

# Unexpected Formation of Bisadducts in 1,3-Dipolar Cycloadditions to 7-(R<sup>1</sup>,R<sup>2</sup>-Methylene)bicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylates

<sup>a</sup>V. ONDRUŠ, <sup>a</sup>L. FIŠERA\*, <sup>b</sup>N. PRÓNAYOVÁ, and <sup>c</sup>P. ERTL

<sup>a</sup>Department of Organic Chemistry, Faculty of Chemical Technology, Slovak Technical University, SK-812 37 Bratislava

<sup>b</sup>Central Laboratory of Chemical Techniques, Faculty of Chemical Technology, Slovak Technical University, SK-812 37 Bratislava

<sup>c</sup>Institute of Chemistry, Comenius University, SK-842 15 Bratislava

Received 7 July 1993

Dedicated to Professor Ing. P. Kristián, DrSc., in honour of his 65th birthday

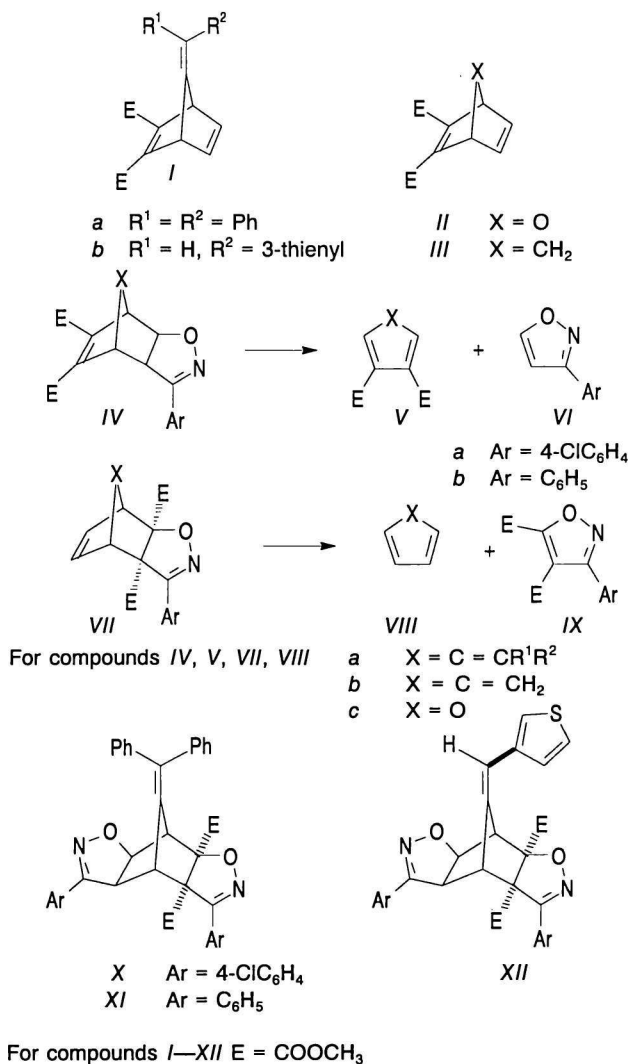
The cycloaddition of aryl nitrile oxides to dimethyl 7-(R<sup>1</sup>,R<sup>2</sup>-methylene)bicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylates proceeds under the formation of bisadducts and retroproducts. The other expected retroproducts were not formed. Semiempirical quantum-mechanical methods AM1 were used to rationalize this formation of bisadducts. The results are confronted with the site selectivity of 7-oxabicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylate and dimethyl derivative of the title compound.

Recently we have found that the selectivity of the condensed isoxazolines possessing a methylene bridge to enamino aldehydes [1] is due to a stabilization of the biradical by the overlap of the radical electron with  $\pi$ -electrons of the bridge C=C double bond. With our effort to investigate the influence of substituent in 7-methylene position on the photorearrangement we have paid our attention to the preparation of dimethyl 7-(R<sup>1</sup>,R<sup>2</sup>-methylene)bicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylates *I* and their behaviour in the cycloaddition with nitrile oxides. In this paper, we describe in detail the site- and stereoselectivity of the 1,3-dipolar cycloaddition of methylenebicyclo derivatives *I* with aryl nitrile oxides, together with AM1 calculations.

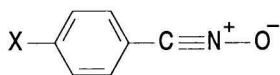
The dimethyl 7-(R<sup>1</sup>,R<sup>2</sup>-methylene)bicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylates *Ia*, *Ib* were prepared from the corresponding fulvenes and dimethyl ester of acetylenedicarboxylic acid. Although, the Diels—Alder reactions of fulvenes are known [2, 3] and some 7-substituted bicyclo[2,2,1]hept-2,5-dienes are precursors for the preparation of  $\beta$ -substituted fulvenes [4, 5], the synthesis of *Ia*, *Ib* has not been published yet.

1,3-Dipolar cycloaddition of 4-chlorobenzenitrile oxide with *Ia* gave bisadduct *X* (21 %) as well as dimethyl 6,6-diphenylfulvene-2,3-dicarboxylate (*V*, 21 %) and 3-(4-chlorophenyl)isoxazole (*VIa*, 15 %), both originating from the cycloaddition product *IV*. The cycloaddition of benzenitrile oxide to *Ia* proceeds fully analogously giving bisadduct *XI* (18 %), 3-phenylisoxazole (*VIb*, 18 %), and fulvene *V* (21 %).

\*The author to whom the correspondence should be addressed.



The products *VIII* and *IX*, originating from the cycloaddition product *VII* have not been detected in the crude reaction mixture by NMR spectroscopy.



In our previous work [6] we have found that benzenenitrile oxide reacted with dimethyl 7-isopropylidenebicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylate (*I*,  $R^1 = R^2 = \text{CH}_3$ ) under formation of primary cycloadducts of the type *IV*, which underwent subsequent aromatization to 3-phenylisoxazole (*Vib*). Cristina *et al.* [7] found the ratio of products *Vla* to *IXa*  $x_r = 90 : 10$  in favour of *Vla* in the case of the cycloaddition to norbornadiene *III* ( $X = \text{CH}_2$ ). Nitrile oxide cycloadditions to 7-oxabicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylate (*II*) showed similar site selectivity [7, 8]. Benzenenitrile oxides attack preferentially electron-deficient double bond of *II* and the intermediate cycloadducts *IVc* and *VIIc* undergo the Diels–Alder cycloreversion to form the derivatives *Vc*, *VI*, *VIIIc*, and *IX*. Although all aforementioned cycloadditions [6–8] were carried out in a mole ratio, formation of any bisadduct has not been observed.

The assignment of the structure of *X* to the bisadduct possessing *exo-syn-exo* configuration was made on the basis of spectroscopic data, in particular using NOE experiments. The prefixes *exo* showed a relationship between isoxazoline moiety and methylene bridge; the second prefix *syn* a relationship between two isoxazoline oxygen atoms. The EI mass spectrum of *X* showed molecular ion peak at  $m/z = 680$  and  $^{13}\text{C}$  NMR spectrum the presence of singlets at  $\delta = 97.45$  and  $71.53$ , for C-2 and C-6 carbon atoms, which revealed the 1,3-dipolar cycloaddition to both double bonds of *Ia*. NMR spectrum of *X* is uniquely diagnostic for the *exo-syn-exo* arrangement, e.g. irradiation of H-8 caused NOE's for H-7 (5.3 %), H-12 (15.6 %), and  $\text{CH}_3$  at C-6 position. Irradiation of H-12 results in signal enhancement of H-1 (6.8 %). The assignment of the structure of *XI* to *exo-syn-exo* was elucidated analogously.

By the cycloaddition of BNO to dimethyl 7-(3-thienylmethylene)bicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylate (*Ib*) the bisadduct *XII* has been obtained possessing the same *exo-syn-exo* configuration. The *anti* assignment between isoxazoline oxygens and thiophene ring was made on the basis of the SINEPT-DQ method, mainly owing to that the irradiation of H-7 caused the change of the following interaction constants  $J_{\text{H-7,C-8}} = 3.0$  Hz,  $J_{\text{H-7,C-6}} = 1.4$  Hz, and  $J_{\text{H-7,C-2}} = 5.0$  Hz.

In order to rationalize the above cycloadditions, we have carried out quantum-mechanical calculations. Inspection of energy levels of benzenenitrile oxide

(BNO) as well as *II* and 7-methylenebicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylate (*III*,  $X = \text{CH}_2$ ) calculated by the AM1 method [9] shows that the cycloaddition is governed by the  $\text{LUMO}_{\text{DIPOLE}}$  ( $\text{HOMO}_{\text{III}} = -10.03$  eV,  $\text{HOMO}_{\text{II}} = -10.42$  eV, and  $\text{LUMO}_{\text{BNO}} = -0.51$  eV). The HOMO orbitals of *II* and *III* are shown in Figs. 1 and 2. In both cases the orbital is localized on both double bonds, therefore the 1,3-dipole

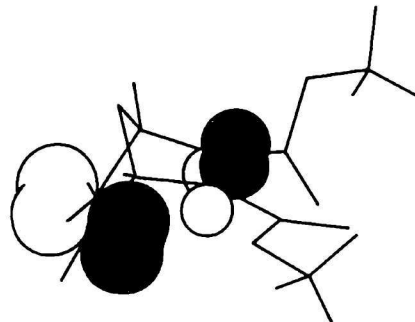


Fig. 1. HOMO *II*.

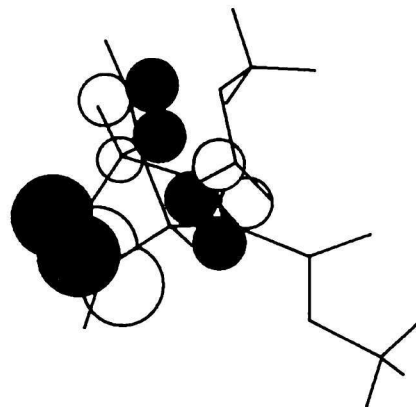


Fig. 2. HOMO *III*.

can attack unsubstituted as well as deactivated double bond in *II* and *III*. In the HOMO of both dipolarophiles the carbons of unsubstituted double bond have large orbital coefficients (0.53 vs. 0.31 for *III*; 0.57 vs. 0.34 for *II*). In contrast to oxygen in *II*, the HOMO in *III* is localized also at the methylene bridge (Fig. 1), since the exocyclic double bond mixes its  $\pi$  orbitals with both substituted and unsubstituted double bond in *III*. In addition, this overlap in *I* can favour the exclusive *exo* attack of the dipole related to the methylene bridge through the secondary orbital interactions between  $\text{LUMO}_{\text{DIPOLE}}$  and  $\text{HOMO}_0$ .

We tried to elucidate the unexpected formation of bisadducts through the relative thermodynamic stability of the possible products *IV–IX*, mainly from the stability of primarily formed cycloadducts *IV* and *VII* to the Diels–Alder cycloreversion. The geometries of all compounds *IV–IX* were fully optimized by the AM1 method. The thermodynamic stabilities of the components in the Diels–Alder cycloreversion are listed below.

**Relative Stabilities/(kJ mol<sup>-1</sup>) of IV—IX Calculated by AM1**

<i>IVb</i> - 194.9	<i>VIIb</i> 286.7	<i>VIIIb</i> 261.9
<i>IVc</i> - 406.8	<i>VIIc</i> - 124.2	<i>VIIIc</i> 12.4
<i>Vb</i> - 415.3	<i>VIIc</i> - 337.0	<i>IXb</i> - 83.6
<i>Vc</i> - 661.9		

The total energy differences/(kJ mol<sup>-1</sup>) of Diels—Alder cycloreversions are expressed in the following manner:

<i>IVb</i> → <i>Vb</i> + <i>VIIb</i> 66.3	<i>VIIb</i> → <i>VIIIb</i> + <i>IXb</i> 36.7
<i>IVc</i> → <i>Vc</i> + <i>VIIc</i> 31.6	<i>VIIc</i> → <i>VIIIc</i> + <i>IXb</i> - 0.1

AM1 calculations showed the cycloadducts formed by the attack of the BNO on the double bond substituted with methoxycarbonyl groups *VIIb*, *VIIc* to be less stable than the other isomers *IVb*, *IVc*. On the other hand, the presence of oxygen atom in the bridge significantly decreases the stability of the products *IVc* and *VIIc* in comparison to the products *IVb* and *VIIb* possessing a methylene bridge. AM1 calculations of compounds *IVb*, *IVc* and *VIIb*, *VIIc* reveal that the cycloadduct *IVb* is more stable than the three other cycloadducts. Thus, greater thermodynamic stability of *IVb* can explain the formation of bisadducts *X—XII*. The absence of products *VIII* and *IX* suggests that the cycloaddition of nitrile oxides to *I* proceeds only to the unsubstituted double bond, which is in accord with AM1 calculations of atomic orbital coefficients in *III*. Thus, AM1 results are in a very good agreement with experimental results.

**EXPERIMENTAL**

Melting points are uncorrected, the <sup>1</sup>H and <sup>13</sup>C NMR spectra of deuteriochloroform solutions were measured with Varian VXR 300 instrument, tetramethylsilane being the internal reference. Mass spectra were recorded at 70 eV on an AEI MS 902 spectrometer equipped with direct inlet system. All reagents were purified and dried if necessary prior to use. TLC analyses were carried out with Lachema UV<sub>254</sub> silica gel plates.

The corresponding fulvenes were prepared according to Refs. [10, 11].

**Dimethyl 7-(R<sup>1</sup>,R<sup>2</sup>-Methylene)bicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylate (*I*)**

The substituted fulvene was added to a stirred solution of dimethyl acetylenedicarboxylate (50 mmol) in chloroform (100 cm<sup>3</sup>). The reaction mixture was stirred at room temperature for 5—7 d. Chloro-

form was removed from the mixture under reduced pressure, and the remaining crude residue was separated on a silica gel column by using chloroform as the solvent. The obtained product was crystallized from diethyl ether.

*Dimethyl 7-(diphenylmethylene)bicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylate (Ia)*, yield = 44 %, m.p. = 144—146 °C. For C<sub>24</sub>H<sub>20</sub>O<sub>4</sub> (*M<sub>r</sub>* = 372.40) *w<sub>i</sub>*(calc.): 77.40 % C, 5.41 % H; *w<sub>i</sub>*(found): 77.65 % C, 5.36 % H. <sup>1</sup>H NMR spectrum, δ: 7.24—7.31 (m, 6H, H<sub>arom</sub>), 7.11 (m, 2H, H-5 and H-6), 7.08 (m, 4H, H<sub>arom</sub>), 4.92 (m, 2H, H-1 and H-4), 3.81 (s, 6H, 2 × COOCH<sub>3</sub>). <sup>13</sup>C NMR spectrum, δ: 164.16 (s, C=O), 163.78 (s, C=O), 151.21, 142.29, 139.19, 130.01, 129.69, 128.13, 128.09, 127.21, 126.86, 112.91 (C<sub>arom</sub> and C<sub>vinyl</sub>), 54.71 (d, C-1 and C-4), 52.19 (q, CH<sub>3</sub>).

*Dimethyl 7-(3-thienylmethylene)bicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylate (Ib)*, yield = 40 %, oil. For C<sub>16</sub>H<sub>14</sub>O<sub>4</sub>S (*M<sub>r</sub>* = 302.33) *w<sub>i</sub>*(calc.): 63.55 % C, 4.66 % H; *w<sub>i</sub>*(found): 63.71 % C, 4.87 % H. <sup>1</sup>H NMR spectrum, δ: 7.03—7.25 (m, 5H, H<sub>thiophene</sub>, H-5 and H-6), 5.38 (s, 1H, H-8), 4.75 (m, 1H, H-1), 4.05 (m, 1H, H-4), 3.83 (s, 6H, 2 × COOCH<sub>3</sub>).

**1,3-Dipolar Cycloaddition — General Procedure**

Triethylamine (13 mmol) in ether (30 cm<sup>3</sup>) was added to a stirred solution of arylhydroximoyl chloride (10 mmol) and the dipolarophile (10 mmol) in ether at 0—5 °C within 1 h. The reaction mixture was stirred overnight at room temperature, the separated triethylammonium chloride was filtered off, removed by dissolving in water and organic material was evaporated under diminished pressure, dried, and separated by chromatography on a silica gel column and purified by crystallization.

Cycloaddition of 4-chlorobenzenenitrile oxide to *Ia* afforded:

*Bisadduct X*, yield = 21 %, m.p. = 249—252 °C. For C<sub>38</sub>H<sub>28</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>6</sub> (*M<sub>r</sub>* = 679.52) *w<sub>i</sub>*(calc.): 67.17 % C, 4.15 % H, 4.12 % N; *w<sub>i</sub>*(found): 66.98 % C, 4.24 % H, 4.32 % N. <sup>1</sup>H NMR spectrum, δ: 7.00—7.31 (m, 18H, H<sub>arom</sub>), 5.84 (d, *J*<sub>8,12</sub> = 8.4 Hz, 1H, H-12), 4.08 (d, 1H, H-8), 3.94 (s, 3H, COOCH<sub>3</sub>-2), 3.72 (s, 1H, H-1), 3.67 (s, 3H, COOCH<sub>3</sub>-6), 3.41 (s, 1H, H-7). <sup>13</sup>C NMR spectrum, δ: 168.01 (s, C=O), 167.02 (s, C=O), 141.23, 139.26, 139.15, 136.48, 135.91, 133.63, 128.81, 128.79, 128.64, 128.61, 127.79, 127.77, 127.71, 127.67, 127.26, 126.63, 125.47 (C<sub>arom</sub> and C<sub>vinyl</sub>), 97.45 (s, C-2), 82.04 (d, C-12), 71.53 (s, C-6), 53.52 (d, C-8), 53.07 (d, C-1), 52.89, 51.39 (q, q, 2 × CH<sub>3</sub>), 49.90 (d, C-7). Mass spectrum, *m/z*: 680 (M<sup>+</sup>).

3-(4-Chlorophenyl)isoxazole (VI), yield = 15 %, oil, Ref. [12] oil.  $^1\text{H}$  NMR spectrum,  $\delta$ : 8.47 (d, 1H, H-5), 7.45—7.70 (m, 4H,  $\text{H}_{\text{arom}}$ ), 6.64 (d, 1H, H-4).

Cycloaddition of benzenenitrile oxide to *la* afforded:

*Bisadduct XI*, yield = 18 %, m.p. = 248—250 °C. For  $\text{C}_{38}\text{H}_{30}\text{N}_2\text{O}_6$  ( $M_r = 609.36$ )  $w_i(\text{calc.})$ : 74.74 % C, 4.95 % H, 4.59 % N;  $w_i(\text{found})$ : 75.07 % C, 5.08 % H, 4.76 % N.  $^1\text{H}$  NMR spectrum,  $\delta$ : 6.90—7.42 (m, 20H,  $\text{H}_{\text{arom}}$ ), 5.88 (d,  $J_{8,12} = 8.5$  Hz, 1H, H-12), 4.12 (d, 1H, H-8), 3.95 (s, 3H,  $\text{COOCH}_3$ -2), 3.76 (s, 1H, H-1), 3.63 (s, 3H,  $\text{COOCH}_3$ -6), 3.42 (s, 1H, H-7).  $^{13}\text{C}$  NMR spectrum,  $\delta$ : 168.62 (s, C=O), 167.62 (s, C=O), 141.23, 139.62, 139.13, 137.03, 136.91, 135.34, 133.34, 128.92, 128.90, 128.75, 128.64, 127.77, 127.71, 127.65, 127.31, 126.64, 125.47, 124.89 ( $\text{C}_{\text{arom}}$  and  $\text{C}_{\text{vinyl}}$ ), 95.51 (s, C-2), 82.22 (d, C-12), 71.64 (s, C-6), 53.40 (d, C-8), 53.00 (d, C-1), 52.74, 51.71 (q, q,  $2 \times \text{CH}_3$ ), 48.99 (d, C-7). Mass spectrum,  $m/z$ : 610 ( $\text{M}^{+}$ ) (35).

3-Phenylisoxazole (VI), yield = 18 %, visc. oil, Ref. [13] oil.  $^1\text{H}$  NMR spectrum,  $\delta$ : 8.45 (d, 1H, H-5), 7.45—7.81 (m, 4H,  $\text{H}_{\text{arom}}$ ), 6.65 (d, 1H, H-4).

*Dimethyl 6,6-diphenylfulvene-2,3-dicarboxylate (V)*, yield = 21 %, m.p. = 164—166 °C. For  $\text{C}_{22}\text{H}_{30}\text{O}_4$  ( $M_r = 346.36$ )  $w_i(\text{calc.})$ : 76.68 % C, 5.24 % H;  $w_i(\text{found})$ : 76.43 % C, 5.32 % H.  $^1\text{H}$  NMR spectrum,  $\delta$ : 7.26—7.43 (m, 10H,  $\text{H}_{\text{arom}}$ ), 6.91 (s, 2H, H-1 and H-4), 3.85 (s, 6H,  $2 \times \text{COOCH}_3$ ).

Cycloaddition of benzenenitrile oxide to *lb* afforded:

*Bisadduct XII*, yield = 25 %, m.p. = 249—252 °C. For  $\text{C}_{30}\text{H}_{24}\text{N}_2\text{O}_6\text{S}$  ( $M_r = 540.47$ )  $w_i(\text{calc.})$ : 66.66 % C, 4.10 % H, 5.18 % N;  $w_i(\text{found})$ : 66.78 % C, 4.23 % H, 5.34 % N.  $^1\text{H}$  NMR spectrum,  $\delta$ : 7.22—7.42 (m,

11H, H-5' and  $\text{H}_{\text{arom}}$ ), 6.93 (dd, 1H, H-2'), 6.64 (d, 1H, H-14), 6.20 (dd,  $J_{4',5'} = 2.5$  Hz, 1H, H-4'), 5.22 (d,  $J_{8,12} = 8.7$  Hz, 1H, H-12), 5.07 (d, 1H, H-8), 3.94 (s, 3H,  $\text{COOCH}_3$ -2), 3.93 (s, 1H, H-7), 3.88 (s, 3H,  $\text{COOCH}_3$ -6), 3.08 (s, 1H, H-1).  $^{13}\text{C}$  NMR spectrum,  $\delta$ : 168.38 (s, C=O), 168.00 (s, C=O), 156.53 (s, C=N), 151.91 (s, C=N), 136.96, 136.41, 134.38, 133.98, 131.32, 131.20, 130.87, 130.63, 129.69, 128.13, 127.89, 127.20, 126.71, 126.54, 126.13, 124.26, 122.03 ( $\text{C}_{\text{arom}}$  and  $\text{C}_{\text{vinyl}}$ ), 92.41 (s, C-2), 82.50 (d, C-12), 75.23 (s, C-6), 53.81 (d, C-8), 53.50 (d, C-7), 53.08 (q,  $2 \times \text{CH}_3$ ), 50.81 (d, C-1).

## REFERENCES

1. Fišera, L., Ondruš, V., and Timpe, H.-J., *Collect. Czech. Chem. Commun.* 55, 512 (1990).
2. Bergmann, E. D., *Chem. Rev.* 1968, 41.
3. Wagner-Jauregg, T., *Synthesis* 1980, 165.
4. Wilson, W. S. and Warrener, R. N., *J. Chem. Soc., Chem. Commun.* 1972, 211.
5. Prinzbach, H. and Rivier, R., *Helv. Chim. Acta* 53, 2201 (1970).
6. Zálupský, P., Pirická, Z., and Fišera, L., *Chem. Papers* 39, 795 (1985).
7. Cristina, D., de Amici, M., de Micheli, C., and Gandolfi, R., *Tetrahedron* 37, 1349 (1981).
8. Fišera, L., Kováč, J., Zálupský, P., Považanec, F., and Pavlovič, D., *Collect. Czech. Chem. Commun.* 48, 3144 (1983).
9. Dewar, M. J. S., Zuebisch, E. G., Healy, E. F., and Stewart, J. J. P., *J. Am. Chem. Soc.* 107, 3902 (1985).
10. Sternbach, S. D. and Ensinger, C. L., *J. Org. Chem.* 55, 2725 (1990).
11. Griesbeck, A. G., *Synthesis* 1990, 144.
12. Sokolov, S. D., Yuditseva, I. M., and Petrovskii, P. V., *Zh. Org. Khim.* 6, 2584 (1970).
13. Auwers, K. and Ottens, B., *Ber.* 58, 2079 (1935).

Translated by L. Fišera