Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2012, **22**, 35–36
Mendeleev Communications

Synthesis of fused isoindoles *via* 1,3-dipolar cycloaddition of 1,3-oxazolium-5-olates (münchnones) with nitro benzazoles

Sergey Yu. Pechenkin, Aleksei M. Starosotnikov,* Maxim A. Bastrakov, Vadim V. Kachala and Svyatoslav A. Shevelev

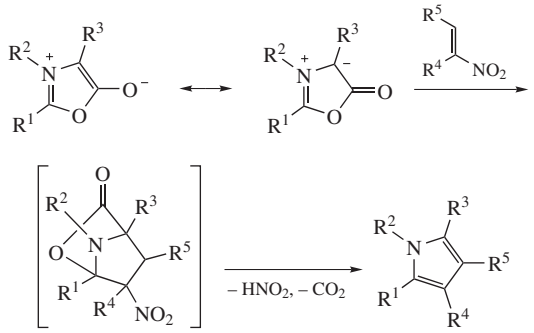
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: alexey41@list.ru

DOI: 10.1016/j.mencom.2012.01.013

1,3-Dipolar cycloaddition of 1,3-oxazolium-5-olates at benzazoles nitrated at the benzene ring affords the corresponding azoloisoindole derivatives.

Although the 1,3-dipolar cycloaddition of dipoles to nitro alkenes is well-known,[1] there is only a few examples of similar reactions involving aromatic nitro compounds, mostly nitro hetarenes.[2] The first examples of the [3+2]-cycloaddition to nitroarenes, namely, reactions between nonstabilized *N*-methyl azomethine ylide and mono- and dinitrobenzene fused with azoles and azines, were published recently by our group.[3] In all cases cycloaddition by one or two C=C bond(s) activated by the nitro group occurred giving rise to the loss of aromaticity of the nitrobenzene ring and formation of tetrahydroisoindole or isoindoline systems.[3] Later, Lee *et al*. described[4] 'facile dearomatization of nitrobenzene derivatives and other nitroarenes' under the action of *N*-benzyl azomethine ylide.

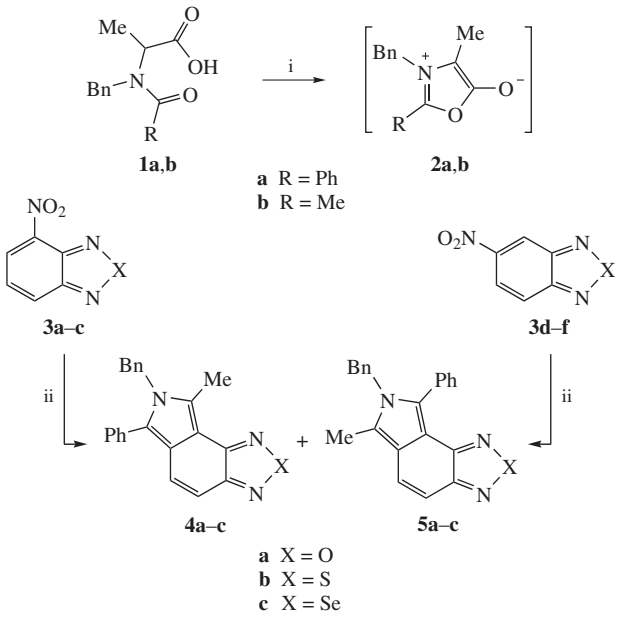
1,3-Oxazolium-5-olates (münchnones) are known to undergo 1,3-dipolar cycloaddition at conjugated nitro alkenes[5] as well as at nitro heteroaromatics, *e.g.*, 2- and 3-nitroindoles.[6] Since münchnone molecule contains the cyclic azomethine ylide fragment (Scheme 1), its reaction with nitro alkene affords bicyclic intermediate which is prone to eliminate HNO_2 and carbon dioxide leading to pyrrole derivatives.[1,5]



Scheme 1

In this connection it was of interest to verify nitroarene behaviour in [3+2]-cycloadditions with münchnones. Available nitrated benzofurazans, benzothiadiazoles and benzoselenadiazoles were used as dipolarophiles. 1,3-Oxazolium-5-olates **2a**,**b** were synthesized *in situ* from *N*-benzyl-*N*-benzoyl- **1a** or *N*-benzyl-*N*-acetylalanine **1b**[6] under the action of dicyclohexyl carbodiimide (DCC) (Scheme 2).

Heating of münchnone **2a** in the presence of nitro benzazoles **3a–f** resulted in formation of the mixtures of isomeric isoindoles **4a–c** and **5a–c** (Scheme 2, Table 1). Here the reactions proceed similarly to those of nitro alkenes.



Scheme 2 *Reagents and conditions:* i, DCC (1 equiv.), THF, reflux; ii, **2a** (3 equiv.), THF, reflux.

In most cases the cycloadditions appeared to be regioselective, the selectivity being dependent on the nature of heteroatom in starting nitro compound **3**. The best selectivity was observed in case of thiadiazole derivatives. The resulting isomers **4** and **5** are quite difficult to separate since they had almost identical R_f values in a wide range of common eluents. However, it was possible to isolate and fully characterize the major isomers excluding **4c**. The ratio of the isomers in each case was determined from ^{1}H NMR data of the crude mixture using the ratio of integral intensities of characteristic signals of benzyl CH_2 groups or methyl groups.

Table 1 Reaction of münchnone **2a** with compounds **3a–f**.

Compound	X	Reaction time/h	Products	Yield of the mixture (%)	Isomer ratio **4**:**5**	Isolated yield of major isomer (%)
3a	O	0.5	**4a** + **5a**	88	58:42	29 (**4a**)
3b	S	0.75	**4b** + **5b**	79	87:13	45 (**4b**)
3c	Se	2	**4c** + **5c**	50	79:21	Not isolated
3d	O	0.5	**4a** + **5a**	85	41:59	13 (**5a**)
3e	S	0.75	**4b** + **5b**	64	13:87	20 (**5b**)
3f	Se	2	**4c** + **5c**	67	35:65	41 (**5c**)

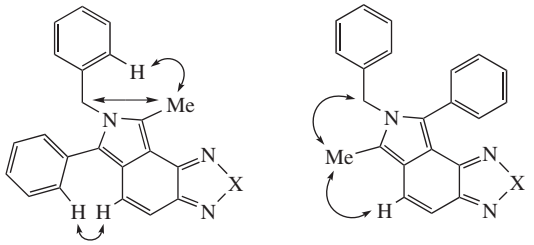


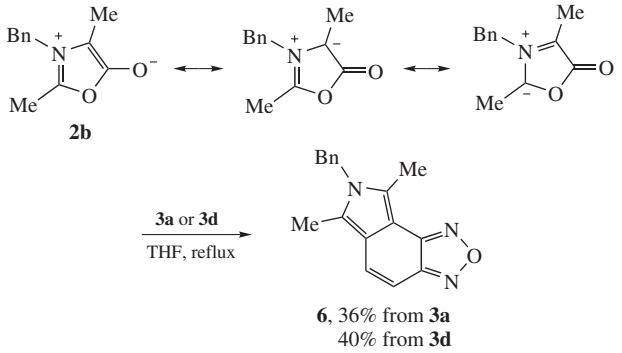
Figure 1 Selected connectivities found in 2D NOESY spectra of the products **4** and **5**.

The structures of each isolated isomer were assigned based on 1D and 2D NOESY experiments (Figure 1).

In case of münchnone **2b** containing two methyl groups the reaction with nitrobenzofurazans **3a** and **3d** resulted in formation of the individual isoindole **6** (Scheme 3). Surprisingly, thia- and selenadiazole derivatives **3b**,**c**,**e**,**f** did not undergo cycloaddition reactions with **2b** under standard conditions.

The structures of the polycyclic compounds obtained were proved by NMR spectroscopy and microanalysis.†

In summary, a number of new isoindole derivatives fused with azoles were synthesized on the basis of the previously unknown 1,3-dipolar cycloaddition reactions of 1,3-oxazolium-5-olates (münchnones) with nitro benzazoles. This can be regarded as a new method for the annelation of pyrrole ring to benzene moiety.



Scheme 3

This work was supported by the Russian Foundation for Basic Research (project no. 10-03-00185-a), and the President of the Russian Federation (The program of state support for young scientists, grant MK-220.2011.3).

References

1 (*a*) A. Padwa and W. H. Pearson, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, Wiley, New York, 2002; (*b*) A. Padwa, *1,3-Dipolar Cycloaddition Chemistry*, John Wiley & Sons, New York, 1984.

2 S. Roy, T. L. Kishbaugh, J. P. Jasinski and G. W. Gribble, *Tetrahedron Lett*., 2007, **48**, 1313, and references cited therein.

3 (*a*) M. A. Bastrakov, A. M. Starosotnikov, S. Yu. Pechenkin, V. V. Kachala, I. V. Glukhov and S. A. Shevelev, *J. Heterocycl. Chem.*, 2010, **47**, 893; (*b*) A. M. Starosotnikov, M. A. Bastrakov, S. Yu. Pechenkin, M. A. Leontieva, V. V. Kachala and S. A. Shevelev, *J. Heterocycl. Chem.*, 2011, **48**, 824; (*c*) L. S. Konstantinova, M. A. Bastrakov, A. M. Starosotnikov, I. V. Glukhov, K. A. Lysov, O. A. Rakitin and S. A. Shevelev, *Mendeleev Commun*., 2010, **20**, 353.

4 S. Lee, I. Chataigner and S. R. Piettre, *Angew. Chem. Int. Ed*., 2011, **50**, 472.

5 M. Avalos, R. Babiano, A. Cabanillas, P. Cintas, J. L. Jimenez and J. C. Palacios, *J. Org. Chem.*, 1996, **61**, 7291.

6 G. W. Gribble, E. T. Pelkey, W. M. Simon and H. A. Trujillo, *Tetrahedron*, 2000, **56**, 10133.

7 (*a*) P. B. Ghosh and M. W. Whitehouse, *J. Med. Chem.*, 1968, **11**, 305; (*b*) T. Murashima, D. Shiga, K. Nishi, H. Uno and N. Ono, *J. Chem. Soc., Perkin Trans. 1*, 2000, **16**, 2671; (*c*) E. Sawicki and A. Carr, *J. Org. Chem.*, 1957, **22**, 503; (*d*) T. Murashima, K. Fujita, K. Ono, T. Ogawa, H. Uno and N. Ono, *J. Chem. Soc., Perkin Trans. 1*, 1996, **12**, 1403.

Received: 15th July 2011; Com. 11/3765

† Melting points were measured on a Boetius apparatus and are uncorrected. NMR spectra were recorded on a Bruker DRX-500 spectrometer using TMS as a standard. All reactions were monitored by TLC using Silufol UV-254 plates which were visualized with UV light. Flash column chromatography was performed with MN Kieselgel 60 (0.04–0.063 mm/230–400 mesh) as the stationary phase and toluene as an eluent. For all new compounds satisfactory microanalyses were obtained. Compounds **3a–f** were prepared according to the described procedures.[7]

Compounds **4–6** *(general procedure)*. A mixture of compound **1a** or **1b** (3 mmol), nitro compound **3** (1 mmol) and DCC (0.61 g, 3 mmol) in 20 ml of dry THF was heated under reflux for the time indicated in Table 1. After the starting material disappeared (TLC) the mixture was cooled to room temperature and filtered. The solvent was evaporated under reduced pressure and the residue was recrystallized from EtOH to give a mixture of isomers **4** and **5**. The major isomer was isolated from the mixture by column chromatography (SiO_2/toluene).

*7-Benzyl-8-methyl-6-phenyl-7*H*-[1,2,5]oxadiazolo[3,4-*e*]isoindole* **4a**: yellow crystals, mp 131–132 °C. ^{1}H NMR ($CDCl_3$) δ: 2.70 (s, 3H, Me), 5.32 (s, 2H, CH_2), 6.92 (d, 2H, *J* 6.7 Hz), 7.07 (d, 1H, *J* 9.6 Hz), 7.29–7.45 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 12.3, 48.4, 105.6, 108.3, 119.1, 125.6, 127.6, 128.4, 128.5, 128.8, 130.0, 130.4, 130.5, 130.7, 137.1, 146.0, 150.0. Found (%): C, 78.10; H, 5.13; N, 12.06. Calc. for $C_{22}H_{17}N_3O$ (%): C, 77.86; H, 5.05; N, 12.38.

*7-Benzyl-8-methyl-6-phenyl-7*H*-[1,2,5]thiadiazolo[3,4-*e*]isoindole* **4b**: brown crystals, mp 90–91 °C. ^{1}H NMR ($CDCl_3$) δ: 2.83 (s, 3H, Me), 5.38 (s, 2H, CH_2), 6.90 (d, 2H, *J* 6.8 Hz), 7.18–7.53 (m, 11H). ^{13}C NMR ($CDCl_3$) δ: 11.9, 48.4, 112.9, 115.6, 118.4, 120.0, 125.7, 126.0, 127.0, 127.6, 128.1, 128.8, 128.9, 130.4, 131.1, 137.5, 152.3, 155.6. Found (%): C, 74.60; H, 4.61; N, 11.59. Calc. for $C_{22}H_{17}N_3S$ (%): C, 74.34; H, 4.82; N, 11.82.

*7-Benzyl-8-methyl-6-phenyl-7*H*-[1,2,5]selenadiazolo[3,4-*e*]isoindole* **4c**: not isolated. ^{1}H NMR (DMSO-d_6) δ: 2.73 (s, 3H, Me), 5.40 (s, 2H, CH_2), 6.84 (d, 2H, *J* 7.2 Hz), 7.04 (d, 1H, *J* 9.5 Hz), 7.08–7.51 (m, 9H).

*7-Benzyl-6-methyl-8-phenyl-7*H*-[1,2,5]oxadiazolo[3,4-*e*]isoindole* **5a**: yellow crystals, mp 125–126 °C. ^{1}H NMR ($CDCl_3$) δ: 2.39 (s, 3H, Me), 5.32 (s, 2H, CH_2), 6.92 (d, 2H, *J* 6.1 Hz), 7.08 (d, 1H, *J* 9.4 Hz), 7.27–7.52 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 10.6, 48.6, 105.4, 107.3, 119.2, 125.7, 126.9, 127.6, 127.8, 128.8, 128.9, 129.1, 130.0, 130.6, 131.6, 137.22, 145.77, 150.2. Found (%): C, 77.65; H, 4.92; N, 12.57. Calc. for $C_{22}H_{17}N_3O$ (%): C, 77.86; H, 5.05; N, 12.38.

*7-Benzyl-6-methyl-8-phenyl-7*H*-[1,2,5]thiadiazolo[3,4-*e*]isoindole* **5b**: brown crystals, mp 61–62 °C. ^{1}H NMR ($CDCl_3$) δ: 2.44 (s, 3H, Me), 5.32 (s, 2H, CH_2), 6.89 (d, 2H, *J* 6.7 Hz), 7.27–7.60 (m, 11H). ^{13}C NMR ($CDCl_3$) δ: 10.6, 48.4, 112.7, 114.5, 119.8, 124.2, 125.0, 125.7, 127.5, 128.4, 128.6, 129.0, 129.6, 130.8, 131.4, 137.6, 151.6, 156.0. Found (%): C, 74.50; H, 4.68; N, 11.97. Calc. for $C_{22}H_{17}N_3S$ (%): C, 74.34; H, 4.82; N, 11.82.

*7-Benzyl-6-methyl-8-phenyl-7*H*-[1,2,5]selenadiazolo[3,4-*e*]isoindole* **5c**: brown crystals, mp 137–138 °C. ^{1}H NMR (DMSO-d_6) δ: 2.37 (s, 3H, Me), 5.26 (s, 2H, CH_2), 6.83 (d, 2H, *J* 7.0 Hz), 7.04 (d, 1H, *J* 9.5 Hz), 7.15–7.65 (m, 9H). ^{13}C NMR (DMSO-d_6) δ: 11.8, 47.48, 114.1, 118.2, 118.9, 119.7, 124.1, 125.6, 126.0, 127.3, 127.9, 128.1, 128.9, 130.0, 130.4, 137.5, 156.7, 160.7. Found (%): C, 65.49; H, 4.13; N, 10.65. Calc. for $C_{22}H_{17}N_3Se$ (%): C, 65.67; H, 4.26; N, 10.44.

*7-Benzyl-6,8-dimethyl-7*H*-[1,2,5]oxadiazolo[3,4-*e*]isoindole* **6**: orange crystals, mp 136–137 °C. ^{1}H NMR ($CDCl_3$) δ: 2.38 (s, 3H, Me), 2.66 (s, 3H, Me), 5.25 (s, 2H, CH_2), 6.90 (d, 2H, *J* 7.0 Hz), 7.98 (d, 1H, *J* 9.5 Hz), 7.27–7.38 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 10.3, 12.1, 47.6, 104.6, 106.6, 117.9, 125.2, 125.7, 127.2, 127.8, 127.9, 129.1, 136.4, 146.1, 150.1. Found (%): C, 73.48; H, 5.58; N, 14.90. Calc. for $C_{17}H_{15}N_3O$ (%): C, 73.63; H, 5.45; N, 15.15.