# Regioselectivity in the 1,3-Dipolar Cycloaddition Reaction of Unsymmetric Pyridinium Dicyanomethylides with Dimethyl Acetylenedicarboxylate and Methyl Propiolate: An Example of Dipole-Dipole Control of Regioselectivity?



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**Dedicated to Professor Norman H. Cromwell**

A study of the cycloaddition behavior of a series of unsymmetric pyridinium dicyanomethylides with dimethyl acetylenedicarboxylate and methyl propiolate has been carried out. The 1,3-dipolar cycloaddition proceeds in good yield with high regioselectivity to produce the corresponding indolizines and 1:1 adducts. The reactions of isoquinolinium dicyanomethylide follow frontier orbital predictions. In contrast, polar 3-substituted pyridinium dicyanomethylides gave predominantly the corresponding 8-isomers regardless of the substituents. The results can be explained by dipole-dipole interactions.

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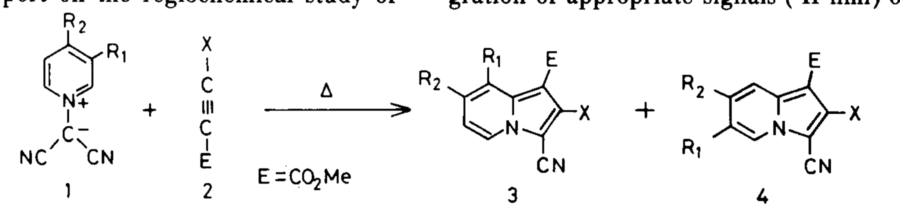
1,3-Dipolar cycloaddition of heteroaromatic *N*-ylides [1] with activated alkenes and alkynes provides a convenient route to novel nitrogen bridged heterocycles such as indolizines [2-4], quinolizines [3], [2.2.3]cyclazines [5], mono- [6] and dibenzo[2.2.3]cyclazines [7]. Although stereochemical aspect of this reaction has been recently investigated systematically [8], only a few reports have been devoted to the regiochemical study of the reaction, neither of them being intensive nor extensive, especially regarding the ylide side regiochemistry [9,10].

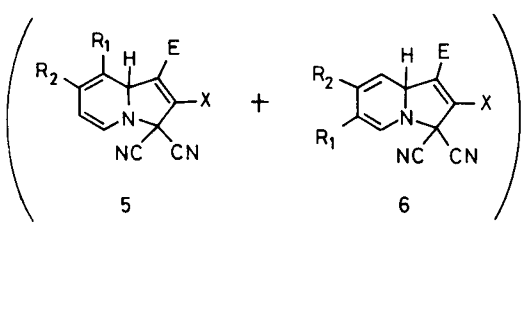
We now briefly report on the regiochemical study of 1,3-dipolar reactions of unsymmetrically substituted pyridinium dicyanomethylides **1** with dimethyl acetylenedicarboxylate (**2a**) and methyl propiolate (**2b**).

The reactions were performed in acetonitrile in a sealed tube at 40-50° for 20-40 hours. The isomeric products were separated by medium-pressure liquid chromatography using a column (25 × 310 mm) prepacked with siliga gel (Lobar, LiChroprep Si 60, Merck). The regiochemical assignment of **3** and **4** is made on the basis of their $^1$H nmr spectra [11]. The isomeric ratios were determined by integration of appropriate signals ($^1$H nmr) of the crude pro-



| | $R_1$ | $R_2$ |
|---|---|---|
| a: | Me | H |
| b: | Me | Me |
| c: | $CO_2Me$ | H |
| d: | CN | H |
| e: | COMe | H |
| f: | -(CH=CH)$_2$- | |

| | X |
|---|---|
| a: | $CO_2Me$ |
| b: | H |
| c: | Ph |



ducts. The results are summarized in Table 1. The reaction of 3-substituted pyridinium dicyanomethylides **1** with

Table 1

Reactions of Ylides **1** with Alkynes **2**

| Entry No. | Ylide $R^1$ | Ylide $R^2$ | Alkyne X | Total Yield % | Ratio 3 | Ratio 4 |
|---|---|---|---|---|---|---|
| 1 | Me | H | $CO_2Me$ | 40 | 76 | 24 [a] |
| 2 | $CO_2Me$ | H | $CO_2Me$ | 61 | 73 | 27 |
| 3 | CN | H | $CO_2Me$ | 96 | 80 | 20 |
| 4 | COMe | H | $CO_2Me$ | 57 | 100 | 0 |
| 5 | -(CH=CH)$_2$- | | $CO_2Me$ | 61 | 100 | 0 |
| 6 | Me | Me | H | 100 | 62 | 38 |
| 7 | Me | H | H | 80 | 66 | 34 |
| 8 | $CO_2Me$ | H | H | 63 [b] | 100 | 0 |
| 9 | CN | H | H | 62 [b] | 100 | 0 |
| 10 | COMe | H | H | 77 [b] | 100 | 0 |
| 11 | -(CH=CH)$_2$- | | H | 94 | 100 | 0 |
| 12 | -(CH=CH)$_2$- | | Ph | 99 | 94 | 6 |

[a] Taken from ref [9]. [b] The product was 1:1 adduct **5**.

**2a** in acetonitrile at *ca.* 55° took place smoothly to give the corresponding indolizines **3** and **4**, **3** being predominantly formed in all the cases examined (entries 1-4). Particularly, 3-acetylpyridinium dicyanomethylide (**1e**) produced the 8-acetyl isomer **3ea** exclusively.

Methyl propiolate (**2b**) that is generally known as a less reactive dipolarophile than **2a** also reacted smoothly with 3-substituted pyridinium dicyanomethylides **1** to give either the corresponding indolizines **3** and **4** or 1:1 adducts **5** depending on the nature of the substituents. Interaction of pyridinium ylides **1c-e** possessing an electron withdrawing group with **2b** gave rise to a single 1:1 adduct **5cb-eb**. These adducts were converted to the corresponding indolizines **3cb-eb** upon treatment with Pd/C in refluxing toluene. The regiochemical assignment with respect to 1,2-position rest on their $^1$H nmr spectra [12]. Isoquinolinium dicyanomethylide (**1f**) with **2a** and **2b** gave regiospecifically **3fa** and **3fb** respectively (entries 5 and 11).

It is now well documented that, to a more or less extent, most 1,3-dipolar cycloadditions receive contribution from HOMO-LUMO interaction [1,13]. The results of CNDO/2 calculations [14] both for the ylides and alkynes are depict-

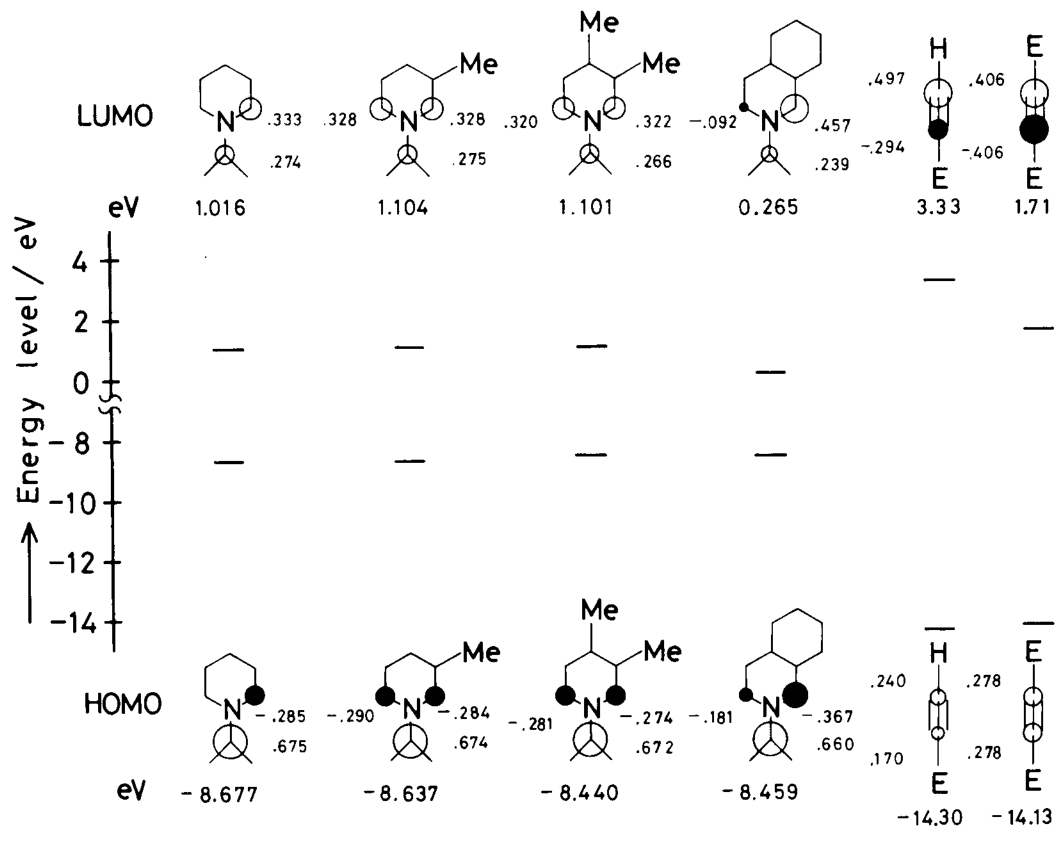



Figure 1. Frontier molecular orbital interaction in 1,3-dipolar cycloaddition of **1a,b,f** with **2a** and **2b**.

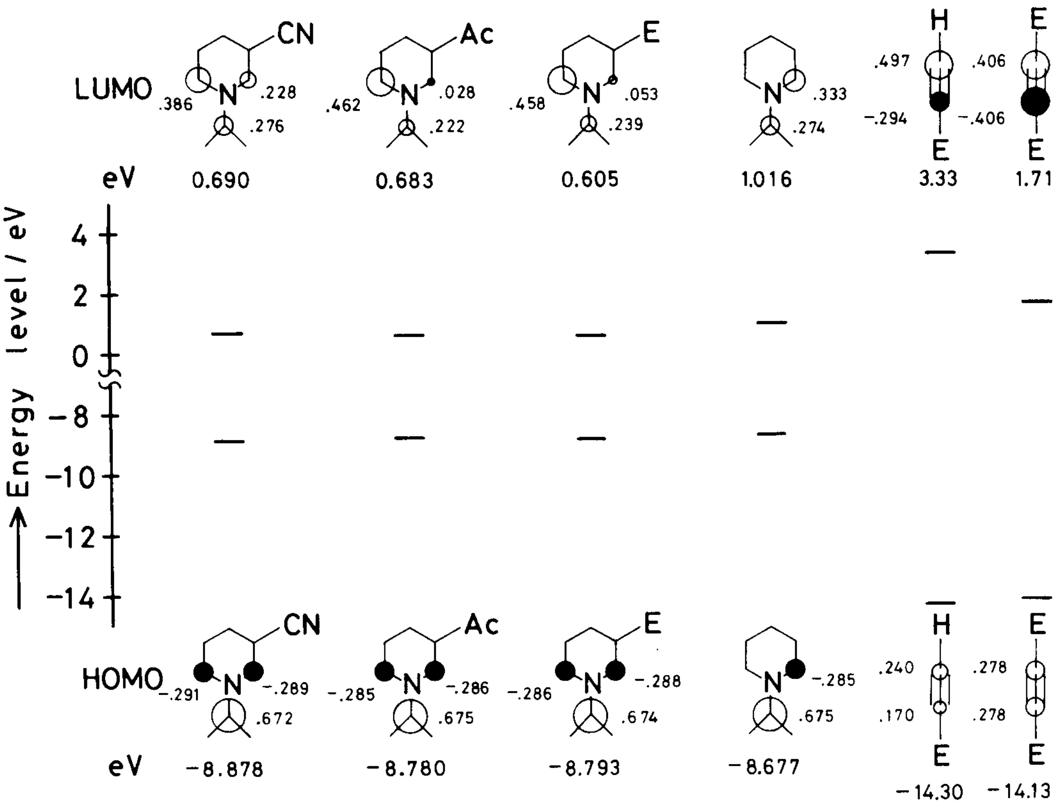



Figure 2. Frontier molecular orbital interaction in 1,3-dipolar cycloaddition of **1b-d** with **2a** and **2b**.

ed in Figures 1 and 2, an inspection of which clearly shows that the present reaction is predominantly HOMO(1,3-dipole)-LUMO(dipolarophile) controlled. Indeed, the regiochemical consequence with respect to **2b** is in agreement with the FMO interactions. The exclusive formation of **3fa** and **3fb** is also in accord with such considerations. The slightly reduced regioselectivity in the reaction of **1f** with **2c** is likely steric (by phenyl) in origin (entry 12). However, the coefficients of 2- and 6-positions of polar 3-substituted pyridinium dicyanomethylides **1a-e** are almost of the same magnitude. This does not explain the observed regioselectivity, that is, predominant formation of the 8-isomers **3**.

Since the answer to this regiochemical control does not seem (at present) to be attributable to FMO factors, we examined simple dipole-dipole interactions [1], as depicted in Figure 3. The interaction of the apparently more dipolar azomethine ylides **1c-e** with **2** will afford predominantly **3**, while the less dipolar azomethine ylides **1a,b** would result in less regioselectivity. We assume here the dipole is induced more efficiently by 3-substituent *through the 2-position* rather than the 6-position. The regiochemical outcome with respect to **2b** is also in agreement with dipole-dipole interaction. Thus, regiochemical control in the cycloaddition of polar 3-substituted ylides with **2a,b** appears to be dipole-dipole interactions rather than FMO interactions. Recognition of the importance of dipole-dipole factors in controlling the regiochemistry of ylide cycloaddition sets the stage for further studies with related systems.

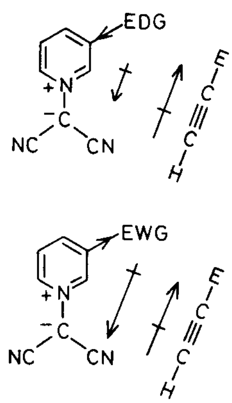



Figure 3. Dipole-dipole interaction in the 1,3-dipolar cycloaddition of polar 3-substituted pyridinium dicyanomethylides with methyl propilate.

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[11] *E.g.*, $^1$H nmr (deuteriochloroform, 90 MHz); **3da**, 3.97 (s, 6H, $CH_3O \times 2$), 7.07 (bt, J = 7.1 Hz, 1H, H-6), 7.66 (dd, J = 7.1, 1.1 Hz, 1H, H-7), 8.45 (dd, J = 7.0, 1.1 Hz, 1H, H-5); **4da**, 3.90, 3.98 (each s, 3H × 2, $CH_3O \times 2$), 7.34 (bd, J = 9.0 Hz, 1H, H-7), 8.30 (bd, J = 9.0 Hz, 1H, H-8), 8.63 (bs, 1H, H-5).

[12] *E.g.*, $^1$H nmr (deuteriochloroform, 90 MHz): **3ab**, 2.76 (s, 3H, $CH_3$), 3.83 (s, 3H, $CH_3O$), 6.90 (q, J = 7.4, 7.5 Hz, 1H, H-6), 7.02 (bd, J = 7.5 Hz, H-7), 7.73 (s, 1H, H-2), 8.16 (bd, J = 7.4 Hz, H-5); **4ab**, 2.38 (s, 3H, $CH_3$), 3.87 (s, 3H, $CH_3O$), 7.13 (dd, J = 10, 1.5 Hz, H-7), 7.66 (s, 1H, H-2), 8.10 (bs, 1H, H-5), 8.13 (d, J = 10 Hz, H-8).

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