HETEROCYCLES, Vol 16, No 8, 1981

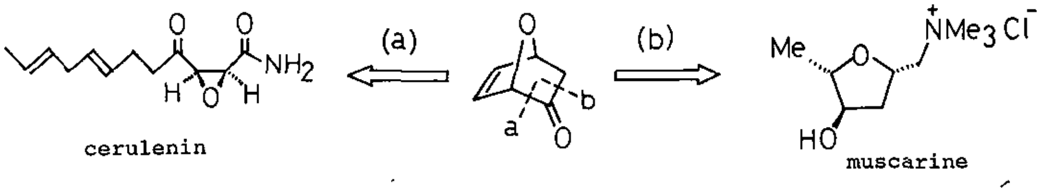
HIGH-PRESSURE DIELS-ALDER REACTIONS OF FURANS WITH α-CHLORO- AND α-ACETOXYACRYLONITRILE[1]

Hiyoshizo Kotsuki* and Hitoshi Nishizawa
Department of Chemistry, Faculty of Science
Kochi University, Akebono-cho, Kochi 780, Japan

Abstract: The Diels-Alder reactions of furans with α-chloro- and α-acetoxyacrylonitrile very nicely proceeded under the conditions of 15 kbar and 30 °C in dichloromethane. The adducts were proved to be a useful precursor for the synthesis of 7-oxa-bicyclo[2.2.1]heptanone derivatives.

Recent investigations from our laboratory and others have shown that the use of high pressure is a very valuable tool for synthetic organic chemistry.[2, 3] In this communication, we wish to report the successful Diels-Alder reactions of furans with α-chloro- and α-acetoxyacrylonitrile by the application of high pressure techniques.

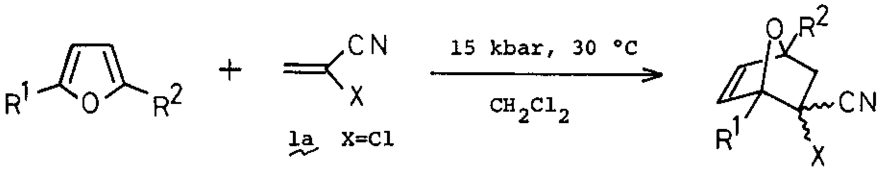
In connection with our studies toward the total synthesis of cerulenin and muscarine, we envisaged 7-oxa-bicyclo[2.2.1]heptenones as a common key intermediate as designed in the following scheme:



Consequently, we set out to develop a general method for the preparation of 7-oxa-bicyclo[2.2.1]heptanones.[4]

The most direct route to this compound would be Diels-Alder reactions between furan and ketene equivalents such as α-chloro- or α-acetoxyacrylonitrile.[5] Although the diene character of furan was well recognized,[6] the reactions with these dienophiles have not been reported. Not unexpectedly, all attempts of the Diels-Alder reactions under conventional conditions (*e.g.* refluxed in ether

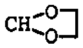
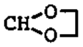
Table. Diels-Alder reactions of furans with α-chloro- and α-acetoxy-acrylonitrile[a)]



1a X=Cl

1b X=OAc

2a X=Cl; 2b X=OAc

Run	1	R^1	R^2	Time, hr	Yield, %[b)]	IR(neat or $CHCl_3$) cm^{-1}
1	a	H	H	8	83	2245, oil
2	a	CH_3	H	8	85	2245, oil
3	a	CH_3	CH_3	8	85	2245, oil
4	a	CH_2OAc	H	8	70[c)]	2245, 1750, oil
5	a		H	8	66[c)]	2245, oil
6	b	H	H	15	70	2240, 1750, oil
7	b	CH_3	H	15	88	1750,[d)] mp 84-86 °C
8	b	CH_3	CH_3	15	90	2240, 1755, oil
9	b	CH_2OAc	H	15	72	1750,[d)] mp 110-112.5 °C
10	b		H	15	65	1755,[d)] mp 158 °C[e)]

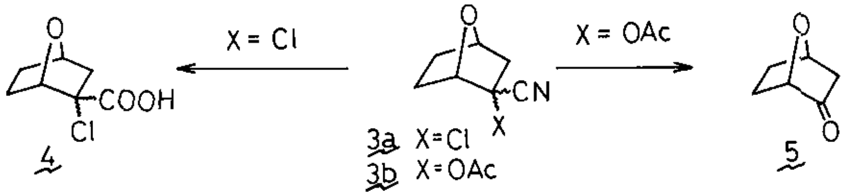
a) All the reactions were performed at a concentration of 3 M of the reactants. The structures of all adducts were confirmed by elemental analysis, NMR, and IR. b) Crude yields by NMR unless otherwise noted. The values are the average of two or more runs. c) Isolated yields after short column chromatography on neutral alumina. d) A very weak absorption of $\nu_{C\equiv N}$ was observed. *Cf.* R. M. Silverstein, G. C. Bassler, and T. C. Morrill, "Spectrometric Identification of Organic Compounds," 3rd ed, Wiley, New York, N.Y., 1974, p 110. e) The *ortho* adduct was obtained as crystals, whereas the *meta* one as an oil.

without or with the catalysis of $BF_3 \cdot OEt_2$) were fruitless. And we have found the reactions in dichloromethane proceeded very nicely at 15 kbar and 30 °C.[7, 8] The results are summarized in Table.

The spectral evidences showed that the reactions proceeded almost regioselectively to form *ortho* adducts with both dienophiles(Runs 2, 4, 7, 9). Exceptionally in the case of furfural ethyleneacetal, an approximately 1 : 1 regioisomeric mixture was obtained(Runs 5, 10). With respect to the stereochemistry of the adducts the *endo/exo* ratios of those with 1a were found to be around 3 : 1 from the NMR integrals or GLC analysis of hydrogenated compounds.[9] In the case of 1b *endo* isomers were obtained mostly.[10]

Although furfural, 5-methylfurfural, and 2-acetylfuran were unreactive even at high pressures, the reactions occurred with the protected furfural in moderate yields(Runs 5, 10).

With the cycloaddition accomplished, we attempted hydrolysis of masked ketone function after hydrogenation because of the relative instability of adducts. The hydrolysis of 3a under a variety of conditions(Na_2S-EtOH or KOH-DMSO) was unsuccessful and gave only a carboxylic acid 4,[11] 3b was smoothly converted to the corresponding ketone 5 (2N NaOH-EtOH, IR 1755 cm^{-1}).



Thus we have demonstrated a simple approach to 7-oxa-bicyclo[2.2.1]heptanones by an application of high-pressure Diels-Alder reactions. We are presently developing the utility of these adducts to natural product synthesis.

Acknowledgements: We thank Professors M. Ochi and K. Matsuoka, Kochi University, and T. Tokoroyama, Osaka City University, for their helpful discussions and continuous encouragements.

References and Notes

1. High Pressure Organic Chemistry. 4.
2. H. Kotsuki, H. Nishizawa, S. Kitagawa, M. Ochi, N. Yamasaki, K. Matsuoka, and T. Tokoroyama, Bull. Chem. Soc. Jpn., 52, 544(1979), and references cited therein.
3. For a recent review see, Kagaku Sosetsu, No. 22, Chap. 7(1979).

4. For the other approaches to this skeleton, see: a) T. A. Eggelte, H. de Koning, and H. O. Huisman, Heterocycles, **4**, 19(1976); b) H.-D. Scharf, P. Friedrich, and A. Linckens, Synthesis, 256(1976); c) A. P. Kozikowski, W. C. Floyd, and M. P. Kuniak, J. C. S. Chem. Commun., **1977**, 582. In ref. 4a, these compounds have been prepared from the adduct of furan with nitroethylene. However, this route is unsatisfactory due to the concomitant Michael type reaction. *Cf.* D. Ranganathan, C. B. Rao, S. Ranganathan, A. K. Mehrotra, and R. Iyengar, J. Org. Chem., **45**, 1185(1980).

5. For a review of ketene equivalents, see S. Ranganathan, D. Ranganathan, and A. K. Mehrotra, Synthesis, 289(1977).

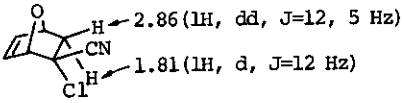
6. A. S. Onishenko, "Diene Synthesis," Israel Program for Scientific Translations Ltd., Jerusalem, Israel, 1964, p 556-566; W. G. Dauben and H. O. Krabbenhoft, J. Am. Chem. Soc., **98**, 1992(1976).

7. Attempted reaction between furan and vinyl acetate was failed and gave only recovery of starting materials.

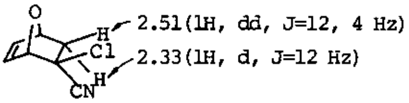
8. A typical isolated yield is 580 mg of adducts from 328 mg of 2-methylfuran and 350 mg of **1a**. For a description of our high-pressure apparatus and general procedure for high pressure reactions, see ref. 2. α-Acetoxyacrylonitrile was prepared according to the literature: R. M. Nowak, J. Org. Chem., **28**, 1182(1963).

9. The major isomer of *endo* adducts was assigned as having a Cl or OAc group in *endo* orientation based on the ^{1}H NMR data (δ, CDCl$_3$):

endo:



exo:



Preferential *endo* orientation of halide group in the reaction at high pressure was reported: K. Seguchi, A. Sera, and K. Maruyama, Tetrahedron Lett., **1973**, 1585; T. Asano and W. J. Le Noble, Chem. Rev., **78**, 407(1978). See also B. C. C. Cantello and J. M. Mellor, Tetrahedron Lett., **1968**, 5179.

10. **2b**(R^1=R^2=H); ^{1}H NMR (CDCl$_3$): δ 1.66(1H, d, J=13 Hz), 2.01(3H, s), 2.63(1H, dd, J=13, 5 Hz), 5.02(1H, dd, J=5, 1.5 Hz), 5.49(1H, d, J=1.5 Hz), 6.15(1H, dd, J=6, 1.5 Hz), 6.55(1H, dd, J=6, 1.5 Hz).

11. Similar result was reported in the case of isobenzofurans: J. G. Smith, S. S. Welankiwar, B. S. Shantz, E. H. Lai, and N. G. Chu, J. Org. Chem., **45**, 1817(1980).

Received, 11th April, 1981