Pyridazines. XXVI [1]. A Novel Synthesis of Pyrano[2,3-*d*]pyridazines

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A novel approach to the title ring system starting with conveniently available cinnamoylacetonitrile (**1**) is proposed. It involves the Japp-Klingemann reaction of **1** followed by thermally induced cyclisation of hydrazones **2** and subsequent addition of the resulting pyridazine derivatives **3** to 2-substituted cinnamonitriles **4a, 4b**. The structures of the pyrano[2,3-*d*]pyridazines **5a, 5b**, thus obtained, were established on basis of spectroscopic data.

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In the course of a program directed to the synthesis of pyridazines annelated with various five and six membered heterocycles, derivatives of pyrano[2,3-*d*]pyridazines became an object of interest. A search of the literature showed that preparation of this ring system so far was achieved either starting with vicinally disubstituted pyranes [3,4], or by ring-closure reactions of 3-(4-pyridazinyl)acrylic acid derivatives bearing an oxygen-function in position 5 of the diazine system [5,6]. We now report on a novel approach to pyrano[2,3-*d*]pyridazines characterized by addition of tetrahydro-4-oxopyridazines to 2-substituted cinnamonitriles.

α-Methylene ketones have been found to represent suitable precursors for the formation of pyrans as they smoothly react with benzylidenemalononitrile or ethyl benzylidenecyanoacetate, respectively, affording 2-amino-4*H*-pyrans [7,8]. This reaction sequence has also been applied in the synthesis of pyrano[2,3-*c*]pyrazoles [7,9]. According to reports in the literature [10,11,12], appropriately substituted β,γ-unsaturated hydrazones **2a-d** now could be anticipated to cyclize smoothly yielding 4-oxo-1,4,5,6-tetrahydropyridazine-4-carbonitriles **3a-d**.

Thus, 3-oxo-5-phenyl-4-pentenenitrile (**1**), easily available by condensation of ethyl cinnamate with acetonitrile [13], was treated with various aryl diazonium salts in a Japp-Klingemann type reaction, affording the arylhydrazones **2a-d** in nearly quantitative yields [14]. The ir and ^{13}C-nmr spectra (*c.f.* Table 2) of the new compounds unequivocally preclude their existence in enolic forms; furthermore, considering the findings of Prasad *et al.* [15], the marked downfield shift of the N-H resonance signals in the ^{1}H-nmr spectra clearly indicates N-H···O=C bridges. In turn, the hydrazones **2a-d** were found to cyclize simply

Scheme 1

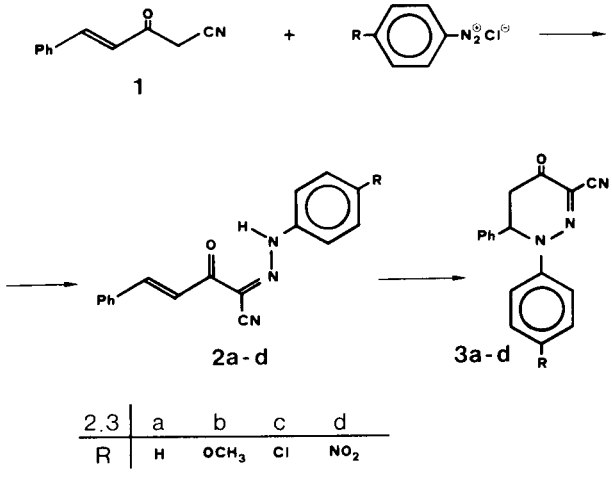


Table 1

2-Arylhyrazono-3-oxo-5-phenyl-4-pentenenitriles **2a-d**

Compound No.	R	% Yield	Mp (°C) [14]	Recrystallisation Solvent	Molecular Formula	Elemental Analyses % Calcd./Found C	H	N
2a	H	97	155-158	MeOH	$C_{17}H_{13}N_3O$	74.17	4.76	15.26
						73.96	4.88	15.35
2b	OCH_3	88	145-148	MeOH	$C_{18}H_{15}N_3O_2$	70.81	4.95	13.76
						70.52	5.10	13.69
2c	Cl	94	148-160	MeOH	$C_{17}H_{12}ClN_3O$	65.92	3.91	13.57
						65.91	4.07	13.59
2d	NO_2	91	181-185	$CHCl_3$	$C_{17}H_{12}N_4O_3$	63.75	3.78	17.49
						63.52	3.91	17.09

Table 2

Spectroscopic Data of Compounds **2a-d**

Compound No.	IR, cm^{-1} ν C=O	ν C≡N	ν N-H	MS m/e (% base peak)	NMR, δ (ppm)
2a	1655	2230	3200	275 (M^+, 45), 198 (100), 131 (40), 103 (33), 77 (56)	^{1}H-nmr [a]: 7.1-7.8 (m, aromatic H, H-4, H-5, 12H), 12.2 (s, NH, 1H, [c]); ^{13}C-nmr [a]: 111.1 (C-2 or C≡N), 114.2 (C≡N or C-2), 116.5 (C-2, C-6 of N-phenyl), 119.7 (C-4), 125.1, 128.7, 129.0, 129.4, 130.6 (C-2, C-3, C-4, C-5, C-6 of C-phenyl, C-3, C-4, C-5 of N-phenyl), 134.4 (C-1 of C-phenyl), 141.9 (C-1 of N-phenyl), 182.6 (C=O)
2b	1655	2230	3200	305 (M^+, 49), 228 (82), 131 (37), 103 (62), 77 (100)	^{1}H-nmr [b]: 3.8 (s, OCH_3, 3H), 6.9-7.9 (m [d], aromatic H, H-4, H-5, 11H), 15.8 (s, NH, 1H [c])
2c	1645	2220	3230 3190	309 (M^+, 21), 232 (56), 131 (52), 103 (89), 77 (100)	^{1}H-nmr [b]: 7.2-7.9 (m [d], aromatic H, H-4, H-5, 11H), 15.3 (s, NH, 1H [c])
2d	1650	2220	3200	320 (M^+, 14), 243 (24), 131 (33), 104 (100), 103 (49), 77 (41)	^{1}H-nmr [a]: 7.2-8.3 (m, aromatic H, H-4, H-5, 11H), 12.5-13.7 (s, NH, 1H [c])

[a] Deuteriodimethylsulfoxide-solution. [b] Deuteriochloroform-solution. [c] Exchangeable with deuterium oxide. [d] Part of the AB-system of H-4/H-5 appears at 7.70-7.87 ppm (**2b** and **2c**), $J_{H\text{-}4/H\text{-}5}$ = 15 Hz, indicating *trans*-configuration in compounds **2**.

Table 3

1-Aryl-4-oxo-6-phenyl-1,4,5,6-tetrahydropyridazine-3-carbonitriles **3a-d**

Compound No.	R	% Yield	Mp (°C)	Recrystallization Solvent	Molecular Formula	Elemental Analyses % Calcd./Found C	H	N
3a	H	91	170-172	1-BuOH	$C_{17}H_{13}N_3O$	74.17	4.76	15.26
						73.97	4.93	15.38
3b	OCH_3	87	126-127	1-PrOH	$C_{18}H_{15}N_3O_2$	70.81	4.95	13.76
						70.85	5.04	13.71
3c	Cl	81	163-165	1-BuOH	$C_{17}H_{12}ClN_3O$	65.92	3.91	13.57
						65.70	4.13	13.30
3d	NO_2	51	153-155	1-PrOH	$C_{17}H_{12}N_4O_3$	63.75	3.78	17.49
						63.83	4.00	17.39

Table 4

Spectroscopic Data of Compounds **3a-d**

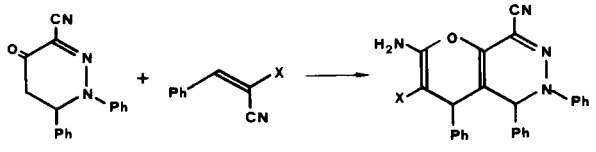
Compound No.	IR, cm^{-1} ν C=O	ν C≡N	MS m/e (% base peak)	NMR, δ (ppm)
3a	1680	2235	275 (M^+, 100), 198 (75), 104 (77), 77 (58)	^{1}H-nmr [b]: 2.8-3.4 (m, H-5, 2H), 5.8-6.0 (m, H-6, 1H), 7.0-7.5 (m, phenyl H, 10H); ^{13}C-nmr [a]: 39.3 (C-5), 60.6 (C-6), 114.2 (C≡N or C-3), 116.4 (C-3 or C≡N), 117.9 (C-2, C-6 of *N*-phenyl), 125.7, 126.3, 128.3, 129.3, 129.5 (C-2, C-3, C-4, C-5, C-6 of *C*-phenyl, C-3, C-4, C-5 of *N*-phenyl), 134.4 (C-1 of *C*-phenyl) 143.6 (C-1 of *N*-phenyl), 181.8 (C=O)
3b	1680	2230	305 (M^+, 34), 228 (17), 173 (38), 121 (100), 104 (25), 77 (35)	^{1}H-nmr [b]: 2.8-3.4 (m, H-5, 2H), 3.8 (s, OCH_3, 3H), 5.8-6.0 (m, H-6, 1H), 6.8-7.5 (m, aromatic H, 9H)
3c	1685	2240	309 (M^+, 11), 232 (12), 104 (36), 47 (100)	^{1}H-nmr [b]: 2.9-3.5 (m, H-5, 2H), 5.8-6.0 (m, H-6, 1H), 7.0-7.5 (m, aromatic H, 9H)
3d	1700	2240	320 (M^+, 28), 243 (41), 104 (100), 77 (19)	^{1}H-nmr [b]: 3.0-3.6 (m, H-5, 2H), 5.9-6.1 (m, H-6, 1H), 7.0-8.3 (m, aromatic H, 9H)

[a] Deuteriodimethylsulfoxide-solution. [b] Deuteriochloroform-solution.

on refluxing in 1-butanol or 1-propanol affording the desired pyridazine derivatives **3a-d** in high yields (*c.f.* Table 3). Similar to the hydrazones **2a-d**, compounds **3a-d** exclusively exist as ketones in solid state as well as in chloroform- or dimethylsulfoxide-solution. This follows unambiguously from ir spectra (ν C=O at 1680-1690 cm^{-1}), ^{13}C-nmr spectra (δ C=O = 181 ppm) and appearance of three-proton-ABX-systems in the ^{1}H-nmr spectra attributable to the CH_2-CH moieties.

As observed in attempts to employ the activated methylene group of compounds **3** in aldol-type condensation reactions with aromatic carbaldehydes, the N-1/C-6 bond in these compounds is split with remarkable ease. Thin layer chromatograms indicate that even on treatment with diluted sodium hydroxide solution at room temperature compounds **3** are converted quantitatively to the starting hydrazones **2**. However, the pyridazine ring proved to be stable on action of weak bases like piperidine. Thus, preparation of pyrano[2,3-*d*]pyridazinedicarbonitrile **5a** could be achieved simply by refluxing **3a** with benzylidenemalononitrile (**4a**) in ethanolic solution in presence of catalytic amounts of piperidine. Application of ethyl benzylidenecyanoacetate (**4b**) instead of **4a** permits easy access to the corresponding ester as examplified in the conversion of **3a** to **5b**.

Scheme 2



3a **4a,b** **5a,b**

4,5	a	b
X	CN	$COOC_2H_5$

Elemental analyses as well as spectroscopic data of compounds **5a,5b** (see Experimental) are in full agreement with the formulated structures. Besides signals of the aromatic protons (7.2-7.5 ppm) and the NH_2-protons (7.1 ppm) the ^{1}H-nmr spectrum of **5a** exhibits only two one-proton-singlets (3.8 and 5.7 ppm). The chemical shift of the downfield signal corresponds well with those of the C-6 protons in compounds **3**, whereas the δ-value of the less deshielded proton is in good accordance with chemical shifts of the C-4 protons in 2-amino-4-phenyl-4*H*-pyrane-3,5-dicarbonitriles [7,8,16,17]. The ^{1}H-nmr spectrum of compound **5b** differs significantly from that of **5a** only with respect to the chemical shift of the NH_2-protons. This, however, easily can be interpreted in terms of interaction of the amino group with the ester carbonyl group. Additionally, the ir spectra of **5a** and **5b** are characterized by strong C=C absorption bands at ~ 1690 cm^{-1}. It is well documented in the literature [16,17,18] that in 2-amino-4*H*-pyrans this type of stretching vibration band occurs at extremely high frequency.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded on a Jasco IRA-1 spectrometer. The ^{1}H-nmr spectra were obtained on a Varian EM 390 (90 MHz) and a Varian WM 250 (250 MHz), the ^{13}C-nmr spectra on a Varian WM 250 (62.9 MHz). Chemical shifts are reported in ppm from TMS as an internal standard and are given in δ units. Electron impact mass spectra were obtained at 70 eV using a Varian MAT CH-7. For analytical tlc, DC-Alufolien, Kieselgel 60F254 (Merck) were used, preparative separations were performed using PSC-Fertigplatten (20 × 20 cm), Kieselgel 60F254 (Merck).

General Procedure for the Preparation of 2-Arylhydrazono-3-oxo-5-phenyl-4-pentenenitriles **2a-d**.

To a stirred suspension of 10 mmoles of aniline, 4-methoxyaniline, 4-chloroaniline or 4-nitroaniline in 5 ml of 6*N* hydrochloric acid a solution of 0.69 g (10 mmoles) of sodium nitrite in 5 ml of water was added over a period of 15 minutes, keeping the temperature of the reaction mixture at 0-5°. After stirring for additional 5 minutes the diazonium salt solution was poured into a cooled mixture of 1.71 g (10 mmoles) **1** and 5 g of sodium acetate trihydrate in 30 ml of dioxane. The resulting mixture was stirred for 30 minutes, then 100 ml of water was added. The precipitate was filtered with suction, washed several times with water and dried *in vacuo* at 40-50°. The products thus obtained were employed for the synthesis of compounds **3a-d** without further purification. Analytical samples were obtained by recrystallisation (*c.f.* Table 1). Melting points, yields and analytical data were summarized in Table 1, for spectroscopic data see Table 2.

General Procedure for the Preparation of 1-Aryl-4-oxo-6-phenyl-1,4,5,6-tetrahydropyridazine-3-carbonitriles **3a-d**.

A mixture of 10 mmoles of **2a, 2c, 2d** and 150 ml of 1-butanol or 10 mmoles of **2b** and 200 ml of 1-propanol was refluxed for 1.5 hours. To obtain **3a-c** half of the solvent was evaporated *in vacuo*. The precipitates obtained on cooling were washed with 1-butanol and dried *in vacuo*. To isolate **3d** the solvent was removed completely and the residue was filtered over a short column packed with silica gel using dichloromethane as eluent. Yields, melting points, recrystallisation solvents and analytical data are summarized in Table 3, for spectroscopic data see Table 4.

2-Amino-5,6-dihydro-4,5,6-triphenyl-4*H*-pyrano[2,3-*d*]pyridazine-3,8-dicarbonitrile (**5a**).

A mixture of 137.5 mg (0.5 mmoles) of **3a**, 77 mg (0.5 mmoles) of **4a** and one drop of piperidine in 8 ml of absolute ethanol was refluxed for 2 hours. The residue obtained after evaporation *in vacuo* was subjected to preparative tlc using dichloromethane-ethyl acetate 15:1 as eluent. The product obtained was recrystallized from ethanol yielding 75 mg (35%) of orange-yellow crystals, mp 220° dec; ^{1}H-nmr (deuteriodimethylsulfoxide): δ 3.8 (s, H-4, 1H), 5.7 (s, H-5, 1H), 7.1 (s, NH_2, 2H), 7.2-7.5 (m, phenyl H, 15H); ir: cm^{-1} 1640, 1695 (C=C), 2200, 2240 (C≡N), 3320, 3470 (N-H); ms: m/e 429 (M^+, 13), 352 (37), 287 (11), 191 (10), 77 (100).

Anal. Calcd. for $C_{27}H_{19}N_5O$: C, 75.51; H, 4.46; N, 16.31. Found: C, 75.43; H, 4.57; N, 16.28.

Ethyl 2-Amino-8-cyano-5,6-dihydro-4,5,6-triphenyl-4*H*-pyrano[2,3-*d*]pyridazine-3-carboxylate (**5b**).

A mixture of 137.5 mg (0.5 mmoles) of **3a** and 100.5 mg (0.5 mmoles) of **4b** was reacted as described in preparation of **5a**. Purification of the crude reaction product was achieved by preparative tlc, using dichloromethane as eluent. Recrystallisation from ethanol yielded 110 mg (46%) of yellow crystals, mp 224-228° dec; ^{1}H-nmr (deuteriodimethylsulfoxide): δ 0.8-1.0 (m, CH_3, 3H), 3.7-4.0 (m [19], CH_2, 2H), 4.0 (s, H-4, 1H), 5.6 (s, H-5, 1H), 7.2-7.5 (m, phenyl H, 15H), 7.8 (s, NH_2, 2H); ir: cm^{-1} 1620, 1680 (C=C), 1700 (C=O), 2240 (C≡N), 3300, 3410 (N-H); ms: m/e 476 (M^+, 17), 400 (11), 399 (39), 286 (10), 77 (100).

Anal. Calcd. for $C_{29}H_{24}N_4O_3$: C, 73.08; H, 5.08; N, 11.76. Found: C, 72.94; H, 5.19; N, 11.82.

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[14] Analytically pure samples of compounds **2** show relatively large melting intervals due to cyclisation reactions taking place at elevated temperatures.

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[19] Due to the chirality of the C-4 atom of the ring system, the protons of the ester-ethyl group form an ABX_3-system.