Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2022, **32**, 221–223

Mendeleev Communications

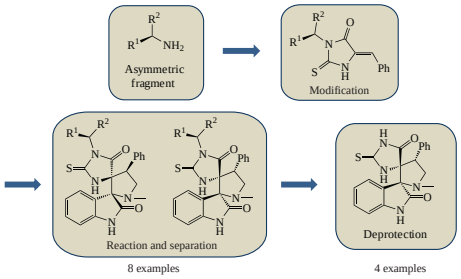
Diastereoselective cycloaddition of isatin azomethine ylides to 5-arylidene-2-thiohydantoins bearing 3-positioned chiral substituent

Alexander A. Barashkin,* Vladislav S. Polyakov, Nikita L. Shikut, Anastasia D. Putilova, Anton R. Gorovoy, Anton D. Degtiarev, Victor A. Tafeenko, Boris N. Tarasevich, Nikolai V. Zyk and Elena K. Beloglazkina

Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. E-mail: aleksandr.baraskin@gmail.com

DOI: 10.1016/j.mencom.2022.03.022

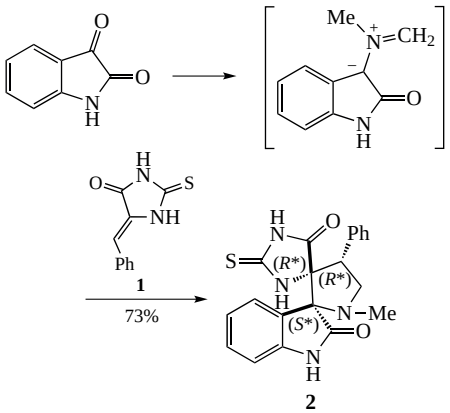
1,3-Dipolar cycloaddition of azomethine ylide, generated from isatin and sarcosine, with 5-arylidene-2-thiohydantoins equipped with various chiral substituents at the N^3 atom occurs diastereoselectively. The highest selectivity with *dr* = 5 : 1 was observed for the 2-thiohydantoin bearing 1,2-diphenylethyl substituent.



Keywords: azomethine ylide, chiral substituent, isatin, spirooxindole, spiro compound, thiohydantoin, diastereoselectivity.

Spiroindolinones demonstrate cytotoxic activity on different cancer cell lines. For instance, compound SAR405838 with a value IC_{50} = 0.27 μM on LNCaP cell line is one of the promising inhibitors of the protein–protein p53–MDM2 interaction.[1] The spirooxindole fragment is present in molecules proposed for the treatment of colorectal cancer and inhibiting tankyrases (TNKS1/TNKS2).[2] Similar spirooxindoles can be potentially used for the treatment of type 2 diabetes.[3] Noticeably, their enantiomers differ significantly in cytotoxic activity,[4] which emphasizes the importance of finding ways to separate spiro- and dispiroderivatives of indoline into individual stereoisomers.

1,3-Dipolar cycloaddition is one of the principal approaches to spiroindolinones. Reactions of 5-arylidene-2-thiohydantoins with azomethine ylides, generated in turn from isatin and sarcosine, proceed diastereoselectively (Scheme 1),[5–8] the selectivity has been found to be determined by an attack of the azomethine ylide planar moiety from two possible sides of the exocyclic C=C bond of 5-benzylidene-2-thiohydantoin **1**.[9] Thus, the reaction product of *N*-unsubstituted compound **1**, isatin and sarcosine was dispiroindolinone **2** with relative (2′*S**,3′*R**,4′*R**) configuration of the pyrrolidine ring (see Scheme 1) as confirmed by NMR spectroscopy and X-ray crystallography data.[10]



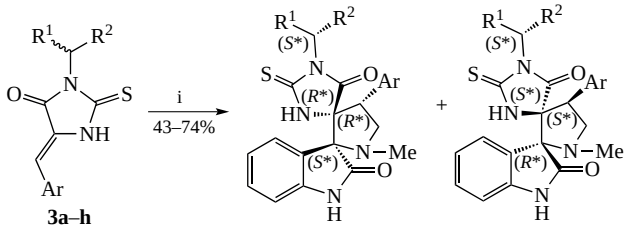
Scheme 1 *Reagents and conditions*: i, $MeNHCH_2CO_2H$, EtOH, reflux, 8 h.

We propose herein a convenient synthetic approach to individual racemic stereoisomeric spiroindolinones of type **2**. It consists in the introduction of an auxiliary chiral substituent into the molecule and subsequent separation of diastereomeric mixture. The removal of the auxiliary group should afford stereochemically pure products. For the introduction of the auxiliary asymmetric substituent, we chose a nitrogen atom in the position 3 in the thiohydantoin ring, which was easy to modify during thiohydantoins prepatation from suitable amines and thioureas.[11,12]

A series of racemic (*Z*)-configured 2-thiohydantoins **3a–h** with an additional stereocenter at the N^3 atom was synthesized (see Online Supplementary Materials) to study the influence of the substituent on diastereoselectivity of the 1,3-dipolar cycloaddition. Benzyl type Ar(Alk)CH groups with various fragments at the chiral α-carbon atom were chosen as asymmetric moieties since the groups could be easily removed by hydrogenolysis or acidolysis.[13] The cycloaddition of these reactants afforded racemic dispiroindolinones as the mixtures of diastereomers **4a–h** and **4′a–h**, where the dominant product had (2′*S**,3′*R**,4′*R**) pyrrolidine ring configuration assuming the asymmetric auxiliary substituent was (*S**)-configured (Scheme 2).

Diastereomeric ratios of the products were derived from ^{1}H NMR spectra. Under the conditions used, the cycloaddition with bulky α-(2-naphthyl)benzyl- and α-cyclopentylbenzyl-substituted substrates did not proceed possibly due to steric restrictions. The highest diastereomeric ratio of 5 : 1 was observed for 5-benzylidene-2-thiohydantoin **3d** with 1,2-diphenylethyl substituent, leading to dispiroindolinones **4d** and **4′d**.

In the 1,3-dipolar cycloaddition under study, the major products were diastereomers **4** with the relative configuration shown in Scheme 2. The structure of the representative



a Ar = R^1 = Ph, R^2 = Me, *dr* = 3.4
b Ar = R^1 = Ph, R^2 = Et, *dr* = 3.2
c Ar = R^1 = Ph, R^2 = Pr^i, *dr* = 1.5
d Ar = R^1 = Ph, R^2 = $PhCH_2$, *dr* = 5.0
e Ar = Ph, R^1 = 4-$MeOC_6H_4$, R^2 = Me, *dr* = 3.0
f Ar = Ph, R^1 = 2,4-$(MeO)_2C_6H_3$, R^2 = Me, *dr* = 3.0
g Ar = Ph, R^1 = 2-BnO-4-$MeOC_6H_3$, R^2 = Me, *dr* = 2.8
h Ar = 4-ClC_6H_4, R^1 = Ph, R^2 = Me, *dr* = 3.4

dr = **4a–h**/**4′a–h**

no reaction for:
R^1 = Ph,
R^2 = *cyclo*-C_5H_9
R^1 = Ph,
R^2 = 2-naphthyl

Scheme 2 *Reagents and conditions*: i, isatin, $MeNHCH_2CO_2H$, EtOH, reflux, 8 h; ii, CF_3CO_2H, reflux.

dispiroindolinone **4h** was established by X-ray crystallography (Figure 1).† Comparison of the characteristic signals of pyrrolidine ring in the ^{1}H NMR spectra of the reaction mixtures and individual stereoisomers with the data of X-ray crystallography made it possible to correlate spectral signals for the major and minor diastereomers.

The presence of a stereocenter in the dipolarophile **3** molecule apparently lead to partial blocking of the dipole approach from on one side of the double C=C bond plane (Figure 2), which provides the reaction diastereoselectivity. In the absence of stereocenter in the 2-thiohydantoin molecule, the dipole approach is equiprobable for both sides of the plane.

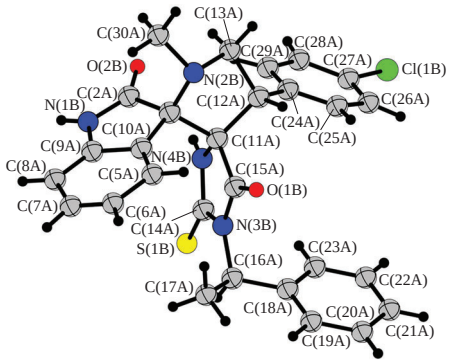


Figure 1 Molecular structure of dispiroindolinone **4h**.

Most of the diastereomeric mixtures synthesized could be purified by recrystallization from ethanol (Table S1, see Online Supplementary Materials). However, for compounds **4f**,**g** with 1-(2,4-dimethoxyphenyl)ethyl and 1-(2-benzyloxy-4-methoxyphenyl)ethyl substituents a column chromatography had to be employed.

At the final stage of synthesis, the conditions for removal of the asymmetric substituent from nitrogen atom by hydrogenolysis or acidolysis were optimized (Table S2). It was found that the hydrogenolysis of benzylic amines **4a**–**g** under 10 atm of H_2 at 50 °C did not occur. Luckily, the target unsubstituted dispiroindolinones **2** were obtained from substances **4d**–**g** using acidolysis with trifluoroacetic acid, while from their analogues **4a**–**c** no product was formed. The main reason is that the Ar(Alk)CH substituent cannot be removed by hydrogenolysis without electron-donating substituents in the aryl moiety (see Table S2).

In summary, diastereoselective 1,3-dipolar cycloaddition of isatin-derived azomethine ylide was accomplished for 5-arylidene-2-thiohydantoins equipped with N^3-positioned

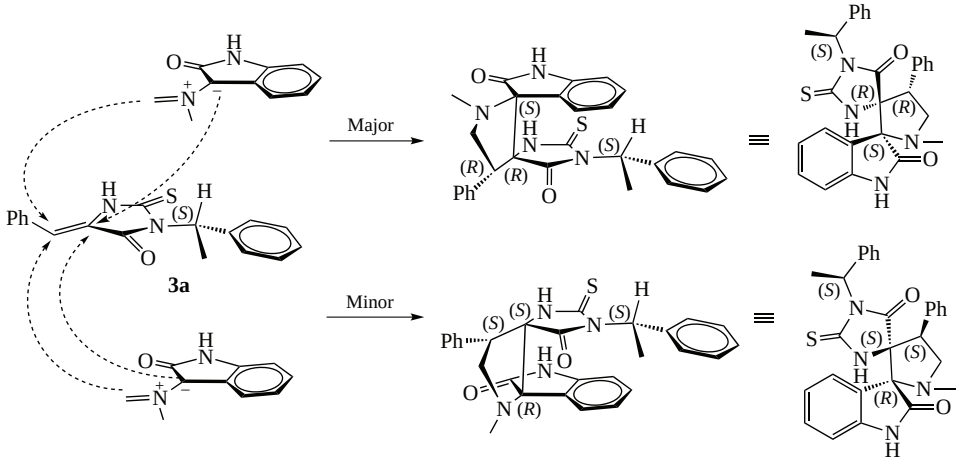


Figure 2 Attack of azomethine ylide from two sides of the exocyclic C=C bond plane of 5-benzylidene-2-thiohydantoin with an auxiliary asymmetric substituent (for compound **4a**).

† *Crystal data for* **4h**. $C_{28}H_{25}ClN_4O_2S$ (M = 517.03), orthorhombic, space group $P2_12_12_1$, at 293(2) K: a = 9.0648(3), b = 22.4610(10) and c = 29.5280(10) Å, V = 6012.0(4) Å^3, Z = 8, d_{calc} = 1.142 g cm^{-3}. Absorption coefficient 2.002 mm^{-1}, F(000) = 2160, 3.936 ⩽ θ ⩽ 60.788° for data collection. Index ranges –10 ⩽ h ⩽ 3, –25 ⩽ k ⩽ 25, –32 ⩽ l ⩽ 33, 36023 reflections collected, 8965 independent reflections (R_{int} = 0.2065). Completeness to θ is 60.788° (99.1%). Refinement method: full-matrix least-squares on F^2. Data/restraints/parameters: 8965/60/629. Goodness-of-fit on F^2 = 0.565. Final R indices [$I > 2\sigma(I)$]: R_1 = 0.0536, wR_2 = 0.0855, R indices (all data) R_1 = 0.2099, wR_2 = 0.1147, absolute structure parameter 0.01(3), largest difference peak and hole is 0.181 and –0.178 e Å^{-3}, respectively.

The data were collected using a STOE diffractometer (STOE & Cie) with a PILATUS100K detector, focusing on the mirror collimation CuKα (1.54086 Å) radiation in rotation method mode. The STOE X-Area software was used for the cell refinement, data reduction, data collection and image processing. Intensity data were scaled with Lana as a part of X-Area in order to minimize the differences in the intensities of symmetry equivalent reflections (multiscan method). Structures were solved with SHELXT and refined using SHELX software. The non-hydrogen atoms were refined using the anisotropic full-matrix least-squares procedure. All the hydrogen atoms were placed in the calculated positions and allowed to ride on their parent atoms [C–H 0.93–0.98; U_{iso} = 1.2 U_{eq} (parent atom)].

CCDC 2100527 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.

chiral auxiliary. The best diastereomeric ratio of 5:1 was obtained for 5-benzylidene-3-(1,2-diphenylethyl)-2-thiohydantoin **3d**. The method of resolution of dispiroindolinone stereoisomers is proposed consisting in introduction of additional groups with asymmetric atoms and the following removal of these groups by acidolysis. The highest yield of the individual diastereomer was observed for 1-(2,4-dimethoxyphenyl)ethyl-substituted product **4f**. It may be expected that 5-arylidene-2-thiohydantoins **3** obtained from enantiomerically pure amines will afford enantiomerically pure dispiroindolinones of type **2** using the approach proposed here.

This work was supported by the Russian Foundation for Basic Research (grant no. 19-33-90237), the Russian Science Foundation (grant no. 21-13-00023), and in the part of NMR and X-ray study 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.2022.03.022.

References

1 S. Wang, W. Sun, Y. Zhao, D. McEachern, I. Meaux, C. Barrière, J. A. Stuckey, J. L. Meagher, L. Bai, L. Liu, C. G. Hoffman-Luca, J. Lu, S. Shangary, S. Yu, D. Bernard, A. Aguilar, O. Dos-Santos, L. Besret, S. Guerif, P. Pannier, D. Gorge-Bernat and L. Debussche, *Cancer Res*., 2014, **74**, 5855.

2 F. Shirai, A. Mizutani, Y. Yashiroda, T. Tsumura, Y. Kano, Y. Muramatsu, T. Chikada, H. Yuki, H. Niwa, S. Sato, K. Washizuka, Y. Koda, Y. Mazaki, M.-K. Jang, H. Yoshida, A. Nagamori, M. Okue, T. Watanabe, K. Kitamura, E. Shitara, T. Honma, T. Umehara, M. Shirouzu, T. Fukami, H. Seimiya, M. Yoshida and H. Koyama, *J. Med. Chem*., 2020, **63**, 4183.

3 C. Teja, S. N. Babu, A. Noor, J. A. Daniel, S. A. Devi and F. R. N. Khan, *RSC Adv*., 2020, **10**, 12262.

4 K. Zak, A. Pecak, B. Rys, B. Wladyka, A. Dömling, L. Weber, T. A. Holak and G. Dubin, *Expert Opin. Ther. Pat*., 2013, **23**, 425.

5 I. B. Kutyashev, I. A. Kochnev, A. A. Cherepkova, N. S. Zimnitskiy, A. Yu. Barkov, V. Yu. Korotaev and V. Ya. Sosnovskikh, *Chem. Heterocycl. Compd*., 2020, **56**, 1302.

6 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.

7 R. Singh and R. Vince, *Chem. Rev*., 2012, **112**, 4642.

8 V. K. Novotortsev, M. E. Kukushkin, V. A. Tafeenko, N. V. Zyk and E. K. Beloglazkina, *Mendeleev Commun*., 2020, **30**, 320.

9 M. E. Kukushkin, D. A. Skvortsov, M. A. Kalinina, V. A. Tafeenko, V. V. Burmistrov, G. M. Butov, N. V. Zyk, A. G. Majouga and E. K. Beloglazkina, *Phosphorus, Sulfur Silicon Relat. Elem*., 2020, **195**, 544.

10 A. Beloglazkina, A. Barashkin, V. Polyakov, G. Kotovsky, N. Karpov, S. Mefedova, B. Zagribelny, Ya. Ivanenkov, M. Kalinina, D. Skvortsov, V. Tafeenko, N. Zyk, A. Majouga and E. Beloglazkina, *Chem. Heterocycl. Compd*., 2020, **56**, 747.

11 O. O. Krasnovskaya, V. M. Malinnikov, N. S. Dashkova, V. M. Gerasimov, I. V. Grishina, I. I. Kireev, S. V. Lavrushkina, P. A. Panchenko, M. A. Zakharko, P. A. Ignatov, O. A. Fedorova, G. Jonusauskas, D. A. Skvortsov, S. S. Kovalev, E. K. Beloglazkina, N. V. Zyk and A. G. Majouga, *Bioconjugate Chem*., 2019, **30**, 741.

12 J. Ryczek, *J. Heterocycl. Chem*., 2003, **40**, 665.

13 S. G. Davies, R. Huckvale, J. A. Lee, T. J. A. Lorkin, P. M. Roberts and J. E. Thomson, *Tetrahedron*, 2012, **68**, 3263.

Received: 12th August 2021; Com. 21/6641