Mendeleev Communications

Mendeleev Commun., 2025, **35**, 18–21

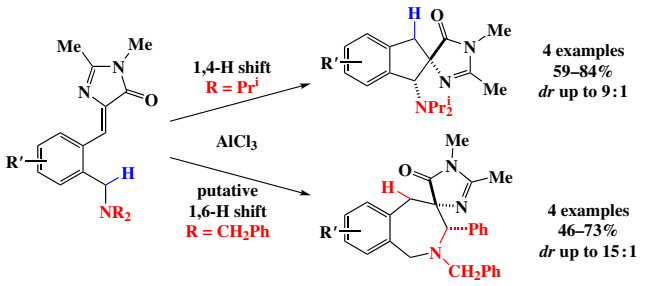
Study on 1,4-hydride shift triggered spirocyclization of arylidene imidazolones: substituent control on formation of indane or tetrahydrobenzazepine systems

Amir M. Al Mufti,[a,b] Viktoria A. Ikonnikova,[a] Alexander Yu. Smirnov,[a,c] Vladislav A. Lushpa,[a] Pavel N. Solyev,[d] Mohamad Nurul Azmi,[e] Mikhail S. Baranov[a,c] and Andrey A. Mikhaylov*[a,c]

[a] *M. M. Shemyakin–Yu. A. Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, 117997 Moscow, Russian Federation. E-mail: mikhaylov_andrey@yahoo.com*
[b] *D. I. Mendeleev University of Chemical Technology of Russia, 125047 Moscow, Russian Federation*
[c] *N. I. Pirogov Russian National Research Medical University, 117997 Moscow, Russian Federation*
[d] *V. A. Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, 119991 Moscow, Russian Federation*
[e] *Natural Products and Synthesis Organic Research Laboratory (NPSO), School of Chemical Sciences, Universiti Sains Malaysia, 11800 Minden, Penang, Malaysia*

DOI: 10.71267/mencom.7550

A rare process of 1,4-hydride or formal 1,6-hydride shift occurs in the (*o*-dialkylaminomethyl)arylidene imidazolones under the action of aluminum chloride. Only sterically hindered amino derivatives are able to enter the spirocyclization reaction, and the substituent would control this direction. Either five-membered indane in case of diisopropylamino derivatives, or seven-membered tetrahydrobenzazepines in case of dibenzylamino derivatives are formed in 46–84% yield.

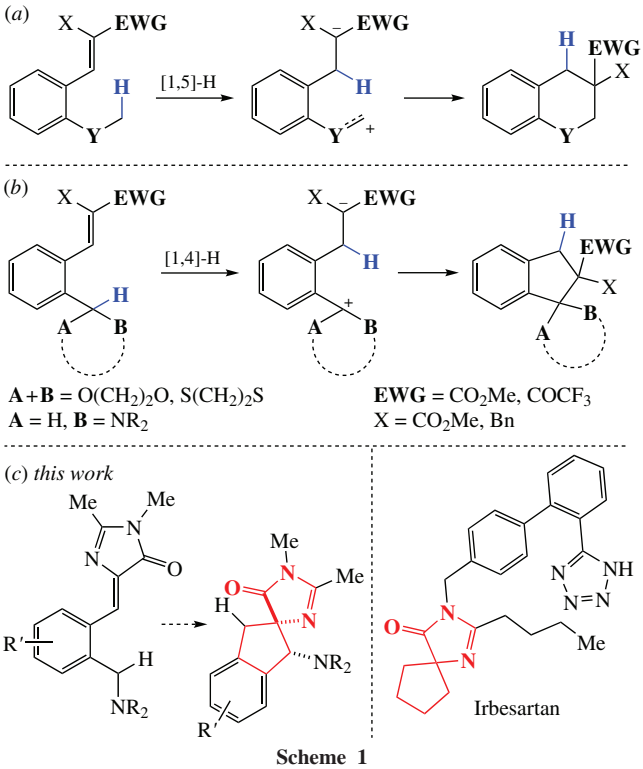


Keywords: spiro compounds, hydride-shift triggered cyclization, indane, benzazepine, imidazolones, Lewis acid catalysis.

Trends in atom and step economy are defining the shape of modern organic chemistry. C–H activation methods,[1,2] solving selectivity issues[3] and minimization of redox steps[4–6] are in the streamline of the current stage of development. In this view, intramolecular redox-neutral transformations and, in particular, those which enable inert C–H bond activation, witness renaissance.[7–9] One of such progressing direction is associated with 1,5-hydride shift triggered cyclization reaction,[10–12] for which new catalysts, including asymmetric,[13–19] tandem processes,[20–27] extended and generalized substrate scopes have been developed.[28–33] The classic variant of the reaction could be described as 1,5-shift of unactivated hydrogen from an *ortho*-substituent in arylidene group of a Knoevenagel adduct, followed by ring closure into 6-membered cycle, *i.e.* '*tert*-amino effect reaction' [Scheme 1(*a*)].

An obvious limitation of the above method is the predetermined six-membered size of the ring. In order to overcome it, several extensions have been developed recently. Governed by the elaboration of the efficient catalysts, it was shown that 1,4-, 1,6-, 1,7- or even higher hydride shifts, although are less-profound, but still could proceed.[9,31,32,34] Among them, 1,4-shift, which provides access to five-membered cycles, is the least developed, and, to the best of our knowledge, there are only four precedents in literature [Scheme 1(*b*)],[23,35–37] and one report[38] in which such process is claimed but, in fact, the data is misinterpreted (for details, see Online Supplementary Materials). In this view, extension of the substrate scope for this methodology is desired.

In this work we envisioned application of 1,4-hydride shift to the creation of spiro heterocyclic structures. The latter are highly valuable for drug development, since they combine rigidity with increased degree of sp^3-hybrid carbon atoms and



Scheme 1

3-dimentionality. Inspired by the structure of antihypertensive drug Irbesartan,[39,40] we aimed to develop efficient method for synthesis of 1,3-diazaspiro[4.4]non-1-en-4-ones by means of 1,4-hydride shift triggered cyclization [Scheme 1(*c*)].

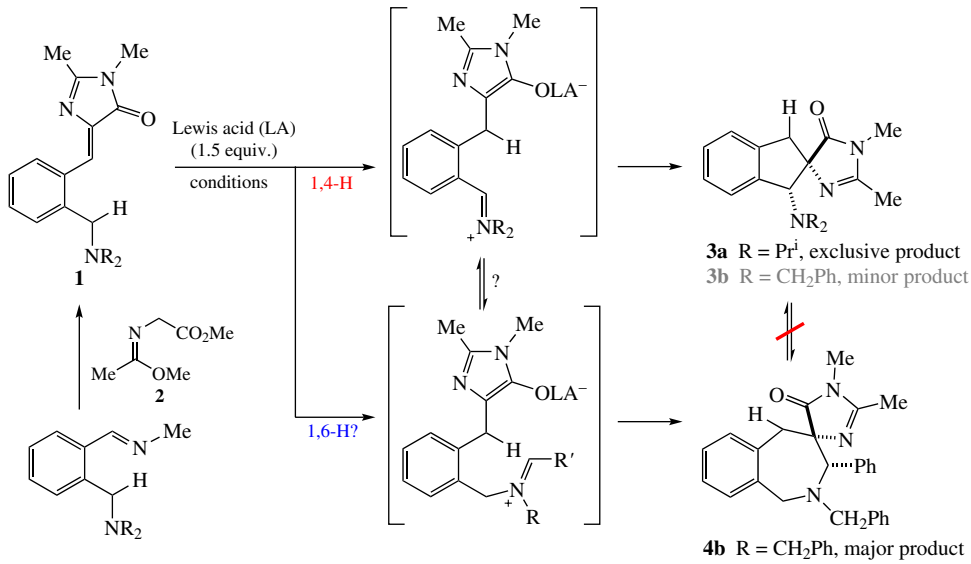
Arylidene imidazolones **1**, starting materials in the current investigation, could be accessed by a number of methods.[41] The one chosen herein is the most straightforward and general, that is cycloaddition of imines with methyl (*Z*)-2-[(1-methoxyethylidene)amino]acetate **2**.[42–45] By these means using previously established route to 2-(dialkylaminomethyl)benzaldehydes,[36] we have synthesized series of starting materials **1** containing various substituents in aromatic ring and at nitrogen atom (for details, see Online Supplementary Materials).

Study of the spirocyclization (Scheme 2, Table 1) of derivatives **1** started with screening of the Lewis acid promotor on the substrates **1a** (R = H, R′ = Pr^i) and **1b** (R = H, R′ = CH_2Ph). As in our previous studies on 1,5-hydride shift, $TiCl_4$ and $AlCl_3$ were found to be catalysts of choice ($SnCl_4$ had less profound activity), providing relatively fast consumption of starting material and robust transformation. However, to our surprise, depending on the starting material, different products were obtained. A product of 1,4-hydride shift, 2-aminoindane **3a**, was formed in case of diisopropylamino derivative **1a** whereas tetrahydrobenzazepine product **4b** was obtained in case of dibenzylamino derivative **1b**. Along with major product **4b**, small quantities of the five-membered by-product **3b** were detected in the reaction with $AlCl_3$. In order to elucidate, whether 5-membered product **3b** is a primary kinetic product, which upon time rearranges into its isomer **4b**, we performed additional experiment. When isolated compound **3b** was heated with the catalyst under the reaction conditions, almost no conversion was observed. This indicates that compounds **3b** and **4b** are formed independently. Moreover, upon processing diisopropylamino derivatives **1a**, **3a** no seven-membered cyclic products similar to **4b** were detected even during prolonged reaction times.

Thus, we decided to optimize both reactions – formation of five-membered cycle **3** for diisopropylamino derivatives, and formation of 7-membered cycle **4** for dibenzylamino derivatives. For both substrate series identical conditions were found to be effective: heating in a sealed tube with $AlCl_3$ in dichloroethane at 100 °C (oil bath temperature) provided 83% yield of indane derivative **3a** (*dr* 9 : 1) and 73% yield of tetrahydroazepine derivative **4b** (*dr* 9 : 1).

Products **3a** and **4b** were formed in good stereoselectivity. Their structure determination was performed based on standard set of NMR and HRMS analysis. Due to the presence of quaternary spiro center and putative stereodynamic process (which we assume to be 7-membered cycle's inversion), NOE-analysis was uninformative. However, based on the mechanism, for both products formation of kinetic *trans*-isomers with minimized steric repulsion in the transition state could be outlined. Indeed, the kinetic nature of major stereoisomer for compound **4b** is experimentally proved (for details, see Online Supplementary Materials), as it epimerizes upon staying in the solution giving rise to a 3 : 1 mixture. In case of indanes **3**, kinetic isomer should be also thermodynamically preferred due to rigidity of 5-membered cycle, providing eclipsed conformation.

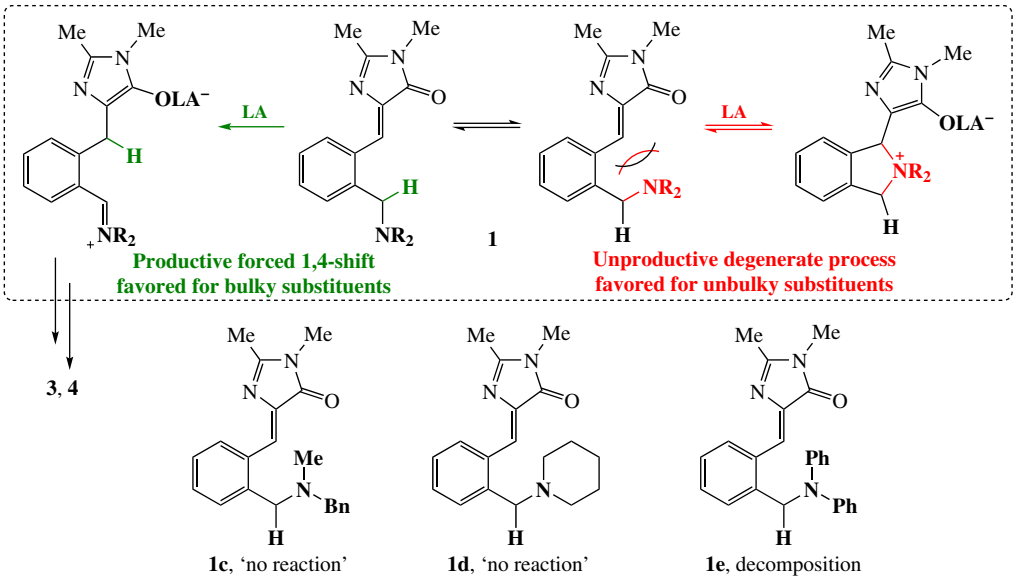
Next, we studied the effect of the substitution at nitrogen atom. In the previous work of Mori and Akiyama,[36] it was brilliantly shown, that bulky substituents at nitrogen atom facilitated hydride shift due to steric repulsion of two *ortho*-substituents in the benzene ring. It provoked conformational switch of the aminomethyl substituent to the form, which was responsible for that process (Scheme 3). With smaller substituents, the hydride shift did not occur due to competing



Scheme 2

Table 1 Spirocyclization of arylidene imidazolones **1a**,**b** under varied reaction conditions.

Entry	**1** (R)	Conditions	**1**, conversion	**3**, yield	**4**, yield
1	**1a** (Pr^i)	$TiCl_4$, 100 °C, 2 h	100%	**3a**, 65% (*dr* 9 : 1)	–
2	**1a** (Pr^i)	$AlCl_3$, 100 °C, 2 h	100%	**3a**, 83% (*dr* 9 : 1)	–
3	**1b** (Bn)	$TiCl_4$, 100 °C, 3 h	100%	**3b**, traces	**4b**, 67% (*dr* 6 : 1)
4	**1b** (Bn)	$TiCl_4$, 100 °C, 1 h	60%	**3b**, traces	**4b**, 40% (*dr* 7 : 1)
5	**1b** (Bn)	$TiCl_4$, 100 °C, 2 h	90%	**3b**, traces	**4b**, 64% (*dr* 6 : 1)
6	**1b** (Bn)	$AlCl_3$, 100 °C, 3 h	92%	**3b**, 10% (*dr* 4 : 1)	**4b**, 73% (*dr* 9 : 1)
7	**1b** (Bn)	$AlCl_3$, 100 °C, 1 h	80%	**3b**, 12%, (*dr* 4 : 1)	**4b**, 46% (*dr* 15 : 1)

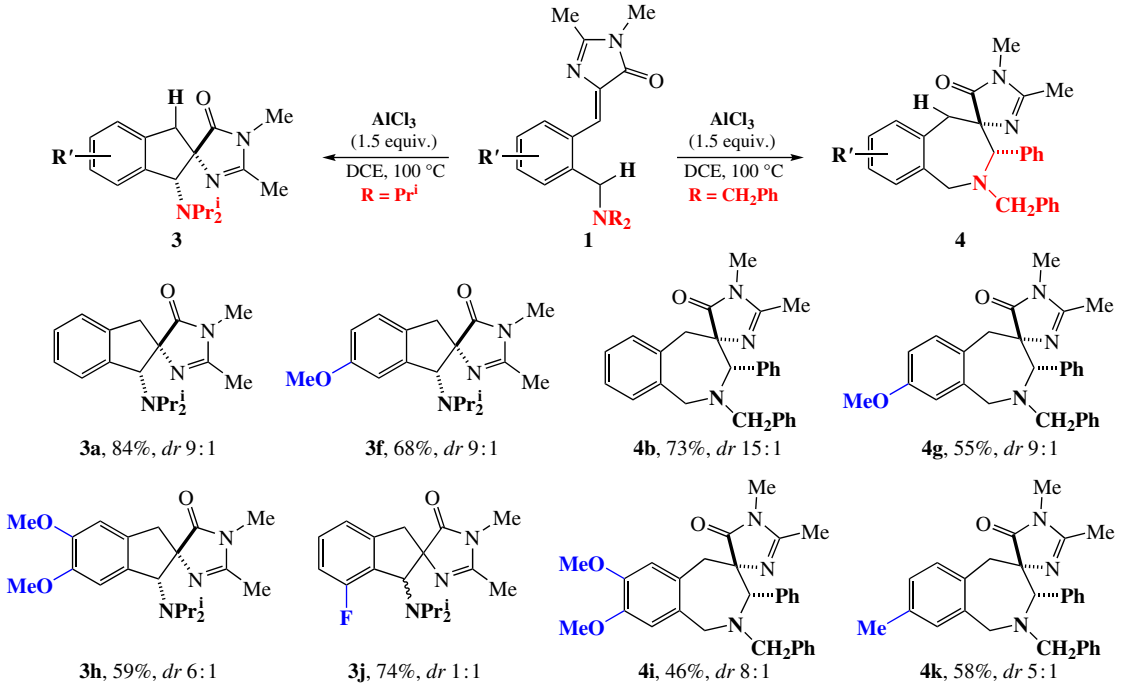


Scheme 3

nitrogen lone pair nucleophilic attack. This consideration could be fully applied to this work, namely, neither methylbenzylamino derivative **1c**, nor piperidine derivative **1d** did undergo transformation and only starting materials were recovered (>85%) after the final work up. In case of diphenylamino derivative **1e** the degradation was observed and no hydride shift product could be isolated.

Next, we examined effect of the substitution in the aromatic ring on the reaction outcome (Scheme 4). Derivatives with 4-methoxy (**f**, **g**), 4,5-dimethoxy (**h**, **i**), 3-fluoro (**j**) and 4-methyl (**k**) substitution pattern were studied. As expected, in all cases indanes **3** were obtained from diisopropylamino derivatives **1a**,**f**,**h**,**j**, while tetrahydroazepines **4** were formed from dibenzylamino derivatives **1b**,**g**,**i**,**k**. For mono-methoxy substituted derivatives **1f**,**g** there was almost no effect on the reaction course except for slightly decreased yields of products **3f** (68%, 9 : 1 *dr*) and **4g** (55%, 9 : 1 *dr*). Dimethoxy derivatives **1h**,**i** readily reacted but a number of by-products was formed, which we associate with highly donating nature of these substituents. However, we were able to isolate in both series products **3h** (59% yield, 6 : 1 *dr*) and **4i** (46% yield, 8 : 1 *dr*). Product **3j** with fluorine in the aromatic ring was formed in a good yield of 74%, but surprisingly no stereoselectivity was observed. At the moment, we cannot rationalize this observation, although it could be attributed to proximal lone pair of fluorine, which may expand lifetime of iminium cation and lead to slow cyclization and thus lack of stereoselectivity. Finally, tetrahydrobenzazepine **4k** with methyl substituent was also obtained in 58% yield.

In summary, a study on 1,4-hydride shift in arylidene imidazolone series was performed. As in our previous reports on the related processes, classic Lewis acids such as $AlCl_3$ were found to be reagents of choice. Only sterically hindered amino derivatives are able to enter such spirocyclization reaction, and critical substituent effect is found. For diisopropylamino derivatives only 1,4-hydride shift/cyclization takes places, providing indane derivatives, while for dibenzylamino derivatives we propose, that more feasible 1,6-hydride shift is likely to occur, giving rise to tetrahydrobenzazepines.



Scheme 4

The authors gratefully acknowledge support from the Russian Science Foundation (grant no. 20-73-10195).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7550.

References

1 T. Rogge, N. Kaplaneris, N. Chatani, J. Kim, S. Chang, B. Punji, L. L. Schafer, D. G. Musaev, J. Wencel-Delord, C. A. Roberts, R. Sarpong, Z. E. Wilson, M. A. Brimble, M. J. Johansson and L. Ackermann, *Nat. Rev. Methods Primers*, 2021, **1**, 43; https://doi.org/10.1038/s43586-021-00041-2.

2 T. Dalton, T. Faber and F. Glorius, *ACS Cent. Sci.*, 2021, **7**, 245; https://doi.org/10.1021/acscentsci.0c01413.

3 Z. Huang and G. Dong, *Acc. Chem. Res.*, 2017, **50**, 465; https://doi.org/10.1021/acs.accounts.6b00476.

4 N. Z. Burns, P. S. Baran and R. W. Hoffmann, *Angew. Chem., Int. Ed.*, 2009, **48**, 2854; https://doi.org/10.1002/anie.200806086.

5 J. Feng, Z. A. Kasun and M. J. Krische, *J. Am. Chem. Soc.*, 2016, **138**, 5467; https://doi.org/10.1021/jacs.6b02019.

6 L. B. Smith, R. J. Armstrong, D. Matheau-Raven and T. J. Donohoe, *J. Am. Chem. Soc.*, 2020, **142**, 2514; https://doi.org/10.1021/jacs.9b12296.

7 B. Peng and N. Maulide, *Chem. – Eur. J.*, 2013, **19**, 13274; https://doi.org/10.1002/chem.201301522.

8 M. C. Haibach and D. Seidel, *Angew. Chem., Int. Ed.*, 2014, **53**, 5010; https://doi.org/10.1002/anie.201306489.

9 K. Mori, *Bull. Chem. Soc. Jpn.*, 2022, **95**, 296; https://doi.org/10.1246/bcsj.20210420.

10 S. J. Kwon and D. Y. Kim, *Chem. Rec.*, 2016, 1191; https://doi.org/10.1002/tcr.201600003.

11 A. Yu. Platonova, T. V. Glukhareva, O. A. Zimovets and Yu. Yu. Morzherin, *Chem. Heterocycl. Compd.*, 2013, **49**, 357; https://doi.org/10.1007/s10593-013-1257-6.

12 H. Liu, Y. Quan, L. Xie, X. Li and X. Xie, *Front. Chem.*, 2022, **10**, Article 840934; https://doi.org/10.3389/fchem.2022.840934.

13 M. Wang, *ChemCatChem*, 2013, **5**, 1291; https://doi.org/10.1002/cctc.201200692.

14 K. Mori, K. Ehara, K. Kurihara and T. Akiyama, *J. Am. Chem. Soc.*, 2011, **133**, 6166; https://doi.org/10.1021/ja2014955.

15 S. Murarka, I. Deb, C. Zhang and D. Seidel, *J. Am. Chem. Soc*., 2009, **131**, 13226; https://doi.org/10.1021/ja905213f.

16 J. Yu, N. Li, D.-F. Chen and S.-W. Luo, *Tetrahedron Lett.*, 2014, **55**, 2859; https://doi.org/10.1016/j.tetlet.2014.03.089.

17 W. Cao, X. Liu, J. Guo, L. Lin and X. Feng, *Chem. – Eur. J.*, 2015, **21**, 1632; https://doi.org/10.1002/chem.201404327.

18 N. S. Baleeva, A. Yu. Smirnov, E. R. Zaitseva, D. S. Ivanov, A. I. Sokolov, A. A. Mikhaylov, I. N. Myasnyanko and M. S. Baranov, *New J. Chem.*, 2023, **47**, 12536; https://doi.org/10.1039/d3nj01837g.

19 Z. Wang, H. Liu, T. Jiang and H. Huang, *Org. Chem. Front.*, 2024, **11**, 864; https://doi.org/10.1039/D3QO01637D.

20 K. Mori, R. Isogai, Y. Kamei, M. Yamanaka and T. Akiyama, *J. Am. Chem. Soc.*, 2018, **140**, 6203; https://doi.org/10.1021/jacs.8b02761.

21 E. R. Zaitseva, D. S. Ivanov, A. Yu. Smirnov, A. A. Mikhaylov, N. S. Baleeva and M. S. Baranov, *Molecules*, 2022, **27**, 5270; https://doi.org/10.3390/molecules27165270.

22 X. Yang, L. Wang, F. Hu, L. Xu, S. Li and S. S. Li, *Org. Lett.*, 2021, **23**, 358; https://doi.org/10.1021/acs.orglett.0c03863.

23 K. Mori, K. Kurihara, S. Yabe, M. Yamanaka and T. Akiyama *J. Am. Chem. Soc.*, 2014, **136**, 3744; https://doi.org/10.1021/ja412706d.

24 S. Liu, W. Zhang, J. Qu and B. Wang, *Org. Chem. Front.*, 2018, **5**, 3008; https://doi.org/10.1039/c8qo00875b.

25 K. Amano, T. Kawasaki-Takasuka and K. Mori, *Org. Lett.*, 2024, **26**, 1824; https://doi.org/10.1021/acs.orglett.3c04355.

26 R. Koyama, M. Anada, S. Sueki, K. Makino, T. Kojima, T. Kawasaki-Takasuka and K. Mori, *Chem. Commun.*, 2024, **60**, 3822; https://doi.org/10.1039/D4CC00797B.

27 D. D. Borisov, R. A. Novikov and Y. V. Tomilov, *Org. Lett.*, 2024, **26**, 1022; https://doi.org/10.1021/acs.orglett.3c04097.

28 L. Cao, F. Hu, J. Dong, X.-M. Zhang and S.-S. Li, *Org. Chem. Front.*, 2023, **10**, 1796; https://doi.org/10.1039/D3QO00035D.

29 E. R. Zaitseva, A. Y. Smirnov, V. I. Timashev, V. I. Malyshev, E. A. Zhigileva, A. A. Mikhaylov, M. G. Medvedev, N. S. Baleeva and M. S. Baranov, *Eur. J. Org. Chem.*, 2022, e202200547; https://doi.org/10.1002/ejoc.202200547.

30 H. Okawa, T. Kawasaki-Takasuka and K. Mori, *Org. Lett.*, 2024, **26**, 1662; https://doi.org/10.1021/acs.orglett.4c00140.

31 P. Bottino, P. Dunkel, M. Schlich, L. Galavotti, R. Deme, G. Regdon, A. Bényei, K. Pintye–Hódi, G. Ronsisvalle and P. Mátyus, *J. Phys. Org. Chem.*, 2012, **25**, 1033; https://doi.org/10.1002/poc.3007.

32 P. Dunkel, D. Bogdán, R. Deme, Á. Zimber, V. Ballayová, E. Csizmadia, B. Kontra, E. Kalydi, A. Bényei and P. Mátyus, *RSC Adv.*, 2024, **14**, 16784; https://doi.org/10.1039/D3RA08974F.

33 D. Szalóki Vargáné, L. Tóth, B. Buglyó, A. Kiss-Szikszai, A. Mándi, P. Mátyus, S. Antus, Y. Chen, D. Li, L. Tao, H. Zhang and T. Kurtán, *Molecules*, 2020, **25**, 1265; https://doi.org/10.3390/molecules25061265.

34 Á. Polonka-Bálint, C. Saraceno, K. Ludányi, A. Bényei and P. Mátyus, *Synlett*, 2008, **4**, 2846; https://doi.org/10.1055/s-0028-1083537.

35 M. Alajarin, M. Marin-Luna and A. Vidala, *Adv. Synth. Catal.*, 2011, **35**, 557; https://doi.org/10.1002/adsc.201000812.

36 K. Mori, K. Kurihara and T. Akiyama, *Chem. Commun.*, 2014, **50**, 3729; https://doi.org/10.1039/c4cc00894d.

37 J. Nagaki, T. Kawasaki-Takasuka and K. Mori, *Synlett*, 2024, **35**, 2143; https://doi.org/10.1055/a-2287-9391.

38 A. P. Gorulya, A. V. Tverdokhlebov, A. A. Tolmachev, O. V. Shishkin and S. V. Shishkina, *Tetrahedron*, 2011, **67**, 1030; https://doi.org/10.1016/j.tet.2010.11.101.

39 J. C. Gillis and A. Markham, *Drugs*, 1997, **54**, 885; https://doi.org/10.2165/00003495-199754060-00007.

40 H.-H. Parving, H. Lehnert, J. Bröchner-Mortensen, R. Gomis, S. Andersen and P. Arner, *N. Engl. J. Med.*, 2001, **345**, 870; https://doi.org/10.1056/NEJMoa011489.

41 N. S. Baleeva and M. S. Baranov, *Chem. Heterocycl. Compd.*, 2016, **52**, 444; https://doi.org/10.1007/s10593-016-1909-4.

42 J. Baldridge and L. M. Tolbert, *Synthesis*, 2010, 2424; https://doi.org/10.1055/s-0029-1218796.

43 A. I. Sokolov, I. N. Myasnyanko, N. S. Baleeva and M. S. Baranov, *ChemistrySelect*, 2020, **5**, 7000; https://doi.org/10.1002/slct.202001782.

44 J. M. Lerestif, J. Perrocheau, F. Tonnard, J. P. Bazureau and J. Hamelin, *Tetrahedron*, 1995, **51**, 6757; https://doi.org/10.1016/0040-4020(95)00321-X.

45 E. R. Zaitseva, A. Y. Smirnov, I. N. Myasnyanko, K. S. Mineev, A. I. Sokolov, T. N. Volkhina, A. A. Mikhaylov, N. S. Baleeva and M. S. Baranov, *New J. Chem.*, 2021, **45**, 1805; https://doi.org/10.1039/D0NJ05738J.

Received: 24th June 2024; Com. 24/7550