Monatshefte für Chemie 122, 1035–1045 (1991)

Monatshefte für Chemie
Chemical Monthly

Furylvinylhalogenides, XII [1]: Reactions of β-Chloro-α-cyano-β-(5-nitrofur-2-yl)-acrylic Acid Derivatives with Malonic Acid Derivatives

Siegfried Vieth[1], **Egon Gründemann**[1], **Klaus Jähnisch**[1,*], **Gabriele Winter**[2], and **Günter Reck**[2]

[1] Central Institute of Organic Chemistry, Rudower Chaussee 5, D-O-1199 Berlin, Federal Republic of Germany
[2] Analytical Center Berlin-Adlershof, Rudower Chaussee 5, D-O-1199 Berlin, Federal Republic of Germany

Summary. Reactions of β-chloro-α-cyano-β-(5-nitrofur-2-yl)-acrylic acid derivatives with malonic acid derivatives in the presence of collidine yield the allyl anions **3a–d**. The pyridines **4**, **8** or **9** are formed by cyclization of **3** under acidic conditions. The 2-chloropyridine **4a** reacts with nucleophiles under substitution. The treatment of ethyl dichloropropionate **1b** with C–H-acidic compounds provided the cyclopropanes **11** or **12**, the configurations of which were determined by ^{13}C-NMR spectroscopy. The results of the X-ray structure analysis of **8c** are discussed.

Keywords. Nitrofurylacrylic acid compounds; Allyl anions; Pyridines; Cyclopropanes.

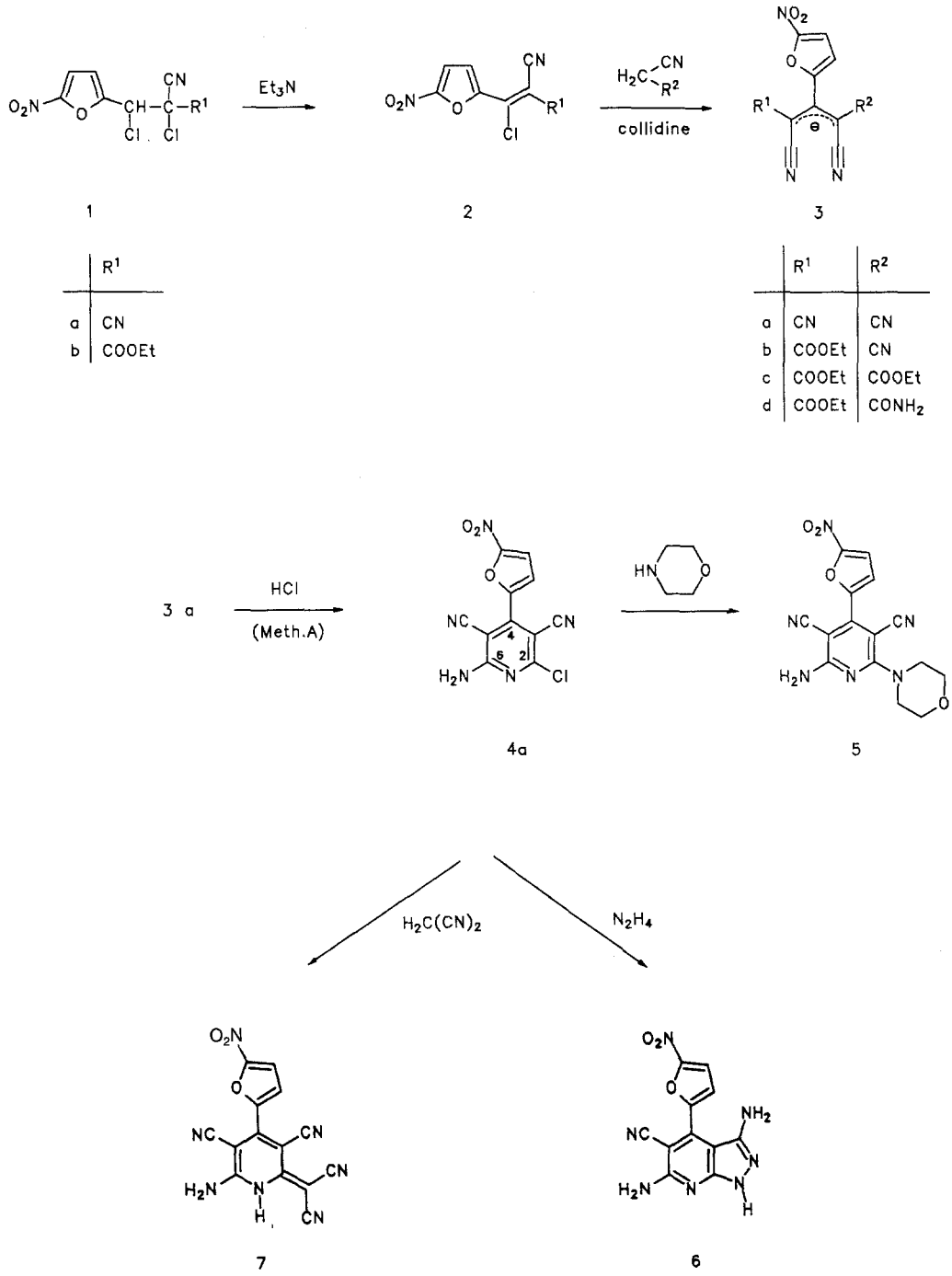
Furylvinylhalogenide, 12. Mitt.: Reaktionen von β-Chlor-β-(5-nitrofur-2-yl)-α-cyanacrylsäurederivaten mit Malonsäurederivaten

Zusammenfassung. Die Umsetzung von β-Chlor-α-cyan-β-(5-nitrofur-2-yl)-acrylsäurederivaten mit Malonsäurederivaten in Gegenwart von Collidin führt zu Allylanionen **3a–d**. Unter sauren Bedingungen cyclisiert **3** zu den Pyridinen **4**, **8** oder **9**. Das 2-Chlorpyridin **4a** reagiert mit Nukleophilen unter Substitution. Setzt man den Dichlorpropionsäureester **1b** mit C–H-aciden Verbindungen in Gegenwart von Collidin um, so werden die Cyclopropane **11** bzw. **12** gebildet, deren Konfigurationen mit Hilfe der ^{13}C-NMR-Spektroskopie bestimmt wurden. Die Ergebnisse der Röntgenkristallstrukturanalyse von **8c** werden diskutiert.

Introduction

Nitrofuryl-substituted heterocycles are known for their biological activity [2]. β-Chloro-α-cyano-β-(5-nitrofur-2-yl)-acrylic acid derivatives **2** [1, 3] offer a new access to these compounds. So, e.g. the treatment of **2** with hydrazines provides the hardly known 3-(5-nitrofur-2-yl)-pyrazoles [4]. In this paper we report on the reactions of **2** with malonic acid derivatives to 4-(5-nitrofur-2-yl)-pyridines which have not yet been described in literature. The corresponding compounds without nitro group can be prepared from furylacrylonitriles with geminate dithiols in the

presence of diethylamine [5]. On the other hand, the cyclization of Michael-adducts from malonic acid derivatives and furylacrylic compounds gives 4-furylpyrane derivatives which can be rearranged in some cases to 4-furylpyridines [6–8].

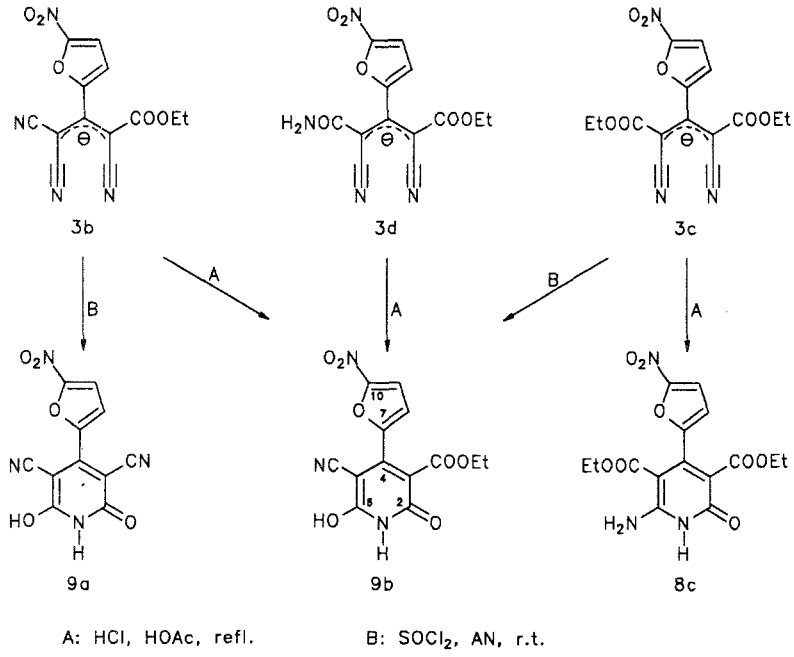


	R¹
a	CN
b	COOEt

	R¹	R²
a	CN	CN
b	COOEt	CN
c	COOEt	COOEt
d	COOEt	CONH2

1 2 3 4a 5 6 7

Scheme 1



Scheme 1 (continued)

Results and Discussion

Our investigations show that using **2 a, b** as synthetic building blocks the preparation of nitrofurylpyridines is possible under mild conditions. The chloroacrylic acid derivatives **2 a, b**, generated from the appropriate dichloropropionic acid derivative **1 a, b** and triethylamine [3, 4], are treated with the C−H-acidic compound and two equivalents of collidine. The reaction products are the allylic anions **3 a–d**. It is noteworthy that the 1,1,3-tricyano-3-ethoxycarbonylallyl anion **3 b** can be obtained from **2 a** and ethyl cyanoacetate as well as from **2 b** and malononitrile (Scheme 1).

The 1,1,3,3-tetracyano-2-(5-nitrofur-2-yl)-allyl anion **3 a** was isolated and characterized as collidinium salt. The structure of **3 a** is in particular proved by ^{13}C-NMR-spectroscopy. The small number of signals shows the high symmetry of this ion and the chemical shifts of the allyl signals (1-C, 3-C: 52.4 ppm; 2-C: 151.9 ppm) reflect the expected distribution of electron density [9].

Cyclization of cyano-substituted allylic salts or propenes to pyridines is possible under both basic and acidic conditions [9–11]. Due to the sensitivity of nitrofurans to bases we only used the second method. The treatment of the tetracyanoderivative **3 a** with a mixture of hydrochloric acid and acetic acid provides the chloropyridine **4 a** in 90% yield. Surprisingly, hydrolysis does not take place. But **4 a** reacts with nucleophiles under chlorine substitution. So the reaction with morpholine yields the diaminopyridine **5.** The treatment with hydrazine provides pyridinopyrazole **6.** In the reaction of **4 a** with malononitrile the dicyanomethylene-pyridine **7** is formed.

We developed two regioselective methods for the cyclization of the ethoxycarbonyl-substituted anions **3 b, c** to pyridines. If **3 b, c** was heated with hydrochloric acid in acetic acid (method A), the ring was closed between two cyano groups. In these cases not the appropriate chloropyridines have been isolated but their hy-

Table 1. Reaction course of pyridine synthesis

Starting compounds		Method	Product	Yield [%]
R^1 (2)	R^2 ($NC-CH_2-R^2$)			
CN	CN	A	**4a**	90
CN	COO*Et*	A	**9b**	65
COO*Et*	$CONH_2$	A	**9b**	47
COO*Et*	CN	A	**9b**	65
COO*Et*	COO*Et*	A	**8c**	60
COO*Et*	COO*Et*	B	**9b**	78
CN	COO*Et*	B	**9a**	61

drolysis products **8c** and **9b**, respectively. Under the same conditions **3d** cyclizes between the amide function and a nitrile group. The product is also **9b** (Scheme 1).

A different reaction course was observed if the allylic anions **3b, c** were treated with thionyl chloride (method B). In this case, cyclization occurred between the ester and cyano group. Thus, **3b** provided after aqueous work-up the hydroxy pyridone **9a**. The reaction of **3c** yielded again **9b**, also obtained from **3b** or **3d** using method A. Altogether, there are four synthetic routes to **9b**, because the allyl anion **3b** can be prepared by two methods (see Table 1).

The pyridine derivatives **4–9** have been characterized by MS, ^{1}H-NMR and especially ^{13}C-NMR spectroscopy (see Tables 3 and 4). A characteristic feature of these compounds is the high field shift of the C-3 and C-5 signal ($\delta = 70$–90 ppm) due to push-pull systems created by electron-withdrawing substituents at C-3 and

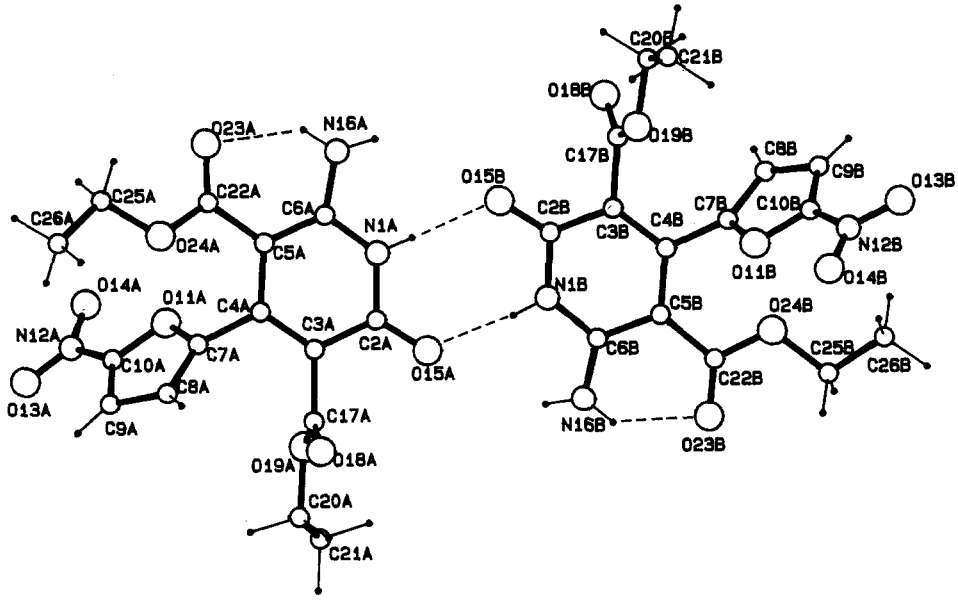


Fig. 1. PLUTO plot [19] of the molecules A and B of **8c** with numbering of atoms (intra- and intermolecular hydrogen bonds are indicated by broken lines)

C-5 and donating groups at C-6 and C-2. The bisethoxycarbonyl derivative **8c** shows a C-3 signal at 113.9 ppm. One reason for this deviating value is the presence of two ester groups in the molecule causing a smaller high field shift at C-3 and C-5 than CN groups. Another reason is the steric situation of the molecule. X-ray structure analysis of **8c** (see below) shows that the carboxylate function at C-3 is out of the pyridine ring plane. Therefore, it is not involved in the conjugation system and causes a high-field shift at C-3. Dramatic changes of chemical shifts of push-pull systems due to steric hindrance are known [12].

In the hydroxypyridone **9a** the signals of C-2 and C-6 as well as of C-3 and C-5 are not identical. This indicates that tautomeric processes leading to merged signals are very slow. Acceleration of proton exchange by rise of temperature is not possible because **9a** is thermically unstable.

The ^{13}C-NMR signals of the dicyanomethylene substituent in pyridine **7** are in good agreement with the structure given but not with the tautomeric dicyanomethylpyridine. The exocyclic methylene carbon atom shows a weak signal at 48.8 ppm. The two CN groups provide a broadened singlet at 118.8 ppm.

Table 2. Atomic parameters ($\times 10^4$) of $C_{15}H_{15}N_3O_8$ (esd's in parentheses)

Atom	Molecule A			Molecule B		
	x/a	*y/b*	*z/c*	*x/a*	*y/b*	*z/c*
N1	4530(2)	396(3)	2775(2)	5204(2)	1317(3)	4825(2)
C2	4015(3)	1303(4)	2751(2)	5858(2)	629(3)	4814(2)
C3	3349(2)	1492(2)	2028(2)	6583(2)	623(3)	5517(2)
C4	3259(2)	804(3)	1404(2)	6609(2)	1300(3)	6134(2)
C5	3865(2)	−47(3)	1442(2)	5895(2)	1951(3)	6124(2)
C6	4513(2)	−224(3)	2155(2)	5180(2)	1935(3)	5432(2)
C7	2476(3)	912(4)	716(2)	7422(3)	1334(4)	6797(2)
C8	2081(3)	1762(4)	260(3)	7878(3)	569(4)	7308(3)
C9	1304(4)	1308(5)	−284(4)	8612(3)	1109(5)	7804(3)
C10	1319(4)	222(5)	−98(4)	8548(4)	2154(5)	7551(4)
O11	2019(2)	−60(3)	514(2)	7836(2)	2341(2)	6925(2)
N12	724(4)	−651(6)	−407(4)	9083(3)	3107(5)	7823(4)
O13	76(4)	−417(5)	−928(4)	9704(3)	2959(4)	8420(3)
O14	886(4)	−1578(5)	−118(5)	8901(3)	3982(4)	7480(4)
O15	4124(2)	1868(3)	3355(2)	5811(2)	118(2)	4211(2)
N16	5137(3)	−973(4)	2284(2)	4464(2)	2505(4)	5315(2)
C17	2778(3)	2467(4)	2001(2)	7305(3)	−127(4)	5526(2)
O18	2963(2)	3416(3)	1927(2)	7257(2)	−1125(3)	5503(2)
O19	2061(2)	2147(3)	2071(2)	7983(2)	466(3)	5556(2)
C20	1442(4)	3032(6)	2022(5)	8741(3)	−187(6)	5627(5)
C21	957(6)	2739(8)	2448(6)	9373(5)	522(9)	5662(8)
C22	3925(3)	−577(4)	747(3)	5845(3)	2608(4)	6784(2)
O23	4333(2)	−1420(3)	743(2)	5261(2)	3233(3)	6743(2)
O24	3521(2)	−8(3)	99(2)	6500(2)	2459(3)	7443(2)
C25	3541(5)	−448(6)	−642(3)	6506(3)	3151(5)	8107(3)
C26	3139(5)	316(7)	−1258(3)	7333(4)	3046(7)	8715(4)

Furthermore, the molecular structure of the bisethoxycarbonylpyridine **8c** was determined by X-ray analysis. The crystals of **8c** contain two independent molecules (A and B). Table 2 summarizes the fractional coordinates.

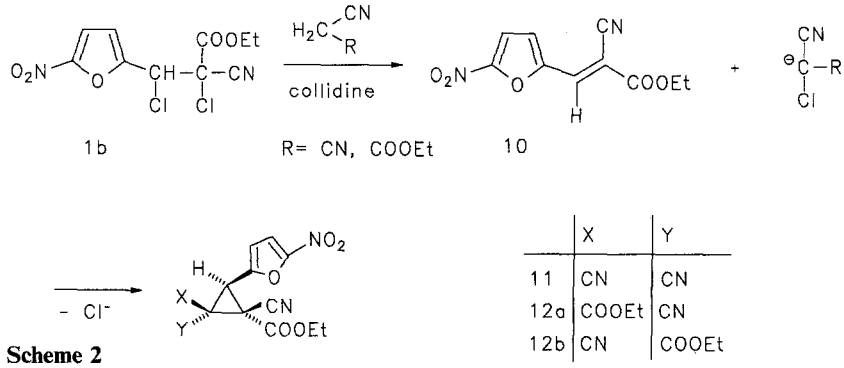
The bond distances and angles correspond to the expected values. The average C2–O15 distance of 1.241 A is a little too large for a carbonyl group. Similar distances occur in other hydropyridones [13]. The present structure features a strong intramolecular hydrogen bond between N16 of the amino group and the adjacent carboxyl oxygen O23 with an average distance between H161 and O23 of 2.036 A. A quasi six-membered ring is formed. This ring makes a dihedral angle of 23.13° (A) and 6.41° (B) with the hydropyridine system. In contrast to this, the ester group at C3 is nearly perpendicular to the hydropyridine ring. The dihedral angle between the plane through C17, C20, O18, O19, and through the pyridine ring is 99.5° (A) and 113.47° (B), respectively. The hydropyridine ring and the furyl ring enclose dihedral angles of 124.9° (A) and 115.5° (B).

The symmetry independent molecules are related by a non-crystallographic centre of symmetry. As shown in Fig. 1, the two molecules form dimers due to strong non-linear hydrogen bonds of type N–H...O (average distance H1...O15 1.973 A).

An interesting divergency from the normal synthetic pathway has been observed in the reaction of ethyl dichloropropionate **1b** with malonic acid derivatives in presence of collidine. Instead of allylic anions **3** cyclopropanes **11** and **12** were isolated (Scheme 2). The treatment of **1b** with malononitril gave **11** as single product. On the other side, the reaction with ethyl cyanoacetate provides a 1:1 mixture of the isomers **12a** and **12b** which can be separated by column chromatography.

The steric arrangement of substituents at the cyclopropane ring has been ascertained by ^{13}C-NMR spectroscopy, especially by the estimation of the vicinal coupling constants of the cyano or carbonyl-carbon atom with the C-2 proton. The $^3J_{H-CN}$ coupling constant is about 5 Hz for the *trans*-configuration and approximately 6 Hz for the *cis*-configuration. The $^3J_{H-CO}$ constants are about 4 and 5 Hz; these values are in good agreement with literature data [14].

The synthesis of cyclopropanes from α,β-dihalogenopropionic acid derivatives is described in literature, but little is known about mechanism and steric course of that reaction [15, 16]. Our investigations show that the cyclopropanes **11** and **12** contain the *cis*-arrangement of H- and COO*Et*-substituents in every case. This provides a stereochemical argument for the reaction mechanism discussed earlier



	X	Y
11	CN	CN
12a	COOEt	CN
12b	CN	COOEt

Scheme 2

[15]. Thus, in the first step a chloro malonate anion and ethyl β-(5-nitrofur-2-yl)-α-cyanoacrylate **10** in (*E*)-configuration [17] are formed. Michael addition of the carbanion to **10** followed by intramolecular substitution gives the cyclopropanes **11** and **12**, respectively. Provided the cyclization reaction is very fast, the reaction yields the products with the geometry found.

Experimental Part

^{1}H-NMR spectra (*HMDS* as internal standard): Tesla BS 567 (80 MHz). ^{13}C-NMR spectra (*HMDS* as internal standard): Bruker MSL 400. Mass spectra: Hewlett Packard HP 5985. Melting points: Corrected values.

X-Ray Determination of **8c**

A crystal with the dimension of 0.4 × 0.4 × 0.1 mm was selected for X-ray analysis. The compound crystallizes in the monoclinic space group $P2_1/c$ with eight (two symmetry-independent) molecules per unit cell. The cell dimensions are $a = 16.752(6)$, $b = 11.941(3)$, $c = 18.295(6)$ A, $\beta = 110.35(3)$ and $D_c = 1.41(3)\,g\,cm^{-3}$.

In the X-ray diffraction experiment performed with an ENRAF-NONIUS CAD-4 diffractometer using MoKα radiation and ω/20 scan mode the intensities of 6227 independent reflections were measured in the range $1.5 \leqslant \Theta \leqslant 25°$. Lattice constants were determined by least-squares refinement of setting angles of 25 reflections. 3547 reflections with $I \geqslant 3\sigma(I)$ were used for structure analysis. The intensities were corrected for Lorentz and polarization effects, absorption corrections were not made. The structure was solved by MULTAN 11/82 [18]. Full-matrix least-squares procedure minimized $|\Delta F|^2$. The final discrepancy index obtained was $R = 0.061$.

α-Cyano-α,β-dichloro-β-(5-nitrofur-2-yl)-propionic Acid Derivatives **1a, b**

Were prepared according to [1, 3, 4].

β-Chloro-α-cyano-β-(5-nitrofur-2-yl)-acrylic Acid Derivatives **2a, b**

Were generated from the appropriate dichloro compound **1a, b** and used for further reactions without isolation [4].

Cyano-Substituted Collidinium 2-(5-Nitrofur-2-yl)-propenates **3a–d** *(Crude Products) and Collidinium 2-(5-Nitrofur-2-yl)-1,1,3,3-tetracyanopropenate* (**3a**)

To freshly prepared stirred solutions of **2** (from 2 mmol of **1**) in acetonitrile (10 ml) 2.1 mmol of the malonic acid derivative and collidine (0.52 ml, 4 mmol) is added at room temperature. Further stirring for 3 h at room temperature affords a dark red solution which is used for the synthesis of the pyridines **4**, **8**, and **9**.

For isolation of **3a** 3% hydrochloric acid (20 ml) is added to the solution. The formed solid is filtered off, washed with water and heated in ethanol (10 ml) for 5 min under reflux. After cooling to room temperature the solution is filtered from the residue and mixed with water (10 ml). The precipitate is filtered off and washed with water yielding 0.48 g (71%).

3a. ^{1}H-NMR: δ = 7.77 (d, 1 H, H-4, *Fu*), 7.60 (s, 2 H, H-3.5, *Coll*), 7.33 (d, 1-H, H-3, *Fu*), 2.58 (s, 6 H, 2.6-CH_3), 2.45 (s, 3 H, 4-CH_3). ^{13}C-NMR: 158.9 (C-2.6, *Coll*), 152.0 (C-5, *Fu*), 151.9 (C-2), 151.2 (2-C, *Fu*), 148.8 (C-4, *Coll*), 125.2 (C-3.5, *Coll*), 118.2 (C-4, *Fu*), 117.5 and 115.3 (CN), 113.2 (C-3, *Fu*), 52.4 (C-1), 21.4 (4-CH_3), 18.9 (2.6-CH_3). MS: 253 (M^+, 1,1,3,3-Tetracyano-2-(5-nitrofur-2-yl)-propene), 121 (M^+, *Coll*). $C_{19}H_{14}N_6O_3$ (300.2); calcd. C 60.96, H 3.77, N 22.45; found C 60.83, H 3.75, N 22.42.

4-(5-Nitrofur-2-yl)-pyridines **4**, **8** *and* **9**

Method A. From the reaction solution cointaining **3a–d** (from 2 mmol of **1**) the solvent is removed by evaporation. Then the residue is heated with acetic acid (1.2 ml) and conc. hydrochloric acid (0.6 ml) for 5 min under reflux. After cooling to room temperature water (5 ml) is added. The solid is filtered off, washed with water and ethanol and recrystallized from acetonitrile.

Method B. To the stirred solution of **3b, c** (from 2 mmol of **1**) in acetonitrile (10 ml) thionylchloride (0.24 g, 2 mmol) is added at room temperature. The solution is stirred for further 2 h and then refluxed for 5 min. After cooling to room temperature water (20 ml) is added. The solid is filtered off, washed with water and ethanol and crystallized from acetonitrile. For data see Tables 3 and 4.

2-Amino-3,5-dicyano-6-(morpholin-1-yl)-4-(5-nitrofur-2-yl)-pyridine (**5**)

To a stirred suspension of **4a** (0.58 g, 2 mmol) in acetonitrile (8 ml) morpholine (0.35 ml, 4.5 mmol) is added at room temperature. Stirring is continued for further 3 h. Then water (20 ml) is added. The product **5** is filtered off, washed with water and ethanol and recrystallized from dioxane yielding 0.720 g (94%). For data see Tables 3 and 4.

3,6-Diamino-5-cyano-4-(5-nitrofur-2-yl)-pyrido[2,3-c]pyrazol (**6**)

4a (0.58 g, 2 mmol), 20% hydrazine (1.25 ml, 4.5 mmol), *DMF* (6 ml) and acetic acid (6 ml) are heated for 5 min under reflux. After cooling to room temperature 2% hydrochloric acid (15 ml) is added. The solid is filtered off and washed with water and ethanol. The product **6** is further purified by washing with hot aceton yielding 0.450 g (79%). For data see Tables 3 and 4.

Table 3. Melting points, MS-data and elemental analysis of **4–9**

No.	M.P. [°C]	MS *m/z* (%)	Mol. formula (Mol. weight)	Elemental analysis calculated/found		
				C	H	N
4a	258–260	289[a] (M^+, 100)	$C_{11}H_4N_5O_3Cl$ (289.6)	45.62 45.74	1.39 1.40	24.18 24.61
5	230	339 (M^+, 100)	$C_{17}H_{16}N_6O_5$[b] (383.3)	53.12 53.09	4.20 4.22	21.87 22.07
6	310 (dec.)	285 (M^+, 100)	$C_{11}H_7N_7O_3$ (285.2)	46.32 46.32	2.47 2.48	34.38 33.99
7	310 (dec.)	319 (M^+, 40)	$C_{14}H_7N_7O_3$[c] (337.3)	49.86 50.20	2.09 2.26	29.07 28.40
8c	230	365 (M^+, 30)	$C_{15}H_{15}N_3O_8$ (365.3)	49.32 48.90	4.14 4.11	11.50 11.30
9a	235	272 (M^+, 80)	$C_{11}H_6N_4O_6$[c] (290.2)	45.53 45.59	2.08 2.08	19.30 19.20
9b	219–221	319 (M^+, 40)	$C_{13}H_9N_3O_7$ (319.2)	48.91 48.93	2.84 2.85	13.16 13.22

[a] M^+ for ^{35}Cl

[b] Contains ½mol of dioxane

[c] Contains 1 mol of water

Table 4. ^{13}C-chemical shifts of nitrofurylpyridines **4–9** (in *DMSO-d_6*)

No.	C-2[a]	C-3[b]	C-4	C-5[b]	C-6[a]	C-7	C-8	C-9	C-10	Further signals
4a	156.5	93.4	143.9	87.1	160.5	146.1	118.8	113.6	152.2	114.5 and 113.8 (3.5-$(CN)_2$)
5	160.9	79.8	145.7	79.9	160.0	148.1	115.5	113.5	152.0	115.2 and 113.5 (3.5-$(CN)_2$), 66.9 and 47.9 (morpholine), 65.9 (dioxane)
6	153.0	96.4	148.0	82.6	159.0	148.3	117.3	113.6	152.3	117.3 (CN), 135.2 (C-3), (pyrazole)
7	157.8	84.2	144.7	79.0	160.1	148.2	118.8	113.3	151.9	118.8 (br. s, 2C, $C(CN)_2$), 115.2 and 114.9 [3,5-$(CN)_2$], 48.8 [**C**$(CN)_2$]
8c	155.2	113.9	139.3	86.9	157.7	151.0	114.2	112.5	152.8	165.0 and 164.3 ($2\times C{=}O$), 60.8 and 60.1 ($2\times OCH_2$), 13.7 and 13.4 ($2\times CH_2$)
9a	156.0	79.5	145.8	69.8	167.0	148.7	119.6	113.3	152.3	114.7 and 113.8 [3,5-$(CN)_2$]
9b	155.8	88.8	149.1	83.0	163.4	149.8	115.8	113.8	151.7	165.7 (C=O), 114.8 (CN), 60.9 (OCH_2), 13.4 (CH_3)

[a, b] Assignments with the same letter may be exchangeable

2-Amino-3,5-dicyano-6-dicyanomethylene-1,6-dihydro-4-(5-nitrofur-2-yl)-pyridine (**7**)

A suspension of **4a** (0.58 g, 2 mmol), K_2CO_3 (0.5 g, 3.6 mmol), malononitrile (0.165 g, 2.5 mmol) and *DMF* (5 ml) is stirred 6 h at room temperature. Then conc. hydrochloric acid (2 ml), acetic acid (2 ml) and water (1 ml) are added and the mixture is refluxed for 5 min. The product **7** is precipitated by addition of water (20 ml). The solid is filtered off, washed with water and ethanol and crystallized from *DMF*/acetonitrile yielding 0.520 g (77%). For data see Tables 3 and 4.

Ethyl 1,1,3-Tricyano-2-(5-nitrofur-2-yl)-cyclopropane-3-carboxylates **11**, *Diethyl trans-1,3-Dicyano-2-(5-nitro-fur-2-yl)-cyclopropanedicarboxylate* (**12a**) *and Diethyl cis-1,3-Dicyano-2-(5-nitro-fur-2-yl)-cyclopropanedicarboxylate* (**12b**)

To a stirred solution of **1b** (0.614 g, 2 mmol) and 2.1 mmol of the C – H-acidic compound in acetonitrile (8 ml) collidine (0.52 ml, 4 mmol) in acetonitrile (4 ml) is added at room temperature. Stirring is continued (**11**: 1 h; **12**: 2 h), then 3% hydrochloric acid (15 ml) is added and the mixture is extracted with chloroform (3 × 10 ml). The combined organic layers are washed with water (10 ml), dried (Na_2SO_4), the chloroform is removed and the residue is treated with ethanol (5 ml). The crystals formed are filtered off, washed with water and ethanol and crystallized from acetonitrile/ethanol.

11. Yield 0.300 g (50%). M.p. 138–144°C. ^{1}H-NMR (*DMSO-d*$_6$): 7.77 (d, 1 H, 4-H, *Fu*), 7.12 (d, 1 H, 3-H, *Fu*), 4.60 (s, 1 H, 2-H), 4.32 (q, 2 H, OCH_2), 1.31 (t, 3 H, CH_3). ^{13}C-NMR (*DMSO-d*$_6$): 159.8 (m, J_{CH} = 4.7 Hz, *cis*-CO), 151.3 (C-5, *Fu*), 146.2 (C-2, *Fu*), 115.5 (C-3, *Fu*), 113.5 (C-4, *Fu*), 111.4 (d, J_{CH} = 5.1) and 110.1 (d, J_{CH} = 5.3 Hz) (2 *trans*-CN), 109.5 (d, J_{CH} = 6.1 Hz, *cis*-CN), 64.7 (CH_2), 13.7 (CH_3). MS: 255 (M^+-*Et*O). $C_{13}H_8N_4O_5$ (300.2); calcd. C 52.01, H 2.69, N 18.66; found C 52.04, H 2.65, N 18.72.

12a, b (1 : 1) diastereomeric mixture. Yield 0.650 g (94%). M.p. 134–138°C ^{1}H-NMR (*DMSO-d*$_6$): 7.56 (d) and 7.49 (d) (1 H, 4-H, *Fu*), 7.09 (d) and 6.97 (d) (1 H, 3-H, *Fu*), 4.5–4.0 (m, 5 H, 2-H and OCH_2), 1.4–1.1 (m, 6 H, CH_3). MS: 347 (M^+). $C_{15}H_{13}N_3O_7$ (347.3); calcd. C 51.88, H 3.77, N 12.10; found C 51.76, H 3.76, N 12.11.

Isolation of the Isomers **12a** *and* **12b**

0.2 g of the 1 : 1 diastereomeric mixture **12** is chromatographed over silica gel (Merck silica gel 60; 0.063–0.200 mm, 40 g) and the pure isomers **12a** and **12b** are eluted with chloroform.

12a. Yield 0.05 g (50%). M.p. 144–146°C. ^{13}C-NMR (*DMSO-d*$_6$): 160.9 (m, J_{CH} = 5.4 Hz, *cis*-CO), 159.4 (m, J_{CH} = 3.8 Hz, *trans*-CO), 151.3 (C-5, *Fu*), 146.2 (C-2, *Fu*), 115.6 (C-3, *Fu*), 113.5 (C-4, *Fu*), 112.4 (d, J_{CH} = 6.3 Hz, *cis*-CN), 110.8 (d, J_{CH} = 4.9 Hz, *trans*-CN), 64.6 and 64.2 (2 CH_2), 33.0 (C-2), 32.4 and 31.8 (C-1 and C-3), 13.7 and 13.4 (2 CH_3).

12b. Yield 0.05 g (50%). M.p. 162–163°C. ^{13}C-NMR (*DMSO-d*$_6$): 159.3 (m, J_{CH} = 5.0, *cis*-CO). 151.9 (C-5, *Fu*), 146.0 (C-2, *Fu*), 115.2 (C-3, *Fu*), 113.4 (C-4, *Fu*), 111.8 (d, J_{CH} = 5.2 Hz, *trans*-CN), 64.8 (CH_2), 33.6 (C-1.3), 31.6 (C-2), 13.6 (CH_3).

References

[1] Part XI: Vieth S., Jähnisch K. (1990) J. Prakt. Chem. **332**: 687
[2] Ehrhardt G., Ruschig H. (1972) Arzneimittel, Vol. 4, 2nd Ed. Verlag Chemie, Weinheim, p. 194
[3] Jähnisch K., Schwertner S., Seeboth H. (1988) J. Prakt. Chem. **330**: 361
[4] Jähnisch K., Schwertner S. (1989) J. Prakt. Chem. **331**: 552
[5] Sharanin Yu., Shestopalov A. M., Promonenkov B. K. (1984) Zh. Org. Khim. **20**: 2002
[6] Sharanin Yu. (1980) Zh. Org. Khim. **16**: 2188
[7] Elgemeie G. E. H., Gohar A. E. M., Regaila H. A., Elfahham H. A. (1988) Arch. Pharm. [Weinheim] **321**: 131

[8] Marchalin S., Iljavski D., Kovac J., Bruncko, M. (1990) Coll. Czech. Chem. Comm. **55**: 718
[9] Pochat F. (1983) Tetrahedron Lett. **24**: 5073
[10] Gottis G., Tieckmann H. (1961) J. Org. Chem. **26**: 79
[11] Mittelbach M., Junek H. (1986) Liebigs Ann. Chem.: 533
[12] Sandström J. (1983) Top. Stereochem. **14**: 83
[13] Reck G., Hagen V., Höhne E. (1986) Pharmazie **41**: 181
[14] Kingsbury C. H., Durham D. L. (1978) J. Org. Chem. **43**: 4696
[15] Schollberg K. (1963) Dissertation. Techn. Hochschule, Dresden
[16] Smith M. (1962) In: Coffey S. (ed.) Rodd's Chemistry of Carbon Compounds, Vol. 2 A. Elsevier, Amsterdam, 1967, p. 19
[17] Dandarova M., Vegh D., Kovac J., Goljer I., Pronayova N., Spirkova K. (1986) Coll. Czech. Chem. Comm. **51**: 889
[18] Main P., Fiske S. J., Hull S. E., Lessinger L., Germain G., Declercq J. P., Woolfson M. M. (1982) Multan 82. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data. Univs. of York, England, and Louvain, Belgium
[19] Motherwell F. (1978) PLUTO-Programs for Plotting Molecular and Crystal Structures. University of Cambridge

Received January 28, 1991. Accepted April 9, 1991