Nucleophilic vinyl substitution
Synthesis and stereochemistry of new enamino ketones of furan series

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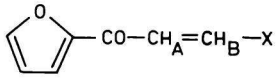
On nucleophilic displacement of chlorine in (*E*)-1-(2-furyl)-3-chloro-2--propen-1-one with primary aromatic amines and secondary aliphatic and alicyclic amines enamino ketones have been obtained. While the products with secondary amines retained the original *E* configuration of the molecule, the configuration of the products with aromatic primary amines was changed totally. Alternative methods for the preparation of some enamino ketones, utilizing the reactions of 2-acetylfuran and furfurylideneacetone with dimethylformamide dimethyl acetal and Gold salt, respectively, are presented. Stereochemistry of the prepared enamino ketones has been studied by ^{1}H NMR spectroscopy.

В результате нуклеофильного замещения хлора в (*E*)-1-(2-фурил)--3-хлор-2-пропен-1-оне первичными ароматическими аминами и вторичными алифатическими и алициклическими аминами были получены енаминокетоны. Продукты реакции со вторичными аминами сохраняли исходную *E* конфигурацию молекулы, в то время, как конфигурация продуктов замещения ароматическими первичными аминами была полностью изменена. Приводятся альтернативные методы получения некоторых енаминокетонов с помощью реакций 2-ацетилфурана и фурфурилиденацетона с диметилацеталем диметилформамида или солью Голда соответственно. Стереохимия полученных енаминокетонов изучалась с помощью ^{1}H ЯМР спектроскопии.

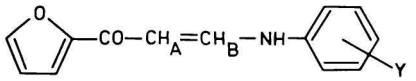
Chlorovinyl ketones readily react in S_NV reactions with amines [1—4] giving highly reactive enamino ketones, stable equivalents of 1,3-aldehydo ketones [3]. Enamino ketones of furan series have not been studied so far, except for the works of *Saikachi* [5] and *Vereshchagin* [6].

(*E*)-1-(2-Furyl)-3-chloro-2-propen-1-one (*I*) was used as model compound for the study of S_NV reaction with secondary aliphatic and alicyclic and primary aromatic amines. This compound enters the reaction with secondary amines in aprotic nonpolar solvents at room temperature already under formation of 85 to

90 % enamino ketones *III*—*VI*. The synthesized enamino ketones have retained the (*E*) configuration of the molecule *I* (Scheme 1).



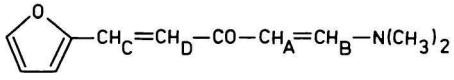
I–*VI*



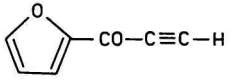
VII–*X*

	X
I	Cl
II	$\overset{+}{N}(CH_3)_3 \cdot Cl^-$
III	$N(CH_3)_2$
IV	
V	
VI	

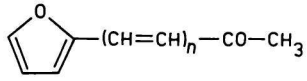
	Y
VII	H
VIII	3-CH_3
IX	4-CH_3
X	4-Cl



XI

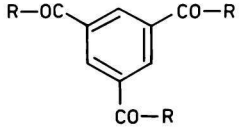


XII



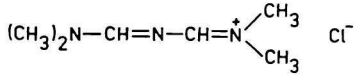
XIII $n = 0$

XIV $n = 1$



XV

R = 2-furyl



XVI

Scheme 1

The problem of proving the mechanism of S_NV reaction of ketovinyl halides with secondary amines was studied by several authors [1—3, 7] and the data obtained point to addition-elimination way [3]. *Popov* and *Kostenko* [7] assumed on the basis of kinetic measurements that the reactions of ketovinyl halides with secondary amines proceed through a low-polar transition state under formation of hydrogen bond between the addition product and oxygen of the keto group. On

Table 1

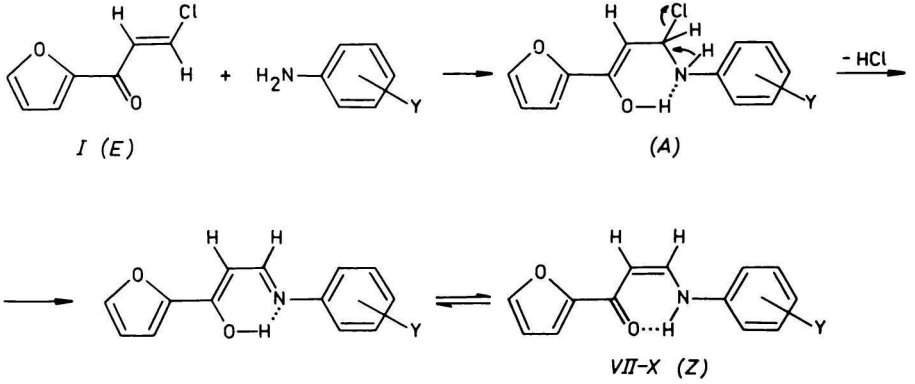
^{1}H NMR data (δ/ppm; J/Hz) of the compounds *III*—*XI*

Compound	Isomer	Solvent	H-3[a]	H-4[a]	H-5[a]	H_A	H_B	$J_{A,B}$	NH	$J_{NH,B}$	Other signals
III	*E*	*b*	7.06	6.49	7.48	5.67 d	7.78 d	12.5	—	—	3.03 $N(CH_3)_2$
IV	*E*	*b*	7.05	6.43	7.48	5.78 d	7.76 d	12.5	—	—	3.36 $N(CH_2—)_2$; 1.66 $(—CH_2—)_2$
V	*E*	*b*	7.06	6.43	7.41	5.63 d	7.99 d	12.5	—	—	3.44 $N(CH_2—)_2$; 1.98 $(—CH_2—)_3$
VI	*E*	*b*	7.07	6.47	7.49	5.83 d	7.70 d	12.1	—	—	3.38 $N(CH_2—)_2$; 3.74 $O(CH_2—)_2$
VII	*Z*	*b*	7.06	6.47	7.50	5.89 d	7.43 dd	7.8	11.90 d	12.0	6.70—7.20 m (H_{arom})
VII[d]	*Z*	*c*	7.18	6.67	7.88	5.94 d	7.82 bd	7.8	11.70 bs	*f*	6.90—7.50 m (H_{arom})
	E	*c*	*e*	6.67	7.78	6.37 d	8.19 bd	12.6	10.10 bs	*f*	6.90—7.50 m (H_{arom})
VIII	*Z*	*b*	7.08	6.50	7.50	5.88 d	7.42 dd	7.7	11.90 d	12.5	6.96 d; 7.11 d (H_{arom}); 2.25 (CH_3)
VIII[d]	*Z*	*c*	7.23	6.65	7.87	5.87 d	7.95 dd	7.7	11.76 d	12.5	7.08 bs (H_{arom}); 2.25 (CH_3)
	E	*c*	7.10	6.65	7.87	6.27 d	8.08 dd	12.5	10.07 d	12.5	7.16 bs (H_{arom}); 2.25 (CH_3)
IX	*Z*	*b*	7.10	6.50	7.52	5.90 d	7.47 dd	7.7	11.90 d	12.5	6.75—7.25 m (H_{arom}); 2.33 (CH_3)
IX[d]	*Z*	*c*	7.26	6.67	7.88	5.94 d	7.83 dd	7.8	11.80 d	12.5	6.75—7.35 m (H_{arom}); 2.30 (CH_3)
	E	*c*	7.22	6.67	7.88	6.39 d	8.22 dd	12.6	10.17 d	12.5	6.75—7.35 m (H_{arom}); 2.30 (CH_3)
X	*Z*	*b*	7.08	6.49	7.51	5.89 d	7.36 dd	7.8	11.90 d	12.0	6.95 d; 7.24 d (H_{arom})
X[d]	*Z*	*c*	*e*	6.67	7.82	5.93 d	7.82 d	8.0	11.62 bs	*f*	7.17 d; 7.37 (H_{arom})
	E	*c*	7.23	6.67	7.82	6.33 d	8.09 d	12.5	10.10 bs	*f*	7.35 d; 7.35 (H_{arom})
XI	*E*	*b*	6.53	6.43	7.43	5.12 d	7.69 d	12.2	—	—	7.35 (H_C); 6.70 (H_D); $J_{A,B}$ = 15.5

a) $J_{3,4}$ = 3.5 Hz, $J_{4,5}$ = 1.7 Hz, $J_{3,5}$ = 0.8 Hz; *b*) deuteriochloroform; *c*) hexadeuteriodimethyl sulfoxide; *d*) data for the mixture of *Z* and *E* isomers; *e*) in multiplet H_{arom}; *f*) undistinguished.

the basis of the experiments in formation of *III—VI* we assume, in accordance with the papers [2, 7], a multi-step addition-elimination mechanism in the studied S_Nv reactions. The product of elimination-addition way [2], 1-(2-furyl)-2-propin--1-one (*XII*) [6], was not observed. In the reaction of *I* with secondary amines in aqueous medium partial hydrolysis of *I* took place, giving 1,3,5-tri-(2-furoyl)benzene (*XV*) [8].

Aromatic primary amines react with *I* at room temperature already. ^{1}H NMR studies of stereochemistry of the formed products showed that the configuration of enamino ketones *VII—X* was changed against that of the starting compound *I*, which was *E* isomer. The ^{1}H NMR spectral data are presented in Table 1. These compounds occurred in deuteriochloroform solution as *Z* isomers, as proved by the values of coupling constants of vicinal protons of the double bond $J_{A,B} = 7.7—7.8$ Hz. The signal of the NH group appeared as a doublet at $\delta = 11.90$ ppm with coupling constant $J_{NH,B} = 12.5$ Hz. The value of this constant confirms the *trans* arrangement of the NH and H_B protons [9, 10]. The chemical shift of the signal for the NH group has not changed either by increasing the temperature or by diluting the solution. This fact points to intramolecular hydrogen bond between the carbonyl and NH groups. Total change of configuration by formation of *Z* isomers of the compounds *VII—X* can be explained on the basis of addition-elimination mechanism of the S_Nv reaction of *I* with primary aromatic amines through the low-polar transition state (*A*) under formation of intramolecular hydrogen bond (Scheme 2). The strength of this bond can be evidenced also by the fact that isomerization of *Z* to *E* isomer has not taken place even on crystallization from methanol.



Scheme 2

When recording the ^{1}H NMR spectra of the compounds *VII—X* in hexadeuteriodimethyl sulfoxide both *Z* and *E* isomers were found in the ratio of

~1:1, which did not change on heating or standing of the solution for longer time. The coupling constant of *E* isomers was found to be $J_{A,B} = 12.6$ Hz and that of *Z* isomers $J_{A,B} = 7.8$—8.0 Hz. In DMSO-d_6 solution the signal for the NH group appeared with both *Z* and *E* isomers as a doublet with coupling constant $J_{NH,B} = 12.5$ Hz, confirming the *trans* arrangement of NH—CH_B protons in both isomers. The signal of NH proton in *E* isomers appeared at higher magnetic field than that of NH proton in *Z* isomers and, contrary to *Z* isomers, increased temperature or dilution of the solution brought about a shift of this signal to higher field. Isomerization of *Z* to *E* isomer is a consequence of formation of intermolecular hydrogen bond between dimethyl sulfoxide and hydrogen of the amino group which eliminated the intramolecular stabilization of *Z* isomers.

The synthesized enamino ketones as important stable equivalents of 1,3--aldehydo ketones were utilized in synthesis of furyl-substituted heterocycles [11]. For preparative purposes also other methods for the preparation of these compounds were investigated. Preparation of *III* in high yield was solved by condensation of 2-acetylfuran (*XIII*) [12] with dimethylformamide dimethyl acetal at 120 °C and Gold salt (*XVI*), respectively. These reactions were applied also in preparation of the vinyl analogue *III* of the compound *XI*. Condensation of the easily available furfurylideneacetone (*XIV*) [13] with dimethylformamide dimethyl acetal resulted in 92 % while with Gold salt in 87 % yield of the enamino ketone *XI*.

Experimental

Melting points were determined on a Kofler block. UV spectra were measured on a Specord UV VIS (Zeiss, Jena) spectrophotometer in methanol and ^{1}H NMR spectra were recorded on a Tesla BS 487 C spectrometer at 80 MHz in deuteriochloroform and hexadeuteriodimethyl sulfoxide using tetramethylsilane as internal standard. The INDOR technique was used to assign the signals.

1-(2-Furyl)-3-chloro-2-propen-1-one (*I*) [4, 14], 3-(2-furyl)-3-oxo-1-propenyl-trimethylammonium chloride (*II*) [4, 5], 1-(2-furyl)-2-propin-1-one (*XII*) [6], 2-acetylfuran (*XIII*) [12], and furfurylideneacetone (*XIV*) [13] were prepared according to the literature given at the individual compounds.

1-(2-Furyl)-3-X-2-propen-1-ones III—VI

Method A

To the solution of *I* (1.56 g; 0.01 mol) in benzene (25 cm^3) the respective secondary amine (0.02 mol) was added under cooling and the reaction mixture was stirred at room temperature for 6 h. After filtration of ammonium chloride the solvent was distilled off *in vacuo* and the residue was purified by crystallization. Characterization of the compounds is presented in Tables 1 and 2.

Table 2

Physicochemical properties of the compounds *IV*—*XI*

Compound	Formula M_r	w_i(calc.)/% w_i(found)/%			Yield	M.p./°C Solvent[a]	λ_{max}/nm log (ε/(m^2 mol^{-1}))			
		C	H	N	%					
III	$C_9H_{11}NO_2$	65.48	6.66	8.48	*b*	85—87	206	229	280	355
	165.0	65.46	6.65	8.46		n-Heptane	3.68	3.64	3.95	4.47
IV	$C_{11}H_{13}NO_2$	69.13	6.80	7.33	87	90—92	206	230	280	360
	191.1	69.11	6.77	7.32		n-Heptane	3.68	3.64	3.90	4.46
V	$C_{12}H_{15}NO_2$	70.27	7.31	6.83	85	97—99	207	230	280	363
	205.1	70.25	7.30	6.83		Benzene	3.72	3.76	3.98	4.53
VI	$C_{11}H_{13}NO_3$	63.80	6.23	6.76	89	146—148	207	230	280	358
	207.1	63.79	6.23	6.74		Benzene	3.73	3.70	3.93	4.49
VII	$C_{13}H_{11}NO_2$	73.26	5.16	6.57	89	124—126	206	240	288	388
	213.1	73.23	5.13	6.55		Methanol	3.96	3.89	3.90	4.49
VIII	$C_{14}H_{13}NO_2$	74.03	5.28	6.17	91	99—100	207	244	288	399
	227.1	74.00	5.26	6.14		Methanol	4.20	3.94	3.94	4.53
IX	$C_{14}H_{13}NO_2$	74.03	5.28	6.17	87	143—144	207	244	288	392
	227.1	74.01	5.28	6.15		Methanol	4.05	3.92	3.92	4.51
X	$C_{13}H_{10}ClNO_2$	74.03	5.28	6.17	85	139—140	206	253	289	389
	247.5	73.99	5.27	6.15		Methanol	4.03	3.90	3.92	4.56
XI	$C_{11}H_{13}NO_2$	69.13	6.80	7.33	*c*	126—128	207	255	—	377
	191.1	69.12	6.79	7.30		n-Heptane	3.78	3.70	—	4.45

a) Solvent used for crystallization; *b*) 90 (*A*), 80 (*B*), 60 (*C*), 85 (*D*), (*A*, *B*, *C*, *D* = methods of preparation described in Experimental); *c*) 92 (*B*), 87 (*D*).

1-(2-Furyl)-3-(N,N-dimethylamino)-2-propen-1-one (III)

Method B

The compound *XIII* (1.1 g; 0.01 mol) was dissolved in dimethylformamide dimethyl acetal (3 g) and the solution was heated at 120 °C for 2 h. Then water (20 cm^3) was added and the crystalline precipitate was filtered off and recrystallized from n-heptane. Yield = 1.3 g (80 %), m.p. = 85—86 °C.

Method C

The compound *II* (2.1 g; 0.01 mol) was suspended in the mixture of water (20 cm^3) and xylene (10 cm^3). After 20 h reflux 1 g (60 %) of *III* was obtained.

Method D

To the solution of sodium (1.5 g) in methanol (100 cm^3) acetylfuran (5.5 g; 0.05 mol) was added at room temperature and the solution was stirred for 10 min. After addition of Gold salt (*XVI*) (10.6 g) [12] the solution was stirred and refluxed for 8 h. After cooling the solvent was distilled off *in vacuo*. The residue was dissolved in chloroform (100 cm^3) and extracted twice with saturated aqueous solution of sodium carbonate (30 cm^3). The chloroform layer was dried with Na_2SO_4, the solvent was distilled off, and the residue was crystallized from n-heptane.

1-(2-Furyl)-3-(Y-anilino)-2-propen-1-ones VII—X

To the solution of *I* (1.56 g; 0.01 mol) in benzene (25 cm^3) the respective substituted aniline (0.02 mol) in benzene (25 cm^3) was added at room temperature. The reaction mixture was stirred at this temperature for 24 h and then the respective anilinium chloride was filtered off. After distillation of the solvent the residue was crystallized from methanol. Characterization of the compounds obtained is presented in Tables 1 and 2.

1-(2-Furyl)-5-dimethylamino-1,4-pentadien-3-one (XI)

Method B

Furfurylideneacetone (*XIV*) (1.36 g; 0.01 mol) was suspended in dimethylformamide dimethyl acetal (3 g; 0.02 mol) and the mixture was refluxed for 2 h. The residual dimethylformamide dimethyl acetal was distilled off and the compound obtained was crystallized from n-heptane.

Method D

To the solution of sodium (3 g) in methanol (200 cm^3) furfurylideneacetone (13.6 g; 0.1 mol) was added at room temperature and the solution was stirred for 15 min. After cooling the solvent was distilled off *in vacuo*. The residue was dissolved in chloroform (250 m^3) and extracted trice with aqueous saturated solution of sodium carbonate (30 cm^3) and finally with water. The chloroform layer was dried with Na_2SO_4, the solvent was distilled off, and the residue was crystallized from n-heptane.

References

1. Pohland, A. E. and Benson, W. R., *Chem. Rev. 66,* 161 (1966).
2. Rybinskaya, M. I., Nesmeyanov, A. N., and Kochetkov, N. K., *Usp. Khim. 38,* 960 (1969).
3. Rappoport, Z., *Advan. Phys. Org. Chim. 7,* 1 (1969).
4. Kristofčák, J., Kováč, J., Hrabovský, J. and Bánki, J., *Collect. Czechoslov. Chem. Commun.*, in press.
5. Saikachi, H. and Sugimoto, H., *Yakugaku Zasshi 91,* 64 (1971).
6. Vereshchagin, L. I., Korshunov, S. P., Timokhin, B. V., and Katkevich, R. I., *Probl. Poluprod. Prom. Org. Sin. Akad. Nauk SSSR 1967,* 223; *Chem. Abstr. 68,* 21756 (1968).
7. Litvinenko, L. M., Popov, A. F., Kostenko, L. I., and Tormosin, I. I., *Dokl. Akad. Nauk SSSR 211,* 353 (1973).
8. Sasaki, T. and Suzuki, H., *Tetrahedron Lett. 1967,* 3137.
9. Nishigaki, S., Ogiwara, K., and Yoneda, F., *J. Heterocycl. Chem. 8,* 759 (1971).
10. Dudek, G. O. and Volp, G. D., *J. Amer. Chem. Soc. 85,* 2697 (1963).
11. Kristofčák, J., *Thesis.* Slovak Technical University, Bratislava, 1985.
12. Gupton, J. T., Colon, C., Harrison, Ch. R., Lizzi, M. J., and Polk, D. E., *J. Org. Chem. 45,* 4522 (1980).
13. Ponomarev, A. A., *Sintezy i reaktsii furanovykh veshchestv,* p. 55. Izdateľstvo Saratovskogo universiteta, Saratov, 1960.
14. Kochetkov, N. K., Nifantev, E. E., and Nifanteva, L. V., *Zh. Obshch. Khim. 30,* 241 (1960).

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