ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 9, pp. 1340–1343. © Pleiades Publishing, Inc., 2006.
Original Russian Text © O.A. Amal'chieva, A.Yu. Egorova, 2006, published in Zhurnal Organicheskoi Khimii, 2006, Vol. 42, No. 9, pp. 1358–1361.

Reaction of Furan-2(3*H*)-ones with 1,2-Binucleophiles

O. A. Amal'chieva and A. Yu. Egorova

Chernyshevskii Saratov State University, ul. Astrakhanskaya 83, Saratov, 410012 Russia
e-mail: amalchiev@mail.ru

Received July 26, 2005

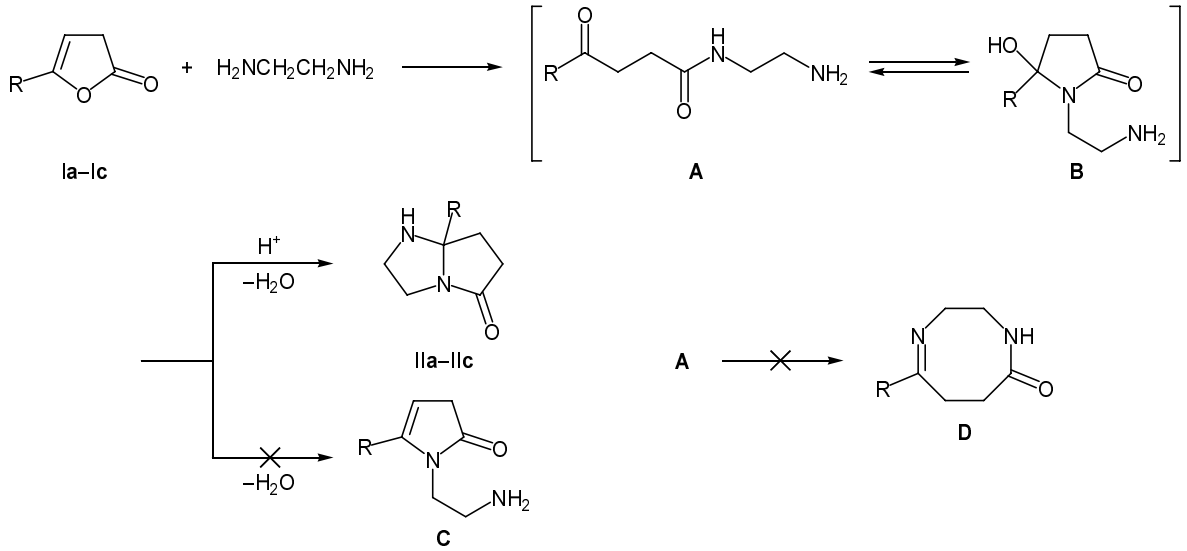
Abstract—Reactions of 5-substituted furan-2(3*H*)-ones with ethylenediamine, 2-aminoethanol, and *o*-aminophenol do not stop at the stage of formation of the corresponding 4-oxoalkanoic acid amides but lead to new bi- and tricyclic structures as a result of double intramolecular cyclodehydration.

DOI: 10.1134/S1070428006090144

In the recent years much attention is given to the synthesis of fused nitrogen-, sulfur-, and oxygen-containing heterocycles which constitute pharmacophoric fragments of known medical agents or natural biologically active organic compounds. Pyrrolidin-2-one derivatives are known to exhibit versatile biological activity [1–3]. Sedavkina et al. [4] previously reported a procedure for the preparation of such compounds from γ-oxocarboxylic acid esters.

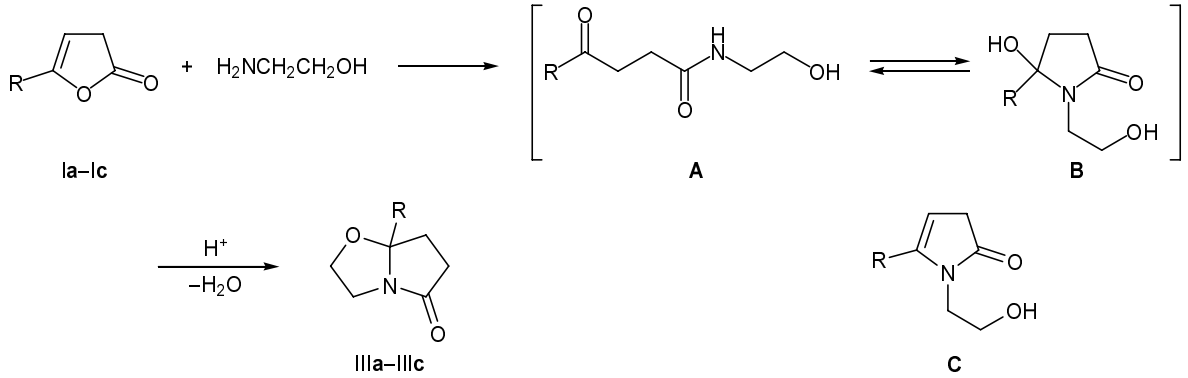
We were the first to examine reactions of 5-substituted furan-2(3*H*)-ones with difunctional 1,2-nucleophiles belonging to both aliphatic and aromatic series. Initial compounds **Ia**–**Id** having various substituents in the 5-position (R = 4-MeC_6H_4, Pr, Ph, Me) were synthesized in good yields by intramolecular cyclization of 4-oxoalkanoic acids [5]. Furanones **Ia**–**Ic** are capable of reacting with difunctional nucleophiles in both protic and aprotic solvents under different conditions. The best results were obtained by carrying out the reactions in benzene with continuous removal of the liberated water by azeotropic distillation. Good results were also obtained in the presence of KU-2 ion exchanger. The reactions of **Ia**–**Ic** with an equimolar amount of ethylenediamine in ethanol in the presence of KU-2 involved double intramolecular cyclization with participation of both nitrogen atoms and gave bicyclic products **IIa**–**IIc** in good yield (Scheme 1). Their formation was favored by flexibility of the substituent on the nitrogen atom and enhanced nucleophilicity of the second amino group.

Scheme 1.



R = 4-MeC_6H_4 (**a**), Ph (**b**), Pr (**c**).

Scheme 2.

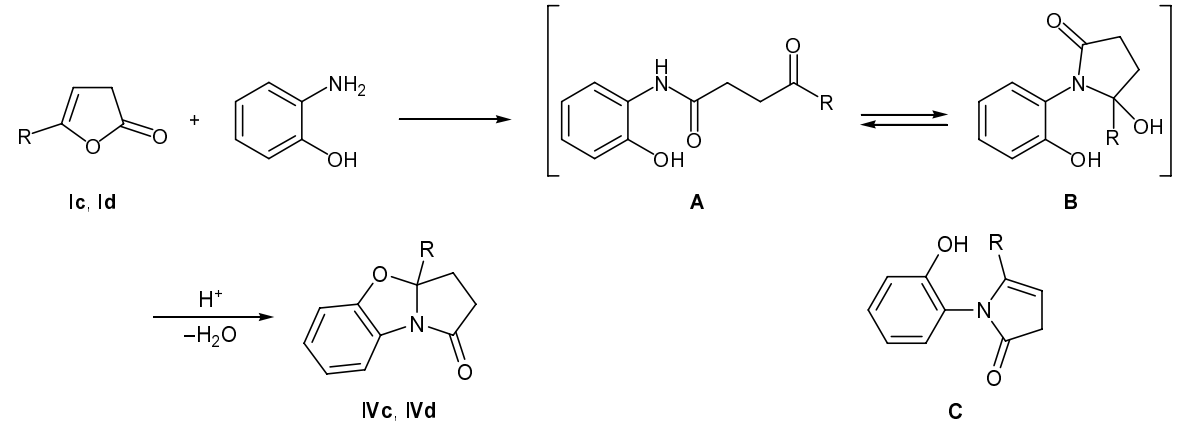


R = 4-MeC$_6$H$_4$ (**a**), Ph (**b**), Pr (**c**).

Presumably, linear intermediate **A** formed in the first stage undergoes cyclization to tautomeric 5-substituted 5-hydroxypyrrolidin-2-one **B**. Dehydration of intermediate **B** could give rise to bicyclic structure or *N*-substituted pyrrol-2(3*H*)-one **C**; in addition, cyclization of **A** to give eight-membered heterocycle **D** is possible [6]. The structure of the products was determined on the basis of the IR and ^{1}H NMR data. The IR spectra of **IIa**–**IIc** lacked absorption bands typical of ketone carbonyl group (which excludes open-chain structure amide **A**), but those characteristic of lactam carbonyl were present in the region 1700–1680 cm^{-1}. In the ^{1}H NMR spectra of **IIa**–**IIc** we observed no vinyl proton signals (which should be present in the spectrum of structure **C**); the spectra contained multiplet signals at δ 3.20–3.40 and 3.42–3.50 ppm (2H each) from the methylene protons on C^7 and C^6, respectively, and signals from those on C^2 and C^3 were located at δ 3.62–4.10 and 3.52–3.60 ppm (2H each). Downfield signals in the region δ 7.22–7.30 ppm were assigned to aromatic protons in the substituent on C^{7a} in compounds **IIa** and **IIb**, and the NH proton gave a broadened singlet at δ 5.2 ppm (1H). These data indicated that the isolated products have the structure of hexahydro-1*H*-pyrrolo[2,1-*a*]imidazol-5-ones **II**.

The reactions of furan-2(3*H*)-ones **Ia**–**Ic** with 2-aminoethanol were performed under analogous conditions. In this case, the formation of cyclic structure **C** or bicyclic compounds **IIIa**–**IIIc** may also be expected (Scheme 2). The ^{1}H NMR spectra of the products contained no vinyl proton signals; therefore, structure **C** can be ruled out. In the IR spectra we observed absorption bands typical of lactam carbonyl group (1700–1670 cm^{-1}) and a band at 1086–1070 cm^{-1} due to C–O–C group, while absorption bands assignable to stretching vibrations of ketone carbonyl and hydroxy group were absent. Compounds **IIIa**–**IIIc** displayed in the ^{1}H NMR signals from the methylene protons at δ 3.30–3.45, 3.55–3.70 (oxazolidine ring) and 2.18–2.28, 2.30–2.55 ppm (pyrrolidine ring) and signals from aromatic protons at δ 6.80–7.20 ppm.

Scheme 3.



R = Pr (**c**), Me (**d**).

Furan-2(3*H*)-ones **Ic** and **Id** were brought into reaction with an aromatic difunctional nucleophile, *o*-aminophenol, with a view to obtain tricyclic compounds possessing an oxazolidine ring fused to a benzene ring. As in the reactions with ethylenediamine and 2-aminoethanol, we isolated cyclization products **IVc** and **IVd** in up to 70% yield (Scheme 3). Here, the formation of N-substituted pyrrol-2(3*H*)-one **C** could not be ruled out *a priori*. The product structure was determined on the basis of spectral data. The IR spectra lacked ketone carbonyl and OH absorption, but contained a band at 1700–1680 cm^{-1} typical of lactams. Neither vinyl nor hydroxy proton signals were present in the ^1H NMR spectra of **IVc** and **IVd**. Multiplets from the methylene protons on C^2 and C^3 were located in the regions δ 2.50–2.67 and 2.30–2.40 ppm, respectively. The alkyl groups on C^{3a} gave a set of signals at δ 0.86–1.78 ppm (**IVc**) or a singlet at δ 1.35 ppm (**IVd**). Protons in the fused benzene ring appeared at δ 6.80–7.10 ppm. These data allowed us to assign compounds **IVc** and **IVd** the structure of 3a-substituted 1,2,3,3a-tetrahydropyrrolo[2,1-*b*][1,3]-benzoxazol-1-ones.

Thus we have shown that 5-substituted furan-2(3*H*)-ones readily react with 1,2-difunctional nucleophiles to give bi- and tricyclic structures having an oxazolidine or imidazolidine fragments.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer from samples dispersed in mineral oil or hexachlorobutadiene. The ^1H NMR spectra were measured on a Varian FT-600 instrument from solutions in $CDCl_3$ using tetramethylsilane as internal reference. The purity of the products was checked by thin-layer chromatography on Silufol plates using ethyl acetate–hexane–chloroform (2:2:1) as eluent; development with iodine vapor.

7a-(4-Methylphenyl)-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolo[2,1-*a*]imidazol-5-one (IIa). A mixture of 3 mmol of compound **Ia**, 3 mmol of ethylenediamine, and 0.2 g of KU-2 ion exchanger in 25 ml of anhydrous benzene was heated under reflux with continuous removal of the liberated water as azeotrope. The solution was evaporated, and the product was isolated by column chromatography on silica gel using ethyl acetate–hexane (2:1) as eluent. Yield 0.28 g (47%). Oily liquid. IR spectrum, ν, cm^{-1}: 3392 (N–H), 1688 (C=O), 3020–2910 (C–H). ^1H NMR spectrum, δ, ppm: 7.18–7.25 m (4H, H_{arom}), 2.35 s (3H, Me), 3.20–3.40 m and 3.42–3.50 m (2H each, C^6H_2, C^7H_2), 3.62–4.10 m and 3.52–3.60 m (2H each, C^2H_2, C^3H_2), 5.2 br.s (1H, NH). Found, %: C 70.85; H 7.15; N 14.32. $C_{12}H_{14}N_2O$. Calculated, %: C 71.26; H 6.93; N 13.86.

Compounds **IIb**, **IIc**, **IIIa**–**IIIc**, **IVc**, and **IVd** were synthesized in a similar way.

7a-Phenyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolo-[2,1-*a*]imidazol-5-one (IIb). Yield 0.43 g (70%). Oily liquid. IR spectrum, ν, cm^{-1}: 3380 (N–H), 1698 (C=O), 3020–2910 (C–H). ^1H NMR spectrum, δ, ppm: 7.29–7.70 m (5H, H_{arom}), 3.15–3.30 m and 3.36–3.49 m (2H each, C^6H_2, C^7H_2), 3.56–3.70 m and 3.79–4.10 m (2H each, C^2H_2, C^3H_2), 5.0 br.s (1H, NH). Found, %: C 72.53; H 7.05; N 13.25. $C_{13}H_{16}N_2O$. Calculated, %: C 72.22; H 7.41; N 12.96.

7a-Propyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolo-[2,1-*a*]imidazol-5-one (IIc). Yield 0.92 g (69%), n_D^{20} = 1.0490. IR spectrum, ν, cm^{-1}: 3370 (N–H), 1720 (C=O), 3000–2910 (C–H). ^1H NMR spectrum, δ, ppm: 0.98–1.49 m (7H, C_3H_7), 3.11–3.30 m and 3.39–3.45 m (2H each, C^6H_2, C^7H_2), 3.48–3.62 m and 3.70–3.95 m (2H each, C^2H_2, C^3H_2), 5.2 br.s (1H, NH). Found, %: C 63.85; H 9.13; N 16.93. $C_9H_{16}N_2O$. Calculated, %: C 64.29; H 9.52; N 16.67.

7a-(4-Methylphenyl)-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*][1,3]oxazol-5-one (IIIa). Yield 0.25 g (42%). Oily liquid. IR spectrum, ν, cm^{-1}: 1670 (C=O), 1070 (C–O–C), 3000–2910 (C–H). ^1H NMR spectrum, δ, ppm: 2.45 s (3H, Me), 2.20–2.28 m and 2.35–2.55 m (2H each, C^6H_2, C^7H_2), 3.30–3.45 m and 3.55–3.70 m (2H each, C^2H_2, C^3H_2), 6.99–7.07 m (4H, H_{arom}). Found, %: C 70.48; H 6.36; N 6.85. $C_{12}H_{13}NO_2$. Calculated, %: C 70.94; H 6.40; N 6.70.

7a-Phenyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]-[1,3]oxazol-5-one (IIIb). Yield 0.27 g (44%). Oily liquid. IR spectrum, ν, cm^{-1}: 1675 (C=O), 1079 (C–O–C), 3000–2910 (C–H). ^1H NMR spectrum, δ, ppm: 7.19 m (5H, H_{arom}), 2.20–2.34 m and 2.43–2.60 m (2H each, C^6H_2, C^7H_2), 3.38–3.45 m and 3.62–3.74 m (2H each, C^2H_2, C^3H_2). Found, %: C 71.54; H 6.72; N 6.62. $C_{13}H_{15}NO_2$. Calculated, %: C 71.89; H 6.91; N 6.45.

7a-Propyl-2,3,5,6,7,7a-hexahydropyrrolo[2,1-*b*]-[1,3]oxazol-5-one (IIIc). Yield 0.27 g (44%), n_D^{20} = 1.4890. IR spectrum, ν, cm^{-1}: 1695 (C=O), 1086 (C–O–C), 3000–2910 (C–H). ^1H NMR spectrum, δ, ppm: 0.92–1.70 m (7H, C_3H_7), 1.96–2.23 m and 2.32–

2.40 m (2H each, C^6H_2, C^7H_2), 3.35–3.50 m and 3.60–3.75 m (2H each, C^2H_2, C^3H_2). Found, %: C 63.71; H 8.54; N 8.44. $C_9H_{15}NO_2$. Calculated, %: C 63.91; H 8.88; N 8.28.

3a-Propyl-1,2,3,3a-tetrahydropyrrolo[2,1-*b*]-[1,3]benzoxazol-1-one (IVc). Yield 1.14 g (75%). Oily liquid. IR spectrum, ν, cm^{-1}: 1700 (C=O), 1080 (C–O–C), 3000–2910 (C–H). ^1H NMR spectrum, δ, ppm: 0.86–1.78 m (7H, C_3H_7), 6.82–7.13 m (4H, H_{arom}), 2.30–2.40 m (2H, CH_2), 2.50–2.67 m (2H, CH_2). Found, %: C 71.53; H 6.85; N 6.54. $C_{13}H_{15}NO_2$. Calculated, %: C 71.89; H 6.91; N 6.45.

3a-Methyl-1,2,3,3a-tetrahydropyrrolo[2,1-*b*]-[1,3]benzoxazol-1-one (IVd). Yield 1.25 g (66%). Oily liquid. IR spectrum, ν, cm^{-1}: 1720 (C=O), 1090 (C–O–C), 3000–2910 (C–H). ^1H NMR spectrum, δ, ppm: 2.26–2.36 m (2H, CH_2), 2.47–2.55 m (2H, CH_2), 1.70 s (3H, Me), 6.80–6.10 s (4H, H_{arom}). Found, %: C 69.67; H 5.70; N 7.65. $C_{11}H_{11}NO_2$. Calculated, %: C 69.84; H 5.82; N 7.40.

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 05-03-32196).

REFERENCES

1. Stezhko, T.V., Granik, V.G., Glushkov, R.G., Roshchina, L.F., Polezhaeva, A.I., and Mashkovskii, M.D., *Khim.-Farm. Zh*., 1984, p. 290.
2. Stezhko, T.V., Granik, V.G., Glushkov, R.G., Roshchina, L.F., Polezhaeva, A.I., and Mashkovskii, M.D., *Khim.-Farm. Zh*., 1984, p. 823.
3. Stezhko, T.V., Granik, V.G., Glushkov, R.G., Roshchina, L.F., Polezhaeva, A.I., and Mashkovskii, M.D., *Khim.-Farm. Zh*., 1984, p. 1198.
4. Sedavkina, V.A., Lizak, I.V., and Sorokin, N.N., *Khim. Geterotsikl. Soedin*., 1987, p. 1405.
5. Sedavkina, V.A., Morozova, N.A., and Egorova, A.Yu., *Khim. Geterotsikl. Soedin*., 1993, p. 456.
6. Sulkowski, T.S., US Patent no. 3293243, 1966; *Ref. Zh., Khim*., 1968, no. 14N415P.