*Chemistry of Heterocyclic Compounds, Vol. 40, No. 6, 2004*

# ADDITION OF NITRILE OXIDES TO ARYL ALLYL ETHERS

**E. Alksnis, V. Muravenko, V. Dirnens, and E. Lukevics**

*3,5-Disubstituted isoxazolines with an aryloxymethyl group in position 5 have been synthesized. The [2+3] cycloaddition reaction of benzonitrile oxide to a 5-chlorosalicylic acid derivative containing two allyl groups occurs to give a compound with an oxazolinylmethyl fragment both in the ester and the ether parts of the molecule. The addition of nitrile oxides to the aryl allyl ethers occurs regiospecifically to give the 5-substituted isomer.*

**Keywords:** aryl allyl ethers, isoxazolines, nitrile oxides, hydroxamic acid chlorides.

An isoxazoline heterocycle is a valuable synthon in organic chemistry for the preparation of β-hydroxy ketones [1-7], γ-amino alcohols [8,9], α,β-unsaturated oximes [10, 11], and β-hydroxy nitriles [12, 13]. Amongst isoxazolines there are found compounds with such pharmacological properties as analgesic [14], anti-inflammatory [15], antibacterial [16], and GPIIb/IIIa inhibiting [17, 18] activity. In biogenic amines an isoxazoline ring is an important part of the molecule for interaction with different receptors [19].

One of the basic methods for the synthesis of these heterocycles is the [2+3] cycloaddition of nitrile oxides, generated from hydroxamic acid chlorides in the presence of triethylamine, or of silylnitronates to alkenes [20-23].

3-Acetyl(benzoyl)-5-phenoxymethylisoxazolines were prepared by the addition of nitrile oxides, generated from acetone and acetophenone in the presence of ammonium cerium(IV) sulfate, to phenyl allyl ether [24].

The 3-aryl-5-aryloxymethylisoxazolines **12-19** were synthesized by the addition of the arylnitrile oxides **9-11** to the substituted aryl allyl ethers **1-8**.

The "one-pot" reactions were carried out in the sequence: 1) reaction of an aryloxime with N-chlorosuccinimide in chloroform to give the corresponding arylhydroxamic acid chloride, 2) addition of the unsaturated compound, and 3) addition of triethylamine as dehydrohalogenating agent for generation of the nitrile oxide.

The [2+3] cycloaddition occurs regiospecifically and always forms the single 5-substituted isoxazoline regioisomer.

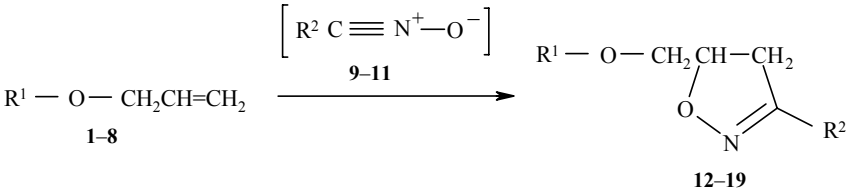
Addition of benzonitrile to compound **8** occurs at both allyl groups to give compound **19** which contains isoxazolinomethyl fragments in both the ester and the ether parts of the molecule (Scheme 1).

The starting ethers **1-8** were prepared by the alkylation of substituted phenols by allyl bromide under phase-transfer catalysis conditions (PTC) [25]. In the case of 5-chlorosalicylic acid, compound **8** was obtained and this contained allyl groups in both the ester and in the ether fragments of the molecule.

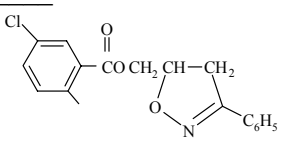
---

Latvian Institute of Organic Synthesis, Riga LV 1006; e-mail: dirnens@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 928-931, June, 2004. Original article submitted April 14, 2004.

Scheme 1




| Compound | $R^1$ | $R^2$ | Compound | $R^1$ | $R^2$ |
|---|---|---|---|---|---|
| **12** | 4,6-$Br_2C_6H_3$– | $C_6H_5$– | **16** | 2,4,6-$Cl_3C_6H_2$– | 4-$BrC_6H_4$– |
| **13** | 4-$ClC_6H_4$– | 4-$BrC_6H_4$– | **17** | 4-$O_2NC_6H_4$– | $C_6H_5$– |
| **14** | 2-Me-4-$ClC_6H_3$– | 4-$ClC_6H_4$– | **18** | 4-$EtOOCC_6H_4$– | 4-$ClC_6H_4$– |
| **15** | 2,4,5-$Cl_3C_6H_2$– | $C_6H_5$– | **19** | —* | $C_6H_5$– |

* 

## EXPERIMENTAL

$^1$H NMR spectra for compounds **13, 14, 16-19** were recorded on a Bruker WP-90 instrument (90 MHz) and for compound **12, 15** on a Varian Mercury-200BB (200 MHz) instrument using $CDCl_3$ solvent and with TMS as internal standard.

The general method for preparing the isoxazolines **12-19** is given in the study [26]. Characteristics for the compounds synthesized are given in Tables 1 and 2.

TABLE 1. Characteristics of the Isoxazoline Derivatives **12-19**

| Compound | Empirical formula | Molecular weight | Found, % / Calculated, % | | | mp, °C | Yield, % |
|---|---|---|---|---|---|---|---|
| | | | C | H | N | | |
| **12** | $C_{16}H_{13}Br_2NO_2$ | 411.10 | 46.90 / 46.75 | 3.20 / 3.19 | 3.40 / 3.41 | 90 | 45 |
| **13** | $C_{16}H_{13}BrClNO_2$ | 366.64 | 52.41 / 52.42 | 3.55 / 3.57 | 3.83 / 3.82 | 134 | 61 |
| **14** | $C_{17}H_{15}Cl_2NO_2$ | 336.22 | 60.88 / 60.73 | 4.52 / 4.50 | 4.20 / 4.17 | 119 | 48 |
| **15** | $C_{16}H_{12}Cl_3NO_2$ | 356.64 | 54.01 / 53.89 | 3.37 / 3.39 | 3.92 / 3.93 | 140 | 41 |
| **16** | $C_{16}H_{11}BrCl_3NO_2$ | 435.53 | 44.01 / 44.13 | 2.58 / 2.55 | 3.25 / 3.22 | 113 | 47 |
| **17** | $C_{16}H_{14}N_2O_4$ | 298.30 | 64.19 / 64.42 | 4.71 / 4.73 | 9.42 / 9.39 | 142 | 65 |
| **18** | $C_{19}H_{18}ClNO_4$ | 359.81 | 63.30 / 63.43 | 5.02 / 5.04 | 3.91 / 3.89 | 96 | 57 |
| **19** | $C_{27}H_{23}ClN_2O_5$ | 490.95 | 65.81 / 66.06 | 4.74 / 4.72 | 5.73 / 5.71 | 154 | 51 |

TABLE 2. $^1$H NMR Spectra of the Isoxazolines **12-19**

| Com-pound | Chemical shifts, δ, ppm (SSCC, *J,* Hz) |
|---|---|
| **12** | 3.56 (1H, dd, *J* = 8.3, *J* = 17.1, CH); 3.60 (1H, dd, *J* = 9.3, *J* = 17.1, CH); 4.17 (1H, dd, *J* = 5.1, *J* = 10.0, CH); 4.21 (1H, dd, *J* = 4.4, *J* = 10.0, CH); 5.05-5.21 (1H, m, CH); 6.84 (1H, d, *J* = 8.8, $H_{arom.}$); 7.37 (1H, dd, *J* = 2.4, *J* = 8.8, $H_{arom.}$); 7.42-7.47 (3H, m, $H_{arom.}$); 7.68 (1H, d, *J* = 2.4, $H_{arom.}$); 7.74-7.80 (2H, m, $H_{arom.}$) |
| **13** | 3.28 (1H, dd, *J* = 7.4, *J* = 15.2, CH); 3.49 (1H, dd, *J* = 9.2, *J* = 15.2, CH); 4.01(1H, dd, *J* = 5.6, *J* = 10.1, CH); 4.16 (1H, dd, *J* = 4.2, *J* = 10.1, CH); 4.94-5.25 (1H, m, CH); 6.81 (2H, d, *J* = 8.6, $H_{arom.}$); 7.18 (2H, d, *J* = 8.6, $H_{arom.}$); 7.52 (4H, s, $H_{arom.}$) |
| **14** | 2.03 (3H, s, $CH_3$); 3.32 (1H, dd, *J* = 7.4, *J* = 16.6, CH); 3.52 (1H, dd, *J* = 9.2, *J* = 16.6, CH); 4.03 (2H, m, $CH_2$); 4.96-5.27 (1H, m, CH); 6.69 (1H, d, *J* = 8.8, $H_{arom.}$); 6.98-7.14 (2H, m, $H_{arom.}$); 7.36 (2H, d, *J* = 8.4, $H_{arom.}$); 7.61 (2H, d, *J* = 8.4, $H_{arom.}$) |
| **15** | 3.51 (1H, dd, *J* = 7.3, *J* = 17.0, CH); 3.61 (1H, dd, *J* = 10.2, *J* = 17.0, CH); 4.16 (1H, dd, *J* = 5.1, *J* = 9.9, CH); 4.22 (1H, dd, *J* = 4.2, *J* = 9.9, CH); 5.02-5.21 (1H, m, CH); 7.08 (1H, s, $H_{arom.}$); 7.45-7.47 (4H, m, $H_{arom.}$); 7.72-7.77 (2H, m, $H_{arom.}$) |
| **16** | 3.43 (1H, dd, *J* = 9.8, *J* = 16.3, CH); 3.58 (1H, dd, *J* = 10.3, *J* = 16.3, CH); 4.09 (1H, dd, *J* = 5.9, *J* = 9.9, CH); 4.21 (1H, dd, *J* = 4.8, *J* = 9.9, CH); 4.55-5.29 (1H, m, CH); 7.25 (2H, s, $H_{arom.}$); 7.52 (4H, s, $H_{arom.}$) |
| **17** | 3.32 (1H, dd, *J* = 7.2, *J* = 14.2, CH); 3.58 (1H, dd, *J* = 9.6, *J* = 14.2, CH); 4.14 (1H, dd, *J* = 5.2, *J* = 8.4, CH); 4.25 (1H, dd, *J* = 4.2, *J* = 8.4, CH); 4.98-5.29 (1H, m, CH); 6.94 (2H, d, *J* = 9.2, $H_{arom.}$); 7.32-7.45 (3H, m, $H_{arom.}$); 7.54-7.69 (2H, m, $H_{arom.}$); 8.14 (2H, d, *J* = 9.2, $H_{arom.}$) |
| **18** | 1.34 (3H, t, *J* = 7.0, $CH_3$); 3.29 (1H, dd, *J* = 7.6, *J* = 15.4, CH); 3.49 (1H, dd, *J* = 9.4, *J* = 15.4, CH); 4.07 (1H, dd, *J* = 5.8, *J* = 9.2, CH); 4.21 (1H, dd, *J* = 4.4, *J* = 9.2, CH); 4.32 (2H, q, *J* = 7.0, $CH_2$); 4.96-5.27 (1H, m, CH); 6.85 (2H, d, *J* = 8.0, $H_{arom.}$); 7.34 (2H, d, *J* = 8.4, $H_{arom.}$); 7.58 (2H, d, *J* = 8.4, $H_{arom.}$); 7.94 (2H, d, *J* = 8.0, $H_{arom.}$) |
| **19** | 3.12 (1H, dd, *J* = 7.2, *J* = 16.3, CH); 3.18 (1H, dd, *J* = 8.2, *J* = 16.8, CH); 3.43 (1H, dd, *J* = 10.3, *J* =16.3, CH); 3.49 (1H, dd, *J* = 13.5, *J* = 16.8, CH); 4.12-4.16 (2H, m, $CH_2$); 4.29-4.36 (2H, m, $CH_2$); 4.81-5.29 (2H, m, 2×CH); 6.94 (1H, d, *J* = 8.6, $H_{arom.}$); 7.32-7.40 (6H, m, $H_{arom.}$); 7.58-7.72 (6H, m, $H_{arom.}$) |

## REFERENCE


1. A. P. Kozikowski and P. D. Stein, *J. Amer. Chem. Soc.*, **104**, 4023 (1982).
2. D. P. Curran, *J. Amer. Chem. Soc.*, **105**, 5826 (1983).
3. B. H. Kim, Y. J. Chung, and E. J. Ryu, *Tetrahedron Lett.*, **34**, 8465 (1993).
4. S. H. Andersen, K. K. Sharma, and K. B. G. Torssell, *Tetrahedron*, **39**, 2241 (1983).
5. P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, and D. Simoni, *Synthesis*, 276 (1987).
6. J. W. Bode and E. M. Carreira, *Org. Lett.*, **3**, 1587 (2001).
7. A. P. Kozikowski and M. Adamczyk, *Tetrahedron Lett.*, **23**, 3123 (1982).
8. A. P. Kozikowski and Y. Y. Chen, *J. Org. Chem.*, **46**, 5248 (1981).
9. J. Müller and V. Jäger, *Tetrahedron Lett.*, **23**, 4777 (1982).
10. V. Jäger and H. Grund, *Angew. Chem. Int. Ed. Engl.*, **15**, 50 (1976).
11. S. Y. Lee, B. S. Lee, C. W. Lee, and D. Y. Oh, *J. Org. Chem.*, **65**, 256 (2000).
12. G. W. Moersch, E. L. Wittle, and W. A. Neuklis, *J. Org. Chem.*, **32**, 1387 (1967).
13. A. Yashiro, Y. Nishida, K. Kobayashi, and M. Ohno, *Synlett*, 361 (2000).
14. A. Mishra, S. K. Jain, and J. G. Asthana, *Orient. J. Chem.*, **14**, 151 (1998).
15. D. H. Ko, M. F. Maponja, M. A. Khalil, E. T. Oriaku, Z. You, and J. Lee, *J. Med. Chem. Res.*, **8**, 313 (1998).

16. Y. Y. Kang, K. J. Shin, K. H. Yoo, K. J. Seo, C. Y. Hong, C. S. Lee, S. Y. Park, D. J. Kim, and S. W. Park, *Bioorg. Med. Chem. Lett.*, **10**, 95 (2000).
17. L. H. Zhang, J. C. Chung, T. D. Kostello, J. Valvis, P. Ma, S. Kauffman, and R. Ward, *J. Org. Chem.*, **62**, 2466 (1997).
18. P. N. Confalone, F. Jin, and S. A. Mousa, *Bioorg. Med. Chem. Lett.*, **9**, 55 (1999).
19. A. A. Patchett and R. P. Nargund, *Ann. Rep. Med. Chem.*, **35**, 289 (2000).
20. R. Huisgen, *Angew. Chem.*, **75**, 604 (1963).
21. G. Grundmann, *Synthesis*, 344 (1970).
22. K. Torssell and O. Zenthen, *Acta Chem. Scand.*, **B32**, 118 (1978).
23. S. C. Sharma and K. Torssell, *Acta Chem. Scand.*, **B33**, 379 (1979).
24. Ken-ichi Itoh and C. Akira Horiuchi, *Tetrahedron*, **60**, 1671 (2004).
25. A. McKillop, J. C. Fiaud, and R. P. Hug, *Tetrahedron*, **30**, 1379 (1974).
26. V. Dirnens, O. Slyadevskaya, and E. Lukevics, *Khim. Geterotsikl. Soedin.*, 499 (2002).