

Synthesis of new heterylmethylidene derivatives of isomeric imidazo[4,5-*e*]thiazolo-fused [1,2,4]triazines

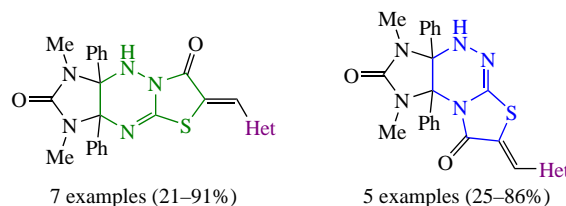
Maksim E. Lugovoi,^a Alexei N. Izmet'sev,^{a,b} Natalya G. Kolotyrkina,^b Ekaterina S. Izmalkova,^b Angelina N. Kravchenko^b and Galina A. Gazieva^{*b}

^a National University of Science and Technology 'MISIS', 119049 Moscow, Russian Federation

^b N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. E-mail: gaz@ioc.ac.ru

DOI: 10.1016/j.mencom.2024.06.029

Novel 6-heterylmethylidene-3a,9a-diphenylimidazo[4,5-*e*]thiazolo[3,2-*b*][1,2,4]triazines were synthesized by the three-component condensation of imidazo[4,5-*e*][1,2,4]triazine-3-thione derivative with bromoacetic acid and heteroaromatic aldehydes. The following MeONa-induced skeletal rearrangement gave the recycled isomeric products, viz. 7-heterylmethylidene-3a,9a-diphenylimidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazines.



Keywords: heteroaromatic aldehydes, thiazolidin-4-ones, 1,2,4-triazines, skeletal rearrangement, imidazothiazolotriazines, imidazo[4,5-*e*][1,2,4]triazine-3-thiones.

The heterocyclic thiazolidin-4-one system is a well-known pharmacophore fragment and is widely used in the synthesis of biologically active compounds.^{1,2} Special attention is paid to thiazolidin-4-ones functionalized at the position 5, many of which are used in medicine as neurotropic (epalrestat),³ antidiabetic (rosiglitazone),⁴ diuretic (ethozoline),⁵ anti-inflammatory (darbufelon)⁶ and anticonvulsant (ralitoline)⁷ agents (Figure 1). In recent years, considerable attention has been paid to the study of antitumor activity of a number of structurally related aryl- and heterylmethylidene derivatives of thiazolidinones.^{8–10} The high alkylating ability of the α,β -unsaturated carbonyl system of 5-benzylidenethiazolidin-4-one

in relation to biological nucleophiles is assumed to be one of the mechanisms of therapeutic action.^{11,12}

Our recent studies on antiproliferative properties of oxindolylidene- and heterylmethylidene derivatives of imidazo[4,5-*e*]thiazolo[2,3-*c*]triazine showed their high activity against a wide number of human cancer cell lines and low toxicity relatively healthy ones (see Figure 1).^{13–15} These compounds can be prepared by skeletal rearrangement of their regioisomeric derivatives of imidazo[4,5-*e*]thiazolo[3,2-*b*][1,2,4]triazine, proceeding upon treatment with KOH. We have also shown that isomerization of similar imidazothiazolotriazines containing two 3a,9a-positioned phenyl substituents is ineffective under these conditions and required the action of a stronger base, i.e., NaOMe. Using this approach, a series of oxindolylidene derivatives of 1,3-dimethyl-3a,9a-diphenylimidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazine was synthesized, which remained unavailable for a long time.¹⁶

Taking into account the high practical significance of the synthesis and study of the biological activity of new functionalized imidazothiazolotriazines, the present work was aimed at the synthesis of a number of 1,3-dimethyl-3a,9a-diphenylimidazo[4,5-*e*]thiazolo[3,2-*b*]triazine heterylmethylidene derivatives of linear structure and their rearrangement into corresponding isomeric imidazo[4,5-*e*]thiazolo[2,3-*c*]triazines upon treatment with sodium methoxide. Imidazothiazolotriazines **1a–g** arranged in a linear fashion were synthesized *via* the three-component condensation of imidazo[4,5-*e*][1,2,4]triazine-3-thione **2**, bromoacetic acid and heteroaromatic aldehydes in acetic acid under reflux according to earlier elaborated procedure (Scheme 1).¹⁷ The wide range of the product yields is probably related to the different nature and reactivity of the aldehydes used, as well as the stability of heterocyclic systems in boiling acetic acid. For example, the reaction with the 1*H*-pyrrole-2-carbaldehyde afforded product **1f** in 32% yield because it was accompanied by polymerization/resinification. Using the

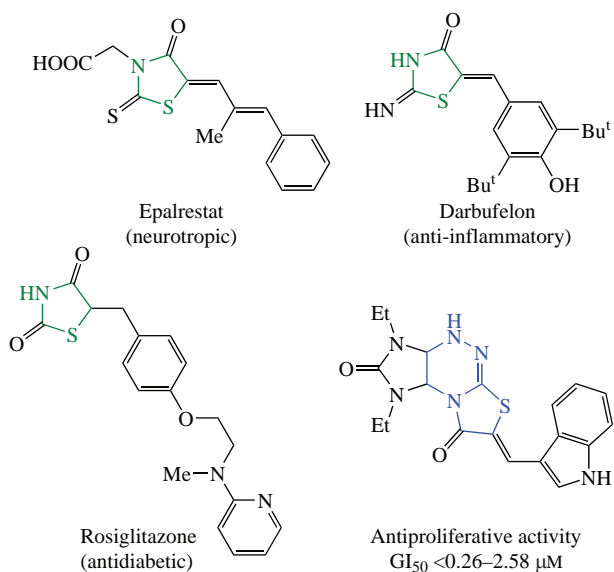
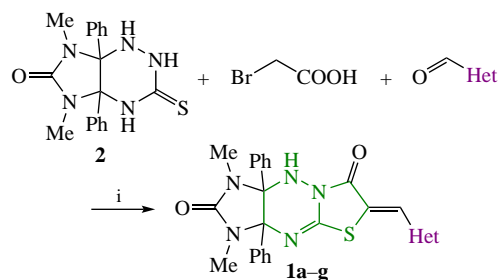


Figure 1 Examples of biologically active functionalized thiazolidin-4-ones and imidazothiazolotriazines.



- | | |
|---|--------------------------------|
| a Het = 3-pyridyl, 52% | e Het = 2-thienyl, 91% |
| b Het = 4-pyridyl, 21% | f Het = 2-pyrrolyl, 32% |
| c Het = 1,2-dimethylimidazol-5-yl, 74% | g Het = 3-indolyl, 58% |
| d Het = 2-furyl, 52% | |

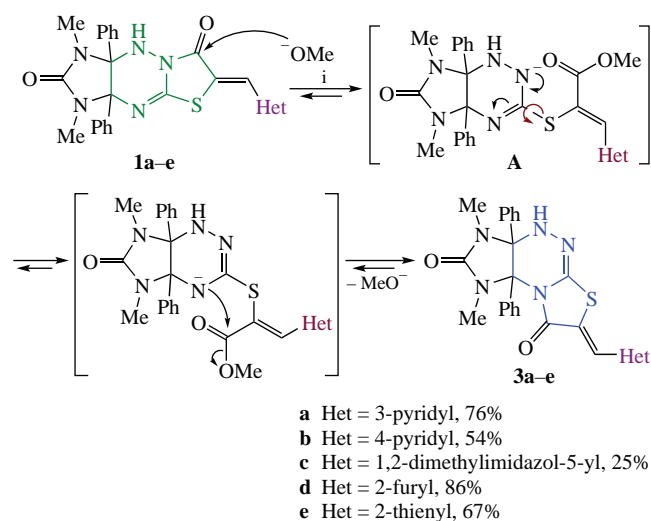
Scheme 1 Reagents and conditions: i, AcONa (1 equiv.), AcOH, reflux, 8 h.

example of the synthesis of compound **1d**, it is shown that the stepwise conducting of the reaction between imidazotriazine **2** and bromoacetic acid, and the consequent aldol condensation of the isolated imidazothiazolotriazine with furfural lead to a slight decrease in the overall yield of the product **1d** (44%) compared with the one-pot three-component condensation (52%).

Rearrangement of thus prepared imidazothiazolotriazines **1a–g** was carried out under basic catalysis using different amounts of sodium methoxide (Scheme 2). It turned out that complete conversion of compounds **1a–e** was achieved by refluxing the starting compounds in methanol with an equivalent amount of NaOMe. In this way, the corresponding regioisomeric imidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazines **3a–e** arranged in an angular fashion were obtained in 25–86% yields. Compounds **1f,g** with *NH* function in the heterocycles did not undergo similar isomerization even in the presence of 4 equiv. of sodium methoxide and were recovered from the reaction mixtures unchanged.

The rearrangement mechanism apparently includes a nucleophilic attack of the methoxide anion at the carbonyl group of compound **1** followed by opening of the thiazolidine ring with formation of the intermediate ester **A**. Further intramolecular cyclization involving the nitrogen atom *N*⁴ of the triazine ring leads to elimination of the methoxide anion and formation of the imidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazine system **3** (see Scheme 2).

The structures of compounds **1a–g** and **3a–e** were confirmed by the IR, ¹H NMR, ¹³C NMR spectroscopy including {¹H–¹³C} HSQC and {¹H–¹³C} HMBC 2D experiments for compound **1c** as well as HRMS spectral data. The ¹H NMR spectra of ‘linear’



- | |
|---|
| a Het = 3-pyridyl, 76% |
| b Het = 4-pyridyl, 54% |
| c Het = 1,2-dimethylimidazol-5-yl, 25% |
| d Het = 2-furyl, 86% |
| e Het = 2-thienyl, 67% |

Scheme 2 Reagents and conditions: i, MeONa (1 equiv.), MeOH, reflux, 1 h.

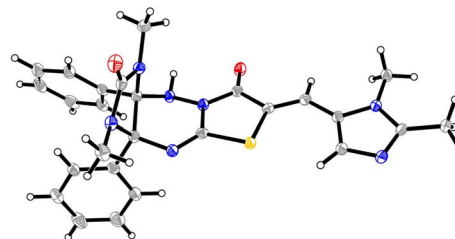


Figure 2 General view of **1c** in crystal in thermal ellipsoid representation (p = 50%).

products **1a–g** exhibit a system of two *ortho*-proton doublets (for two benzene rings) characteristic of phenyl substituents in the range of 6.74–6.87 ppm and triplets of *meta*- and *para*-protons combined into a multiplet at 7.04–7.21 ppm, while in the spectra of compounds **3a–e** *ortho*- and *para*-protons resonate as two broadened singlets at 6.71–7.14 ppm (see Online Supplementary Materials). The singlet of the NH group proton of compounds **3a–e** is shifted to the downfield region (8.21–8.35 ppm) compared to the signal of the same group in products **1a–g** (7.55–7.75 ppm), which is typical of pairs of regioisomeric imidazothiazolotriazines and was observed earlier.^{13,16} The proton signals for the methyldene fragment are shifted downfield in a rather wide range of chemical shift values due to the deshielding effect of the carbonyl group (7.38–8.20 ppm), which confirmed the *Z*-configuration of the double bond.^{13,17}

The structure of compound **1c** was ultimately proved by X-ray analysis of its single crystal (Figure 2).[†]

In summary, the application scope of the skeletal rearrangement catalyzed by sodium methoxide in the series of functionalized imidazo[4,5-*e*]thiazolo[3,2-*b*][1,2,4]triazine derivatives was expanded and a diastereoselective synthesis of previously inaccessible hetaryl-methyldene derivatives of 1,3-dimethyl-3a,9a-diphenylimidazo[4,5-*e*]thiazolo[2,3-*c*][1,2,4]triazine was developed.

Crystal structure determination for compound **1c** was performed in the Department of Structural Studies of the N. D. Zelinsky Institute of Organic Chemistry, Moscow.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.06.029.

References

- N. Agrawal, *Curr. Chem. Lett.*, 2021, **10**, 119.
- A. K. Jain, A. Vaidya, V. Ravichandran, S. K. Kashaw and R. K. Agrawal, *Bioorg. Med. Chem.*, 2012, **20**, 3378.

[†] Crystal data for **1c**. The crystals were obtained from methanol solution. C₂₆H₂₅N₇O₂S, *M* = 499.59, triclinic, space group *P* $\bar{1}$, 100 K, *a* = 7.4357(2), *b* = 9.7514(2) and *c* = 17.7464(8) Å, α = 85.942(3), β = 82.650(3) and γ = 69.591(2)°, *V* = 1195.61(7) Å³, *Z* = 2, *d*_{calc} = 1.388 g cm^{−3}, *F*(000) = 524. Total of 25266 reflections were measured and 5036 independent reflections (*R*_{int} = 0.0341) were used in a further refinement. *R*₁ = 0.0373 [from 4797 unique reflections with *I* > 2σ(*I*)] and *wR*₂ = 0.1011 (from all 5036 unique reflections). X-ray diffraction data were collected at 100 K on a Rigaku Synergy S four-circle diffractometer equipped with a HyPix6000HE area-detector (kappa geometry, shutterless ω-scan technique), using monochromatized Cu Kα-radiation. The intensity data were integrated and corrected for absorption and decay by the CrysAlisPro program.¹⁸ The structure was solved by direct methods using SHELXT¹⁹ and refined on *F*² using SHELXL-2018²⁰ in the OLEX2 program.²¹

CCDC 2288431 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Center via <http://www.ccdc.cam.ac.uk>.

- 3 N. Hotta, Y. Akanuma, R. Kawamori, K. Matsuoka, Y. Oka, M. Shichiri, T. Toyota, M. Nakashima, I. Yoshimura, N. Sakamoto and Y. Shigeta, *Diabetes Care*, 2006, **29**, 1538.
- 4 J. M. Malinowski and S. Bolesta, *Clin. Ther.*, 2000, **22**, 1151.
- 5 H. Knauf, R. Liebig, P. Schollmeyer, J. Rosenthal, E. U. Kölle and E. Mutschler, *Eur. J. Clin. Pharmacol.*, 1984, **26**, 687.
- 6 X. Ye, W. Zhou, Y. Li, Y. Sun, Y. Zhang, H. Ji and Y. Lai, *Cancer Chemother. Pharmacol.*, 2010, **66**, 277.
- 7 W. Fischer, R. Bodewei and G. Satzinger, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 1992, **346**, 442.
- 8 R. Romagnoli, P. G. Baraldi, M. K. Salvador, M. E. Camacho, J. Balzarini, J. Bermejo and F. Estévez, *Eur. J. Med. Chem.*, 2013, **63**, 544.
- 9 A. N. Izmet'sev, G. A. Gazieva, N. G. Kolotyrykina, E. D. Daeva and A. N. Kravchenko, *Chem. Heterocycl. Compd.*, 2020, **56**, 1569.
- 10 A. S. Agarkov, A. K. Shiryaev, S. E. Solovieva and I. S. Antipin, *Russ. J. Org. Chem.*, 2023, **59**, 337 (*Zh. Org. Khim.*, 2023, **59**, 285).
- 11 B. Z. Ahn and D. E. Sok, *Curr. Pharm. Des.*, 1996, **2**, 247.
- 12 F. F. Gan, K. K. Kaminska, H. Yang, C.-Y. Liew, P.-C. Leow, C.-L. So, L. N. L. Tu, A. Roy, C.-W. Yap, T.-S. Kang, W.-K. Chui and E.-H. Chew, *Antioxid. Redox Signaling*, 2013, **19**, 1149.
- 13 A. N. Izmet'sev, G. A. Gazieva, L. V. Anikina, S. A. Pukhov, V. A. Karnoukhova, N. G. Kolotyrykina and A. N. Kravchenko, *New J. Chem.*, 2021, **45**, 12271.
- 14 A. N. Izmet'sev, L. V. Anikina, I. E. Zanin, N. G. Kolotyrykina, E. S. Izmalkova, A. N. Kravchenko and G. A. Gazieva, *New J. Chem.*, 2022, **46**, 11632.
- 15 A. N. Izmet'sev, A. N. Kravchenko and G. A. Gazieva, *Chem. Heterocycl. Compd.*, 2022, **58**, 531.
- 16 A. N. Izmet'sev, A. N. Kravchenko and G. A. Gazieva, *Mendeleev Commun.*, 2022, **32**, 678.
- 17 G. A. Gazieva, S. A. Serkov, N. V. Sigai, N. N. Kostikova, Yu. V. Nelyubina, E. A. Shishkova and A. N. Kravchenko, *Chem. Heterocycl. Compd.*, 2013, **49**, 1097 (*Khim. Geterotsikl. Soedin.*, 2013, **49**, 1176).
- 18 *CrysAlisPro, Version 1.171.42*, Rigaku Oxford Diffraction, 2022.
- 19 G. M. Sheldrick, *Acta Crystallogr.*, 2015, **A71**, 3.
- 20 G. M. Sheldrick, *Acta Crystallogr.*, 2015, **C71**, 3.
- 21 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339.

Received: 27th February 2024; Com. 24/7406