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(1H)-pyridone; high-pressure Diels-Alder cycloaddition; azapolycyclic ring system; β-lactam

The photoisomers, 3-oxo-2-azabicyc[2.2.0]hex-5-enes, of 2(1H)-pyridones contain β-lactam and cyclobutane, and therefore have great potential as synthetic intermediates. Thus, photo-2(1H)-pyridones may become synthons of β-lactam antibiotics1) and a potent inhibitor of human immunodeficiency virus (HIV).2) In contrast to the substantial amount of experimental work on photoisomerization of 2(1H)-pyridones having electron-donating groups in the ring,3) little attention has been focused on similar reactions of 2(1H)-pyridones possessing electron-withdrawing substituents, except for the reactions of 3-cyano-4-methoxy-1-methyl,3a) or monochloro-4)2(1H)-pyridones. Herein we report the photoisomerization of 1-unsubstituted 2(1H)-pyridones having a methoxycarbonyl substituent in the ring; the reaction of the 2(1H)-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(1H)-pyridones (1a,b) (10-2M) in benzene with a 400-W high-pressure mercury lamp through a Pyrex vessel were carried out for 24h. The reaction of the 2(1H)-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(1H)-pyridine (1b) afforded the photodimer (80%, mp 184-186°C).

In general, photopyridones are all liquids or low melting solids, and revert readily to 2(1H)-pyridones under appropriate thermal conditions. Likewise, the photopyridone (2a) also gradually returned to the 2(1H)-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.

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1a,b

a: R\(^1\) = H, R\(^2\) = CO\(_2\)Me
b: R\(^1\) = CO\(_2\)Me, R\(^2\) = H

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 (6.5 kbar, 50°C, 24 h, 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 ¹H-NMR NOE enhancement between Hα and Hβ, and the absence of any NOE between Hα and Hc. All new compounds (2a and 4a-e) were characterized by IR, ¹H-NMR spectroscopy, elemental analysis, mass and high-resolution mass spectrometry.

REFERENCES AND NOTES

5) 2a: ¹H-NMR (400 MHz, CDCl₃) δ, 7.21 (1H, d, C₅-H), 6.45 (1H, br s, NH), 4.59 (1H, dd, C₁-H), 4.20 (1H, br s, C₄-H). The decoupling experiments gave J₁,₄ = 2.2 Hz, J₁,₅ = 2.9 Hz, and J₄,₅ = 0.7 Hz.

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