Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2020, **30**, 320–321

Mendeleev Communications

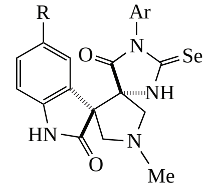
New spiro-linked indolinone pyrrolidine selenoxoimidazolones

Vladimir K. Novotortsev, Maxim E. Kukushkin, Viktor A. Tafeenko, Nikolai V. Zyk and Elena K. Beloglazkina*

Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation.
E-mail: bel@org.chem.msu.ru

DOI: 10.1016/j.mencom.2020.05.020

New 2-selenoxodispiro[imidazolidine-4,3′-pyrrolidine-4′,3′′-indoline]-2′′,5-dione system was accessed by addition of azomethine ylide at the double bond of (*Z*)-(2-oxoindolin-3-ylidene)-2-selenoxoimidazolidin-4-one derivatives. The latter were stereoselectively obtained in two steps from ethyl isoselenocyanatoacetate and isatins.

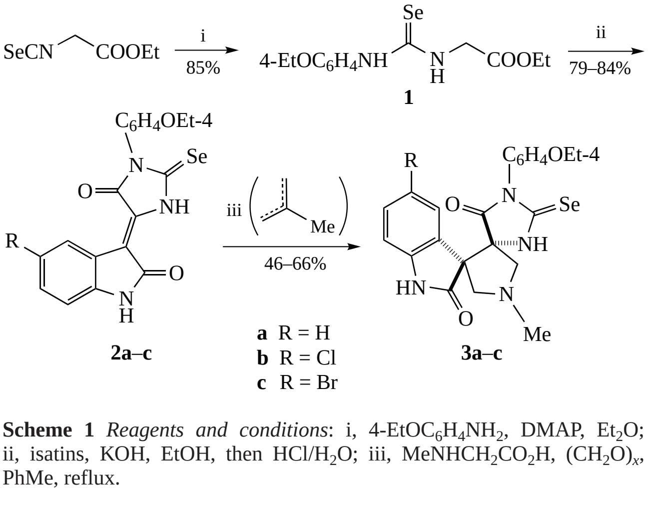


Keywords: dispiro compounds, spiro compounds, indolinones, selenohydantoins, azomethine ylides, pyrrolidines, X-ray.

A promising direction in the treatment of cancer is the development of compounds that affect the interaction of p53–MDM2 proteins. Tumor suppressor p53, not being complexed with its MDM2 inhibitor, can trigger cell apoptosis.[1,2] It was previously established that the Trp23 fragment of p53 protein which plays a key role in the p53–MDM2 binding can be effectively replaced by indolinone fragment.[3] It was also shown that compounds with a spiro-linked structure are capable of better binding to MDM2 by limiting the conformational mobility of the molecule.[3]

Hydantoin and thiohydantoin derivatives containing spiro-linked indolinone fragments showed significant *in vitro* cytotoxic activity.[4–6] The ability of organoselenium compounds to exhibit antioxidant properties[7,8] mimicking the action of the glutathione peroxidase enzyme[9] allows one to use them in anticancer therapy as auxiliary antioxidants to neutralize the oxidizing agents produced by certain anticancer drugs.[10] Taken this into consideration, here we report the synthesis of spiro derivatives of 2-selenohydantoin containing an imidazolone fragment (Scheme 1).

Selenourea **1** (obtained from ethyl isoselenocyanatoacetate[11] and 4-ethoxyaniline) was chosen as a starting material providing easy access to highly functionalized ‘biheterylidenes’ **2a**–**c** (see Scheme 1). Compound **1** was introduced into Knoevenagel condensation with isatins; in the course of these reactions, cyclization of selenourea moiety into selenohydantoin one also occurred to give 5-indolidene-substituted selenohydantoins **2a**–**c**. The reactions of the latter with sarcosine and paraformaldehyde provided the target spiro derivatives **3a**–**c** (the details of experimental procedures are given in Online Supplementary Materials). The best yields were achieved using toluene as a solvent, whereas in boiling methanol or ethanol the 1,3-dipolar cycloaddition did not proceed.



Scheme 1 *Reagents and conditions*: i, 4-EtOC$_6$H$_4$NH$_2$, DMAP, Et$_2$O; ii, isatins, KOH, EtOH, then HCl/H$_2$O; iii, MeNHCH$_2$CO$_2$H, (CH$_2$O)$_x$, PhMe, reflux.

The formation of dispiroindolinones **3a**–**c** occurs according to the [3+2] cycloaddition mechanism.[4] The reaction is believed to include the following steps: (1) the reaction between isatin and amino acid with the formation of the iminium intermediate; (2) cyclization of the iminum intermediate, followed by the loss of CO$_2$ with the formation of a 1,3-dipole; (3) regioselective addition of a 1,3-dipole at the C=C bond of compound **2**. Importantly, single diastereomers of the products **3a**–**c** with (R^*,S^*)-configuration of asymmetric carbon atoms were formed.

The structures of compounds **3** were confirmed by NMR spectroscopy. A characteristic part of the ^{1}H NMR spectra of compounds **3** is located in the region of 3.50–2.90 ppm where four doublets with J ~ 11 Hz corresponding to the hydrogen atoms of the central pyrrolidine cycle are observed. In addition, the structure of compound **3b** was proved by X-ray diffraction analysis (Figure 1).[†] Since compound **3b** was crystallized from

---

[†] *Crystallographic data for* **3b**. C$_{23}$H$_{25}$ClN$_4$O$_4$Se, M = 535.88, triclinic, space group $P\bar{1}$, a = 8.1758(3), b = 15.9583(5) and c = 18.8004(6) Å, V = 2429.57(14) Å^3, Z = 4, d_{calc} = 1.465 g cm^{-3}, μ = 3.413 mm^{-1}, F(000) = 1096, the final R = 0.0465, wR = 0.1216 and S = 0.797 for 2684 observed reflections with $I > 2\sigma(I)$. The measurements were performed on a STOE diffractometer with Pilatus100K detector and CuKα radiation (λ = 1.54186 Å). The structure was solved by direct methods, and the non-hydrogen atoms were located from the trial structure and then refined anisotropically with SHELXTL using full-matrix least-squares procedures based on F^2 values. Hydrogen atom positions were fixed geometrically at calculated distances and allowed to ride on the parent atoms.

CCDC 1967512 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.

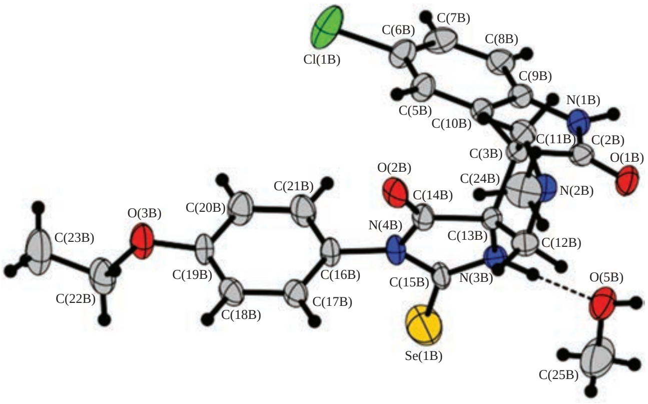


Figure 1 Molecular structure of compound **3b**. Thermal ellipsoids are given with a probability of 40%. Selected bond lengths (Å) and angles (°): C(3)–C(2) 1.552, C(3)–C(10) 1.486, C(3)–C(11) 1.552, C(3)–C(13) 1.570, C(13)–C(12) 1.515, C(13)–N(3) 1.449, C(13)–C(14) 1.516, N(3)–C(13)–C(14) 101.1, C(12)–C(13)–C(3) 103.6, C(10)–C(3)–C(2) 103.2, C(11)–C(3)–C(13) 100.1.

methanol, the solvate methanol molecule in the crystal is bonded to the hydrogen atom of the N–H fragment of the selenohydantoin ring. Dihedral angles between the planes of the cycles at spiro junction are close to 80° (the dihedral angle between the pyrrolidine and selenohydantoin cycles is 81.5°, and that between the pyrrolidine and indolinone fragments is 78.9°).

Comparing the results obtained in the synthesis of spiro derivatives of selenohydantoins with previously obtained data for similar hydantoins[6] and thiohydantoins,[4] it can be noted that in the case of selenoxo imidazolones, the yields of 1,3-dipolar cycloaddition products are generally lower (46–66%) than those for oxygen and sulfur analogues (77–90%), but in all cases the reaction proceeds with high diastereoselectivity.

In summary, a diastereoselective synthesis of a new spiro derivatives of 2-selenoxotetrahydro-4*H*-imidazol-4-ones and indolinones by the reaction of [3+2] cycloaddition of azomethine ylide generated from sarcosine and paraformaldehyde to 5-indolidene-substituted selenohydantoins has been accomplished. The compounds obtained may be further investigated as cytotoxic agents, similar to the previously described oxygen and sulfur-containing analogues; their possible antioxidant properties characteristic of selenium-containing compounds can provide them with less toxicity to non-cancer cells.

This work was supported by the Russian Foundation for Basic Research (project no. 19-03-00201). The work in part of NMR and X-ray study was supported by the M. V. Lomonosov Moscow State University Program of Development.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.05.020.

References

1 X. Wu, J. H. Bayle, D. Olson and A. J. Levine, *Genes Dev*., 1993, **7**, 1126.

2 B. Vogelstein, D. Lane and A. J. Levine, *Nature*, 2000, **408**, 307.

3 K. Ding, Y. Lu, Z. Nikolovska-Coleska, S. Qiu, Y. Ding, W. Gao, J. Stuckey, K. Krajewski, P. P. Roller, Y. Tomita, D. A. Parrish, J. R. Deschamps and S. Wang, *J. Am. Chem. Soc*., 2005, **127**, 10130.

4 Y. A. Ivanenkov, S. V. Vasilevski, E. K. Beloglazkina, M. E. Kukushkin, A. E. Machulkin, M. S. Veselov, N. V. Chufarova, E. S. Chernyagina, A. S. Vanzcool, N. V. Zyk, D. A. Skvortsov, A. A. Khutornenko, A. L. Rusanov, A. G. Tonevitsky, O. A. Dontsova and A. G. Majouga, *Bioorg. Med. Chem. Lett*., 2015, **25**, 404.

5 A. A. Beloglazkina, D. A. Skvortsov, V. A. Tafeenko, A. G. Majouga, N. V. Zyk and E. K. Beloglazkina, *Russ. Chem. Bull*., *Int. Ed*., 2018, **67**, 562 (*Izv. Akad. Nauk, Ser. Khim*., 2018, 562).

6 A. A. Beloglazkina, N. A. Karpov, S. R. Mefedova, V. S. Polyakov, D. A. Skvortsov, M. A. Kalinina, V. A. Tafeenko, A. G. Majouga, N. V. Zyk and E. K. Beloglazkina, *Russ. Chem. Bull*., *Int. Ed*., 2019, **68**, 1006 (*Izv. Akad. Nauk, Ser. Khim*., 2019, 1006).

7 T. Wirth, *Angew. Chem., Int. Ed*., 2015, **54**, 10074.

8 A. Müller, E. Cadenas, P. Graf and H. Sies, *Biochem. Pharmacol*., 1984, **33**, 3235.

9 T. Schewe, *Gen. Pharmacol*., 1995, **26**, 1153.

10 G. Batist, A. G. Katki, R. W. Klecker, Jr. and C. E. Myers, *Cancer Res*., 1986, **46**, 5482.

11 Y. A. Ivanenkov, M. S. Veselov, I. G. Rezekin, D. A. Skvortsov, Yu. B. Sandulenko, M. Polyakova, D. S. Bezrukov, S. V. Vasilevsky, M. E. Kukushkin, A. A. Moiseeva, A. V. Finko, V. E. Koteliansky, N. L. Klyachko, L. A. Filatova, E. K. Beloglazkina, N. V. Zyk and A. G. Majouga, *Bioorg. Med. Chem*., 2016, **24**, 802.

Received: 25th November 2019; Com. 19/6064