Chem. Pharm. Bull. **40**(10) 2876—2878 (1992)

DIELS-ALDER CYCLOADDITION OF 1-UNSUBSTITUTED 2(1*H*)-PYRIDONE HAVING AN ELECTRON-WITHDRAWING GROUP ACTING AS DIENE AND ITS APPLICATION TO SYNTHESES OF NEW TYPE HETEROCYCLIC RING SYSTEMS

Hiroto NAKANO, Yuki SAITO, and Hiroshi HONGO*
Tohoku College of Pharmacy, 4-4-1 Komatsushima, Aoba-ku, Sendai 981, Japan

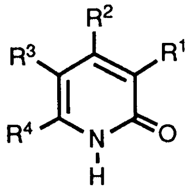
The first examples are presented of Diels-Alder cycloadditions using, as dienes, 1-unsubstituted 2(1*H*)pyridones substituted by an electron-withdrawing group in the ring. Furthermore, the Diels-Alder adduct obtained is a potentially valuable synthetic intermediate leading to new heterocyclic ring systems, 4,5-benzo-3-oxo-2,6-diazatricyclo[6.2.2.0^{2,7}]dodecanes and 4,5-benzo-3-oxo-2,6-diazatetracyclo[6.6.2.0.^{2,7}0^{9,14}]hexadecanes.

KEYWORDS Diels-Alder cycloaddition; 1-unsubstituted 2(1*H*)-pyridone; diene; aza-polycyclic ring system

2(1*H*)-Pyridones are classified as aromatic heterocycles, and generally do not proceed effectively into Diels-Alder cycloaddition. Nevertheless, the Diels-Alder adducts from the reactions of 2(1*H*)-pyridones with dienophiles have an isoquinuclidine skeleton, and therefore have great potential as synthetic intermediates.[1g)] In contrast to the substantial amount of experimental work on the Diels-Alder cycloadditions of 1-substituted 2(1*H*)-pyridones with a variety of dienophiles,[1)] little attention has been focussed on similar reactions of 1-unsubstituted tautomeric 2(1*H*)-pyridones.[2)] Although the Diels-Alder cycloadditions of 1-substituted 2(1*H*)-pyridones possessing electron-withdrawing substituents in the ring, acting as dienes, were reported by the two groups of Posner[3a)] and Hongo,[3b)] there are few publications relating to Diels-Alder cycloadditions of 1-unsubstituted 2(1*H*)-pyridones.

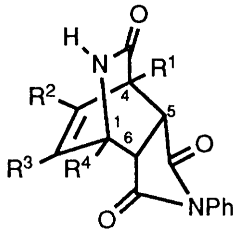
Herein we report the reactions of 1-unsubstituted 2(1*H*)-pyridones **1a-d** having a methoxycarbonyl substituent in the ring with *N*-phenylmaleimide **2** and the versatility of the Diels-Alder adduct **5** for the preparation of a new type of heterocyclic ring system, 4,5-benzo-3-oxo-2,6-diazatricyclo[6.2.2.0^{2,7}]dodecanes **9a,b**, and a new aza-polycyclic ring system **10a,b,** 4,5-benzo-3-oxo-2,6-diazatetracyclo[6.6.2.0.^{2,7}0^{9,14}]hexadecanes. These compounds, **9a,b** and **10a,b,** are expected to possess pharmacological activities.

Diels-Alder cycloadditions of **1a-d** and the dienophile **2** (4 eq) were carried out at 110°C for 72h . In the reaction of **1a** with **2,** only the Michael-type adduct **3** was obtained, and the same reaction of **1b** gave the two *endo* Diels-Alder-type adducts, **4a** and **4b**. Treatment of **4a** with **2** under the same reaction conditions recovered starting materials, and therefore **4b** is deduced as deriving from the Michael-type adduct of **1b** and **2.** Cycloaddition of **1c** with **2** produced stereoselectively the *endo* Diels-Alder-type adduct **5** in a good yield, while the same reaction of **1d** afforded the *endo* and *exo* Diels-Alder-type adducts, **6a** and **6b**. The stereochemistry of the *endo* (**4a** and **6a**: $J_{4,5}$= 4Hz, **5** and **4b:** $J_{1,6}$= 4Hz) and the *exo* (**6b**: $J_{4,5}$= 3Hz) adducts follows from the coupling constants. In general, the coupling constants of *endo*-H and *exo*-H coupling with bridgehead protons are 3.5Hz and under[1d,j,3b)] and 3.5-



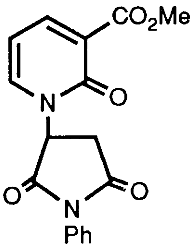
1

a: $R^1 = CO_2Me$, $R^2 = R^3 = R^4 = H$
b: $R^1 = R^3 = R^4 = H$, $R^2 = CO_2Me$
c: $R^1 = R^2 = R^4 = H$, $R^3 = CO_2Me$
d: $R^1 = R^2 = R^3 = H$, $R^4 = CO_2Me$

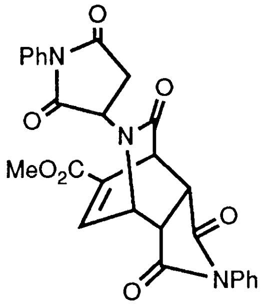


4a,5,6a ***endo***

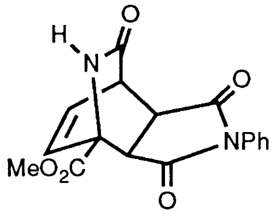
4a: $R^2 = CO_2Me$, $R^1 = R^3 = R^4 = H$ (29 %)
5 : $R^1 = R^2 = R^4 = H$, $R^3 = CO_2Me$ (67 %)
6a: $R^1 = R^2 = R^3 = H$, $R^4 = CO_2Me$ (22 %)



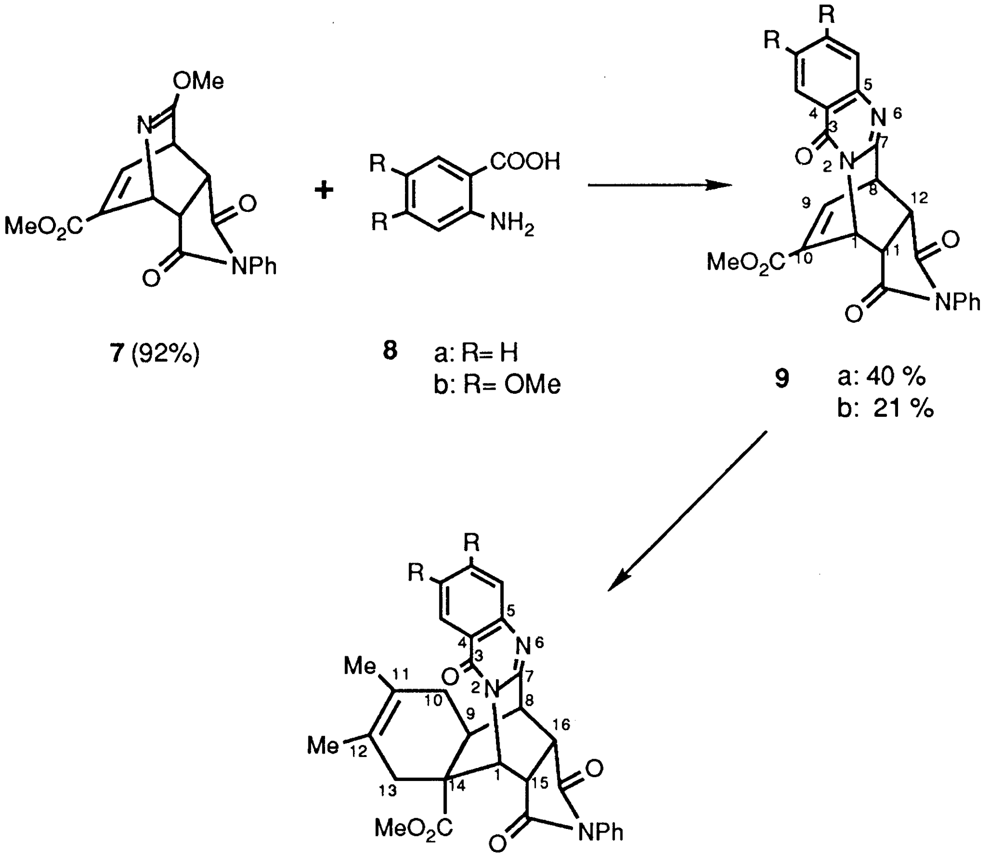
3(59 %)



4 b(49 %) ***endo***



6 b(10 %) ***exo***



7 (92%)

8 a: R= H
b: R= OMe

9 a: 40 %
b: 21 %

1 0 ***cis-anti-cis*** a: 67 %
b: 62 %

4.5Hz,[1d,j,3b] respectively, in isoquinuclidine derivatives.

The conversion of **5** into imino ether **7** was achieved by reaction with trimethyloxonium tetrafluoroborate in dichloromethane at room temperature for 24 h according to known methods[4] in an excellent yield. A mixture of **7** with anthranilic acids, **8a** in benzene or **8b** in acetonitrile, was refluxed for 48 h to give a new type ring system, **9a** and **9b**, respectively. Diels-Alder cycloadditions of the heterocycles, **9a** and **9b**, with 2,3-dimethylbuta-1,3-diene (3 eq) in *p*-dioxane at 120°C for 72 h stereoselectively produced the corresponding *cis-anti-cis* polycyclic aza-compounds, **10a** and **10b**, in good yields. The *cis-anti*-stereochemistry (C-9 and C-14 positions) was determined from the coupling constant (400 MHz; $CDCl_3$, $J_{8,9}$Hz), which was 1.0 Hz[1d,j,3b] in the adducts, **10a** and **10b**, respectively.

All new compounds, **3, 4a,b, 5, 6a,b, 7, 9a,b,** and **10a,b,** were characterized by IR and ^{1}H-NMR spectroscopy, and gave satisfactory elemental analyses.

REFERENCES

1) *a*) E. B. Sheinin, G. E. Wright, C. L. Bell, and L. Bauer, *J. Heterocyclic Chem.*, **5**, 859 (1968); *b*) H. Tomisawa, and H. Hongo, *Tetrahedron Lett.*, **1969** 2465 ; *c*) U. Heep, *Tetrahedron*, **31**, 77 (1975); *d*) K. Somekawa, T. Watanabe, and S. Kumamoto, *Nippon Kagaku Kaishi*, 412 (1978); *e*) P. S. Mariano, P. L. Huesman, and R. L. Beamer, *Tetrahedron*, **34**, 2617 (1978); *f*) G. P. Gisby, S. E. Royall, and P. G. Sammes, *J. Chem. Soc., Chem. Commun.*, **1979**, 501; *g*) H. Tomisawa, H. Hongo, H. Kato, K. Sato, and R. Fujita, *Heterocycles*, **16**, 1947 (1981); *h*) G. P. Gisby, S. E. Royall, and P. G. Sammes, *J. Chem. Soc., Perkin Trans 1*, **1982**, 169; *i*) M. Kuzuya, A. Noguchi, E. Mano, and T. Okuda, *Bull. Chem. Soc. Jpn.*, **58**, 1149 (1985); *j*) H. Tomisawa, H. Nakano, and H. Hongo, *Heterocycles*, **30**, 359 (1990).

2) *a*) L. B. Vetaneli, N. P. Shusherina, A. V. Stepaniants, and E. A. Tarkhanova, *Zh. Org. Khim.*, **13**, 1926 (1977); *b*) K. Somekawa, H. Uemura, T. Shimou, and S. Kumamoto, *Nippon Kagaku Kaishi*, 1071 (1979); *c*) M. Kuzuya, E. Mano, M. Adachi, A. Noguchi, and T. Okuda, *Chem. Lett*, **1982**, 475.

3) *a*) G. H. Posner and C. Switzer, *J. Org. Chem.*, **52**, 1642 (1987); *b*) H. Nakano, H. Tomisawa, and H. Hongo, *J. Chem. Soc., Chem. Commun.*, **1990**, 1775.

4) R. Gompper and A. Schmidt, *Angew. Chem. Int. Ed. Engl.*, **19**, 463 (1980) .

(Received June 8, 1992)