Spiro heterocyclization of pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones under the action of 1,3,3-trimethyl-3,4-dihydroisoquinoline

Irina V. Mashevskaya,[a] Aleksei V. Duvalov,[a] Yuliya S. Rozhkova,[b] Yurii V. Shklyaev,[b] Nadezhda L. Racheva,[a] Kseniya S. Bozdyreva[a] and Andrei N. Maslivets*[a]

[a] *Department of Chemistry, Perm State University, 614990 Perm, Russian Federation. Fax: +7 3422 39 6367; e-mail: koh2@psu.ru*
[b] *Institute of Technical Chemistry, Urals Branch of the Russian Academy of Sciences, 614990 Perm, Russian Federation. Fax: +7 3422 12 6237; e-mail: cheminst@mpm.ru*

10.1070/MC2004v014n02ABEH001897

1,3,3-Trimethyl-3,4-dihydroisoquinoline reacts with pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones to give substituted pyrrolo[2,1-*a*]-isoquinoline-2-spiro-2-pyrroles.

The reactions of the enamino derivatives of isoquinoline with highly electrophilic 2,3-dioxo heterocycles are poorly understood. Thus, Andreichikov *et al.*[1] found that 1,3,3-trimethyl-3,4-dihydroisoquinoline reacts with 5-aryl-2,3-dihydro-2,3-furandiones to form the products of N-acylation of an isoquinoline ring, namely, 2-aroylpyruvoyl-3,3-dimethyl-1-methylene-1,2,3,4-tetrahydroisoquinolines. The decyclization of 5-phenyl-2,3-dihydro-2,3-furandione under the action of 1-methyl-3,3-pentamethylene-3,4-dihydroisoquinoline gave rise to a product of the β-C acylation of the isoquinoline enamine moiety, 1-(3-hydroxy-2,5-dioxo-5-phenylhept-*Z*-3-ene-*Z*-1-ylidene)-3,3-pentamethylene-1,2,3,4-tetrahydroisoquinoline.[2] The interaction of 1,3,3-trimethyl-3,4-dihydroisoquinoline with 6-nitro-2-polyfluoroalkylchromones afforded the products of an electrophilic attack on the β-C atom of the enamino fragment.[3] Taking into consideration the interaction of 3,4-dihydroisoquinoline derivatives[4–6] with highly electrophilic olefins and perfluorocarbonyl compounds, we can confirm that the alkylation and hydroxyalkylation of these systems occur at the β-C atom of the enamino system. It is clear that, with increasing steric hindrances of an electrophilic centre, an attack on the enamine form of the isoquinoline derivatives occurs at the β-C atom.

We found that the interaction of 3-aroyl-2,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **1a**,**b** with 1,3,3-trimethyl-3,4-dihydroisoquinoline **2** performed by short-term heating (2–3 min) in dry acetonitrile yielded 9,9-dimethyl-1-oxo-1,2,8,9-tetrahydropyrrolo[2,1-*a*]isoquinoline-2-spiro-2-(3-aroyl-4-hydroxy-1-*o*-hydroxyphenyl-5-oxo-2,5-dihydropyrroles) **3a**,**b**.†

The spectroscopic characteristics of resulting spiro adducts **3a**,**b** are much similar to those of model compounds, 6,6-dimethyl-2,4-dioxo-2,3,4,5,6,7-hexahydro-1*H*-indole-3-spiro-2-(3-aroyl-4-hydroxy-1-*o*-hydroxyphenyl-5-oxo-2,5-dihydropyrroles). The structure of these compounds was proved by X-ray analysis.[7] A computer simulation (AM1 method, Hyperchem 6.0) of spiro heterocycle **3a** shows that the dihydropyridine ring exists in the form of a flat 'arm-chair' and the C(9) atom is approximately 10° beyond the plane of this ring. This explains the presence of two Me-group singlets at 1.40 (pseudoeq.) and 1.55 ppm (pseudoax.) and the typical AB system of methylene protons (2.63–2.82 ppm) in the ^{1}H NMR spectra of **3a**.

Most likely, at the first stage of the interaction, an activated methylene group of enamine **2** adds to the C(3a) atom of pyrrolobenzoxazinetriones **1a**,**b**, as described for the reactions of these compounds with mono-[9] and binucleophiles.[10,11] This step is followed by pyrrole ring closing, the result of a *sec*-amino group attack (isoquinoline ring) onto lacton carbonyl group (benzoxazine ring) and its opening by C(4)–C(5) bond cleavage. An analogous reaction, which was observed previously for binucleophiles such as *o*-phenylenediamine[10] and *o*-aminothiophenole,[11] did not yield stable spiro heterocycles because it was accompanied by subsequent intramolecular proton transfer from the NH group adjacent to the spiro C atom onto the N atom of a spiro-pyrrole ring and its further opening. Such a disclosure does not take place in our case apparently because there is no possibility of a proton transfer in spiro products **3a**,**b**. The described reaction presents an example of the regioselective formation of a functionalised spiro-bis-heterocycle system of pyrroloisoquinoline-spiro-pyrrole, which was inaccessible formerly.

This work was supported by the Russian Foundation for Basic Research (project no. 04-03-96033).

† *A typical experimental procedure*. Enamine **2** (0.173 g, 1 mmol) was added dropwise to a solution of pyrrolobenzoxazinetrione **1** (1 mmol) in dry MeCN (20 ml). The solution was heated at 60 °C for 2–3 min and then allowed to cool. The precipitated product was filtered off and recrystallised from benzene.

*9,9-Dimethyl-1-oxo-1,2,8,9-tetrahydropyrrolo[2,1-*a*]isoquinoline-2-spiro-2-(3-benzoyl-4-hydroxy-1-*o*-hydroxyphenyl-5-oxo-2,5-dihydropyrrole)* **3a**: yield 72%, mp 215–216 °C. ^{1}H NMR (400 MHz, [$^2H_6$]DMSO) δ: 1.40 [s, 3H, Me (pseudoeq.)], 1.55 [s, 3H, Me (pseudoax.)], 2.63, 2.82 (dd, 2H, CH_2, AB system, J 15.7 Hz), 5.61 (s, 1H, CH=), 6.69–7.79 (m, 13H, Ph + 2C_6H_4), 9.39 [s, 1H, OH (phenol.)], 11.93 [s, 1H, OH (enol.)]. ^{13}C NMR (100.62 MHz, [$^2H_6$]DMSO) δ: 188.40 (COPh), 174.12 [C(1)=O], 165.40 [C(5)=O], 154.51 [C(4)–OH], 142.81 (N–C=), 137.88 (C–OH), 132.61 [C(3′)], 132.44–116.47 (CAr), 97.35 [C(3)], 72.39 [C(9)], 53.60 [C(2)], 43.21 [C(8)], 26.39 (Me), 25.42 (Me). IR (Nujol, ν/cm^{-1}): 3210 (O–H), 1705 (N–C=O), 1640 (C=OPh). Found (%): C, 73.14; H, 4.81; N, 5.64. Calc. for $C_{30}H_{24}N_2O_5$ (%): C, 73.16; H, 4.91; N, 5.69.

*9,9-Dimethyl-1-oxo-1,2,8,9-tetrahydropyrrolo[2,1-*a*]isoquinoline-2-spiro-2-(3-benzoyl-4-hydroxy-1-*o*-hydroxyphenyl-3-*p*-methoxybenzoyl-5-oxo-2,5-dihydropyrrole)* **3b**: yield 77%, mp 197–199 °C (from benzene). ^{1}H NMR (400 MHz, [$^2H_6$]DMSO) δ: 1.38 [s, 3H, Me (pseudoeq.)], 1.49 [s, 3H, Me (pseudoax.)], 2.59, 2.79 (dd, 2H, CH_2, AB system, J 15.9 Hz), 3.85 (s, 3H, OMe), 5.68 (s, 1H, CH=), 6.76–8.16 (m, 12H, 3C_6H_4), 9.62 [s, 1H, OH (phenol.)], 12.00 [s, 1H, OH (enol.)]. ^{13}C NMR (100.62 MHz, [$^2H_6$]DMSO) δ: 186.93 (COC_6H_4), 174.15 [C(1)=O], 165.48 [C(5)=O], 162.91 (C–OMe), 154.54 [C(4)–OH], 151.37 (N–C=), 142.85 (C–OH), 132.62 [C(3)], 131.46–113.41 (CAr), 97.16 [C(3)], 75.52 [C(9)], 55.48 (OMe), 53.57 [C(2)], 43.22 [C(8)], 26.37 (Me), 25.47 (Me). IR (Nujol, ν/cm^{-1}): 3200 (O–H), 1704 (N–C=O), 1645 (C=OC_6H_4). Found (%): C, 71.24; H, 5.07; N, 5.34. Calc. for $C_{31}H_{26}N_2O_6$ (%): C, 71.25; H, 5.02; N, 5.36.

References

1 Yu. S. Andreichikov, V. S. Shklyaev, B. B. Alexandrov, Y. V. Ionov and M. I. Vahrin, *Khim. Geterotsikl. Soedin.*, 1982, 420 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1982, **18**, 320].

2 Yu. V. Shklyaev and A. N. Maslivets, *Zh. Org. Khim.*, 1996, **32**, 319 (*Russ. J. Org. Chem.*, 1996, **32**, 302).

doi 3 V. Ya. Sosnovskikh, B. I. Usachev, A. Yu. Sizov, I. I. Vorontsov and Yu. V. Shklyaev, *Org. Lett.*, 2003, **5**, 3123.

4 N. D. Chkanikov, V. D. Sviridov, M. V. Galahov, Yu. V. Shklyaev, B. B. Alexandrov, M. S. Gavrilov and V. S. Shklyaev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 1405 (*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 1268).

5 V. Yu. Tutin, N. D. Chkanikov, Yu. V. Shklyaev, A. F. Colomiets and A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1992, 1888 (*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 1474).

6 V. D. Sviridov, N. D. Chkanikov, Yu. V. Shklyaev, A. F. Colomiets and A.V. Fokin, *Khim. Geterotsikl. Soedin.*, 1990, 1689 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1990, **26**, 1405].

7 I. V. Mashevskaya, I. A. Tolmachova, O. Yu. Tiunova, Z. G. Aliev and A. N. Maslivets, *Khim. Geterotsikl. Soedin.*, 2002, 565 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2002, **38**, 500].

8 Yu. V. Shklyaev, Yu. V. Nifontov, S. I. Firgang and A. S. Shashkov, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 2075 (*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 2234).

9 A. N. Maslivets, I. V. Mashevskaya, O. P. Krasnykh, S. N. Shurov and Yu. S. Andreichikov, *Zh. Org. Khim.*, 1992, **28**, 2545 (*Russ. J. Org. Chem.*, 1992, **28**, 2056).

10 A. N. Maslivets, I. V. Mashevskaya and Yu. S. Andreichikov, *Zh. Org. Khim.*, 1995, **31**, 616 (*Russ. J. Org. Chem.*, 1995, **31**, 569).

11 I. V. Mashevskaya, S. V. Koltsova and A. N. Maslivets, *Khim. Geterotsikl. Soedin.*, 2001, 705 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2001, **37**, 652].

Received: 26th January 2004; Com. 04/2223