

HIGH PRESSURE DIELS-ALDER REACTIONS OF PYRIDONES WITH CYCLOOCTYNE

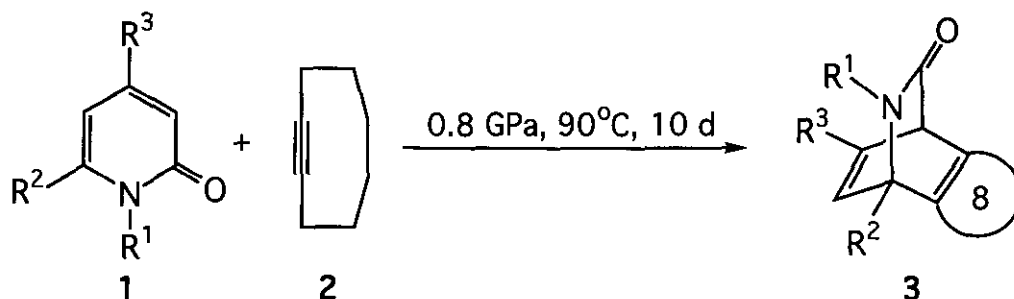
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Abstract - The high-pressure (0.8 GPa) Diels-Alder reactions of *N*-methyl-2(1*H*)-pyridones with cyclooctyne have afforded the corresponding stable bridged tricyclic 1:1 cycloadducts in moderate to good yields.

Since it was reported that 2(1*H*)-pyridones possess only *ca.* 35% of the aromaticity of benzene,¹ there have been many attempts to show that their conjugated system can act as dienes in Diels-Alder cycloaddition reactions.² The cycloadditions of *N*-methylated pyridones (unsubstituted pyridones gave the competing nucleophilic Michael addition of the amide group to the acceptor dienophiles)³ with dimethyl acetylenedicarboxylate occurred only under very vigorous reaction conditions to give low yields of the cycloadducts due to the ready loss of methyl isocyanate.⁴ We have showed that the use of high pressure is of great help for the reactions of *N*-alkyl- and *N*-methoxy-2(1*H*)-pyridones with dimethyl acetylenedicarboxylate.⁵ Better results were reported for the cycloadditions of 2(1*H*)-pyridones with electron deficient alkenes such as *N*-phenylmaleimide.^{2, 6} Particularly, Diels-Alder cycloadditions using electrophilic⁷ as well as nucleophilic⁸ 2(1*H*)-pyridones have been successful. However, examples of 1:1 adducts from pyridones and alkynes are rare apart from those with benzyne.⁹ We now report on high-pressure Diels-Alder cycloadditions of a series of *N*-substituted 2(1*H*)-pyridones with cyclooctyne. The reactions were performed at 0.8 GPa and 90 °C, allowing the separation of the new bridged tricyclic Diels-Alder adducts (**3**)¹⁰ in yields that vary from poor to good. The results are summarised in Table 1. Only 6% yield of the adduct (**3a**) was obtained at 1 bar in refluxing toluene, whereas no adduct has been isolated in the reactions of

Table 1. Diels-Alder Reactions of Pyridones (**1a-f**) with Cyclooctyne (**2**)

Pyridones 1	R ¹	R ²	R ³	Pressure (GPa)	Temp (°C)	Reaction Time (d)	Yield of 3 (%)
a	CH ₃	H	H	0.8	90	10	77
b	CH ₂ Ph	H	H	0.8	90	10	80
c	CH(CH ₃) ₂	H	H	0.8	90	10	62
d	CH ₃	H	CH ₃	0.8	90	10	70
e	CH ₃	CH ₃	H	0.8	90	10	16
f	CH ₃	OCH ₃	H	0.8	60	5	4
f	CH ₃	OCH ₃	H	0.8	90	10	24

N-benzyl-2(1*H*)-pyridone (**1b**) and *N*-methyl-6-methoxy-2(1*H*)-pyridone (**1f**) with cyclooctyne. It is remarkable that under these conditions no products arising from the breakdown of the cycloadducts, by extrusion of methyl isocyanate, were formed. The good yields of the cycloadducts (**3**) were obtained with the pyridones (**1a-c**) and (**1d**) while poor yields were obtained with the 1,6-disubstituted pyridones (**1e**, **f**). These results suggest that, as observed by Sammes *et al.*,^{4c} the steric effect of the 6-substituent is of primary importance for the reaction rate. However, the influence of the 6-substituent that we have observed is opposite to that they previously reported. Thus, Sammes *et al.* obtained the best results with the most sterically congested pyridones, particularly with 1,5,6-trimethyl-2(1*H*)-pyridone. They explained these results by suggesting that the cycloaddition across the 3- and 6-positions of the pyridone ring helps to relieve the strain, caused by the buttressing effect of the methyl substituents, as the reaction sites rehybridise from sp² to sp³.^{4c} In our case, the best results were obtained with the pyridones which allow the most favourable steric interaction during the transition state. The good yields of the present reactions are caused not only by kinetic factors but the eight-membered ring also can stabilize the cycloadducts, otherwise thermodynamically unstable under the reaction conditions. Thus, the combined use of high pressure and appropriate cyclic dienophiles has successfully allowed the preparation of the previously

unknown stable bridged tricyclic 1:1 cycloadducts of *N*-methyl-2(1*H*)-pyridones, which are not available by conventional thermal methods.

According to the consideration made by Sustmann, the poor results obtained in several cases⁴ from the cycloadditions reactions of 2(1*H*)-pyridones suggest that the classical compatibility of electron-rich diene and electron-deficient dienophile is not operating for these pyridone systems which might act as "neutral dienes".¹² Indeed, the semiempirical calculations using PM3 method¹³ showed the values of energy difference between 2(1*H*)-pyridones (LUMO) and cyclooctyne (HOMO) are almost comparable to those between 2(1*H*)-pyridones (HOMO) and cyclooctyne (LUMO).

ACKNOWLEDGMENTS

This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan (Nos. 07304047 and 08221214).

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10. Typical procedure: A mixture of *N*-methyl-2(1*H*)-pyridone ((**1a**); 0.25 g, 2.29 mmol) and cyclooctyne

(0.45 g, 4.16 mmol) in dichloromethane (*ca.* 5 ml) was compressed to 0.8 GPa (8 kbar) and heated at 90 °C for 9 d. After evaporation of the solvent, the residue was chromatographed on silica gel using ethyl acetate as eluent to give the adduct (**3a**).

11. With the exception of 10,11-dimethyl-11-azatricyclo[8.2.2.0^{2,9}]tetradeca-2(9),13-dien-12-one (**3d**), which is a colorless solid with mp 151.0 °C, all the products (**3**) were isolated as colorless oils. All new compounds gave satisfactory spectral (ir, ¹H and ¹³C nmr, and mass) and combustion analytical data.

11-Benzyl-11-azatricyclo[8.2.2.0^{2,9}]tetradeca-2(9),13-dien-12-one (**3b**) (80%); colorless oil; ir (KBr) ν (cm⁻¹) 2930 (m), 2850 (s), 1670 (s), 1650 (s), 1600 (m), 1215 (m); ¹H nmr (CDCl₃) δ 1.27-1.30 (m, 5H, H-4eq, 5, 6), 1.36-1.38 (m, 1H, H-4ax), 1.50-1.59 (m, 2H, H-7), 2.07-2.15 (m, 2H, H-8), 2.35 (t, $J = 6.5$ Hz, 2H, H-3), 4.13 (dd, $J = 5.5, 1.2$ Hz, 1H, H-10), 4.30 (d, $J = 14.6$ Hz, 1H, N-CH₂), 4.34 (dd, $J = 4.9, 1.9$ Hz, H-1), 4.41 (d, $J = 14.6$ Hz, 1H, N-CH₂), 6.62 (ddd, $J = 6.7, 4.9, 1.8$ Hz, 1H, H-13), 6.82 (ddd, $J = 6.7, 5.5, 1.2$ Hz, 1H, H-14), 7.15 (d, $J = 7.3$, 2H, Ph: H-o), 7.25-7.32 (m, 3H, Ph: H-m,p); ¹³C nmr (CDCl₃) δ 25.8, 25.9, 28.0, 28.1, 28.9, 29.8 (C-3, 4, 5, 6, 7, 8), 48.9 (CH₂), 59.5 (C-1), 62.5 (C-10), 127.4, 128.3, 128.5 (Ph: C), 136.9 (Ph: *ipso*-C), 135.5, 136.4 (C-13, 14), 140.5, 141.2 (C-2, 9), 173.1 (C=O). Anal. Calcd for C₂₀H₂₃NO: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.83; H, 7.93; N, 4.81.

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13. PM3 Calculations were performed using CAChe MOPAC (CAChe Scientific, Oxford Molecular Group); J. J. P. Stewart, *J. Comp. Chem.*, 1989, **10**, 209. The HOMO energy (eV): (**1a**), -8.786; (**1b**), -8.790; (**1c**), -8.766; (**1d**), -8.747; (**1e**), -8.685; (**1f**), -8.637; (**2**), -10.165; the LUMO energy (eV): (**1a**), -0.329; (**1b**), -0.314; (**1c**), -0.282; (**1d**), -0.289; (**1e**), -0.336; (**1f**), -0.208; (**2**), 1.171.

Received, 2nd October, 1996