THE DIELS-ALDER REACTION OF PYRIDAZINONES AS DIENOPHILES

Péter Mátyus,*[1] Kaoru Fuji, and Kiyoshi Tanaka*

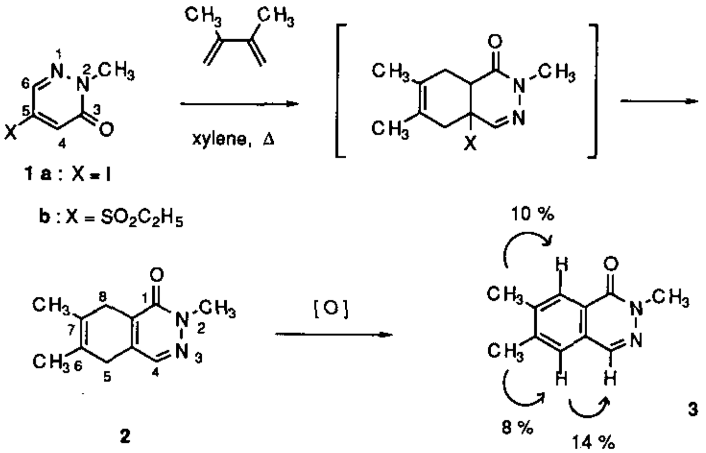
Institute for Chemical Research, Kyoto University, Uji, Kyoto-Fu 611, Japan

Abstract - The Diels-Alder reaction of 5-iodo- (**1a**) and 5-ethylsulfonyl-2-methyl-3(2*H*)-pyridazinone (**1b**) with 2,3-dimethyl-1,3-butadiene afforded phthalazinone (**3**) and dihydrophthalazinone (**2**) as isolable products, respectively. The cycloadditions are well interpreted by the theoretical considerations based on the calculated AM1 data.

Pyridazines have been shown to undergo Diels-Alder cycloaddition as dienes with inverse electron demand, and the versatility of this methodology has been well demonstrated by numerous examples in inter- and intramolecular versions for this series of compounds.[2] On the other hand, only a few precedents have appeared in the literature,[3] in which the pyridazine derivative was involved as a dienophile. In these particular cycloadditions, an azo compound, which was derived *in situ* from the corresponding pyridazinedione by oxidation, was employed as a highly reactive dienophilic component.

In connection with our recent studies on [4,5]-annulated pyridazines,[4] a Diels-Alder approach was investigated for the construction of phthalazinone ring system. The 3(2*H*)-pyridazinones substituted with electron-withdrawing group were expected to be reactive enough on the basis of relevant quantum-chemical data on the related pyridazinones[5] as well as of their reactivities with diazoalkanes in 1,3-dipolar cycloaddition.[6] In this study, the 5-substituted 3(2*H*)-pyridazinones were chosen as candidates for dienophiles of [4+2]cycloaddition. The 5-iodo derivative (**1a**)[7] was treated with 2,3-dimethyl-1,3-butadiene (DMB) in a sealed tube at 165-170 °C for 65 h to give phthalazinone (**3**)[8] in 9 % yield and a trace of the dihydro derivative(**2**)together with 70 % of the unreacted **1a** (Scheme 1). After unsuccessful attempts with **1a** for improvement of the yields of **2** and/or **3**, 5-ethylsulfonyl-3(2*H*)-pyridazinone (**1b**)[9] was employed as a dienophile. Thus, **1b** was allowed to react with the same diene at 140-150 °C for 48 h under an atmosphere of argon. Dihydrophthalazinone (**2**)[10] was isolated in 70 % yield concomitant with a trace amount of **3**. An independent experiment showed that **2** was quantitatively aromatized to **3** in the presence of atmospheric oxygen at room temperature. The structures of **2** and **3** were unambiguously elucidated by spectroscopic data. In the ^{1}H nmr spectrum of **2**, the methylene protons appeared as a broad singlet with 4H intensity, while one proton as a singlet at the aromatic region. The signals of each two methylenic and olefinic carbons and the most intense peak[11] at *m/z* 189 (M^+-1) in its ms, were consistent with the proposed structure. The observed nOes of cycloadduct (**3**) are included in Scheme 1.

Scheme 1



Experimental results could be qualitatively rationalized by considerations based on the FMO theory.[12] Coefficients and energies were obtained by AM1 method[13] and are tabulated.

Table 1. HOMO/LUMO coefficients and energies for compounds (**1**) and DMB.[a]

compounds	HOMO/LUMO p_z coefficients							orbital energy (eV)
	1	2	3	4	5	6	7[b]	
1a	-.27	.52	.10	.36	.11	-.45	-.41	-9.60
	.37	-.30	.18	.56	-.54	-.11	-.16	-0.88
1b	-.22	.45	.08	.26	.08	-.39	-.33	-9.82
	-.23	.23	-.15	-.49	.42	.01	.15	-1.49
DMB[c]	-.52	-.38	.38	.52	.10	-.10		-9.06
	-.53	.40	.40	-.53	.01	.01		0.50

[a] Calculated by AM1 Method. [b] For **1**, atom-7 is oxygen; for DMB, atoms-5,6 relate to the methyl groups. Contributions of other atoms to HOMO and LUMO are negligible in all compounds. [c] *s-cis* conformer.

FMO theory: i) The LUMO (**1**)-HOMO (DMB) gaps (for **1a** 8.18, for **1b** 7.57 eV) are much smaller than the LUMO (DMB)-HOMO (**1**) separations (10.10 and 10.32 eV) indicating that the reaction might take place with normal electron demand. On the basis of the above values, a higher rate for **1b** might be expected, and was actually observed. ii) In the LUMO of **1**, the 4- and 5-positions have the largest orbital coefficients, so an overlap between the LUMO of **1** and the HOMO of DMB through the 4,5 and 1,4 positions, respectively, should be preferred to the other combinations. This overlapping is perfectly in phase and the same orientation has been found experimentally.

Since neither the HOMO nor LUMO is degenerated in these compounds, perturbations involving the next five orbitals to the HOMO and LUMO contribute substantially to the total perturbation energy, and they are of more representing value in approximation of this energy. This approach led to the same conclusion as above. Subsequently, products formed under thermodynamic control were considered. Heat of formation values of adducts formed by reacting the 1,6- or 5,6-positions of **1a** with 1,4-positions of DMB are 49.6 and 67.0 kcal/mol, respectively. These values indicate the thermodynamically disfavored formations of these compounds as compared with that of the 4,5-adduct (22.0 kcal/mol). Furthermore, cycloadducts by bond formations between 1,4-positions of **1a** and the 1,2- or 2,1-positions of DMB, turned out to be also less stable ($\Delta H^f = 70.0$ and 71.2 kcal/mol) than the 4,5-adduct. Finally, the regiochemistry in the elimination step could also be well understood by theoretic consideration based on AM1 data. Formation of the 5,8-dihydro compound (**2**) is preferred thermodynamically to that of 8,8a-dihydro derivative ($\Delta H^f = 13.0$ and 20. 0 kcal/mol, respectively) and this agrees with the result from the conformational analysis indicating the absence of antiperiplanarly oriented hydrogens at C-5 in the intermediate (dihedral angles are 143 and -29°).

In conclusion, our results demonstrate a new and well predictable approach to polycyclic pyridazines, including otherwise hardly accessible derivatives, and underscore the high potency of the Diels-Alder reaction in using heterocycles as dienophiles. Further work in this field is now in progress.

ACKNOWLEDGMENT

P. M. wishes to thank CIBA-GEIGY Foundation (Japan) for the Promotion of Science for a fellowship (1992/93).

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7. Obtained from 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone with hydrogen iodide by heating at 150 °C for 24 h (mp 182-183 °C): K. Czakó and P. Mátyus, unpublished results.
8. **3**: mp 139-140 °C (from 2-propanol); ^{1}H nmr (400 MHz, $CDCl_3$): δ 2.44 (3H, s, 6-CH_3), 2.46 (3H, s, 7-CH_3), 3.84 (3H, s, N-CH_3), 7.44 (1H, s, 5-CH), 8.06 (1H, s, 4-CH), 8.18 (1H, s, 8-CH); ^{13}C nmr (100 MHz, $CDCl_3$): δ 20.2 (2 x CH_3), 39.3 (N-CH_3), 126.0 (C-8a), 126.2 (C-5), 126.6 (C-8), 128.3 (C-4a), 137.4 (C-4), 141.9, 143.1 (C-6,7), 159.8 (C-1); ms (*m/z*): 188 (M^+), 160 (base); HRms for $C_{11}H_{12}N_2O$ (M^+): found *m/z* 188.097; calcd 188.095.
9. Prepared from **1a** using the same procedures as described from 5-bromo-2-methyl-3(2*H*)-pyridazinone, see F. Farina, M. V. Martin, M. Romanach, and F. Sanchez, *An. Quim.*, 1988, **84C**, 173.
10. **2**: mp 181-182 °C (from *n*-hexane-2-propanol); ^{1}H nmr (200 MHz, $CDCl_3$): δ 1.74, 1.76 (3H, s, 2 x CH_3), 3.13 (4H, br, 2 x CH_2), 3.78 (3H, s, N-CH_3), 7.54 (1H, s, 4-CH); ^{13}C nmr (50 MHz, $CDCl_3$): δ 18.2, 18.4 (2 x CH_3), 30.8, 33.3 (2 x CH_2), 39.9 (N-CH_3), 120.9, 123.4 (C-6,7), 126.2 (C-8a), 134.4 (C-4a), 136.9 (C-4), 160.4 (C-1); ms (*m/z*): 190 (M^+), 189 (base); HRms for $C_{11}H_{12}N_2O$ (M^+): found *m/z* 190.113, calcd 190.111.
11. *Cf.* Ms data of 1,4-cyclohexadiene: J. S. Shannon, *Aust. J. Chem.*, 1962, **15**, 265.
12. The FMO theory is discussed e.g. in I. Fleming, 'Frontier Orbitals and Organic Chemical Reactions', Wiley and Sons, London, 1976.
13. For AM1, see M. J. J. Dewar, E. G. Zoebisch, E. F. Mealy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902. A UNICHEM version (3.1) was used on a Cray supercomputer. Calculations for **1b** were done with 'IPAROK' = 1 option, while for DBM both the *s-cis* and *s-trans* conformers were calculated to give ΔH^f = 17.5 and 17.7 kcal/mol values. It is reasonable to expect that activation barrier for the transformation of *s*-trans DMB to the *s-cis* conformer is far less than the barrier for the cycloaddition reaction. We used the parameters obtained for the *s-cis* DMB.

Received, 22nd April, 1993