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# NEW SYNTHESIS OF KARAHANA ETHER

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A new synthesis of karahana ether by employing the intramolecular Diels-Alder adduct of furan and β,β-dimethylacrylamide components is described. The facile oxidation of the adduct to N-nitrosoamide is the most significant step of the present synthetic scheme.

In the previous paper,[1] we have reported an efficient method for the acceleration of the intramolecular Diels-Alder reaction by the internal coordination of the metal salts. The cycloadduct of furan and β,β-dimethylacrylamide components, which had not been obtained by the conventional Diels-Alder reaction, was readily obtained according to this procedure.

In this communication, we wish to report an efficient transformation of this cycloadduct to one of monoterpenoid, karahana ether 1, which was isolated from Japanese hop, "Shinshu Wase." [2],[3]

In order to utilize the cycloadducts as intermediates for natural products synthesis, for example, terpenoids, it is necessary to remove the 2-hydroxyphenyl group introduced for the acceleration of the Diels-Alder reaction. The removal of this group under oxidative conditions was tried based on the notes that aminophenol is easily oxidized to quinone.

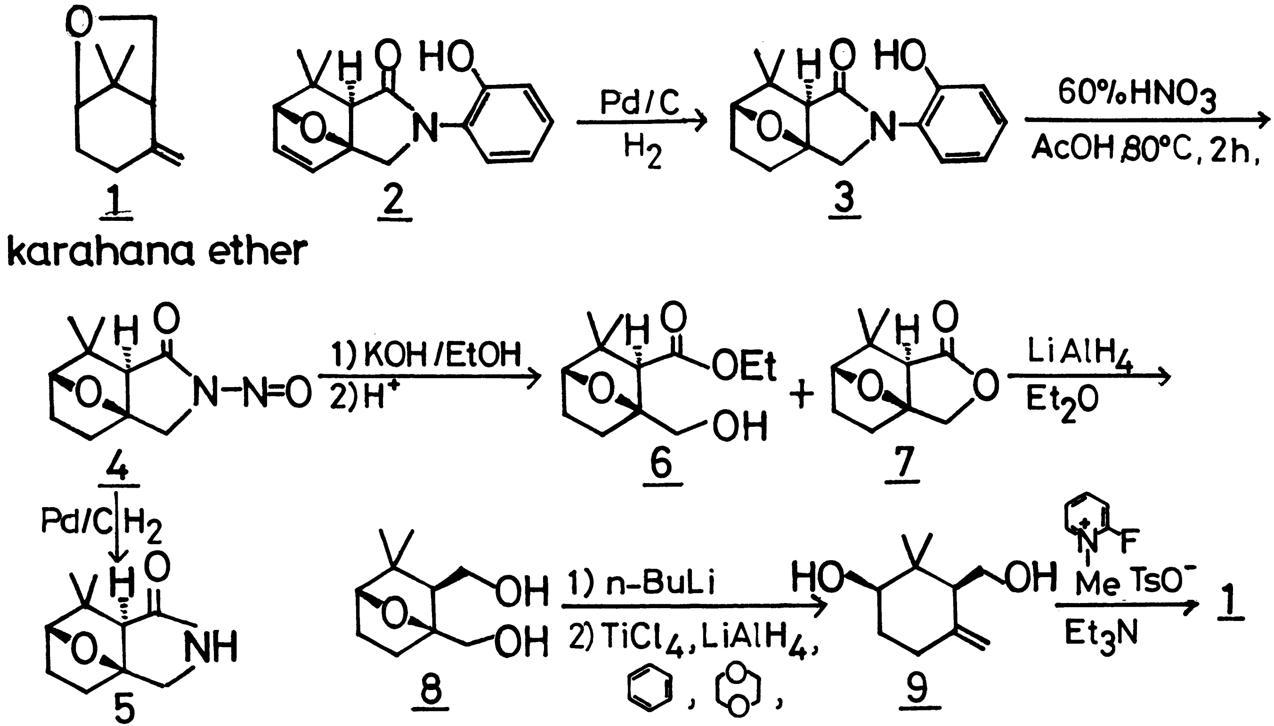
At first, the cycloadduct 2 was catalytically hydrogenated to form 3 almost quantitatively. Then, 3 was treated with lead tetraacetate or ceric ammonium nitrite, commonly used for the oxidation of phenol derivatives, but the desired product was not obtained.

The oxidation was successfully achieved by heating a mixture of 3, acetic acid, and 60% nitric acid at 80°C for 2 hours. After neutralization with aqueous $NaHCO_3$, N-nitrosoamide 4[4] was obtained in 83% yield based on 2. The structure of 4 was further confirmed by deriving to γ-lactam 5[4] by catalytic hydrogenation.

It is generally known that N-nitrosoamide is converted to diazocarboxylic acid under alkaline condition.[5] Then, the ethanol solution of 4 was made alkaline by ethanolic potassium hydroxide at 0°C and successive addition of 2N HCl gave the mixture of hydroxyester 6[4] and γ-lactone 7[4]. The mixture of 6 and 7 was reduced by $LiAlH_4$ in ether at 0°C to give diol 8[4] in 82% yield from 4.

The reductive elimination of the diol 8 to cis-diol 9 was attempted by using low-valent titanium complexes.[6] Benzene solution of the lithium salt of 8 was added to the low valent titanium reagent, prepared by the procedure described in reference 6), and the reaction mixture was refluxed for 30 hours. Thus, the cis-diol 9[7)] was isolated in 63% yield.

Karahana ether was obtained by the dehydration of the cis-diol 9 by employing 1-methyl-2-fluoropyridinium salt.[8)] When pyridinium salt was added to the methylene chloride solution of 9 and triethylamine at 0°C and stirred for an additional 2 hours at room temperature, karahana ether 1[7)] was isolated in 50% yield.



## References and Notes

1) T. Mukaiyama, T. Tsuji, and N. Iwasawa, Chem. Lett., 697 (1979).
2) Y. Naya and M. Kotake, Tetrahedron Lett., 1645 (1968).
3) R. M. Coates and L. S. Melvin, Jr., J. Org. Chem., 35, 865 (1970).
4) The nmr and ir spectra of these compounds are as follows,

N-nitrosoamide 4: IR (KBr) 1740, 1640 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=1.27 (6H, s), 1.77-2.00 (4H, m), 2.53 (1H, s), 3.50 (1H, d, J=14Hz), 4.03 (1H, d, J=14Hz), 4.00 (1H, d).

$\gamma$-lactam 5: IR (KBr) 3200, 1680 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=1.17 (3H, s), 1.22 (3H, s), 1.67-1.83 (4H, m), 2.00 (1H, s), 3.47 (2H, s), 3.85 (1H, d).

hydroxyester 6: IR (neat) 3450, 1735 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=1.02 (3H, s), 1.18 (3H, s), 1.25 (3H, t), 1.60-1.88 (4H, m), 2.35 (1H, s), 2.82 (1H, br), 3.88--4.23 (5H, m).

$\gamma$-lactone 7: IR (KBr) 1755 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=1.20 (6H, s), 1.73-1.90 (4H, m), 2.25 (1H, s), 3.97 (1H, d), 4.20 (1H, d, J=12Hz), 4.43 (1H, d, J=12Hz).

diol 8: IR (neat) 3400 $cm^{-1}$; NMR ($CDCl_3$) $\delta$=0.92 (3H, s), 1.07 (3H, s), 1.50-2.00 (5H, m), 3.40-3.97 (5H, m), 4.40(2H, br).

5) K. Heyns and O. Woyrsch, Chem. Ber., 86, 76 (1953).
6) Y. Watanabe, M. Shiono, and T. Mukaiyama, Chem. Lett., 871 (1975).
7) The nmr and ir spectra of these compounds coincide with the spectra described in reference 3).
8) T. Mukaiyama, S. Ikeda, and S. Kobayashi, Chem. Lett., 1159 (1975).

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