SYNTHESIS OF HETEROCYCLIC COMPOUNDS FROM THE PRODUCTS OF ADDITION OF POLYHALOALKANES TO UNSATURATED SYSTEMS

4.* SYNTHESIS OF SUBSTITUTED FURO[2,3-D]PYRIMIDINES

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2-Amino-5-methyl-4-(2,2,2-trichloroethyl)-3-furonitrile was synthesized from 3,5,5,5-tetrachloropentan-2-one, a product of the radical addition of CCl_4 to methyl vinyl ketone, according to a scheme known for α-haloketones. The product was converted via the corresponding imino-ether into N^2-substituted N^1[5-methyl-4-(2,2,2-trichloroethyl)-3-cyano-2-furyl]formamidines. Cyclization of these formamidines gave 2-methyl-3-(2,2,2-trichloroethyl)-5-R-4-imino-4,5-dihydrofuro[2,3-d]pyrimidines, which readily regroup according to Dimroth into 2-methyl-3-(2,2,2-trichloroethyl)-4-R-aminofuro[2,3-d]pyrimidines.

We have previously shown that the available products of addition of CCl_4 to α,β-unsaturated carbonyl compounds having a labile chlorine atom in the α-position can be used in the syntheses of various heterocyclic compounds, proceeding by schemes known for α-halocarbonyl compounds [2]. As a result, compounds are obtained having a 2,2,2-trichloroethyl group as a substituent, which creates the possibility of modification of these compounds into hetarylacetic acids and compounds containing a dichlorovinyl group, which can be used in the synthesis of biologically active compounds. The presence of additional substituents makes it possible to carry out annelation. In the present work 3,5,5,5-tetrachloropentan-2-one (I), obtained by the radical addition of CCl_4 to methyl vinyl ketone in the presence of a $RuCl_2(Ph_3P)_3$ complex [3], was used for the synthesis of substituted 4-aminofuro[2,3-d]pyrimidines (for preliminary communication, see [4]).

2-Amino-5-methyl-4-(2,2,2-trichloroethyl)-3-furonitrile (II) was obtained in a 72% yield in the reaction of chloroketone I with malonodinitrile in the presence of sodium ethylate. The reaction proceeds via the acyclic derivative (III), which can be isolated by the accurate addition of an equimolar mixture of malonodinitrile and sodium ethylate to the chloroketone solution. The action of morpholine on the intermediate product (III), without isolation of the latter, generally leads to the furan derivative (II).

The latter aminofuran II is a fairly labile compound, which readily resinifies in the presence of traces of acid. Moreover, the presence of the trichloroethyl group does not allow the use of strongly basic agents for its further condensation into furopyrimidines. Thus, attempts to condense compound II with nitriles on prolonged boiling in a saturated alcoholic solution of KOH [5] resulted in resinification. Boiling of cyanoaminofuran II in formamide in the presence of Ac_2O (cf. [6]) and the attempts to carry out the condensation of the aminonitrile with nitriles under acid catalysis conditions [7] also did not lead to the expected products.

Considering the above data, a path was used for the synthesis of furo[2,3-d]pyrimidines, which was previously proposed for the preparation of condensed pyrimidines from ortho-aminonitriles [8], which includes several stages. As an intermediate compound, the corresponding amino ester (IV) was obtained from amine II by the action of orthoformic ester. By the action of ammonia or primary amines on (IV), formamidines (Va-i) were obtained, most of which were found to be stable compounds, which in the presence of sodium ethylate readily cyclized into the corresponding 5-R-4-imino-4,5-dihydrofuro[2,3-d]pyrimidines (VI). Some of the amidines (Vj-*l*, having R = isopropyl, n-butyl, cyclohexyl) could not be isolated, since they cyclize under the conditions of formation.

*For communication 3, see [1].

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TABLE 1. Chemical Shifts in the ^1H NMR Spectra of 5-R-4-Imino-4,5-dihydrofuro[2,3-d]pyrimidines (VI) and 4-R-Aminofuro[2,3-d]-pyrimidines (VII)

Compound	R	Chemical shifts, δ, ppm*				
		2-Me[2*]	3-CH_2[2*]	6-CH[2*]	4-NH[3*]	5-R and other signals
VI b	Me	2,41	4,32	8,02	7,0	3,35 s
VI e	$PhCH_2$	2,40	4,31	8,21	6,85	5,20 s, 7,2...7,4 m
VI f	Ph	2,44	4,34	7,92	6,15	7,38...7,65 m
VI g	*p*-$Et_2NC_6H_4$	2,46	4,35	7,86	6,05	1,11 t, 3,35 qv[5*], 6,78...7,15 m
VI h	*p*-ClC_6H_4	2,44	4,32	7,91	6,25	7,38...7,70 m
VI j	*i*-Pr	2,40	4,30	8,08	7,18	1,33 d[5*], 5,20 br
VI k	*n*-Bu	2,40	4,32	8,00	—	0,89 t, ',27 m, 1,61 m 3,39 t[5*]
VI ℓ	C_6H_{11}	2,38	4,30	8,05	7,18	1,45 m, 4,82 br.
VII a	H[4*]	2,52	4,30	8,12	6,55	—
VII b	Me	2,48	4,39	8,21	7,30 qv	2,97 d[6*]
VII e	$PhCH_2$	2,49	4,44	8,17	7,62 dd	4,74 d[6*], 7,24 m
VII f	Ph	2,56	4,58	8,30	8,68	7,35 m
VII g	*p*-$Et_2NC_6H_4$	2,50	4,48	8,40	8,13	1,07 t, 3,30 qv[5*], 6,64 d, 7,20 d
VII h	*p*-ClC_6H_4	2,57	4,61	8,35	8,76	7,41...7,65 m
VII j	*i*-Pr	2,48	4,49	8,18	6,51	1,21 d[5*], 4,5 m
VII k	*n*-Bu	2,48	4,42	8,16	7,00	0,89 t, 1,31 m, 1,57 m, 3,49 d. t[5*]
VII ℓ	C_6H_{11}	2,48	4,48	8,17	6,48 d[6*]	1.48 m, 4,14 br.
XI b	Me	—	—	8,18	6,11	3,30 s, 7,2...7,6 m
XI c	Ph	—	—	8,08	6,10	7,2...7,7 m
XII a	H	—	—	8,28	6,10	7,2...7,7 m
XII b	Me	—	—	8,37	5,28 qv	2,87 d, 7,3...7,6 m
XII c	Ph	—	—	8,31	6,00	7,2...7,7 m

*Solvent — DMSO-d_6.

2*Singlets.

3*Broadened singlets or broad signals.

4*Solvent — acetone-D_6.

5*J = 7 Hz.

6* J = 6 Hz.

TABLE 2. N^1-[5-Methyl-4-(2,2,2-trichloroethyl)-3-cyano-2-furyl]-N^2-R-formamidines (V) and N^1-(4,5-Diphenyl-3-cyano-2-furyl]-N^2-R-formamidines (X)*

Compound	R	mp, °C	IR spectrum, cm^{-1} (with KBr)		Yield, %
			νNH	νC-N	
Va	H	210...212	3376...3152	2216, 1680, 1580	75
Vb	Me	166...168	3356	2218, 1626, 1590	94
Vc	*i*-Bu	126...127	3312	2224, 1624, 1580	85
Vd	*t*-Bu	132...135	3226	2226, 1646, 1596	98
Ve	$PhCH_2$	130...132	3320	2240, 1614, 1592	82
Vf	Ph	159...160	3344	2216, 1624, 1584	85
V g	*p*-$Et_2NC_6H_4$	159...161	3180	2218, 1652, 1550	25
Vh	*p*-ClC_6H_4	189...190	3320, 3128	2216, 1620, 1590	70
Vi	*p*-AcC_6H_4	228...230	3284	1660, 1640, 1584, 1574	50
Xa	H	222...223	3368, 3108	2220, 1676, 1564	89
Xb	Me	160...161	3408	2206, 1620, 1600, 1580	94
Xc	Ph	162...165	3452, 3180	2216, 1654, 1654, 1600	90

*The second amidine band (1500-1596 cm^{-1}) is overlapped by bands of the C=C bonds of the furan and benzene rings. The table includes the most intense bands; bands with frequencies lower than 1500 cm^{-1} are not given.

TABLE 3. 5-R-4-Imino-4,5-dihydrofuro[2,3-d]pyrimidines (VI and XI).

Compound	R	mp, °C	IR spectrum, cm^{-1} (KBr)			Yield, %
			ν_{NH}	$\nu_{C=NH}$	ν pyridine	
VIb	Me	148...150	3372	1636	1604, 1546	85
VIe	$PhCH_2$	90...91	3330	1634	1600, 1540	88
VIf	Ph	135...138	3310	1666	1634, 1536	60
VIg	p-$Et_2NC_6H_4$	153...154	3200	1663	1610, 1535	82
VIh	p-ClC_6H_4	192...195	3300	1658	1610, 1540	75
VIj	i-Pr	139...141	3364	1640	1606, 1548	96
VIk	n-Bu	106...108	3338	1632	1600, 1544	70
VIℓ	C_6H_{11}	169...171	3365	1638	1606, 1540	94
XIb	Me	118...120	3312	1638	1610, 1554	94
XIc	Ph	170...173	3408	1678	1586, 1488	85

TABLE 4. 4-R-Aminofuro[2,3-d]pyrimidines (VII, XII)

Compound	R	mp, °C	IR spectrum, cm^{-1} (KBr)		Yield, %
			ν_{NH}	νpyrimidine, other	
VIIa	H	209*	3464, 3314	1642 (δ_{NH}), 1586	55
VIIb	Me	236	3320	1620 sh, 1580, 1512	95
VIIe	$PhCH_2$	157...159	3336	1590 sh, 1580, 1502	96
VIIf	Ph	143...144	3380	1600, 1580, 1510, 1495, 1460	68
VIIg	p-$Et_2NCH_6H_4$	163...165	3326	1612 w, 1580, 1518	95
VIIh	p-ClC_6H_4	149...150	3408	1600 w, 1584, 1568, 1492	95
VIIj	i-Pr	190	3384	1580 sh,1488	93
VIIk	n-Bu	124...125	3344	1584 sh,1508	86
VIIℓ	C_6H_{11}	208	3384	1584 sh,1496	98
XIIa	H	263[2*]	3470, 3330	1648, 1596, 1578, 1480	95
XIIb	Me	203...205	3340, 3210	1656, 1598, 1480	90
XIIc	Ph	195...198[3*]	3356, 3196	1660, 1596, 1456	98

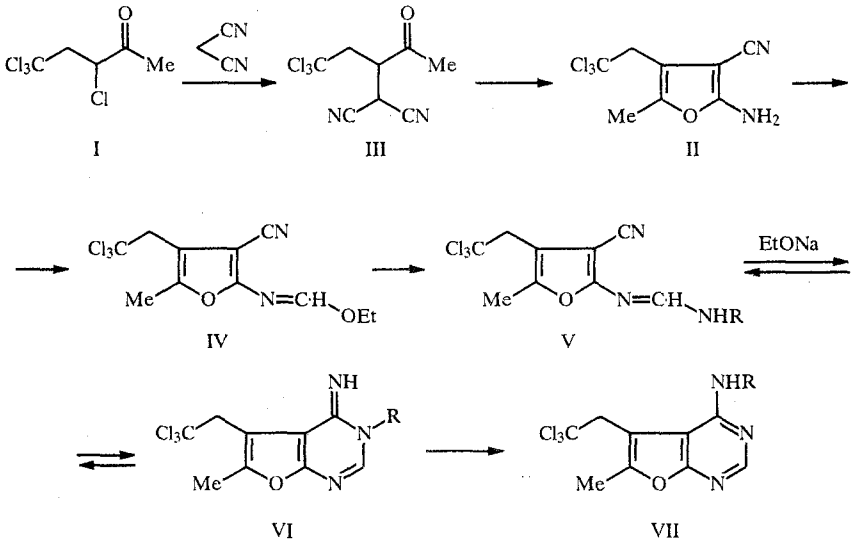
*Compound VIIa could not be isolated in an analytically pure state. It was characterized by its derivatives. The hydrochloride was obtained by the action of a double molar amount of conc. HCl in methanol, yield 85%, mp 245-246°C. The phthalimide derivative was obtained by the action of an equimolar amount of phthaloyl dichloride in the presence of a double excess of triethylamine (100°C, 1.5 h, in N-methylpyrrolidone), yield 75%, mp 139-140°C (from dioxane). The melting points were determined in a sealed capillary.

[2*]Literature data, see [6, 10].

Formamidines V exist in the form of E-isomers, whereby, as seen from the NMR and x-ray diffraction analysis data, the Z-isomers were in no case detected [1]. The cyclization of amidines V into furopyrimidines can be realized, by by-passing the Z/E isomerization, through the stage of deprotonation, the case of which is determined by the acid properties of the amidine fragment, depending on the nature of the substituents and the basicity of the medium. In the case of the tert-butyl-substituted formamidine (Vd), the corresponding furopyrimidine could not be obtained, which is probably due to considerable steric hindrances produced by the tert-butyl group.

Under thermodynamic control conditions (during a prolonged boiling in an aqueous dioxane), the furopyrimidinone-imines (VI) undergo a Dimroth rearrangement: they recyclize with the formation of the aminopyrimidine structure (VII). Furopyrimidines (VII) with substituents at the exocyclic nitrogen atom were obtained for R = Me, i-Pr, n-Bu, $PhCH_2$, cyclo-C_6H_{11}, Ph, p-$Et_2NC_6H_4$. The cyclization of amidine Va (R = H) leads directly to the amino form of furopyrimidine (VIIa). The possibility of separation of amidines, intermediately formed during annelation by the method used in the case of furan II,

was also studied for the previously described 2-amino-4,5-diphenyl-3-furonitrile (VIII), obtained according to Gewald [9]. Starting from cyanoaminofuran VIII, the corresponding imino-ether (IX) and formamidines (Xa-c) were obtained. The latter, like amidines V, were found to be fairly stable compounds, and their cyclization into furopyrimidinoneimines (IX) and the



a R = H, b R = Me, c R = *i*-Bu, d R = *t*-Bu, e R = $PhCH_2$, f R = Ph, g R = *p*-$Et_2NC_6H_4$, h R = *p*-ClC_6H_4, i R = *p*-AcC_6H_4, j R = *i*-Pr, k R = *n*-Bu, l R = *cyclo*-C_6H_{11}

subsequent Dimroth rearrangement led to the previously described [6, 9, 10] aminofuropyrimidines (XII).

All three isomeric structures (V, VI, VII, and their diphenylsubstituted analogs) were characterized by spectral data which differ from one another in accordance with the attributed structure. Thus, in the PMR spectra, with increase in the conjugation chain on transition from amidines V to furopyrimidinone-imines VI and further to aminofuropyrimidines (VII), a weak-field shift is observed of signals of the methyl (2.3-2.5 ppm) and methylene (3.9-4.45 ppm) groups, and for imines VI and amines VII — also of the pyrimidine ring protons (8.0-8.2 ppm). The NMR spectra of amidines V will be discussed in detail in a separate article in relation to their structure and stereochemistry. The ^1H NMR data of imines VI, XI and amines VII, XII are given in Table 1.

All the compounds were characterized by mass spectra whereby the isomeric compounds (V-VII and X-XII) form ionized particles with the same m/e, but the intensities of the corresponding peaks differ notably.

Valuable information is obtained from the IR spectra. In particular, in the spectra of substituted formamidines (V and X) there is a nitrile group band at 2210-2220 cm^{-1}, which is absent in other structures, and also two amidine bands at 1600-1680 and 1550-1596 cm^{-1}, the identification of which was carried out in accordance with the data in [11], whereby the latter band is overlapped by bands of the C=C bond of the furan ring. Imines VI and XII together with ν_{NH} are characterized by an intense broad band of the exocyclic C=N bond in the 1630-1640 cm^{-1} region. For amines VII and XII intense absorption bands of both ν_{NH} and the conjugated pyrimidine ring at 1584-1596 and 1488-1512 cm^{-1} are characteristic. The IR spectral data are given in Tables 2-4, which include mainly the most intense bands, while bands with frequencies below 1480 cm^{-1} are not shown.

EXPERIMENTAL

The PMR spectra were run on a Bruker WM-250 radiospectrometer (250 MHz) in DMSO-d_6. The IR spectra were obtained on Perkin-Elmer 577 and Specord M-80-spectrophotometers of KBr tablets and in the form of a solution in $CHCl_3$. The mass spectra were run on a Varian MAT CH-6 spectrometer with direct introduction of the sample into the ionic source, at an ionizing voltage of 70 eV and emission current of 100 μA.

The course of the reactions were monitored by TLC on Silufol UV-254 plates, using the ethyl acetate — hexane (1:3) chromatographic system.

4-Oxo-3-(2,2,2-trichloroethyl)-2-cyanovaleronitrile (III). A 0.2 g portion of sodium was dissolved in 10 ml of absolute ethanol, then 0.6 g of malonodinitrile was added, and the mixture was heated at 60°C to complete dissolution, the solution obtained containing 9 mmoles of the sodium derivative was added dropwise with stirring to a cooled (0°C) solution of 2 g (9 mmoles) of 3,5,5,5-tetrachloropentan-2-one in absolute ethanol. The reaction mixture was stirred for 2 h at room temperature, and then was poured into 20 ml of water and extracted with ether. The extract was dried over magnesium sulfate and evaporated. The oil obtained was ground with cooling with hexane, and recrystallized from alcohol with water. Yield 0.47 g (21%) of white plate-like crystals, mp 86-88°C.

2-Amino-5-methyl-4-(2,2,2-trichloroethyl)-3-furonitrile (II). A 1.2 g portion (48 g-at.) of metallic sodium was dissolve in 100 ml of absolute ethanol, and then 3.2 g (48 mmoles) of malonodinitrile was added, and the mixture was heated at 60°C for 15 min. It was then cooled with an ice–salt mixture and 10 g (45 mmoles) of chloroketone I was added with stirring. The reaction mixture was held at a temperature of about 0°C for 1 h, and after the addition of 4 ml of morpholine (46 mmoles), was allowed to stand 3 h, allowing the temperature to rise to room temperature. The product was precipitated from the reaction mixture by the addition of water (about 100 ml). The white needle-like crystals that separated out were washed 3 times with water, recrystallized from alcohol with water, and dried over P_2O_5. Yield 8.2 g (72%) of compound II, mp 100-102°C (dec.), R_f = 0.6.

An identical product was obtained by adding a decimolar amount of morpholine to a solution of compound III in a small volume of ethanol at room temperature. Yield, 75%.

The product was also characterized in the form of an acetyl derivative (obtained by the action of AcCl in dry pyridine, 20°C, 24 h), mp 193-194°C (from aqueous alcohol), yield 80%.

5-Methyl-4-(2,2,2-trichloroethyl-2-ethoxymethylimino-3-furonitrile (IV). A solution of 4 g (16 mmoles) of aminofuran (II) was boiled for 4 h in 50 ml of orthoformic ester in the presence of 1 ml of acetic anhydride. The excess of orthoformic ester was evaporated on a rotary evaporator, and the remaining brown oil was dissolved in a small volume of ether and precipitated with hexane. Yield, 3.78 g (77.7%) of a crystalline compound, mp 70-71°C, R_f 0.85.

N′-[5-Methyl-4-(2,2,2-trichloroethyl)-3-cyano-furyl]-N²-R-formamidines (V). A double molar excess of amine RNH_2 was added to a solution of imino-ether IV in a minimal amount of absolute ethanol. The reaction mixture was stirred and allowed to stand at room temperature for 2 h. The reaction product was precipitated with water, and recrystallized from aqueous alcohol. Compounds Va, d, f, h, i were thus synthesized.

Compound Va was obtained by passing through a gaseous ammonia for 15 min, while in the case of compounds, Vb, c, e the amine was generated during the reaction by adding equimolar amounts of anhydrous sodium acetate and the hydrochloride or sulfate (for Vg) of the corresponding amine. The yields, melting points, and IR spectral data of the amidines are given in Table 2.

4,5-Diphenyl-2-ethoxymethyliminofuronitrile (IX) was synthesized similarly to the imino-ether IV from the corresponding 2-amino-3-furonitrile (VIII) in a yield of 84.6%, pm 93-94°C.

5-R-4-Imino-2-methyl-3-(2,2,2-trichloroethyl)-4,5-dihydrofuro-[2,3-d]pyrimidines (VI). A decimolar amount of a solution of sodium ethylate in alcohol was added to a solution of formamidines V in a minimal amount of absolute ethanol, and the mixture was allowed to stand at room temperature for 12 h. The cyclization product (VI) crystallized out from the reaction mixture. Additional amounts of the product were precipitated from the mother liquor by water, and recrystallized from aqueous alcohol.

Compounds Vj-*l* cyclize under the conditions of their preparation from ethoxyiminofuronitrile IV and the corresponding amine. The characteristics of imines VI are given in Table 3.

4-Amino-2-methyl-3-(2,2,2-trichloromethyl)furo[2,3-d]pyrimidines (VII). Furo[2,3-d]pyrimidines (VI) were boiled for 15-20 h in a minimal amount of aqueous dioxane (1:1). On cooling the rearrangement product separated out and was recrystallized from aqueous dioxane.

The yields and melting points of imines (VI) and amines (VII) are given in Table 3.

N′-(4,5-Diphenyl-3-cyano-2-furyl)-N²-R-formamidines (X) were obtained in a similar way as compounds V from imino-ether IX and the corresponding amines. The yields and melting points are given in Table 2.

5-R-4-Imino-2,3-Diphenyl-4,5-dihydrofuro[2,3-d]pyrimidines (XI) and 4-R-Amino-2,3-diphenylfuro[2,3-d]-pyrimidines (XII). A decimolar amount of sodium ethylate was added to the solution of imino-ether IX in absolute ethanol, and the mixture was allowed to stand at room temperature for 12 h. The 3-R-imino-3,4-dihydrofuro[2,3-d]pyrimidine (XI) obtained was precipitated and washed thrice with water and dried over P_2O_5. After boiling the solutions of compounds XI in a minimal amount of aqueous dioxane for 20 h, the corresponding furo[2,3-d]pyrimidines (XII) with a substituent attached to

the exocyclic nitrogen atom were separated. Furopyrimidines XIIa and XIIc were described previously [6, 10]. The characteristics of compounds XI and XII are given in Tables 3 and 4.

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