1,3-Dipolar Cycloaddition of Heterocycles XXXII.* Cycloadditions of Nitrones to *N*-(2,6-dialkylphenyl)maleimides

L. JAROŠKOVÁ, M. KONOPÍKOVÁ, and Ľ. FIŠERA**

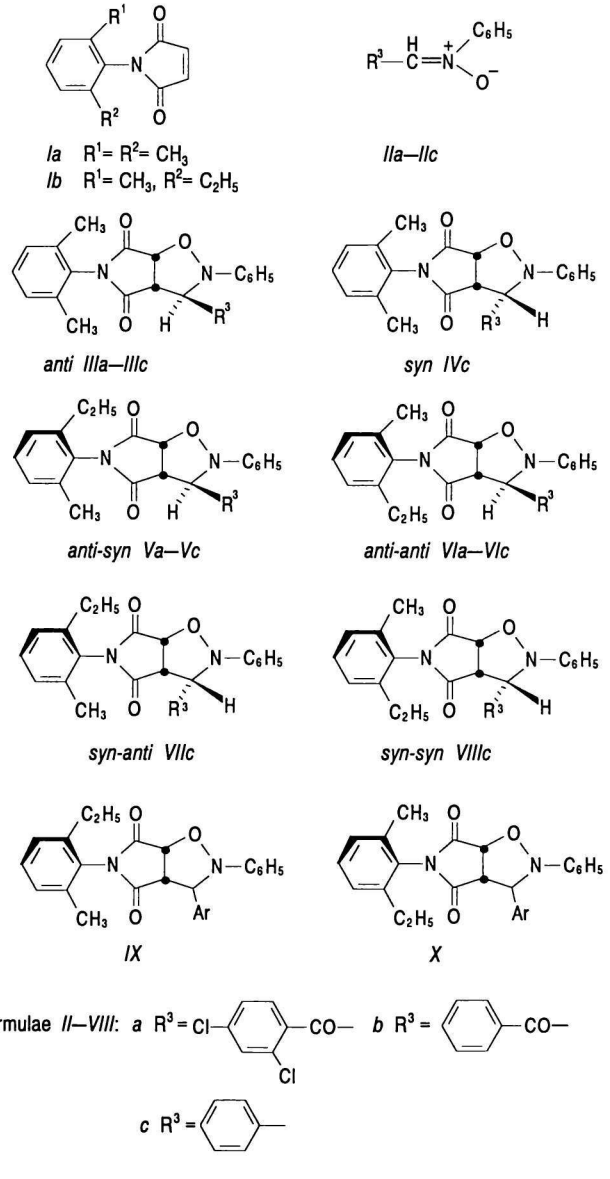
Department of Organic Chemistry, Faculty of Chemical Technology, Slovak Technical University, SK-812 37 Bratislava

Received 10 November 1992

The 1,3-dipolar cycloadditions of nitrones to *N*-(2,6-dialkylphenyl)maleimides give mainly *anti*-adducts. The *Z*/*E* isomerization of nitrones and the sterically preferred *exo* attack avoiding the repulsions between *N*-arylmaleimide and *N*-phenyl moiety of nitrone was proposed. The reaction of *N*-(2-ethyl-6-methylphenyl)maleimide with nitrone gave, due to hindered rotation, two or four types of diastereoisomers characterized by different spatial arrangement of alkyl groups *vs*. bridgehead hydrogen atoms.

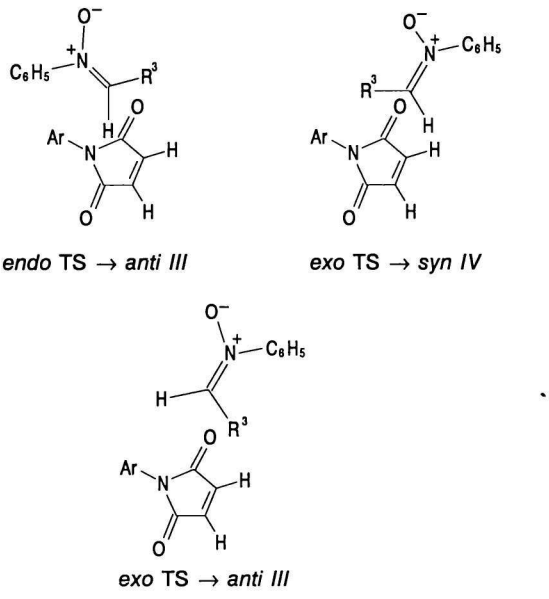
Some compounds of dicarboximide type are reported to reveal effective systemic activity against *Botrytis cinerea*, *Cochliobolus miyabeanus*, and *Pellicularia sasaci* [1]. Within the scope of our ongoing research aimed at utilization of 1,3-dipolar cycloadditions to heterocycles we have recently found [2] that the reaction of *N*-(2-ethyl-6-methylphenyl)maleimide with nitrile oxide gave, due to hindered rotation, two diastereoisomers characterized by different spatial arrangement of alkyl groups *vs*. bridgehead hydrogen atoms [3]. Since that is a very rare phenomenon we have focused our attention to the cycloaddition of nitrones to *N*-(2,6-dialkylphenyl)-maleimides.

1,3-Dipolar cycloaddition of *C*-(2,4-dichlorobenzoyl)-*N*-phenyl nitrone (*IIa*) and *N*-(2,6-dimethylphenyl)maleimide (*Ia*) in benzene at room temperature afforded the *anti*-isoxazolidine *IIIa* (Scheme 1, H-3, H-3a *anti* relationship) in 88 % yield. The NMR analysis of the crude mixture showed the presence of the second isomer *IVa*, but in the amount less than 10 %. This compound could not be isolated from the major product in pure form. Similarly, treatment of the corresponding *C*-benzoylnitrone *IIb* with *Ia* gave *anti*-isoxazolidine *IIIb*. On the other hand, it was found that *C*,*N*-diphenylnitrone (*IIc*) reacted with *Ia* in benzene at 80 °C to give a mixture of *anti IIIc* and *syn IVc* cycloadducts. The crude residue was chromatographically separated, and each cycloadduct *IIIc* and *IVc* could be obtained in pure form. The NMR analysis of the crude mixture gave the mass ratio 72 : 28 in favour of *IIIc*. There are two possible adducts of *Ia* and nitrones *IIa*—*IIc*, two diastereoisomers *III* and *IV*. The distinction between them was possi-



Scheme 1

*For Part XXXI see *Monatsh. Chem. 124*, 1019 (1993).
**The author to whom the correspondence should be addressed.



Scheme 2

ble by means of spectroscopic data. Stereochemical assignments of H-3, H-3a, and H-6a atoms were made to the condensed isoxazolidines on the basis of the $J_{3,3a}$ and $J_{3a,6a}$ coupling constant. The ring junction between two rings was always *cis*, which was indicated by coupling constants and an examination of molecular models. Moreover, all up-to-date known 1,3-dipolar cycloadditions of nitrones to alkenes proceeded with *cis* stereospecificity [4]. For instance, in the compounds *IIIa* the coupling constant for the *cis* ring junction protons H-6a and H-3a $J_{3a,6a}$ = 8.4 Hz and in *IIIc* $J_{3a,6a}$ = 7.2 Hz; in *IVc* $J_{3a,6a}$ = 8.1 Hz, which is indicative of nearly eclipsed dihedral angles between H-3a and H-6a.

Proton NMR analysis of isoxazolidines *IIIa—IIIc* revealed that each diastereoisomer has a H-3, H-3a *anti* relationship. In *IIIa,* for example, the signal for H-3a proton appears as a doublet at δ = 4.71 with a coupling constant of $J_{3a,6a}$ = 8.4 Hz from coupling solely to the H-6a proton. In the H-3, H-3a *anti*-adducts the protons H-3 and H-3a fail to display coupling since ϕ = 90°. This feature of NMR spectrum is uniquely diagnostic of the H-3, H-3a *anti* relationship [5]. In *IIIa* and *IIIc* the 0—1 Hz coupling constant between bridgehead H-3a and isoxazolidine H-3 (in *IIIa* $J_{3,3a}$ = 0.0 Hz, in *IIIc* $J_{3,3a}$ = 1.2 Hz) is consistent only with *anti* stereochemistry, since in a *syn*-isomer *IV* the two hydrogens would be nearly eclipsed and would give rise to a much larger coupling constants. Indeed, the isolated adduct *IVc* from the cycloaddition of *C,N*-diphenylnitrone showed $J_{3,3a}$ = 8.1 Hz, which is in the range expected for a H-3, H-3a *syn* relationship. Further support for this *syn* relationship is the signal for the H-3a proton appearing as a doublet of doublets.

The diastereomeric isoxazolidines *III* and *IV* were formed *via* different two-plane orientation complexes (Scheme 2). The *anti*-isoxazolidines *III* arise from the cycloaddition of *Z*-nitrone *II* through an *endo* transition state (*N*-Ph and *N*-aryl groups are on the same sides), or from the *E*-nitrone in an *exo* mode (*N*-Ph and *N*-aryl groups are on the opposite sides).

Conversely the *syn*-isoxazolidines *IV* could be formed by the *Z*-nitrone reacting in the *exo* fashion or the *E*-nitrone in an *endo* mode [6, 7]. The ratio of diastereoisomers should reflect secondary orbital interactions and repulsive interactions caused by steric hindrance [4]. An examination of both transition states in these terms reveals that secondary orbital interactions are not significant and that repulsions between the phenyl and aryl groups on nitrogens are minimized in the *exo* transition state. There is strong evidence that nitrones derived from aromatic aldehydes possess a configuration in which the *C*-aryl and *C*-aroyl, respectively, and *N*-phenyl groups are in a *trans* relationship (*Z*-configuration of nitrone) [8]. The isomeric *E*-nitrones (*cis* relationship between aryl groups) could not be isolated, but since it has been postulated that isomerization of *Z*-nitrones to the more reactive nitrones can precede cycloaddition [9], it is not possible to exclude that either *Z*- or *E*-nitrones are involved in cycloadditions [10].

Therefore, the major isoxazolidines *III* should arise from cycloaddition of *Z*-nitrone *II* through *endo* transition state (Scheme 2). Molecular models suggest that an attack *via endo* mode is at least sterically unlikely. For *endo* transition state severe steric interactions occur between the incoming *N*-arylmaleimide as a consequence of the hindered rotation and *N*-phenyl moiety of nitrone *II*. We propose that the aforementioned nitrones undergo $Z \rightarrow E$ isomerization, since both *anti III* and *syn IV* cycloadducts obtained in these cycloadditions using *N*-(2,6-dimethylphenyl)maleimide as the dipolarophile must arise from the *exo* transition state; the *E*-isomer of the nitrone *IIa—IIc* yields the *anti*-adduct *III*, while the *Z*-isomer of *IIc* yields the *syn*-adduct *IVc*. The proposed *Z/E* nitrone isomerization was involved by many authors to account for the diastereoselectivity of 1,3-dipolar cycloaddition of nitrones with alkenes [9—12].

1,3-Dipolar cycloaddition of nitrone *IIa* and *N*-(2-ethyl-6-methylphenyl)maleimide (*Ib*) in benzene at room temperature affords the isoxazolidines *Va* and *VIa* as a mixture of diastereoisomers, from which only the preponderant *anti*-isomer *Va* could be isolated in the pure state (see Experimental). The ratio of *Va* to *VIa* 80 : 20 was determined by integration of the H-3, H-3a, and H-6a signals in the ^{1}H NMR spectra.

Similarly, *C*-benzoylnitrone *IIb* with *Ib* gave only *anti*-isoxazolidines *Vb* and *VIb* in the ratio of 50 : 50. The possible stereoisomers *VIIa*, *VIIb* as well as

VIIIa, *VIIIb* have not been detected in the crude reaction mixture by NMR spectroscopy. In contrast to the mentioned examples the cycloaddition of *C*,*N*-diphenylnitrone to *Ib* gave the *anti*-isoxazolidines *Vc* + *VIc* together with *syn*-isoxazolidines *VIIc* + *VIIIc*, the ratio 72 : 28 was determined by NMR spectroscopy. The crude residue after cycloaddition was chromatographed, but only the mixture of *anti*-adducts *Vc* + *VIc* and of *syn*-adducts *VIIc* + *VIIIc* both indicating a 1 : 1 ratio of stereoisomers could be obtained.

As a consequence of the hindered rotation and unsymmetrical substitution of the *N*-phenyl ring of maleimide four diastereomeric transition states of 1,3-cycloaddition can be envisioned. The attack of the dipole at the double bond can in principle be carried out from the *syn* side of the methyl group (derivatives *anti-syn V* and *syn-anti VII*; the first prefix *anti* or *syn* showed a relationship between H-3 and H-3a atoms and the second a relationship between H-3 and methyl group bound directly to the benzene ring) or from the opposite side (derivatives *anti-anti VI* and *syn-syn VIII*). Consequently, the diastereomeric cycloadducts (atropisomers) differ in the spatial arrangement of their alkyl groups towards the bridgehead proton H-3a and H-6a. The attempted chromatographic separation of atropisomers was successful only in case of *anti-syn Va*; this isomer could be isolated in a pure state. The assignment of structure of *Va* was done based on comparison with derivatives *IX* and *X* [2] and mainly by the fact that the repulsion of an alkyl group located in proximity to bridgehead protons causes their deshielding, an effect which indeed is substantiated by the measured values (see Experimental). Thus, the triplets of methyl protons of the ethyl groups in *anti-syn Va* were found at δ = 1.13, whereas in *anti-anti VIa* at δ = 0.85. Singlets of methyl group protons bound directly to the benzene ring in *Va* were found at δ = 1.30, those of *VIa* at higher value, δ = 2.06. Similar differences are observed also in quartets of the methylene groups protons as well as in signals of ^{13}C NMR spectra.

EXPERIMENTAL

Melting points are not corrected. ^1H and ^{13}C NMR spectra of deuterochloroform solutions were measured with Varian VXR 300 instrument, tetramethylsilane being the internal reference. ^1H and ^{13}C NMR spectra of the raw reaction mixture were recorded on a Tesla BS 487 C (80 MHz) spectrometer.

The progress of the cycloaddition was monitored by thin-layer chromatography on silica gel, impregnated by a fluorescence indicator (254 nm). *N*-(2,6-Dialkylphenyl)maleimides *I* were prepared by the reaction of maleic anhydride with 2,6-dialkylanilines [13]. *C*-(2,4-Dichlorobenzoyl)-*N*-phenylnitrone and *C*-benzoyl-*N*-phenylnitrone were prepared according to Ref. [14]. *C*,*N*-Diphenylnitrone was prepared from the benzaldehyde by treatment with *N*-phenylhydroxylamine [4].

2,5-Diaryl-3-aroyl-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-*d*]isoxazoles *III—VI*

C-Aroyl-*N*-phenylnitrone *IIa* or *IIb* (10 mmol) and the appropriate dipolarophile *I* (10—50 mmol) in benzene (50 cm^3) or chloroform (50 cm^3) were stirred at room temperature for 12—24 h (TLC monitoring). In some cases the cycloadduct was precipitated from the reaction mixture. The solvent was evaporated under reduced pressure, the residue was purified on silica gel to give the product. Characteristic data for compounds are as follows:

2-Phenyl-3-(2,4-dichlorobenzoyl)-5-(2,6-dimethylphenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo-[3,4-d]isoxazole (IIIa), yield = 88 % (benzene) or 64 % (chloroform), m. p. = 192—194 °C (decomp.). For $C_{26}H_{20}Cl_2N_2O_4$ (M_r = 495.35) w_i(calc.): 62.99 % C, 4.07 % H, 5.65 % N; w_i(found): 62.62 % C, 4.08 % H, 5.66 % N. ^1H NMR spectrum, δ: 7.01—7.41 (m, 11H, H_{arom}), 5.93 (s, 1H, H-3), 5.24 (d, 1H, H-6a, $J_{3a,6a}$ = 8.4 Hz), 4.71 (d, 1H, H-3a), 2.06 (s, 3H, CH_3), 1.27 (s, 3H, CH_3). ^{13}C NMR spectrum, δ: 196.10 (s, C=O), 173.41 (s, C=O), 172.17 (s, C=O), 146.73, 137.94, 136.46, 135.64, 134.84, 131.40, 130.56, 130.02, 129.69, 129.56, 129.48, 128.39, 127.58, 123.72, 114.63 (C_{arom}), 77.67 (d, C-6a), 71.73 (d, C-3), 50.19 (d, C-3a), 17.91 (q, CH_3), 16.35 (q, CH_3).

2-Phenyl-3-(benzoyl)-5-(2,6-dimethylphenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]isoxazole (IIIb), yield = 36 % after column chromatography, eluent heptane—ethyl acetate mixture (φ_r = 2 : 1), m. p. = 186—187 °C. For $C_{26}H_{22}N_2O_4$ (M_r = 426.45) w_i(calc.): 73.22 % C, 5.20 % H, 6.57 % N; w_i(found): 74.01 % C, 5.34 % H, 6.68 % N. ^1H NMR spectrum, δ: 6.97—8.02 (m, 13H, H_{arom}), 6.01 (s, 1H, H-3), 5.25 (d, 1H, H-6a, $J_{3a,6a}$ = 8.4 Hz), 4.69 (d, 1H, H-3a), 2.04 (s, 3H, CH_3), 1.29 (s, 3H, CH_3). ^{13}C NMR spectrum, δ: 192.65 (s, C=O), 174.21 (s, C=O), 172.44 (s, C=O), 146.92, 136.52, 134.85, 134.35, 134.01, 129.74, 129.68, 129.52, 129.01, 128.85, 128.67, 128.37, 123.69, 114.79 (C_{arom}), 77.76 (d, C-6a), 68.17 (d, C-3), 50.77 (d, C-3a), 17.90 (q, CH_3), 16.36 (q, CH_3).

2-Phenyl-3-(2,4-dichlorobenzoyl)-5-(2-ethyl-6-methylphenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]isoxazole (Va), yield = 65 % after column chromatography, eluent chloroform—heptane—ethyl acetate mixture (φ_r = 3 : 5 : 1), m. p. =

144—147 °C. For $C_{27}H_{22}Cl_2N_2O_4$ (M_r = 509.38) w_i(calc.): 63.66 % C, 4.35 % H, 5.50 % N; w_i(found): 63.72 % C, 4.59 % H, 5.37 % N. ^{1}H NMR spectrum, δ: 6.93—7.39 (m, 11H, H_{arom}), 5.93 (s, 1H, H-3), 5.25 (d, 1H, H-6a, $J_{3a,6a}$ = 8.4 Hz), 4.70 (d, 1H, H-3a), 2.33 (q, 2H, CH_2), 1.30 (s, 3H, CH_3), 1.13 (t, 3H, CH_3). ^{13}C NMR spectrum, δ: 196.10 (s, C=O), 173.41 (s, C=O), 172.17 (s, C=O), 146.50, 140.54, 137.90, 136.43, 135.64, 134.84, 131.40, 130.51, 129.99, 129.92, 129.51, 128.32, 127.54, 126.51, 123.71, 114.70 (C_{arom}), 77.52 (d, C-6a), 71.62 (d, C-3), 50.18 (d, C-3a), 24.46 (t, CH_2), 16.35 (q, CH_3), 14.20 (q, CH_3).

Some relevant signals corresponding to a minor isomer *VIa* were also clearly observed in the other enriched fraction.

^{1}H NMR spectrum, δ: 5.90 (s, 1H, H-3), 5.24 (d, 1H, H-6a, $J_{3a,6a}$ = 8.4 Hz), 4.69 (d, 1H, H-3a), 2.06 (q, 2H, CH_2), 1.23 (s, 3H, CH_3), 0.85 (t, 3H, CH_3). ^{13}C NMR spectrum, δ: 77.57 (d, C-6a), 71.69 (d, C-3), 50.23 (d, C-3a), 22.68 (t, CH_2), 17.97 (q, CH_3).

2-Phenyl-3-(benzoyl)-5-(2-ethyl-6-methylphenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]-isoxazole (the mixture of Vb and VIb), yield = 50 %. For $C_{27}H_{24}N_2O_4$ (M_r = 440.48) w_i(calc.): 73.62 % C, 5.49 % H, 6.36 % N; w_i(found): 73.87 % C, 5.42 % H, 6.19 % N. ^{1}H NMR spectrum, δ: 6.99—8.00 (m, 26H, H_{arom}), 5.99 (s, 1H, H-3), 5.98 (s, 1H, H-3), 5.26 (d, 1H, H-6a, $J_{3a,6a}$ = 9.0 Hz), 5.23 (d, 1H, H-6a, $J_{3a,6a}$ = 8.7 Hz), 4.66 (d, 1H, H-3a, $J_{3a,6a}$ = 9.0 Hz), 4.64 (d, 1H, H-3a, $J_{3a,6a}$ = 8.7 Hz), 2.32 (q, 2H, CH_2), 2.04 (s, 3H, CH_3), 1.56 (q, 2H, CH_2), 1.32 (s, 3H, CH_3), 1.11 (t, 3H, CH_3), 0.88 (t, 3H, CH_3). ^{13}C NMR spectrum, δ: 192.68 (s, C=O), 174.58 (s, C=O), 174.52 (s, C=O), 172.81 (s, C=O), 146.81, 146.66, 142.15, 140.54, 136.51, 134.69, 134.40, 133.99, 129.91, 129.68, 129.59, 128.98, 128.84, 128.61, 128.33, 126.51, 123.69, 123.64, 114.89, 114.86 (C_{arom}), 77.63 (d, C-6a), 77.59 (d, C-6a), 68.19 (d, C-3), 68.11 (d, C-3), 50.93 (d, C-3a), 50.83 (d, C-3a), 24.45 (t, CH_2), 22.58 (t, CH_2), 17.97 (q, CH_3), 16.38 (q, CH_3), 14.24 (q, CH_3), 14.19 (q, CH_3).

2,3,5-Triaryl-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-*d*]isoxazoles *IIIc—VIIIc*

C,N-Diphenylnitrone *IIc* (10 mmol) and the appropriate dipolarophile *I* (10—50 mmol) in dry benzene (50 cm^3) were heated under reflux for 5—24 h (TLC). Concentration under reduced pressure and chromatography using the cyclohexane—ethyl acetate mixture (φ_r = 2 : 1) gave corresponding cycloadducts. Characteristic data for compounds are as follows:

2,3-Diphenyl-5-(2,6-dimethylphenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]isoxazole (IIIc), yield = 56 %, m. p. = 185—189 °C. For $C_{25}H_{22}N_2O_3$ (M_r = 398.45) w_i(calc.): 75.35 % C, 5.56 % H, 7.03 % N; w_i(found): 75.30 % C, 5.54 % H, 7.00 % N. ^{1}H NMR spectrum, δ: 6.87—7.38 (m, 13H, H_{arom}), 5.33 (d, 1H, H-3), 5.23 (d, 1H, H-6a, $J_{3a,6a}$ = 7.2 Hz), 4.00 (dd, 1H, H-3a, $J_{3,3a}$ = 1.2 Hz), 2.06 (s, 3H, CH_3), 1.80 (s, 3H, CH_3). ^{13}C NMR spectrum, δ: 174.03 (s, C=O), 172.75 (s, C=O), 146.67, 137.42, 136.29, 135.13, 129.63, 129.55, 128.81, 128.72, 128.38, 128.20, 127.45, 122.77, 116.07 (C_{arom}), 76.29 (d, C-6a), 70.37 (d, C-3), 57.38 (d, C-3a), 17.78 (q, CH_3), 17.08 (q, CH_3).

2,3-Diphenyl-5-(2,6-dimethylphenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]isoxazole (IVc), yield = 22 %, m. p. = 171—176 °C. For $C_{25}H_{22}N_2O_3$ (M_r = 398.45) w_i(calc.): 75.35 % C, 5.56 % H, 7.03 % N; w_i(found): 75.39 % C, 5.57 % H, 7.02 % N. ^{1}H NMR spectrum, δ: 7.04—7.42 (m, 13H, H_{arom}), 5.23 (d, 1H, H-6a), 4.97 (d, 1H, H-3, $J_{3a,6a}$ = $J_{3,3a}$ = 8.1 Hz), 4.12 (dd, 1H, H-3a), 2.05 (s, 3H, CH_3), 1.99 (s, 3H, CH_3). ^{13}C NMR spectrum, δ: 172.94 (s, C=O), 171.37 (s, C=O), 146.66, 136.17, 135.09, 133.71, 129.55, 129.13, 128.93, 128.84, 128.76, 128.67, 128.54, 128.48, 128.37, 127.74, 125.43, 120.10, 116.97 (C_{arom}), 76.40 (d, C-6a), 70.64 (d, C-3), 54.67 (d, C-3a), 17.99 (q, CH_3), 17.85 (q, CH_3).

2,3-Diphenyl-5-(2-ethyl-6-methylphenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]isoxazole (the mixture of Vc and VIc), yield = 58 %. For $C_{26}H_{24}N_2O_3$ (M_r = 412.47) w_i(calc.): 75.70 % C, 5.88 % H, 6.79 % N; w_i(found): 75.72 % C, 5.88 % H, 6.80 % N. ^{1}H NMR spectrum, δ: 6.90—7.38 (m, 26H, H_{arom}), 5.32 (s, 2H, H-3), 5.26 (d, 2H, H-6a, $J_{3a,6a}$ = 8.0 Hz), 4.05 (d, 2H, H-3a), 2.51 (q, 2H, CH_2), 2.20 (q, 2H, CH_2), 2.10 (s, 3H, CH_3), 1.86 (s, 3H, CH_3), 1.13 (t, 3H, CH_3), 0.97 (t, 3H, CH_3). ^{13}C NMR spectrum, δ: 174.57 (s, C=O), 173.94 (s, C=O), 146.37, 141.79, 137.51, 135.81, 129.81, 128.47, 128.84, 128.23, 126.62, 121.98, 116.04 (C_{arom}), 76.30 (d, C-6a), 68.69 (d, C-3), 56.71 (d, C-3a), 23.59 (t, CH_2), 14.55 (q, CH_3).

2,3-Diphenyl-5-(2-ethyl-6-methylphenyl)-4,6-dioxo-2,3,3a,4,6,6a-hexahydropyrrolo[3,4-d]isoxazole (the mixture of VIIc and VIIIc), yield = 22 %. For $C_{26}H_{24}N_2O_3$ (M_r = 412.47) w_i(calc.): 75.70 % C, 5.88 % H, 6.79 % N; w_i(found): 75.72 % C, 5.87 % H, 6.78 % N. ^{1}H NMR spectrum, δ: 7.00—7.45 (m, 26H, H_{arom}), 5.22 (d, 2H, H-6a), 5.00 (d, 2H, H-3,), 4.12 (dd, 2H, H-3a, $J_{3a,6a}$ = $J_{3,3a}$ = 8.0 Hz), 2.42 (q, 2H, CH_2), 2.10 (q, 2H, CH_2), 2.07 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.16 (t, 3H, CH_3), 1.08 (t, 3H, CH_3). ^{13}C NMR spectrum, δ: 173.81 (s, C=O), 172.15 (s, C=O), 146.43, 141.51, 141.30, 137.36, 135.66, 135.36, 134.23, 129.44, 128.74, 128.02, 127.74, 127.32, 126.41, 125.71, 121.04, 115.70 (C_{arom}), 76.30 (d, C-6a), 69.75 (d, C-3), 54.16 (d, C-3a), 23.44 (t, CH_2), 17.56 (q, CH_3), 17.37 (t, CH_2), 14.58 (q, CH_3).

REFERENCES

1. Matocsy, G., Nádasy, M., and Adriska, V., *Pesticide Chemistry*. Akadémiai Kiadó, Budapest, 1988.
2. Konopíková, M., Fišera, Ľ., Goljer, I., Varkonda, Š., Hýblová, O., Šturdík, E., and Ujhélyová, R., *Chem. Papers 45*, 789 (1991).
3. Jedlovská, E., Fišera, Ľ., Goljer, I., Konopíková, M., and Belen´kii, L. I., *Collect. Czech. Chem. Commun. 56*, 673 (1991).
4. Tufariello, J. J., in *1,3-Dipolar Cycloaddition Chemistry*, Vol. 2. (Padwa, A., Editor.) P. 83. Wiley, New York, 1984.
5. DeShong, P., Dicken, C. M., Leginus, J. M., and Whittle, R. R., *J. Am. Chem. Soc. 106*, 5598 (1984).
6. Fišera, Ľ., Al-Timari, U. A. R., and Ertl, P., *Cycloadditions in Carbohydrate Chemistry*, ACS Monograph. P. 158. Am. Chem. Soc., Washington, 1992.
7. Al-Timari, U. A. R., Fišera, Ľ., Ertl, P., Goljer, I., and Prónayová, N., *Monatsh. Chem. 123*, 999 (1992).
8. Folting, K., Lipscomb, W. N., and Jerslev, B., *Acta Chem. Scand. 17*, 2138 (1963).
9. Kametani, T., Huang, S.-P., Nakayama, A., and Honda, T., *J. Org. Chem. 47*, 2328 (1982).
10. Fišera, Ľ., Al-Timari, U. A. R., Ertl, P., and Prónayová, N., *Monatsh. Chem., 124*, 1019 (1993).
11. Vasella, A. and Voeffray, R., *J. Chem. Soc., Chem. Commun. 1981*, 97.
12. Huber, R., Knierzinger, A., Obrecht, J. P., and Vasella, A., *Helv. Chim. Acta 68*, 1730 (1985).
13. Bublitz, D. E., *U.S.* 3394145 (1968); *Chem. Abstr. 69*, 76972p (1968).
14. Huisgen, R., Hauck, H., Seidl, H., and Burger, M., *Chem. Ber. 102*, 1117 (1969).

Translated by Ľ. Fišera

Synthesis of 2-Acylaminobenzimidazoles from Acyl Isothiocyanates and *o*-Phenylenediamine

P. KUTSCHY, V. FICERI, and M. DZURILLA

Department of Organic Chemistry, Faculty of Natural Sciences, P. J. Šafárik University, SK-041 67 Košice

Received 4 December 1992

Acyl isothiocyanates react with *o*-phenylenediamine in anhydrous acetonitrile in the presence of dicyclohexylcarbodiimide as cyclodesulfurizing agent with the formation of acyl derivatives of 2-aminobenzimidazole. Intermediates of the reaction are corresponding *N*-(2-aminophenyl)-*N'*-acylthioureas readily formed at laboratory temperature, which cyclize to benzimidazole derivatives by the action of dicyclohexylcarbodiimide in boiling acetonitrile.

Amongst 2-aminobenzimidazole derivatives there are some compounds exhibiting an expressive biological activity. For instance, methyl *N*-(2-benzimidazolyl)carbamate is used as broad spectrum systemic fungicide [1] and some of its derivatives are known as anthelmintics [2]. These compounds can be prepared by the reaction of *o*-phenylenediamine derivatives with methyl *N*-cyanocarbamate [3]. In the year 1977 appeared a paper reporting on the preparation of 2-alkylamino- and 2-arylaminobenzimidazoles from *N*-(2-aminophenyl)-*N'*-substituted thioureas by the action of dicyclohexylcarbodiimide as cyclodesulfurizing agent in boiling benzene [4]. This approach was later applied in the synthesis of pyrimidine analogues of benzimidazoles from 4,5-diaminopyrimidine derivatives and methoxycarbonyl isothiocyanate under reflux in acetonitrile in the presence of dicyclohexylcarbodiimide [5]. Starting from this knowledge and in continuation of our previous research on acyl isothiocyanates we have studied the possibility of employment of different acyl isothiocyanates in the synthesis of 2-acylaminobenzimidazoles *via* the reaction with *o*-phenylenediamine and subsequent cyclodesulfurization by dicyclohexylcarbodiimide. We found that acyl isothiocyanates *I* readily react with *o*-phenylenediamine in dry acetonitrile at laboratory temperature with the formation of *N*-(2-aminophenyl)-*N'*-acylthioureas (*II*). Thioureas *IId* and *IIf* were also prepared independently by the reaction of *o*-phenylenediamine with isothiocyanates *Id* and *If* in benzene. Addition of dicyclohexylcarbodiimide to a solution of independently prepared thiourea or to a solution of not isolated thiourea in acetonitrile at 50 °C and following reflux of the reaction mixture for 2 h afforded 2-acylaminobenzimidazoles *III* (Scheme 1). The above-mentioned work [5] does not describe a detailed procedure. According to our experience for