A SYNTHESIS OF PYRANO[2,3-c]PYRROLES FROM CINNAMOYLOXIMINOACETONITRILE

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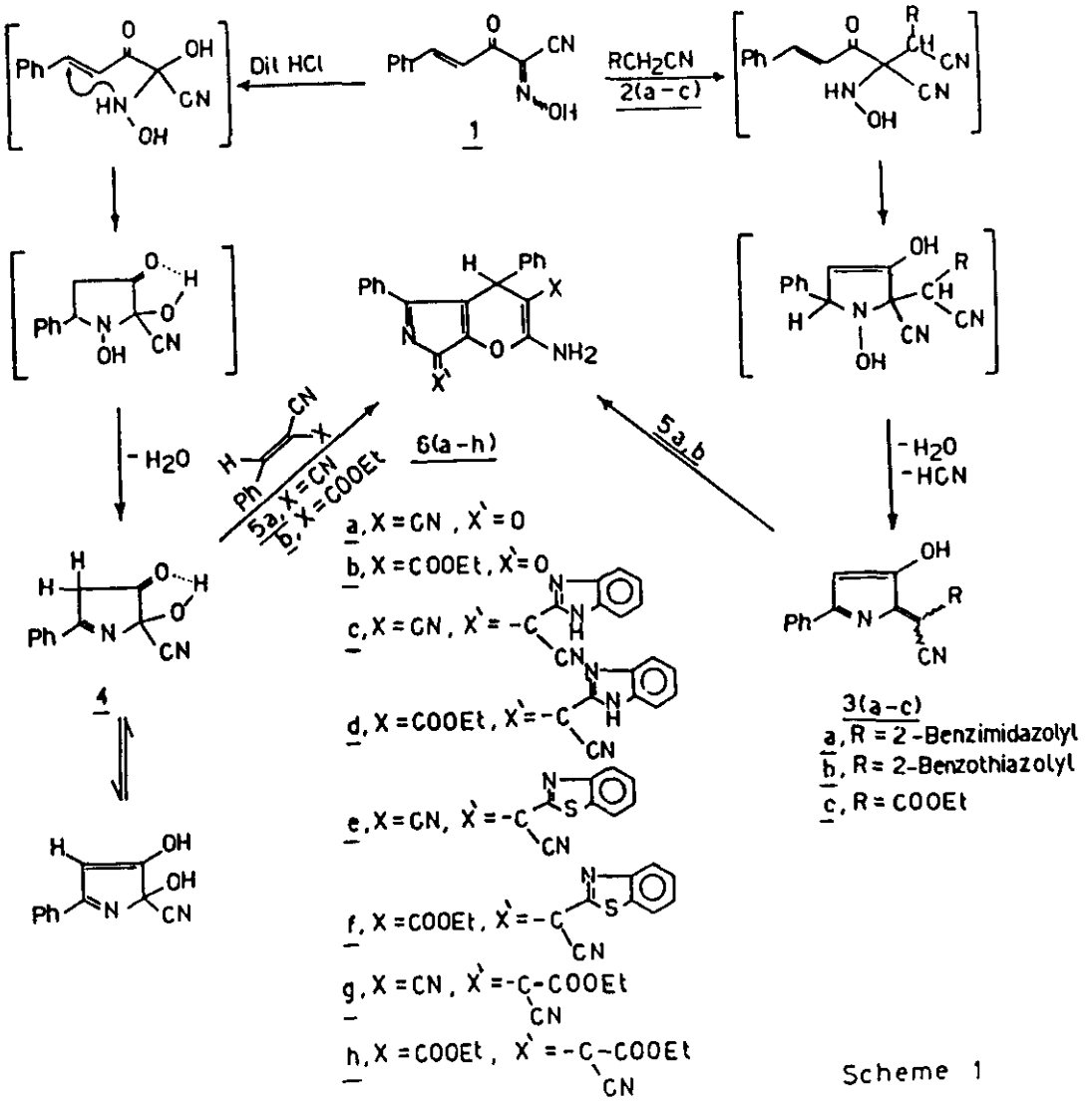
Abstract - An approach to the title ring system starting with the available cinnamoyloximinoacetonitrile (1) is proposed. It involves its reaction with various nucleophiles and subsequent addition of the resulting pyrrole derivatives (3,4) to 2-substituted cinnamonitriles (5), in a Micheal type reaction, thus affording the pyrano[2,3-c]pyrroles (6).

In the course of a program directed to develop new, efficient procedures for the synthesis of functionally substituted and condensed heterocycles, using readily obtainable materials,[1-3] we have reported earlier a simple synthesis of pyrrole from the reaction of 3-hydroxyimino-5-phenyl-4-pentenenitrile (1).[4] In the present work, the utility of such pyrrole in the synthesis of pyrano[2,3-c]pyrroles, through a facile approach, is investigated. We have been particularly interested to see if reactions of this type can be extented to constitute more general method for the preparation of polysubstituted pyrrole derivatives, the title ring system. Also, the mechanistic pathway of the pyrrole formation was reconsidered.

The oxime (1) was refluxed with benzimidazole or benzothiazole-2-acetonitriles (2a,b), respectively, in ethanolic piperidine. The reaction afforded products with a characteristic red colour, resembling the colour

of 3c[4] and showing similar spectral features where their ^{1}H-nmr spectra revealed the pyrrole H-4 at δ 6.2-6.3 ppm and the mass spectral data of the product obtained from the reaction of 1 with 2a gave a molecular formula compatible with $C_{19}H_{12}N_4O$ (m/z 312). Accordingly, the 2-(1-cyanoarylidene)-3-hydroxy-5-phenylpyrrole structure (3) was assigned to these products. Careful inspection of the pyrrole H-4 proton resonance revealed its appearance in the form of two singlets of close chemical shift values



Scheme 1

(which was thought to be a doublet as previously reported for 3c).[4] The appearance of these two singlets (integrated together to one proton) suggested the presence of two distinct stereoforms of structure (3).

The chemical behaviour of 3a-c also emphasized the given structure. Thus, they reacted with cinnamonitriles (5a,b), in a Micheal type reaction, affording the pyrano[2,3-c]pyrroles (6c-h). Structure (6) was established from elemental analyses and spectral data. Their ^{1}H-nmr spectra revealed the characteristic pyranopyrrole H-4 signal at δ 4.4-4.8 ppm range.[5,6]

Moreover, their ir spectra are characterized by strong C=C absorption bands at ν 1690 cm^{-1}. This character was previously noticed in several 2-amino-4H-pyrans where this type of stretching vibration band occurs at extremely high frequency.[6,7]

During the preparation of the oxime (1) in aqueous acidic medium,[4] we have observed the formation of another product, mp 262°C, when the reaction medium was left overnight. This product had the same molecular formula of the oxime (1) and showed a cyano group absorption in its ir spectrum which could not be detected in the spectrum of 1.[4]

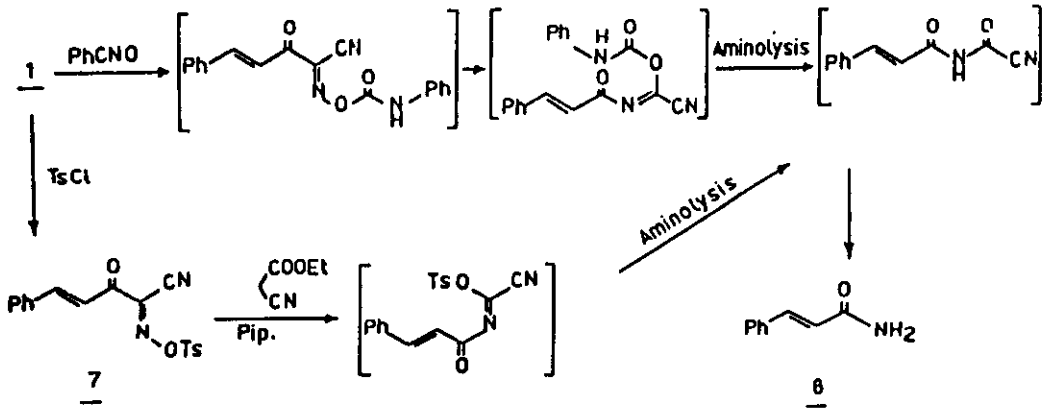
Moreover, its ^{1}H-nmr showed a characteristic signal at δ 6.2 ppm similar to that previously detected for the reported pyrrole (3c).[4] These data could be assigned to the 2-cyano-2-hydroxy-5-phenylpyrrolin-3-one(4).

The behaviour of 4 towards cinnamonitriles (5a,b) was found to be parallel to that of the pyrroles (3a-c). The reaction afforded the corresponding pyrano[2,3-c]pyrroles (6a,b) thus adding further proof to the given structure.

However, the pyrrole formation as in compound (4) could not be explained in terms of a base catalysed Beckmann rearrangement as we have reported concerning the reaction of 1 with ethyl cyanoacetate.[4] A more plausible

mechanism suggesting hydration on the oximino C=N of the starting compound with acidic water - as a nucleophile - followed by self cyclization to the final isolable product (4) could be postulated instead. This interpretation could be also extended to explain the pyrrole formation in compounds (3a-c).

To verify this postulation, the tosylate (7) (prepared by treating 1 with tosyl chloride) reacted with ethyl cyanoacetate under the same experimental conditions previously used to prepare the pyrrole (3c).[4] However, the reaction afforded a colourless product identified as cinnamamide (mp and mixed mp 248-250°C)[8] rather than the reported pyrrole (3c).[4]



Scheme 2

Also, cinnamamide could be detected by tlc when the tosylate (7) was boiled in ethanol/piperidine in absence of ethyl cyanoacetate or when the oxime (1) was treated with phenyl isocyanate.

In all these cases, the cinnamamide could be only explained in terms of a base catalysed Beckmann rearrangement[9] and a mechanistic pathway is suggested in Scheme 2.

Thus, it could be concluded that the polysubstituted pyrroles and the pyrano[2,3-c]pyrroles could be obtained through simple procedures and from an available starting compound.

Table 1. Analytical data for pyrroles (3a-c,4), pyranopyrroles (6a-h) and tosylate (7).

Compound	Solvent of recryst./ colour	mp (°C)	Yield (%)	Mol. formula	Analysis % Calc. / Found C	H	N	S	M^+ m/z
3a	butanol	>300	50	$C_{19}H_{12}N_4O$	73.06	3.87	17.94	-	312
	red				72.85	3.60	17.62	-	
3b	EtOH	224	50	$C_{19}H_{11}N_3OS$	69.28	3.37	12.76	9.73	329
	red				69.07	3.29	12.50	9.48	
3c	EtOH	189	70	$C_{15}H_{12}N_2O_3$	67.15	4.51	10.44	-	268
	red				66.92	4.30	10.16	-	
4	EtOH	262	50	$C_{11}H_8N_2O_2$	65.99	4.03	13.99	-	200
	brown				65.73	3.87	13.65	-	
6a	dioxane	246	50	$C_{20}H_{13}N_3O_2$	73.38	4.00	12.83	-	327
	yellow				73.12	3.82	12.59	-	
6b	EtOH	225	55	$C_{22}H_{18}N_2O_4$	70.57	4.84	7.48	-	374
	yellow				70.38	4.70	7.22	-	
6c	DMF/H_2O	280	40	$C_{29}H_{18}N_6O$	74.66	3.89	18.02	-	466
	brown				74.53	3.70	17.74	-	
6d	dioxane	267	68	$C_{31}H_{23}N_5O_3$	72.50	4.51	13.63	-	513
	brown				72.34	4.22	13.41	-	
6e	dioxane	279	55	$C_{29}H_{17}N_5OS$	72.03	3.54	14.48	6.63	483
	yellow				71.84	3.33	14.21	6.35	
6f	dioxane	232	60	$C_{31}H_{22}N_4O_3S$	70.17	4.18	10.56	6.04	530
	yellow				70.02	3.96	10.28	5.80	
6g	dioxane	256	60	$C_{25}H_{18}N_4O_3$	71.08	4.29	13.26	-	422
	yellow				70.96	4.06	12.98	-	
6h	dioxane	234	65	$C_{27}H_{23}N_3O_5$	69.07	4.93	8.95	-	469
	yellow				68.85	4.71	8.66	-	
7	EtOH	156	70	$C_{18}H_{14}N_2O_4S$	61.00	3.96	7.90	9.04	354
	yellow				60.82	3.76	7.68	8.78	

Table 2. Spectroscopic data for compounds listed in Table 1.

Compound	Ir ν (cm^{-1})	^{1}H-Nmr (DMSO-d_6) δ (ppm)
3a	3250 (NH); 2210 (CN); 1660 (CO)	6.3(s,1H, pyrrole H-4); 7.4(m,2H, benzimidazole H-5 and H-6); 7.6(m, 5H,Ph); 8.0(m,2H,benzimidazole H-4 and H-7); 14.0(br s,1H,NH); 15.8 (br s,1H,OH)
3b	2210 (CN); 1690 (CO)	6.2(s,1H, pyrrole H-4); 7.2-8.0(m, 9H,ArH); 11.3(br s,1H,OH)
4	3400 (OH); 2200 (CN); 1640 (CO hydrogen bonded)	6.2(s,1H, pyrrole H-4); 7.4-7.6(m, 5H,Ph); 8.2(br s,1H,OH); 9.0(br s, 1H,OH).
6a	3400, 3200 (NH_2); 2210 (CN); 1700 (CO)	4.8(s,1H, pyranopyrrole H-4); 7.3-7.9(m,10H,2Ph); 10.9(s,2H,NH_2)
6b	3395,3340 (NH_2); 1710 (CO ester); 1700 (CO pyrrole)	1.2(t,J=7 Hz,3H,CH_3); 4.1(q,J=7 Hz, 2H,CH_2); 4.7(s,1H, pyranopyrrole H-4); 6.5(s,2H,(D_2O) exchangeable NH_2); 7.3-7.9(m,10H,2Ph)
6c	3300-2890 (NH_2 and NH); 2210 (CN)	4.7(s,1H, pyranopyrrole H-4); 7.0 (s,2H,NH_2); 7.4-8.0(m,14H,ArH); 11.2(br s,1H, benzimidazole NH)
6d	3400-2890 (NH_2 and benzimidazole ring NH); 2220 (CN); 1705 (CO); 1680 (C=C)[9]	0.8-1.0(t,J=7 Hz,3H,CH_3); 3.7-3.9 (m,2H,CH_2), 4.4(s,1H, pyranopyrrole H-4); 7.3-8.2(m,16H,ArH and NH_2)
6e	3440, 3300 (NH_2); 2215 (CN)	4.7(s,1H,pyranopyrrole H-4); 7.1 (s,2H,NH_2); 7.4-8.0(m,14H,ArH)
6f	3400, 3280 (NH_2); 2220 (CN); 1705 (CO); 1675 (C=C)	1.0(s,3H,CH_3); 3.8-4.6(m,2H,CH_2); 4.6(s,1H, pyranopyrrole H-4); 7.2-8.2(m,16H,ArH and NH_2)

Table (2) Cont.

Compound	Ir ν (cm^{-1})	^{1}H-Nmr (DMSO-d_6) δ (ppm)
6g	3300-3200 (NH_2); 2200 (CN); 1690 (CO)	1.5(t,J=7 Hz,3H,CH_3); 4.5(q,J=7 Hz, 2H,CH_2); 4.8(s,1H, pyranopyrrole H-4); 7.0(br s,2H,NH_2); 7.4-7.6(m, 10H,ArH)
6h	3400, 3270 (NH_2); 2220 (CN); 1715 (CO); 1705 (CO); 1680 (C=C)	1.0-1.1(2t,J=7 Hz,6H,2CH_3); 3.8-4.2 (m,4H,2CH_2); 4.4(s,1H,pyranopyrrole H-4); 7.4-7.6(m,10H,2C_6H_5); 7.8 (s,2H,NH_2)
7	1705 (CO)	2.8(s,3H,CH_3); 7.4-7.8(m,11H,ArH)

EXPERIMENTAL

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ir spectra (KBr) were determined on a Pye-Unicam SP-1000 spectrophotometer. ^{1}H-Nmr spectra were run on a Varian EM 390 (90 MHz) or a GEMINI-200 spectrometers using tetramethylsilane as an internal reference. The mass spectra were recorded at 70 ev with a Varian MAT 311 A mass spectrometer. Elemental analyses were performed by the Central Service Laboratory in the National Research Centre. Compounds (3c) was prepared according to literature procedure.[4]

Preparation of 2-(1-cyanoarylidene)-3-hydroxy-5-phenylpyrroles (3a,b); 2-amino-3,7-disubstituted 4,5-diphenyl-4H-pyrano[2,3-c]pyrroles (6a-h). General method - A mixture of the oxime (1) (2.0 g, 1 mmol) with each of (2a,b) (1 mmol) or a mixture of each of compounds (3a-c) or (4) (1 mmol) and the nitriles (5a,b) (1 mmol) was refluxed in ethanol (30 ml) in presence of piperidine (1 ml) as a catalyst for 4-5 h. The reaction was then

concentrated, left to precipitate and the solid product obtained was collected and recrystallized (see Table 1).

Concerning the reaction of 1 with 2a no catalyst was added and the product (3a) precipitated from the reaction mixture while hot. Also, in case of the reactions of 3a-c with 5a,b dimethylformamide was used as a solvent instead of ethanol.

Preparation of 2-hydroxy-2-cyano-5-phenylpyrrolin-3-one (4). To a solution of 3-oxo-5-phenyl-4-pentenenitrile (1.7 g, 1 mmol) in dioxane (20 ml) in presence of 33% HCl (1.1 ml), a solution of sodium nitrite (1.7 g in 2 ml H_2O) was added portionwise with stirring at 5°C. After stirring for 2 h, the reaction mixture was left overnight at room temperature. A solid product separated out of the solution, it was filtered off and recrystallized (see Table 1).

Preparation of 1-(O-p-tosylisonitroso)-1-cinnamoylacetonitrile (7). To a stirred solution of the oxime (1) (2.0 g, 1 mmol) and triethylamine (2.0 g, 2 mmol) in dry toluene (40 ml), a solution of tosyl chloride (1.9 g, 1 mmol) in dry toluene (25 ml) was added dropwise over a period of 20 minutes at 25°C and stirring was kept for another 8 h. The solid product was filtered off, washed with H_2O and recrystallized (see Table 1).

Preparation of cinnamamide (8)

Method A

The tosylate (7) (3.2 g, 1 mmol) was refluxed with ethyl cyanoacetate (1.1 g, 1 mmol) in ethanol (50 ml) in presence of piperidine (3 drops) as a catalyst for 4 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 0.1 N hydrochloric acid (5 ml/3 times), 5% sodium bicarbonate solution (5 ml/3 times) then

with water and finally dried over anhydrous sodium sulphate. To the dried solution, n-hexane was added dropwise till it became turbid and left overnight to precipitate. The solid product was filtered off and recrystallized.

Method B

The tosylate (7) (3.2 g, 1 mmol) was refluxed in ethanol (50 ml) in presence of piperidine (3 drops) for 4 h. Tlc (ethyl acetate : n-hexane 1:1 v/v) indicated the presence of 8 and absence of 3c.

Method C

The tosylate (7) (3.2 g, 1 mmol) was refluxed with phenyl isocyanate (1.2 g, 1 mmol) in benzene (40 ml) in presence of triethylamine (1 ml) for 6 h. Tlc of the reaction mixture in ethyl acetate : n-hexane (1:1 v/v) as eluant showed the presence of 8.

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