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Synthesis and structure of 4,6a-diaryl-3,3:6,6-dipropano-tetrahydro-2*H*-furo[3,2-*b*]pyrrole-2,5(3*H*)-diones

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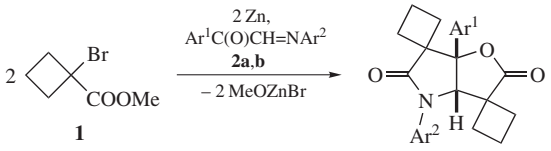
Reaction of methyl 1-bromocyclobutanecarboxylate with zinc and 1-aryl-2-(arylimino)ethanones leads to 4,6a-diaryl-3,3:6,6-dipropano-tetrahydro-2*H*-furo[3,2-*b*]pyrrole-2,5(3*H*)-diones. Structure of one of these compounds is confirmed by X-ray analysis.

Spiro-compounds can be constructed from a cyclic substrate bearing at one carbon atom two suitable functional substituents, *e.g.*, ester group.[1,2] The Reformatsky reagents, derived from α-bromocycloalkylcarboxylic esters satisfy these conditions thus allowing to synthesize various spiro-heterocyclic systems.[3–6]

Reformatsky reagents can add to both carbonyl group and C=N bond of azomethines to form the corresponding adducts.[7,8] Herein, we performed reactions of the Reformatsky reagent, derived from methyl 1-bromocyclobutanecarboxylate **1**, with 1-aryl-2-(arylimino)ethanones **2a**,**b**, which contain carbonyl and azomethine groups. As a result, 4,6a-diaryl-3,3:6,6-dipropano-tetrahydro-2*H*-furo[3,2-*b*]pyrrole-2,5(3*H*)-diones **3a**,**b** were obtained (Scheme 1).†



a Ar^1 = Ph, Ar^2 = 4-BrC_6H_4
b Ar^1 = 4-BrC_6H_4, Ar^2 = 4-$MeOC_6H_4$

Scheme 1

Compounds **3a**,**b** were isolated as a racemic mixture of one diastereomer in 60–63% yields.

The structure of compounds **3a**,**b** was confirmed by the elemental analysis, IR and ^{1}H NMR spectroscopy. The IR spectra of **3a**,**b** contain the characteristic absorption bands of lactam carbonyl groups in the range of 1700–1705 cm^{-1}, and lactone carbonyl groups at 1750–1775 cm^{-1}. The ^{1}H NMR spectra contain characteristic singlets of methine protons at 4.73–4.86 ppm.

Formation of compounds **3a**,**b** may be exemplified on the imine **2a** (Scheme 2).

In order to evaluate the plausibility of this mechanism we carried out nonempirical quantum-chemical calculations of energy and structural characteristics of precursors, intermediates and reaction products by the B3LYP/6-31(d) method for imine **2a** [calculated values of total energies (*E*, a.u.) are shown in Scheme 2].

According to calculations, C=O and C=N bonds in the molecule of imine **2a** has *trans*-orientation: corresponding dihedral angle is 174.8°. In the molecule of imine **2a** there are two potentially electrophilic centers: carbon atoms of carbonyl and imine groups. Carbonyl carbon atom has greater positive Mulliken charge (q_{tot} = 0.381 a.u.) than the imine carbonyl atom (q_{tot} = = 0.034 a.u.). However, summarized contribution of compact and diffuse components of $2p_z$ orbitals of the last in LUMO is higher (c = 0.501) in comparison with alternative (c = 0.485). Thus, evaluation of distribution of the electron density in the substrate does not allow one to determine the location of primary attack of the Reformatsky reagent. The latter very likely reacts in the form of zinc enolate **IA**, in spite of greater (for 42.3 kJ mol^{-1}) energy of this form in comparison with **I**. The Reformatsky reagent in enolate form has an efficient nucleophilic center – formally sp^2-hybridized carbon atom of cyclobutane ring (total q_{tot} and π-electron charges are 0.044 a.u. and –0.124 a.u., respectively).

Addition of the Reformatsky reagent to the carbonyl group of compound **2a** should lead to intermediate **II**, which is stabilized

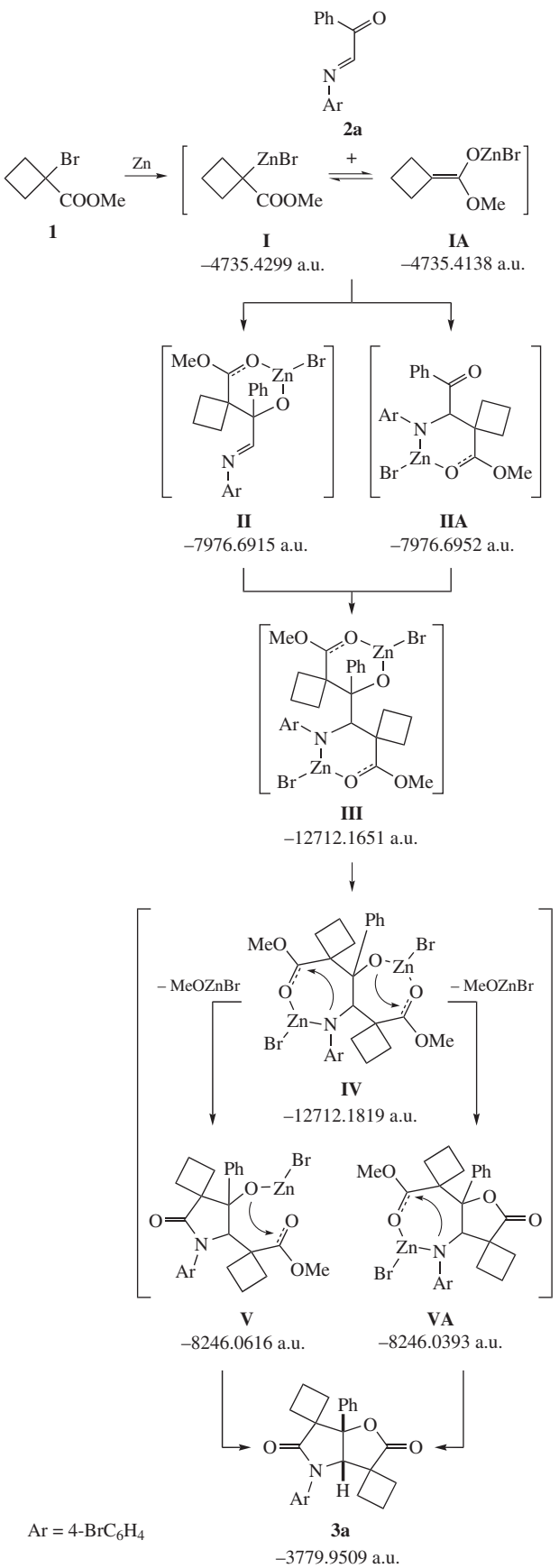
† The IR spectra of compounds **3a**,**b** from mulls in mineral oil were measured on a Spectrum Two PerkinElmer Fourier-spectrometer. ^{1}H NMR spectra were recorded at 300 MHz on a Varian Mercury Plus-300 instrument in $CDCl_3$ with TMS as an internal standard.

Quantum-chemical calculations with all geometric parameters full optimization were carried out using program package Firefly[10] on the supercomputer PSU-Tesla with hybrid architecture based on platform T. Blade 1.1 and processors NVidia Tesla S 2050 of Scientific-educational Center of Parallel and Distributive Calculations of Perm State University.

*4,6a-Diaryl-3,3:6,6-dipropanotetrahydro-2*H*-furo[3,2-*b*]pyrrole-2,5(3*H*)-diones* **3a**,**b**. A mixture of methyl 1-bromocyclobutanecarboxylate (0.022 mol) and 1-aryl-2-(arylimino)ethanone (0.01 mol) in 10 ml of anhydrous toluene was added dropwise with stirring to a mixture of 2.0 g of powdered zinc, catalytic amount of $HgCl_2$, 20 ml of anhydrous toluene and 2 ml HMPA. The mixture was refluxed for 3 h, cooled and decomposed with 5% acetic acid. The organic layer was separated, the water layer was twice extracted with toluene. The combined extracts were dried with anhydrous sodium sulfate. The solvent was removed and the product was twice recrystallized from ethanol.

*4-(4-Bromophenyl)-3,3:6,6-dipropano-6a-phenyltetrahydro-2*H*-furo-[3,2-*b*]pyrrole-2,5(3*H*)-dione* **3a**. Yield 63%, mp 219–220 °C. IR (ν/cm^{-1}): 1705, 1775 (C=O). ^{1}H NMR, δ: 1.48–2.45 [m, 12 H, 2(CH_2)$_3$], 4.86 (s, 1H, CH), 7.40–7.45 (m), 7.57 (d, *J* 8.7 Hz) (9 H, Ph, 4-BrC_6H_4). Found (%): C, 63.88; H, 4.96; Br, 17.93; N, 3.18. Calc. for $C_{24}H_{22}BrNO_3$ (%): C, 63.73; H, 4.90; Br, 17.66; N, 3.10.

*6a-(4-Bromophenyl)-4-(4-methoxyphenyl)-3,3:6,6-dipropanotetra-hydro-2*H*-furo[3,2-*b*]pyrrole-2,5(3*H*)-dione* **3b**. Yield 60%, mp 162–163 °C. IR (ν/cm^{-1}): 1700, 1750 (C=O). ^{1}H NMR, δ: 1.45–2.37 [m, 12 H, 2(CH_2)$_3$], 3.83 (s, 3H, MeO), 4.73 (s, 1H, CH), 6.95 (d, *J* 9.0 Hz), 7.30 (d, *J* 9.0 Hz) (4 H, $MeOC_6H_4$), 7.37 (d, *J* 8.7 Hz), 7.56 (d, *J* 8.7 Hz) (4 H, 4-BrC_6H_4). Found (%): C, 62.43; H, 5.08; Br, 16.68; N, 2.84. Calc. for $C_{25}H_{24}BrNO_4$ (%): C, 62.25; H, 5.01; Br, 16.57; N, 2.90.



Scheme 2

by coordination of the zinc atom and the ester oxygen atom (calculated interatomic distance Zn···O=C is 1.822 Å). Intermediate **IIA** may be formed as a result of addition of the Reformatsky reagent to the C=N bond of molecule of compound **2a**. As calculations show, intermediate **IIA** is more stable than **II** by 9.5 kJ mol^{-1}. In the intermediate **IIA**, coordination of zinc atom with the oxygen of the COOMe group can also occur (calculated interatomic distance Zn···O=C is 1.881 Å). As established earlier, interaction of the Reformatsky reagent with imines affords β-lactams,[9] therefore, the primary addition to C=N bond is less probable in spite of formally greater stability of intermediate **IIA**.

Addition of the Reformatsky reagent to intermediate **II** (or **IIA**) leads to species **III**. However, conditions for ring-closure to furan and pyrrole are absent. Therefore, we supposed that intermediate **III** transforms into intermediate **IV**, in which formation of N–C and O–C bonds and elimination of MeOZnBr molecules are possible. Indeed, intermediate **IV** is more stable than **III** by 44.1 kJ mol^{-1}. According to calculations, the N···C distance is 3.489 Å, and total Mulliken charges of atoms are $q_N = –0.795$ a.u., $q_C = 0.693$ a.u., the O···C distance is 3.336 Å (charges of atoms $q_O = –0.845$ a.u., $q_C = 0.677$ a.u.). Attack of the nitrogen atom at the ester carbon atom should result in pyrrole ring-closure and formation of intermediate **V**, and alternatively in attack providing furan ring closure (intermediate **VA**). As it appears from the calculations, intermediate **V** is more stable than intermediate **VA** by 58.5 kJ mol^{-1} and its generation is more preferable. Increase in the interatomic distance O···C up to 3.433 Å in intermediate **V** does not obstruct closing of furan ring and formation of the reaction product **3a**.

In furopyrrole **3a**, phenyl substituent and hydrogen atom are in s-*cis*-position relative to central C^{3a}–C^{6a} bond (corresponding dihedral angle is 16.2°). Alternative furopyrrole with s-*trans* orientation of the abovementioned groups (dihedral angle H–C^{3a}–C^{6a}–Ph is –174.2°, $E_{tot} = –3779.9139$ a.u.) is less stable by 97.1 kJ mol^{-1}.

To ultimately establish the structure of compounds **3a**,**b**, we performed X-ray diffraction investigation of the crystal of compound **3a**. According to the X-ray data,‡ the compound crystallizes in the centrosymmetric space group monoclinic system (Figure 1). Bond lengths and bond angles are close to the standard values. Atom C(12) of cyclobutane cycle, spiro-connected with the pyrrolidine cycle, is characterized by strong thermal disordering, which is shown in strong anisotropy of thermal ellipsoid. Substituents at the bridged nitrogen atoms of bicyclic fragment are in conformation which is intermediate between synplanar and synclinal [torsion angle H(5A)C(5)C(1)C(4) is 35.2°]. Thus, calculation data on the preferability of s-*cis* position of substituents at the bridged atoms of bicyclic fragment are confirmed. Divergence in the calculated and observed angles may be referred to influence of the environment of crystal package. The lactone and lactame cycles are in envelope conformation with deviation from the plane of the C(5) and C(1) atoms, respectively. There are no essential deviations from van der Waals interaction lengths of intermolecular contacts in the crystal packing.

‡ *Crystal data for* **3a**. The XRD analysis of compound **3a** was performed on an automatic Xcalibur S diffractometer by standard procedure [λ(MoKα) = = 0.71073 Å, $T = 295(2)$ K, ω-scanning with 1° step and crystal–detector distance 50 mm]. Reflections collected: 11384, among them independent: 5936 ($R_{int} = 0.0371$) and 2267 with $I > 2\sigma(I)$. Completeness for $\theta = 26°$ is 98.3%. Empirical correction for extinction is introduced ($\mu = 2.044$ mm^{-1}). Crystal is monoclinic, space group $P2_1/c$, $a = 15.6689(13)$, $b = 6.0765(4)$ and $c = 21.602(2)$ Å, $\beta = 97.990(7)°$. The solution and refinement of the structure were carried out using the SHELXTL[11] software package. The final refinement parameters are $R_1 = 0.1395$, $wR_2 = 0.0684$ (for all reflections); $R_1 = 0.0423$, $wR_2 = 0.0637$ for the reflections with $I > 2\sigma(I)$ by quality factor $S = 1.008$. Maximum and minimum of residual electronic density are 0.578 and –0.561 eÅ^{-3}.

CCDC 1005599 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2014.

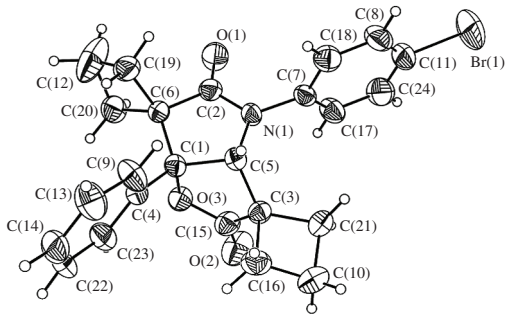


Figure 1 General view of the molecule of **3a** according to the X-ray data with 50% probability thermal ellipsoids.

In conclusion, reaction of α-iminoketones with the carbocyclic Reformatsky reagents opens an access to 2*H*-furo[3,2-*b*]-pyrrole-2,5(3*H*)-diones with spiro-carbon atoms.

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