

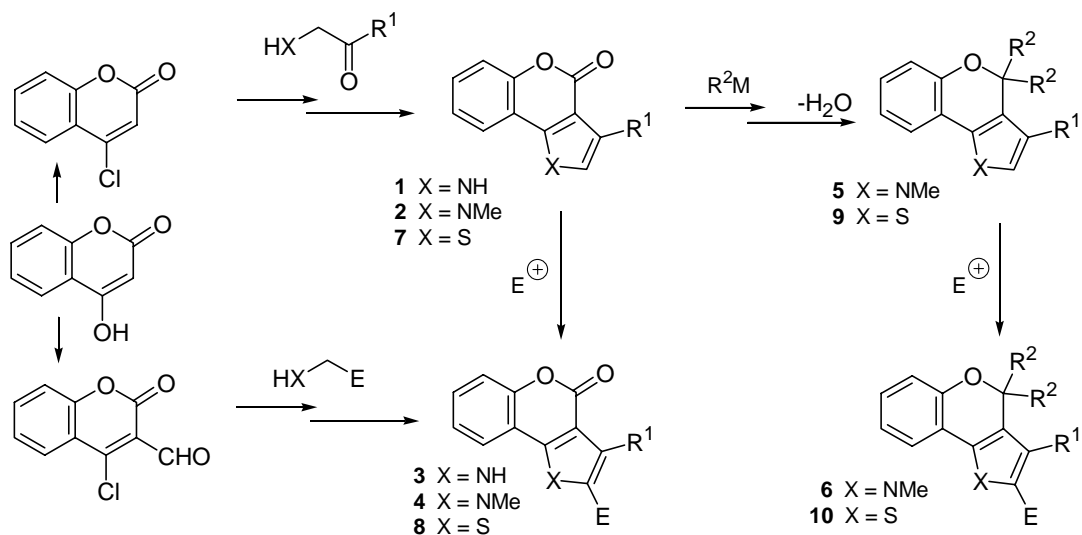
SYNTHESIS OF 1*H*-[1]BENZOPYRANO[4,3-*b*]PYRROLE AND 4*H*-THIENO[3,2-*c*][1]BENZOPYRAN DERIVATIVES. FUNCTIONALISATION BY AROMATIC ELECTROPHILIC SUBSTITUTION

Rocío Álvaro Navarro, Luis Calvo Bleye, Alfonso González-Ortega,^{*} and M. Carmen Sañudo Ruíz

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid, Prado de la Magdalena s/n. 47005 Valladolid, Spain. E-mail algon@qo.uva.es

Abstract – 4,4-dialkyl-1*H*-[1]benzopyrano[4,3-*b*]pyrroles were prepared starting from [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-ones and organometallic reagents. Subsequently, both types of polycyclic compound and their analogous 4*H*-thieno[3,2-*c*][1]benzopyrano derivatives were functionalized at C-2 by aromatic electrophilic substitution (bromination, nitration, acetylation and formylation).

In previous studies¹⁻³ we have described synthetic methods for preparing [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-ones (**1-4**) by Knorr or Fischer-Fink type reactions starting from 4-chlorocoumarin or 4-chloro-3-formylcoumarin (Scheme 1).



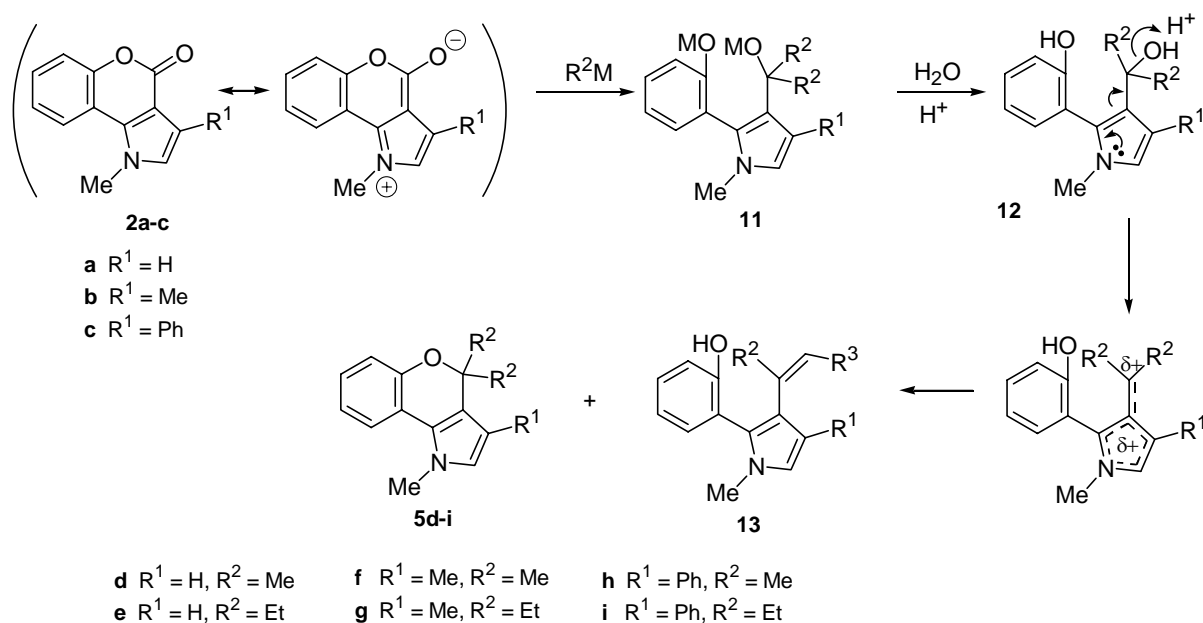
Scheme 1

In this paper, we report the transformation of **2** to 1*H*-[1]benzopyrano[4,3-*b*]pyrroles (**5**) by reaction with organometallic compounds and the incorporation of new functions by aromatic electrophilic substitution in **1**, **2** and **5** to give **3**, **4** and **6**, respectively. We have, thus, completed a comprehensive project regarding different alternative paths for the synthesis of pyrroles fused to coumarins or chromenes starting from 4-hydroxycoumarin as an only remote precursor. Furthermore, due to the pharmacological interest which the thiophenes fused to 1-benzopyrans possess,⁴ in this paper we have included and compared aromatic electrophilic substitutions in 4*H*-thieno[3,2-*c*]benzopyrano derivatives (**7**) and (**9**) which present structures referable to **2** and **5**.

REACTION OF [1]BENZOPYRANO[4,3-*b*]PYRROL-4(1*H*)-ONES (**2**) WITH ORGANO-METALLIC REAGENTS. SYNTHESIS OF 1*H*-[1]BENZOPYRANO[4,3-*b*]PYRROLES (**5**).

Grignard and organolithium reagents

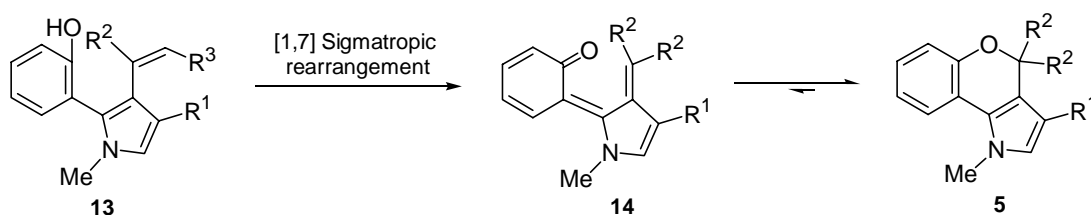
The [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-ones (**2**) reacted with Grignard and organolithium reagents *via* a 1,2 double addition (Scheme 2) in a similar manner to other coumarins.⁵⁻⁸ As a differential characteristic, we should point out that the electron-donating character of the fused pyrrole decreased the reactivity of the lactone and, on the other hand, increased the reactivity and instability of the reaction products.



Scheme 2

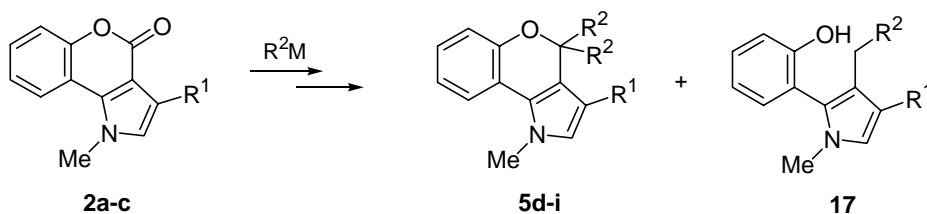
The deactivation of the carboxylate group toward the attack of the organometallic reagents meant that the solvent (tetrahydrofuran, ether or toluene) acquired a greater influence than that expected. In fact, it was the tetrahydrofuran in which **2** was most easily transformed to the intermediate (**11**). Conversely, the high reactivity and instability of the 3-hydroxymethylpyrrole derivatives (**12**), resulting from the hydrolysis of

11, did not allow their isolation and purification. They were easily dehydrated to the olefins (**13**) and the expected 4,4-dialkyl-1*H*-[1]benzopyrano[4,3-*b*]pyrroles (**5**). The formation of the olefins (**13**) was not a synthetic limitation for the preparation of 4,4-dialkyl-1*H*-[1]benzopyrano[4,3-*b*]pyrroles (**5**), given that when **13** was heated to 150 °C, it was transformed to **5**, presumably *via* a [1,7] sigmatropic rearrangement followed by an electrocyclic reaction^{9,10} (Scheme 3). In short, the experimental procedure consisted in the reaction of **2** with organometallic reagents, hydrolysis, heating of the reaction concentrates and the final purification of **5**. The optimum yields are shown in Table 1.



Scheme 3

Table 1 Reaction of [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-ones (**2a-c**) with organometallic reagents

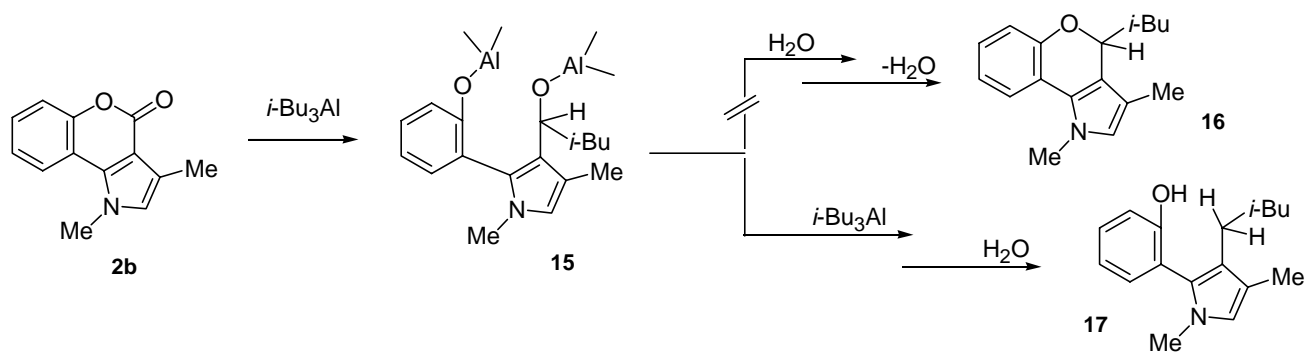


Starting	R ² M	R ¹	R ²	Compound	Yield (%)
2a	MeLi	H	Me	5d	25
2a	MeMgI	H	Me	5d	72
2a	Me ₃ Al	H	Me	5d	40
2a	EtMgBr	H	Et	5e	81
2a	Et ₃ Al	H	Et	5e	28
2b	MeMgI	Me	Me	5f	73
2b	EtMgBr	Me	Et	5g	83
2b	<i>i</i> -Bu ₃ Al	Me	<i>i</i> -Bu	17	88
2c	MeLi	Ph	Me	5h	77
2c	MeMgI	Ph	Me	5h	80
2c	Me ₃ Al	Ph	Me	5h	42
2c	EtMgBr	Ph	Et	5i	62

Organoaluminum Compounds

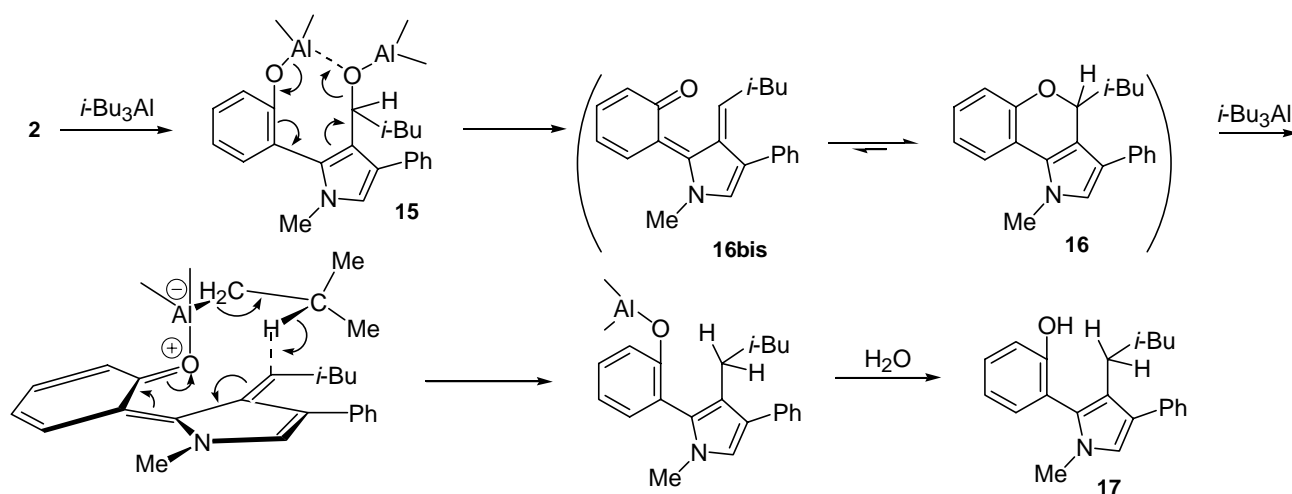
The triorganoaluminum compounds, which in their reaction with coumarins^{11,12} show a reductive power greater than that of the Grignard reagents, deserve a special mention.

In the first place, we should point out that the reactivity of **2** towards the organoaluminum compounds was very low in electron-donating solvents (tetrahydrofuran or ether), and that the use of toluene at 80-100°C was necessary in order to obtain the total transformation of the substrate. In the above conditions, the trimethylaluminum, which does not possess a reductive character, only yielded 40-42% of 4,4-dimethylbenzopyran derivatives (**5d** 40%, **5h** 42%). The triethylaluminum, with a greater reductive power, led to complex reaction mixtures in which the yields of 4,4-dialkylbenzopyrans were even lower (28-30%). Starting from triisobutylaluminum, a reagent with greater steric demands and with a strong reductive power, we tried to obtain the corresponding 4-monoalkyl-1-benzopyrano[4,3-*b*]pyrrole (**16**), but the process was not detained at the intermediate (**15**) and evolved toward the compound (**17**) (88%), resulting from one alkylation and two reductions which does not occur with other coumarins (Scheme 4).



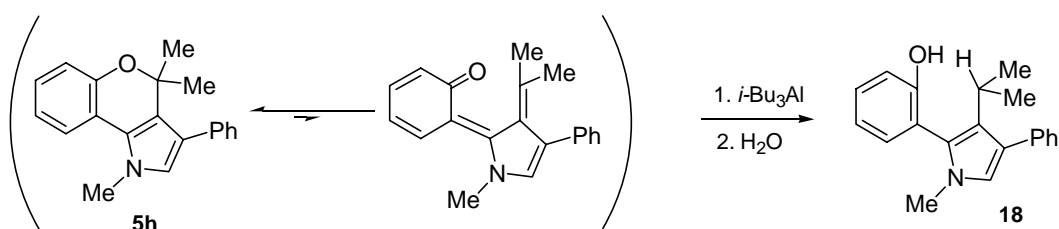
Scheme 4

The preparation of alkylpyrroles starting from ethoxycarbonylpyrroles and metal hydrides has been described exclusively for *N*-unsubstituted pyrroles which are capable of *N*-deprotonating and evolving by means of an azafulvene intermediate.¹³ This path, consequently, would not be appropriate for our *N*-substituted pyrroles. Among the many possible alternatives for the formation of **17**, in Scheme 5 we describe a hypothetical mechanism which takes into account both the high reactivity of the hydroxymethylpyrroles in the presence of Lewis acids (e.g. R_3Al) as well as the reaction of organometallic compounds with *o*-quinonemethide structures in equilibrium with 2*H*-1-benzopyrans.^{14,15} In our case, the intermediate (**15**) would experience aluminoxane elimination giving the *o*-quinonemethide (**16bis**) (in equilibrium with the benzopyran (**16**)), which would be reduced toward **17** in the presence of triisobutylaluminum.



Scheme 5

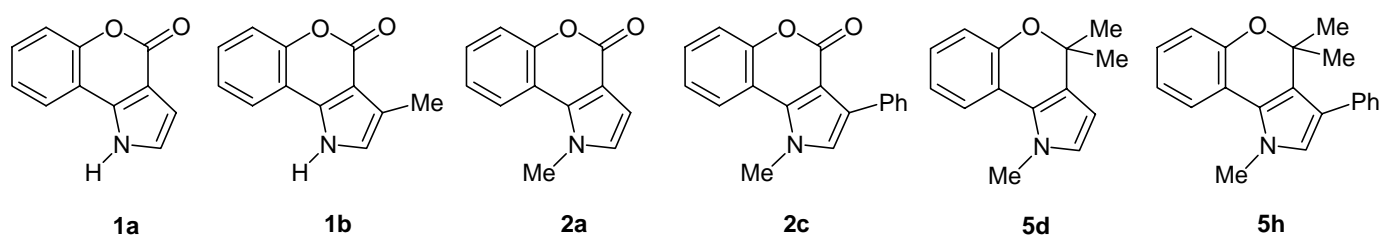
Although this can not be considered as conclusive proof, the previous hypothesis was supported by a complementary experiment in which the 3-phenyl-1,4,4-trimethyl-4*H*-[1]benzopyrano[4,3-*b*]pyrrole (**5h**) was directly transformed to **18** by reaction with triisobutylaluminum in toluene at 100 °C (Scheme 6).



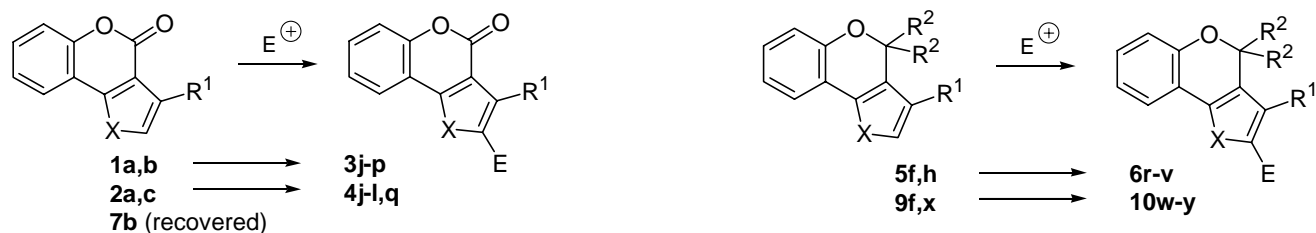
Scheme 6

AROMATIC ELECTROPHILIC SUBSTITUTION IN 1*H*-[1]BENZOPYRANO[4,3-*b*]PYRROLES (**5**) AND [1]BENZOPYRANO[4,3-*b*]PYRROL-4(1*H*)-ONES (**1** AND **2**).

We selected six different substrates (Scheme 7) which underwent bromination, nitration, acetylation and formylation. The series of experiments provided interesting information regarding the stability of the polyheterocyclic system, the substitution regiochemistry and the scope of the synthetic method.



Scheme 7

Table 2 Aromatic Electrophilic Substitution

Starting	Reactant-Solvent	Temp. °C	Time (h)	X	R ¹	R ²	E	Product	Yield (%)
1a	NBS-AcOH	20	4	NH	H	-	Br	3j	10 ^a
1a	HNO ₃ -Ac ₂ O	-5	5	NH	H	-	NO ₂	3k	65
1a	Ac ₂ O/TiCl ₄ -Ac ₂ O	20	24	NH	H	-	Ac	3l	10
1a	POCl ₃ /DMF-CH ₂ Cl ₂	20	5	NH	H	-	CHO	3m	81
1b	NBS-AcOH	20	2	NH	Me	-	Br	3n	52
1b	HNO ₃ -Ac ₂ O	-5	4	NH	Me	-	NO ₂	3o	53
1b	POCl ₃ /DMF-CH ₂ Cl ₂	20	2	NH	Me	-	CHO	3p	82
2a	NBS-AcOH	20	10	NMe	H	-	Br	4j	78 ^b
2a	HNO ₃ -Ac ₂ O	-5	4	NMe	H	-	NO ₂	4k	89
2a	Ac ₂ O/TiCl ₄ -Ac ₂ O	20	48	NMe	H	-	Ac	4l	72
2c	Ac ₂ O/TiCl ₄ -Ac ₂ O	20	12	NMe	Ph	-	Ac	4q	75
5d	... ^c			NMe	H	Me	Br	-	0
5d	HNO ₃ -Ac ₂ O	-5	1	NMe	H	Me	NO ₂	6r	18
5d	Ac ₂ O/TiCl ₄ -Ac ₂ O	20	1	NMe	H	Me	Ac	6s	85 ^d
5d	POCl ₃ /DMF-CH ₂ Cl ₂	0	1	NMe	H	Me	CHO	6t	62
5h	... ^c			NMe	Ph	Me	Br	-	0
7b	... ^e			S	Me	-	... ^e	-	0
9f	NBS-AcOH	20	1	S	Me	Me	Br	10u	71 ^f
9f	HNO ₃ -Ac ₂ O	-5	2	S	Me	Me	NO ₂	10v	86 ^g
9f	Ac ₂ O/TiCl ₄ -Ac ₂ O	20	1	S	Me	Me	Ac	10w	41
9f	POCl ₃ /DMF-CH ₂ Cl ₂	20	1	S	Me	Me	CHO	10x	85
9y	POCl ₃ /DMF-CH ₂ Cl ₂	20	1	S	H	H	CHO	10z	25

^a 2,3-Dibromo-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (**19**) was isolated (<5%). ^b 2,3-Dibromo-1-methyl-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (**20**) was isolated (<10%). ^c The substrate was degraded in all the conditions employed. ^d 3-Acetyl-1,4,4-trimethyl-1*H*-[1]benzopyrano[4,3-*b*]pyrrole (**21**) was isolated (<5%). ^e The substrate was recovered practically untransformed in the bromination, acetylation nitration and formylation reactions. ^f 2,8-Dibromo-3,4,4-trimethyl-4*H*-thieno[3,2-*c*][1]benzopyran (**22**) was isolated (<5%). ^g 2,8-Dinitro-3,4,4-trimethyl-4*H*-thieno[3,2-*c*][1]benzopyran (**23**) was isolated (<5%).

The bromination (Br_2/AcOH or NBS/AcOH) was without doubt the process in which the substrates showed the greatest instability and in which the results depended decisively on the reaction conditions (temperature and electrophilic equivalents) and on the pyrrole ring substituents. Thus, when starting from pyrroles (**5**), degradation exclusively occurred. But, starting from pyrroles (**1**) and (**2**), with an electron withdrawing group ($-\text{COO}-$), we were able to prepare the corresponding bromo derivatives, obtaining better yields with NBS/AcOH than with Br_2/AcOH . In these last two series, the stability of the substrates and the yield of the processes increased with the presence of additional substituents, above all if they were located at N-1 (e.g.: NH , $\text{R}^1 = \text{H}$, **3j** 10%; NH , $\text{R}^1 = \text{Me}$, **3n** 52%; NMe , $\text{R}^1 = \text{H}$, **4j** 78%;). Although with slightly less influence than in the bromination, the stability of the heterocycle and the rigorous control of the reaction conditions were also decisive in the nitrations (-5°C , $\text{HNO}_3/\text{Ac}_2\text{O}$) and in the acetylations (20°C , $\text{Ac}_2\text{O}/\text{TiCl}_4$). On the other hand, the Vilsmeier reagent (20°C , $\text{POCl}_3/\text{N,N-DMF}$) was without doubt the least aggressive of all and with which even the most unstable pyrroles (*N*-unsubstituted pyrroles, series **1**) were formylated with good yields.

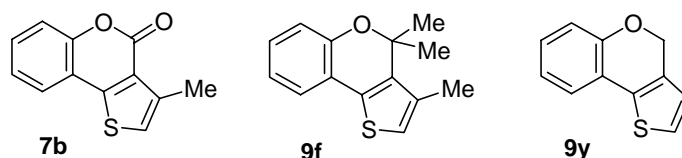
The electrophile always attacked the pyrrole ring and we were unable to confirm that it occurred in the 3-phenyl substituent (in **2c**) or in the fused benzene ring. Starting from the substrates (**1a**, **2a** and **5d**), unsubstituted at the positions C-2 and C-3, we verified that the substitution took place preferentially or exclusively at C-2. In fact, only in the acetylation of **5d** was 3-acetyl-1,4,4-trimethyl-1*H*-[1]benzopyrano[4,3-*b*]pyrrole (**21**, <5%) isolated, resulting from the exclusive attack at C-3. In all the cases, the position of the incorporated substituent was confirmed by NOES experiments. As often occurs in pyrroles, polybrominations in **1a** and **2a** were observed to give respectively 2,3-dibromo-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (**19**, <5%) and 2,3-dibromo-1-methyl-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (**20**, <10%). Nevertheless, the 2-bromo derivatives (**3j**) and (**3n**) were obtained as major products when an equivalent of the bromination reagent was used.

From a synthetic point of view, we can conclude that, with the exception of the bromination of **5f**, **5h** and **1a**, these compounds could be functionalised at C-2 by aromatic electrophilic substitution. In some cases (e.g. **3l** 10% or **6r** 18%) the low yield was due to the insolubility of the substrates and the impurities, which made their isolation and purification difficult.

AROMATIC ELECTROPHILIC SUBSTITUTION IN 4*H*-THIENO[3,2-*c*]BENZOPYRANS (**9**) AND THIENO[3,2-*c*]BENZOPYRAN-4(4*H*)-ONES (**7**).

In this last section three substrates have been studied: **7b**, **9f** and **9y** (Scheme 8). The 3-methylthieno[3,2-*c*][1]benzopyran-4(4*H*)-one (**7b**) was prepared by cyclization of the 4-acetylmercaptocoumarin in polyphosphoric acid.¹⁶ The compound (**7b**) reacted with methylmagnesium iodide to give 3,4,4-trimethyl-

4*H*-thieno[3,2-*c*][1]benzopyran (**9f**). 4*H*-Thieno[3,2-*c*][1]benzopyran (**9y**) was obtained by decarboxylation of the thieno[3,2-*c*][1]benzopyran-2(4*H*)-carboxylic acid.¹⁷



Scheme 8

The lower reactivity of the thiophene with respect to the pyrrole, together with the presence of the electron withdrawing group (-COO-), meant that the 3-methylthieno[3,2-*c*][1]benzopyran-4(4*H*)-one (**7b**) remained unaltered towards the electrophiles which did react with the pyrroles (**1**) or (**2**) analogues of **7b**. As for the 4*H*-thieno[3,2-*c*]benzopyrans (**9f**) and (**9y**), aromatic electrophilic substitution did occur at C-2 (bromination, nitration, acetylation and formylation) with moderate to good yields, with the exception of the formylation of **9y** which only reached 25%. From these results we would emphasise: a) that the greater stability of the polycyclic system meant that brominations were possible which in **5** gave rise to degradations; b) although the directing effect continued to appear especially at C-2, additional electrophilic substitutions were observed in low yield at the C-8 position of the fused benzene: 2,8-dibromo-3,4,4-trimethyl-4*H*-thieno[3,2-*c*][1]benzopyran (**22**), <5%; 2,8-dinitro-3,4,4-trimethyl-4*H*-thieno[3,2-*c*][1]benzopyran (**23**), <5%.

As a final comment we should point out that although our essential aim was synthetic, the different behavior of **1**, **3**, **5** and **7** which was observed in the aromatic electrophilic substitutions make these substrates a group of polycyclic systems in which the differences concerning the stability and reactivity existing between the pyrroles and the thiophenes are clearly shown to stand out.

EXPERIMENTAL

Melting points were measured on a Reichert-Jung Thermo Galen and are uncorrected. Boiling points correspond to the oven temperature in a Kugelrohr GKR-51. IR spectra were obtained on a Perkin Elmer 1720 X spectrophotometer. NMR spectra were recorded on a Bruker AC300 spectrometer, and chemical shifts are given downfield from SiMe₄ as an internal standard; ¹³C-NMR spectra were carried out with complete ¹H decoupling and the assignments were made by additional DEPT experiments. MS spectra were measured on a Hewlett-Packard 5988A mass spectrometer.

The starting compounds (**1a,b**,¹ **2a-c**,¹ **7b**¹⁶ and **9y**¹⁷) were synthesized by literature procedures.

Reaction of compounds 2a-c with organomagnesium or organolithium reagents. General procedure for the preparation of compounds (5d-i). To a magnetically stirred solution of [1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-ones (**2a-c**) (5 mmol) in dry THF (40 mL) at 20 °C under nitrogen was added dropwise (30 min) the organometallic compound (20 mmol). At the end of the reaction, monitored by TLC (2-3 hours, Table 1), the mixture was hydrolyzed, extracted with CH₂Cl₂ (3 x 50 mL) and the extracts were washed with saturated aqueous NaHCO₃, and dried (MgSO₄). After removal of the solvent, the concentrate was heated at 150°C for one hour and the residue was flash chromatographed on silica gel using CH₂Cl₂/pentane (1:3) as eluent. The following compounds were thus prepared.

1,4,4-Trimethyl-1*H*-[1]benzopyrano[4,3-*b*]pyrrole (5d). Yield 72%, mp 51-52 °C (from hexane); IR(film) 1505, 1440, 1261, 1228, 1121, 1105, 930, 752, 691 cm⁻¹; δ_{H} (300 MHz; CDCl₃) 1.56 (6H, s), 3.75 (3H, s), 5.88 (1H, d, *J* 2.7, H-3), 6.47 (1H, d, *J* 2.7, H-2) and 6.78-7.45 (4H, m, Ar); δ_{C} (75.4 MHz; CDCl₃) 28.3 (2CH₃), 36.4 (CH₃), 77.6 (C), 101.9 (CH), 117.8 (CH), 119.0 (C), 119.8 (CH), 120.8 (CH), 122.3 (C), 124.7 (CH), 125.6 (C), 126.4 (CH) and 151.7 (C); *m/z* 213 (M⁺, 16%) and 198 (100). Anal. Calcd for C₁₄H₁₅NO: C, 78.84; H, 7.09; N 6.57. Found: C, 79.00; H, 6.95; N 6.42.

4,4-Diethyl-1-methyl-1*H*-[1]benzopyrano[4,3-*b*]pyrrole (5e). Yield 81%, mp 73-74 °C (from hexane); IR(KBr) 1517, 1476, 1445, 1232, 1113, 934, 755, 693 cm⁻¹; δ_{H} (300 MHz; CDCl₃) 0.93 (6H, t, *J* 7.4), 1.86 (4H, q, *J* 7.4), 3.91 (3H, s), 5.88 (1H, d, *J* 2.5, H-3), 6.59 (1H, d, *J* 2.5, H-2) and 6.87-7.44 (4H, m, Ar); δ_{C} (75.4 MHz; CDCl₃) 8.4 (2CH₃), 32.0 (2CH₂), 36.9 (CH₃), 83.4 (C), 103.4 (CH), 117.3 (CH), 118.7 (C), 119.6 (CH), 120.3 (CH), 122.3 (C), 123.4 (C), 124.7 (CH), 126.4 (CH) and 152.5 (C); *m/z* 241 (M⁺, 24%) and 212 (100). Anal. Calcd for C₁₆H₁₉NO: C, 79.63; H, 7.94; N 5.80. Found: C, 79.48; H, 7.81; N 5.96.

1,3,4,4-Tetramethyl-1*H*-[1]benzopyrano[4,3-*b*]pyrrole (5f). Yield 73%, mp 108 °C (from hexane); IR(nujol mull) 1502, 1438, 1262, 1143, 770, 761 cm⁻¹; δ_{H} (300 MHz; CDCl₃) 1.56 (6H, s), 2.06 (3H, s), 3.75 (3H, s), 6.93 (1H, s, H-2) and 6.85-7.45 (4H, m, Ar); δ_{C} (75.4 MHz; CDCl₃) 11.5 (CH₃), 28.1 (2CH₃), 36.3 (CH₃), 78.6 (C), 112.3 (C), 117.6 (CH), 119.0 (C), 119.8 (CH), 120.7 (CH), 122.7 (C), 123.6 (C), 124.2 (CH), 126.2 (CH) and 151.7 (C); *m/z* 227 (M⁺, 29%) and 212 (100). Anal. Calcd for C₁₅H₁₇NO: C, 79.26; H, 7.54; N 6.16. Found: C, 79.42; H, 7.44; N 6.03.

4,4-Diethyl-1,3-dimethyl-1*H*-[1]benzopyrano[4,3-*b*]pyrrole (5g). Yield 83%, mp 55 °C (from hexane); IR(nujol mull) 1497, 1439, 1251, 1232, 1112, 940, 745, 732 cm⁻¹; δ_{H} (300 MHz; CDCl₃) 0.88 (6H, t, *J* 7.2), 1.85 (4H, q, *J* 7.4), 1.99 (3H, s), 3.74 (3H, s), 6.88 (1H, s, H-2) and 6.87-7.42 (4H, m, Ar); δ_{C} (75.4 MHz; CDCl₃) 8.3 (2CH₃), 11.1 (CH₃), 31.6 (2CH₂), 36.4 (CH₃), 83.9 (C), 111.3 (C), 116.4 (CH), 118.3 (C), 119.2 (C), 119.8 (CH), 120.4 (CH), 122.9 (C), 125.0 (CH), 126.0 (CH) and 152.1 (C); *m/z* 255 (M⁺, 23%) and 226 (100). Anal. Calcd for C₁₇H₂₁NO: C, 79.96; H, 8.29; N 5.49. Found: C, 80.15; H, 8.39; N 5.24.

1,4,4-Trimethyl-3-phenyl-1*H*-[1]benzopyrano[4,3-*b*]pyrrole (5h). Yield 80%, mp 95-97 °C (from hexane); IR(KBr); 1502, 1245, 1102, 745, 702 cm⁻¹; δ_{H} (300 MHz; CDCl₃) 1.50 (6H, s), 3.90 (3H, s), 6.56 (1H, s, H-2) and 6.92-7.49 (9H, m, Ar); δ_{C} (75.4 MHz; CDCl₃) 28.4 (2CH₃), 36.6 (CH₃), 78.5 (C), 117.9 (CH), 119.2 (C), 120.4 (CH), 120.5 (C), 121.0 (CH), 123.0 (C), 123.1 (C), 124.2 (CH), 126.4 (CH), 126.8 (CH), 128.0 (2CH), 129.7 (2CH), 136.5 (C) and 151.5 (C); m/z 289 (M⁺, 18%) and 274 (100). Anal. Calcd for C₂₀H₁₉NO: C, 83.01; H, 6.62; N 4.84. Found: C, 82.85; H, 6.71; N 4.90.

4,4-Dimethyl-1-methyl-3-phenyl-1*H*-[1]benzopyrano[4,3-*b*]pyrrole (5i). Yield 62%, mp 73-74 °C (from hexane); IR(KBr) 1478, 1250, 935, 749, 740, 700 cm⁻¹; δ_{H} (300 MHz; CDCl₃) 0.92 (6H, t, *J* 7.3), 1.84 (4H, q, *J* 7.3), 3.96 (3H, s), 6.59 (1H, s, H-2) and 6.94-7.56 (9H, m, Ar); δ_{C} (75.4 MHz; CDCl₃) 8.4 (2CH₃), 32.3 (2CH₂), 36.9 (CH₃), 84.2 (C), 117.8 (CH), 118.7 (C), 120.0 (CH), 120.1 (C), 120.3 (CH), 120.5 (C), 124.0 (C), 124.4 (CH), 126.5 (CH), 126.6 (CH), 127.8 (2CH), 129.7 (2CH), 136.7 (C) and 152.9 (C); m/z 317 (M⁺, 6%) and 288 (100). Anal. Calcd for C₂₂H₂₃NO: C, 83.24; H, 7.30; N 4.41. Found: C, 83.06; H, 7.28; N 4.62.

3-(1-Ethylpropenyl)-2-(2-hydroxyphenyl)-1-methyl-4-phenylpyrrole (13i).¹⁸ δ_{H} (300 MHz; DMSO-*d*₆) 0.72 (3H, t, *J* 7.6), 1.51 (3H, d, *J* 6.6), 1.96 (2H, m), 3.40 (3H, s), 5.21 (1H, q, *J* 6.6), 6.89 (1H, s), 6.72-7.51 (9H, m, Ar) and 9.30 (1H, br, OH).

Reaction of 3-methylthieno[3,2-*c*][1]benzopyran-4(4*H*)-one (7b) with methylmagnesium iodide. Preparation of 3,4,4-trimethyl-4*H*-thieno[3,2-*c*][1]benzopyran (9y).

By the previous procedure starting from 0.30 g (1.4 mmol) of 3-methylthieno[3,2-*c*][1]benzopyran-4(4*H*)-one (7b) and 5.6 mmol of methylmagnesium iodide, was obtained a reaction mixture which was chromatographed on silica gel using CH₂Cl₂/hexane (1:5) as eluent. 0.26 g (82%) of 3,4,4-trimethyl-4*H*-thieno[3,2-*c*][1]benzopyran (9y) was obtained as a pale yellow oil, bp 125 °C at 1 mmHg. IR(film) 1581, 1488, 1460, 1253, 1132, 750 cm⁻¹. δ_{H} (300 MHz; DMSO-*d*₆) 1.58 (6H, s), 2.22 (3H, d, *J* 1.0), 6.88-7.30 (4H, m, Ar) and 7.05 (1H, d, *J* 1.0, H-2); δ_{C} (75.4 MHz; DMSO-*d*₆) 16.3 (CH₃), 27.4 (2CH₃), 79.4 (C), 116.6 (CH), 119.5 (C), 121.3 (CH), 121.6 (CH), 122.1 (CH), 128.5 (CH), 131.1 (C), 134.4 (C), 137.9 (C) and 150.2 (C); m/z 230 (M⁺, 16%) and 215 (100). Anal. Calcd for C₁₄H₁₄OS: C, 76.01; H, 6.13. Found: C, 75.88; H, 6.27.

Reaction of compound (2b) with triisobutylaluminum. Preparation of 2-(2-hydroxyphenyl)-1,4-dimethyl-3-(3-methylbutyl)pyrrole (17). A mixture of 1,3-dimethyl[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (2b) (1.065 g, 5 mmol) and triisobutylaluminum (12.5 mL, 2M in toluene, 25 mmol) in dry toluene (40 mL) at 100°C was magnetically stirred for 1 h under nitrogen. It was then hydrolyzed, extracted with CH₂Cl₂ and the organic layer was washed with saturated aqueous NaHCO₃, dried (MgSO₄) and

evaporated under reduced pressure. The residue was flash chromatographed on silica gel using CH₂Cl₂/pentane (1:2) as eluent to yield 1.131 g (88%) of 1,4-dimethyl-2-(2-hydroxyphenyl)-3-(3-methylbutyl)pyrrole (**17**) as a pale yellow oil, bp 150 °C at 15 mmHg; IR(film) 3234, 1668, 1601, 1456, 1241, 754 cm⁻¹; δ_{H} (300 MHz; CDCl₃) 0.75 (3H, d, *J* 6.5), 0.76 (3H, d, *J* 6.5), 1.26 (2H, m), 1.42 (1H, m), 2.07 (3H, s), 2.27 (2H, m), 3.29 (3H, s), 5.43 (1H, br, OH), 6.48 (1H, s) and 6.89-7.28 (4H, m, Ar); δ_{C} (75.4 MHz; CDCl₃) 10.3 (CH₃), 22.2 (CH₃), 22.4 (CH₃), 22.7 (CH₂), 27.7 (CH₂), 33.7 (CH₃), 40.3 (CH₂), 115.0 (CH), 117.3 (C), 119.0 (C), 120.0 (CH), 121.2 (CH), 123.4 (C), 123.6 (C), 129.8 (CH), 131.9 (CH) and 154.5 (C); *m/z* 257 (M⁺, 25%) and 200 (100). Anal. Calcd for C₁₇H₂₃NO: C, 79.33; H, 9.01; N 5.44. Found: C, 79.15; H, 9.06; N 5.59.

Reaction of 1,4,4-trimethyl-3-phenyl-[1]benzopyrano[4,3-*b*]pyrrole (5h**) with triisobutylaluminum.**

Preparation of 2-(2-hydroxyphenyl)-3-isopropyl-4-phenylpyrrole (18**).** By the previous procedure, starting from **5h** (0.578 g, 2 mmol), was obtained 0.436 g (75%) of 2-(2-hydroxyphenyl)-3-isopropyl-4-phenylpyrrole (**18**) as a colorless oil. IR (film) 3369, 1683, 1457, 1388, 1285, 756, 701 cm⁻¹; δ_{H} (300 MHz; CDCl₃) 1.05 (3H, d, *J* 7.1), 1.12 (3H, d, *J* 7.1), 3.05 (1H, m, *J* 7.1), 3.34 (3H, s), 5.31 (1H, br, OH), 6.77 (1H, s) and 6.99-7.46 (9H, m, Ar); δ_{C} (75.4 MHz; CDCl₃) 23.2 (CH₃), 24.2 (CH₃), 25.6 (CH), 33.8 (CH₃), 115.0 (CH), 119.9 (C), 120.1 (CH), 121.3 (CH), 122.8 (C), 124.2 (C), 125.8 (CH), 128.1 (2CH), 128.7 (C), 129.3 (2CH), 130.5 (CH), 132.8 (CH), 136.7 (C) and 154.9 (C); *m/z* 291 (M⁺, 34%) and 276 (100).

Bromination of compounds (1, 2, 5, 7 and 9). General procedure. To a solution of **1a**, **1b**, **2a**, **5d**, **5h**, **7b**, or **9f** (2 mmol) in 10 mL of glacial acetic acid was added dropwise with stirring at rt under nitrogen a solution of *N*-bromosuccinimide (0.35 g, 2 mmol) in 8 mL of anhydrous glacial acetic acid. At the end of the reaction (monitored by TLC, see Table 2) the solution was poured into a mixture of ice-water (80 mL) and sodium hydroxide (13 g). The solution was decanted and extracted with ethyl acetate. The organic layer, after drying over MgSO₄, was concentrated at rt. The concentrate was chromatographed on silica gel. The following compounds were thus prepared.

2-Bromo-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (3j**).** Chromatographed on silica gel using CH₂Cl₂/pentane (1:2) as eluent. Yield 10%; mp 251-252 °C (from acetic acid); IR(KBr) 3195, 1691, 1475, 741 cm⁻¹; δ_{H} (DMSO-*d*₆) 6.76 (1H, s, H-3), 7.32-8.0 (4H, m, Ar) and 13.30 (1H, br, NH); δ_{C} (DMSO-*d*₆) 106.0 (C), 108.5 (CH), 109.4 (C), 112.9 (C), 116.9 (CH), 121.3 (CH), 124.3 (CH), 129.1 (CH), 136.4 (C), 151.2 (C) and 156.9 (C); *m/z* 265 (M⁺+2, 100) and 263 (M⁺, 90%). Anal. Calcd for C₁₁H₆NO₂Br: C, 50.03; H, 2.29; N 5.30. Found: C, 50.12; H, 2.22; N 5.33.

2-Bromo-3-methyl-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (3n**).** Chromatographed on silica gel using

CH₂Cl₂/pentane (1:2) as eluent. Yield 52%; mp >300 °C (from acetic acid); IR(nujol mull) 3205, 1688, 745 cm⁻¹; δ_{H} (DMSO-d₆) 2.23 (3H, s), 7.34-7.98 (4H, m, Ar) and 13.45 (1H, br, NH); δ_{C} (DMSO-d₆) 10.2 (CH₃), 105.2 (C), 107.4 (C), 118.2 (C), 116.9 (CH), 117.5 (C), 121.2 (CH), 124.2 (CH), 128.8 (CH), 135.4 (C), 151.1 (C) and 157.6 (C); m/z 277 (M⁺, 100) and 279 (M⁺+2, 96%). Anal. Calcd for C₁₂H₈NO₂Br: C, 51.83; H, 2.90; N 5.04. Found: C, 51.71; H, 2.93; N 5.12.

2-Bromo-1-methyl-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (4j). Chromatographed on silica gel using CH₂Cl₂/pentane (1:2) as eluent. Yield 78%; mp 203-204 °C (from MeOH); IR(nujol mull) 1708, 1470, 1162, 1091, 748 cm⁻¹; δ_{H} (DMSO-d₆) 4.06 (3H, s), 6.83 (1H, s) and 7.32-8.13 (4H, m, Ar); δ_{C} (CDCl₃) 35.2 (CH₃), 108.6 (CH), 109.3(C), 111.7 (C), 113.8 (C), 117.2 (CH), 121.5 (CH), 124.0 (CH), 128.6 (CH), 134.9 (C), 151.3 (C) and 156.8 (C); m/z 277 (M⁺, 100) and 279 (M⁺+2, 97%). Anal. Calcd for C₁₂H₈NO₂Br: C, 51.83; H, 2.90; N 5.04. Found: C, 51.92; H, 2.88; N 4.96.

2-Bromo-3,4,4-trimethyl-4*H*-thieno[3,2-*c*]benzopyran (10u). Chromatographed on silica gel using CH₂Cl₂/pentane (1:5) as eluent. Yield 71%; bp 150-152 °C at 1 mmHg; IR(film) 1490, 1459, 1258, 1141, 752 cm⁻¹; δ_{H} (DMSO-d₆) 1.57 (6H, s), 2.19 (3H, s) and 6.85-7.24 (4H, m, Ar); δ_{C} (DMSO-d₆) 15.4 (CH₃), 27.25 (2CH₃), 79.36 (C), 109.3 (C), 116.7 (CH), 118.3 (C), 121.7 (CH), 122.3 (CH), 129.3 (CH), 130.6 (C), 134.3 (C), 137.8 (C) and 150.0 (C); m/z 309 (M⁺+1, 100), 311 (M⁺+3, 97%) and 263 (M⁺+5, 5%). Anal. Calcd for C₁₄H₁₃OBrS: C, 54.38; H, 4.24. Found: C, 54.50; H, 4.25.

2,3-Dibromo-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (19). Chromatographed on silica gel using CH₂Cl₂/pentane (1:2) as eluent. Yield <5%; mp >300 °C (from acetic acid); IR(KBr) 1699, 753 cm⁻¹; δ_{H} (DMSO-d₆) 7.34-8.01 (4H, m, Ar), 13.77 (1H, br, NH); δ_{C} (DMSO-d₆) 96.9 (C), 107.1 (C), 108.8 (C), 112.8 (C), 117.0 (CH), 121.5 (CH), 124.5 (CH), 129.6 (CH), 136.4 (C), 151.2 (C) and 155.5 (C); m/z 341 (M⁺, 49%), 343 (M⁺+2, 100) and 345 (M⁺+4, 50%). Anal. Calcd for C₁₁H₅NO₂Br₂: C, 38.52; H, 1.47; N 4.08. Found: C, 38.68; H, 1.29; N 4.19.

2,3-Dibromo-1-methyl-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (20). Chromatographed on silica gel using CH₂Cl₂/pentane (1:2) as eluent. Yield 10%; mp 273-274 °C (from MeOH); IR(nujol mull) 1719, 1154, 980, 751 cm⁻¹; δ_{H} (DMSO-d₆) 4.14 (3H, s), 7.25-7.93 (4H, m, Ar); δ_{C} (DMSO-d₆) 36.7 (CH₃), 97.5 (C), 107.2 (C), 113.1 (C), 114.4 (C), 117.2 (CH), 122.2 (CH), 124.1 (CH), 129.2 (CH), 135.3 (C), 151.1 (C) and 154.7 (C); m/z 355 (M⁺, 57%), 357 (M⁺+2, 100) and 359 (M⁺+4, 50%). Anal. Calcd for C₁₂H₇NO₂Br₂: C, 40.37; H, 1.98; N 3.92. Found: C, 40.11; H, 2.09; N 3.81.

2,8-Dibromo-3,4,4-trimethyl-4*H*-thieno[3,2-*c*]benzopyran (22). Chromatographed on silica gel using CH₂Cl₂/pentane (1:2) as eluent. Yield <5%; mp 127-129 °C (from EtOH); IR(nujol mull) 1477, 1269, 1251, 1045, 810 cm⁻¹; δ_{H} (DMSO-d₆) 1.60 (6H, s), 2.21 (3H, s) and 6.85-7.45 (3H, m, Ar); δ_{C} (DMSO-d₆) 15.4 (CH₃), 27.24 (2CH₃), 80.0 (C), 111.2 (C), 113.0 (C), 119.0 (CH), 120.5 (C), 124.5 (CH), 129.8 (C), 131.6 (CH), 134.4 (C), 138.6 (C) and 149.3 (C); m/z 386 (M⁺, 9%), 388 (M⁺+2, 18%), 390 (M⁺+4, 10%)

and 373 (100). Anal. Calcd for $C_{14}H_{12}OBr_2S$: C, 43.32; H, 3.12. Found: C, 43.19; H, 3.25.

Nitration of compounds (1, 2, 5, 7 and 9). General procedure. The pyrrole (**1a,1b, 2a, 5d,**) or thiophene (**7b, 9f**) (1.0 mmol) was dissolved in 8 mL of acetic anhydride and chilled to -5°C . To this was added under nitrogen a cold mixture of fuming nitric acid (0.124 mL) in 4 mL of acetic anhydride at such a rate as to prevent the temperature from rising above 0°C . When the reaction, which was monitored by TLC, was completed (Table 2), the mixture was poured into ice-water, neutralized with sodium hydroxide (3.7 g) and extracted with ethyl acetate. The extract was evaporated to dryness at rt and the residue was recrystallized or chromatographed on silica gel. The following compounds were thus prepared.

2-Nitro-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (3k). Recrystallized from toluene/hexane (1:1). Yield 65%, mp $>300^{\circ}\text{C}$; IR(nujol mull) 3140, 1710, 1505, 1320, 972, 760 cm^{-1} ; δ_{H} (DMSO- d_6) 7.61 (1H, s, H-3), 7.35-8.27 (4H, m, Ar) and 14.21 (1H, br, NH); δ_{C} (DMSO- d_6) 109.0 (C), 109.3 (CH), 113.5 (C), 117.4 (CH), 123.2 (CH), 124.8 (CH), 131.0 (CH), 138.4 (C), 142.4 (C), 152.8 (C) and 157.5 (C);. Anal. Calcd for $C_{11}H_6N_2O_4$: C, 57.40; H, 2.63; N 12.17. Found: C, 57.19; H, 2.50; N 12.30.

3-Methyl-2-nitro-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (3o). Chromatographed on silica gel using $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ (40:1) as eluent. Yield 53%, mp $>300^{\circ}\text{C}$ (from acetic acid); IR(nujol mull) 1715, 1453, 1328, 972, 758 cm^{-1} ; δ_{H} (DMSO- d_6) 2.70 (3H, s), 7.39-8.37 (4H, m, Ar) and 14.13 (1H, br, NH); m/z 244 (M^+ , 82%) and 185 (100). Anal. Calcd for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N 11.47. Found: C, 59.21; H, 3.15; N 11.40.

1-Methyl-2-nitro-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (4k). Chromatographed on silica gel using CH_2Cl_2 as eluent. Yield 89%, mp $235-236^{\circ}\text{C}$ (from MeOH); IR(nujol mull) 1733, 1505, 1453, 1350, 1303, 1285, 970 cm^{-1} ; δ_{H} (DMSO- d_6) 4.35 (3H, s), 7.70 (1H, s, H-3) and 7.38-8.26 (4H, m, Ar); δ_{C} (DMSO- d_6) 36.2 (CH_3), 107.6 (C), 110.9 (CH), 112.3 (C), 117.7 (CH), 123.1 (CH), 124.3 (CH), 130.8 (CH), 137.5 (C), 141.3 (C), 152.7 (C) and 156.4 (C); m/z 244 (M^+ , 100). Anal. Calcd for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N 11.47. Found: C, 59.25; H, 3.40; N 11.22.

1,4,4-Trimethyl-2-nitro-1*H*-[1]benzopyrano[4,3-*b*]pyrrole (6r). Recrystallized from toluene/hexane. Yield 18%, mp $145-146^{\circ}\text{C}$; IR(KBr) 1440, 1392, 1297, 1271, 1200 cm^{-1} ; δ_{H} (300 MHz; CDCl_3) 1.57 (6H, s), 4.20 (3H, s), 7.10 (1H, s, H-3) and 7.02-7.60 (4H, m, Ar); δ_{C} (75.4 MHz; CDCl_3) 27.5 (2 CH_3), 36.3 (CH_3), 77.2 (C), 109.2 (CH), 115.8 (C), 119.2 (CH), 121.7 (CH), 122.9 (CH), 125.6 (C), 130.5 (CH), 131.2 (C), 139.3 (C) and 154.6 (C); m/z 258 (M^+ , 17%) and 243 (100). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N 10.85. Found: C, 65.30; H, 5.28; N 10.97.

3,4,4-Trimethyl-2-nitro-4*H*-thieno[3,2-*c*]benzopyran (10v). Chromatographed on silica gel using $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ (40:1) as eluent. Yield 86%, mp $126-127^{\circ}\text{C}$ (from EtOH); IR(KBr) 1486, 1457, 1308, 1296,

1240, 745 cm^{-1} ; δ_{H} (DMSO- d_6) 1.67 (6H, s), 2.65 (3H, s) and 6.95-7.58 (4H, m, Ar); δ_{C} (DMSO- d_6) 15.1 (CH₃), 27.3 (2CH₃), 79.1 (C), 116.5 (C), 117.4 (CH), 122.2 (CH), 124.0 (CH), 132.5 (CH), 136.6 (C), 138.8 (C), 139.9 (CH), 145.1 (CH) and 151.6 (C); m/z 275 (M^+ , 19%), 277 ($\text{M}^+ + 2$, 1%) and 260 (100). Anal. Calcd for C₁₄H₁₃NO₃S: C, 61.07; H, 4.76; N 5.09. Found: C, 60.91; H, 4.82; N 5.22.

3,4,4-Trimethyl-2,8-dinitro-4*H*-thieno[3,2-*c*]benzopyran (23). Chromatographed on silica gel using CH₂Cl₂ as eluent. Yield <5%, mp 233-235 °C (from EtOH); IR(KBr) 1510, 1341, 1312, 1283 cm^{-1} ; δ_{H} (DMSO- d_6) 1.74 (6H, s), 2.66 (3H, s) and 7.17-8.40 (4H, m, Ar); δ_{C} (DMSO- d_6) 15.1 (CH₃), 27.8 (2CH₃), 81.6 (C), 116.5 (C), 118.2 (CH), 119.6 (C), 127.4 (CH), 128.7 (C), 131.5 (C), 133.6 (C), 139.4 (CH), 141.8 (C) and 156.7 (C); m/z 320 (M^+ , 16%), 322 ($\text{M}^+ + 2$, 1%) and 305 (100). Anal. Calcd for C₁₄H₁₂N₂O₅S: C, 52.49; H, 3.78; N 8.75. Found: C, 52.28; H, 3.90; N 8.91.

Acetylation of compounds (1, 2, 5, 7 and 9). General procedure. A solution of **1a**, **2a**, **2c**, **5d**, **7b**, or **9f** (0.5 mmol) in 2 mL of Ac₂O was added to a solution of 0.17 mL (1.5 mmol) of TiCl₄ in 4 mL of Ac₂O and the mixture was stirred at rt under nitrogen. When the reaction was completed, monitored by TLC, the mixture was hydrolyzed and neutralized with NaOH/ice/water, and then extracted with ethyl acetate. The extract, after drying (Na₂SO₄), was evaporated and chromatographed on silica gel. The following compounds were thus prepared.

2-Acetyl-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (3l). Chromatographed on silica gel using CH₂Cl₂/Et₂O (10:1) as eluent. Yield 10%, mp 292-294 °C (from MeOH) (lit.,³ mp 292-294 °C), IR(KBr) 3286, 3020, 1735, 1640, 1461, 753; δ_{H} (300 MHz; DMSO- d_6) 2.51 (3H, s), 7.31-8.39 (4H, m, Ar), 7.64 (1H, d, *J* 1.6, H-3), 13.27 (1H, br, NH); δ_{C} (75.4 MHz; DMSO- d_6) 26.0 (CH₃), 109.2 (C), 113.0 (C), 115.5 (CH), 117.1 (CH), 123.1 (CH), 124.4 (CH), 130.5 (CH), 135.4 (C), 138.6 (C), 152.3 (C), 157.8 (C) and 188.8 (C); m/z 227 (M^+ , 90%), 212 (100).

2-Acetyl-1-methyl-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (4l). Chromatographed on silica gel using CH₂Cl₂/Et₂O (30:1) as eluent. Yield 72%, mp 202-204 °C (from MeOH) (lit.,³ mp 202-204 °C), IR(KBr) 1724, 1652, 750; δ_{H} (300 MHz; CDCl₃) 2.55 (3H, s), 4.39 (3H, s), 7.32-8.04 (4H, m, Ar), 7.54 (1H, s, H-3); δ_{C} (75.4 MHz; CDCl₃) 27.9 (CH₃), 35.8 (CH₃), 108.9 (C), 113.4 (C), 117.7 (CH), 118.1 (CH), 122.2 (CH), 124.1 (CH), 130.0 (CH), 134.0 (C), 139.0 (C), 152.7 (C), 157.9 (C) and 189.6 (C); m/z 241 (M^+ , 82%), 226 (100).

2-Acetyl-1-methyl-3-phenyl-1*H*-[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (4q). Chromatographed on silica gel using CH₂Cl₂/Et₂O (30:1) as eluent. Yield 75%, mp 198-200 °C (from MeOH); IR(KBr) 1780, 1638, 1366, 1195, 1090, 758 cm^{-1} ; δ_{H} (300 MHz; CDCl₃) 1.96 (3H, s), 4.28 (3H, s) and 7.26-8.10 (9H, m, Ar); δ_{C} (75.4 MHz; CDCl₃) 31.0 (CH₃), 36.6 (CH₃), 108.1 (C), 113.7 (C), 118.3 (CH), 122.6 (CH), 124.0 (CH), 128.2 (2CH), 128.3 (CH), 128.4 (CH), 130.0 (2CH), 132.3 (C), 133.2 (C), 134.1 (C), 138.0 (C),

153.1 (C), 157.4 (C) and 192.7 (C); m/z 317 (M^+ , 100%). Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N 4.41. Found: C, 75.52; H, 4.80; N 4.20.

2-Acetyl-1,4,4-trimethyl-1*H*-[1]benzopyrano[4,3-*b*]pyrrole (6s). Chromatographed on silica gel using CH_2Cl_2 as eluent. Yield 85%, mp 150-152 °C (from EtOH); IR(KBr) 1639, 1455, 1365, 1228, 112, 930 cm^{-1} ; δ_H (300 MHz; $CDCl_3$) 1.58 (6H, s), 2.46 (3H, s), 4.20 (3H, s), 6.75 (1H, s, H-3) and 6.96-7.61 (4H, m, Ar); δ_C (75.4 MHz; $CDCl_3$) 27.6 (CH_3), 27.8 ($2CH_3$), 35.7 (CH_3), 77.0 (C), 113.6 (CH), 117.2 (C), 118.6 (CH), 121.3 (CH), 122.5 (CH), 125.4 (C), 129.0 (CH), 131.1 (C), 132.0 (C), 153.7 (C) and 188.1 (C); m/z 255 (M^+ , 19%) and 240 (100). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N 5.49. Found: C, 75.40; H, 6.83; N 5.56.

2-Acetyl-3,4,4-trimethyl-4*H*-thieno[3,2-*c*]benzopyran (10w). Chromatographed on silica gel using CH_2Cl_2 /pentane (1:1) as eluent. Yield 41%, mp 84-85 °C (from EtOH); IR(KBr) 1646, 1405, 1293, 1238, 750 cm^{-1} ; δ_H (DMSO- d_6) 1.64 (6H, s), 2.50 (3H, s), 2.53 (3H, s) and 6.92-7.48 (4H, m, Ar); δ_C (DMSO- d_6) 15.6 (CH_3), 27.5 ($2CH_3$), 30.2 (CH_3), 79.5 (C), 117.0 (CH), 117.9 (C), 121.9 (CH), 123.3 (CH), 131.0 (CH), 135.2 (C), 135.4 (C), 140.4 (C), 141.1 (C), 151.0 (C) and 190.8 (C); m/z 272 (M^+ , 18%), 272 (M^++2 , 1%) and 257 (100). Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.56; H, 5.92. Found: C, 70.72; H, 5.81.

3-Acetyl-1,4,4-trimethyl-1*H*-[1]benzopyrano[4,3-*b*]pyrrole (21). Chromatographed on silica gel using CH_2Cl_2 as eluent. Yield <5%, mp 140-142 °C (from toluene); IR(KBr) 1648, 1360, 1251, 1102, 751 cm^{-1} ; δ_H (300 MHz; $CDCl_3$) 1.73 (6H, s), 2.40 (3H, s), 3.91 (3H, s), 7.22 (1H, s, H-2) and 6.87-7.44 (4H, m, Ar); δ_C (75.4 MHz; $CDCl_3$) 27.7 ($2CH_3$), 27.9 (CH_3), 38.7 (CH_3), 79.5 (C), 116.8 (C), 116.9 (CH), 119.1 (C), 120.7 (CH), 120.8 (CH), 123.2 (C), 124.2 (C), 127.5 (CH), 134.6 (CH), 151.3 (C) and 192.0 (C); m/z 255 (M^+ , 14%) and 240 (100). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N 5.49. Found: C, 75.40; H, 6.59; N 5.32.

Formylation of compounds (1, 5, 7 and 9). General procedure. To 0.34 mL (0.32 g, 4.4 mmol) of *N,N*-dimethylformamide cooled in an ice bath was added dropwise 0.41 mL (0.676 g, 4.4 mmol) of phosphorous oxychloride at such a rate as to maintain the internal temperature at 10-15°C. The ice bath was removed, and the mixture was stirred for 15 min at rt. The ice bath was replaced, and 8 mL of ethylene dichloride were added to the mixture. When the internal temperature dropped to 10-15°C, a solution of 4 mmol of pyrrole (**1a**, **b**, **5d**) or thiophene (**7b**, **9f**, **9y**) in 8 mL of ethylene dichloride was added. After the addition was completed, the mixture was stirred at rt until the reaction was complete (monitored by TLC, Table 2). To this was added 3 g (22 mmol) of sodium acetate trihydrate in 30 mL of water and the reaction mixture was again refluxed for 15 min.

The cooled mixture was decanted and extracted with ethyl acetate. The organic layer, was washed with saturated aqueous sodium carbonate solution, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was

recrystallized or chromatographed on silica gel. The following compounds were thus prepared.

4-Oxo-[1]benzopyrano[4,3-*b*]pyrrole-2(1*H*)-carboxaldehyde (3m). Recrystallized from acetone. Yield 81%, mp >300 °C; (lit.,³ mp >300 °C), IR(KBr) 3260, 1729, 1643, 1163, 753 cm⁻¹; δ_{H} (300 MHz; DMSO-*d*₆) 7.35-8.33 (4H, m, Ar), 7.63 (1H, s, H-3), 9.76 (1H, s, CHO) and 13.52 (1H, br, NH); δ_{C} (75.4 MHz; DMSO-*d*₆) 109.5 (C), 112.8 (C), 117.1 (CH), 119.5 (CH), 123.0 (CH), 124.4 (CH), 130.8 (CH), 135.8 (C), 139.4 (C), 152.4 (C) 157.5 (C) and 181.3 (CH); *m/z* 213 (M⁺, 100%).

3-Methyl-4-oxo-[1]benzopyrano[4,3-*b*]pyrrole-2(1*H*)-carboxaldehyde (3p). Recrystallized from THF. Yield 82%, mp >300 °C; IR(KBr) 3230, 1722, 1639, 1611, 1455, 760 cm⁻¹; δ_{H} (300 MHz; DMSO-*d*₆) 2.63 (3H, s), 7.27-8.31 (4H, m, Ar), 9.86 (1H, s, CHO) and 12.97 (1H, br, NH); δ_{C} (75.4 MHz; DMSO-*d*₆) 8.8 (CH₃), 108.1 (C), 112.6 (C), 116.4 (CH), 122.7 (CH), 123.7 (CH), 130.1 (CH), 131.3 (C), 131.6 (C), 138.3 (C), 152.2 (C) 157.3 (C) and 178.9 (CH); *m/z* 227 (M⁺, 100%). Anal. Calcd for C₁₃H₉NO₃: C, 68.72; H 3.99; N 6.16. Found: C, 68.56; H, 4.12N 6.22.

1,4,4-Trimethyl-[1]benzopyrano[4,3-*b*]pyrrole-2(1*H*)-carboxaldehyde (6t). Recrystallized from toluene/hexane (1:1). Yield 62%, mp 139-141 °C; IR(KBr) 1749, 1450, 1367, 1255, 1150, 747 cm⁻¹; δ_{H} (300 MHz; CDCl₃) 1.58 (6H, s), 4.24 (3H, s), 6.68 (1H, s, H-3), 6.97-7.63 (4H, m, Ar) and 9.49 (1H, s, CHO); δ_{C} (75.4 MHz; CDCl₃) 27.8 (2CH₃), 34.8 (CH₃), 77.0 (C), 116.7 (C), 118.1 (CH), 118.6 (CH), 121.3 (CH), 122.6 (CH), 126.6 (C), 129.6 (CH), 132.5 (C), 132.8 (C), 153.9 (C) and 178.9 (CH); *m/z* 241 (M⁺, 13%), 226 (100). Anal. Calcd for C₁₅H₁₅NO₂: C, 74.67; H 6.27; N 5.81. Found: C, 74.51; H, 6.38; N 5.91.

3,4,4-Trimethylthieno[3,2-*c*]benzopyran-2(4*H*)-carboxaldehyde (10x). Chromatographed on silica gel using CH₂Cl₂/pentane (1:1) as eluent. Yield 85%, mp 120-122 °C (from EtOH); IR(KBr) 1635, 1466, 1384, 1298, 1233, 1193, 751 cm⁻¹; δ_{H} (300 MHz; CDCl₃) 1.69 (6H, s), 2.59 (3H, s), 6.89-7.41 (4H, m, Ar) and 10.04 (1H, s, CHO); δ_{C} (75.4 MHz; CDCl₃) 14.3 (CH₃), 27.8 (2CH₃), 79.2 (C), 117.3 (CH), 118.3 (C), 121.6 (CH), 123.7 (CH), 131.2 (CH), 137.1 (C), 139.8 (C), 141.3 (C), 143.5 (C), 151.6 (C) and 181.8 (CH); *m/z* 258 (M⁺, 17%), 260 (M⁺+2, 1%), 243 (100). Anal. Calcd for C₁₅H₁₄O₂S: C, 69.74; H 5.46. Found: C, 69.91; H, 5.30.

Thieno[3,2-*c*]benzopyran-2(4*H*)-carboxaldehyde (10z). Chromatographed on silica gel using CH₂Cl₂/pentane (1:1) as eluent. Yield 25%, mp 116-117 °C (from EtOH); IR(KBr) 1652, 1451, 1433, 1230, 1146, 1108, 748 cm⁻¹; δ_{H} (300 MHz; CDCl₃) 5.30 (2H, s), 6.96-7.4 (4H, m, Ar) 7.50 (1H, s, H-3) and 9.87 (1H, s, CHO); δ_{C} (75.4 MHz; CDCl₃) 65.6 (CH₂), 117.2 (CH), 119.1 (C), 122.4 (CH), 124.2 (CH), 131.3 (CH), 132.1 (C), 132.9 (C), 141.9 (C), 142.5 (C), 153.1 (C) and 182.3 (CH); *m/z* 216 (M⁺, 74%), 218 (M⁺+2, 4%), 215 (100). Anal. Calcd for C₁₂H₈O₂S: C, 66.65; H 3.73. Found: C, 66.82; H, 3.61.

REFERENCES AND NOTES

- 1 A. Alberola, R. Álvaro, J. M. Andrés, B. Calvo, and A. González Ortega, *Synthesis*, 1994, 279.
- 2 A. Alberola, R. Álvaro, A. González Ortega, M. L. Sádaba, and M. C. Sañudo, *Tetrahedron*, 1999, **55**, 13211.
- 3 A. Alberola, L. Calvo, A. González-Ortega, A. P. Encabo, and M. C. Sañudo, *Synthesis*, 2001, 1941
- 4 Selected references. (a) Antipyretic, antiinflammatory and antiallergic drugs: Y. Makisumi, *Jpn Kokai*, 73 00,596 (*Chem. Abstr.*, 1973, **78**, 72097v); 74 75,599 (*Chem. Abstr.*, 1975, **83**, 164152r); (b) Analgesic and sedative-hypnotic potency: R. K. Razdan, G. R. Handrickc, H. C. Dalzell, J. F. Howes, M. Winn, N. P. Plotnikoff, P. Dodge, W. Patrick, A. T. Dren, and T. Anthony, *J. Med. Chem.*, 1976, **19**, 552. (c) Analgesic properties: A. Xicluna, J. E. Ombetta, J. Navarro, J. F. Robert, and J. Panouse, *J. Med. Chem. Chim. Ther.*, 1979, **14**, 523; F. Manna, F. Chimenti, A. Bolasco, M. L. Conicola, M. D'Amico, C. Parrillo, F. Rossi, and E. Marco, *Eur. J. Med. Chem.*, 1991, **27**, 633 (d) Diuretic action: J. E. Ombetta, A. Xicluna, J. F. Robert, and J. J. Panouse, *Ann. Pharm. Fr.*, 1986, **44**, 107. (e) Mucoregulatory drugs: C. G. Rimbault, *Eur. Pat. Appl.*, EP 193,493 (*Chem. Abstr.*, 1987, **106**, 67282u); S. E. Webber, and J. G. Widdicombe, *Agents Actions*, 1988, **24**, 65; D. F. Rogers, R. W. A. Rogers, K. Castro, S. Majumdar, and P. K. Jeffery, *Agents Actions*, 1991, **33**, 359.
- 5 L. Merlini, 'Advances in Heterocyclic Chemistry: Advances in the Chemistry of Chrom-3-enes', Vol. 18, ed. by A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1976, pp. 168-169.
- 6 M. S. Kharasch and O. Reinmuth, 'Grignard Reactions of Nonmetallic Substances', ed. by W. M. Latimer, Prentice-Hall, Inc., New York, 1954, pp. 574-576 and Table VIII-III.
- 7 A. Alberola, B. Calvo, A. González Ortega, and R. Pedrosa, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3075.
- 8 A. Alberola, B. Calvo, A. González Ortega, C. López, and F. Villafañe, *Heterocycles*, 1994, **38**, 819.
- 9 L. Merlini, "Advances in Heterocyclic Chemistry: Advances in the Chemistry of Chrom-3-enes", Vol. 18, ed. by A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1976, pp. 162,176-190.
- 10 R. Hug, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, 1972, **55**, 1675 and 1828.
- 11 A. Alberola, F. A. Cermeño, and A. González Ortega, *An. Quim*, 1982, **78C**, 9.
- 12 A. Alberola, A. González Ortega, R. Pedrosa, J. L. P. Bragado, and J. F. R. Amo, *J. Heterocycl. Chem.*, 1983, **20**, 715.
- 13 T. P. Toubé, "The Chemistry of Heterocyclic Compounds: Acylpyrroles", Vol. 48, Part. 2, ed. by R. A. Jones, John Wiley and Sons, Inc., New York, 1992, p. 67.
- 14 J. Kolc and R. S. Becker, *J. Phys. Chem.*, 1967, **71**, 4045.
- 15 A. Alberola, A. González Ortega, R. Pedrosa, J. L. P. Bragado, and J. F. R. Amo, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1209.

- 16 M. Darbarwar and V. Sundaramurthy, *Synthesis*, 1982, 377.
- 17 A. Ricci, D. Balucani, C. Rossi, and A. Croisy, *Boll. Soc. Ital. Biol. Sper.*, 1969, **27**, 279.
- 18 Compounds (**13**) were not isolated. We have selected the ^1H -NMR of the compound (**13i**), precursor of the pyrrole (**5i**), as a representative example of these intermediates.