STEREOSELECTIVE 1,3-DIPOLAR CYCLOADDITION OF A NITRILE YLIDE PHOTOCHEMICALLY GENERATED FROM 2,3-DIPHENYL-2*H*-AZIRINE TO SUBSTITUTED METHYLENE LACTONES

Jakub ČASTULÍK[1], Jaroslav JONAS[2] and Ctibor MAZAL[3,*]

Department of Organic Chemistry, Faculty of Science, Masaryk University, Kotlářská 2, 611 37 Brno, Czech Republic; e-mail: [1] jakub@chemi.muni.cz, [2] jonas@chemi.muni.cz, [3] mazal@chemi.muni.cz

Received March 1, 2000
Accepted April 6, 2000

Dedicated to Professor Otakar Červinka on the occasion of his 75th birthday.

The nitrile ylide photochemically generated from 2,3-diphenyl-2*H*-azirine adds to both isomers of 3-(tosyloxymethylene)tetrahydrofuran-2-one with excellent regio- and stereoselectivity giving spiroheterocyclic products in moderate yields. X-Ray structure determination showed dibutolactone to have the *E*-configuration; the corresponding *Z*-isomer was prepared photochemically.

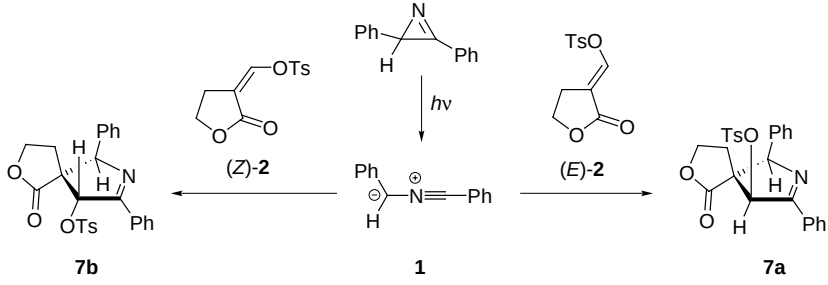
Key words: Methylene lactones; Nitrile ylide; Dipolar cycloadditions; Spiro compounds; Photoisomerizations; NMR spectroscopy; X-Ray diffraction.

Although many α-methylene lactones are well known for a wide range of their biological activities[1], their structure offers some interesting potential of further synthetic utilization, too[2]. Recently, an investigation of reactivity of methylene lactones in 1,3-dipolar cycloadditions brought several reports on additions of diazomethane[3], nitrile oxides[4] and diphenyl nitrile imine[5]. Of the features studied in these reactions, stereoselectivity and regioselectivity played, clearly, a very important role. The opening work on nitrile ylides additions to methylene lactones has been published by de March *et. al.*[6] who studied the 1,3-dipolar cycloaddition of nitrile ylides, generated *in situ* by thermal decomposition of corresponding imidoyl chlorides, to various α,β-unsaturated esters including 3-(methylidene)tetrahydrofuran-2-one. They found that it added nitrile ylides regioselectively with some extent of stereoselectivity. In this paper we report on a stereoselective and regioselective cycloaddition of the photochemically generated nitrile ylide

1 to both isomers of 3-(tosyloxymethylidene)tetrahydrofuran-2-one ((*E*)- and (*Z*)-**2**).

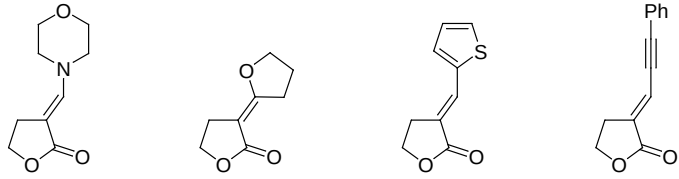
RESULTS AND DISCUSSION

Nitrile ylides have traditionally been prepared either by treatment of imidoyl halides with a base[7], or by elimination of phosphoric esters from 2,3-dihydro-1,4,2-oxazaphospholes[8], or by photolysis of aryl substituted azirines[9]. We have chosen the last mentioned method because of easy accessibility of arylazirines[10]. Thus, irradiation of 2,3-diphenyl-2*H*-azirine led to an *in situ* formation of the nitrile ylide **1** that could be trapped with a methylene lactone dipolarophile (Scheme 1). Since ylides rank among electron-rich dipoles, they prefer electron-deficient reaction partners. From our previous research[11,12], we had ready a set of methylene lactone derivatives substituted on exocyclic double bond with various substituents covering a wide range of electronic effects; some of them were chosen for investigation of their reactivity towards **1**.

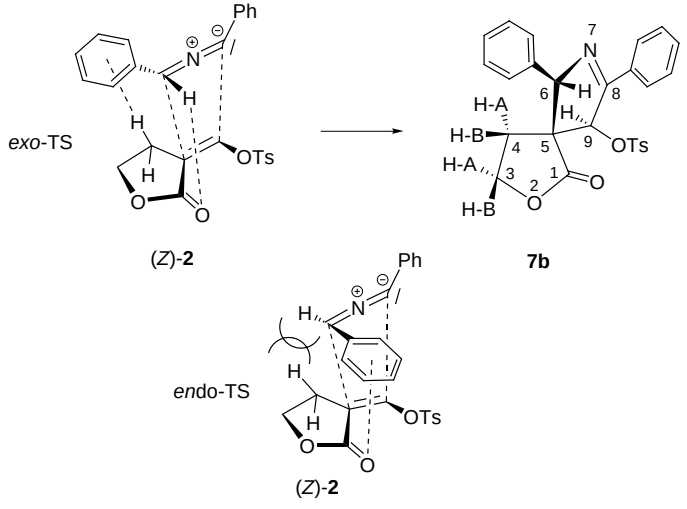


SCHEME 1

Morpholinomethylidene, tetrahydrofuran-2-ylidene, (2-thienyl)methylidene, 3-phenylpropynylidene, and tosyloxymethylene derivatives (**3**–**6** and **2**, respectively) were tried, but only the tosylates (*E*)- and (*Z*)-**2**, with the most electron-deficient double bonds, showed a satisfactory reactivity. Both isomers of **2** added nitrile ylide **1** in a regioselective fashion, in agreement



with de March's results; moreover, an excellent stereoselectivity of the dipole approach has been observed. In fact, only one diastereomer of 1-oxo-6,8-diphenyl-2-oxa-7-azaspiro[4.4]non-7-en-9-yl tosylate (**7**) has been detected in each reaction mixture by ^{1}H NMR: *E*-isomer of tosylate **2** yielded the racemate **7a** with relative configuration 5*R**,6*R**,9*R**, whereas (*Z*)-**2** gave **7b**, the (5*R**,6*R**,9*S**)-diastereomer, which differs from **7a** only in the configuration of the carbon atom bearing the tosyloxy group. This indicates a synchronous dipole addition in both the reactions preferring the *exo* approach to the double bond as depicted in Scheme 2. The corresponding transition state probably profits from attractive interactions of β-hydrogens of the lactone moiety and the phenyl ring of the dipole (C–H...π interaction), and an additional dipole–dipole interaction of the C=O double bond of the dipolarophile and the C–H bond of the nitrile ylide. The *endo* transition state is, despite attractive interactions between the ylide phenyl ring and the lactone carbonyl, disfavored by repulsion of the lactone and nitrile ylide protons. Such explanation also corresponds with de March's results[6]. In that case, the substitution of ylide phenyl ring by an electronwithdrawing nitro group increases the attractive interaction in the *endo* TS decreasing the C–H...π interaction in *exo* TS. This results in a decreased stereoselectivity with the *exo/endo* ratio 58 : 11.



SCHEME 2

2D NMR spectroscopy has been a main tool used for elucidation of the structure of **7**. Regioselectivity of the cycloaddition resulted in the formation of the regioisomer with protons in positions 2 and 4 of 3,4-dihydro-

2*H*-pyrrole ring of **7**. The other regioisomer would display a significant vicinal coupling interaction[6]. The configurations of the diastereomers were determined from NOESY experiments. In **7a**, a NOE was found between the aromatic *ortho* protons of the phenyl group in position 6, and H-3 and H-4 of the lactone ring. Also, there was no significant interaction of the latter protons with H-6, and only a weak interaction with H-4B. Similarly, H-9, located in **7a** on the same side of the ring as H-6, interacts with H-4A. The interactions of those two protons are substantially different in the diastereomer **7b**. Whereas H-6 gives almost the same picture, H-9 interacts with H-4 as well as with H-3A. The atom numbering and lettering of **7** are shown in Scheme 2.

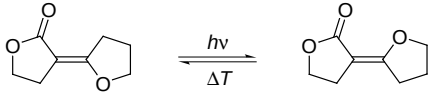
There are also further features in the NMR spectra that support the configuration assignment. The long range coupling of protons H-6 and H-9 is observable only in **7a**, where the four bonds mediating the coupling have a "W" configuration, which facilitates the coupling ($^4J_{H,H}$ = 1.7 Hz). Identification of signals of the lactone ring protons was more complicated. The methylene in position 4, which in **7b** appears as only one multiplet, is splitted, in **7a**, into two distinct multiplets. A NOESY experiment showed that the proton H-4B remained at 1.8 ppm, whereas H-4A was shifted downfield to 2.5 ppm. NOESY helped also in the assignment of signals of the protons in position 3, especially in **7b**, where NOE was detected between H-3A and H-9. No such interaction was present in **7a**. Our assignment is, therefore, based only on a weak NOE with *ortho* protons of the phenyl in position 6. The reason for the relatively large differences in chemical shifts of the lactone ring protons most probably lies in different conformation of the spiro system which changes locations of aromatic substituents effecting thus a local magnetic field as a result of magnetic anisotropy of these substituents.

In contrast to the excellent regio- and stereoselectivity, a somewhat weak point of the cycloaddition reaction was its 50% conversion. Neither increasing excess of the starting tosylate, nor longer irradiation, nor solvent change (benzene, acetonitrile) did improve it. The unreacted tosylates could be isolated from the reaction mixtures. The reaction is irreversible as proven by irradiation and/or heating the product **7a** in benzene. Apparently, more detailed investigation would be required to find the reason for such relatively low conversion.

It is also worth mentioning that in unsuccessful cycloaddition experiments, *E–Z* isomerizations of starting lactone dipolarophiles were observed. An exception was the enamine **3** which decomposed, but about 15% of (*Z*)-3-[(2-thienyl)methylidene]tetrahydrofuran-2-one[11b] ((*Z*)-**5**) was, for in-

stance, detected after 12 h irradiation of the corresponding (*E*)-isomer in the reaction mixture with 2,3-diphenyl-2*H*-azirine. We also observed isomerization of dibutolactone **4** and thus had an opportunity to study, to the best of our knowledge for the first time, both isomers of this compound. Therefore, we scaled up the isomerization in a separate reaction isolating and characterizing both isomers of **4**. In this connection, we realized that the configuration assignment in the literature[13a] failed to hit the target. A comparison of physicochemical data of **4** prepared by different procedures and taken now for (*Z*)-**4** (refs[13a–13d]) now for (*E*)-**4** (refs[13e–13i]) showed that always the same isomer has been dealt with, namely (*E*)-**4**. This was proved by X-ray structure analysis of a sample prepared according to Spencer[13g] (*cf.* Fig. 1 and Table I). It was also found that (*Z*)-**4** isomerizes thermally to (*E*)-**4** at 30 °C with a half-time $t_{1/2} \approx 230$ h. Acid impurities facilitate the isomerization.

Interconversions of the dibutolactone isomers are illustrated in Scheme 3. ^{1}H NMR spectra of (*E*)- and (*Z*)-**4** were assigned by 2D experiments (COSY).



(*E*)-**4** (*Z*)-**4**

SCHEME 3

Most significant is the difference in chemical shifts of methylene protons in position 8 (for numbering, see Fig. 1), which in (*E*)-**4** are shifted to the lower field by 0.4 ppm.

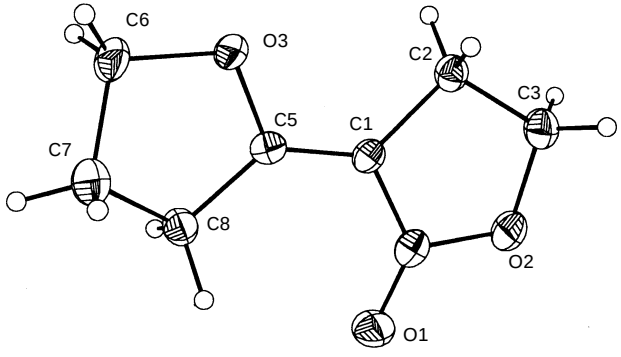


FIG. 1
ORTEP representation of compound (*E*)-**4**

In conclusion, the first photochemically initiated cycloaddition of a nitrile ylide on methylene lactone derivatives has been reported which displayed an excellent regio- and stereoselectivity giving spiroheterocyclic products in moderate yields. Additionally, configuration of dibutolactone **4** was unambiguously determined by X-ray analysis and its as yet unknown isomer was prepared.

EXPERIMENTAL

Melting points were obtained on a Kofler block and are uncorrected. ^{1}H and ^{13}C NMR spectra (δ, ppm; *J*, Hz) were obtained on an Avance Bruker DRX 500 spectrometer (500 MHz) in deuteriochloroform with tetramethylsilane as internal standard. Ultraviolet spectra were recorded on a UV-VIS spectrophotometer UV-101 Shimadzu. IR spectra (wavenumbers in cm^{-1}) were measured in KBr pellets on a Genesis series FTIR, ATI Matson spectrometer. Elemental analyses were performed by analytical laboratory of Lachema Brno. Literature procedures were used for preparations of (*E*)- and (*Z*)-3-[(tosyloxy)methylidene]tetrahydrofuran-2-ones[12] (**2**), 2,3-diphenyl-2*H*-azirine[10b], and (*E*)-2,3′-bi(tetrahydrofuranylidene)-2′-one[13g] (**4**). A medium presure mercury lamp (125 W, Teslamp) with Simax glass filter and argon atmosphere were used in photochemical experiments. Dibutolactone photoisomerization was carried out in a quartz immersion reactor using the same lamp.

Photoinduced Cycloaddition of 2,3-Diphenyl-2*H*-azirine to Tosylates **2**. General Procedure

A mixture of tosylate **2** (100 mg, 0.3 mmol) and diphenylazirine (144 mg, 0.6 mmol) in benzene (100 ml) was irradiated for 2 h. A solid residue after evaporation of the solvent was shaken with pre-cooled diethyl ether giving a crystalline residue of tosylate **2** and the product **7** only. This was isolated by suction and separated by column chromatography on silica gel (CCl_4–diethyl ether 1 : 1 for the reaction of (*E*)-**2** and $CHCl_3$ for (*Z*)-**2**). The crude product **7** was recrystallized from ethanol. The reaction of (*E*)-**2** gave product **7a**, whereas (*Z*)-**2** gave **7b**.

(5R,6R*,9R*)-1-Oxo-6,8-diphenyl-2-oxa-7-azaspiro[4.4]non-7-en-9-yl tosylate* (**7a**): 64 mg (50%); m.p. 119–120 °C. ^{1}H NMR: 7.86 d, 2 H, *J* = 8.4 (H-Ar); 7.54 d, 2 H, *J* = 7.3 (H-Ar); 7.40 m, 6 H (H-Ar); 7.32 m, 4 H (H-Ar); 6.19 s, 1 H (H-4′); 5.42 s, 1 H (H-2′); 4.09 m, 1 H (H-5A); 3.37 m, 1 H (H-5B); 2.53 m, 1 H (H-4A); 2.49 s, 3 H (CH_3); 1.81 m, 1 H (H-4B). ^{13}C NMR: 179.0 (2), 169.1 (5′), 146.2, 136.9, 131.8, 131.4, 131.2, 130.2, 128.8, 128.7, 128.6, 128.4, 128.1, 127.5, 86.7 (2′), 78.7 (4′), 66.5 (5), 59.5 (3), 24.0 (4), 21.7 (CH_3). IR: 2 975, 2 917, 2 877, 1 763, 1 631, 1 370, 1 189, 1 019, 1 033, 836, 763, 698, 672, 554. UV: 251.2, 232.8 nm. For $C_{26}H_{23}NO_5S$ (461.5) calculated: 67.7% C, 5.0% H, 3.0% N; found: 67.5% C, 4.9% H, 3.1% N.

(5R,6R*,9S*)-1-Oxo-6,8-diphenyl-2-oxa-7-azaspiro[4.4]non-7-en-9-yl tosylate* (**7b**): 68 mg (52%); m.p. 146–147 °C. ^{1}H NMR: 8.05 d, 2 H, *J* = 7.3 (H-Ar); 7.83 d, 2 H, *J* = 8.4 (H-Ar); 7.52 m, 1 H (H-Ar); 7.44 m, 2 H (H-Ar); 7.37 m, 2 H (H-Ar); 7.33 m, 3 H (H-Ar); 7.24 d, 2 H, *J* = 6.9 (H-Ar); 6.11 s, 1 H (H-4′); 5.96 s, 1 H (H-2′); 4.44 m, 1 H (H-5A); 4.16 m, 1 H (H-5B); 2.49 s, 3 H (CH_3); 1.82 m, 2 H (H-3). ^{13}C NMR: 174.6 (2), 166.5 (5′), 145.7, 137.5, 132.3, 131.7, 131.1, 129.8, 128.9, 128.8, 128.5, 128.4, 128.1, 127.2, 84.2 (4′), 78.7 (2′), 65.5 (5), 57.1 (3), 29.8 (4), 21.7 (CH_3). IR: 2 997, 2 924, 2 877, 1 772, 1 620, 1 369, 1 179, 1 026, 942,

843,762, 699, 676. UV: 254.4, 237.8 nm. For $C_{26}H_{23}NO_5S$ (461.5) calculated: 67.7% C, 5.0% H, 3.0% N; found: 67.3% C, 5.1% H, 3.2% N.

(*E*)-2,3′-Bi(tetrahydrofuranylidene)-2′-one ((*E*)-**4**)

Samples of **4** prepared according to refs[13a,13g] were found to be identical. ^{1}H NMR ($CDCl_3$): 4.262 t, *J* = 7.7, 2 H (H-3); 4.260 t, *J* = 7.0, 2 H (H-6); 3.06 tt, *J* = 7.7, 2.4, 2 H (H-8); 2.84 tt, *J* = 7.7, 2.4, 2 H (H-2); 2.09 quasiquint., 2 H (H-7). ^{1}H NMR (C_6D_6): 3.73 t, 2 H, *J* = 7.7 (H-3); 3.53 t, 2 H, *J* = 7.0 (H-6); 2.89 tt, 2 H, *J* = 7.7, 2.4 (H-8); 2.48 tt, 2 H, *J* = 7.7, 2.4 (H-2); 1.27 quasiquint., 2 H (H-7). ^{13}C NMR ($CDCl_3$): 173.1 (C-4), 169.4 (C-5), 93.1 (C-1), 72.4 (C-6), 65.2 (C-3), 28.9 (C-8), 25.1 (C-2), 24.1 (C-7). ^{13}C NMR (C_6D_6): 172.2 (C-4), 168.5 (C-5), 93.7 (C-1), 71.8 (C-6), 64.6 (C-3), 28.9 (C-8), 25.4 (C-2), 24.0 (C-7). X-Ray data obtained with a single crystal from diethyl ether are presented in Table I and Fig. 1.

X-Ray Structural Analysis

Crystals of (*E*)-**4** suitable for X-ray analysis were obtained by careful recrystallization from diethyl ether. Experimental data were collected with a KUMA KM-4 kappa-axis four-circle diffractometer with graphite-monochromatized radiation. The data were corrected for Lp factor but no absorption correction was applied. The structure was solved by a direct method in a straightforward manner. The H atoms were placed in calculated positions with the temperature factors $1.2U_{eq}$ of the parent atoms and refined by using a "ride-on" model. The structure was solved and refined using the SHELX97 program[14] system and the drawing (Fig. 1) was prepared by ORTEP (ref.[15]). Crystal data and other details concerning the data collection are summarized in Table I. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-142958. Copies of the data can be obtained free of charge on application to CCDC, e-mail: deposit@ccdc.cam.ac.uk.

E–*Z* Photoisomerization of **4** and Isolation of *Z*-Isomer

A solution of (*E*)-**4** (500 mg, 3.25 mmol) in dry dichloromethane (100 ml) was irradiated with a UV lamp. Photostationary state was reached in 3 h and the reaction mixture composition, as determined by ^{1}H NMR, was (*E*)-**4**/(*Z*)-**4** 3 : 2. After evaporation of the solvent, the residue was dissolved in chloroform (5 ml) and chromatographed on silica gel (ethyl acetate–chloroform 1 : 9) yielding, besides 300 mg of (*E*)-**4** (eluted first), 200 mg of (*Z*)-**4** as a white waxy solid. (*Z*)-**4**: For $C_8H_{10}O_3$ (154.2) calculated: 62.33% C, 6.54% H; found: 62.27% C, 6.62% H. ^{1}H NMR ($CDCl_3$): 4.46 t, 2 H, *J* = 7.0 (H-6); 4.30 t, 2 H, *J* = 7.7 (H-3); 2.83 tt, 2 H, *J* = 7.7, 1.6 (H-8); 2.66 tt, *J* = 7.7, 1.6, 2 H (H-2); 2.13 quasiquint., 2 H (H-7). ^{13}C NMR ($CDCl_3$): 169.9 (C-4), 166.9 (C-5), 92.2 (C-1), 74.5 (C-6), 65.1 (C-3), 31.4 (C-8), 26.6 (C-2), 23.2 (C-7). Attempts to prepare a single crystal of (*Z*)-**4** suitable for X-ray analysis failed.

Thermal Isomerization of (*Z*)-**4**

A solution of (*Z*)-**4** in deuteriochloroform was kept at 303 K in a sealed NMR tube and analyzed by NMR in regular intervals. At this temperature (*Z*)-**4** isomerized into (*E*)-**4** with a half-life of approximately 230 h and, after two months, could not be detected any longer.

TABLE I
Crystallographic parameters, data collection and refinement for (*E*)-**4**

Empirical formula	$C_8H_{10}O_3$
Formula weight	154.16
Temperature, K	150(2)
Wavelength, Å	0.71073
Crystal system; space group	monoclinic; *Pc*
Unit cell dimensions:	
a, Å	9.054(5)
b, Å	4.674(3)
c, Å	9.528(6)
α, °	90
β, °	115.88(5)
γ, °	90
Volume, Å^3; *Z*	362.8(4); 2
Calculated density, g cm^{-3}	1.411
Absorption coefficient, mm^{-1}	0.108
F(000)	164
Crystal size, mm	0.35 × 0.25 × 0.20
θ range for data collection, °	2.50 to 28.68
Range of *hkl*	–11→10, –6→6, 0→11
Reflections collected	1 599
Independent reflections	853 (R_{int} = 0.0426)
Max. and min. transmission	0.9787 and 0.9632
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	853/2/100
Goodness-of-fit on F^2	1.061
Final *R* indices [$I > 2\sigma(I)$]	*R*1 = 0.0322, *wR*2 = 0.0794
R indices (all data)	*R*1 = 0.0481, *wR*2 = 0.0852
Absolute structure parameter	0.1(13)
Largest difference peak and hole, e Å^{-3}	0.233 and –0.177

We thank Prof. Z. Žák and Dr O. Humpa for X-ray and NMR measurements, respectively. This work was supported by grant-in-aid (No. 391/99) from the Fund of the Development of Universities.

REFERENCES

1. Kupchan S. M., Eakin M. A., Thomas A. M.: *J. Med. Chem.* **1971**, *14*, 1147.
2. Lee J., Sharma R., Wang S.: *J. Med. Chem.* **1996**, *39*, 36.
3. Jonas J., Głowiak T., Žák Z., Trška P., Mazal C.: *Collect. Czech. Chem. Commun.* **1991**, *56*, 973.
4. a) Štverková S., Žák Z., Jonas J.: *Liebigs Ann. Chem.* **1993**, 1169; b) Micuch P., Fišera L., Ondruš V., Ertl P.: *Molecules* **1997**, *2*, 57; c) Alonso-Perarnau D., de March P., el Arrad M., Figueredo M., Font J., Parella T.: *Tetrahedron* **1997**, *53*, 14763; d) de March P., Figueredo M., Font J.: *Heterocycles* **1999**, *50*, 1213.
5. Štverková S., Žák Z., Jonas J.: *Liebigs Ann. Chem.* **1995**, 497.
6. de March P., el Arrad M., Figueredo M., Font J.: *Tetrahedron* **1998**, *54*, 11613.
7. Huisgen R., Stangle H., Sturm H. J., Wagenhofer H.: *Angew. Chem.* **1962**, *74*, 31.
8. Burger K., Fehn J.: *Chem. Ber.* **1972**, *105*, 3814.
9. Padwa A., Dharan M., Smolanoff J., Wetmore S. I.: *J. Am. Chem. Soc.* **1973**, *98*, 1945.
10. a) Perocheau J., Danion-Bougot R., Carrie R.: *Bull. Soc. Chim. Fr.* **1994**, 973; b) Fowler F. W., Hassner A., Levy L. A.: *J. Am. Chem. Soc.* **1967**, *89*, 2077.
11. a) Mazal C., Jurka Z., Jonas J.: *Collect. Czech. Chem. Commun.* **1984**, *49*, 2509; b) Častulík J., Mazal C.: *Tetrahedron Lett.*, in press.
12. Jonas J.: *Collect. Czech. Chem. Commun.* **1984**, *49*, 1907.
13. a) Minami T., Matsumoto M., Suganuma H., Agawa T.: *J. Org. Chem.* **1978**, *43*, 2149; b) Dědek V., Trška P.: *Collect. Czech. Chem. Commun.* **1970**, *35*, 651; c) Lipkin M. A., Markevich V. S., Kirsanov A. T., Yurkevich A. M.: *Khim. Farm. Zh.* **1988**, *22*, 1465; *Pharm. Chem. J. (Engl. Transl.)* **1988**, *22*, 911; d) Bukowska M., Prejzner J.: *Pol. J. Chem.* **1986**, *60*, 957; e) Dale J., Schwartz J.-E.: Acta Chem. Scand., Ser. B **1986**, 40, 559; f) Casy G., Furber M., Richardson K. A., Stephenson R. G., Taylor R. J. K.: *Tetrahedron* **1986**, 5849; g) Spencer E. Y., Wright G. F.: *J. Am. Chem. Soc.* **1941**, *63*, 1281; h) Stepanov F. N., Smirnov O. K.: *Zh. Obshch. Khim.* **1957**, *27*, 1042 (Engl. Transl. p. 1124); i) Kochetkov N. K., Likhosherstvov A. M., Budovskii E. I.: *Zh. Obshch. Khim.* **1960**, *30*, 2077 (Engl. Transl. p. 2058).
14. Sheldrick G. M.: *SHELX97, Program for Structure Solution and Refinement*. University of Göttingen, Göttingen 1997.
15. Johnson C. K.: *ORTEP*. Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee 1965.