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1,3-DIPOLAR CYCLOADDITION OF AROMATIC N-OXIDES TO N-PHENYLMALEIMIDES. STEREOSELECTIVE CYCLOADDITION AND ITS KINETIC AND MECHANISTIC ASPECTS

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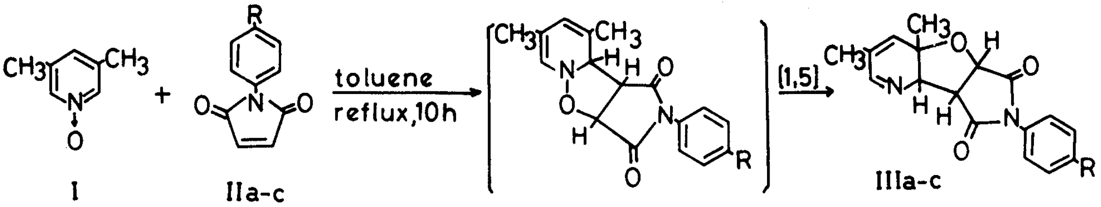
Pericyclic reactions of 3,5-dimethylpyridine N-oxide to N-phenylmaleimides were investigated. The exo 1:1 cycloadducts were formed stereoselectively as primary products. The reaction behavior is discussed in terms of frontier molecular orbital theory, based on kinetic and MO calculation data.

KEYWORDS —— 1,3-dipolar cycloaddition; pyridine N-oxide; N-phenylmaleimide; frontier molecular orbital; exo addition; 1,5-sigmatropy

A number of attempts have been made to explain and predict the various mechanistic aspects of cycloaddition reaction.$^{1)}$ Particularyl, the Frontier Molecular Orbital (FMO) method$^{2)}$ furnished a clue to the problem of reactivity, regioselectivity, periselectivity and stereoselectivity of cycloaddition reactions for complex systems. In a continuing work on the 1,3-dipolar cycloaddition reaction of aromatic N-oxides to various dipolarophiles,$^{3)}$ we have studied the reactions of pyridine N-oxides to phenyl isocyanates and explained the reaction behavior by the FMO theory.$^{4)}$ On the basis of MINDO/3$^{5)}$ and CNDO/2$^{6)}$ molecular orbital calculation data, we have sought for new and more reactive components that can be applied to the 1,3-cycloaddition. In this paper, we report the first example of the cycloaddition of aromatic N-oxides to N-phenylmaleimide derivatives, wherein the exo-adducts are formed stereoselectively.$^{7)}$



a: R=H, b: R=CH$_3$, c: R=Cl

Chart 1

Refluxing a mixture of 3,5-dimethylpyridine N-oxide (I) and a slight excess of the N-phenylmaleimide derivatives (IIa-c) in toluene for 10 h resulted in the formation of crystalline products (IIIa-c), respectively (Chart 1).

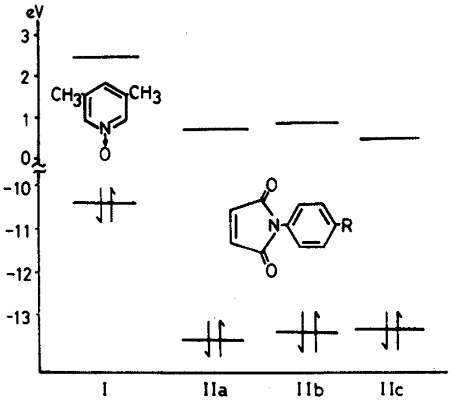


Fig. 1. Frontier Orbital Energy Levels Calculated by CNDO/2 MO Method

It is forecasted that the first step of the cycloaddition proceeds via the exo-[4+2]π or endo[4+2]π transition state. In other words, if IIIa-c are the primary exo[4+2]π cycloadducts, their structures are A, whereas if IIIa-c are the primary endo[4+2]π cycloadducts, their structures are C. The structures B and D are 1,5-sigmatropic shifted products arising from A or C, respectively.

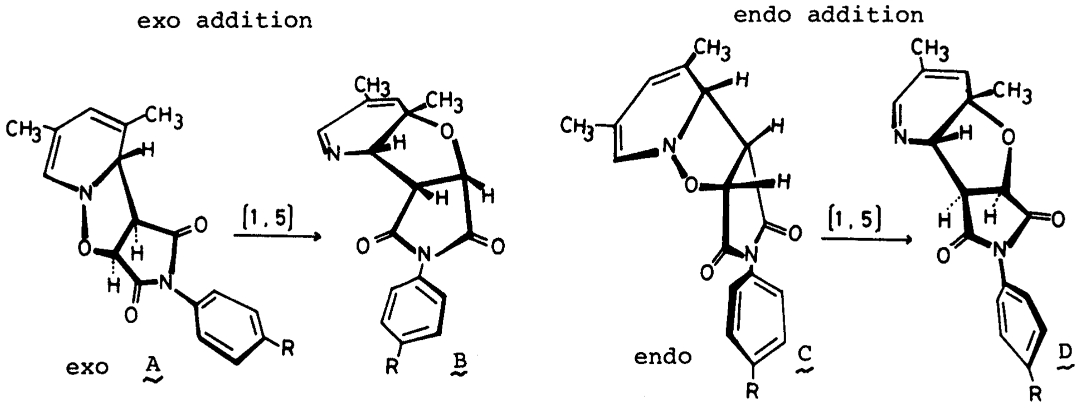


Chart 2

The infrared (IR) spectra of IIIa-c showed characteristic carbonyl bands at 1715-1710 cm^{-1}, suggesting the presence of unconjugated imide carbonyl group. The mass spectra (MS) of IIIa-c exhibited molecular peaks corresponding to the 1:1 cycloadducts. Four sp^3 carbons were observed in the ^{13}C nuclear magnetic resonance (CMR) spectrum of IIIb. Consequently, it was assumed that IIIa-c were not primary cycloadducts (A or C) but 1,5-sigmatropic rearranged products (B or D). Further the proton magnetic resonance (PMR) spectra of IIIa-c exhibited A_2M patterns due to three cis oriented methine protons (J=8 and 9 Hz). From these data, the structures of IIIa-c were considered to be 2,3-dihydropyridine type 1:1 cycloadducts (B) arising from primary exo[4+2]π cycloadducts by 1,5-sigmatropic shift.

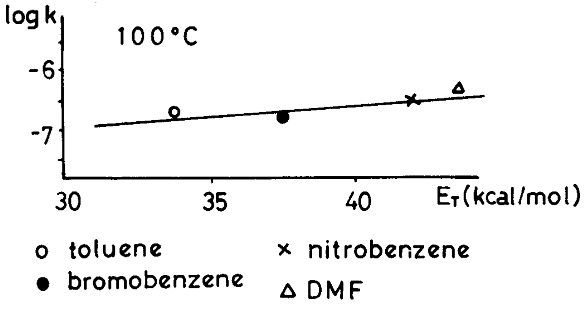


Fig. 2. Plots of log k vs. E_T for the Cycloaddition of I to IIa

The second-order rate constants were obtained in several solvents at 100°C, following the disappearance of IIa by gas liquid chromatography (GLC).8)

The E_T values of Dimroth9) were used as a scale of solvent ionizing power in studying the effect of solvent on the rate of reaction. As illustrated in Fig. 2, plots of log k vs. E_T values show a linear relationship. The magnitude of slope has been used as a measure of the sensitivity of a reaction to the ionizing power of the solvent.9) The value is only 2.73×10^{-2}, comparable to those of typical concerted reactions.10) The small response to variation of polarity of the solvent rules out an intermediate involving any significant degree of charge separation. The activation energy for the reaction of I and IIa, 19 kcal/mol, lies within the range reported for the typical 1,3-dipolar cycloaddition reaction, while the entropy of activation, $\Delta S^{*}=-50$ e.u., considerably lower than that for the average 1,3-dipolar cycloaddition,10) suggests a highly ordered transition state.

Fig. 3 shows transition tates for exo[4+2]π and endo[4+2]π cycloadditions, respectively. In the endo[4+2]π transition state, the secondary orbital interaction is out of phase, therefore the exo[4+2]π transition state is considered to be more stable than the endo[4+2]π transition state. This agrees with the experimental results for the reaction of I to IIa-c.

So far as we know, this is the first example of the isolation of a product which can be used to understand the stereochemical course of the reaction of aromatic amine N-oxides to various dipolarophiles.

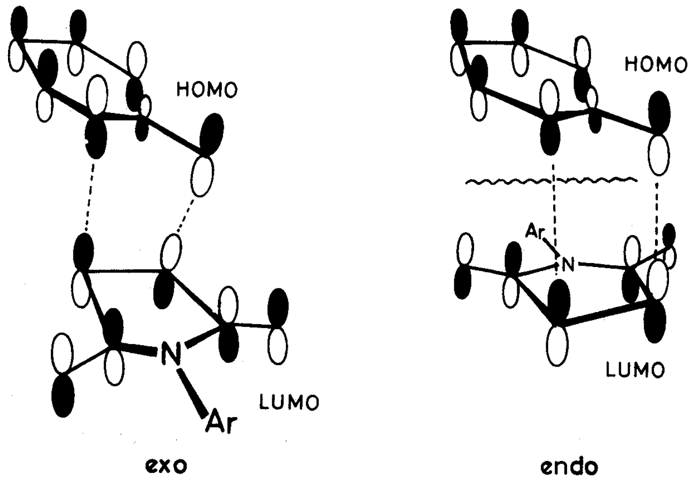


Fig. 3. Transition States of the Cycloaddition of I to II

The facile 1,5-rearrangement of the primary cycloadduct may be predicted by the reactant dissection method.$^{2)}$ A HOMO-LUMO interaction is depicted in Fig. 4. The amide carbonyl group lowers the σLUMO, whereas the two methyl groups raise the πHOMO, thus the FMO interaction becomes quite favorable for the rearrangement.

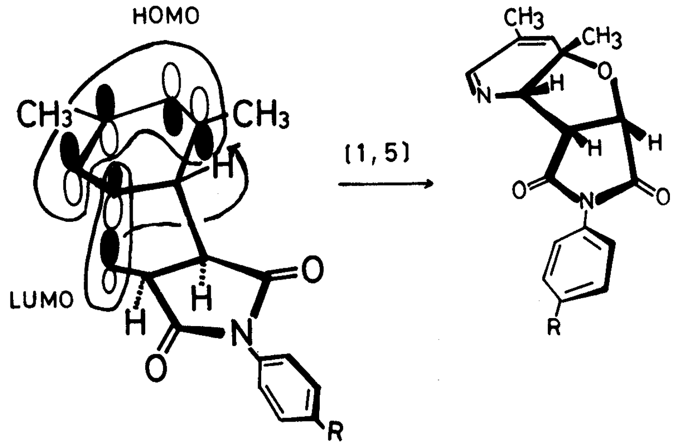


Fig. 4. 1,5-Sigmatropic Rearrangement of the Primary exo[4+2]π Cycloadduct

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7) IIIa: yield 51%; mp 172.5-173.5°C; IR(KBr): 1715(C=O)cm^{-1}; MS m/e: 296(M$^+$).
IIIb: yield 55%; mp 187-188°C; IR(KBr): 1715(C=O)cm^{-1}; MS m/e: 310(M$^+$).
IIIc: yield 55%; mp 199-201°C; IR(KBr): 1710(C=O)cm^{-1}; MS m/e: 330(M$^+$), 332(M$^+$+2).
8) Quantitative analyses were performed by Yanagimoto G80 gas chromatograph using Fluoxylate K (2%) on Uniport HP (Gasukuro Kogyo Inc. Japan) as stationary phase and hydrogen as carier gas.
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