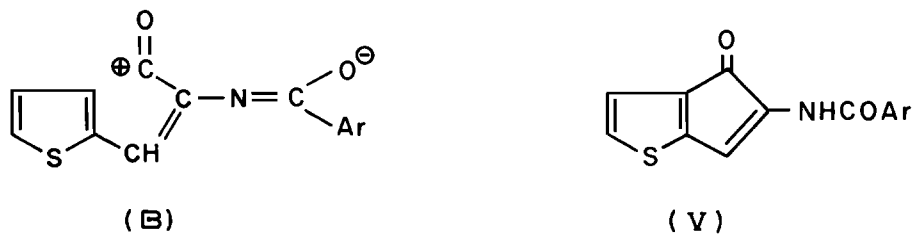
The oxazolinones (IIa-f) underwent an intramolecular Friedel-Crafts reaction upon treatment with anhydrous aluminium chloride in excess of benzene to give satisfactory yields of the 4-arylthieno [3,2-c] pyridine-6-carboxylic acids (IIIa-f) (Table 1).

It is believed that the oxazolinones (II) are converted via an alkyl-oxygen fission to the highly resonance-stabilised carbocations (A), which cyclise via position 3 of the thiophene ring to form the corresponding heterocycle (III) (Scheme 1). The possibility of an intramolecular Friedel-Crafts reaction, through an acyl-oxygen fission, to give the intermediate (B) could be ruled out since compounds of type (V) could not be detected (Scheme 2).



Ar = a, C₆H₅; b, p-MeC₆H₄; c, p-MeOC₆H₄;
d, p-ClC₆H₄; e, p-Br.C₆H₄; f, p-NO₂C₆H₄.

Scheme 1.



Scheme 2.

The formation of (III) from (II) through an intramolecular Friedel–Crafts reaction is quite similar to the formation of 3-aryl-fluoranthene-1-carboxylic acids from α -fluorenylidene- γ -aryl $\Delta^{\beta,\gamma}$ butenolides reported earlier (Hashim 1977). Besides, the i.r. spectra of compounds (III) lacked the characteristic stretching and deformation bands of the —NHCO— group but showed a broad absorption at 2850–3050 cm^{-1} , characteristic of the —OH moiety of the carboxyl group, as well as a band for the carbonyl group at 1690 cm^{-1} . The presence of a carboxyl group could also be seen from the acidic properties of these compounds which are soluble in base and can be reprecipitated by acid. Their u.v. spectra showed the four main absorption bands of substituted thienopyridines (Barker 1977), and their n.m.r. spectra beside being in accordance with the structures proposed, showed the characteristic singlet of the —COOH group at 11.5–12.5 δ (Table 2).

Table 2. Spectral data

Compound	i.r. (cm^{-1})			u.v. (EtOH)		n.m.r.	
	$\nu\text{C}=\text{N}$	$\nu\text{C}=\text{O}$	νOH	λ_{max} (nm)	(1 g%)	δ	Assignment (No. of protons)
II _a	1650	1795		284(3.40)	270(2.81)	5.29(s)	(1) —CH=
				232(3.11)	225(3.59)	8.18–7.82(m)	(8) ArH
II _b	1640	1785		294(3.45)	269(2.73)	2.60(s)	(3) ArCH ₃
				234(3.40)	229(3.60)	5.30(s)	(1) —CH=
						7.95–7.49(m)	(7) ArH
II _c	1650	1780		309(3.41)	272(2.80)	4.05(s)	(3) —OCH ₃
				231(3.38)	228(3.63)	5.29(s)	(1) —CH=
						8.10–7.35(m)	(7) ArH
II _d	1650	1790		280(3.38)	269(2.81)	5.16(s)	(1) —CH=
				234(3.28)	227(3.59)	8.20–7.20(m)	(7) ArH
II _e	1645	1795		279(3.39)	271(2.83)	5.23(s)	(1) —CH=
				233(3.30)	229(3.60)	8.17–7.25(m)	(7) ArH
II _f	1650	1795		316(3.43)	270(2.92)	5.28(s)	(1) —CH=
				235(3.28)	228(3.61)	8.30–7.15(m)	(7) ArH
III _a		1690	2950	395(4.32)	310(3.90)	8.40–7.35(m)	(8) ArH
			(br)	327(4.00)	226(4.12)	11.55(s)	(1) —COOH
III _b		1695	2850	394(4.55)	273(3.94)	2.45(s)	(3) ArCH ₃
			(br)	240(3.94)	225(4.27)	8.45–7.40(m)	(7) ArH
						11.85(s)	(1) —COOH
III _c		1695	2980	410(4.40)	395(4.45)	3.90(s)	(3) —OCH ₃
			(br)	283(4.07)	224(4.29)	8.35–7.20(m)	(7) ArH
						11.95(s)	(1) —COOH
III _d		1690	2950	394(4.50)	325(4.12)	8.10–7.25(m)	(7) ArH
			(br)	235(3.11)	225(4.13)	12.40(s)	(1) —COOH
III _e		1685	3050	396(3.38)	324(4.07)	8.00–7.25(m)	(7) ArH
			(br)	235(4.04)	226(4.22)	12.25(s)	(1) —COOH
III _f		1695	3040	420(4.01)	295(3.51)	8.30–7.45(m)	(7) ArH
			(br)	277(3.48)	277(4.44)	11.95(s)	(1) —COOH
IV _a				296(3.27)	280(3.47)	8.53–7.50(m)	(9) ArH
				263(3.44)	224(4.32)		
IV _c				300(3.30)	281(3.53)	4.10(s)	(3) —OCH ₃
				265(3.71)	228(4.23)	8.60–7.58(m)	(8) ArH

Refluxing (IIIa,c) in benzene with hydroquinone and copper chromite gave the corresponding decarboxylated products, 4-arylthieno [3,2-c] pyridines (IVa,c) in very good yields. The analytical and spectral data of compounds (IV) were also in accordance with their structures (Tables 1 and 2).

EXPERIMENTAL

All melting points were determined on an Electrothermal melting point apparatus, and are uncorrected. Elemental analyses were performed by Professor Dr H. Malissa and G. Reuter, Elbach über Engelskirchen, West Germany. Spectra were recorded with a Unicam SP1000 infrared spectrophotometer (KBr Wafer technique), and Unicam SP8000 visible and ultraviolet spectrophotometer (in ethanol). ¹H-n.m.r. spectra in CDCl₃ were recorded on a Varian T-60A spectrometer using TMS as external standard.

Preparation of the oxazolinones (II)

A mixture of thiophene-2-aldehyde (0.05 mole), the appropriate N-arylglycine (Ia-f) (0.05 mole), freshly fused sodium acetate (0.05 mole), and acetic anhydride (16 ml) was heated on a hot-plate until a complete solution was obtained. The mixture was then transferred to a steam-bath and heating was continued until crystals separated. The reaction mixture was then poured into water, the solid product filtered off, and successively washed with water. Crystallisation from ethanol gave the 2-aryl-4-(2-thenylidene)-2-oxazolin-5-ones (IIa-f). Analytical and spectral data of compounds (II) are shown in Tables 1 and 2.

Preparation of the thieno [3,2-c] pyridine carboxylic acids (III)

The oxazolinone (Ia-f) (0.01 mole) in dry benzene was added dropwise to a stirred mixture of anhydrous aluminium chloride (0.03 mole) and dry benzene (50 ml). After complete addition, the reaction mixture was refluxed with stirring for 2 hr. The complex formed was decomposed with hydrochloric acid and the mixture steam-distilled whereby a solid product separated out. The solid was filtered off, washed with water, recrystallised from a suitable solvent to give 4-arylthieno [3,2-c] pyridine-6-carboxylic acids (IIIa-f). A summary of the analytical and spectral data of compounds (III) is shown in Tables 1 and 2.

Decarboxylation of (IIIa,c) to the thieno [3,2-c] pyridines (IV)

4-Arylthieno [3,2-c] pyridine-6-carboxylic acid (IIIa,c) (0.01 mole), hydroquinone (0.2 g), copper chromite (0.5 g) and benzene (75 ml) were refluxed for 6 hr. Separation and evaporation of the organic layer gave a resinous residue which was recrystallised from ethanol to give 4-arylthieno [3,2-c] pyridine (IVa,c) (Tables 1 and 2).

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تخليق الحلقيات غير المتجانسة - الجزء الثالث -
مسار ملائم لتخليق ثيينو (٢,٣- c) بيريدينات مستبدلة

نامق فرحات عويس وعائشة على حسني
قسم الكيمياء بجامعة الكويت

تم التوصل الى طريقة بسيطة وذات عائد مرتفع نسبيا لتخليق مركبات ٤- آريل
ثيينو (٢,٣- c) - ٦- كربوكسيل بيريدينات وكذلك ٤- آريل ثيينو (٢,٣- c) بيريدينات .

