Accepted Manuscript

Reactivity of spiroanthraceneoxazolidines with cyclopropanes: an approach to the oxindole alkaloid scaffold

Evgeny M. Buev, Vladimir S. Moshkin, Vyacheslav Y. Sosnovskikh

PII: S0040-4039(18)30970-5
DOI: https://doi.org/10.1016/j.tetlet.2018.08.001
Reference: TETL 50176

To appear in: *Tetrahedron Letters*

Received Date: 13 June 2018
Revised Date: 20 July 2018
Accepted Date: 1 August 2018

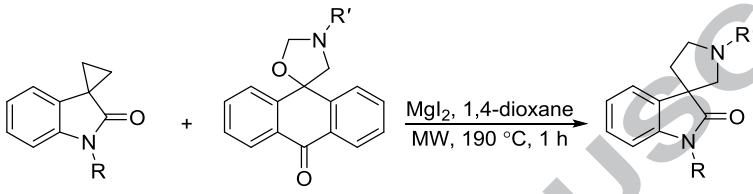
Please cite this article as: Buev, E.M., Moshkin, V.S., Sosnovskikh, V.Y., Reactivity of spiroanthraceneoxazolidines with cyclopropanes: an approach to the oxindole alkaloid scaffold, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.08.001

Graphical Abstract

Reactivity of spiroanthraceneoxazolidines with cyclopropanes: an approach to the oxindole alkaloid scaffold

Leave this area blank for abstract info.

Evgeny M. Buev, Vladimir S. Moshkin*, Vyacheslav Y. Sosnovskikh



R = Me, Et, *n*Pr, Am, Bn, PMB
R′ = Me, Bn

9 examples
29–65% yield

* Corresponding author. Tel: +7 3432616824; fax: +7 3432615978.
E-mail address: mvslc@mail.ru (V. S. Moshkin).

Tetrahedron Letters
journal homepage: www.elsevier.com

Reactivity of spiroanthraceneoxazolidines with cyclopropanes: an approach to the oxindole alkaloid scaffold

Evgeny M. Buev, Vladimir S. Moshkin*, Vyacheslav Y. Sosnovskikh

Institute of Natural Sciences and Mathematics, Ural Federal University, 620000 Ekaterinburg, Russian Federation

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Domino reaction
Spiroanthraceneoxazolidines
Pyrrolidines
Oxindole alkaloids
Horsfiline
Coerulescine

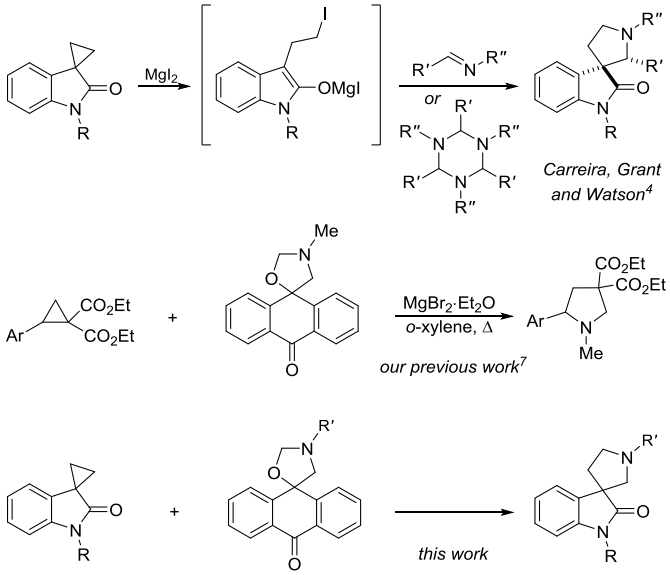
ABSTRACT

The reaction of *N*-methylspiro[anthracene-oxazolidine] with spiro[cyclopropane-3,3′-indolin]-2-ones in the presence of MgI_2 formed the corresponding spiro[pyrrolidine-3,3′-indolin]-2-ones in 42–65% yields. The use of *N*-benzylspiro[anthracene-oxazolidine] in this reaction led to the formation of a mixture of the corresponding *N*-methyl- and *N*-benzylpyrrolidines.

The pyrrolidine core is one of the most important building blocks in organic synthesis and is a popular fragment in medicinal chemistry.[1] In particular, compounds which are spiro-fused at the 3-position of the indolin-2-one pyrrolidine ring constitute the basis for naturally occurring oxindole alkaloids.[2] The oxindole motif is present in the core of numerous biologically active compounds such as coerulescine and horsfiline (Fig. 1). The latter were isolated from the Malaysian medicinal plant *Horsfieldia superba* and have attracted significant attention as analgesic medicinal compounds.[3]

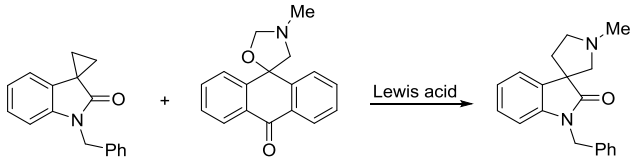
Figure 1. Examples of naturally occurring alkaloids containing an oxindole framework.

Straightforward approaches for the synthesis of the oxindole framework based on a formal [3+2]-cycloaddition of imines to cyclopropanes were reported by the Carreira, Grant and Watson groups (Scheme 1).[4] These works are based on the high strain energy of the cyclopropane ring which allows its facile ring-opening with formation of an iodide-enolate. The latter possesses a dipolar nature and successfully forms the pyrrolidine ring after reaction with imines or 1,3,5-triazinanes. It should be noted that such an approach has been effectively applied to the chemistry of donor-acceptor cyclopropanes, whose structure promotes an easier ring-opening of the cyclopropane ring.[5] In particular, previously we reported that the reaction of D-A cyclopropanes[6] with spiro[anthracene-oxazolidine] resulted in diethyl 5-arylpyrrolidine-3,3-dicarboxylates.[7] Thus, the spiroanthraceneoxazolidine system[8] unexpectedly appeared to be a synthetic equivalent of *N*-methylmethanimine. Herein, we report the reactivity of spiro[anthracene-oxazolidines] and its application in the synthesis of a valuable natural oxindole scaffold.



Scheme 1. Selected reactions of cyclopropanes.

* Corresponding author at: Institute of Natural Sciences and Mathematics, Ural Federal University, 620000 Ekaterinburg, Russian Federation.
e-mail address: mvslc@mail.ru (V. S. Moshkin).



Scheme 2. Synthesis of spiro-pyrrolidine **3a**.

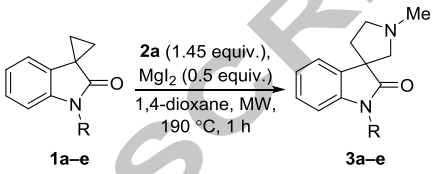
Table 1. Optimisation of the reaction conditions.[a]

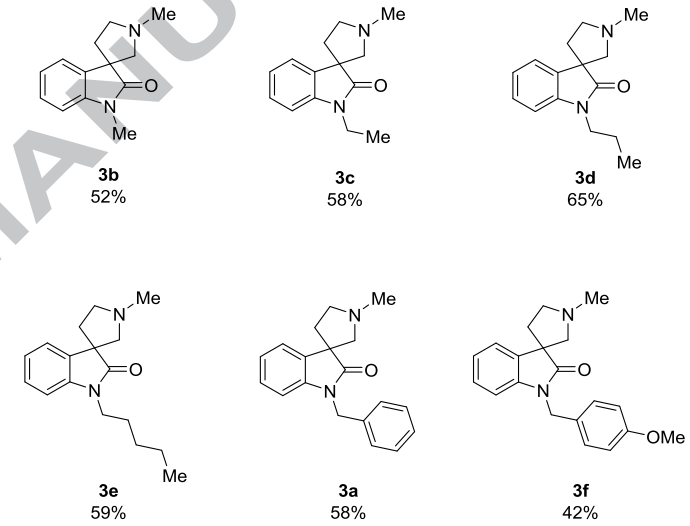
Entry	Conditions	Solvent	Lewis acid (equiv.)	Yield **3a** (%)[b]
1	**2a** (1.7 equiv.), reflux, 4 h	*o*-xylene	$MgBr_2 \cdot Et_2O$ (1.0)	–[c]
2	**2a** (2.25 equiv.), MW, 210 °C, 2 h	*o*-xylene	$MgBr_2 \cdot Et_2O$ (1.0)	25[d]
3	**2a** (1.1 equiv.), MW, 120 °C, 30 min	THF	MgI_2 (0.1)	recovered **2a**
4	**2a** (1.3 equiv.), MW, 170 °C, 1 h	1,4-dioxane	MgI_2 (0.2)	29[d]
5	**2a** (1.45 equiv.), MW, 210 °C, 1 h	DMF	MgI_2 (0.2)	27[d]
6	**2a** (1.2 equiv.), MW, 150 °C, 15 min	THF	BBr_3 (1.0)	–[c]
7	**2a** (1.2 equiv.), MW, 170 °C, 1 h	1,4-dioxane	MgI_2 (1.1)	40[d]
8	**2a** (1.3 equiv.), MW, 170 °C, 1 h	THF	$MgBr_2$ (0.2)	30[d]
9	**2a** (1.2 equiv.), MW, 170 °C, 1 h	1,4-dioxane	$MgBr_2$ (1.1)	27
10	**2a** (**1.45 equiv.**), **MW, 190 °C, 1 h**	**1,4-dioxane**	**MgI_2 (0.5)**	**58**

[a] Reactions were performed on a 0.8 mmol scale.
[b] Isolated yields of product **3a** based on cyclopropane **1a**.
[c] Complex mixture of products.
[d] NMR yield: product was contaminated by the starting oxazolidine.

We commenced our study with optimization of the reaction conditions using the model reaction of *N*-benzyloxindole cyclopropane **1a** with spiroanthraceneoxazolidine **2a** (Scheme 2). Unfortunately, it was discovered that the previously developed conditions for the reactions of D-A cyclopropanes (*o*-xylene, $MgBr_2 \cdot Et_2O$, reflux, 3.5 h)[7] were not appropriate (Table 1, entry 1). The same experiment at higher temperature (210 °C) in a microwave reactor led to the desired *N*-benzylcoerulescine (**3**) in low yield with an admixture of starting oxazolidine **2** (Entry 2). As mentioned above, Carreira and co-workers reported the successful reaction of oxindole cyclopropane with 1,3,5-trimethyl-1,3,5-triazinane catalyzed by MgI_2 in THF at 125 °C.[4b] Nevertheless, we found that under the same conditions spiroanthraceneoxazolidine **2a** did not lead to the formation of product **3a**, and the crude mixture was contaminated with oxazolidine **2** (Entry 3). At this stage, it was clear that the reaction of spiro-oxazolidine **2** requires higher temperatures than the reactions of imines and 1,3,5-triazinanes. For this reason, we chose higher boiling 1,4-dioxane and after variation of the reaction temperature and equivalents of MgI_2 (Entries 4, 7) we found optimal conditions for this process: heating the reagents in 1,4-dioxane with MgI_2 (0.5 equiv.) in a microwave reactor at 190 °C for 1 h (Entry 10). At the same time, attempts to use other solvents or Lewis acids did not improve the yield (Entries 5, 6, 8, 9).

Table 2. Synthesis of spiro[pyrrolidine-3,3′-indolin]-2-ones **3a–e**.



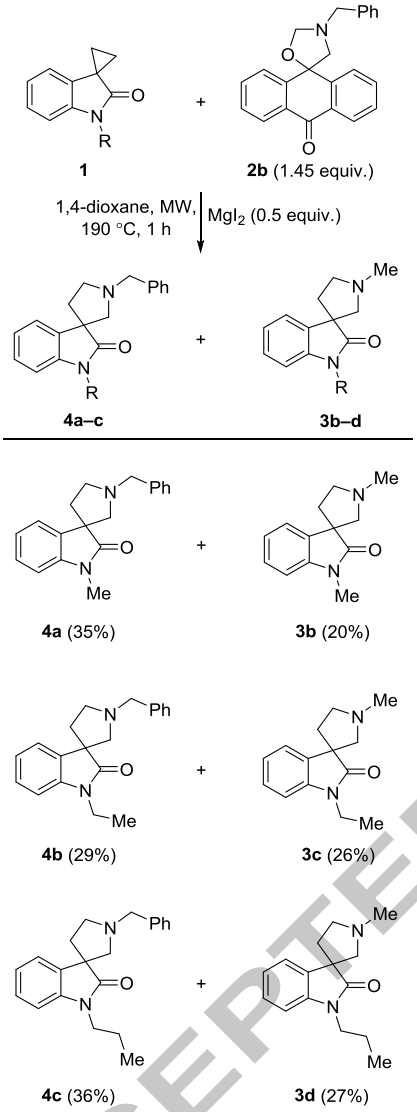


Further efforts were directed toward an extension of the starting substrates. For this purpose, we synthesized a number of cyclopropanes **1** from commercially available isatin. The first stage was alkylation of isatin with an alkyl halide in the presence of K_2CO_3 in DMF, the second, Wolff–Kishner reduction of *N*-substituted isatin at reflux in hydrazine-hydrate (65% water solution). The third stage was the ethylenation of oxindoles by treatment with 1,2-dibromoethane and NaH in DMF (see ESI for details). With the optimized conditions for ring expansion in hand, we synthesized a number of oxindole pyrrolidines **3b**–**f** *via* the reaction of *N*-substituted spiro[cyclopropane-oxindoles] **1** with spiro[anthracene-oxazolidine] **2a** in 42–65% yield (Table 2). Remarkably, the desired spiro[pyrrolidine-3,3′-oxindoles] **3** could be easily purified from the side products by conversion into water soluble hydrochlorides. Subsequent extraction of the non-basic admixtures using PhMe and basification with $NaHCO_3$ resulted in pure pyrrolidines **3**. Thus, the proposed approach appears to be an attractive method due to its simple implementation.

Interestingly, the reaction of *N*-benzylspiroanthraceneoxazolidine **2b** led to an unexpected result. Thus, heating **2b** with 1-methylspiro[cyclopropane-indolinone] (**1**, R = Me) using the previously developed conditions resulted in the formation of a mixture of *N*-benzyl- and *N*-methyl[pyrrolidine-oxindoles] **4a** and **3b** in a 1.7 : 1 ratio according to the NMR data. Subsequent chromatographic purification allowed the isolation of *N*-benzylpyrrolidine **4a** and *N*-methylpyrrolidine **3b** in 35% and 20% yields, respectively.

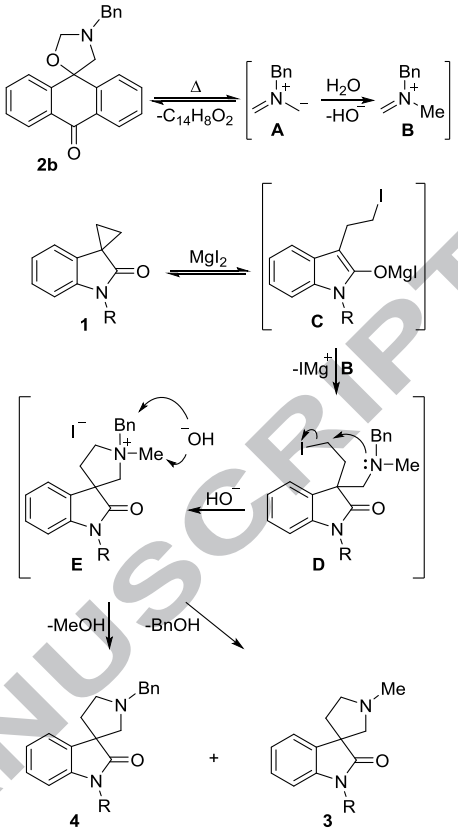
The same result was obtained in the reactions of *N*-ethyl and *N*-propyl substituted spiro[cyclopropane-3,3′-oxindoles] **1** (Table 3).

Table 3. Reaction of *N*-benzylspiroanthraceneoxazolidine **2b** with spiro[cyclopropane-3,3′-indolinones].[a]

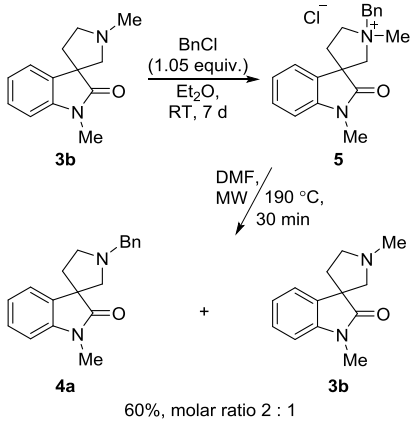


[a] Isolated yields of chromatographically purified products.

The reaction of spiroanthraceneoxazolidines **2** with spiro[cyclopropane-3,3′-indolinones] **1** differs significantly from the known reactions of cyclopropanes with imines and triazinanes.[5] Presumably, oxazolidine **2b** initially underwent cycloreversion to form nonstabilised azomethine ylide **A**. Then ylide **A** was protonated by trace water in the reaction mixture and reacted with enolate **C**. Subsequent intramolecular cyclization of intermediate **D** leads to quaternary ammonium base **E** (Scheme 3). The latter possesses a benzyl moiety and, presumably, competition between dealkylation of the Me and Bn groups takes place. As the result, the mixture of pyrrolidines **3** and **4** forms when the starting compound is *N*-benzylspiroanthraceneoxazolidine **2b**. *N*-Methylspiro[anthracene-9,5′-oxazolidine] **2a** reacts through the same pathway, however the process results in the single product **3**.



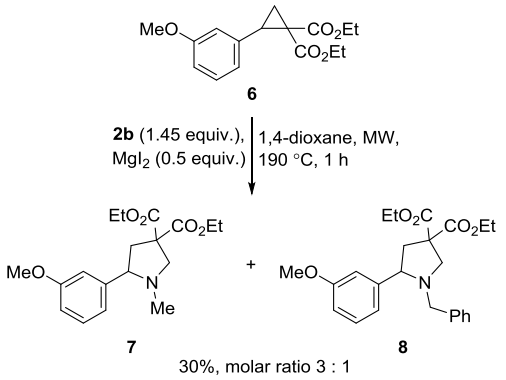
Scheme 3. Proposed mechanism.



Scheme 4. Dealkylation of an *N*-benzyl-*N*-methylammonium quaternary salt.

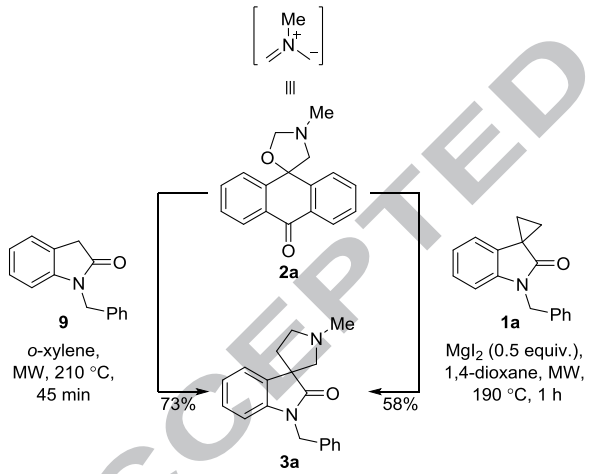
Such a hypothesis is consistent with the recently discovered dealkylation of quaternary ammonium salts due to the fact that dealkylation of *N*-benzyl-*N*-methylammonium salts was not selective.[9] To examine this assumption we obtained quaternary salt **5** from methylpyrrolidine **3b** and benzylchloride (Scheme 4). Heating this salt in DMF at 190 °C for 30 min resulted in the formation of a mixture of **4a** and **3b** in a 2 : 1 ratio (according to the NMR data). This finding is in agreement with the reaction of 1-methylspiro[cyclopropane-indolinone] (**1**, R = Me) and spiro-oxazolidine **2b**.

We also carried out the same reaction with D-A cyclopropane **6** and obtained a similar result (Scheme 5). However, *N*-methylpyrrolidine **7** predominated over *N*-benzyl compound **8** (molar ratio **7** : **8** = 3 : 1 according to the NMR data).



Scheme 5. Reaction of D-A cyclopropane **6** with spiro-oxazolidine **2b**.

It is interesting to note that we recently reported the synthesis of oxindole scaffold **3** from spiroanthraceneoxazolidines **2** by another method.[8b] The reaction of spiro-oxazolidine **2a** (2.3 equiv.) with 1-benzylindolinone **9** occurred as a domino-process: Mannich reaction – elimination of dimethylamine – [3+2]-cycloaddition, and led to the formation of *N*-benzylcoerulescine **3a** in 73% yield (Scheme 6). The reaction of *N*-benzylspiro[cyclopropane-3,3′-indolin]-2-one **1a** described herein resulted in the same product **3a** in 58% yield. In the first case a nonstabilized azomethine ylide derived from oxazolidine **2a** additionally acted as a synthetic equivalent of formaldehyde, in the second, as the synthetic equivalent of *N*-methylmethanimine.



Scheme 6. Synthetic potential of spiroanthraceneoxazolidine system.

In summary, a new method is reported for the synthesis of the spiro[pyrrolidine-3,3′-oxindole] system using spiroanthraceneoxazolidines **2** as an unusual synthetic equivalent of an imine. These spiro-oxazolidines **2**, despite their simple structure, possess wide synthetic capabilities for the construction of various azaheterocycles. Their further application for the synthesis of natural and potentially bioactive compounds is underway in our laboratory and will be reported in due course.

Acknowledgments

This work was financially supported by the Russian Science Foundation (Grant 17-73-20070).

References and notes

1. (a) Plunkett AO. *Nat Prod Rep*. 1994;11:581;
(b) Döndas HA, de Gracia Retamosa M, Sansano JM. *Synthesis*. 2017;49:2819;
(c) Obst U, Betschmann P, Lemer C, Seiler P, Diederich F, Gramlich V, Weber L, Banner DW, Schönholzer P. *Helv Chim Acta*. 2000;83:855;
(d) Pandey G, Dey D, Tiwari SK. *Tetrahedron Lett.* 2017;58:699;
(e) Kawasaki M, Shinada T, Hamada M, Ohfune Y. *Org Lett.* 2005;7:4165;
(f) Hanessian S, Bayrakdarian M, Luo X. *J Am Chem Soc.* 2002;124:4716;
(g) Scott JD, Williams RM. *Chem Rev*. 2002;102:1669;
(h) Dubuffet T, Muller O, Simonet SS, Descombes J-J, Laubie M, Verbeuren TJ, Lavielle G. *Bioorg Med Chem Lett.* 1996;6:349;
(i) Ivanov KL, Villemson EV, Budynina EM, Ivanova OA, Trushkov IV, Melnikov MY. *Chem Eur J*. 2015;21:4975.
2. (a) Bindra JS. In The Alkaloids. In: Manske RHF, ed, Vol. 14. New York: Academic Press; 1973:84;
(b) Marti C, Carreira EM. *Eur J Org Chem.* 2003;2209;
(c) Akaev AA, Villemson EV, Vorobyeva NS, Majouga AG, Budynina EM, Melnikov MY. *J Org Chem.* 2017;82:5689;
(d) Sebahar PR, Williams RM. *J Am Chem Soc*. 2000;122:5666;
(e) Santos MMM. *Tetrahedron*. 2014;70:9735.
3. (a) Jossang A, Jossang P, Hadi HA, Sévenet T, Bodo B. *J Org Chem.* 1991;56:6527;
(b) Pellegrini C, Strässler C, Weber M, Borschberg H-J. *Tetrahedron: Asymmetry*. 1994;5:1979;
(c) Hsieh J-C, Cheng A-Y, Fu J-H, Kang T-W. *Org Biomol Chem.* 2012;10:6404;
(d) Le Goff R, Lawson AM, Daïch A, Comesse S. *Org Biomol Chem.* 2013;11:1818;
(e) Palmisano G, Annunziata R, Papeo G, Sisti M. *Tetrahedron: Asymmetry*. 1996;7:1.
4. (a) Alper PB, Meyers C, Lerchner A, Siegel DR, Carreira EM. *Angew Chem Int Ed.* 1999;38:3186;
(b) Fischer C, Meyers C, Carreira EM. *Helv Chim Acta.* 2000;83:1175;
(c) Helan V, Mills A, Drewry D, Grant D. *J Org Chem.* 2010;75:6693;
(d) Seath CP, Fyfe JWB, Molloy JJ, Watson AJB. *Synthesis*. 2017;49:891.
5. (a) Parsons AT, Smith AG, Neel AJ, Johnson JS. *J Am Chem Soc.* 2010;132:9688;
(b) Garve LKB, Kreft A, Jones PG, Werz DB. *J Org Chem.* 2017;82:9235;
(c) Kang Y-B, Tang Y, Sun X-L. *Org Biomol Chem*. 2006;4:299;
(d) Chu Z-Y, Li N, Liang D, Li Z-H, Zheng Y-S, Liu J-K. *Tetrahedron Lett.* 2018;59:715.
6. (a) Schneider TF, Kaschel J, Werz DB. *Angew Chem Int Ed.* 2014;53:5504;
(b) Tomilov YV, Menchikov LG, Novikov RA, Ivanova OA, Trushkov IV. *Russ Chem Rev*. 2018;87:201;
(c) Melnikov MY, Budynina EM, Ivanova OA, Trushkov IV. *Mendeleev Commun.* 2011;21:293;
(d) Nanteuil F, Simone F, Frei R, Benfatti F, Serrano E, Waser J. *Chem Commun.* 2014;50:10912;
(e) Grover HK, Emmett MR, Kerr MA. *Org Biomol Chem.* 2015;13:655.
7. Buev EM, Moshkin VS, Sosnovskikh VY. *Tetrahedron Lett.* 2016;57:3731.
8. (a) Buev EM, Moshkin VS, Sosnovskikh VY. *Org Lett.* 2016;18:1764;
(b) Buev EM, Moshkin VS, Sosnovskikh VY. *J Org Chem*. 2017;82:12827.
9. Buev EM, Smorodina AA, Stepanov MA, Moshkin VS, Sosnovskikh VY. *Tetrahedron Lett*. 2018;59:1638.

Supplementary data

Supplementary data associated with this article can be found in the online version.

Spiroanthraceneoxazolidines for the synthesis of natural spiro[pyrrolidine-3,3'-oxindole] core.
A new plausible mechanism of the reaction spiroanthraceneoxazolidines with cyclopropanes.
Spiroanthraceneoxazolidines as an unusual synthetic equivalents of imines and triazinanes.