SYNTHESIS AND HIGH-PRESSURE DIELS-ALDER CYCLOADDITIONS OF 6-METHOXYCARBONYL-3-OXO-2-AZABICYCLO[2.2.0]HEX-5-ENE

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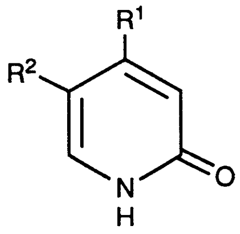
The efficient photochemical synthesis of photopyridone having an electron-withdrawing group and its high-pressure Diels-Alder cycloaddition, the first examples of an application of the technique relating to photopyridone, are reported.

KEYWORDS photoisomerization; photo-2(1*H*)-pyridone; high-pressure Diels-Alder cycloaddition; azapolycyclic ring system; β-lactam

The photoisomers, 3-oxo-2-azabicyclo[2.2.0]hex-5-enes, of 2(1*H*)-pyridones contain β-lactam and cyclobutane, and therefore have great potential as synthetic intermediates. Thus, photo-2(1*H*)-pyridones may become synthons of β-lactam antibiotics[1] and a potent inhibitor of human immunodeficiency virus (HIV).[2] In contrast to the substantial amount of experimental work on photoisomerization of 2(1*H*)-pyridones having electron-donating groups in the ring,[3] little attention has been focused on similar reactions of 2(1*H*)-pyridones possessing electron-withdrawing substituents, except for the reactions of 3-cyano-4-mothoxy-1-methyl-[3a] or monochloro-[4]2(1*H*)-pyridones. Herein we report the photoisomerization of 1-unsubstituted 2(1*H*)-pyridones having a methoxycarbonyl substituent in the ring; the reaction of the 2(1*H*)-pyridone (**1a**) gave the photopyridone (**2a**) with no dimer formation in a good yield. The photopyridone (**2a**) obtained is potentially a valuable synthetic intermediate, and may act as a dienophile leading to richly functionalized, polycyclic ring systems fusing β-lactam (**4a-e**), since it contains an electrophilic group. These compounds (**2a** and **4a-e**) are expected to possess interesting chemical properties and pharmacological activities.

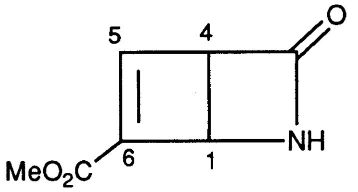
Irradiations of the 2(1*H*)-pyridones (**1a,b**) (10^{-2}M) in benzene with a 400-W high-pressure mercury lamp through a Pyrex vessel were carried out for 24h. The reaction of the 2(1*H*)-pyridone (**1a**) gave the stable photopyridone (**2a**)[5] [52%, mp 68-70°C, IR: 1775 cm^{-1} (β-lactam carbonyl)], which was isolated by column chromatographic separation of the concentrated residue, and the irradiation of 2(1*H*)-pyridone (**1b**) afforded the photodimer (80%, mp 184-186°C).

In general, photopyridones are all liquids or low melting solids, and revert readily to 2(1*H*)-pyridones under appropriate thermal conditions. Likewise, the photopyridone (**2a**) also gradually returned to the 2(1*H*)-pyridone (**1a**) in refluxing benzene. Although a high-pressure strategy has proven extremely useful to surmount the energy barrier imposed by the steric and electronic effects and to reduce the thermal influence in cycloaddition reaction, such as Diels-Alder reaction,[6] an application of the technique relating to photopyridones has not been reported. Diels-Alder cycloadditions of the photopyridone (**2a**) with the synthetically useful dienes (**3a-d**), (**3a**: buta-1,3-diene, **3b**: 2,3-dimethyl-buta-1,3-diene, **3c**: furan, **3d**: anthracene) (2 eq) were carried out under high-pressure conditions (10Kbar, 50°C, 24h, dichloromethane), and the *cis-anti-cis* adducts (**4a-d**) were stereoselectively obtained in excellent or good yields, respectively.

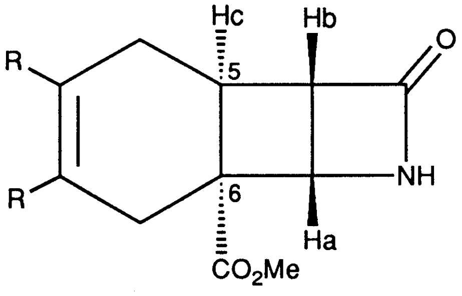


1a,b

a: $R^1 = H$, $R^2 = CO_2Me$
b: $R^1 = CO_2Me$, $R^2 = H$

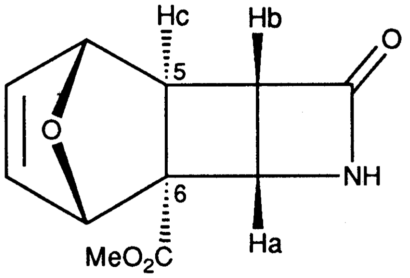


2a

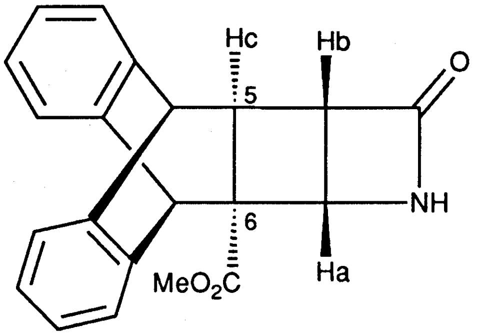


4a,b

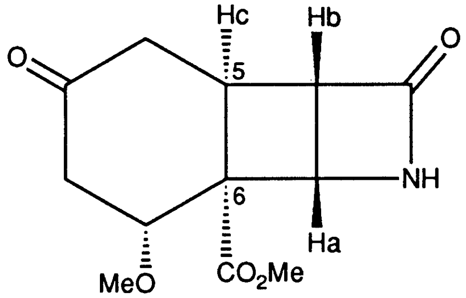
a: R =H, 88%, mp 94-95 °C
b: R =Me, 87%, mp 51-52°C



4c, 73%, mp 170-171°C



4d, 70%, mp 209-210°C



4e, 75%, viscous oil

Furthermore, treatment of the photopyridone (**2a**) with 1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene (Danishefsky's diene) (2 eq) under high-pressure conditions (6.5Kbar, 50°C, 24h, dichloromethane) followed by acid work-up (camphor-10-sulfonic acid) regio- and stereo-selectively gave the *cis-anti-cis* adduct (**4e**)in a good yield. The *cis-anti* stereochemistry (C-5 and C-6 positions) was confirmed by the observation of ^{1}H-NMR NOE enhancement between Ha and Hb, and the absence of any NOE between Ha and Hc. All new compounds (**2a** and **4a-e**) were characteraized by IR, ^{1}H-NMR spectroscopy, elemental analysis, mass and high-resolution mass spectrometry.

REFERENCES AND NOTES

1) *a)* E. J. Corey, J. Streith, *J. Am. Chem. Soc.*, **86**, 950 (1964); *b)* G. Kretschmer, R. N. Warrener, *Tetrahedron Lett.*, **16**, 1335 (1975); *c)* W. J. Begley, G. Lowe, A. K. Cheetham, J. M. Newsam, *J. Chem. Soc., Perkin Trans. I*, **1981**, 2620; *d)* J. Brennan, *J. Chem. Soc., Chem Commun.*, **1981**, 880; *e)* T. Kametani, T. Mochizuki, T. Honda, *Heterocycles*, **19**, 89 (1982); *f)* C. Kaneko, T. Naito, A. Saito, *Tetrahedron Lett.*, **25**, 159 (1984); *g)* N. Katagiri, M. Sato, N. Yoneda, S. Saikawa, T. Sakamoto, M. Muto, C. Kaneko, *J. Chem. Soc., Perkin Trans.I*, **1986**, 1289.
2) N. Katagiri, H. Sato, C. Kaneko, *Chem. Pharm. Bull.*, **38**, 288 (1990).
3 *a)* R. C. De Selms, W. R. Schleigh, *Tetrahedron Lett.*, **1972**, 3563; *b)* H. Furrer, *Chem. Ber.*, **105**, 2780 (1972); *c)* K. Shiba, C. Kaneko, *J. Chem. Soc., Chem Commun.*, **1980**, 537; *d)* J. Kurita, T. Yoneda, N. Kakusawa, T. Tsuchiya, *Chem. Pharm. Bull.*, **38**, 2911 (1990).
4) W. L. Dilling, N. B. Tefertiller, A. B. Mitchell, *Mol. Photochem.*, **5**(4), 371 (1973).
5) **2a**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ, 7.21 (1H, d, C_5-H), 6.45 (1H, br s, NH), 4.59 (1H, dd, C_1-H), 4.20 (1H, br s, C_4-H). The decoupling experiments gave $J_{1,4}$ = 2.2Hz, $J_{1,5}$ = 2.9Hz, and $J_{4,5}$ = 0.7Hz.
6) *a)* K. Matsumoto, A. Sera, T. Uchida, *Synthesis*, **1985**, 1; *b)* K. Matsumoto, A. Sera, *ibid.*, **1985**, 999; *c)* W. J. le. Noble (ed.), " Organic High Pressure Chemistry," Elsevier, Amsterdam, 1988.

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