α, β-Unsaturated Nitriles in Heterocyclic Synthesis:

Synthesis of Several Arylpyridine and Arylpyridazine Derivatives

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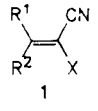
Several new azabiaryls and diazabiaryls were synthesized utilizing readily obtainable α,β-unsaturated nitriles.

α,β-Ungesättigte Nitrile für die Heterocyclen-Synthese: Synthese einiger Arylpyridine und Arylpyridazine

Einige neue Azabiaryle und Diazabiaryle wurden aus leicht zugänglichen α,β-ungesättigten Nitrilen hergestellt.

Several pyridazines and pyridines are well known to be active as herbicides[1]. For example, 1-aryl-4-alkylamino-5-chloropyridazin-6-ones are used as herbicide especially for cotton[2]. Moreover, several azabiaryls (e.g. Diquat) are widely applied as herbicide in spite of its toxicity to mammals[3]. Since toxicity is a major problem with Dequat it was thought of value to prepare less toxic and similarly effective herbicides. In the present paper we report synthesis of several pyridazines and azabiaryls of potential herbicidal activity utilizing readily obtainable nitriles.



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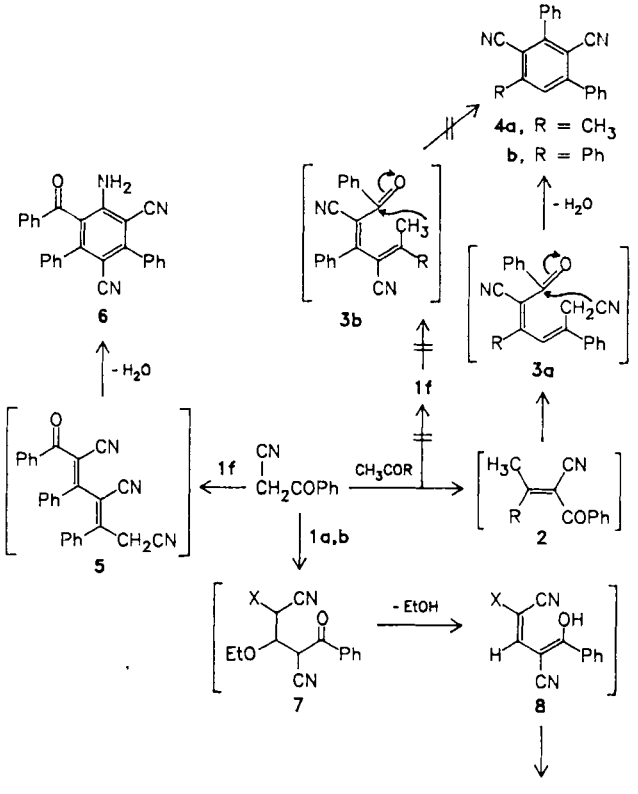
	R^1	R^2	X
a	H	OC_2H_5	CN
b	H	OC_2H_5	COOEt
c	CH_3	CH_2COOEt	CN
d	CH_3	CH_2COOEt	COOEt
e	Ph	CH_2CN	CN
f	Ph	CH_2CN	COPh

The α,β-unsaturated nitriles **1a-f** were selected as starting materials. Lit. survey revealed that the α,β-unsaturated nitriles **2** have not yet been prepared. Attempted preparation of **2** utilizing the reaction of benzoylacetonitrile with aliphatic ketones failed, because under these conditions the formed **2** cyclised into the benzene derivative **4**. The structure of **4a** was confirmed from the MS ($M^{+\cdot}$ at m/z 294) and ^{1}H-NMR-spectra which revealed signals for aryl and methyl protons. Formation of **4a** is assumed to proceed via **2** which condenses with benzoylacetonitrile to yield the diene **3a** which cyclises into the finally isolable **4a**.

If was prepared by heating benzoylacetonitrile with catalytic amounts of ammonium acetate in absence of a solvent at 120°C. Attempts to effect self condensation of benzoylacetonitrile by refluxing in boiling pyridine afforded a product of molecular formula $C_{27}H_{17}N_3O$ ($M^{+\cdot}$ at m/z 399).



Structure **6** was established for this product and is assumed to be formed via **5**.

Compunds **1a,b** reacted with benzoylacetonitrile to yield condensation products by ethanol elimination. four possible isomeric structures **8-11** were considered. The acyclic structure **8** and the pyran **9** were readily ruled out based on ^{1}H-NMR spectra which revealed one proton signal at δ = 8.3 ppm. This signal can be only interpreted in terms of the pyridine structure **11** or possible tautomers **12** and **13**[4]. The

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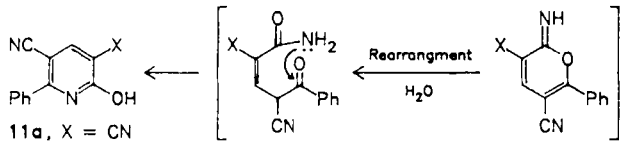
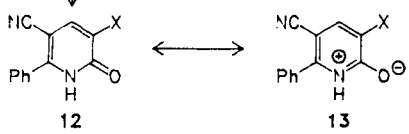
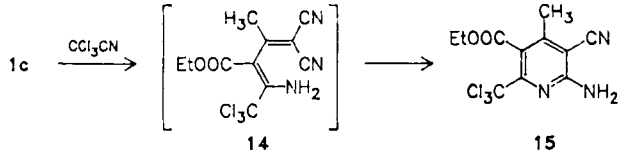
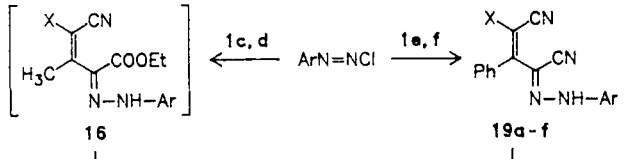
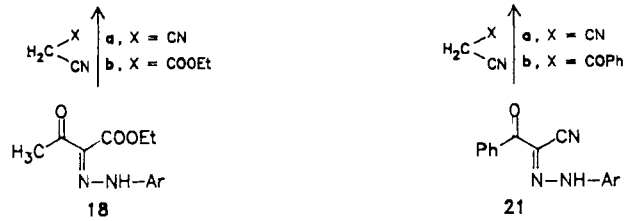






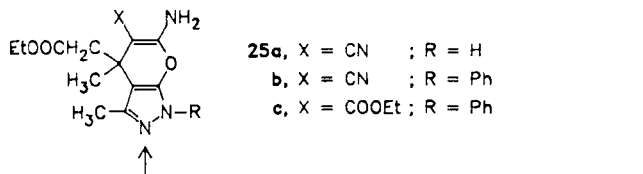


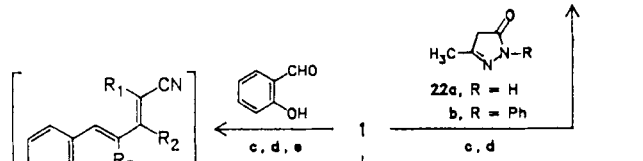


17a-f	20a-f	21a-f
a, X = NH; Ar = C_6H_4Cl-p	a, X = CN ; Ar = C_6H_4Cl-p	
b, X = NH; Ar = $C_6H_4NO_2$-p	b, X = CN ; Ar = $C_6H_4CH_3$-p	
c, X = NH; Ar = $C_6H_4OCH_3$-p	c, X = CN ; Ar = $C_6H_4OCH_3$-p	
d, X = O ; Ar = C_6H_4Cl-p	d, X = COPh; Ar = C_6H_4Cl-p	
e, X = O ; Ar = $C_6H_4NO_2$-p	e, X = COPh; Ar = $C_6H_4CH_3$-p	
f, X = O ; Ar = $C_6H_4OCH_3$-p	f, X = COPh; Ar = $C_6H_4OCH_3$-p	

formation of **11** from **1a,b** and benzoylacetonitrile is assumed to proceed by addition of benzoylacetonitrile to **1a,b** to yield the *Michael* adduct **7**. This loses ethanol affording **8** which would cyclise simultaneously into **9**.Rearrangement of **9** under basic conditions affords the finally isolable stable pyridine **11**.Rearrangement of pyrans into pyridines under basic reaction conditions has been reported [5].

1c reacts with trichloroacetonitrile to yield the pyridine **15**.





	R_1	R_2	X
a	CN	CH_3	O
b	COOEt	CH_3	O
c	CN	Ph	NH

Compounds **1c,d** coupled with aryldiazonium salts to yield pyridazines, formed via arylhydrazone derivatives. This, **1c,d** afforded directly the pyridazines **17a-c** and the pyridazinones **17d-f**. On the other hand, **1e,f** coupled to yield hydrazones **19** which could be cyclised into the corresponding pyridazineimines **20**. The overall yield of pyridazines in these reactions is very low. Thus, these compounds were synthesized alternatively by condensation of the arylhydrazones **21** with active methylene reagents.

Formation of pyranoazoles from reaction of α,β-unsaturated nitriles with pyrazolones has been reported [6]. Similarly, **1c,d** react with pyrazolones **22** to yield the pyrano[2,3-c]pyrazole derivatives **25**. Aminopyrazole **26** reacted with **1c** to yield the pyrazolo[1,5-a]pyrimidine derivative **27**. Compounds **1c,d,e** reacted with salicylaldehyde to yield the coumarine derivatives **29-c**.

These results indicate that compunds **1a-f** can be utilized as starting materials for the synthesis of several, otherwise not easily accessible, heterocyclic derivatives.

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Table 1: List of compounds **17a-f, 19a-f, 20a-f, 25a-c** and **31a-c**.

Compound	Solv.of	M.P.	Yield	Mol. fomula	Found Calcd. %		
(Colour)	cryst.	(°C)	(%)	(Mol. weight)	C	H	N
17a	EtOH	164-66	90	$C_{15}H_{13}ClN_4O_2$	56.5	4.5	17.3
(yellow)				(316.5)	56.9	4.1	17.7
17b	EtOH	188-90	85	$C_{15}H_{13}N_5O_4$	55.3	4.2	21.2
(yellow)				(327)	55.1	4.0	21.4
17c	EtOH	130-32	80	$C_{16}H_{16}N_4O_3$	61.6	5.4	18.4
(yellow)				(312)	61.5	5.1	18.0
17d	EtOH	152-54	82	$C_{15}H_{12}ClN_3O_3$	56.5	4.4	13.0
(yellow)				(317.5)	56.7	4.9	13.2
17e	EtOH	130-32	80	$C_{15}H_{12}N_4O_5$	54.4	4.3	16.7
(yellow)				(328)	54.9	3.9	17.1
17f	EtOH	153-55	85	$C_{16}H_{15}N_3O_4$	61.5	5.0	13.7
(yellow)				(313)	61.3	4.8	13.4
19a	EtOH	200-02	85	$C_{18}H_{10}ClN_5$	64.8	2.8	20.9
(yellow)				(331.5)	65.2	3.0	21.1
19b	EtOH	238-40	88	$C_{19}H_{13}N_5$	73.0	4.0	22.1
(brown)				(311)	73.3	4.2	22.5
19c	EtOH	180-82	83	$C_{19}H_{13}N_5O$	70.0	4.2	21.7
(brown)				(327)	69.7	4.0	21.4
19d	EtOH	194-96	75	$C_{24}H_{15}ClN_4O$	70.5	4.1	13.9
(orange)				(410.5)	70.2	3.7	13.6
19e	EtOH	213-15	95	$C_{25}H_{18}N_4O$	77.2	5.0	14.6
(yellow)				(390)	76.9	4.6	14.4
19f	EtOH	158-60	90	$C_{25}H_{18}N_4O_2$	74.2	4.8	13.5
(yellow)				(406)	73.9	4.4	13.8
20a	AcOH	233-35	77	$C_{18}H_{10}ClN_5$	65.6	3.4	21.4
(brown)				(331.5)	65.2	3.0	21.1
20b	AcOH	190-95	70	$C_{19}H_{13}N_5$	73.0	4.0	22.1
(brown)				(311)	73.3	4.2	22.5
20c	AcOH	148-50	85	$C_{19}H_{13}N_5O$	69.4	3.7	21.0
(brown)				(327)	69.7	4.0	21.4
20d	EtOH	194-96	70	$C_{24}H_{15}ClN_4O$	70.4	4.0	14.0
(yellow)				(410.5)	70.2	3.7	13.6
20e	EtOH	213-15	65	$C_{25}H_{18}N_4O$	77.0	5.0	14.3
(yellow)				(390)	76.9	4.6	14.4
20f	EtOH	213-15	60	$C_{25}H_{18}N_4O_2$	73.6	4.1	13.6
(yellow)				(406)	73.9	4.4	13.8
25a	EtOH	198-200	75	$C_{13}H_{18}N_4O_3$	56.3	5.5	19.9
(colourless)				(276)	56.5	5.8	20.3
25b	EtOH	132-34	85	$C_{19}H_{20}N_4O_3$	64.8	6.0	16.2
(colourless)				(352)	64.8	5.7	15.9
25c	EtOH	136-38	79	$C_{21}H_{25}N_3O_5$	62.9	5.9	10.1
(yellow)				(399)	63.2	6.3	10.5
29a	EtOH	187-90	70	$C_{14}H_8N_2O_2$	70.8	3.1	11.5
(yellow)				(236)	71.2	3.4	11.9
29b	EtOH	192-94	65	$C_{16}H_{13}NO_4$	67.5	4.8	4.7
(yellow)				(283)	67.8	4.6	5.0
29c	EtOH	208-10	70	$C_{19}H_{11}N_3O$	76.8	4.1	13.7
(yellow)				(297)	76.8	3.7	14.1

Experimental Part

Melting points: uncorrected. - IR spectra (KBR): Pye Unicam Sp-1000 spectrophotometer. - ^{1}H-NMR spectra: Varian EM-390 90 MHz spectrometer, DMSO as solvent, TMS as int. reference. Chemical shifts in δ units (ppm). - Mass spectra: Mass spectrometer MS 30 (AEI), at 70 eV. in the Institut für Organische Chemie, Universität Darmstadt, West Germany. - Analytical data: Microanalytical Centre at Cairo University, Egypt. - Compounds **1a-d** were prepared following lit. procedures[7-9].

Propanonitrile derivatives **1e,f**

1e: A mixture of malononitrile (0.01 mol) and benzoylacetonitrile (0.01 mol) in pyridine (30 ml) was refluxed for 3 h. The solvent was evaporated under vacuum and the resulting solid product was collected by filteration and crystallised from ethanol: brown powder, yield 95%, m.p. 70-71°C. - IR: 2230; 2220; 2210 (3CN). - ^{1}H-NMR: 4.02 (s, br, 2H, CH_2), 7.55 (s, 5H, C_6H_5). - $C_{12}H_7N_3$ (193) Calcd. C 74.6 H 3.6 N 21.8. Found C 74.9 H 4.0 N 22.0.

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

Compound	IR (cm^{-1})(KBr)	^{1}H-NMR (δ ppm)
17b	3500-3300 (NH); 2220 (CN); 1730 (CO)	1.22 (t, 3H, CH_3), 2.68 (s, 3H, CH_3), 4.24 (q, 2H, CH_2), 7.82-7.99 (m, 2H, phenyl H), 8.32-8.44 (m, 2H, phenyl H).
17f	2210 (CN); 1725 (CO); 1680 (CO ring)	1.38 (t, 3H, CH_3); 2.71 (s, 3H, CH_3); 4.82 (s, 3H, OCH_3); 4.48 (q, 2H, CH_2); 6.90-7.09 (m,2H, phenyl H); 7.51-7.68 (m, 2H, phenyl H).
19a	3300 (NH); 2210 (CN)	
20a	3350 (NH); 2220 (CN)	5.23 (s, br, 1H, NH); 7.49-7.88 (m, 9H, phenyl H).
25b	3450; 3350 (NH_2); 2210 (CN); 1710 (CO)	1.12 (t, 3H, CH_3); 1.52 (s, 3H, CH_3), 2.32 (s, 2H, CH_3); 2.67 (s, 2H, CH_2); 4.88 (s, br, 2H, NH_2), 7.22-7.68 (m, 5H, C_6H_5).
29b	2220 (CN); 1750 (CO); 1710 (CO).	1.33 (t, 3H, CH_3), 3.22 (s, 3H, CH_3); 4.24 (q, 2H, CH_2); 5.99 (s, 1H, pyran-H); 7.42-7.77 (m, 4H, aromatic H).

1f: To a solution of benzoylacetonitrile (0.01 mol) in acetic acid (30 ml) were added 2.0 g ammonium acetate. The mixture was refluxed for 4 h. Evaporation of most of acetic acid left a solid residue which was recrystallised from ethanol: yellow crystals, yield 70%, m.p. 160-62°C. - IR: 2220 (CN); 1670 (CO). - ^{1}H-NMR: 7.22-7.77 (m, 11H, 2 C_6H_5, ylidenic CH. - $C_{18}H_{12}N_2O$ (272) Calcd C 79.4 H 4.4 N 10.3). Found C 79.9 H 4.6 N 10.

4-Substituted-2,6-diphenylbenzo-1,3-dicarbonitriles **4a,b**

To 20 ml of dry benzene in a flask containing acetone or acetophenone (0.05 mol), 0.5 g of ammonium acetate and 12 ml of glacial acetic acid, were added 7.25 g (0.05 mol) of benzoylacetonitrile. The mixture was refluxed for 6 h in a device for constant removal of the water formed in the reaction. Evaporation of benzene left a solid product which was recrystallised from ethanol.

4a: yellow crystals, yield 76%, m.p. 260-62°C. - IR: 2220 (CN). - ^{1}H-NMR: 1.52 (s, 3H, CH_3), 7.34-7.68 (m, 11H, phenyl-H) - $C_{21}H_{14}N_2$ (294) MS: m/z 294 ($M^{+\cdot}$). Calcd. C 85.7 H 4.8 N 9.5. - Found C 85.7 H 4.8 N 9.2.

4b: yellow crystals, yield 65%, m.p. 248-50°C. - IR: 2220 (CN). - $C_{26}H_{16}N_2$ (356). Calcd. C 87.6 H 4.5 N 7.9. Found C 87.2 H 4.4 N 8.0.

6-Amino-5-benzoyl-2,4-diphenylbenzo-1,3-dicarbonitrile(**6**)

Benzoylacetonitrile (0.01 mol) in pyridine (30 ml) was refluxed for 3 h. The solvent was evaporated under vacuum and the solid product was collected and crystallised from ethanol. 6 formed yellow crystals, yield 60%, m.p. 285-87°C. - IR: 3300-3100 (NH_2); 2220; 2215 (CN); 1670 (CO). - ^{1}H-NMR: 7.44-8.04 (m, 17H, 3 C_6H_5 and NH_2). $C_{27}H_{17}NO$ (399) MS: m/z 399 ($M^{+\cdot}$) Calcd. C 81.2 H 4.3 N 10.5. Found C. 81.0 H 4.4 N 10.8.

3-substituted-2-hydroxy-6-phenylpyridine-5-carbonitriles **11a,b**

A suspension of benzoylacetonitrile (0.01 mol) in EtOH (30 ml) was treated with ethoxymethylenemalononitrile or ethyl ethoxymethylenecyanoacetate (0.01 mol) and two drops of piperidine. The mixture was refluxed for 6 h and then left to cool at room temp. The crystals, separated on cooling, were crystallised from ethanol. **11a**: colourless crystals, yield 90%, m.p. 256-58°C. - IR: 3500-3400 (OH); 2220 (CN). - ^{1}H-NMR: 4.78 (s, br, 1H, OH); 7.52-7.77 (m, 5H, C_6H_5; 7.98 (s, 1H, pyridine-H). - $C_{13}H_7N_3O$ (221) Calcd. C 70.6 H 3.2 N 19.0. Found C 70.4 H 3.0 N 18.6.

11b: colourless crystals, yield 90%, m.p. 212-14°C. - IR: 3500 (OH); 2220 (CN); 1700 (CO). - ^{1}H-NMR: 1.33 (t, 3H, CH_3); 3.34 (s, br, 1H, OH); 4.23 (q, 2H, CH_2); 7.67-7.88 (m, 5H, C_6H_5), 8.35 (s, 1H, pyridine-H). - $C_{15}H_{12}N_2O_3$ (268) MS: m/z 268 ($M^{+\cdot}$) Calcd. C 67.2 H 4.5 N 10.5. Found C 67.5 H 4.1 N 10.2.

Ethyl 2-amino-3-cyano-4-methyl-6-trichloromethylpyridine-5-carboxylate (**15**)

To a solution of 1c (0.01 mol) in EtOH (30 ml), trichloroacetonitrile (0.01 mol) and two drops of piperidine were added. The mixture was refluxed for 6 h. The resulting solid was collected by filtration.

15: colourless crystals from ethanol, yield 73%, m.p. 226-28°C. - IR: 3330 (NH_2); 2220 (CN); 1680-1660 (CO). - $C_{11}H_{10}N_3O_2Cl_3$ (322.5). Calcd. C 40.9 H 3.1 N 13.0. Found C 41.2 H 3.5 N 12.6.

Ethyl 2-aryl-4-cyano-5-methyl1-2,3-dihydro-pyridazin-6-carboxylates **17a-f**

A solution of **1c,d** (0.01 mol) in ethanol (100 ml) containing sodium acetate (3 g) was cooled to 0°C, stirred and treated gradually with a cooled solution of aryldiazonium chloride (prepared from 0.01 mol of amine and the appropriate quantities of HCl and $NaNO_2$. the solid product formed on standing was collected and crystallised from the proper solvent (cf. Tables 1 and 2).

1-substituted-3-arylhydrazono-1,3-dicyano-2-phenyl-pent-2-enes **19a-f**

The above experimental procedure was followed (cf. Tables 1 and 2)

4-substituted-2,3-dihydro-imino-2-phenyl-pyridazin-6-carbonitriles **20a-f**

A suspension of **19a-f** (0.01) mol in AcOH (30 ml) was refluxed for 3 h and then evaporated under vacuum. The resulting solid product was collected and crystallised from the proper solvent (cf. Tables 1 and 2).

Pyrano[2,3-c]pyrazoles **25a-c**

A suspension of **1c,d** (0.01 mol) in EtOH (30 ml) was treated with 3-methylpyrazol-5-one (0.01 mol) and a few drops of piperidine. The mixture was refluxed for 5 h. The resulting solid product was collected (cf. Tables 1 and 2).

5-Amino-4,7-dihydro-7-ethoxycarbonylmethyl-7-methyl-2-phenyl-pyrazolo[1,5-a]pyrimidine-6-carbonitrile (**27**)

The above experimental procedure was followed. 27 formed yellow crystals from ethanol, yield 85%, m.p. 132-34C. - IR: 3400; 3300 (NH_2); 2220 (CN). - $C_{18}H_{19}N_5O_2$ (337). Calcd. C 64.1 H 5.2 N 20.8. Found C 64.1 H 5.6 N 21.0.

Coumarin-3-ylcrotonitrile derivatives **29a-c**

To a solution of each of **1c,d,e** (0.01 mol) in EtOH (30 ml), salicylaldehyde (0.01 mol) and two drops of piperidine were added. The mixture was refluxed for 5 h and the resulting solid product was collected and crystallised from the proper solvent (cf. Tables 1 and 2).

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