

1,3-Dipolar Cycloaddition of Azolium Dicyanomethylides

Enrique Díez-Barra and Carmen Pardo *

Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, Madrid 3, Spain

José Elguero

Instituto de Química Médica, C.S.I.C., Juan de la Cierva 3, Madrid 6, Spain

Jean Arriau

Département de Chimie Structurale, Faculté des Sciences, Université de Pau et des Pays de l'Adour, 64000 Pau, France

1,3-Dipolar cycloaddition of azolium *N*-dicyanomethylides, which have an azomethine ylide structure, to acetylenic dipolarophiles affords azolopyridine derivatives. The initial cycloadduct has been isolated for the first time. Using unsymmetrical dipolarophiles, only one of the two possible regioisomers has been obtained. The orientation problem has been approached theoretically by a second-order perturbational treatment, which also gives good results in the case of the reaction of an azomethine imine, 1-ethylbenzo-triazolium 3-dicyanomethylide.

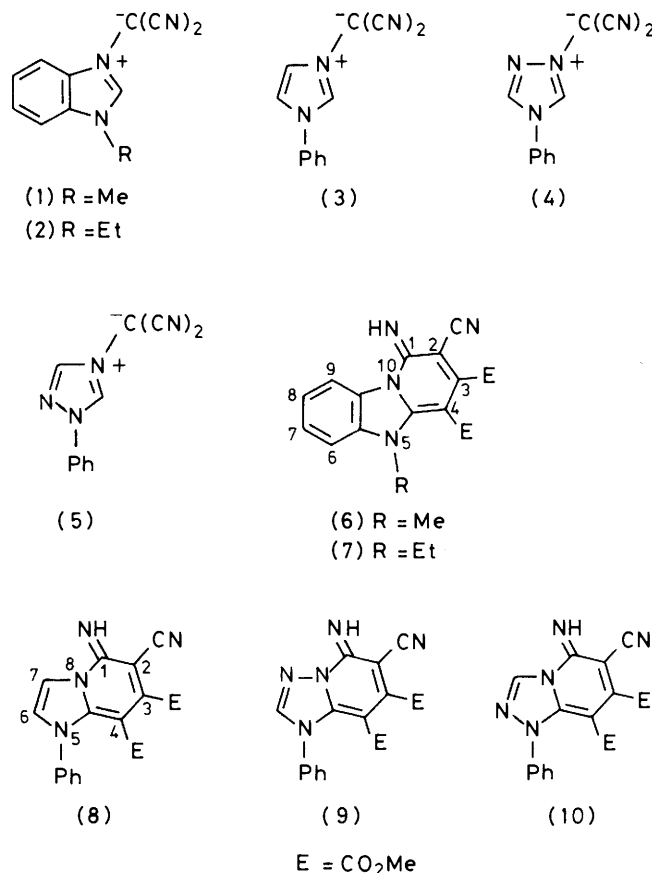
Reaction of azinium dicyanomethylides with acetylenic esters yields indolizine derivatives by loss of HCN from the initial cycloadduct; ¹⁻⁵ however, reactions of 1-methylimidazolium and thiazolium dicyanomethylides with dimethyl acetylenedicarboxylate (DMAD) afford imidazo[1,2-*a*] and thiazolo[3,2-*a*]pyridine derivatives. Boekelheide and Fedoruk have explained the formation of these products assuming an opening of the initial cycloadduct and a subsequent six-membered ring closure.⁶ The aim of this work is to investigate the reactions of a series of azolium dicyanomethylides with symmetrical and unsymmetrical acetylenic dipolarophiles.

Results and Discussion

(1) *Reaction of Azomethine Ylides.*—(a) *Reaction with DMAD.* Reactions of 1-methyl- (1) and 1-ethyl-benzimidazolium (2), 1-phenylimidazolium (3), and 4-phenyl- (4) and 1-phenyl-1,2,4-triazolium (5) dicyanomethylides with DMAD afford respectively the azolopyridines (6)—(10).† The i.r. spectra of these compounds show four characteristic absorptions at 3 220—3 310 (νNH), 2 210—2 220 (νCN conjugated), 1 690—1 710, and 1 720—1 740 cm⁻¹ (νCO). The highest νCO absorption has been assigned to the ester group at the 3-position conjugated with the electron-withdrawing cyano-group.

The ¹H n.m.r. spectra of these compounds are summarized in Table 1. The singlets at δ 2.08 in compounds (8) and (10) and 3.03 in compound (9) have been assigned to the methoxy-group of the ester at the 4-position contiguous to the five-membered ring, which is shielded by the *N*-phenyl group in an almost orthogonal conformation. The chemical shifts of the methoxy groups in compounds (6) and (7) have been assigned by comparison with those of (8)—(10).

In the reaction of (5) with DMAD an intermediate, which by gentle heating was transformed into (10), was isolated. The i.r. spectrum of this intermediate shows two νCO absorptions at 1 725 and 1 735 cm⁻¹, but no absorptions corresponding to the imino and cyano groups. Its ¹H n.m.r. spectrum shows signals at δ (CDCl₃) 3.70 (3 H, s, CO₂CH₃), 3.93 (3 H, s, CO₂CH₃), 6.63 (1 H, s, 3a-H), 7.00—7.66 (6 H, m, 6-H and phenyl group). The ¹³C n.m.r. spectrum (CDCl₃) shows the corresponding signals at δ 51.4 and 53.5 (CH₃ of the ester groups), 52.5 (C-3a), 123.4 (both CN groups), 124.4, 129.7, 129.9 and 138.9 (*ortho*-, *meta*-, *para*-, and *ipso*-carbons of the

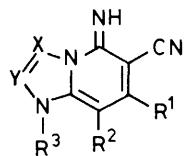


phenyl group), 134.7 (C-6), 128.0 and 149.6 (C-2 and C-3), and 161.6 and 165.0 p.p.m. (CO of the ester groups). All these data are in agreement with structure (11) corresponding to the initial cycloadduct, isolated for the first time for this class of reactions.

(b) *Reactions with unsymmetrical acetylenic dipolarophiles.* Reactions of ylides (2)—(4) with methyl propiolate (MP) yield only one of the two possible regioisomers, the azolopyridines (12)—(14), respectively.

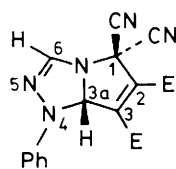
In their i.r. spectra the ν(CO) absorptions at 1 680—1 710 cm⁻¹ correspond to the lowest observed in compounds with two ester groups (that for the ester group at the 4-position

† In order to facilitate the i.r. and n.m.r. discussion a non-conventional atom numbering [see (6)—(8)] has been used.

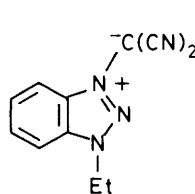
Table 1. ^1H N.m.r. chemical shifts for adducts (6)–(10) and (12)–(16) [δ (CDCl_3); internal standard Me_4Si]

(6)–(10), (12)–(16)

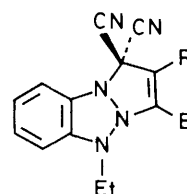
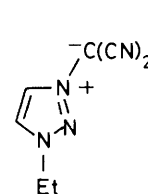
| Adducts | X | Y | R ¹ | R ² | R ³ | R ¹ | R ² | R ³ | Other |
|---------|-------|----|--------------------------|-----------------------------------|------------------------|----------------|----------------|----------------|----------------------|
| (6) | Benzo | | CO_2CH_3 | CO_2CH_3 | CH_3 | 3.83 | 4.00 | 3.80 | ArH, 7.30–7.83 |
| (7) | Benzo | | CO_2CH_3 | CO_2CH_3 | C_2H_5 | 3.83 | 4.00 | 4.43, 1.47 | ArH, 7.33–7.87 |
| (8) | CH | CH | CO_2CH_3 | CO_2CH_3 | Ph | 3.81 | 2.88 | 7.50 | 6-H, 7.90; 7-H, 8.20 |
| (9) | N | CH | CO_2CH_3 | CO_2CH_3 | Ph | 3.81 | 2.88 | 7.56 | 6-H, 9.31 |
| (10) | CH | N | CO_2CH_3 | CO_2CH_3 | Ph | 3.95 | 3.03 | 7.40–7.50 | 7-H, 9.08 |
| (12) | Benzo | | H | CO_2CH_3 | C_2H_5 | 8.07 | 3.87 | 4.65, 1.48 | ArH, 7.30–7.45 |
| (13) | CH | CH | H | CO_2CH_3 | Ph | 7.87 | 3.03 | 7.48 | 6-H, 7.83; 7-H, 8.17 |
| (14) | N | CH | H | CO_2CH_3 | Ph | 8.02 | 3.05 | 7.55 | 6-H, 9.28 |
| (15) | Benzo | | Ph | H | CH_3 | 7.30–7.67 | 5.67 | 3.70 | ArH, 7.30–7.67 |
| (16) | Benzo | | Ph | $\text{CO}_2\text{C}_2\text{H}_5$ | CH_3 | 7.30–7.58 | 3.88, 0.78 | 3.70 | ArH, 7.30–7.58 |



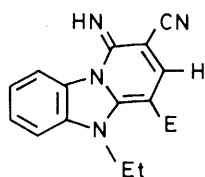
(11)



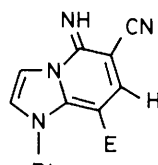
(17)

(18) R = E
(19) R = H

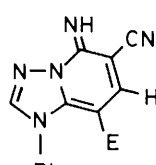
(20)



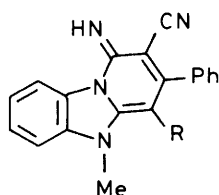
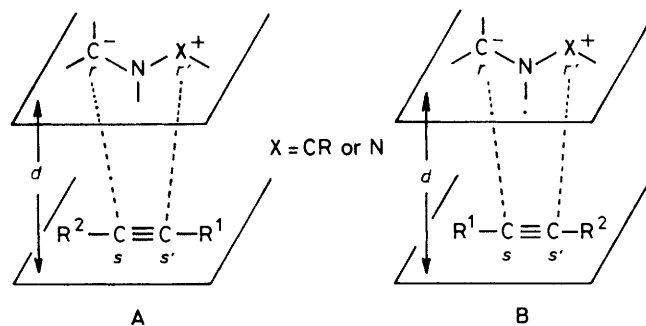
(12)



(13)



(14)

(15) R = H
(16) R = E

Theoretical model for approach in cycloaddition

appears at $1\,690\text{--}1\,710\text{ cm}^{-1}$). With this value of the νCO absorption and the chemical shifts of the methoxy groups in the n.m.r. spectra (see Table 1) it is possible to establish the structure of these products.

Reactions of ylide (1) with phenylacetylene and ethyl phenylpropionate yield the azolopyridines (15) and (16), respectively. The ^1H n.m.r. spectrum of (15) shows the signal corresponding to 4-H as a singlet at δ 5.67; structure (15) has been assigned to this regioisomer by comparing this value with those of 3-H in compounds (12)–(14), at δ ca. 8. The structure of (16) has been established by comparing the

chemical shifts of the *N*-methyl groups of (6), (15), and (16). In the other regioisomer this group would be affected by the neighbouring phenyl group at C-4.

The structures of the regioisomers (12)–(16) show that the nucleophilic extreme of the dipole in compounds (1)–(5) is the carbon atom which supports the two cyano groups, which is the usual polarization of azomethine ylides with electron-withdrawing substituents.⁷

(2) *Reactions of Azomethine Imines.*—Reactions of 1-ethylbenzotriazolium 3-dicyanomethylide (17) with DMAD and MP afford the cycloadducts (18) and (19), respectively.⁸ Experiments with 1-ethyl-1,2,3-triazolium 3-dicyanomethylide (20) yield only tars.

(3) *Regioselectivity in 1,3-Dipolar Cycloadditions. Theoretic-*

Table 2. Stabilisation energies

| Dipole | 2 | 4 | 5 | R ¹ | R ² | 10 ³ ΔE _A * | 10 ³ ΔE _B * | 10 ³ ΔΔE* | Exp. |
|----------|----|-------|----|----------------|----------------|-----------------------------------|-----------------------------------|----------------------|-----------|
| (1), (2) | CH | Benzo | | H | E | -3.60 | -4.51 | -0.91 | 100% (12) |
| (1), (2) | CH | Benzo | | Ph | E | -3.88 | -4.54 | -0.66 | 100% (16) |
| (1), (2) | CH | Benzo | | Ph | H | -2.79 | -2.94 | -0.15 | 100% (15) |
| (3) | CH | CH | CH | H | E | -3.52 | -4.48 | -0.96 | 100% (13) |
| (3) | CH | CH | CH | Ph | E | -3.83 | -4.54 | -0.71 | |
| (3) | CH | CH | CH | Ph | H | -2.80 | -2.97 | -0.17 | |
| (4) | CH | N | CH | H | E | -3.85 | -4.65 | -0.80 | 100% (14) |
| (4) | CH | N | CH | Ph | E | -4.11 | -4.80 | -0.69 | |
| (4) | CH | N | CH | Ph | H | -2.95 | -3.20 | -0.25 | |
| (5) | CH | CH | N | H | E | -3.34 | -4.34 | -1.00 | 100% (19) |
| (5) | CH | CH | N | Ph | E | -3.68 | -4.44 | -0.76 | |
| (5) | CH | CH | N | Ph | H | -2.73 | -2.95 | -0.22 | |
| (17) | N | Benzo | | H | E | -3.23 | -4.05 | -0.82 | 100% (19) |
| (17) | N | Benzo | | Ph | E | -3.51 | -3.88 | -0.37 | |
| (17) | N | Benzo | | Ph | H | -2.48 | -2.38 | 0.10 | |
| (20) | N | CH | CH | H | E | -2.74 | -3.77 | -1.03 | 100% (19) |
| (20) | N | CH | CH | Ph | E | -3.22 | -3.54 | -0.32 | |
| (20) | N | CH | CH | Ph | H | -2.44 | -2.18 | 0.26 | |

* Energies are given in atomic units. Italicised values correspond to the experimental reactions.

al Approach.—1,3-Dipolar cycloaddition, both of azomethine ylides and azomethine imines, has been examined by using Sustmann's second-order perturbational treatment [equation (1)]⁹ which is a good model for the study of the regioselectivity of these reactions.¹⁰⁻¹²

$$\Delta E = 2 \times \left[\frac{(C_r^{\text{HO}} C_s^{\text{LU}} \beta_{rs} + C_r^{\text{HO}} C_s^{\text{LU}} \beta_{r's'})^2}{E_R^{\text{HO}} - E_S^{\text{LU}}} + \frac{(C_r^{\text{LU}} C_s^{\text{HO}} \beta_{rs} + C_r^{\text{LU}} C_s^{\text{HO}} \beta_{r's'})^2}{E_S^{\text{HO}} - E_R^{\text{LU}}} \right] \quad (1)$$

C_r^{HO} , atomic orbital coefficient of the highest occupied molecular orbital (HOMO)

C_s^{LU} , atomic orbital coefficient of the lowest unoccupied molecular orbital (LUMO)

β_{rs} , resonance integral between r and s atoms¹³

$E_R^{\text{HO}}, E_R^{\text{LU}}$, dipole HOMO and LUMO energies

$E_S^{\text{HO}}, E_S^{\text{LU}}$, dipolarophile HOMO and LUMO energies

We have used a model in which the reagents are placed in two parallel planes at d 2.5 Å (Figure).^{11,13} Each stabilization energy has been estimated by applying equation (1); the more negative the values of ΔE the greater the expected stabilization of the transition state.

The molecular energies and the atomic orbital coefficients were obtained from molecular wave functions calculated by the CNDO/2 method.* The calculations have been carried out on the N -methyl instead of the N -phenyl ylides, since our

program is limited to 70 orbitals. However, we have checked that this approximation did not introduce any significant change in the $\Delta \Delta E$ values, by studying theoretically the cycloaddition of pairs of N -methyl and N -phenyl ylides with only one cyano group [$N^+-\text{CH}(\text{CN})$].¹⁴

Table 2 summarizes the stabilization energies for a large group of reactions. It can be seen that the experimental results always agree with the calculated values. Approach B is always favoured. The $|\Delta \Delta E|$ value decreases in the order $\text{HC}\equiv\text{CE} > \text{PhC}\equiv\text{CE} > \text{PhC}\equiv\text{CH}$, even if the reaction is always stereospecific. For the azomethine imines, the lower values of ΔE_A and ΔE_B can be correlated with a lower reactivity. One can note that the calculations predict an inversion of the orientation in the case of phenylacetylene.

Experimental

M.p.s were determined on a Buchi 510 apparatus and are uncorrected. I.r. spectra were obtained for KBr discs and n.m.r. spectra for solutions in CDCl_3 using tetramethylsilane as an internal standard. Microanalyses were performed at Centro Nacional de Química Orgánica, C.S.I.C., Madrid.

Ylides (1)–(5), (17), and (20) were available from earlier work.¹⁵

Reactions of Azomethine Ylides with DMAD.—DMAD (1 mmol) was added to a solution of ylide (1 mmol) in dimethylformamide (5 ml) at 0 °C. The mixture was allowed to stand at 0 °C for 4 h, and then dropped into water and the precipitated filtered off. Recrystallization from the appropriate solvent gave the pure product.

2-Cyano-1-imino-5-methyl-3,4-bismethoxycarbonyl-1,5-dihydroprido[1,2-a]benzimidazole (6). This was formed in

* The corresponding molecular geometries are available on request to the author.

68% yield, m.p. 210—211 °C (from acetonitrile); ν_{\max} . 3 280 (NH), 2 215 (CN), 1 730, and 1 710 (CO) cm^{-1} (Found: C, 60.6; H, 4.2; N, 16.6. $\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_4$ requires C, 60.3; H, 4.4; N, 16.3%).

2-Cyano-5-ethyl-1-imino-3,4-bismethoxycarbonyl-1,5-dihydropyrido[1,2-a]benzimidazole (7). This was formed in 63% yield, m.p. 209—210 °C (from acetonitrile); ν_{\max} . 3 220 (NH), 2 220 (CN), 1 730, and 1 700 (CO) cm^{-1} (Found: C, 60.8; N, 4.5; N, 15.7. $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_4$ requires C, 61.3; H, 4.5; N, 15.8%).

6-Cyano-5-imino-7,8-bismethoxycarbonyl-1-phenyl-1,5-dihydroimidazo[1,2-A]pyridine (8). This was formed in 61% yield, m.p. 177—178 °C (from ethanol); ν_{\max} . 3 220 (NH), 2 210 (CN), 1 720, and 1 690 (CO) cm^{-1} (Found: C, 61.9; H, 4.1; N, 15.7. $\text{C}_{18}\text{H}_{14}\text{N}_4\text{O}_4$ requires C, 61.7; H, 4.0; N, 16.0%).

6-Cyano-5-imino-7,8-bismethoxycarbonyl-1-phenyl-1,5-dihydro-1,2,4-triazolo[1,5-a]pyridine (9). This was formed in 62% yield, m.p. 185—187 °C (from ethanol); ν_{\max} . 3 300 (NH), 2 220 (CN), 1 740, and 1 700 (CO) cm^{-1} (Found: C, 58.0; H, 3.7; N, 20.2. $\text{C}_{17}\text{H}_{13}\text{N}_5\text{O}_4$ requires C, 58.1; H, 3.7; N, 19.9%).

6-Cyano-5-imino-7,8-bismethoxycarbonyl-1-phenyl-1,5-dihydro-1,2,4-triazolo[4,3-a]pyridine (10). The crude product (11) cannot be purified since it affords by simple crystallization from benzene compound (10), in 56% yield, m.p. 172—174 °C (from benzene); ν_{\max} . 3 310 (NH), 2 220 (CN), 1 740, and 1 700 (CO) cm^{-1} (Found: C, 57.9; H, 3.7; N, 20.2. $\text{C}_{17}\text{H}_{13}\text{N}_5\text{O}_4$ requires C, 58.1; H, 3.7; N, 19.9%).

Reactions of Azomethine Ylides with MP.—The reactions were carried out in the same way as those with DMAD, but at room temperature and a reaction time of 72 h.

2-Cyano-5-ethyl-1-imino-4-methoxycarbonyl-1,5-dihydropyrido[1,2-a]benzimidazole (12). This was formed in 25% yield, m.p. 172—173 °C (from benzene); ν_{\max} . 3 310 (NH), 2 210 (CN), and 1 710 (CO) cm^{-1} (Found: C, 65.2; H, 4.7; N, 19.2. $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_2$ requires C, 65.3; H, 4.8; N, 19.0%).

6-Cyano-5-imino-8-methoxycarbonyl-1-phenyl-1,5-dihydroimidazo[1,2-a]pyridine (13). This was formed in 27% yield, m.p. 205—206 °C (from ethanol); ν_{\max} . 3 300 (NH), 2 220 (CN), and 1 680 (CO) cm^{-1} (Found: C, 65.3; H, 4.5; N, 19.3. $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}_2$ requires C, 65.7; H, 4.1; N, 19.2%).

6-Cyano-5-imino-8-methoxycarbonyl-1-phenyl-1,5-dihydro-1,2,4-triazolo[2,3-a]pyridine (14). This was formed in 24% yield, m.p. 171—173 °C (from ethanol); ν_{\max} . 3 300 (NH), 2 220 (CN), and 1 680 (CO) cm^{-1} (Found: C, 61.4; H, 3.9; N, 23.5. $\text{C}_{15}\text{H}_{11}\text{N}_5\text{O}_2$ requires C, 61.4; H, 3.8; N, 23.9%).

Reactions of 1-Methylbenzimidazolium 3-Dicyanomethylide (1) with Ethyl Phenylpropiolate and Phenylacetylene.—A solution of (1) (1 mmol) and the dipolarophile (1 mmol) in dioxane (5 ml) was refluxed for 48 h ($\text{PhC}\equiv\text{CCO}_2\text{Et}$) and 72 h ($\text{PhC}\equiv\text{CH}$). The crude product was precipitated by cooling, filtered off, and recrystallized.

2-Cyano-1-imino-5-methyl-3-phenyl-1,5-dihydropyrido[1,2-a]benzimidazole (15). This was formed in 8% yield, m.p. 312—314 °C (from acetonitrile); ν_{\max} . 3 300 (NH) and 2 180 (CN) cm^{-1} (Found: C, 76.7; H, 4.8; N, 18.5. $\text{C}_{19}\text{H}_{14}\text{N}_4$ requires C, 76.5; H, 4.7; N, 18.8%).

2-Cyano-4-ethoxycarbonyl-1-imino-5-methyl-3-phenyl-1,5-dihydropyrido[1,2-a]benzimidazole (16). This was formed in 22% yield, m.p. 227—228 °C (from acetonitrile); ν_{\max} . 3 300 (NH), 2 220 (CN), and 1 710 (CO) cm^{-1} (Found: C, 71.6; H, 5.0; N, 14.7. $\text{C}_{22}\text{H}_{18}\text{N}_4\text{O}_2$ requires C, 71.4; H, 4.9; N, 15.1%).

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Received 22nd October 1982; Paper 2/1801