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Synthesis of frame pyrazolines based on azabicyclo[2.2.1]heptenes and nitrilimines

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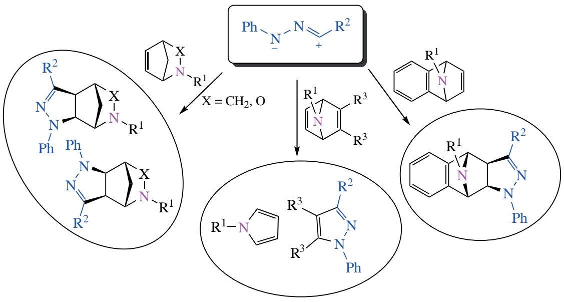
The stereo- and regiochemical features of the reaction of nitrilimines (generated *in situ* from *N*-hydrazonoyl chlorides) with derivatives of 2-aza-, 2-oxa-3-azanorbornenes, 7-aza-benzonorbornadiene and 7-azanorbornadiene have been explored. The cycloaddition products contain pyrazoline moiety fused to bicyclic skeleton; in some cases the products undergo further retro-Diels–Alder fragmentation to form pyrazole derivatives.

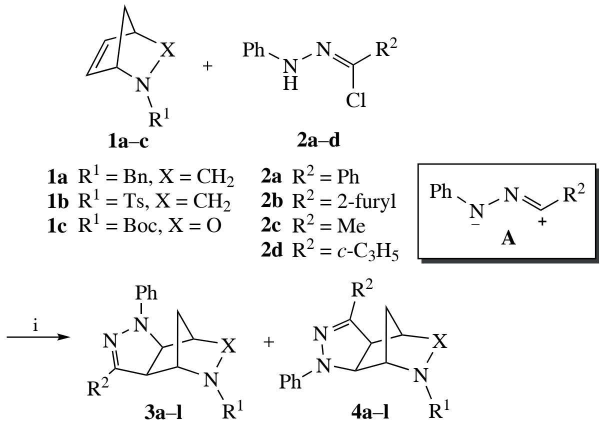


Keywords: azabicyclo[2.2.1]heptenes, azabicyclo[2.2.1]heptadienes, nitrilimines, 1,3-dipolar cycloaddition, *N*-hydrazonoyl chlorides, norbornene, pyrazolines.

Recently, interest in pyrazoline derivatives has sharply increased since they exhibit a wide range of biological activities.[1–7] One of the convenient methods for their synthesis is the 1,3-dipolar cycloaddition of nitrilimines (usually generated *in situ* by dehydrohalogenation of *N*-hydrazonoyl chlorides) to alkenes.[8–12] The reactions of norbornene and norbornadiene derivatives with hydrazonoyl chlorides in the presence of bases make it possible to obtain pyrazolines fused with a bicyclic skeleton.[13–20] In cases of norbornene, products with an *exo*-arrangement of a heterocyclic ring are formed. In the case of norbornadiene, the *exo*-isomer is also the main one; however, when electron-withdrawing substituents are introduced into both nitrilimine[19] and norbornadiene,[20] the yield of the *endo*-isomer increases. It was found that the reactions of some 7-azabenzonorbornadiene derivatives with nitrilimines are accompanied by the retro-Diels–Alder reaction.[21]

In order to obtain new pyrazolines fused with azabicyclic skeleton and to continue our work on the behavior of aza-bicycloalkenes in 1,3-dipolar cycloaddition reactions,[22] we studied herein the regio- and stereochemical features of the reaction of nitrilimines (generated *in situ* from the corresponding hydrazonoyl chlorides) with derivatives of 2-aza-, 2-oxa-3-aza- and 7-azabicyclo[2.2.1]heptenes. We found that 2-azabicyclo[2.2.1]heptenes **1a**,**b** and 2-oxa-3-azabicyclo[2.2.1]heptene **1c** on treatment with hydrazonoyl chlorides **2a–d** in the presence of triethylamine were transformed into mixtures of regioisomers **3a–l** and **4a–l** (Scheme 1). Apparently, the reaction proceeds through the formation of species **A** formed upon the action of the base on reactants **2a–c**. The total yields of products **3** + **4** relate to those purified by column chromatography while their ratios were determined by ^{1}H NMR in the crude materials.

7-Azabenzonorbornadiene **5** with Boc protection reacts with nitrilimines (generated from **2a–d**) to form single isomers **6a–d** with an *exo*-arrangement of the pyrazoline ring (Scheme 2). It should be noted that pyrazolines **6a–d** readily undergo the retro-Diels–Alder reaction: signals of pyrazoles **7a–d** (~10%) are present in the ^{1}H NMR spectra of the reaction mixtures, and their yield would increase with the reaction prolongation (the second possible product, isoindole **8**, was not detected). Also, the formation of noticeable amounts of pyrazoles **7a–d** is observed in samples of individual pyrazolines **6a–d** (isolated by



1a–c

2a–d

1a R^1 = Bn, X = CH_2
1b R^1 = Ts, X = CH_2
1c R^1 = Boc, X = O

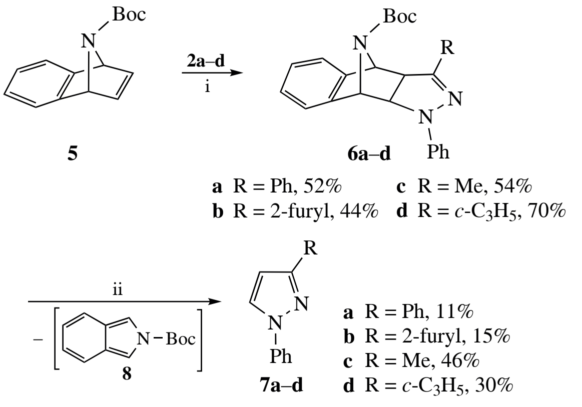
2a R^2 = Ph
2b R^2 = 2-furyl
2c R^2 = Me
2d R^2 = *c*-C_3H_5

A

3a–l **4a–l**

		Yield (%) (**3**/**4** ratio)
3a, **4a**	R^1 = Bn, R^2 = Ph, X = CH_2	94 (58:42)
3b, **4b**	R^1 = Bn, R^2 = 2-furyl, X = CH_2	36 (50:50)
3c, **4c**	R^1 = Bn, R^2 = Me, X = CH_2	70 (53:47)
3d, **4d**	R^1 = Bn, R^2 = *c*-C_3H_5, X = CH_2	40 (50:50)
3e, **4e**	R^1 = Ts, R^2 = Ph, X = CH_2	68 (56:44)
3f, **4f**	R^1 = Ts, R^2 = 2-furyl, X = CH_2	73 (52:48)
3g, **4g**	R^1 = Ts, R^2 = Me, X = CH_2	61 (57:43)
3h, **4h**	R^1 = Ts, R^2 = *c*-C_3H_5, X = CH_2	93 (55:45)
3i, **4i**	R^1 = Boc, R^2 = Ph, X = O	78 (50:50)
3j, **4j**	R^1 = Boc, R^2 = 2-furyl, X = O	54 (50:50)
3k, **4k**	R^1 = Boc, R^2 = Me, X = O	74 (50:50)
3l, **4l**	R^1 = Boc, R^2 = *c*-C_3H_5, X = O	50 (50:50)

Scheme 1 *Reagents and conditions*: i, Et_3N, CH_2Cl_2, room temperature, ~18 h.



Scheme 2 *Reagents and conditions*: i, Et_3N, CH_2Cl_2, room temperature, ~18 h; ii, room temperature, storage.

chromatography) when they were kept for a week while after two months the pyrazolines completely dissociate.

The same phenomenon is better expressed in the case of products of 1,3-dipolar addition of nitrilimines to 7-azanorbornadienes **9a**,**b**: primary adducts **10a–d** and **11a–d** cannot be isolated (Scheme 3). The main products are pyrazoles **12** and pyrroles **13** whereas the signals for compounds **7** and **14** were recorded in the ^{1}H NMR spectra of reaction mixtures in minor amounts. The composition and ratio of the products suggest that the 1,3-cycloaddition of nitrilimines to 7-azanorbornadienes **9** occurs mainly at the C=C bond containing electron acceptor substituents (see Scheme 3, path *a*). This reaction direction is in argeement with the data on the cycloaddition of diphenyl nitrilimine **2a** to 7-carbo- and 7-oxa-analogs of compounds **9a**,**b**.[23]

The *exo*-location of the pyrazoline cycle in compounds **3**, **4** and **6** was established based on NMR spectroscopy data: the spin–spin interaction constant of protons in the positions 2 and 6 is *ca.* 8 Hz, which is typical for the *cis-endo*-positioned protons in the norbornane skeleton.[24] The structure of the **3c** isomer was established using the NOESY experiment: the observed correlation of the singlet with a chemical shift of 3.41 ppm with the signals of protons of the CH_2 benzyl group allows us to attribute this signal to the HC^7 proton, and, in turn, the correlation of the HC^7 proton signal with the signal of protons of the CH_3 group (δ 1.96 ppm) confirms the structure of the **3c** isomer. There is also a correlation between the signal of *ortho*-protons for the phenyl group at the pyrazoline ring (δ 7.01 ppm) and the signals of protons HC^1 (δ 2.81 ppm) and HC^2 (δ 4.04 ppm) that are spatially close to it. Consequently, the signal for proton HC^2 of isomer **3c** is shifted upfield compared to the similar signal of isomer **4c**, and the HC^6 proton signal of the **3c** isomer is shifted downfield compared to the analogous signal of the **4c** isomer. Based on these data, the structures of the **3a–h** and **4a–h** isomers were determined. The structure of the **3i–l** and **4i–l** isomers has not been unambiguously determined by NMR spectroscopy.

To summarize, the addition of nitrilimines to 2-aza-, 2-oxa-3-azabicyclo[2.2.1]heptenes and 7-azabenzonorbornadiene proceeds stereospecifically from the *exo* side. Two regioisomers are formed in the case of 2-azanorbornenes and 2-oxa-3-azanorbornene. The [3+2] cycloaddition to 2,3,7-tris(alkoxycarbonyl)-7-azabicyclo[2.2.1]hept-2,5-dienes is accompanied by the retro-Diels–Alder reaction, which leads to the formation of monocyclic pyrazoles and pyrroles.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7723.

References

1 S. Kumar, S. Bawa, S. Drabu, R. Kumar and H. Gupta, *Recent Pat. Anti-Infect. Drug Discovery*, 2009, **4**, 154; https://doi.org/10.2174/157489109789318569.

2 D. D. Korablina, N. I. Vorozhtsov, L. A. Sviridova, E. I. Kalenikova and O. S. Medvedev, *Pharm. Chem. J.*, 2016, **50**, 281; https://doi.org/10.1007/s11094-016-1438-6.

3 B. Nehra, S. Rulhania, S. Jaswal, B. Kumar, G. Singh and V. Monga, *Eur. J. Med. Chem.*, 2020, **205**, 112666; https://doi.org/10.1016/j.ejmech.2020.112666.

4 Q.-S. Li, B.-N. Shen, Z. Zhang, S. Luo and B.-F. Ruan, *Curr. Med. Chem.*, 2021, **28**, 940; https://doi.org/10.2174/0929867327666200306120151.

5 T. M. Rangarajan and B. Mathew, *Curr. Top. Med. Chem.*, 2021, **21**, 2695; https://doi.org/10.2174/1568026621999210902123132.

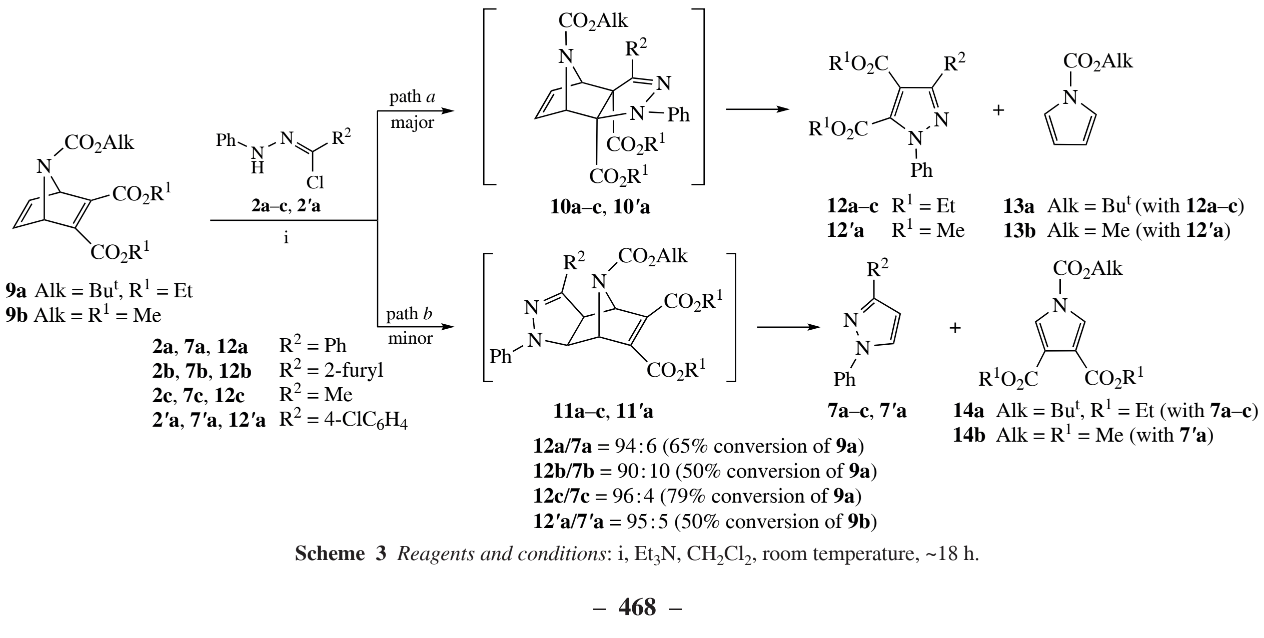
6 D. Choudhary, R. Kaur, T. G. Singh and B. Kumar, *Curr. Top. Med. Chem.*, 2024, **24**, 401; https://doi.org/10.2174/0115680266280249240126052505.

7 D. Matiadis and M. Sagnou, *Int. J. Mol. Sci.*, 2020, **21**, 5507; https://doi.org/10.3390/ijms21155507.

8 R. Huisgen, *J. Org. Chem.*, 1976, **41**, 403; https://doi.org/10.1021/jo00865a001.

9 A. S. Shawali, *Chem. Rev.*, 1993, **93**, 2731; https://doi.org/10.1021/cr00024a007.

10 T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2015, **115**, 5366; https://doi.org/10.1021/cr5007182.



Scheme 3 *Reagents and conditions*: i, Et_3N, CH_2Cl_2, room temperature, ~18 h.

11 N. P. Belskaya, A. I. Eliseeva and V. A. Bakulev, *Russ. Chem. Rev.*, 2015, **84**, 1226; https://doi.org/10.1070/RCR4463.

12 C. Jamieson and K. Livingstone, *The Nitrile Imine 1,3-Dipole. Properties, Reactivity and Applications*, Springer, 2020; https://doi.org/10.1007/978-3-030-43481-6.

13 R. Huisgen, M. Seidel, G. Wallbillich and H. Knupfer, *Tetrahedron*, 1962, **17**, 3; https://doi.org/10.1016/S0040-4020(01)99001-5.

14 R. Huisgen, H. Knupfer, R. Sustmann, G. Wallbillich and V. Weberndörfer, *Chem. Ber.*, 1967, **100**, 1580; https://doi.org/10.1002/cber.19671000525.

15 H. Taniguchi, T. Ikeda, Y. Yoshida and E. Imoto, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 2694; https://doi.org/10.1246/bcsj.50.2694.

16 D. E. Shybanov, M. E. Filkina, M. E. Kukushkin, Y. K. Grishin, V. A. Roznyatovsky, N. V. Zyk and E. K. Beloglazkina, *New J. Chem.*, 2022, **46**, 18575; https://doi.org/10.1039/D2NJ03756D.

17 A. V. Popova, A. Kanaa, V. S. Vavilova, M. A. Mironova, P. A. Slepukhin, E. Benassi and N. P. Belskaya, *New J. Chem.*, 2021, **14**, 6315; https://doi.org/10.1039/D0NJ06287A.

18 K. K. Mahalanabis and A. Mukherjee, *Heterocycles*, 2009, **78**, 911; https://doi.org/10.3987/COM-08-11531.

19 K. Tanaka, H. Masuda and K. Mitsuhashi, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 3901; https://doi.org/10.1246/bcsj.59.3901.

20 C. De Micheli, R. Gandolfi and R. Oberti, *J. Org. Chem.*, 1980, **45**, 1209; https://doi.org/10.1021/jo01295a008.

21 P. S. Anderson, M. E. Christy, E. L. Engelhardt, G. F. Lundell and C. S. Ponticello, *J. Heterocycl. Chem.*, 1977, **14**, 213; https://doi.org/10.1002/jhet.5570140209.

22 T. A. Solodovnikova, N. V. Zyk and A. Yu. Gavrilova, *Mendeleev Commun.*, 2022, **32**, 549; https://doi.org/10.1016/j.mencom.2022.07.038.

23 D. Cristina, M. De Amici, C. De Micheli and R. Gandolfi, *Tetrahedron*, 1981, **37**, 1349; https://doi.org/10.1016/S0040-4020(01)92451-2.

24 A. J. Gordon and R. A. Ford, *The Chemist's Companion: A Handbook of Practical Data, Techniques, and References*, John Wiley and Sons, New York, 1972.

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