A New, General Synthesis of 1-Substituted 2-Amino-4-aroyl-5-methylthiopyrroles using α-Ketoketene *S,S*-Acetals[1]

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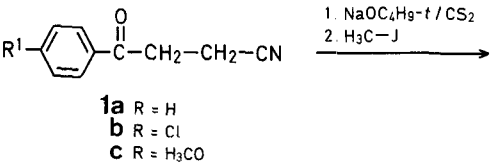
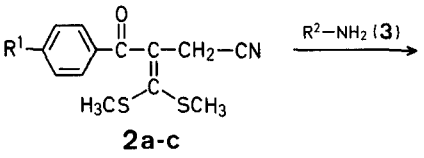
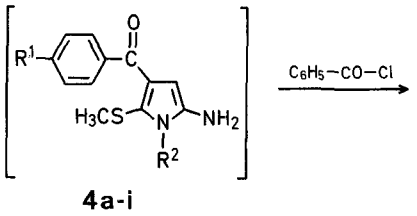
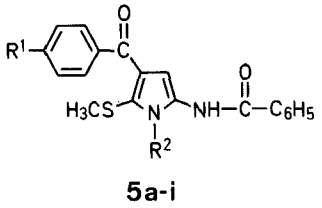
The importance of 2- and 3-aminopyrroles without any substituents in their respective adjacent positions has been recently demonstrated by the conversion of 1-substituted 2-amino-4-cyanopyrroles to 7-azaindole derivatives[2]. This method proved to be superior to the conventional approach of construction of the pyrrole moiety on a suitably substituted pyridine ring. Several methods have been reported[3] for the preparation of 2- and 3-aminopyrroles, which involve either functional group transformations on the pyrrole ring or their total ring synthesis from two carbon units. The aminopyrroles obtained by these methods are unsuitable for further synthetic eloboration as their adjacent positions are blocked. The only methods available for the synthesis of 2- and 3-aminopyrroles with such structural features, involve (a) self-condensation of α-aminocarbonyl compounds in dilute acid to give 2-unsubstituted 3-aminopyrroles[4] and (b) the enamines derived from succinonitrile which undergo intramolecular nucleophilic attack upon the cyano group to give 3-unsubstituted 2-aminopyrroles[2,5]. In continuation of our interest[6] in the studies of α-ketoketene *S,S*-acetals, we now report a convenient, general synthesis of 1-substituted 2-amino-4-aroyl-5-methylthiopyrroles **5** in good yields from **2a-c**.









The previously unreported ketene *S,S*-diacetals **2a-c** were prepared by slight modification of an earlier report[7] from the 4-aryl-4-oxobutanenitriles **1a-c**. The I.R. and N.M.R. data are consistent with the assigned structures (Table 1).

Treatment of **2a** with methylamine (**3**, $R^2 = CH_3$) in refluxing ethanol for 45 min gave **4a** in 46% yield. The other compounds **4b-i** were similarly prepared in 41–61% overall yields[8]. The aminopyrroles, **4**, thus obtained, were found to develop a dark colour after purification by column chromatography and were thus characterized as their mono-*N*-benzoyl derivatives (Table 2; **5a-i**).

4-Aryl-3-(bis[methylthio]methylene)-4-oxobutanenitriles 2a-c; General Procedure:

A mixture of 4-aryl-4-oxobutanenitrile[9] **1** (0.1 mol) and carbon disulfide (6 ml, 0.1 mol) is added to a well stirred and cooled suspension of sodium *t*-butoxide (19.2 g, 0.2 mol) in dry benzene (150 ml) and dry dimethylformamide (10 ml). After stirring of the reaction mixture at 5–10 °C for 5 h, methyl iodide (14.5 ml, 0.22 mol) is gradually added with external cooling. The reaction mixture is stirred at room temperature for 5 h, left overnight, and again stirred at 30–35 °C for 3 h. Work-up of the reaction mixture as reported earlier[7] gives crude **2a-c**, which are purified by column chromatography over silica gel using benzene/hexane (25:75) as eluent (Table 1).

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Table 1. Ketene *S,S*-Acetals **2a–c** prepared

Product No.	R^1	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	I.R. (nujol) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. m/e (M^+)
2a	H	45	68° ($CHCl_3/C_6H_{14}$)	$C_{13}H_{13}NOS_2$ (263.4)	2240; 1648	2.05 (s, 3H, SCH_3); 2.40 (s, 3H, SCH_3); 3.78 (s, 2H, CH_2); 7.4–7.9 (m, 5H_{arom})	263
2b	Cl	41	111–112° ($CHCl_3$)	$C_{13}H_{12}ClNOS_2$ (297.8)	2250; 1650	2.02 (s, 3H, SCH_3); 2.32 (s, 3H, SCH_3); 3.69 (s, 2H, CH_2); 7.36 (d, 2H_{arom}); 7.75 (d, 2H_{arom})	297
2c	H_3CO	48	98–99° (C_2H_5OH)	$C_{14}H_{15}NO_2S_2$ (293.3)	2243, 1645	2.20 (s, 3H, SCH_3); 2.48 (s, 3H, SCH_3); 3.84 (s, 2H, CH_2); 3.96 (s, 3H, OCH_3); 7.10 (d, 2H_{arom}); 8.00 (d, 2H_{arom})	293

[a] Satisfactory microanalyses obtained: C ±0.35, H ±0.26, N ±0.30.

Table 2. *N*-Substituted 4-Aroyl-5-benzoylamino-5-methylthiopyrroles **5a–i**

Product No.	R^1	R^2	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b]	I.R. (nujol) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]	M.S. m/e (M^+)
5a	H	CH_3	46	108–109° ($CHCl_3$/hexane)	$C_{20}H_{18}N_2O_2S$ (350.4)	3330; 1673; 1632	2.05 (s, 3H, SCH_3); 3.40 (s, 3H, NCH_3); 7.12 (s, 1H, H-3); 7.2–7.7 (m, 10H_{arom})[c]	350
5b	H	C_2H_5	55	146–147° (C_2H_5OH)	$C_{21}H_{20}N_2O_2S$ (364.5)	3300; 1663; 1620	1.23 (t, 3H, CH_2CH_3); 2.20 (s, 3H, SCH_3); 3.82 (q, 2H, CH_2); 6.90 (s, 1H, H-3); 7.4 (m, 6H_{arom}); 7.8 (m, 4H_{arom}); 8.42 (s, 1H, NH)	364
5c	H	$C_6H_5CH_2$	59	175° (C_2H_5OH)	$C_{26}H_{22}N_2O_2S$ (426.5)	3295; 1672; 1620	2.34 (s, 3H, SCH_3); 5.06 (s, 2H, CH_2); 7.00 (s, 1H, H-3); 7.1–9.9 (m, 15H_{arom}); 7.90 (s, 1H, NH)	426
5d	4-Cl	CH_3	46	154° ($CHCl_3$/hexane)	$C_{20}H_{17}ClN_2O_2S$ (384.5)	3305; 1688; 1620	2.23 (s, 3H, SCH_3); 3.50 (s, 3H, NCH_3); 6.93 (s, 1H, H-3); 7.3–8.1 (m, 9H_{arom}); 8.44 (s, 1H, NH)	384
5e	4-Cl	C_2H_5	41	170° ($CHCl_3$/hexane)	$C_{21}H_{19}ClN_2O_2S$ (398.5)	3210; 1685; 1615	1.36 (t, 3H, CH_2CH_3); 2.23 (s, 3H, SCH_3); 3.84 (q, 2H, CH_2); 6.97 (s, 1H, H-3); 7.2–8.0 (m, 9H_{arom}); 8.30 (s, 1H, NH)	398
5f	4-Cl	$C_6H_5CH_2$	54	209° (C_2H_5OH)	$C_{26}H_{21}ClN_2O_2S$ (460.5)	3300; 1678; 1618	2.04 (s, 3H, SCH_3); 4.95 (s, 2H, CH_2); 6.6–7.7 (m, 15H_{arom} and H-3)[c]	460
5g	4-H_3CO	CH_3	61	154° ($CHCl_3$/hexane)	$C_{21}H_{20}N_2O_3S$ (380.5)	3307; 1678; 1620	1.98 (s, 3H, SCH_3); 3.22 (s, 3H, NCH_3); 3.56 (s, 3H, OCH_3); 6.7–7.9 (m, 9H_{arom}); 8.67 (s, 1H, NH)	380
5h	4-H_3CO	C_2H_5	45	185° ($CHCl_3$/hexane)	$C_{22}H_{22}N_2O_3S$ (394.5)	3305; 1667; 1612	1.10 (t, 3H, CH_2CH_3); 2.03 (s, 3H, SCH_3); 3.65 (s, 3H, OCH_3); 3.82 (q, 2H, CH_2); 6.85 (s, 1H, H-3); 7.0–8.0 (m, 9H_{arom})[c]	394
5i	4-H_3CO	$C_6H_5CH_2$	57	173° ($CHCl_3$/hexane)	$C_{27}H_{24}N_2O_3S$ (456.5)	3260; 1670; 1615	2.38 (s, 3H, SCH_3); 3.90 (s, 3H, OCH_3); 5.12 (s, 2H, CH_2); 6.9–7.9 (m, 16H_{arom} and NH)	456

[a] Yield of pure, isolated product.
[b] Satisfactory microanalyses obtained: C ±0.40, H ±0.37, N ±0.40; exceptions: **5a**, C −0.44%; **5h**, C −0.47%.
[c] In trifluoroacetic acid solution.

1-Substituted 2-Amino-4-aroyl-5-methylthiopyrroles 4a–i and 1-Substituted 4-Aroyl-2-benzoylamino-5-methylthiopyrroles 5a–i; General Procedure:

A solution of **2** (0.01 mol) and amine **3** (0.011 mol) in ethanol (15 ml) is refluxed for 1–1.5 h. Removal of solvent under reduced pressure gives the crude aminopyrroles **4a–i** which are dissolved in dry benzene (50 ml) and treated with anhydrous potassium carbonate (0.01 mol) and benzoyl chloride (0.015 mol) with vigorous stirring and cooling. After stirring for 2 h at room temperature the mixture is poured over crushed ice (200 g). The benzene layer is separated, the aqueous layer further extracted with benzene (2 × 100 ml), and the combined organic layer is dried with magnesium sulfate. Evaporation of the benzene gives the crude **5a–i** which are further purified by crystallization (**5b, c,** and **f**) or by column chromatography (**5a, d–e,** and **g–i**) over silica gel using benzene/ethyl acetate (95:5) as eluent (Table 2).

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