



Cite this: *New J. Chem.*, 2017, 41, 1902

Received 29th October 2016,
Accepted 13th January 2017

DOI: 10.1039/c6nj03403a

rsc.li/njc

First synthesis of heterocyclic allenes – benzazecine derivatives†

Leonid G. Voskressensky,^{a*} Alexander A. Titov,^a Maksad S. Dzhankaziev,^a Tatiana N. Borisova,^a Maxim S. Kobzev,^a Pavel V. Dorovatovskii,^b Victor N. Khurstalev,^{a,c} Alexander V. Aksenov^d and Alexey V. Varlamov^a

Benzazecines with an allene fragment were prepared for the first time and in high yields via tandem reaction of 1-phenylethynyl-1-methyl(benzyl)-1,2,3,4-tetrahydroisoquinolines with activated alkynes in trifluoroethanol.

Azecine fragments have been found in a number of natural products. The well-known alkaloids protopine and allocryptopine¹ (Fig. 1) were isolated from plants of the families Berberidaceae, Papaveraceae, Fumariaceae, and Rutaceae. Both compounds play important roles in protecting plants from biotic stress and also exhibit several biological effects in mammals. These compounds expand capillaries, cause analgesia, and disrupt cell division. They are used to treat gout and skin tumors. Protopine was isolated

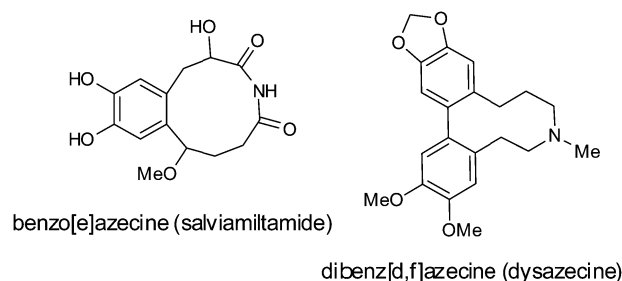
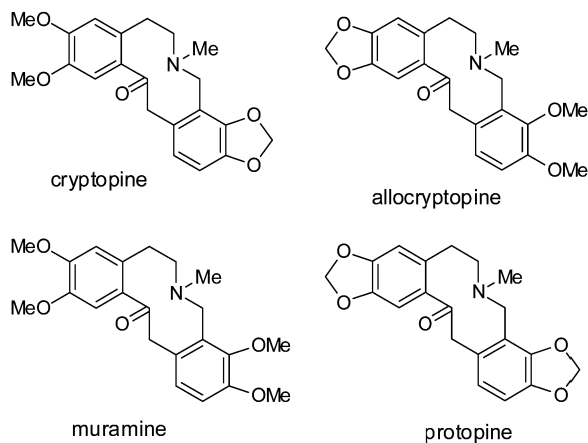


Fig. 1 Natural alkaloids containing an azecine ring.



^a Organic Chemistry Department, Peoples' Friendship University of Russia, 6 Miklukho-Maklaya St., Moscow 117198, Russia. E-mail: lvoskressensky@sci.pfu.edu.ru

^b National Research Center "Kurchatov Institute", 1, Akademika Kurchatova pl., Moscow 123182, Russia

^c Nesmeyanov Institute of Organoelement Compounds of RAS, 28, Vavilova St., GSP-1, Moscow 119991, V-334, Russia

^d North-Caucasus Federal University, 1, Pushkin Street, Stavropol 355009, Russia

† Electronic supplementary information (ESI) available: Experimental procedures, copies of ¹H and ¹³C spectra. CCDC 1507230. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6nj03403a

from celandine. It desensitizes the autonomous nervous system and enhances smooth-muscle tone. Muramine^{1c} is found in several leafy vegetables and is also used for therapeutic purposes (Fig. 1).

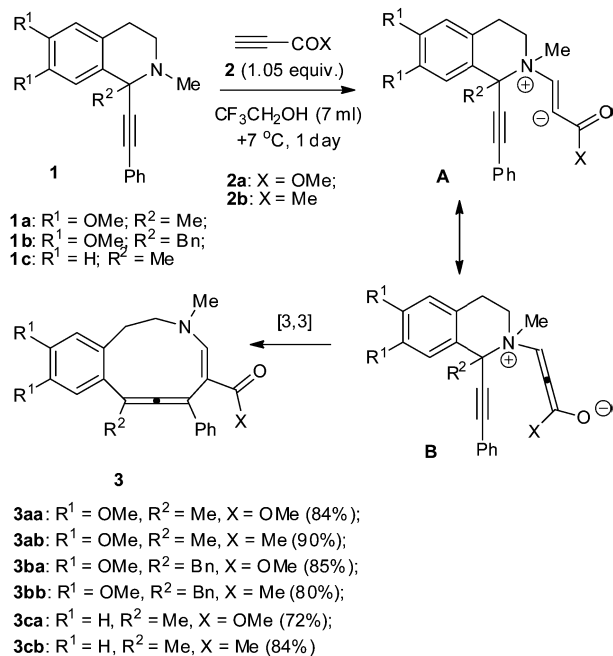
Alkaloids containing an azecine ring, salviamiltamide² and dysazecine,³ were isolated from the plants *Salvia miltiorrhiza* Bunge (Lamiaceae) and *Dysoxylum lenticellare*, respectively. Benzazecines are dopamine 5-HT_{2A} antagonists, could be potential neuroleptics,⁴ and inhibit acetyl- and butyrylcholine esterases.⁵

Only a few synthetic methods for condensed azecines have been published.^{6–8} They all are based on difficult-to-access starting materials and can hardly be considered common. Heterocyclic allenes represent an even less known class of compounds. Stable S-containing cyclic allenes were obtained in moderate yields from a [2,3] sigmatropic rearrangement of 1-ethynylisothiochromenium salts.⁹

Only two examples^{10,11} of the preparation of a cyclic allene with a N atom in the ring have been reported. 10- and 11-membered lactams 3-chloro-4,5-allenylactams¹¹ were prepared by the reactions of 2-phenylethynylpiperidone and 2-phenylethynylazepine with chloroacetylfluoride through [3,3]-sigmatropic rearrangement. These results motivated our interest towards exploring the domino reaction of 1-phenylethynylisoquinolines with activated alkynes.

Our team has worked for many years on domino transformations of tetrahydropyridines with [c]-condensed aromatic fragments with activated alkynes. As a result, preparative





Scheme 1 Synthesis of benzazecines with an allene fragment.

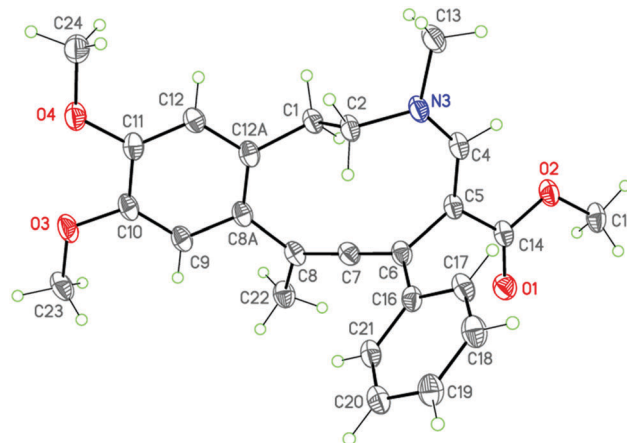
synthetic methods for a series of azocines annelated with pyrrole,¹² chromene,¹³ benzothiophene,¹⁴ thiophene¹⁵ and indole¹⁶ were developed. It was shown that tetrahydroisoquinolines with 1-phenyl substituents reacted with methyl propiolate and acetylacetylene to give the expected benzazocines in good yields.^{17–19} As it turned out, 1,1-disubstituted tetrahydroisoquinolines, 1-methyl- and 1-benzyl-1-phenylethynyl-1,2,3,4-tetrahydroisoquinolines **1a–c** reacted differently with activated terminal alkynes **2a,b** in trifluoroethanol (Scheme 1). The reaction occurred rather quickly in this solvent at +7 °C. The major reaction products benzazecines **3** with allene systems were obtained in high yields.

We suppose that the transformation of **3** began with Michael addition of the tetrahydropyridine N atom to the alkynes **2a,b** to form zwitterion **A**, which converted into intermediate **B**. [3,3] Sigmatropic rearrangement resulted in the formation of the azecine ring.

The structures of **3** were elucidated by ¹H and ¹³C NMR spectroscopy, mass spectrometry, and IR spectroscopy. The IR spectra lacked ethynyl stretching bands and exhibited bands at 1934–1937 cm^{−1} and 1648–1682 cm^{−1}, confirming that the molecules contained an allene system and carbonyls. The ¹H NMR spectra of azecines **3** showed a characteristic singlet for the enamine proton at δ 7.53–7.59 ppm.

The structure of product **3aa** was unambiguously established by an X-ray diffraction study and is shown in Fig. 2 along with the atomic numbering scheme.

Compound **3aa** comprises the benzazecine system containing the C6=C7=C8 allene fragment. The ten-membered azecine ring adopts a chair conformation. As expected, the dihedral angle between the C6=C7=C8(C22)–C8A and C5–C6(C16)=C7=C8 planes is close to 90° [89.01(6)°]. The molecule has the *E*-configuration of substituents at the C4=C5 double bond.

Fig. 2 Molecular structure of **3aa**.

The carboxylate group is almost coplanar with the C4=C5 double bond (rms deviation is 0.027 Å) due to the presence of bond conjugation. The N3 nitrogen atom is in a slightly pyramidal configuration [the sum of the bond angles is 356.9(4)°]. The methoxy substituents lie within the benzene plane (rms deviation is 0.028 Å).

The crystal packing of the molecules includes stacks along the crystallographic *a* axis. The molecules are arranged at van der Waals distances.

Thus, we developed an original synthesis of benzo[*d*]-3-azadeca-4,6,7-triens with an enamine fragment in the α -position relative to the allene system from readily available 1-methyl- and 1-benzyl-1-phenylethynyl substituted tetrahydroisoquinolines and activated terminal alkynes.

Acknowledgements

This work was sponsored by the RF Ministry of Education and Science under the program for improving the competitiveness of RUDN among leading global science-education centers for 2016–2020, and the Russian Foundation for Basic Research (grants 15-33-20187-mol_a_ved, 17-03-00605, 17-53-540001).

Notes and references

- (a) M. Kubala, J. Vacek, I. Popa, M. Janovská, P. Kosina, J. Ulrichová, Z. Trávníček and V. Šimánek, *J. Lumin.*, 2011, **131**, 1340; (b) L. Skarydova, J. Hofman, J. Chlebek, J. Havrankova, K. Kosanova, A. Skarka, A. Hostalkova, T. Plucha, L. Cahlikova and V. Wsol, *J. Steroid Biochem.*, 2014, **143**, 250; (c) Y. Wada, H. Kaga, S. Uchiito, E. Kumazawa, M. Tomiki, Y. Onozaki, N. Kurono, M. Tokuda, T. Ohkuma and K. Orito, *J. Org. Chem.*, 2007, **72**, 7301.
- J. S. Choi, H. S. Kang, H. A. Jung, J. H. Jung and S. S. Kang, *Fitoterapia*, 2001, **72**, 30.
- (a) A. J. Aladesanmi, C. J. Kelley and J. D. Leary, *J. Nat. Prod.*, 1983, **46**, 127; (b) P. Dunkel, G. Túrós, A. Bényei, K. Ludányi and P. Mátyus, *Tetrahedron*, 2010, **66**, 2331.



- 4 (a) M. Decker, K. J. Schleifer, M. Nieger and J. Lehmann, *Eur. J. Med. Chem.*, 2004, **39**, 481; (b) C. Enzensperger, T. Görnemann, H. H. Pertz and J. Lehmann, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3809.
- 5 (a) M. Schulze, F. K. U. Müller, J. M. Mason, H. Görls, J. Lehmann and C. Enzensperger, *Bioorg. Med. Chem.*, 2009, **17**, 6898; (b) M. Schulze, O. Siol, M. Decker and J. Lehmann, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2946.
- 6 (a) T. Witt, F. J. Hock and J. Lehmann, *J. Med. Chem.*, 2000, **43**, 2079; (b) B. Hoefgen, M. Decker, P. Mohr, A. M. Schramm, S. A. F. Rostom, H. El-Subbagh, P. M. Schweikert, D. R. Rudolf, M. U. Kassack and J. Lehmann, *J. Med. Chem.*, 2006, **49**, 760; (c) C. Enzensperger, S. Kilian, M. Ackermann, A. Koch, K. Kelch and J. Lehmann, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1399; (d) L. G. Voskressensky, T. N. Borisova, A. A. Titov, A. V. Listratova, L. N. Kulikova, A. V. Varlamov, V. N. Khrustalev and G. G. Aleksandrov, *Russ. Chem. Bull.*, 2012, **61**, 1231.
- 7 A. M. Jones, M. M. Lorion, T. Lebl, A. M. Z. Slawin, D. Philp and N. J. Westwood, *Tetrahedron*, 2010, **66**, 9667.
- 8 (a) M. H. Weston, K. Nakajima and T. G. Back, *J. Org. Chem.*, 2008, **73**, 4630; (b) Á. González-Gómez, G. Domínguez, U. Amador and J. Pérez-Castells, *Tetrahedron Lett.*, 2008, **49**, 5467; (c) J. B. Bremner and D. F. Perkins, *Tetrahedron*, 2005, **61**, 2659.
- 9 H. Sashida and T. Tsuchiya, *Chem. Pharm. Bull.*, 1986, **34**, 3644.
- 10 H. Sashida and T. Tsuchiya, *Chem. Pharm. Bull.*, 1984, **32**, 4600.
- 11 M. Perscheid, D. Schollmeyer and U. Nubbemeyer, *Eur. J. Org. Chem.*, 2011, 5250.
- 12 A. V. Varlamov, T. N. Borisova, L. G. Voskressensky, T. A. Soklakova, L. N. Kulikova, A. I. Chernyshev and G. G. Alexandrov, *Tetrahedron Lett.*, 2002, **43**, 6767.
- 13 L. G. Voskressensky, L. N. Kulikova, S. V. Gozun, V. N. Khrustalev, T. N. Borisova, A. V. Listratova, M. V. Ovcharov and A. V. Varlamov, *Tetrahedron Lett.*, 2011, **52**, 4189.
- 14 L. G. Voskressensky, S. A. Kovaleva, T. N. Borisova, A. V. Listratova, A. B. Eresko, V. S. Tolkunov, S. V. Tolkunov and A. V. Varlamov, *Tetrahedron*, 2010, **66**, 9421.
- 15 L. G. Voskressensky, A. V. Listratova, T. N. Borisova, S. A. Kovaleva, R. S. Borisov and A. V. Varlamov, *Tetrahedron*, 2008, **64**, 10443.
- 16 A. Carotti, M. de Candia, M. Catto, T. N. Borisova, A. V. Varlamov, E. Méndez-Álvarez, R. Soto-Otero, L. G. Voskressensky and C. Altomare, *Bioorg. Med. Chem.*, 2006, **14**, 7205.
- 17 L. G. Voskressensky, T. N. Borisova, A. V. Listratova, L. N. Kulikova, A. A. Titov and A. V. Varlamov, *Tetrahedron Lett.*, 2006, **47**, 4585.
- 18 L. G. Voskressensky, A. V. Listratova, T. N. Borisova, G. G. Alexandrov and A. V. Varlamov, *Eur. J. Org. Chem.*, 2007, 6106.
- 19 L. G. Voskressensky, A. A. Titov, R. Samavati, T. N. Borisova, E. A. Sorokina and A. V. Varlamov, *Chem. Heterocycl. Compd.*, 2016, **52**, 316.

