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Regioselectivity in the 1,3-Dipolar Cycloaddition Reaction of Pyridinium Dicyanomethylides with Unsymmetric Alkynes#

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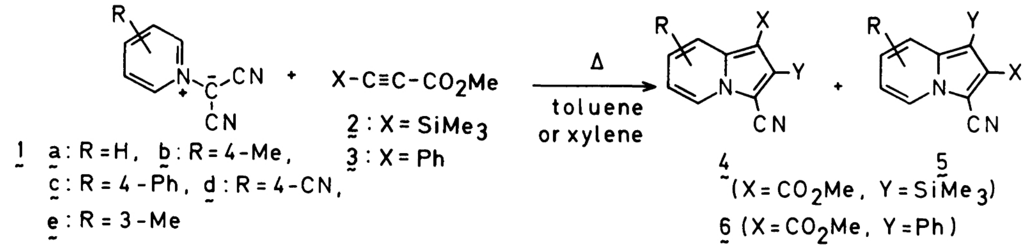
Representative pyridinium dicyanomethylides underwent regioselectively 1,3-dipolar cycloaddition onto methyl 3-trimethylsilyl-2-propynate and methyl 3-phenyl-2-propynate yielding the corresponding indolizines whereby 1-methoxycarbonylindolizines forms either exclusively or predominantly, in agreement with HOMO(ylide)-LUMO(dipolarophile) interaction as revealed by CNDO/2 calculation.

1,3-Dipolar cycloaddition of heteroaromatic N-ylides with activated alkynes constitutes one of the most powerful methods for construction of nitrogen bridged heterocycles such as indolizines.1) Although quite recently, stereochemical aspect of this reaction has been systematically investigated by Tsuge group,2) only a few reports have been devoted to the regiochemical study of the reaction, neither of them being intensive nor extensive.3,4)

We now briefly report on the regiochemical study of 1,3-dipolar reaction of representative pyridinium dicyanomethylides (**1**) with methyl 3-trimethylsilyl-2-propynate (**2**) and methyl 3-phenyl-2-propynate (**3**).

Pyridinium and 4-methylpyridinium dicyanomethylide (**1a** and **1b**) reacted with **2** in refluxing toluene to give the corresponding 1-methoxycarbonyl-2-trimethylsilylindolizines (**4a**, **4b**) and 1-trimethylsilyl-2-methoxycarbonylindolizines (**5a**, **5b**) in the ratio of 49:10 and 48:15, respectively. The less reactive 4-phenyl- and 4-cyanopyridinium ylides (**1c** and **1d**) afforded almost exclusively the 1-methoxycarbonyl isomers (**4c** and **4d**) as summarized in Table 1.5) In the case of 3-methylpyridinium dicyanomethylide (**1e**), a more complex result was obtained owing to the formation of a mixture of 6-methyl and 8-methyl isomer.



#This paper is dedicated to the late Professor Ryozo Goto, Kyoto University.

The less reactive dipolarophile, **3** reacted in refluxing xylene producing the corresponding 1-methoxycarbonyl isomers (**6**) exclusively except in the case of 3-methylpyridinium ylide (**1e**) (Table 1).

Table 1. Reactions of the ylide **1** with ethynes **2** and **3**[a)]

Products	**a**	**b**	**c**	**d**	**e**
4	49	48	19	56	22[b)] + 44[c)]
5	10	15	—[d)]	—[d)]	6[b)]
6	75	69	80	40	79[e)] + 9[f)]

a) Yields; %. b) 6-Methyl isomer. c) 8-Methyl isomer of **4** or **5**. d) Trace. e) A mixture of 6- and 8-methyl isomers in the ratio of 2:1. f) A mixture of 6- and 8-methyl isomers of 2-methoxycarbonyl-1-phenylindolizines in the ratio of 2:1.

It is now documented, to a more or less extent, most 1,3-dipolar cycloadditions receive contribution from HOMO-LUMO interactions.[6)] The results of CNDO/2 calculations both for the ylides and alkynes are depicted in Fig. 1, an inspection of which shows that the present reaction is predominantly HOMO(1,3-dipole)-LUMO(dipolarophile) controlled. The larger energy separation is with **3**, that is less reactive and requires higher temperature. The higher regioselectivity with **3**, compared with **2**, is presumably due to its more efficient overlap. This might be also indeed the case for the high regioselectivity in the reaction of **1c** and **1d** with **2**. In contrast, the decreased regioselectivity in the formation of the 6-methyl isomers from **1e** and **3** may be due to the buttressing effect through the 2-phenyl group to the 6-methyl group; the 8-methyl isomers usually form predominantly[7)] as is also exemplified in the reaction of **1e** with **2**.[8)]

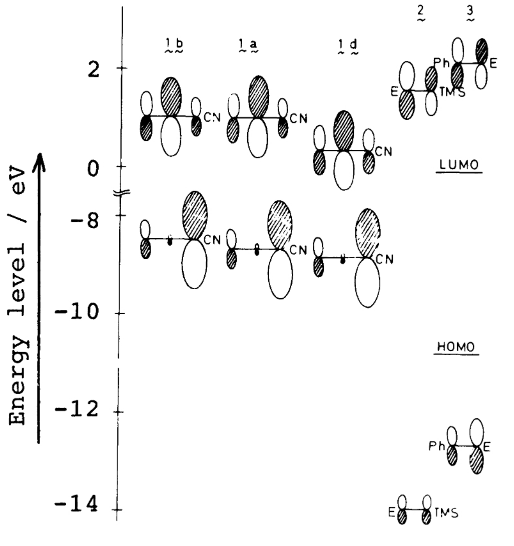


Fig. 1. Energy levels of HOMO and LUMO of **1a**, **b**, **d**, **2**, and **3** calculated by CNDO/2 method.

Although analogous experimental and theoretical results in 1,3-dipolar cycloadditions of pyridinium bis(methoxycarbonyl)methylides have been now available in our hands, the more sophisticated calculations must be performed to understand the subtle differences in the observed regiochemistry.

References

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3) T. Sasaki, K. Kanematsu, and Y. Yukimoto, J. Chem. Soc., C, 1970, 481.
4) C. A. Henrick, E. Ritchie, and W. C. Taylor, Aust. J. Chem., 20, 2467 (1967).
5) All spectral and analytical data are in accord with assigned structure. The regioisomers were able to separate by medium high pressure chromatography.
6) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions," John Wiley & Sons, London (1976) p. 148; "1,3-Dipolar Cycloaddition Chemistry," ed by A. Padwa, John Wiley & Sons, London (1984).
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8) The aspects of the ylide side regiochemistry are under investigation and subject of future communications.

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