4-NITRO- AND 4-CYANOPYRIDAZINES

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Abstract - 3-Aryl-1,2,4,5-tetrazines react with 1-nitro-2-dimethylaminoethene and 1-cyano-2-morpholinoethene by an inverse electron demand Diels-Alder reaction to give, after elimination of nitrogen and the secondary amine, the corresponding 3-aryl-5-nitro- and 3-aryl-5-cyanopyridazines. Besides these compounds, 1-benzylidene-2-dialkylaminomethylenehydrazines were isolated. They are also obtained from reaction of the 3-aryl-1,2,4,5-tetrazines with secondary aliphatic amines. Tetrazines with two electron-withdrawing groups like 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine, 3,6-bis(4-pyridyl)-1,2,4,5-tetrazine and 3,6-bis(piperidinocarbonyl)-1,2,4,5-tetrazine also react with the nitro- or cyanoenamine to give the corresponding 3,6-disubstituted 4-nitro- or 4-cyanopyridazines.

Nitropyridazines are usually not easily accessible. Direct introduction of the nitro group by nitration is limited to compounds containing strong electron-releasing groups, usually pyridazinones and pyridazine N-oxides.[1] Preparation of nitropyridazines from non-cyclic synthons containing the nitro-group has also been achieved.[2,3]

Only a limited number of 4-cyanopyridazines have been described in the literature; they are prepared either from a cyano group containing non-cyclic starting material, by dehydration of a pyridazinecarboxamide[4] or in very low yield by reaction of a pyridazine with dimethyl sulfate, followed by treatment with potassium cyanide.[5] In two reports the synthesis of a 4-cyanopyridazine is described by bichromate oxidation of a dihydropyridazine, obtained from a tetrazine by reaction with acrylonitrile.[6,7]

Many 1,2,4,5-tetrazines give inverse electron demand Diels-Alder reactions with a wide range of dienophiles.[7] Dihydropyridazines are formed with alkenes. With an enamine, however, elimination of an amine from the formed aminodihydropyridazine may occur leading to a pyridazine.

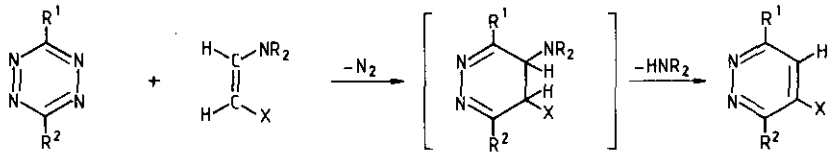
Our recent interest in the reactions of 5-nitropyrimidines with enamines and ynamines,[8] induced us to study the cycloaddition of 1,2,4,5-tetrazines with cyano- and nitroenamines. In this paper we report an elegant synthesis of several 4-nitro- and 4-cyanopyridazines by this cycloaddition.

RESULTS AND DISCUSSION

The 3-aryl-1,2,4,5-tetrazines (**1a-d**) were found to react easily with 1-nitro-2-dimethylaminoethene (**2**) or 1-cyano-2-morpholinoethene (**3**) in refluxing dioxane to give products, which were proven to be 3-aryl-5-nitropyridazines (**4a-d**) or 3-aryl-5-cyanopyridazines (**5a-d**) respectively. The presence of the nitro- or cyano group was clearly evidenced by the CN- or NO_2-absorption frequencies in the infrared spectra. The ^1H nmr coupling constants for the two pyridazine hydrogens are of the magnitude of 1.5-2.5 Hz, indicating that these hydrogens are in a meta position. No trace of the isomeric 3-aryl-4-nitro- or 3-aryl-4-cyanopyridazines was found, showing that the reaction is regioselective. The rules governing the regioselectively of these inverse electron demand Diels-Alder reactions are not quite clear at present, but secondary orbital overlap effects probably play an important role.[9]

A second type of products can be isolated from the reaction of the 3-aryl-1,2,4,5-tetrazines (**1a-d**) with enamines (**2**) and (**3**) by preparative tlc. These compounds were identified as 1-benzylidene-2-dialkylaminoethylenehydrazines (**6**) and are probably formed by reaction of the tetrazines (**1a-d**) with the secondary amine liberated during the conversion of (**1**) into the nitro- or cyanopyridazines (**4**) or (**5**) (see Scheme 1). We found that reaction of the secondary aliphatic amines; dimethylamine and morpholine, with 3-aryl-1,2,4,5-tetrazines in refluxing chloroform does indeed give the 1-benzylidene-2-dialkylaminomethylenehydrazines (**6**) in high yield. The first step in this reaction is probably a reversible addition of the secondary amine to the unsubstituted 6-position of the tetrazine, followed by elimination of nitrogen (see Scheme 2). With ammonia or primary aliphatic amines this addition reaction is known to occur easily at low temperature without loss of

Scheme 1



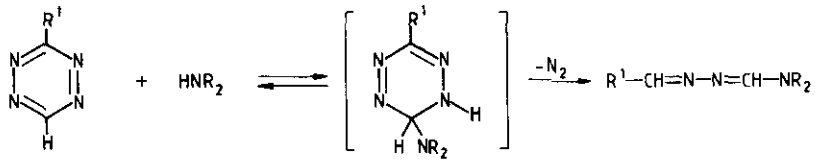
1 **2**, X=NO_2, R=CH_3; **3**, X=CN, R_2=C_4H_8O **4**, X=NO_2; **5**, X=CN

a, R^1=C_6H_5, R^2=H
b, R^1=p-Br-C_6H_4, R^2=H
c, R^1=p-CH_3-C_6H_4, R^2=H
d, R^1=p-OCH_3-C_6H_4, R^2=H
e, R^1=R^2=2-pyridyl
f, R^1=R^2=4-pyridyl
g, R^1=R^2-piperidinocarbonyl

nitrogen.[10] Only a few 1-benzylidene-2-dialkylaminomethylenehydrazines have been described in the literature.[11,12,13] The present synthesis offers a new and facile route to this type of compounds.

In order to avoid the occurrence of these side reactions initiated by the addition of the amine to the unsubstituted C_6-position, we extended our study to reactions of 3,6-disubstituted tetrazines with (**2**) and (**3**). These reactions show that the ring transformations are strongly influenced by the nature of the substituents on the tetrazine. The 3,6-bis(2-pyridyl) and 3,6-bis(4-pyridyl)-1,2,4,5-tetrazines (**1e-f**) react to form the corresponding 3,6-diaryl-4-nitropyridazines (**4e-f**) and 3,6-diaryl-4-cyanopyridazines (**5e-f**), respectively, but 3,6-bis(3-pyridyl)-tetrazines, 3,6-dimethyltetrazine, 3,6-diphenyltetrazine and 3,6-dibenzyltetrazine, failed to react with the enamines (**2**) and (**3**), even at higher reaction temperatures and prolonged reaction times. However, 3,6-bis-(piperidinocarbonyl)tetrazine

Scheme 2



1a-d **6**

Comp.	mp (°C)	Yield of isolated products (%)	mol. form.	Analysis obs. calcd. %C	Analysis obs. calcd. %H	MS (m/e) obs. calcd	^{1}H nmr ($CDCl_3$) H6	^{1}H nmr ($CDCl_3$) H4,5	^{13}C nmr ($CDCl_3$) C4,5 ($^1J_{C-H}$)	^{13}C nmr ($CDCl_3$) C6 ($^1J_{C-H}$)
4a	166–167	42	$C_{10}H_7N_3O_2$	59.80 59.70	3.39 3.51	201.054 201.054	9.82	8.49	115.5(174)	141.6(194)
4b	206–207	46	$C_{10}H_6BrN_3O_2$	43.12 42.88	2.18 2.16	-	9.90	8.90	115.3(174)	141.8(194)
4c	198–200	45	$C_{11}H_9N_3O_2$	61.41 61.39	4.30 4.21	-	9.80	8.45	115.2(176)	141.3(196)
4d	154–155	41	$C_{11}H_9N_3O_3$	56.85 57.14	3.97 3.92	-	9.72	8.38	114.7(174)	140.9(192)
4e	159–160	34	$C_{14}H_9N_5O_2$	60.11 60.21	3.39 3.25	279.076 279.076	-	8.82	117.9(175)	-
4f	198(d)	32	$C_{14}H_9N_5O_2$	60.36 60.21	3.36 3.25	279.076 279.076	-	8.30	117.0(174)	-
4g	oil	39	$C_{16}H_{21}N_5O_4$	-	-	347.160 347.159	-	8.40	121.7(180)	-
5a	193–194	36	$C_{11}H_7N_3$	73.18 72.91	3.82 3.89	-	9.30	8.09	125.2(170)	148.3(192)
5b	241–242	48	$C_{11}H_6BrN_3$	50.89 50.79	2.27 2.33	-	9.62	8.87	129.4(170)	149.8(194)
5c	209–210	52	$C_{12}H_9N_3$	73.97 73.83	4.46 4.65	-	9.28	8.05	124.9(172)	148.1(192)
5d	201–202	40	$C_{12}H_9N_3O$	68.49 68.23	4.35 4.30	-	9.21	7.99	124.4(171)	147.6(191)
5e	203–204 (206–207[6])	60	$C_{15}H_9N_5$	69.30 69.49	3.51 3.50	259.086 259.086	-	9.00	129.8(176)	-
5f	201–202	56	$C_{15}H_9N_5$	69.14 69.49	3.57 3.50	-	-	8.32	127.4(172)	-
5g	135–136	55	$C_{17}H_{21}N_5O_2$	62.42 62.36	6.53 6.47	327.169 327.170	-	8.18	131.0(178)	-

(**1g**) reacted smoothly with the enamines, indicating that the presence of electron-withdrawing substituents at the 3 and 6 position of the disubstituted tetrazines is a prerequisite for reaction with the enamines (**2**) and (**3**).

EXPERIMENTAL SECTION

Melting points are uncorrected. The ^{1}H nmr spectra (deuteriochloroform) were recorded with a Varian EM-390 90-MHz spectrometer using tetramethylsilane as internal reference. ^{13}C nmr spectra were recorded with a Bruker CXP-300 spectrometer. Mass spectra were obtained with a JEOL JMS-D-100 spectrometer. Infrared spectra were recorded on a Hitachi EPI-G3 or a JASCO A-100 spectrophotometer.

*Synthesis of the 3-aryl-5-nitropyridazines (**4a-d**) and the 3-aryl-5-cyanopyridazines (**5a-d**).* A stirred solution of 1.0 mmole of the tetrazine (**1a-e**)[14] and 1.3 mmole of the enamine (**2**)[15] or (**3**)[16] in 5 ml of dry dioxane was refluxed until the red color of the tetrazine had completely disappeared. Reaction times ranged from 1 to 3 days. After removal of the solvent, the pyridazines were isolated by crystallization from methanol or by column chromatography on silica gel with dichloromethane as eluent. The compounds could be recrystallyzed from methanol or toluene/hexane (see Table).

The methanolic mother liquor was concentrated and the 1-benzylidene-2-dialkylaminomethylenehydrazine (**6**) was isolated by preparative tlc using ethyl acetate as eluent. Yields obtained were: **6a**: 28%, **6b**: 25%, **6c**: 26%. Their physical properties are identical with those of the compounds obtained from reaction of the 3-aryltetrazines with the secondary aliphatic amines.

*Synthesis of 3,6-bis(2-pyridyl)-4-nitropyridazine (**4e**) and 3,6-bis(2-pyridyl)-4-cyanopyridazine (**5e**).* These compounds were prepared from 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (**1e**)[17,18] by the procedure described above (see Table).

*Synthesis of 3,6-bis(4-pyridyl)-4-nitropyridazine (**4f**) and 3,6-bis(4-pyridyl)-4-cyanopyridazine (**5f**).* A stirred mixture of 236 mg (1.0 mmole) of 3,6-bis(4-pyridyl)-1,2,4,5-tetrazine (**1f**)[17,18] and 1.5 mmole of the enamine (**2**) or (**3**) in 25 ml of dry toluene was refluxed until the red color of the tetrazine had completely disappeared (1 to 2 weeks). After removal of the solvent, the pyridazines (**4f**) and (**5f**) were isolated by column chromatography on silica gel with ethyl acetate as eluent. Recrystallization from isopropanol gave the pure compounds (see Table).

Synthesis of 3,6-bis(piperidinocarbonyl)-4-nitropyridazine(**4g**). A stirred solution of 304 mg (1.0 mmole) of 3,6-bis(piperidinocarbonyl)-1,2,4,5-tetrazine (**1g**)[19] and 1.5 mmole of 1-nitro-2-dimethylaminoethene (**2**) was refluxed in 5 ml of dioxane for 3 h. After this time the red color of the tetrazine had completely disappeared. After removal of the solvent, the nitropyridazine was separated from the reaction mixture by column chromatography on silica gel with ether/dichloromethane 1:1 as eluent. Evaporation of the solvent from the fractions containing nitropyridazine (**4g**) gave a viscous yellow oil which did not crystallize (134 mg; 39%). nmr spectra showed no impurities. Ms: Calcd. for $C_{16}H_{21}N_5O_4$: 347.1593. Found: 347.1596.

Synthesis of 3,6-bis(piperidinocarbonyl)-4-cyanopyridazine (**5g**). A stirred solution of 304 mg (1.0 mmole) of 3,6-bis(piperidinocarbonyl)-1,2,4,5-tetrazine (**1g**) and 1.5 mmole of 1-cyano-2-morpholinoethene (**3**) in 5 ml of dioxane was refluxed for 1 h. After this time the red color of the tetrazine had completely disappeared. After removal of the solvent the reaction mixture was purified by column chromatography on silica gel with ether/dichloromethane 1:1 as eluent. The cyanopyridazine containing fractions were collected. After evaporation of the solvent the residue was separated by column chromatography on neutral alumina (act. IV). Elution with dichloromethane gave first the excess cyanoenamine (**3**). Subsequent elution with ether gave (**5g**), which crystallized slowly after removal of the solvent (180 mg; 55%).

Synthesis of the 1-benzylidene-2-dialkylaminomethylenehydrazines (**6**). A mixture of 1.0 mmole of the appropriate 3-aryl-1,2,4,5-tetrazine and an excess of the secondary amine was refluxed in 20 ml of chloroform until the red color of the tetrazine had completely disappeared (1-3 h). The solvent was removed and the hydrazine (**6**) was purified by column chromatography on silica gel with ethyl acetate as eluent.

1-Benzylidene-2-morpholinomethylenehydrazine (**6a**): yield 91%. mp 96-97°C (hexane); ^{1}H nmr (deuteriochloroform): 8.34 (s, 1H), 8.14 (s, 1H), 7.8-7.2 (m, aromatic, 5H), 3.3-3.8 (m, morpholine, 8H). ^{13}C nmr (CH=N): 160.2 ($^1J_{C-H}$=176 Hz), 154.0 ($^1J_{C-H}$=161 Hz). ir (potassium bromide): 1640 cm^{-1} (C=N).

Anal.Calcd for $C_{12}H_{15}N_3O$: C, 66.33; H, 6.96. Found: C, 66.54; H, 6.91.

1-(p-Methoxybenzylidene)-2-morpholinomethylenehydrazine (**6b**): yield 75%; mp 105-106°C (hexane); ^{1}H nmr (deuteriochloroform): 8.30 (s, 1H), 8.11 (s, 1H), 7.6-6.8 (m, aromatic, 4H), 3.83 (s, OCH_3, 3H), 3.8-3.4 (m, morpholine, 8H). ^{13}C nmr (CH=N): 159.6 ($^{1}J_{C-H}$=176 Hz), 153.8 ($^{1}J_{C-H}$=161 Hz). ir (potassium bromide): 1630 cm^{-1} (C=N)

Anal.calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93. Found: C, 63.16; H, 6.77.

1-Benzylidene-2-dimethylaminomethylenehydrazine (**6c**): yield 86%. mp 60-62°C (lit.[11]: 47°C). mp 212-213°C (picrate) (lit[11]: 213°). ^{1}H nmr (deuteriochloroform) 8.35 (s, 1H), 8.10 (s, 1H), 7.7-7.2 (m, aromatic, 5H), 2.95 (s, dimethylamine, 6H).

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