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Synthesis of 2- and 3-Acetylfuran Carbethoxyhydrazones and Investigation of Their Reaction with Thionyl Chloride

L. M. Pevzner, Yu. O. Remizov, and M. L. Petrov

St. Petersburg Institute of Technology (Technical University), Moskovskii pr. 26, St. Petersburg, 190013 Russia
e-mail: pevzner_lm@list.ru

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Abstract—By the reaction of 2- and 3-acetylfurans with ethoxycarbonyl hydrazine in presence of acetic acid a series of carboethoxyhydrazones was synthesized. On the basis of the ^{1}H NMR spectra it was shown that in the compounds obtained furyl substituent and ethoxycarbonyl group might be located both in *Z*- and in *E*-position with respect to the C=N bond. The isomer ratio for various types of substitution in the furan ring was established. It was shown that the introduction of two methyl groups in the positions adjacent to the hydrazone group leads to thermal lability of the corresponding hydrazone. 2-Acetyl-, 5-methyl-2-acetyl-, and 3-acetylfuran carbethoxyhydrazones under the action of thionyl chloride undergo cyclization to 4-furyl-1,2,3-thiadiazoles. In the case of 3-methyl-5-acetyl- and 2-methyl-3-acetylfuran a mixture of corresponding thiadiazoles and the products of chlorination of carbethoxyhyrazone fragment was formed. It was shown that the introduction of methyl group in the furan ring leads to thermal lability of furylthiadiazoles.

Keywords: acetylfuran, carbethoxyhydrazones, *cis-trans*-isomerism, 4-furyl-1,2,3-thiadiazoles

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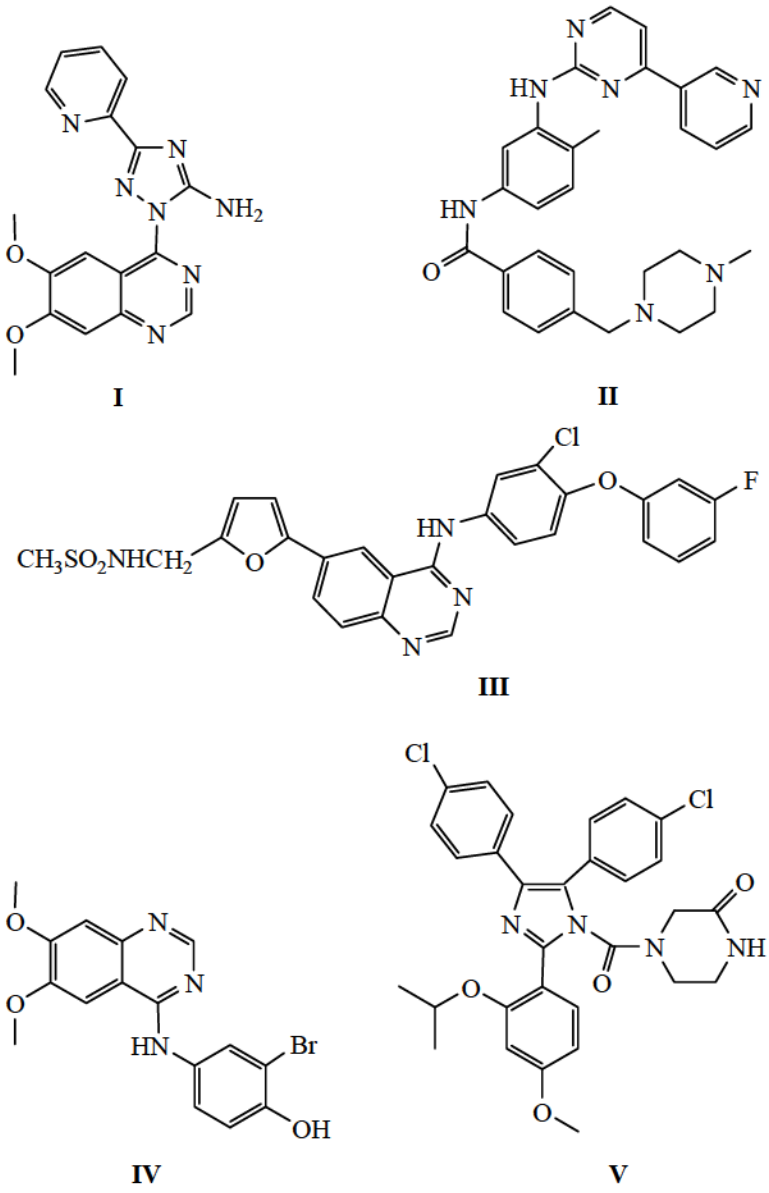
Simultaneous presence of aromatic and heteroaromatic fragments, the intramolecular donors and acceptors of electron density in the structure of a molecule provides it with the ability to bond with protein fragments. On this principle the action of many enzymes inhibitors is based. For example, we present below the structures of CP-466722 ATM-inhibitor (**I**), of protein-tyrosine kinase inhibitors ENMD-2076 (**II**), GW 57016 (**III**), WHIP-154 (**IV**), and of Nutlein-3 (**V**), the antagonist of Mdm2 enzyme taking part in starting of apoptosis [1]. These are commercial products offered for medical studies. As is seen from the presented structures, the role of acceptor fragment belongs to the nitrogen-containing heterocycle. The electron-donating fragment as a rule is the phenyl ring with donor substituents or the furan ring. Nitrogen heterocycles are pyrimidines, benzpyrimidines, 1,2,4-triazoles, pyrazines, and some other structures containing several nitrogen atoms (Scheme 1).

Analogous system may be constructed in another way using π-excessive furan ring as a donor fragment and π-deficient 1,2,3-thiadiazole as an acceptor one. The latter is comparatively easily formed by cyclization of the methyl ketone acylhydrazones under the action of thionyl chloride. 1,2,3-Thiadiazole is a sufficiently strong π-acceptor, while furan is one of the strongest π-donors. Therefore when these cycles are conjugated a high degree of polarization of the system by means of intramolecular electron density transfer can be expected.

Only two compounds of this class, 4-(2-furyl)-1,2,3-thiadiazole and 4-(5-methylfur-2-yl)-1,2,3-thiadiazole, are described [2]. These substances were synthesized from semicarbazones of 2-acetylfuran and its 5-methyl analog by the Hurd–Mori reaction under the treatment with thionyl chloride. But the properties of these compounds were not studied.

In the aromatic series the most common synthetic protocol for preparing 1,2,3-thiadiazoles is the cyclization of carbethoxyhydrazones of the acetophenone derivatives by the same Hurd–Mori reaction [3, 4]. Therefore in our work we have used a similar process. The choice of acetylfuran derivatives as starting substances was made considering the following factors. As known, even small alterations in the structure of furan, for example, the introduction of

Scheme 1.

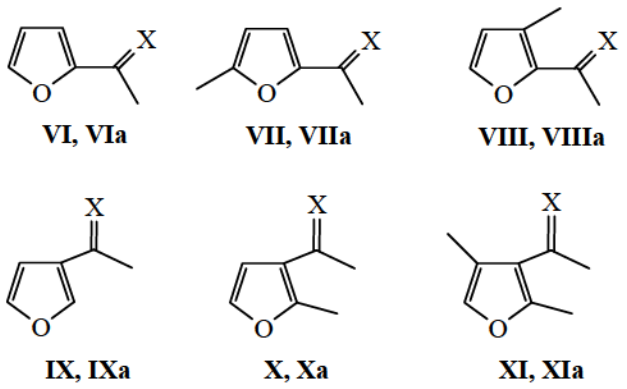


such a weak donor as a methyl group leads to significant increase in its activity in the electrophilic substitution reactions [5]. This means that the electron density in the ring significantly increases. Therefore for the increase of the electron transfer in the furan-thiadiazole pair one or two methyl groups must be introduced in the furan ring, and the series of furylthiadiazoles must be synthesized on the basis of acetylfurans of this structure. Hence, the main problem of our work was the development of a protocol for the preparation of carbohydrazones of 2- and 3-acetylfurans and their methyl derivatives and also the investigation of conditions of their cyclization under the action of thionyl chloride according to the Hurd–Mori reaction.

Acetylfurans **VI**–**XI** were chosen as starting substances (Scheme 2).

The reaction of these ketones with carbethoxy-hydrazine was carried out in ethanol at boiling in the presence of catalytic amounts of acetic acid. The compounds obtained were white or yellowish crystals. In some cases ^{1}H NMR spectra of these substances contained two sets of signals. For establishing the reasons of this effect we have considered spectral data more thoroughly.

Scheme 2.



VI, VIa **VII, VIIa** **VIII, VIIIa**

IX, IXa **X, Xa** **XI, XIa**

X = O (**VI**–**XI**), N–NHCOOEt (**VIa**–**XIa**).

As is known, the aldehyde hydrazones may exist in *syn*- and *anti*-forms characterized by the *cis*- and *trans*-location of substituents with respect to the C=N bond. For the case of hydrazones of methyl ketones *syn*-isomer will correspond to the compound with *trans*-location of methyl group and NHCOOEt fragment. In *anti*-form methyl group will be *cis*-located. It was established in [6–8] that in hydrazones of aliphatic ketones signals of protons of *cis*-located methyl or methylene group were shifted upfield with respect to the signals of *trans*-isomer. Hydrazones of arylmethyl-ketones exist only in a form of one isomer with *cis*-location of methyl group and NH-fragment with respect to the C=N bond. In the case of acetylfuran carbethoxyhydrazones **VIa**–**XIa** it occurred that in some cases isomers of hydrazones can be distinguished spectroscopically and their ratio might be established.

In the ^{1}H and ^{13}C NMR spectra of compound **VIa** only one set of signals of protons and carbon atoms was observed. Protons of the hydrazone methyl group appeared at 2.17 ppm, and the signal of the corresponding carbon atom was observed at 12.19 ppm. The signal of carbon atom from the C=N fragment overlaps with the signal of carbonyl carbon atom of the urethane group at 151.65 ppm. The introduction of additional methyl group in the position 5 of the furan ring in the case of hydrazone **VIIa** unexpectedly changes the spectral pattern. In the upfield range of the ^{1}H NMR spectrum two sets of methyl group signals appear, those at C=N bond and in the position 5 of the furan ring, at 2.13 ppm (CH_3–C=N), 2.35 ppm (CH_3-furan), 2.24 ppm (CH_3–C=N), 2.43 ppm (CH_3-furan) with the intensity ratio 1 : 1.13. Basing on the data [4–6] the signals of the first set may be attributed to isomer with the *cis*-location of methyl group and urethane fragment, and of the second one, to the corresponding *trans*-isomer. Signals of the furan ring protons of the *cis*-isomer are also located upfield with respect to the signals of protons of the *trans*-isomer.

In the ^{13}C NMR spectrum two sets of signals belonging to the corresponding isomers can be also found. Signals of the methyl group carbon atom adjacent to C=N fragment belonging to both isomers overlap, but the signals of methyl groups of the ester group, of azomethine group, and the signals of C^3 and C^4 atoms of the furan ring belonging to the *trans*-isomer are somewhat shifted downfield with respect to the signals of the *cis*-product. The largest difference (Δ 3.41 ppm) is observed for C^3 carbon atom of the furan ring. The presented data show that the structure with cis-location of methyl group and urethane fragment with respect to C=N bond may be also ascribed to the hydrazone **VIa.**

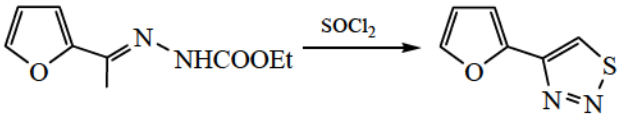
In the case of hydrazone **VIIIa** only one set of signals of protons and carbon atoms is observed in the ^{1}H and ^{13}C NMR spectra. The signal of the methyl group protons from the CH_3–CN fragment is observed at 2.18 ppm, practically in the same range, as in the case of hydrazone **VIa**. Due to that it was considered that compound **VIIIa** should exist in the *cis*-configuration.

In the case of 3-acetylfuran carbethoxyhydrazone **IXa** ^{1}H NMR spectrum also contained two sets of signals with the intensity ratio ~1 : 0.1. The signal of the methyl group protons of the CH_3–C=N fragment of the major isomer was observed at 2.10 ppm, and the corresponding signal of the minor isomer, at 2.27 ppm. Hence, compound **IXa** is present mainly as the *cis*-isomer. In the ^{13}C NMR spectra the signals only of this product were found.

The introduction of methyl group in the position 2 of the furan ring in the case of hydrazone **Xa** shifts the equilibrium to the side of isomer with the *cis*-location of methyl group and urethane fragment. ^{1}H NMR contains only one set of signals. The chemical shift of the methyl group protons from the CH_3–C=N fragment is 2.11 ppm. The reason of this effect is connected with steric hindrances from the methyl group in the position 2 of the ring. It prevents the location of urethane fragment and heteroring on the same side of the C=N bond.

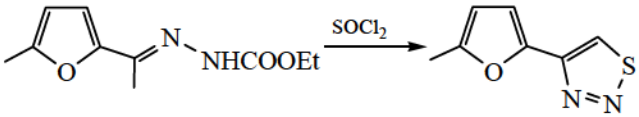
The introduction of one more methyl group in the position 4 of the furan ring in the case of hydrazone **XIa** increases steric hindrances also for the isomer

Scheme 3.



VIa **VIb**

Scheme 4.



VIIa **VIIb**

with *cis*-configuration. It shifts the equilibrium backwards, and in the ^{1}H NMR spectrum of compound **XIa** two sets of signals corresponding to *cis*- and *trans*-isomers appear again. Their attribution was made on the basis of location of the methyl group signals from CH_3–C=N fragment which were observed at 2.12 and 2.18 ppm. According to NMR data the ratio of isomers was 2 : 1.

Large sterical hindrances cause thermal lability of hydrazone **XIa**. It decomposes at storage with the formation of complex mixture of products.

Hence, in the first stage of our work a series of carbethoxyhydrazones **VIa**–**Xa** was synthresized. They were used as starting substances for preparing the derivatives of 4-[2(3)-furyl]-1,2,3-thiadiazoles. Compound **XIa** because of its lability was not brought in the Hurd–Mori reaction.

The reaction of hydrazones **VIa**–**Xa** with thionyl chloride was carried out in chloroform or carbon tetrachloride at elevated temperature at the 1 : (2–3) hydrazone–thionyl molar ratio.

Hydrazone **VIa** under the action of thionyl chloride at 50–55°C and the 1 : 3 molar ratio in the course of 1.5 h undergoes cyclization to give 4-(2-furyl)-1,2,3-thiadiazole **VIb**. After evaporation of the reaction mixture and extraction of the residue with hexane and crystallization light yellow crystals with mp 63°C were obtained. In the ^{1}H NMR spectrum of this substance the signal of the thiadiazole ring proton was observed at 8.61 ppm, and the signals of the furan ring protons, at 6.03 (1H, H^4, J_{HH} 2.0 and 3.6 Hz), 7.18 (1H, H^3, J_{HH} 3.6 Hz), and 7.58 ppm (1H, H^5, broad signal). These data well agree with [2]. Yield of compound **VIb** was 26%, while in the case of cyclization of the corresponding semicarbazone in thionyl chloride it reached 56% [2] (Scheme 3).

To reduce the action of hydrogen chloride liberating in the course of the reaction on the labile furan ring pyridine was added to the reaction mixture. It occurred that under these conditions starting hydrazone **VIa** while performing the reaction in chloroform at 50–55°C and hydrazone : thionyl : pyridine molar ratio 1 : 1 : 2 is consumed in the course of 5 min but no formation of thiadiazole **VIb** takes place. Its appearance was established by TLC only 20 min after the beginning of heating the reaction mixture, and the process came to a standstill. Only after the addition of excess thionyl chloride until the 1 : 2.5 : 2 hydrazone : thionyl : pyridine molar ratio the reaction completed in the course of 30 min. After the workup of the reaction mixture thiadiazole **VIb** was isolated in 39% yield, mp 61°C. Compound **VIb** occurred to be unstable at storage. In the course of 2–3 weeks its crystals became dark brown. ^{1}H NMR spectrum showed the appearance of the impurity signals in the range characteristic of the aliphatic protons. Their intensity increased in time.

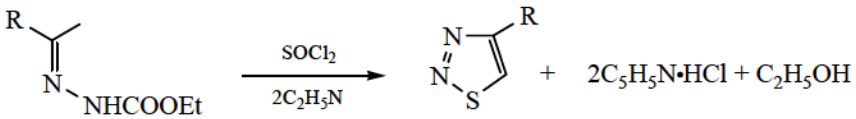
The reaction of carbethoxyhydrazone **VIIa** with thionyl chloride was carried out in carbon tetrachloride at the 1 : 2 : 2 hydrazone : thionyl : pyridine molar ratio. After removing pyridinium salts and evaporation of solvent thiadiazole **VIIb** was obtained in 86% yield (Scheme 4).

^{1}H and ^{13}C NMR spectra of the compound synthesized confirmed its structure and agreed well with the reported data [2]. In [2] compound **VIIb** was obtained in 51% yield by cyclization of the corresponding semicarbazone in thionyl chloride. Its melting point was reported to be 107°C, but we failed to obtain the crystals of this substance.

While heating in a vacuum (1 mmHg) thiadiazole **VIIb** sublimes, but its crystals and all the outer surface of the installation quickly covers with the carbon film. At higher temperatures an explosive-like decomposition of the substance takes place with the liberation of hydrogen sulfide, water, carbon, and probably of nitrogen.

From these two examples of the Hurd–Mori reaction in the furan series it follows that the presence of pyridine significantly increases the yield of furylthiadiazoles, but for the completion of the reaction excess of thionyl chloride is required. At the 1 : 1 : 2 reagent ratio corresponding to the formal equation of the reaction presented below the process stops at the stage of the formation of intermediates (Scheme 5).

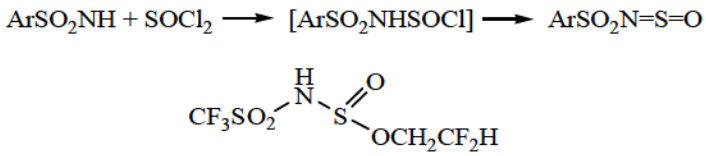
Scheme 5.



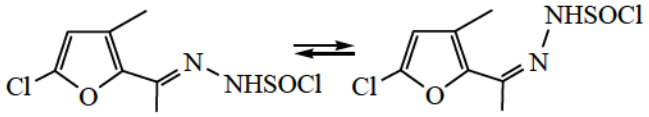
In the case of hydrazone **VIIIa** the reaction with thionyl chloride is more intricate. In the absence of pyridine the starting substance forms tar under the action of thionyl chloride. After keeping a mixture of hydrazone, pyridine, and thionyl chloride in the 1 : 2 : 3 molar ratio in chloroform for 1.5 h at 20°C a yellow crystalline product of mp 110–120°C was isolated from the reaction mixture. While keeping this substance for a week it became dark brown. Evidently it is unstable in deuterochloroform solution because in its ^{1}H NMR spectrum many signals in the range of aliphatic protons, of the furan ring protons and also at 8.5–8.7 ppm are observed. At the same time the signals of the ester ethoxy group at 1.30 ppm (triplet, CH_3, J_{HH} 7.2 Hz) and 4.23 ppm (quartet, CH_2O, J_{HH} 7.2 Hz) were identified. Unlike that the signals in the range 7.30–7.35 (H^5-furan) and 8.20–8.30 ppm (NH, hydrazone) are absent. Hence, methyl and ester group of starting substance under the conditions used do not take part in the reaction, while H^5 proton of the furan ring is evidently substituted by chlorine. From the published data it is known that while cyclization of 2-acetyl-1-hydroxynaphthalene hydrazone under the action of thionyl chloride 4-(4-chloro-1-hydroxy-naphthyl)-1,2,3-thiadiazole is formed. This means that simultaneously with the Hurd–Mori reaction the chlorination of naphthalene ring takes place [9]. The hydrogen atom of the NH fragment is most probably substituted with SOCl group in the first stage of cyclization according to the Hurd–Mori scheme [4]. The keeping of the same mixture of reagents for 1 h at 45–50°C leads to the formation of yellow crystalline product melting with decomposition at 89–90°C. ^{1}H NMR spectrum of this product in $CDCl_3$ showed that in this case several substances are also present in the solution. Signals of the ethoxy group protons, of H^5 from the furan ring, and of the hydrazone NH proton were absent. At the same time ^{13}C NMR data confirmed that the furan ring remained. Among the proton signals basing on their intensities three sets may be selected. The most intense one includes the singlets at 2.18, 2.48, 6.67, and 8.65 ppm with the intensity ratio close to 3 : 3 : 1 : 1. Chemical shift of the most upfield signal is close to that of the methyl group signal in the CH_3–C=N fragment. The second signal belongs to the range where the signals of methyl group at the furan ring are observed. The third signal may be attributed to H^4 of the furan ring. Next set of singlets with lower intensities at 2.34, 2.49, 6.75, and 8.58 ppm and the intensity ratio 3 : 3 : 1 : 1 also corresponds to a compound with methyl groups in the side chain and in the furan ring. The location of signals of the methyl group protons was close to that of 3-methyl-2-acetylfuran (2.34 and 2.42 ppm), but in the ^{13}C NMR spectrum no signal of the ketone carbonyl carbon atom was found. The downfield proton signal at 6.75 ppm in this set corresponds to H^4 atom of the furan ring. Signals of the methyl group carbon atoms in the ^{13}C NMR spectrum of the first compound under consideration were observed at 11.24 (CH_3-furan) and 31.57 ppm. The signal at 154.92 ppm may be attributed to azomethine carbon atom. As compared with the starting hydrazone **VIIIa** the signal of the second methyl group carbon atom shifted downfield to the position characteristic of methyl ketones. This means that acylhydrazone fragment transformed in a functional group with more expressed acceptor properties. Analogous picture is characteristic of the second compound. Signals of the methyl group and azomethine fragment carbon atoms were observed at 11.33 (CH_3-furan), 30.99 (CH_3–C=N), and 154.29 ppm respectively. It may be suggested that in these compounds a substitution of ethoxycarbonyl group with SOCl function takes place. From the reported data [10, 11] it is known that while treating arylsulfamides with thionyl chloride the reaction proceeds analogously, but the intermediate amidochlorosulfite stabilizes by means of hydrogen chloride abstraction. On the other hand it was shown recently [12] that if the atom of tetravalent sulfur is bound to the electron-accepting substituent (with the fluorinated alcohol residue in the reported case) the amidosulfites containing NH fragment became stable. In the ^{1}H NMR spectrum (in CD_3CN) the signal of this proton appears at 6.5–6.6 ppm (Scheme 6).

It is quite possible that in our case analogous effect takes place, but the role of acceptor is played by the chlorine atom. Meanwhile the stability of the products under consideration is quite low even at room

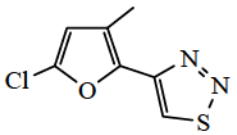
Scheme 6.



temperature. Signals at 8.65 and 8.58 ppm may be attributed to the protons of NHSOCl fragment in isomeric products of ethoxycarbonyl group substitution in 5-chloro-3-methyl-2-acetylfuran carbethoxyhydrazone. If the rule established at the evaluation of hydrazone configuration of [6–8] is fulfilled in this case, CH_3 and NHSOCl groups in the first compound have *cis*-location, and in the second one *trans*-location must take place. NHSOCl fragment is less bulky than NHCOOEt one, and due to that the ontent of *trans*-isomer occurs to be higher than in the starting hydrazone **VIIIa**.



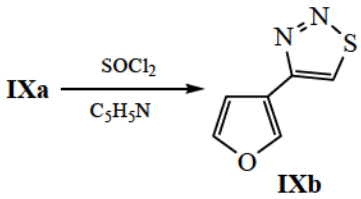
The third set of signals found in the ^{1}H NMR spectrum included three signals at 2.47, 7.04, and 8.69 ppm with the intensity ratio 3 : 1 : 1. First signal unambiguously belongs to methyl group at the furan ring. The second one may be regarded as H^4 of the furan ring, and the third one must be attributed to H^5 of thiadiazole. Signals at 129.24 and at 142.46–142.95 ppm must belong to the carbon atom of thiadiazole ring. These spectral data permit to suggest that in the course of the reaction furylthiadiazole **XII** is formed.



XII

Regretfully, because of the lability of the compounds under consideration we failed to isolate them pure. Attempts to separate the components of crystalline products lead only to tar formation.

The reaction of hydrazone **IXa** with thionyl chloride was carried out in chloroform in the presence of pyridine. Molar ratio of hydrazone, thionyl chloride, and pyridine was 1 : 3 : 2. Just after mixing of reagents the temperature of the reaction mixture spontaneously rose to 40°C. After cooling reaction the reaction mixture was kept for 1 h at room temperature and separated. Brittle carbon powder and viscous syrup were obtained. The latter was identified as 4-(3-furyl)-1,2,3-thiadiazole **IXb**. Yield of the product was 38%. Thiadiazole **IXb** occurred to be thermally unstable and at storage at room temperature it decomposed in a week.

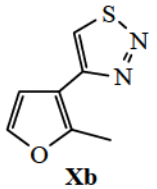


IXb

Reaction of hydrazone **Xa** with thionyl chloride was carried out in the presence of pyridine at the same reagent ratio as in the previous case. Mixing of reagents was carried out under cooling at 25°C. After that the reaction mixture was kept for 30 min at 30°C, for 1 h at 35°C, and for 30 min at 40°C. Pyridine hydrochloride was removed by washing with water. After drying and removing the solvent the syrup was obtained. Its two main components were identified. ^{1}H NMR spectrum of the first component included two singlets at 2.37 ppm (3H, CH_3–CO) and 2.55 ppm (3H, CH_3-furan), and two doublets at 6.59 ppm (1H, H^4-furan, J_{HH} 2.0 Hz) and 7.21 ppm (1H, H^5-furan, J_{HH} 2.0 Hz). Its ^{13}C NMR spectrum contained the signals at 14.28 ppm (CH_3-furan), 29.06 ppm (CH_3–CO), 110.42 (C^4-furan), 121.34 (C^3-furan), 140.24 (C^5-furan), 158.41 (C^2-furan), and 194.06 ppm (C=O). These spectral data are characteristic of 3-acetyl-2-methylfuran formed while the hydrolysis of the product of the reaction between hydrazone **Xa** and thionyl chloride because TLC showed that at the end of maintenance the starting substance was absent in the reaction mixture.

The second component of the mixture, which contained it in smaller amount had the following spectral characteristics. In its ^{1}H NMR spectrum a singlet at 2.63 ppm (3H, CH_3-furan), two doublets at 6.71 ppm (1H, H^4-furan, J_{HH} 1.8 Hz) and 7.35 ppm (1H, H^5-furan, J_{HH} 1.8 Hz), and a singlet at 8.37 ppm (1H, H^5-thiadiazole) were present. In the ^{13}C NMR spectrum signals at 13.65 ppm (CH_3-furan), 110.56 ppm (C^4-furan), 117.95 ppm (C^3-furan), 129.10 ppm

(C^5-thiadiazole), 140.24 (C^5-furan, overlaps with the signal of the first product), 141.09 ppm (C^4-thiadiazole), and 151.10 ppm (C^2-furan) were observed. These spectral data may be attributed to the structure **Xb**.



Xb

We failed to identify minor products of this mixture, but it must be noted that in the ^{1}H NMR spectrum singlets at 2.23 and 2.39 ppm and two downfield singlets at 8.45 and 8.66 ppm were observed. Their intensity ratio was about 3 : 3 : 1 : 1. In the ^{13}C NMR spectrum signals at 31.89, 32.71, 153.69, and 153.87 ppm were found. These signals may be attributed to the CH_3–C=N–NHSOCl structure fragment. This means that in the case of hydrazone **Xa** products of substitution of ethoxycarbonyl group in hydrazone residue similarly to the above-described case of compound **VIIIa** were probably formed.

From the presented data it follows that in the reaction of hydrazone **Xa** with thionyl chloride the main reaction product is the compound which under the action of water gives 2-methyl-3-acetylfuran. We failed to establish whether this substance is the precursor of thiadiazole **Xb** or it was formed in parallel because of accumulation of tar in the course of the process.

Hence, the route of the reaction of carbethoxyhydrazone with thionyl chloride significantly depends on the structure of the furan fragment. If the furan ring contains no substituents or the methyl group is remote from the reaction center the formation of 4-furyl-1,2,3-thiadiazole is observed. The addition of pyridine catalyzes the reaction, and in some cases its presence allows a successful proceeding of the process. If methyl group occupies the position in the furan ring adjacent to the hydrazone fragment, additional reaction pathways competing with the formation of thiadiazole ring appear. In any case furylthiadiazoles are rather thermally unstable, and the increase in electron density in the furan ring enhances this lability. Thermal stability of 4-furyl-1,2,3-thiadiazole fragment can be probably provided by introduction of electron-acceptor groups in the furan ring.

EXPERIMENTAL

Melting points were measured on a Boëtius apparatus. ^{1}H and ^{13}C NMR spectra were taken on a Bruker DPX-400 spectrometer [400.13 MHz (^{1}H), 100.16 MHz (^{13}C)] in $CDCl_3$. Mass spectra were obtained on a FinniganINCOS MAT 95 mass spectrometer with the direct admission of sample (energy of ionizing electrons 70 eV, ionization cell temperature 200°C). The reaction progress was monitored by TLC on Silufol UV-254 plates, development with UV light and iodine vapor. All the solvents used were purified and dried according to the standard procedures.

Synthesis of acetylfuran carbethoxyhydrazones *(general procedure)*. To a solution of 0.025 mol of acetylfuran in 10 mL of ethanol 0.025 mol of ethoxycarbonylhydrazine and 5 drops of acetic acid were added. The mixture obtained was stirred at boiling. The reaction progress was monitored by TLC (Silufol, ethyl acetate–hexane, 3 : 2, development with the iodine vapor). After the reaction was completed the reaction mixture was poured in 50 mL of water. The crystals formed were filtered off and dried in air.

2-Acetylfuran carbethoxyhydrazone (VIa). Reaction time 10 min. Yield 75%, mp 151°C. ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, CH_3, J_{HH} 7.2 Hz), 2.17 s (3H, CH_3-hydrazone), 4.32 q (2H, CH_2O, J_{HH} 7.2 Hz), 6.44 s (1H, H^4-furan), 6.74 s (1H, H^3-furan), 7.47 s (1H, H^5-furan), 8.09 br.s (NH). ^{13}C NMR spectrum, δ_C, ppm: 12.19 (CH_3-hydrazone), 14.54 (CH_3-ethyl), 62.20 (CH_2O), 110.22 (C^4-furan), 111.54 (C^3-furan), 140.75 (C^5-furan), 143.75 (C^2-furan), 151.65 (C=N + C=O). Mass spectrum, *m/z* (I_{rel}, %): 196 (49) $[M]^+$, 150 (6), 137 (18), 123 (17) $[M - CO_2Et]^+$, 108 (10) $[M - NHCO_2Et]^+$, 95 (52), 81 (15), 66 (25), 54 (16), 39 (47), 29 (100). Found, %: C 40.13, 40.18; H 2.41, 2.57. $C_9H_{12}N_2O_3$. Calculated, %: C 55.23; H 6.28, N 14.11. *M* 196.204.

5-Methyl-2-acetylfuran carbethoxyhydrazone (VIIa). Reaction time 10 min, yield 65%, mp 107°C. ^{1}H NMR spectrum, δ, ppm: common signals: 1.35 t (3H, CH_3, J_{HH} 6.8 Hz), 4.31 q (2H, CH_2O, J_{HH} 6.8 Hz),7.85 br.s (NH); *cis*-form: 2.13 s (3H, CH_3-hydrazone), 2.35 s (3H, CH_3-furan), 6.04 d (1H, H^4-furan, J_{HH} 3.2 Hz), 6.62 d (1H, H^3-furan, J_{HH} 3.2 Hz); *trans*-form: 2.24 s (3H, CH_3-hydrazone), 2.43 s (3H, CH_3-furan), 6.13 d (1H, H^4-furan, J_{HH} 3.2 Hz), 6.70 d (1H, H^3-furan, J_{HH} 3.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: *cis*-form: 12.12 (CH_3-hydrazone), 13.89 (CH_3-

furan), 14.54 (CH_3-ethyl), 62.06 (CH_2O), 107.85 (C^4-furan), 111.98 (C^3-furan), 148.08 (C^2-furan), 149.87 (C^5-furan), 154.19 and 154.30 (C=N and C=O); *trans*-form: 12.12 (CH_3-hydrazone), 13.96 (CH_3-furan), 14.65 (CH_3-ethyl), 62.06 (CH_2O), 107.81 (C^4-furan), 115.39 (C^3-furan), 148.08 (C^2-furan), 149.87 (C^5-furan), 154.20 and 154.30 (C=N and C=O). Mass spectrum, *m/z* (I_{rel}, %): 210 (33) $[M]^+$, 137 (8) $[M - CO_2Et]^+$, 109 (52), 93 (25), 68 (21), 53 (25),43 (42), 39 (17), 29 (100). Found, %: C 57.29, H 6.47, N 13.14. $C_{10}H_{14}N_2O_3$. Calculated, %: C 57.13; H 6.71, N 13.33. *M* 210.231.

3-Methyl-2-acetylfuran carbethoxyhydrazone (VIIIa). Reaction time 1 h. Yield 74%, mp 103–104°C. ^{1}H NMR spectrum, δ, ppm: 1.34 t (3H, CH_3, J_{HH} 7.2 Hz), 2.18 s (3H, CH_3-hydrazone), 2.34 s (3H, CH_3-furan), 4.29 q (2H, CH_2O, J_{HH} 7.2 Hz), 6.31 d (1H, H^4-furan, J_{HH} 1.6 Hz), 7.30 d (1H, H^5-furan, J_{HH} 1.6 Hz), 8.24 br.s (NH). ^{13}C NMR spectrum δ_C, ppm: 11.91 and 11.98 (CH_3-hydrazone and CH_3-furan), 14.49 (CH_3-ethyl), 61.89 (CH_2O), 115.52 (C^4-furan), 120.92 (C^3-furan), 141.28 (C^5-furan), 143.23 br.s (C=N), 146.89 (C^2-furan), 154.34 br.s (C=O).

3-Acetylfuran carbethoxyhydrazone (IXa). Reaction time 2 h. Yield 64%, mp 98–99°C. ^{1}H NMR spectrum, δ, ppm: common signals: 1.34 t (3H, CH_3, J_{HH} 7.2 Hz), 4.29 q (2H, CH_2O, J_{HH} 7.2 Hz), 7.95 br.s (NH); *cis*-form: 2.10 s (3H, CH_3-hydrazone), 6.87 br.s (1H, H^4-furan), 7.39 d.d (1H, H^5-furan, J_{HH} 1.6 Hz); 7.66 br.s (H^2-furan); *trans*-form: 2.27 s (3H, CH_3-hydrazone), 6.77 br.s (1H, H^4-furan), 7.44 d.d (1H, H^5-furan, J_{HH} 1.6 Hz); 7.72 br.s (H^2-furan). ^{13}C NMR spectrum, δ_C, ppm.: 13.65 (CH_3-hydrazone), 14.54 (CH_3-ethyl), 61.95 (CH_2O), 108.23 (C^4-furan), 126.62 (C^3-furan), 141.76 (C^5-furan), 143.83 (C^2-furan), 144.36 (C=N), 147.56 (C=O).

2-Methyl-3-acetylfuran carbethoxyhydrazone (Xa). Reaction time 3.5 h. Yield 82%, mp 58–59°C. ^{1}H NMR spectrum, δ, ppm: 1.36 t (3H, CH_3, J_{HH} 7.0 Hz), 2.11 s (3H, CH_3-hydrazone), 2.56 s (3H, CH_3-furan), 4.31 q (2H, CH_2O, J_{HH} 7.0 Hz), 6.51 d (1H, H^4-furan, J_{HH} 1.6 Hz), 7.25 d (1H, H^5-furan, J_{HH} 1.6 Hz), 7.73 br.s (NH). ^{13}C NMR spectrum δ_C, ppm: 14.12 and 14.36 and 14.55 (CH_3-hydrazone and CH_3-furan and CH_3-ethyl), 61.65 (CH_2O), 109.96 (C^4-furan), 119.37 (C^3-furan), 140.02 (C^5-furan), 151.55 (C^2-furan), 155.11 (C=N) 161.49 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 210 (17) $[M]^+$, 137 (8) $[M - CO_2Et]^+$, 109 (27), 79 (17), 68 (24), 52 (12),43 (21), 39 (12), 29 (100). Found, %: C 57.31, H 6.887, N 13.42. $C_{10}H_{14}N_2O_3$. Calculated, %: C 57.13; H 6.71, N 13.33. *M* 210.231.

2,4-Dimethyl-3-acetylfuran carbethoxyhydrazone (XIa). Reaction time 1.5 h. Yield 52%, mp 99–100°C. ^{1}H NMR spectrum, δ, ppm: common signals: 1.36 t (3H, CH_3, J_{HH} 7.2 Hz), 4.29 q (2H, CH_2O, J_{HH} 7.2 Hz); *cis*-form: 2.05 d (3H, CH_3^4-furan, J_{HH} 1.2 Hz), 2.12 s (3H, CH_3-hydrazone), 2.37 s (3H, CH_3^2-furan), 7.03 br.s (H^2-furan), 7.93 br.s (NH); *trans*-form: 1.90 d (3H, CH_3^4-furan, J_{HH} 0.8 Hz), 2.18 s (3H, CH_3-hydrazone), 2.30 s (3H, CH_3^2-furan), 7.18 br.s (H^2-furan), 7.75 br.s (NH). Mass spectrum, *m/z* (I_{rel}, %): 224 (16) $[M]^+$, 151 (13) $[M - CO_2Et]^+$, 136 (8) $[M - NHCO_2Et]^+$, 123 (46), 94 (12), 77 (18),66 (16), 43 (26), 29 (100). Found, %: C 59.13, H 7.43, N 12.17. $C_{10}H_{14}N_2O_3$. Calculated, %: C 58.91; H 7.19, N 12.49. *M* 224.258.

2-(2-Furyl)-1,2,3-thiadiazole (VIb). *a. In the absence of pyridine.* To a solution of 1 g of carbethoxyhydrazone **VIa** in 10 mL of chloroform 1.1 mL of thionyl chloride was added. The mixture obtained was heated at 50–55°C. The reaction progress was monitored by TLC (Silufol, ethyl acetate-hexane, 2 : 3) After the reaction was complete (2 h) the reaction mixture was evaporated, and the residue was extracted with boiling hexane. After removing hexane 0.2 g (26%) of 4-(2-furyl)-1,2,3-thiadiazole, mp 63°C (mp 62°C [2]) was obtained. ^{1}H NMR spectrum, δ, ppm: 6.60 d.d (1H, H^4-furan, J_{HH} 2.0 Hz, 3.6 Hz); 7.18 d (1H, H^3-furan, J_{HH} 3.6 Hz); 7.58 br.s (1H, H^5-furan), 8.61 s (1H, H^5-thiadiazole).

b. In the presence of pyridine. To a solution of 1 g of carbethoxyhydrazone **VIa** in 10 mL of chloroform 0.4 mL of thionyl chloride and 0.8 mL of pyridine were added. The mixture obtained was heated with stirring at 50–55°C. Reaction progress was controlled by TLC (Silufol, ethyl acetate-hexane, 3 : 2). 5 min later additional 0.6 mL of thionyl chloride was added and stirring was continued for 30 min. Then solvent was removed, the residue was extracted with boiling hexane, the extract was washed with water and dried over calcium chloride. After removing hexane 0.3 g (39%) of 4-(2-furyl)-1,2,3-thiadiazole, mp 61°C, was obtained.

4-(5-Methylfur-2-yl)-1,2,3-thiadiazole (VIIb). To a suspension of 3.5 g of carbethoxyhydrazone **VIIa** in 30 mL of carbon tetrachloride 2.7 mL of pyridine and 2.5 mL of thionyl chloride was added. The reaction mixture was stirred at 50°C for 1.5 h. The reaction progress was monitored by TLC (Silufol, ethyl acetate-

hexane, 5 : 2). After the end of the reaction the mixture was cooled to room temperature, diluted with 20 mL of carbon tetrachloride, and washed with 40 mL of water. The obtained emulsion was filtered through a paper filter, and the water layer was separated. The organic layer was washed with water (3 × 10 mL) and dried over calcium chloride. The solvent was removed to give 2.4 g (86%) of thiadiazole **VIIb,** viscous syrup. ^{1}H NMR spectrum, δ, ppm: 2.41 s (3H, CH_3-furan), 6.16 br.s (1H, H^4-furan), 7.02 d (1H, H^3-furan, J_{HH} 3.2 Hz), 8.50 s (1H, H^5-thiadiazole). ^{13}C NMR spectrum δ_C, ppm: 13.09 (CH_3-furan), 107.99 (C^4-furan), 110.50 (C^3-furan), 127.31 (C^5-thiadiazole), 145.03 (C^4-thiadiazole), 153.60 (C^2-furan), 155.04 (C^5-furan).

Reaction of carbethoxyhydrazone (VIIIa) with thionyl chloride. *a. At room temperature.* To a solution of 1 g of carbethoxyhydrazone **VIIIa** in 5 mL of chloroform 0.8 mL of pyridine and 1 mL of thionyl chloride was added. The reaction mixture was stirred at room temperature for 1.5 h, The reaction progress was monitored by TLC (Silufol, ethyl acetate-cyclohexane, 3 : 2). After the end of the reaction the mixture was washed with water (3 × 5 mL) and dried over sodium sulfate. After removing chloroform the residue was dissolved in carbon tetrachloride and the solution obtained was poured in small portions to hexane. Yellow crystals were formed which were filtered off and dried in air. Yield 0.6 g, mp 110–120°C.

b. At 45–50°C. To a solution of 1 g of carbethoxyhydrazone **VIIIa** in 5 mL of chloroform 0.8 mL of pyridine and 1 mL of thionyl chloride was added. After addition of reagents the heating of reaction mixture to 45°C was observed. The mixture obtained was stirred at 45–50°C for 1 h. The reaction progress was monitored by TLC (Silufol, ethyl acetate–cyclohexane, 3 : 2). On completion of the reaction the mixture was washed with water (2 × 3 mL) and dried over calcium chloride. After evaporation of solvent the residual tar was dissolved in small amount of chloroform and poured in hexane. The obtained yellowish orange precipitate was filtered off and dried in air. Yield 0.45 g, mp 89–90°C.

4-(3-Furyl)-1,2,3-thiadiazole (IXb). To a solution of 1 g of carbethoxyhydrazone **IXa** in 6 mL of chloroform 0.8 mL of pyridine and 1.1 mL of thionyl chloride was added. After addition of reagents the heating of reaction mixture to 40°C was observed. The mixture obtained was cooled to 20°C and stirred at this temperature for 5 h. The reaction progress was monitored by TLC (Silufol, ethyl acetate–cyclohexane, 3 : 2). The reaction mixture on completion was washed with water (3 × 4 mL), dried over calcium chloride, and evaporated to dryness. The residue was dissolved in small amount of chloroform, and the solution obtained was poured in small portions with stirring in carbon tetrachloride. The obtained precipitate was filtered off, and the filtrate was evaporated to dryness to give 0.3 g (38%) of thiadiazole **IXb**. ^{1}H NMR spectrum, δ, ppm: 6.83 s (1H, H^4-furan), 7.49 s (1H, H^5-furan), 8.07 s (1H, H^2-furan), 8.45 s (1H, H^5-thiadiazole). ^{13}C NMR spectrum δ_C, ppm: 109.25 (C^4-furan), 117.66 (C^3-furan), 129.37 (C^5-thiadiazole), 143.97 (C^4-thiadiazole), 141.31 (C^5-furan), 155.53 (C^2-furan).

Reaction of carbethoxyhydrazone Xa with thionyl chloride. To a solution of 1 g of carbethoxyhydrazone **Xa** in 7 mL of chloroform 0.8 mL of pyridine and 1 mL of thionyl chloride was added at 25°C. The reaction mixture was stirred for 30 min at 30°C, for 1 h at 35°C, and for 30 min at 40°C. The reaction progress was monitored by TLC (Silufol, ethyl acetate-cyclohexane, 3 : 2). After the reaction was complete, the reaction mixture was cooled to room temperature, washed with water (3 × 5 mL), dried over calcium chloride, and evaporated to dryness. The residue was triturated with carbon tetrachloride, brownish black precipitate was filtered off, and the filtrate was evaporated to give 0.2 g of viscous oil containing 2-methyl-3-acetylfuran and 4-(2-methylfur-3-yl)thiadiazole.

2-Methyl-3-acetylfuran. ^{1}H NMR spectrum, δ, ppm: 2.37 s (3H, CH_3-CO), 2.55 s (3H, CH_3-furan), 6.59 d (1H, H^4-furan, J_{HH} 2.0 Hz), 7.21 d (1H, H^5-furan, J_{HH} 2.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 14.28 (CH_3-furan), 29.06 ($\underline{C}H_3$–CO), 110.42 (C^4-furan), 121.34 (C^3-furan), 140.24 (C^5-furan), 158.41 (C^2-furan), 194.06 (C=O).

4-(2-Methylfur-3-yl)-1,2,3-thiadiazole. ^{1}H NMR spectrum, δ, ppm: 2.63 s (3H, CH_3-furan), 6.73 d (1H, H^4-furan, J_{HH} 1.8 Hz), 7.35 d (1H, H^5-furan, J_{HH} 1.8 Hz), 8.37 s (1H, H^5-thiadiazole). ^{13}C NMR spectrum, δ_C, ppm: 13.65 (CH_3-furan), 110.56 (C^4-furan), 117.95 (C^3-furan), 129.10 (C^5-thiadiazole), 140.24 (C^5-furan), 141.09 (C^4-thiadiazole), 151.11 (C^2-furan).

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