Chemistry of Heterocyclic Compounds, Vol. 49, No. 3, June, 2013 (Russian Original Vol. 49, No. 3, March, 2013)

REGIO- AND STEREOSELECTIVE CYCLOADDITION OF *C*-CARBAMOYLNITRONES TO 1-BENZYLIDENE-3,3-DICHLORO-2,2-DIMETHYLCYCLOPROPANE

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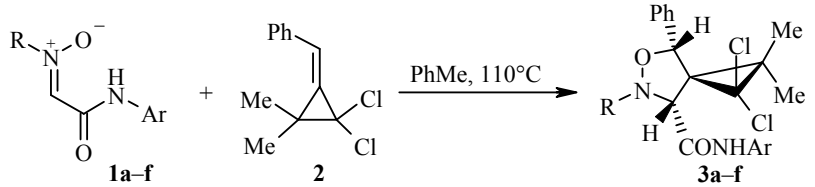
C-Carbamoylnitrones add regio- and stereoselectively to 1-benzylidene-3,3-dichloro-2,2-dimethylcyclopropane with the formation of one diastereomer of 4-spirocyclopropaneisoxazolidine.

Keywords: isoxazolidines, methylenecyclopropanes, nitrones, 1,3-dipolar cycloaddition, stereoselectivity.

1,3-Dipolar cycloaddition of nitrones to carbon–carbon multiple bonds is a widely used method of constructing the isoxazolidine ring [1, 2]. These compounds attract special attention owing to their potential biological activity, and also the possibility of using them to obtain amino alcohols, which are precursors of such natural compounds as β-lactams and alkaloids [3]. Unlike acyclic unsaturated compounds, the methylenecyclopropanes, as a result of significant strain energy, fairly readily entered into cycloaddition reactions with nitrones. As a result, mixtures of 4- and 5-spirocyclopropaneisoxazolidines were formed, the proportions of which depended on substituents both in the nitrone and in the methylenecyclopropane [4].

We have shown previously that on interacting *C,N*-diaryl- and *N*-aryl-*C*-carbamoylnitrones with esters of methylenecyclopropanedicarboxylic acids only 4-spirocyclopropaneisoxazolidines were formed [5-8]. At the same time, the formation of azeto- and pyrroloquinolines, observed on interacting *C,C*-disubstituted nitrones with the same esters, involved 5-spirocyclopropaneisoxazolidine intermediates [9].



1a–f **2** **3a–f**

a R = Ar = Ph; **b** R = Ph, Ar = 4-MeC_6H_4; **c** R = Ph, Ar = 4-ClC_6H_4; **d** R = 4-MeC_6H_4, Ar = Ph; **e** R = 4-MeC_6H_4, Ar = 4-$MeOC_6H_4$; **f** R = Me, Ar = Ph

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 514-518, March, 2013. Original article submitted August 26, 2012.

To expand the range of methylenecyclopropanes involved in reaction with nitrones, we have in this case studied the interaction of *C*-carbamoylnitrones **1a-f** with 1-benzylidene-3,3-dichloro-2,2-dimethyl-cyclopropane (**2**). It was established that on heating the nitrones **1a-e** with dichlorocyclopropane **2** in toluene for 4-5 h, only a single diastereomer of the 4-spirocyclopropaneisoxazolidines **3a-e** was formed, and compounds **3a-e** were isolated in yields of 58-70%. Interaction with the *N*-methylnitrone **1f** required longer heating (25 h).

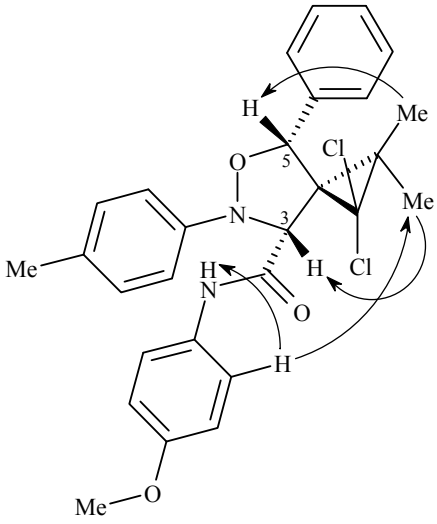
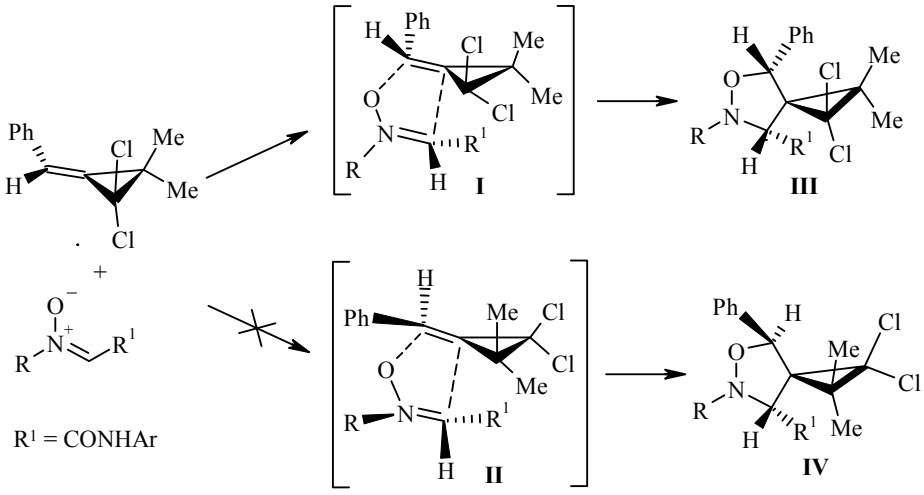


Fig. 1. Main proton interactions in the ^{1}H-^{1}H NOESY spectrum of compound **3e**.

The structures of cycloadducts **3a-f** were established on the basis of spectral data. In the ^{1}H NMR spectra there were singlets for the protons of the two methine groups at 4.18-4.90 and 5.41-5.64 ppm, and a singlet for the amide NH group at 9.25-9.45 ppm. In the ^{13}C NMR spectra of compounds **3a-f** there were three signals for the quaternary carbon atoms of the cyclopropane ring at 32.2-33.4, 49.0-49.9, and 74.6-76.3 ppm, a signal for the methine carbon atom of the isoxazolidine ring, linked with nitrogen, at 74.2-74.7 ppm, and a signal for the methine carbon atom, linked with oxygen, at 84.0-84.9 ppm. In the IR spectra of compounds **3a-f** there were absorption bands of the amide carbonyl groups at 1700-1688 cm^{-1} and of the NH groups at 3370-3340 cm^{-1}. The elemental analysis data confirmed the composition of the obtained products.



The stereochemistry of adduct **3e** was established with the aid of two-dimensional NMR spectroscopy. The main interactions between the protons found in the ^{1}H-^{1}H NOESY spectrum of compound **3e** are shown in Fig. 1 including the cross peaks corresponding to isoxazolidine ring protons H-3 and H-5 interacting with the methyl group protons. Also observed was the interaction of the aromatic protons of the arylcarbamoyl group with the NH proton and with one of the cyclopropane ring methyl groups. At the same time, interaction of only one of the isoxazolidine ring protons with the methyl group protons would be expected for the *trans* isomer. It should be mentioned that in the reaction mixtures no ^{1}H NMR signals were observed which might be ascribed to the other diastereomer.

The *C*-carbamoylnitrones **1a-f** added to benzylidenecyclopropane **2** with analogous stereoselectivity to that observed previously on interacting the same nitrones and methylenecyclopropanes having acceptor ester groups on the three-membered ring. The cycloaddition of nitrones to the methylenecyclopropane **2** could proceed in two directions, through the transition state **I** leading to the observed diastereoisomer **III**, or through the transition state **II**, which would have led to the diastereomer **IV**. The second route was apparently less favored because of the steric repulsion between the *syn*-oriented chlorine atom and the aryl group, and also steric repulsion between the benzylidenecyclopropane phenyl group and the substituent R on the nitrone.

It has therefore been established that the addition of *C*-carbamoylnitrones to 1-benzylidene-3,3-dichloro-2,2-dimethylcyclopropane proceeds regio- and stereoselectively with the formation of a single 4-spirocyclopropaneisoxazolidine diastereomer.

EXPERIMENTAL

The IR spectra were recorded on a Bruker Tensor 27 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 instrument (300 and 75 MHz, respectively) in $CDCl_3$, using the residual solvent signals as a standard (7.26 ppm for the ^{1}H nuclei, 77.2 ppm for the ^{13}C nuclei). Elemental analysis was performed on a Hewlett-Packard 185B C,H,N-analyzer. Melting points were determined on a Boetius hot stage apparatus. *C*-Carbamoylnitrones **1a-f** were obtained according to procedures in [6, 10, 11], and 1-benzylidene-3,3-dichloro-2,2-dimethylcyclopropane (**2**) by the procedure of [12].

Interaction of *C*-Carbamoylnitrones 1a-f with Methylenecyclopropane 2 (General Method). A solution of methylenecyclopropane **2** (272 mg, 1.2 mmol) and nitrone **1a-f** (1.0 mmol) in anhydrous toluene (10 ml) was heated at 110°C (reaction time is given in the procedures for products **3a-f**). Toluene was evaporated in vacuum, and the residue was separated on a silica gel column. Eluent was EtOAc–hexane. The solvent was evaporated and the residue recrystallized from EtOH.

7-(*N*-Phenylcarbamoyl)-1,1-dichloro-2,2-dimethyl-4,6-diphenyl-5-oxa-6-azaspiro[2.4]heptane (3a). Heating time was 5 h. Yield 275 mg (59%), white powder, mp 218-220°C. R_f 0.43 (EtOAc–hexane, 1:7). IR spectrum (KBr), ν, cm^{-1} 3370 (NH), 1700 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.80 (3H, s, CH_3); 1.65 (3H, s, CH_3); 4.90 (1H, s, 7-CH); 5.64 (1H, s, 4-CH); 7.17 (2H, t, *J* = 7.3, H Ar); 7.27-7.47 (11H, m, H Ar); 7.55 (2H, d, *J* = 8.7, H Ar); 9.34 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 23.0 (CH_3), 25.9 (CH_3); 33.4 (C-2); 49.9 (C-3); 74.6 (C-1); 74.7 (C-7); 84.8 (C-4); 116.2; 120.8; 124.3; 125.2; 129.2; 129.4; 129.5; 129.6; 129.7; 136.7; 137.6; 148.2; 167.5. Found, %: C 66.94; H 5.18; N 5.92. $C_{26}H_{24}Cl_2N_2O_2$. Calculated, %: C 66.81; H 5.18; N 5.99.

7-[*N*-(4-Tolyl)carbamoyl]-1,1-dichloro-2,2-dimethyl-4,6-diphenyl-5-oxa-6-azaspiro[2.4]heptane (3b). Heating time was 5 h. Yield 336 mg (70%), white powder, mp 217-218°C. R_f 0.60 (EtOAc–hexane, 1:4). IR spectrum (KBr), ν, cm^{-1}: 3358 (NH), 1693 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.79 (3H, s, CH_3); 1.64 (3H, s, CH_3); 2.35 (3H, s, CH_3); 4.88 (1H, s, 7-CH); 5.63 (1H, s, 4-CH); 7.08-7.47 (14H, m, H Ar); 9.27 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 21.3 (CH_3); 23.0 (CH_3); 25.9 (CH_3); 33.4 (C-2); 49.9 (C-3); 74.7 (C-1); 74.8 (C-7); 84.8 (C-4); 116.2; 120.9; 124.2; 128.8; 129.1; 129.3; 129.5; 129.7; 134.8; 135.1; 136.8; 148.3; 167.4. Found, %: C 66.98; H 5.28; N 5.95. $C_{27}H_{26}Cl_2N_2O_2$. Calculated, %: C 67.36; H 5.44; N 5.82.

7-[*N*-(4-Chlorophenyl)carbamoyl]-1,1-dichloro-2,2-dimethyl-4,6-diphenyl-5-oxa-6-azaspiro[2.4]heptane (3c). Heating time was 5 h. Yield 335 mg (67%), white powder, mp 208-210°C. R_f 0.55 (EtOAc–hexane, 1:4). IR spectrum (KBr), ν, cm^{-1}: 3359 (NH), 1699 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.80 (3H, s, CH_3); 1.64 (3H, s, CH_3); 4.87 (1H, s, 7-CH); 5.64 (1H, s, 4-CH); 7.12-7.52 (14H, m, H Ar); 9.34 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 23.0 (CH_3); 25.8 (CH_3); 33.5 (C-2); 49.8 (C-3); 74.7 (C-1); 74.8 (C-7); 84.8 (C-4); 116.2; 121.9; 124.4; 129.2; 129.4; 129.6; 130.2; 136.2; 136.6; 148.1; 167.6 (C=O). Found, %: C 61.97; H 4.78; N 5.85; $C_{26}H_{23}Cl_3N_2O_2$. Calculated, %: C 62.23; H 4.62; N 5.58.

7-(*N*-Phenylcarbamoyl)-1,1-dichloro-2,2-dimethyl-4-phenyl-6-(4-tolyl)-5-oxa-6-azaspiro[2.4]heptane (3d). Heating time was 4 h. Yield 318 mg (66%), white powder, mp 193-194°C. R_f 0.44 (EtOAc–hexane, 1:7). IR spectrum ($CHCl_3$), ν, cm^{-1}: 3370 (NH), 1700 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.79 (3H, s, CH_3); 1.64 (3H, s, CH_3); 2.39 (3H, s, CH_3); 4.85 (1H, s, 7-CH); 5.63 (1H, s, 4-CH); 7.15-7.24 (5H, m, H Ar); 7.30-7.39 (5H, m, H Ar); 7.43-7.45 (2H, m, H Ar); 7.54 (2H, d, *J* = 8.0, H Ar); 9.36 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 21.2 (CH_3); 23.0 (CH_3); 25.9 (CH_3); 33.3 (C-2); 49.8 (C-3); 74.7 (C-7); 74.8 (C-1); 84.9 (C-4); 116.1; 120.8; 125.1; 129.2; 129.4; 129.5; 129.7; 129.9; 133.7; 136.8; 137.6; 145.8; 167.6 (C=O). Found, %: C 67.49; H 5.38; N 5.87. $C_{27}H_{26}Cl_2N_2O_2$. Calculated, %: C 67.36; H 5.44; N 5.82.

7-[*N*-(4-Methoxyphenyl)carbamoyl]-1,1-dichloro-2,2-dimethyl-4-phenyl-6-(4-tolyl)-5-oxa-6-aza-spiro[2.4]heptane (3e). Heating time was 4.5 h. Yield 296 mg (58%), white powder, mp 171-172°C. R_f 0.30 (EtOAc–hexane, 1:7). IR spectrum ($CDCl_3$), ν, cm^{-1}: 3340 (NH), 1700 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.79 (3H, s, CH_3); 1.63 (3H, s, CH_3); 2.38 (3H, s, CH_3); 3.82 (3H, s, CH_3); 4.84 (1H, s, 7-CH); 5.62 (1H, s, 4-CH); 6.89 (2H, d, *J* = 8.7, H Ar); 7.16 (2H, d, *J* = 8.7, H Ar); 7.22 (2H, d, *J* = 8.7, H Ar); 7.31-7.33 (3H, m, H Ar); 7.41-7.46 (4H, m, H Ar); 9.25 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 20.8 (CH_3); 22.7 (CH_3); 25.5 (CH_3); 32.9 (C-2); 49.4 (C-3); 55.4 (CH_3); 74.3 (C-7); 74.4 (C-1); 84.4 (C-4); 114.2; 115.7; 122.3; 128.7; 129.1; 129.3; 129.5; 130.3; 133.2; 136.5; 145.5; 156.7; 167.1 (C=O). Found, %: C 65.48; H 5.50; N 5.42. $C_{28}H_{28}Cl_2N_2O_3$. Calculated, %: C 65.76; H 5.52; N 5.48.

7-(*N*-Phenylcarbamoyl)-1,1-dichloro-2,2,6-trimethyl-4-phenyl-5-oxa-6-azaspiro[2.4]heptane (3f). Heating time was 25 h. Yield 240 mg (59%), white powder, mp 116-117°C. R_f 0.34 (EtOAc–hexane, 1:7). IR spectrum ($CHCl_3$), ν, cm^{-1}: 3342 (NH), 1703 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.78 (3H, s, CH_3); 1.65 (3H, s, CH_3); 2.99 (3H, s, CH_3); 4.18 (1H, s, 7-CH); 5.41 (1H, s, 4-CH); 7.14 (1H, t, *J* = 7.3, H Ar); 7.26-7.28 (3H, m, H Ar); 7.32-7.38 (4H, m, H Ar); 7.55 (2H, d, *J* = 8.0, H Ar); 9.45 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 22.7 (CH_3); 26.3 (CH_3); 32.3 (C-2); 43.6 (CH_3); 49.0 (C-3); 74.2 (C-7); 76.3 (C-1); 84.0 (C-4); 120.7; 124.9; 129.1; 129.3; 129.4; 129.7; 136.9; 137.8; 167.6 (C=O). Found, %: C 62.34; H 5.40; N 6.84. $C_{21}H_{22}Cl_2N_2O_2$. Calculated, %: C 62.23; H 5.47; N 6.91.

The authors are grateful to the Russian Foundation for Basic Research for financial support (Project 12-03-01008-a).

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