Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2021, **31**, 248–250

Mendeleev Communications

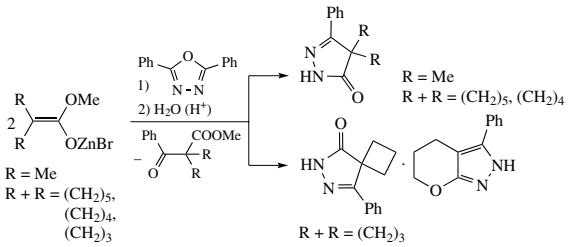
Reaction of Reformatsky reagents with 2,5-diphenyl-1,3,4-oxadiazole

Elena A. Nikiforova,* Nikolay F. Kirillov, Daniil V. Baibarodskikh, Sergey N. Shurov, Maksim V. Dmitriev and Dmitriy P. Zverev

Department of Chemistry, Perm State National Research University, 614990 Perm, Russian Federation. Fax: +7 342 237 1611; e-mail: vikro@ya.ru

DOI: 10.1016/j.mencom.2021.03.035

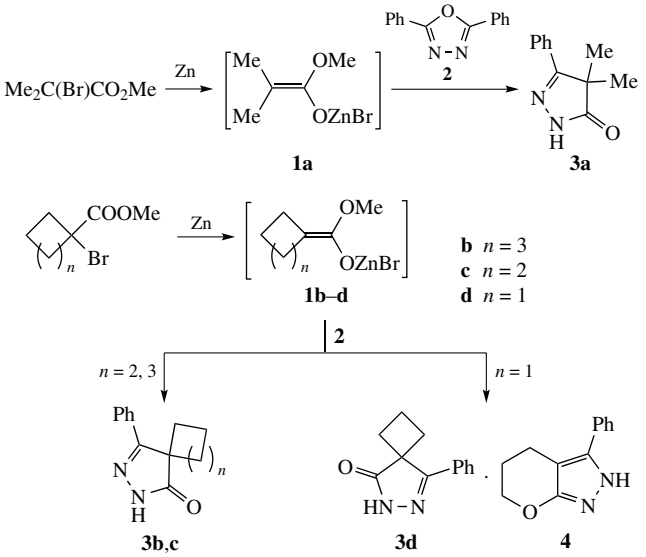
The reaction of methyl α-bromoisobutyrate or 1-bromocycloalkanecarboxylates with zinc and 2,5-diphenyl-1,3,4-oxadiazole leads to 5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one derivatives, with the cycloalkane series affording products of spiro structure. In the case of cyclobutane reactant, 3-phenyl-2,4,5,6-tetrahydropyrano[2,3-*c*]pyrazole is also formed.



Keywords: Reformatsky reaction, alicyclic compounds, organozinc compounds, 1,3,4-oxadiazoles, spiro compounds, pyrazol-3-ones, pyrano[2,3-*c*]pyrazoles, X-ray analysis.

The Reformatsky reagents are known to add at double C=N bonds of azomethines to give intermediates that can undergo further cyclization to afford azetidinones.[1,2] Carbocyclic Reformatsky reagents in such reactions form spiroazetidinones,[3,4] some of them possessing antiviral, antibacterial, antifungal and antimalarial activities.[5–7]

Herein, we performed reactions of the Reformatsky reagents **1a–d** with 2,5-diphenyl-1,3,4-oxadiazole **2** (Scheme 1). Compound **2** contains two double carbon–nitrogen bonds, each of them can be in principle reactive towards organozinc species. Unexpectedly, these reactions gave 1 : 1 products of 2,4-dihydro-3*H*-pyrazol-3-one type **3**. 4,4-Dimethyl-5-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **3a** was the reaction product of compound **2** with reagent **1a** derived from methyl α-bromoisobutyrate and zinc (compound **3a** was obtain earlier[8] *via* reaction of *S*-phenyl 2-phenyl-3,3-dimethylthiolglycidate with hydrazine). Carbocyclic Reformatsky reagents **1b**,**c** reacted with oxadiazole **2** with formation of spiro derivatives **3b**,**c**. Surprisingly, cyclobutane reagent **1d** was converted into co-crystallizate of 8-phenyl-6,7-diazaspiro[3.4]oct-7-en-5-one **3d** with 3-phenyl-1,4,5,6-tetrahydropyrano[2,3-c]pyrazole **4**.†



Scheme 1

The structures of compounds **3** and **4** were confirmed by elemental analysis, IR, ^{1}H and ^{13}C NMR spectra. It was not possible to separate products **3d** and **4** by fractional crystallization, so they were analyzed as co-crystallizate. Separation by chromatographic methods was not performed. Structure of product **3c** was ultimately established by X-ray diffraction (XRD).‡ This compound crystallizes in the centrosymmetric space group belonging to the triclinic crystal system (Figure 1).

† *Compounds* **3a–c** *and* **3d**·**4** *(general procedure).* A solution of methyl 1-bromocycloalkanecarboxylate (or 2-methyl-2-bromopropanoate) **1** (0.022 mol) in anhydrous toluene (10 ml) was added dropwise with stirring to a boiling mixture of 2,5-diphenyl-1,3,4-oxadiazole **2** (0.01 mol), zinc chips (2 g), a catalytic amount of mercury dichloride, anhydrous toluene (20 ml) and HMPA (2 ml). The mixture was refluxed for 3 h, cooled, decanted, and hydrolyzed with 5% acetic acid. The organic layer was separated, and the aqueous one was twice extracted with toluene. The organic phase was dried with anhydrous sodium sulfate, the toluene was distilled off. After that ethanol (10 ml) was added, the solid products were filtered and twice recrystallized from ethanol. For characteristics of compounds **3a–d** and **4**, see Online Supplementary Materials.

‡ Single crystal X-ray analysis of compounds **3c** and **3d**·**4** was performed on an Xcalibur Ruby diffractometer equipped with CCD detector, using Mo X-ray source (MoKα 0.71073 Å), scanning at 295(2) K. The empirical absorption correction was introduced by multi-scan method using SCALE3 ABSPACK algorithm.[11] The structure was solved by the SHELXS-97 software and refined by full-matrix least-squares on all F^2 data using SHELXL-97[12] in conjunction with the WinGX[13] graphical user interface. Hydrogen atoms bound to carbon were located from the Fourier synthesis of the electron density and refined using a riding model. Hydrogen atoms of NH groups were refined independently with isotropic displacement parameters.

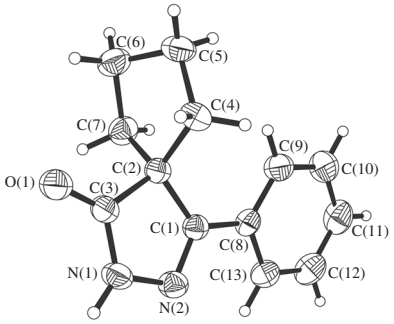


Figure 1 Molecular structure of compound **3c** with thermal ellipsoids drawn at the 50% probability level.

The pyrazolone ring is planar within 0.02 Å. The cyclopentane ring has a distorted envelope conformation with the C(6) atom deviating by 0.60 Å from the plane formed by the other four atoms. The dihedral angle between planes of phenyl and pyrazolone rings is 12.3°. In the crystal, molecules form centrosymmetric dimers by intermolecular hydrogen bonds N(1)–H(1)···O(1) [$-x$, 1$-y$, $-z$] with d(D–H) 0.89(2), d(A···H) 1.98(2), d(D···A) 2.851(1) Å and dihedral angle 167(2)°.

The structure of co-crystallizate **3d**·**4** was also determined by X-ray analysis (Figure 2) showing that symmetrically independent part of unit cell of the crystal consists of two isomeric molecules **3d** and **4**. These compounds crystallize in the centrosymmetric space group belonging to the triclinic crystal system. Geometry of the spiro component is similar to that of **3c** when cyclobutane and pyrazolone rings are planar within 0.02 and 0.01 Å, respectively. The dihedral angle between planes of phenyl and pyrazolone rings is 2.8°. Pyrazole ring of second molecule **4** is planar within 0.01 Å and it represents a heteroaromatic system with delocalized double bonds. Pyran

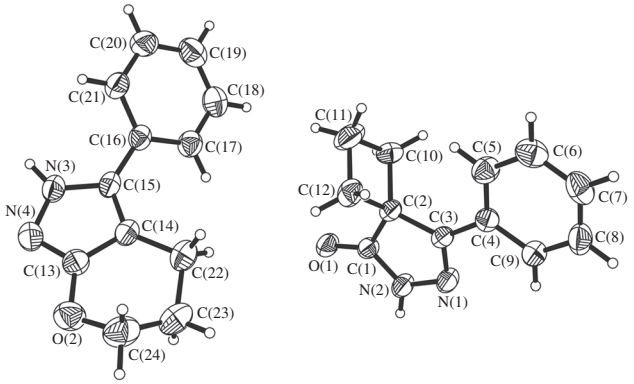


Figure 2 Molecular structure of co-crystallizate **3d**·**4** with thermal ellipsoids drawn at the 50% probability level.

Crystal data for **3c**. $C_{13}H_{14}N_2O$, M = 214.26, triclinic, a = 6.5405(11), b = 8.9877(14) and c = 9.5658(17) Å, α = 81.780(14)°, β = 81.192(14)°, γ = 79.776(13)°, V = 542.97(16) Å^3, T = 295(2) K, space group $P\bar{1}$, Z = 2, μ(MoKα) = 0.085 mm^{-1}. The final refinement parameters: R_1 = 0.0474, wR_2 = 0.1225 [for observed 2101 reflections with $I > 2\sigma(I)$]; R_1 = 0.0560, wR_2 = 0.1300 (for all independent 2499 reflections), R_{int} = 0.0339, S = 1.081.

Crystal data for **3d**·**4**. $C_{12}H_{12}N_2O \cdot C_{12}H_{12}N_2O$, M = 400.47, triclinic, a = 8.0671(10), b = 10.6841(15) and c = 12.3627(16) Å, α = 70.211(12)°, β = 89.890(10)°, γ = 89.551(11)°, V = 1002.6(2) Å^3, T = 295(2) K, space group $P\bar{1}$, Z = 2, μ(MoKα) = 0.087 mm^{-1}. The final refinement parameters: R_1 = 0.0473, wR_2 = 0.1235 [for observed 3604 reflections with $I > 2\sigma(I)$]; R_1 = 0.0638, wR_2 = 0.1359 (for all independent 4656 reflections), R_{int} = 0.0273, S = 1.079.

CCDC 2043375 (**3c**) and 2043377 (**3d**·**4**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

cycle aquires half-chair conformation, C(23) and C(24) atoms deviate to different sides of O(2)C(13)C(14)C(22) plane by 0.30 and –0.41 Å. Phenyl substituent is turned to 36.7° in relation to pyrazole ring plane.

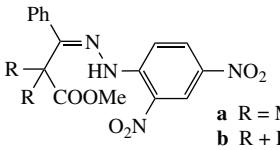
Formation of compounds **3** and **4** (Scheme 2) includes the sequential addition of two molecules of the Reformatsky reagent to the C^2=N^3 and C^5=N^4 bonds of oxadiazole **2** and the sequential generation of intermediates **A** and **B**. Further on, intermediate **B** turns into the key intermediate **C**. The migration of the ZnBr group in it to the carbonyl oxygen atom of the methoxycarbonyl group and the formation of the C–N bond leads to intermediate **D** containing the 3-oxa-1,7-diazabicyclo[2.2.1]heptane fragment. Elimination from this intermediate of either MeOZnBr or HOZnBr *via* the **E1** or **E2** intermediates gives the same species **F**. Migration of a proton from the N^7 nitrogen atom to the N^1 nitrogen atom leads to the reaction products, 2,4-dihydro-3*H*-pyrazol-3-ones **3a–d** and keto esters **5a–d**.

In order to determine the plausibility of this proposed mechanism, we performed quantum-chemical calculations of energy, electronic and geometric characteristics of probable intermediates in the reaction of Reformatsky reagent **1d** with oxadiazole **2** using the B3LYP density functional and the 6-311G(d) basis set[§] (for results of quantum-chemical calculations and their detailed discussion, see Online Supplementary Materials). Based on quantum-chemical calculations, the reaction scheme can be represented as follows:

1d + **2** → **A** → **B** → **C** → **D** → **E2** → **F** → **G** → **3d** + **5d**.

Apparently, the formation of compounds **3a–c** also proceeds according to the given scheme. Formation of compound **4** is probably the result of rearrangement of compound **3d** (see Scheme 2) caused by strain factors of spiro system consisting of cyclobutane and pyrazolone rings (*cf.* refs. 9, 10). The transformation of compound **3d** into pyranopyrazole **4** occurs due to the cleavage of the C^5–C^6 bond and the formation of the C–O bond. According to calculations, in the transition state (**H**, E_{tot} = –649.2628 hartree) the C^5–C^6 bond length increases to 2.661 Å, and the distance between oxygen and carbon atoms of the CH_2 group becomes 2.567 Å. The C^4–C^5 bond length decreased to 1.466 Å, while the C^5–O bond length increased to 1.240 Å. The calculated activation energy is 0.0949 hartree.

As follows from Scheme 2, the secondary reaction products are the corresponding oxo esters **5a–d**. Indeed, after separation of the solid products **3a–c** treatment of the filtrates with 2,4-dinitrophenylhydrazine afforded the corresponding 2,4-dinitrophenylhydrazones of these oxo esters **6a–c** (for details, see Online Supplementary Materials).

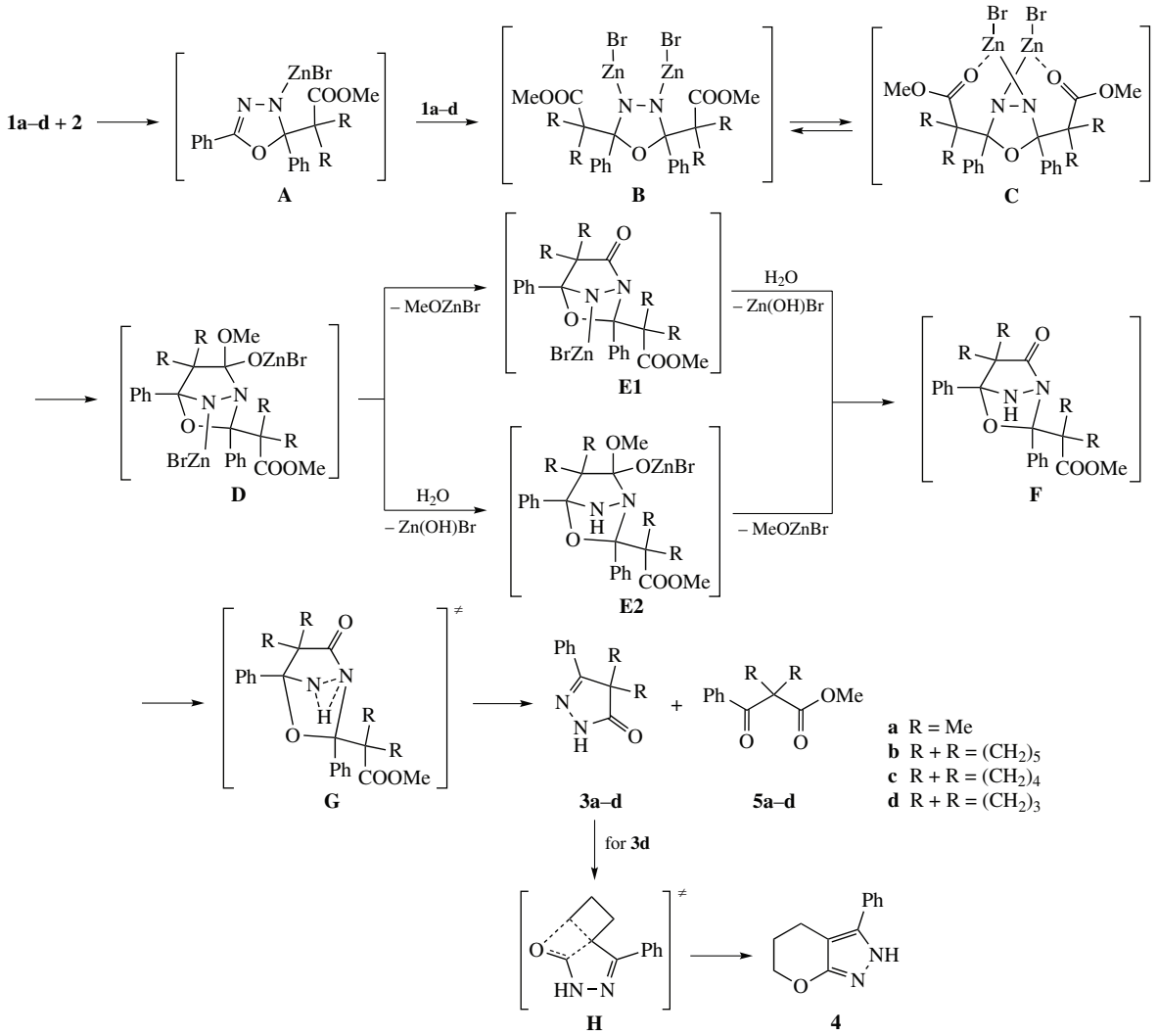


6a–c

a R = Me
b R + R = $(CH_2)_5$
c R + R = $(CH_2)_4$

In summary, the Reformatsky reaction of 2,5-diphenyl-1,3,4-oxadiazole provides compounds of remarkable structures, which can be promising for biological studies. The mechanistic pathways for the transformations seem interesting from the fundamental point of view.

[§] Quantum-chemical calculations with full optimization of all geometric parameters and taking into account the Grimme dispersion correction[14] were performed using the Firefly[15] software package.



Scheme 2

This work was supported by the Government of Perm Region.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.035.

References

1 F. Dardoize, J.-L. Moreau and M. Gaudemar, *Bull. Soc. Chim. Fr.*, 1969, **268**, 2228.
2 A. Brandi, S. Cicchi and F. M. Cordero, *Chem. Rev.*, 2008, **108**, 3988.
3 N. F. Kirillov and V. V. Shchepin, *Russ. J. Gen. Chem.*, 2005, **75**, 590 (*Zh. Obshch. Khim.*, 2005, **75**, 629).
4 E. A. Nikiforova, N. F. Kirillov, V. S. Melekhin and P. A. Slepukhin, *Mendeleev Commun.*, 2019, **29**, 393.
5 G. S. Singh, M. D'hooghe and N. De Kimpe, *Tetrahedron*, 2011, **67**, 1989.
6 A. Jarrahpour, S. Rezaei, V. Sinou, C. Latour and J. M. Brunel, *Iran. J. Sci. Technol.*, 2017, **41**, 337.
7 A. Jarrahpour, E. Ebrahimi, E. De Clercq, V. Sinou, C. Latour, L. D. Bouktab and J. M. Brunel, *Tetrahedron*, 2011, **67**, 8699.
8 D. J. Dagli, R. A. Gorski and J. Wemple, *J. Org. Chem.*, 1975, **40**, 1741.
9 S. J. Etheredge, *J. Org. Chem.*, 1966, **31**, 1990.
10 C. F. Wilcox, Jr., and G. C. Whitney, *J. Org. Chem.*, 1967, **32**, 2933.
11 *CrysAlisPro Software System, version 1.171.37*, Agilent Technologies, Yarnton, Oxfordshire, UK.
12 G. M. Sheldrick, *Acta Crystallogr.*, 2008, **A64**, 112.
13 L. J. Farrugia, *J. Appl. Crystallogr.*, 2012, **45**, 849.
14 S. Grimme, J. Antony, S. Ehrlich and H. Kreig, *J. Chem. Phys.*, 2010, **132**, 154104.
15 A. A. Granovsky, *Firefly, version 8.2.0*, http://classic.chem.msu.su/gran/firefly/index.html.

Received: 9th November 2020; Com. 20/6362