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Thermolysis of 1-Phthalimidoaziridine-2-carbonitriles in the Presence of Dipolarophiles

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Abstract—Thermolysis of *trans*-3-phenyl-1-phthalimidoaziridine-2-carbonitrile and *trans*-1-phthalimidoaziridine-2,3-dicarbonitrile in the presence of several dipolarophiles involves 1,3-dipolar cycloaddition to intermediate azomethine ylides and leads to 1-phthalimidopyrrolidine derivatives with good yields and high stereoselectivity. Thermally induced opening of the three-membered ring in *trans*-2,3-disubstituted 1-phthalimidoaziridines occurs in conrotatory mode to produce the corresponding *cis*-azomethine ylides in keeping with the orbital symmetry conservation rules. The relative configuration of substituents in the dipolarophiles is retained, which implies concerted mechanism of the addition.

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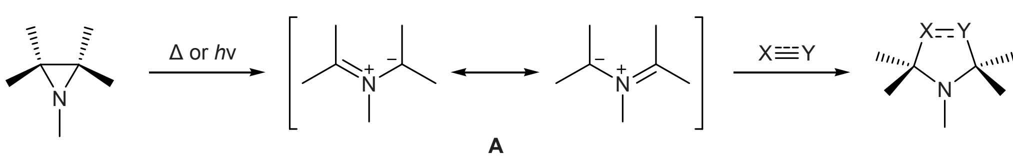
Aziridines are widely used in organic synthesis, and their transformations usually involve opening of the energy-rich three-membered ring. Thermally or photochemically induced cleavage of the C–C bond generates 1,3-dipoles, so-called azomethine ylides **A** [1], and addition of the latter at multiple bonds of dipolarophiles provides a general method for the synthesis of various five-membered nitrogen-containing heterocycles [2] (Scheme 1). Obviously, aziridine ring opening to produce azomethine ylides should be favored by the presence of strong electron-withdrawing groups that are capable of stabilizing partial negative charge on the terminal carbon atoms of the 1,3-dipole thus formed.

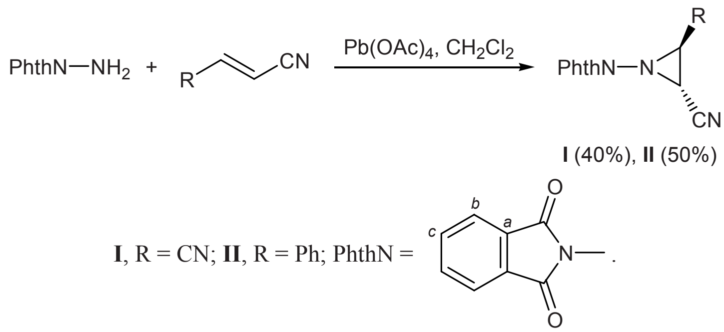
The possibility for generation of azomethine ylides from *N*-aminoaziridine derivatives has been studied very poorly, though this process could give rise in one step to various compounds of the *N*-aminodihydropyrrole and *N*-aminopyrrolidine series. The only series of studies in this field was performed about 25 years ago by Foucaud et al. [3, 4]. These authors showed that some *N*-phthalimidoaziridines having three or four electron-withdrawing substituents on slight heating (or even at room temperature!) in the presence of dipolarophiles are in fact converted into compounds which may be regarded as products of intra- (dihydrooxazoles, oxazoles) and/or intermolecular transformations (dihydropyrroles, azetidines) of the corresponding *N*-phthalimidoazomethine ylides. It was also noted that the activating effect of substituents on the aziridine carbon atoms decreases in the series CN >> COR > COOR. Analogous intramolecular transformations were reported for *N*-succinimidoaziridines [5].

However, the only dipolarophile used in the above studies on [2+3]-cycloaddition of azomethine ylides was strongly reactive dimethyl acetylenedicarboxylate, and the steric structure of a few isolated adducts was not determined rigorously. Therefore, both the scope of application of this reaction series for the synthesis of *N*-aminoazoles and general relations (primarily stereochemical) holding in the process remained unclear. The goal of the present work was to examine thermal transformations of much more stable *trans*-disubstituted *N*-phthalimidoaziridines **I** and **II** in the presence of

Scheme 1.



Scheme 2.



I, R = CN; **II**, R = Ph; PhthN =

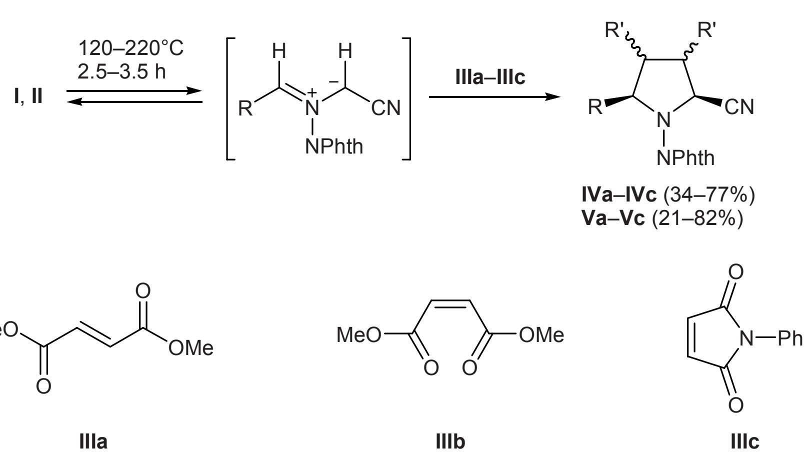
various dipolarophiles and elucidate the mechanism and stereochemical aspects of the formation of possible 1,3-dipolar cycloaddition products.

The choice of substituents in the three-membered ring of aziridines **I** and **II** was dictated by the following reasons. According to published data [4], cyano group which is known as a strong electron acceptor maximally facilitates cleavage of aziridine ring with formation of azomethine ylide, while phenyl group is capable of effectively delocalizing both positive and negative charges. As dipolarophiles we selected extensively studied compounds **IIIa**–**IIIc** possessing electron-deficient double carbon–carbon bonds, which are frequently used as “traps” and are convenient models for studying stereochemistry of the entire transformation sequence.

N-Phthalimidoaziridines **I** and **II** were synthesized from *N*-aminophthalimide and the corresponding unsaturated nitriles according to the standard procedure for oxidative aminoaziridination [6] (Scheme 2). Commercially available fumaronitrile was pure *E* isomer. However, commercial samples of cinnamonitrile from different sources were mixtures of *E* and *Z* isomers whose separation is quite tedious. Therefore, we prepared pure (*E*)-cinnamonitrile from accessible (*E*)-cinnamic acid through the corresponding amide.

The structure of aziridines **I** and **II** was confirmed by the ^{1}H and ^{13}C NMR and mass spectra and elemental analyses. *N*-Aminoaziridine derivatives are characterized by slow (on the NMR time scale) inversion of the endocyclic nitrogen atom [7]. In the case of aziridine **I** this process is degenerate, so that compound **I** displays in the ^{1}H NMR spectrum two doublets from protons in the aziridine ring of a single form at δ 4.8–4.9 ppm. According to the ^{1}H NMR data, aziridine **II** at room temperature exists as a mixture of two invertomers, one of which considerably prevails (~96:4). Signals from the aziridine protons of the major invertomer appear in a stronger field (δ 3.38 and 4.52 ppm; cf. δ 4.12 4.73 ppm for the minor one). In the ^{13}C NMR spectrum of **II**, only signals belonging to the major invertomer could be reliably distinguished. Taking into account that the effective volume of the phenyl group is clearly larger than the volume of the linear cyano

Scheme 3.



IV, R = CN; **V**, R = Ph.

group, the phenyl ring and phthalimide fragment in the major invertomer are likely to be oriented *trans*. *trans* Configuration of both adducts **I** and **II** with respect to the $C^2–C^3$ bond follows from the small vicinal coupling constant for the aziridine protons (^3J = 5.1 Hz for compound **I** and the major invertomer of **II**; ^3J = 5.6 Hz for the minor invertomer of **II**) [7].

Thermolysis of aziridines **I** and **II** was performed in sealed ampules and/or in a hermetically closed heat-resistant reactor in the presence of 1.5 equiv of the corresponding dipolarophile. As solvent we used benzene or more polar and higher-boiling chlorobenzene.

Preliminary experiments were carried out by heating aziridine **I** in the presence of dimethyl fumarate (**IIIa**). Compound **I** is appreciably soluble in benzene only above 150°C, and in chlorobenzene, at 110°C; nevertheless, it was necessary to heat the reaction mixture to 220°C to initiate the process. Likewise, heating to the same temperature was required for the reactions of **I** with dipolarophiles **IIIb** and **IIIc**. Therefore, chlorobenzene was selected as solvent. Monitoring of the reaction course by TLC showed that complete conversion of aziridine **I** into thermolysis products was attained in about 3 h. The reactions of aziridine **II** with dipolarophiles **IIIa–IIIc** were complete in 2.5–3 h even at 120°C, so that this series of experiments was performed using benzene as solvent. Insofar as each of aziridines **I** and **II** started to react with all dipolarophiles **IIIa–IIIc** at the same temperature, we presumed that the rate-determining step in the overall process is just opening of the aziridine ring to generate azomethine ylide.

In all cases, the thermolysis was accompanied by tarring and formation of phthalimide. The latter may appear in the reaction mixture as a result of elimination from both initial aziridine and final product. However, when aziridines **I** and **II** were heated under the same conditions but in the absence of dipolarophile, no decomposition was observed; therefore, elimination of phthalimide fragment from the cycloaddition products seems to be more probable.

Comparison of the thermolysis conditions for aziridines **I** and **II** indicates more facile conversion of phenyl-substituted compound **II** into azomethine ylide, i.e., phenyl ring stabilizes intermediate dipole more effectively than does strong electron-withdrawing cyano group. On the other hand, published data for tri- and tetra-substituted aziridines [4] clearly demonstrate that, as might be expected, reduction in the number of substituents capable of stabilizing azomethine ylide leads to more severe conditions necessary for opening of the aziridine ring.

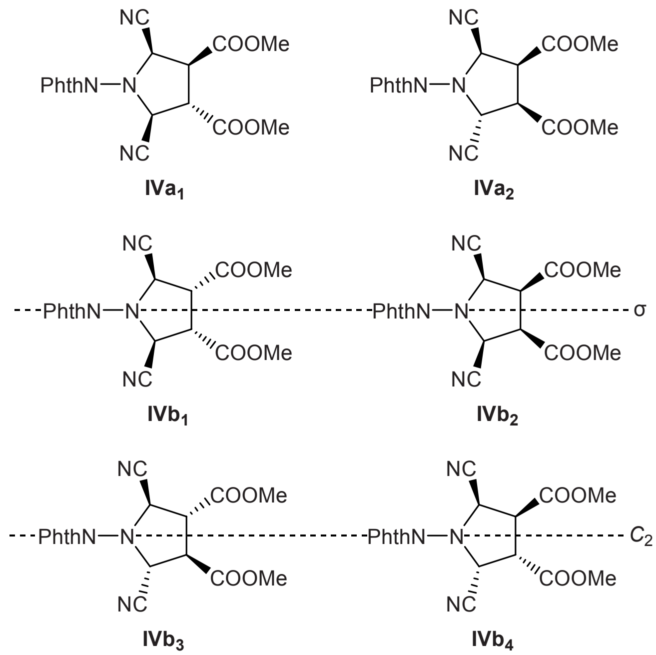
In all cases, thermolysis of aziridines **I** and **II** in the presence of dipolarophiles **IIIa–IIIc** led to the formation of the corresponding 1,3-dipolar cycloaddition products, previously unknown *N*-phthalimidopyrrolidines **IVa–IVc** and **Va–Vc** (Scheme 3). The selectivity of the process was confirmed by the ^{1}H NMR spectra of the reaction mixtures, which were recorded immediately after thermolysis.

The assumed structure of crystalline *N*-phthalimidopyrrolidines **IVa–IVc** and **Va–Vc** was consistent with their ^{1}H and ^{13}C NMR and mass spectra and elemental analyses. The mass spectra of **IVa–IVc** and **Va–Vc** contained the corresponding molecular ion peaks, strong peaks due to $[M - 146]^+$ and/or $[M - 147]^+$ ions (loss of phthalimide fragment), and ion peak with *m/z* 147. In the ^{1}H NMR spectra of these compounds, multiplets typical of phthalimido group were located in the region δ 7.70–8.00 ppm. The imide carbonyl carbon atoms resonated in the ^{13}C NMR spectra at δ_C 164–165 ppm, and carbon atoms in the six-membered aromatic ring gave signals at δ_C 129–130 (C^a), 123–124 (C^b), and 134–135 ppm (C^c). The chemical shifts of protons and carbon nuclei in the cyano, methoxycarbonyl, and phenyl groups had their usual values.

Signals from protons neighboring to the nitrogen atom in the pyrrolidine fragments usually appear in the ^{1}H NMR spectra of adducts **IVa–IVc** and **Va–Vc** as doublets at δ 4.9–5.4 ppm. Protons on C^3 and C^4 resonate at δ 3.5–4.4 ppm, and the number and multiplicity of their signals depend on a particular compound structure. Four protons in the pyrrolidine ring of adducts **IVa** and **Va–Vc** form an *ABXY* spin system, and the 3-H and 4-H signals appear as doublets of doublets which sometimes degenerate into triplets. This is consistent with magnetic nonequivalence of those protons in molecules **Va–Vc** and the absence of any symmetry elements (such as reflection plane or second-order rotation axis) in pyrrolidine **IVa** molecule. The four ring protons in **IVb** and **IVc** give only two signals (*AA'XX'* spin system), indicating the presence of some symmetry elements in their molecules. In the spectrum of bicyclic adduct **IVc**, these signals look like slightly broadened singlets, which corresponds to $^3J_{AX}$ not exceeding 1–2 Hz. The above stated is consistent with the presence of four pyrrolidine carbon signals in the ^{13}C NMR spectrum of adduct **IVa** and only two signals in the spectra of **IVb** and **IVc**.

A fairly difficult problem was to determine steric structure of the isolated compounds. For this purpose, dependences of vicinal coupling constants $^3J_{HH}$ upon dihedral angle (like Karplus equation) are generally used. However, the ranges of $^3J_{HH}$ for *cis*- and *trans*-oriented protons in five-membered heterocycles strongly overlap each other, so that $^3J_{HH}$ values cannot be regarded as reliable criteria for configuration assignment [8]. This is clearly demonstrated by the data for adduct **IVa** obtained from aziridine **I** and dimethyl fumarate (**IIIa**). All vicinal constants for the ring protons in **IVa** are almost similar ($J_{2,3} = J_{4,5} = 9.1$, $J_{3,4} = 9.8$ Hz). It would seem that equal $J_{2,3}$ and $J_{4,5}$ constants imply similar orientations of the H^2/H^3 and H^4/H^5 couples (both *cis* or both *trans*). On the other hand, examination of all six theoretically possible diastereoisomers of **IVa** (structures **IVa₁**, **IVa₂** and **IVb₁**–**IVb₄**) shows that similar orientations of the above proton couples inevitably correspond to the presence of a symmetry element (plane or C_2 axis; structures **IVb₁**–**IVb₄**); this means that these protons and the respective carbon atoms should be enantiotopic or equivalent in pairs. In contrast, all ring protons and carbon atoms in **IVa** are nonequivalent, i.e., molecule **IVa** lacks any symmetry element; therefore, it may have only asymmetric structure like **IVa₁** or **IVa₂**.

Insofar as vicinal coupling constants $^3J_{HH}$ are clearly unsuitable for determination of steric configuration of the isolated adducts, we have resorted to 2D ^{1}H NOESY technique. Figure 1 shows the 2D ^{1}H NOESY spectrum of adduct **IVa**; it is seen that the NOEs for H^2–H^3 and H^4–H^5 sharply differ in magnitude. The observed pattern suggests *cis* orientation of H^4 and H^5 and *trans* orientation of H^2 and H^3. Furthermore, the H^3–H^4 cross peak is very weak, which corresponds to *trans* orientation of these protons. Thus the configuration of molecule **IVa** is given by structure **IVa₁**.



Theoretically, symmetric compound **IVb** may have one of the following four configurations: **IVb₁** and **IVb₂** with a symmetry plane and pairwise enantiotopic protons or **IVb₃** and **IVb₄** with a second-order rotation axis and pairwise equivalent protons. These two structure types may be distinguished provided that the rotation of the phthalimido group about the N–N bond is slow on the NMR time scale. The reason is that diastereosomers **IVb₃** and **IVb₄** retain the C_2 symmetry axis at any conformation of the phthalimide residue, and all protons and carbon atoms therein should remain equivalent in pairs even if the rotation is restricted completely. On the other hand, in the most stable conformers of structures **IVb₁** and **IVb₂** the phthalimido group should be orthogonal to the pyrrolidine ring plane. In this case, provided that the rotation about the N–N bond is restricted, two halves of the

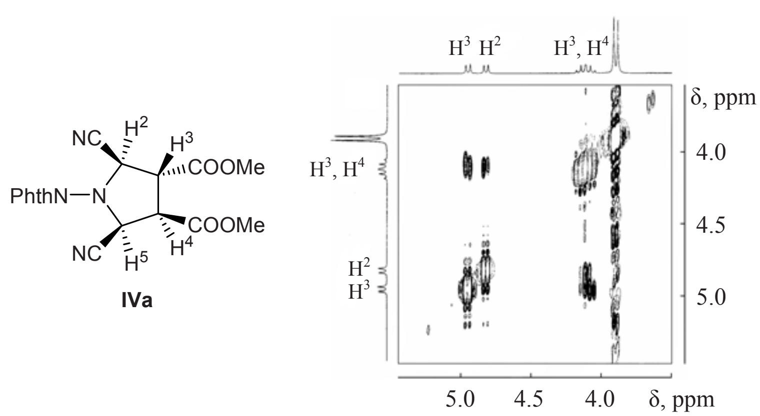


Fig. 1. 2D ^{1}H NOESY spectrum of dimethyl *rel*-(2*R*,3*R*,4*R*,5*S*)-2,5-dicyano-1-phthalimidopyrrolidine-3,4-dicarboxylate (**IVa**).

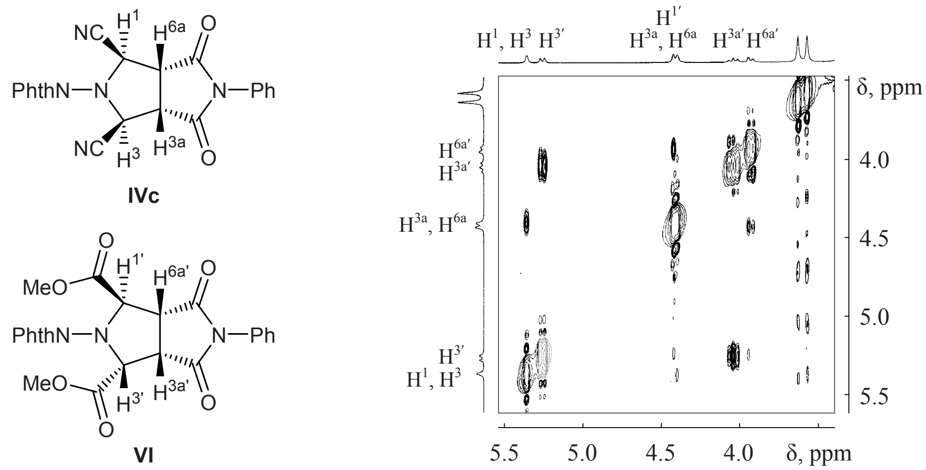


Fig. 2. 2D ^{1}H NOESY spectrum of a mixture of compounds **IVc** and **VI** at a ratio of 1 : 2.

phthalimide fragment become nonequivalent, which should be reflected in a complicated pattern of the corresponding signals in the NMR spectra.

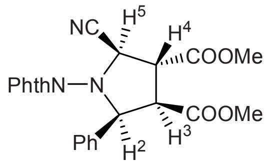
Even at room temperature, the signal from the imide carbonyl carbon atoms in the ^{13}C NMR spectrum of **IVb** (δ_C 164.9 ppm) is very weak and broadened; obviously, this is the result of a slow (on the NMR time scale) dynamic process. Therefore, molecule **IVb** possesses a symmetry plane (structure **IVb$_1$** or **IVb$_2$**) but not symmetry axis. Assuming that strained all-*cis* structure **IVb$_2$** is unlikely to be formed as the only product of intermolecular reaction at 220°C, adduct **IVb** was assigned structure **IVb$_1$**.

The NMR spectra of bicyclic adduct **IVc** also indicate that its molecule is symmetric. It may have configurations analogous to **IVb$_1$–IVb$_4$**. However, *trans*-junction of two five-membered rings is strongly unfavorable; therefore, structures like **IVb$_3$** and **IVb$_4$** may be ruled out. Structures **IVb$_1$** and **IVb$_2$** possess a symmetry plane and differ by orientation of the cyano groups and *N*-phenylmaleimide fragment with respect to the pyrrolidine ring plane. To distinguish between them, we used the “intermolecular” 2D ^{1}H NOESY version and compared NOEs for couples of neighboring protons in pyrrolidine **IVc** and previously synthesized compound **VI** whose configuration unambiguously follows from the absence of symmetry elements in its molecule. In order to take into account equivalence of the H^1–H^{6a} and H^3–H^{3a} couplings in molecule **IVc**, a twofold amount of compound **VI** was taken.

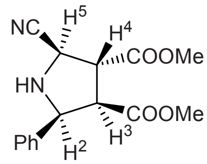
The NOESY spectrum of a 1 : 2 mixture of compounds **IVc** and **VI** (Fig. 2) clearly shows that the NOE for H^1–H^{6a}/H^3–H^{3a} in **IVc** is comparable with the NOE for the *trans*-oriented $H^{1'}$ and $H^{6a'}$ protons and that it is considerably weaker than for the *cis*-oriented $H^{3'}$–$H^{3a'}$ and $H^{3a'}$–$H^{6a'}$ protons in **VI**. These findings unambiguously indicate *trans* orientation of the cyano groups and *N*-phenylmaleimide fragment in molecule **IVc**, i.e., its *exo* configuration.

All products of cycloaddition of aziridine **II** to dipolarophiles **IIIa–IIIc** are characterized by slow (on the NMR time scale) rotation of the phthalimido group about the N–N bond. As a result, the imide carbonyl carbon signals (δ_C 164–165 ppm) are not observed in the ^{13}C NMR spectra of **Va–Vc**, and sometimes C^a signals disappear; in addition, the C^a and C^b signals broaden. Presumably, the phenyl ring in the α-position to the former aziridine nitrogen atom creates strong steric hindrances to rotation of the phthalimide fragment (as compared to cyano-substituted analog).

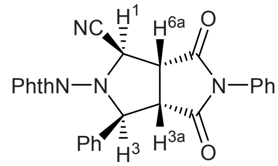
In the ^{1}H NMR spectra of compounds **Va–Vc**, signal from the C**H**Ph proton appears as a doublet in a weaker field than the C**H**CN proton and is broader and lower. Most probably, this is the result of long-range interaction with *ortho*-protons in the benzene ring. The most upfield signal in the spectra is that from the proton in the vicinal position with respect to the phenyl group. Signals from the ring protons in the spectra of adducts **Va–Vc** (with account taken of their multiplicity) were assigned, and their steric structure was determined, using 2D ^{1}H NOESY as well. For example, strong nuclear Overhauser effect between the *ortho*-protons in the phenyl ring, on the one hand, and spatially close 3-H and 3a-H, on the other, allowed us to unambiguously assign signals in the ^{1}H NMR spectrum of compound **Vc**. In addition, the cross peak between the *cis*-oriented protons in the *N*-phenylmaleimide fragment (H^{3a}/H^{6a}) is much greater than the cor-



Va



Vb



Vc

responding NOEs for the *trans*-oriented proton couples H^1–H^{6a} and H^3–H^{3a} (the latter are approximately similar), which confirms the assumed relative arrangement of substituents in molecule **Vc**.

Strong NOEs between *ortho*-protons in the phenyl ring and geminal (H^2) and vicinal (H^3) protons were also observed in the 2D ^{1}H NOESY spectrum of **Vb**, which clearly indicated *cis* orientation of the H^3–H^4 couple and *trans* orientation of H^2–H^3 and H^4–H^5. Therefore, steric configuration of this compound is fairly obvious.

It follows from the 2D ^{1}H NOESY spectrum of adduct **Va** that the *ortho*-protons in the phenyl ring are loated closely to only H^2 and that the vicinal H^3 proton is fairly distant. This means that the phenyl and neighboring ester groups are oriented *cis*. Correspondingly, the H^2–H^3 couple shows a strong NOE. A weaker effect is observed for H^2–H^5 and H^3–H^5. Presumably, the H^2, H^3, and H^5 protons reside at the same side of the pyrrolidine ring. The cross peak for H^3–H^4 is relatively weak, which is also consistent with the structure assigned to **Va**.

Thus we can state that the NOESY method ensures reliable determination of steric structure of the obtained pyrrolidine derivatives and that the use of spin–spin coupling constants is inappropriate.

Our results provide rigorous substantiation of the following mechanism of the observed transformation. The first step is conrotatory opening of the three-membered ring in *trans*-2,3-disubstituted 1-phthalimidoaziridines **I** and **II** to generate the corresponding *cis*-azomethine ylides, which is allowed by the orbital symmetry conservation rules. Next follows concerted cycloaddition of intermediate 1,3-dipoles at the double C=C bond of dipolarophiles **IIIa**–**IIIc**. The complete stereospecificity of both steps is indicated by the facts that the substituents in the initial *trans*-2,3-disubstituted aziridine appear *cis*-oriented in adducts **IVa**–**IVc** and **Va**–**Vc** and that the relative configuration of substituents in dipolarophiles **IIIa**–**IIIc** is retained.

Moreover, the reactions of aziridines **I** and **II** with dimethyl maleate (**IIIb**) and *N*-phenylmaleimide (**IIIc**) gave only one stereoisomer of the two possible for the above mechanism. This means that the cycloaddition of azomethine ylides is stereoselective: the products are exclusively less sterically strained adducts **IVb**, **IVc**, **Vb**, and **Vc** having *exo* configuration. One more evidence for high sensitivity of the reaction to steric factors may be relatively low yields of adducts with dimethyl fumarate (**IIIa**): three substituents in molecules **IVa** and **Va** reside at the one side of relatively small pyrrolidine ring.

To conclude we can state that thermolysis of disubstituted *N*-phthalimidoaziridines **I** and **II** in the presence of dipolarophiles leads to the formation of *N*-aminopyrrolidine derivatives with good yields and high stereoselectively. The described reaction may be regarded as a general method for the synthesis of such difficultly accessible compounds.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer at 300.13 and 75.47 MHz, respectively; the chemical shifts were measured relative to the residual proton ($CHCl_3$, δ 7.26 ppm; DMSO, δ 2.50 ppm; CH_3CN, δ 1.96 ppm) and carbon signals ($CDCl_3$, δ_C 77.16 ppm; DMSO-d_6, δ_C 39.52 ppm; CD_3CN, δ_C 1.32 ppm) of the deuterated solvents. The elemental compositions were determined on an HP-185B automatic CHN analyzer. The mass spectra (electron impact, 70 eV) were obtained on an MKh-1321 instrument, and the ESI (electrospray ionization) mass spectra were run on a Finnigan MAT-90 spectrometer. The reaction mixtures were analyzed, and the purity of the isolated products was checked, by TLC on Alugram sil G/UV_{254} plates. *N*-Aminophthalimide was synthesized according to the procedure described in [9].

(*E*)-Cinnamonitrile. A solution of 5.0 g (30 mmol) of (*E*)-cinnamoyl chloride in 20 ml of methylene chloride was added under vigorous stirring to a mixture of 45 ml (0.6 mol) of 25% aqueous ammonia and 150 g of ice. After 20 min, the white precipitate of (*E*)-cinnamamide was filtered off and dried in air. Yield 4.0 g (90%), mp 146°C; published data [10]: mp 149°C.

A mixture of 4.0 g (27 mmol) of (*E*)-cinnamamide and 4.6 g (32 mmol) of P_2O_5 in 100 ml of toluene was heated for 3 h under reflux, the progress of the reaction being monitored by TLC. The solution was separated by decanting, 50 ml of toluene was added to the solid residue, and the mixture was heated for 1 h under reflux. The solution was separated by decanting, combined with the first solution, and passed through a thin layer of silica gel. The solvent was distilled off under reduced pressure to obtain 2.2 g (63%) of (*E*)-cinnamonitrile as a yellow liquid with a specific odor. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.88 d (1H, CHCN, *J* = 16.7 Hz), 7.40 d (1H, C**H**Ph, *J* = 16.7 Hz), 7.43–7.48 m (5H, H_{arom}) (cf. [11]). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 96.41 (**C**HCN), 118.24 (CN), 127.44 (C^m), 129.20 (C^o), 131.30 (C^p), 133.60 (C^i), 150.65 (**C**HPh).

Oxidative addition of *N*-aminophthalimide to unsaturated nitriles. Potassium carbonate, 1.242 g (9 mmol), was dispersed in a solution of 3 mmol of fumaronitrile or cinnamonitrile in 20 ml of anhydrous methylene chloride, and 486 mg (3 mmol) of *N*-aminophthalimide and 1.329 g (3 mmol) of lead tetraacetate were added in small approximately equal portions over a period of 40 min under stirring and cooling with ice water. When the addition was complete, the mixture was stirred for 20 min and filtered through a thin layer of silica gel, and the precipitate was washed with 40 ml of methylene chloride or chloroform. The filtrate was combined with the washings and treated as indicated below.

***trans*-1-Phthalimidoaziridine-2,3-dicarbonitrile (I).** The solution obtained from 234 mg (3 mmol) of fumaronitrile was evaporated under reduced pressure until crystallization began and was left overnight in a freezing chamber (–15 to –20°C). The white flaky crystals were filtered off and dried in air. Yield 285 mg (40%), mp 198°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.83 d and 4.92 d (1H each, C**H**CN, *J* = 5.1 Hz), 7.84–7.99 m (4H, C_6H_4). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 31.74 and 32.03 (C^2, C^3), 113.39 and 114.58 (CN), 123.65 (C^b), 129.62 (C^a), 135.21 (C^c), 163.74 (C=O). Mass spectrum (ESI): *m*/*z* 238 $[M]^+$. Found, %: C 60.40; H 2.74; N 23.85. $C_{12}H_6N_4O_2$. Calculated, %: C 60.51; H 2.54; N 23.52.

***trans*-3-Phenyl-1-phthalimidoaziridine-2-carbonitrile (II).** The solution obtained from 387 mg (3 mmol) of (*E*)-cinnamonitrile was evaporated under reduced pressure (but not to dryness). A small amount of diethyl ether was added to the residue, and the mixture was left to stand for crystallization. The precipitate was filtered off and dried in air. Yield 433 mg (50%), mp 132°C. According to the ^{1}H NMR data, the product was a mixture of two invertomers at a ratio of 96:4. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.38 d and 4.52 d (*J* = 5.1 Hz, major invertomer), 4.12 d and 4.73 d (*J* = 5.6 Hz, minor invertomer) (total of 2H); 7.42 m (C_6H_5, major invertomer), 7.65 m (C_6H_5, minor invertomer) (total of 5H); 7.74–7.88 m (4H, C_6H_4). ^{13}C NMR spectrum of the major invertomer ($CDCl_3$), δ_C, ppm: 34.80 (C^2), 49.48 (C^3), 114.83 (CN), 123.86 (C^b), 127.21 (C^m), 129.05 (C^o), 129.52 (C^a), 130.19 (C^p), 132.64 (C^i), 134.81 (C^c), 164.82 (C=O). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 289 (31) $[M]^+$, 143 (88) [*M* – PhthN], 142 (51) [*M* – PhthNH], 116 (55), 104 (100) [C_6H_4CO], 89 (11), 84 (12), 76 (75), 51 (11), 50 (28). Found, %: C 70.41; H 3.99; N 14.73. $C_{17}H_{11}N_3O_2$. Calculated, %: C 70.59; H 3.81; N 14.53.

Dimethyl *rel*-(2*R*,3*R*,4*R*,5*S*)-2,5-dicyano-1-phthalimidopyrrolidine-3,4-dicarboxylate (IVa). A dry heat-resistant glass ampule was charged with 225 mg (0.94 mmol) of aziridine **I** and 204 mg (1.40 mmol) of dimethyl fumarate (**IIIa**) in 12 ml of anhydrous chlorobenzene. The ampule was sealed, placed into a metal high-pressure container with a screw cap, and heated for 3.5 h at 220°C in a muffle furnace. After cooling, the ampule was opened, the solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography on 40 g of silica gel using hexane–methylene chloride (1:1) to pure methylene chloride as eluent (gradient elution). Yield 123 mg (34%), mp 205°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.86 s and 3.89 s (3H each, Me), 4.06 d.d and 4.11 d.d (1H each, 3-H, 4-H, *J* = 9.1, 9.8 Hz), 4.79 d and 4.92 d (1H each, 2-H, 5-H, *J* = 9.1 Hz), 7.80–7.96 m (4H, C_6H_4). ^{13}C NMR spectrum (DMSO-d_6–$CDCl_3$, 1:2), δ_C, ppm: 46.51, 47.24 (CH_3); 52.86, 52.94, 54.32, 54.54 (C^2–C^5); 115.11, 115.69 (CN); 123.44 (C^b), 129.14 (C^a), 134.67 (C^c), 164.55 (C=O); 167.08, 167.38 (C=O, ester). Mass spectrum (ESI): *m*/*z*: 382 $[M]^+$. Found, %: C 56.62; H 3.88; N 14.72. $C_{18}H_{14}N_4O_6$. Calculated, %: C 56.55; H 3.69; N 14.65.

Dimethyl *rel*-(2*R*,3*R*,4*S*,5*S*)-2,5-dicyano-1-phthalimidopyrrolidine-3,4-dicarboxylate (IVb). A heat-resistant glass reactor with a screw cap was charged with 227 mg (0.95 mmol) of aziridine **I** and 206 mg (1.40 mmol) of dimethyl maleate (**IIIb**) in 12 ml of anhydrous chlorobenzene and was heated for 3 h at 220°C on a silicone oil bath. After cooling, the solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography on 40 g of silica gel using hexane–ethyl acetate (2:1) to ethyl acetate–ethanol (2 : 1) as eluent (gradient elution). Yield 280 mg (77%), mp 204°C. ^{1}H NMR spectrum (CD_3CN), δ, ppm: 3.80 s (6H, Me), 4.03 m (2H, 3-H, 4-H), 4.91 m (2H, 2-H, 5-H), 7.87–7.94 m (4H, C_6H_4). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 47.56 (CH_3), 53.61 and 54.49 (C^2–C^5), 115.81 (CN), 124.47 (C^b), 129.37 (C^a), 135.48 (C^c), 164.92 br.s (C=O), 167.77 (C=O, ester). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 382 (0.1) $[M]^+$, 324 (10), 147 (100) [PhthNH], 105 (65), 76 (30), 59 (17), 50 (10), 43 (10). Found, %: C 56.54; H 3.66; N 14.66. $C_{18}H_{14}N_4O_6$. Calculated, %: C 56.68; H 3.86; N 14.65.

***exo*,*exo*-4,6-Dioxo-5-phenyl-2-phthalimidoocta-hydropyrrolo[3,4-*c*]pyrrole-1,3-dicarbonitrile (IVc).** A dry heat-resistant glass ampule was charged with 206 mg (0.86 mmol) of aziridine **I** and 224 mg (1.30 mmol) of *N*-phenylmaleimide (**IIIc**) in 12 ml of anhydrous chlorobenzene. The ampule was sealed, placed into a metal high-pressure container with a screw cap, and heated for 3 h at 220°C in a muffle furnace. After cooling, the ampule was opened, the solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography on 40 g of silica gel using methylene chloride to methylene chloride–diethyl ether (10 : 1) as eluent (gradient elution). Yield 206 mg (58%), mp 262°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.39 s (2H, 3a-H, 6a-H), 5.36 s (2H, 1-H, 3-H), 7.44–7.62 m (5H, C_6H_5), 7.89–7.96 m (4H, C_6H_4). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 49.68 (C^{3a}, C^{6a}), 56.49 (C^1, C^3), 118.21 (CN), 123.70 (C^b), 127.08 (C^m), 129.10 (C^p), 129.25 (C^o), 129.73 (C^a), 131.97 (C^i), 135.10 (C^c), 165.21 (C=O), 173.51 (C^4, C^6). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 411 (3) $[M]^+$, 264 (100) [*M* – PhthNH], 147 (49) [PhthNH], 145 (39), 119 (55), 117 (39), 104 (55) [C_6H_4CO], 91 (21), 86 (13), 84 (23), 76 (59), 65 (16), 49 (35). Found, %: C 64.38; H 3.29; N 17.22. $C_{22}H_{13}N_5O_4$. Calculated, %: C 64.23; H 3.19; N 17.02.

Dimethyl *rel*-(2*R*,3*S*,4*S*,5*S*)-5-cyano-2-phenyl-1-phthalimidopyrrolidine-3,4-dicarboxylate (Va). A heat-resistant glass reactor with a screw cap was charged with 289 mg (1.0 mmol) of aziridine **II** and 216 mg (1.5 mmol) of dimethyl fumarate (**IIIa**) in 12 ml of anhydrous benzene, and the mixture was heated for 3.5 h at 120°C on a silicone oil bath. After cooling, the solvent was distilled off under reduced pressure, the oily residue was treated with a small amount of diethyl ether, and the white precipitate was filtered off and dried in air. Yield 91 mg (21%), mp 190°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.20 s (3H, Me), 3.83 d.d (1H, 3-H, *J* = 8.2, 10.3 Hz), 3.83 s (3H, Me), 4.20 d.d (1H, 4-H, *J* = 8.2, 9.7 Hz), 5.05 d (1H, 5-H, *J* = 9.7 Hz), 5.39 d (1H, 2-H, *J* = 10.3 Hz), 7.22–7.31 m (3H, *m*-H, *p*-H), 7.45–7.47 m (2H, *o*-H), 7.69–7.80 m (4H, C_6H_4). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 46.55, 49.49, 52.23, 53.34, 53.53 (CH_3, C^3–C^5); 66.68 (C^2); 116.63 (CN); 123–124 br.s, 124–125 br.s (C^b); 128.36 (C^m, C^o); 129.00 (C^p); 129.64 br.s (C^a); 134.9 br.s (C^i, C^c); 169.49, 169.56 (C=O). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 433 (2) $[M]^+$, 322 (22), 287 (60) [*M* – PhthN], 255 (73), 251 (16), 227 (56), 226 (56), 195 (42), 182 (56), 168 (15), 167 (14), 148 (10), 142 (100), 130 (20), 115 (42), 104 (71) [C_6H_4CO], 90 (15), 76 (56), 59 (53), 51 (12). Found, %: C 63.74; H 4.39; N 9.70. $C_{23}H_{19}N_3O_6$. Calculated, %: C 63.72; H 4.46; N 9.59.

Dimethyl *rel*-(2*R*,3*R*,4*S*,5*S*)-5-cyano-2-phenyl-1-phthalimidopyrrolidine-3,4-dicarboxylate (Vb). A heat-resistant glass reactor with a screw cap was charged with 289 mg (1.0 mmol) of aziridine **II** and 216 mg (1.5 mmol) of dimethyl maleate (**IIIb**) in 12 ml of anhydrous benzene, and the mixture was heated for 2.5 h at 120°C. After cooling, the solvent was distilled under reduced pressure, the oily residue was treated with a small amount of diethyl ether, and the white precipitate was filtered off and dried in air. Yield 221 mg (51%), mp 186°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.55 d.d (1H, 3-H, *J* = 7.3, 9.2 Hz), 3.66 s and 3.71 s (3H each, Me), 4.18 d.d (1H, 4-H, *J* = 8.2, 9.2 Hz), 5.14 d (1H, 5-H, *J* = 8.2 Hz), 5.15 d (1H, 2-H, *J* = 7.3 Hz), 7.24–7.37 m (3H, *m*-H, *p*-H), 7.48–7.51 m (2H, *o*-H), 7.84 m (4H, C_6H_4). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 46.21, 50.63, 52.45, 52.68, 53.58 (CH_3, C^3–C^5); 67.36 (C^2); 117.82 (CN); 123.51 br.s (C^b); 127.60, 128.42 (C^m, C^o); 128.49 (C^p); 135.13 (C^c); 137.65 (C^i); 169.24, 170.28 (C=O). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 433 (1) $[M]^+$, 375 (12), 322 (22), 287 (100), 286 (35) [*M* – PhthNH], 226 (62), 225 (55), 195 (130), 182 (59), 167 (14), 148 (10), 142 (59), 131 (16), 115 (25), 104 (48) [C_6H_4CO]. Found, %: C 63.74; H 4.39; N 9.70. $C_{23}H_{19}N_3O_6$. Calculated, %: C 63.82; H 4.50; N 9.53.

***exo*,*exo*-4,6-Dioxo-3,5-diphenyl-2-phthalimido-octahydropyrrolo[3,4-*c*]pyrrole-1-carbonitrile (Vc).** A heat-resistant glass reactor with a screw cap was charged with 289 mg (1.0 mmol) of aziridine **II** and 260 mg (1.5 mmol) of *N*-phenylmaleimide (**IIIc**) in 12 ml of anhydrous benzene, and the mixture was heated for 3 h at 120°C and left to stand overnight. The white crystals were filtered off and dried in air. Yield 380 mg (82%), mp 255°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.63 d.d (1H, 3a-H, *J* = 8.1, 9.6 Hz), 4.05 d.d

(1H, 6a-H, *J* = 6.3, 9.6 Hz), 5.05 d (1H, 1-H, *J* = 6.3 Hz), 5.17 d (1H, 3-H, *J* = 8.1 Hz), 7.31–7.61 m (10H, C_6H_5), 7.72–7.81 m (4H, C_6H_4). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 46.96, 50.52, 53.78 (C^1, C^{3a}, C^{6a}); 68.75 (C^3); 116.45 (CN); 126.52, 127.69, 129.20, 129.33, 129.45, 129.52, 131.20, 135.70 (C_{arom}); 135.07 br.s (C^s); 172.85, 173.30 (C^4, C^6). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 462 (2) $[M]^+$, 435 (10), 316 (28), 315 (62) [*M* – PhthNH], 168 (28), 147 (11) [PhthNH], 142 (100), 115 (14), 104 (21) [C_6H_4CO], 78 (25), 76 (19). Found, %: C 70.13; H 3.90; N 12.12. $C_{27}H_{18}N_4O_4$. Calculated, %: C 70.03; H 3.87; N 12.09.

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