Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2022, **32**, 549–550

Mendeleev Communications

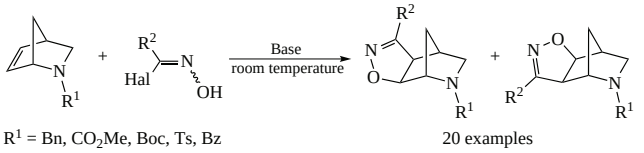
Reaction of 2-azabicyclo[2.2.1]heptenes with nitrile oxides

Tatiana A. Solodovnikova, Nikolai V. Zyk and Anna Yu. Gavrilova*

Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation.
E-mail: augava@gmail.com

DOI: 10.1016/j.mencom.2022.07.038

The reaction of 2-azanorbornene derivatives with nitrile oxides (generated *in situ* by dehydrohalogenation of *N*-hydroxyimoyl halides) affords two regioisomers with the *exo*-arrangement of the isoxazoline ring.



Keywords: 2-azabicyclo[2.2.1]heptanes, nitrile oxides, 1,3-dipolar cycloaddition, hydroxyimoyl halides, norbornene, isoxazolines.

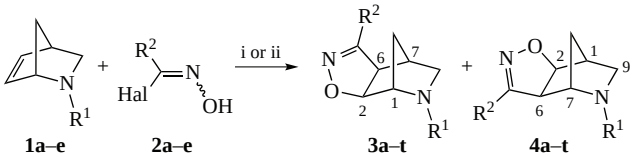
2-Azabicyclo[2.2.1]heptanes are analogues of piperidine, pyrrolidine and cyclopentylamine with a rigidly fixed conformation. Therefore, the study of these compounds is carried out in two directions: the synthesis of new biologically active compounds containing a 2-azanorbornane fragment, and the use of the azabicyclic fragment in the synthesis of monocyclic compounds with a specific configuration of substituents.[1] A promising way to modify azabicyclo[2.2.1]heptenes is their use as dipolarophiles in reactions with nitrile oxides, as this would create an isoxazoline ring that is a hidden equivalent of some functional groups, which can be used at the corresponding stage of the synthesis.[2,3]

The unsubstituted carbocyclic analogue of 2-azabicyclo[2.2.1]heptene, norbornene, has been widely used as a model substrate in the study of 1,3-dipolar cycloaddition reactions of nitrile oxides.[4–25] Regardless of the nature and method of generating the dipole, the addition proceeds exclusively from the *exo* side. For bicyclo[2.2.1]heptene derivatives containing a 2-positioned substituent, the reaction is regiospecific,[23,24] whereas for derivatives containing substituents in the position 5, only a slight predominance of one of the regioisomers is observed.[24] Using the examples of the reaction of 2-azabicyclo[2.2.1]hept-5-en-3-one with cyanogen bromide oxide and alkanenitrile oxides[26–29] as well as *N*-alkyl- and *N*-benzylazanorbornenes with benzonitrile oxide,[30,31] it was shown that, as in the case of 5-substituted norbornenes, two regioisomers are formed with the *exo*-arrangement of the isoxazoline ring. Besides, the reactivity of azanorbornene with phenylnitrile oxide was found to be lower than that of norbornene.[30]

The purpose of this work was to study the effect of the protective group at the nitrogen atom in 2-azabicyclo[2.2.1]hept-5-ene derivatives **1a**–**e** on the regio- and stereochemical outcome of the reaction (Scheme 1). We have found that the addition of bromo- (**2a**), ethoxycarbonyl- (**2b**), and aryl-containing (**2c**–**e**) nitrile oxides to *N*-substituted 2-azanorbornenes proceeds at room temperature with the formation of two regioisomers with the *exo*-position of the isoxazoline ring (Table 1). The predominance of one of the regioisomers is insignificant and may vary slightly depending on the solvent used.[30] Complete conversion of the alkene was observed at a ratio of nitrile oxide/alkene of 1 : 1 only for 4-methoxybenzonitrile oxide (generated from **2d**). As for all other nitrile oxides, the best results were achieved at a ratio of nitrile oxide/alkene of 3 : 2. The product yields were 20–87% and depended on the structure of both dipolarophile and 1,3-dipole. The low yields in some cases can be explained by two reasons. First, furoxans could be formed as the by-products.[32] Secondly, a significant decrease in yield occurs during the chromatographic separation of a mixture of isomers. For example, after chromatographic separation, the total yield of isomers **3k** and **4k** (see Table 1, entry 11) or **3p** and **4p** (entry 16) did not exceed 25%, however, according to the ^{1}H NMR of the reaction mixtures, the yields of the products in both cases were quantitative.

It was not possible to separate regioisomers **3**, **4** in some cases, however the predominance of one of them in the fractions obtained after chromatography allowed us to establish their structure by NMR. The *exo*-arrangement of the isoxazoline ring and, accordingly, the *endo*-arrangement of protons in the positions 2 and 6 follows from the spin–spin coupling constant value of 8 Hz, which is typical for the coupling constant of *cis*-di-*endo*-located protons in the norbornane fragment.[33]

The structure of isomer **4s** was established using the NOESY experiment: a correlation was observed between the signal for the HC^7 proton (δ 4.39 ppm) and the signals of HC^{6}C=N protons spatially close to it (δ 4.20 ppm) as well as the *ortho*-located protons of 4-$O_2NC_6H_4$ (δ 7.92 ppm) and tosyl (δ 7.70 ppm) groups, and the correlation of the signal for the HC^{2}O proton (δ 5.01 ppm) with the signals of the protons from *endo*-HC^9 (δ 2.93 ppm), HC^1 (δ 3.09 ppm) and HC^6 (δ 4.18 ppm). The HCC=N and HCO proton signals of isomer **3s** have chemical



a R^1 = Bn
b R^1 = CO_2Me
c R^1 = Boc
d R^1 = Ts
e R^1 = Bz

a R^2 = Br, Hal = Br
b R^2 = CO_2Et, Hal = Cl
c R^2 = Ph, Hal = Cl
d R^2 = 4-$MeOC_6H_4$, Hal = Cl
e R^2 = 4-$O_2NC_6H_4$, Hal = Cl

Scheme 1 For designation of products **3a–t** and **4a–t**, see Table 1. *Reagents and conditions*: i, $NaHCO_3$, EtOAc, 5 °C, 1 h, then room temperature, 4 h (for **3a–c** + **4a–c**); ii, Et_3N, Et_2O or CH_2Cl_2, room temperature, 0.5–5 h (for **3d–t** + **4d–t**).

Table 1 Yields of products of the reaction between nitrile oxides and 2-azanorbornenes.

Entry	Alkene	Nitrile oxide	R^1	R^2	Product	Yield[a] (%)	**3**/**4** ratio[b]
1	**1a**	**2a**	Bn	Br	**3a** + **4a**	20	53 : 47
2	**1b**	**2a**	CO_2Me	Br	**3b** + **4b**	20	53 : 47
3	**1c**	**2a**	Boc	Br	**3c** + **4c**	29	50 : 50
4	**1a**	**2b**	Bn	CO_2Et	**3d** + **4d**	66	55 : 45
5	**1d**	**2b**	Ts	CO_2Et	**3e** + **4e**	74	49 : 51
6	**1a**	**2c**	Bn	Ph	**3f** + **4f**	63	41 : 59
7	**1b**	**2c**	CO_2Me	Ph	**3g** + **4g**	41	49 : 51
8	**1c**	**2c**	Boc	Ph	**3h** + **4h**	87	52 : 48
9	**1d**	**2c**	Ts	Ph	**3i** + **4i**	71	48 : 52
10	**1e**	**2c**	Bz	Ph	**3j** + **4j**	45	40 : 60
11	**1a**	**2d**	Bn	4-$MeOC_6H_4$	**3k** + **4k**	24	45 : 55
12	**1b**	**2d**	CO_2Me	4-$MeOC_6H_4$	**3l** + **4l**	54	49 : 51
13	**1c**	**2d**	Boc	4-$MeOC_6H_4$	**3m** + **4m**	57	35 : 65
14	**1d**	**2d**	Ts	4-$MeOC_6H_4$	**3n** + **4n**	55	45 : 55
15	**1e**	**2d**	Bz	4-$MeOC_6H_4$	**3o** + **4o**	37	42 : 58
16	**1a**	**2e**	Bn	4-$O_2NC_6H_4$	**3p** + **4p**	24	56 : 44
17	**1b**	**2e**	CO_2Me	4-$O_2NC_6H_4$	**3q** + **4q**	29	49 : 51
18	**1c**	**2e**	Boc	4-$O_2NC_6H_4$	**3r** + **4r**	33	33 : 67
19	**1d**	**2e**	Ts	4-$O_2NC_6H_4$	**3s** + **4s**	46	46 : 54
20	**1e**	**2e**	Bz	4-$O_2NC_6H_4$	**3t** + **4t**	54	34 : 66

[a]Yields after chromatographic separation. [b]From ^{1}H NMR of the reaction mixtures.

shifts of 3.79 and 5.07 ppm, respectively. Thus, the signal for the HC^2O proton of isomer **3s** is shifted downfield compared to the HC^2O proton of isomer **4s**. On the contrary, the $HC^6C{=}N$ proton signal of isomer **3s** is shifted upfield compared to the $HC^6C{=}N$ signal in isomer **4s**. A similar pattern is observed for the pair of isomers **3f** and **4f**.[30] Based on these data, the structures of all isomers containing tosyl and benzyl groups at the nitrogen atom were thus deduced.

In the ^{1}H and ^{13}C NMR spectra of compounds containing CO_2Me, Boc and Bz groups, there are two sets of signals, which is the result of hindered rotation around the N–CO bond.[34] Considering this feature of amides and carbamates, we assumed that the HC^2O proton of isomer **3** will appear as two signals, and the HC^6CAr proton as one; for isomer **4**, the picture will be reversed. Our assumption was confirmed by the example of isomer **4r**: its structure follows from the presence of cross peaks between the signals of the HC^7 proton (δ 4.36 and 4.47 ppm) and the signals of $HC^6C{=}N$ protons spatially close to it (δ 3.87 and 3.98 ppm) and *ortho*-located aromatic ring protons (δ 7.95 and 7.99 ppm), as well as cross peaks between the HC^2O proton signals (two close doublets δ 4.96 and 4.97 ppm) and proton signals from *endo*-HC^9 (δ 2.93 ppm), HC^1 (δ 2.99 ppm) and HC^6 (δ 3.87 and 3.98 ppm) in the NOESY experiment.

In conclusion, 1,3-dipolar cycloaddition of nitrile oxides to 2-azabicyclo[2.2.1]heptenes with electron-withdrawing substituents at the nitrogen atom has been examined. The reaction proceeds non-regioselectively with the formation of two products, both with the *exo*-arrangement of the isoxazoline ring, regardless of the type of protecting group at the nitrogen atom.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.07.038.

References

1 E. Wojaczyńska, J. Wojaczyński, K. Kleniewska, M. Dorsza and T. K. Olszewski, *Org. Biomol. Chem.*, 2015, **13**, 6116.
2 A. P. Kozikowski, *Acc. Chem. Res.*, 1984, **17**, 410.
3 R. P. Litvinovskaya and V. A. Khripach, *Russ. Chem. Rev.*, 2001, **70**, 405.
4 R. Huisgen and M. Christl, *Angew. Chem*., 1967, **79**, 471.
5 R. Huisgen and M. Christl, *Chem. Ber*., 1973, **106**, 3291.
6 F. De Sarlo(rk), A. Brandi, A. Guarna, A. Goti and S. Corezzi, *Tetrahedron Lett.*, 1983, **24**, 1815.
7 F. De Sarlo, A. Guarna, A. Brandi and A. Goti, *Tetrahedron*, 1985, **41**, 5181.
8 P. Caldirola, M. Ciancaglione, M. De Amici and C. De Michel, *Tetrahedron Lett.*, 1986, **27**, 4647.
9 R. Huisgen, P. H. J. Ooms, M. Mingin and N. L. Allinger, *J. Am. Chem. Soc*., 1980, **102**, 3951.
10 G. A. Lee, *Synthesis*, 1982, 508.
11 R. F. Cunico and L. Bedell, *J. Org. Chem*., 1983, **48**, 2780.
12 L. Cecchi, F. De Sarlo and F. Machetti, *Synlett*, 2007, 2451.
13 L. Cecchi, F. De Sarlo and F. Machetti, *Chem. – Eur. J*., 2008, **14**, 7903.
14 P. E. Pigou and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. 2*, 1988, 725.
15 D. Muri, J. W. Bode and E. M. Carreira, *Org. Lett*., 2000, **2**, 539.
16 L. Ma, F. Jin, X. Cheng, S. Tao, G. Jiang, X. Li, J. Yang, X. Bao and X. Wan, *Chem. Sci*., 2021, **12**, 9823.
17 B. A. Mendelsohn, S. Lee, S. Kim, F. Teyssier, V. S. Aulakh and M. A. Ciufolini, *Org. Lett*., 2009, **11**, 1539.
18 H. Liang and M. A. Ciufolini, *Tetrahedron*, 2010, **66**, 5884.
19 T. Jen, B. A. Mendelsohn and M. A. Ciufolini, *J. Org. Chem*., 2011, **76**, 728.
20 B. D. Zlatopolskiy, R. Kandler, D. Kobus, F. M. Mottaghy and B. Neumaier, *Chem. Commun*., 2012, **48**, 7134.
21 C. Xiang, T. Li and J. Yan, *Synth. Commun*., 2014, **44**, 682.
22 G. Molteni and P. Del Buttero, *Tetrahedron*, 2011, **67**, 7343.
23 G. K. Tranmer and W. Tam, *Org. Lett*., 2002, **4**, 4101.
24 P. Mayo, T. Hecnar and W. Tam, *Tetrahedron*, 2001, **57**, 5931.
25 M. Gucma, W. M. Gołębiewski and A. K. Michalczyk, *J. Braz. Chem. Soc*., 2016, **27**, 1925.
26 A. Pinto, L. Tamborini, E. Pennacchietti, A. Coluccia, R. Silvestri, G. Cullia, C. De Micheli, P. Conti and D. De Biase, *J. Enzyme Inhib. Med. Chem*., 2016, **31**, 295.
27 D. P. Curran, S. A. Gothe and S.-M. Choi, *Heterocycles*, 1993, **35**, 1371.
28 D.-C. Chiu, T.-C. Lin, W.-I Huang, T.-J. Cheng, K.-C. Tsaic and J.-M. Fang, *Org. Biomol. Chem*., 2017, **15**, 9910.
29 C.-L. Chen, T.-W. Chiu, Y.-W. Chen and J.-M. Fang, *Tetrahedron*, 2019, **75**, 4458.
30 P. Quadrelli, A. Piccanello, N. V. Martinez, B. Bovio, M. Mella and P. Caramella, *Tetrahedron*, 2006, **62**, 7370.
31 M. G. Memeo, D. (P.) Mantione, B. Bovio and P. Quadrelli, *Synthesis*, 2011, 2165.
32 L. I. Khmelnitsky, S. S. Novikov and T. I. Godovikova, *Khimiya furoksanov: stroenie i svoistva* (*Chemistry of Furoxans: Structure and Properties*), Nauka, Moscow, 1996 (in Russian).
33 A. J. Gordon and R. A. Ford, *The Chemist's Companion*, Wiley-Interscience, New York, 1972.
34 O. A. Reutov, A. L. Kurts and K. P. Butin, *Organicheskaya khimiya* (*Organic Chemistry*), Binom. Laboratoriya znanii, Moscow, 2004, vol. 3 (in Russian).

Received: 17th December 2021; Com. 21/6776