Tetrahedron Letters,Vol.24,No.16,pp 1675-1678,1983 0040-4039/83/161675-04$03.00/0
Printed in Great Britain

INTRAMOLECULAR CYCLOADDITIONS WITH 2-(ω-ALKENYL)-5-HYDROXY-4-PYRONES

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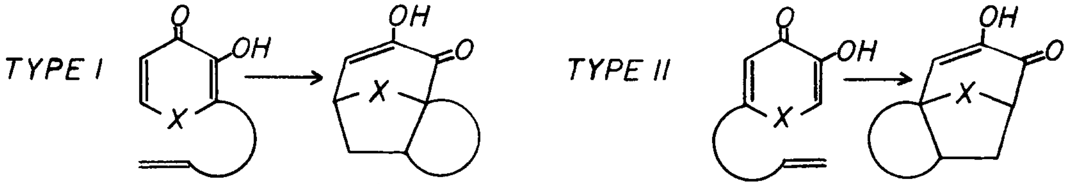
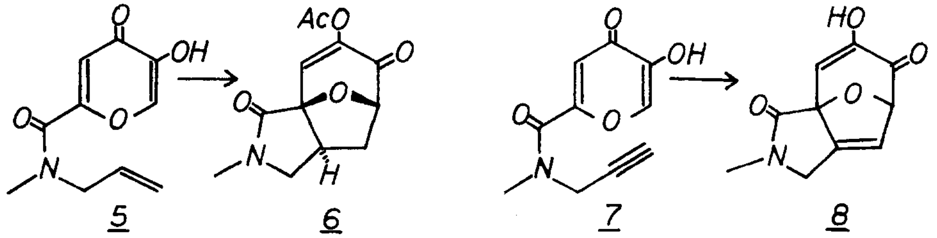
Five 5-hydroxy-4-pyrones, bearing unsaturated side chains at the 2-position, undergo thermal or acid catalyzed cycloaddition to yield bicycloadducts.

The cycloaddition represented by the perezone to pipitzol transformation (Type I, X = CO) has received little attention by synthetic chemists.[1] Büchi[2] has applied an intermolecular variation to the synthesis of three natural product structures while three other groups have examined related betaine reactions.[3,4] Structural modifications of perezone might yield a general route to highly functionalized tricyclic structures such as 2 or 4. These alterations might include removal of the peripheral methyl groups of perezone and increasing the length of the side chain (Type I, X = CO). Mechanistic considerations suggest that the hydroxyl group and the side chain might be in a 1,4 relationship and that the spectator carbonyl might be replaced with a heteroatom. All of these changes are represented in the Type II addition. The recent communication by Sammes[4] prompts us to report independent examples of the Type II reaction (X = O).[5]

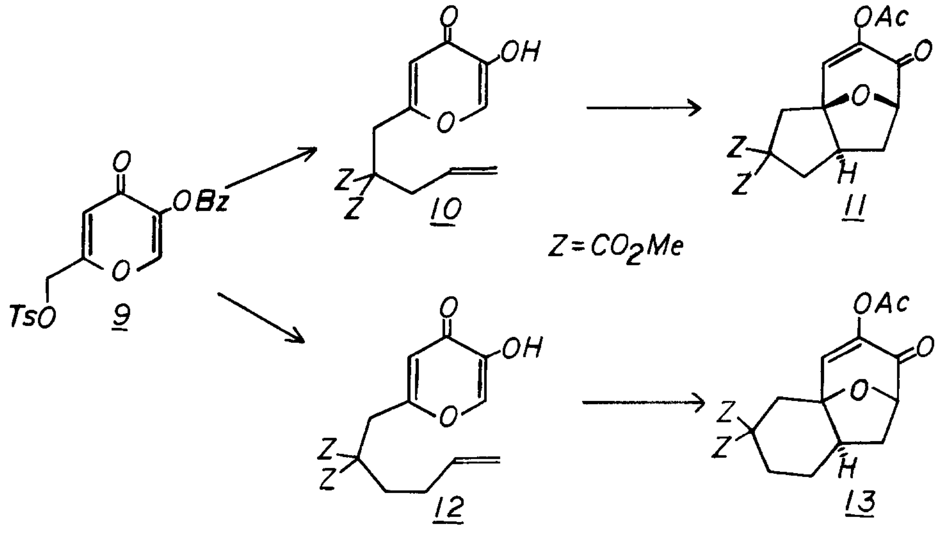


1 2 3 4

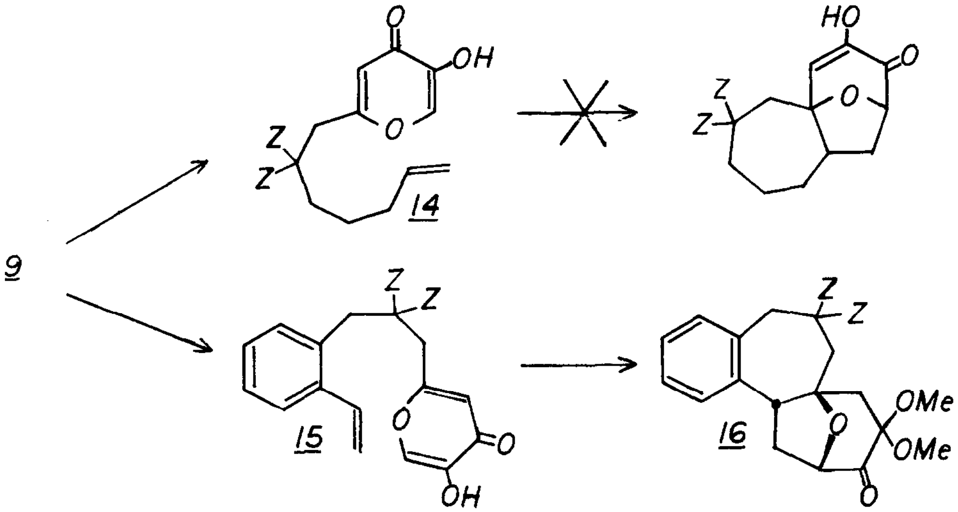
To test these modifications comenic acid[6] was converted into amides 5 and 7 by standard techniques.[7,8] Pyrolysis of amide 5 in refluxing benzene for 12 h followed by acetylation provided a 55% yield of acetate 6, readily identified by its distinctive NMR and ^{13}C NMR spectral data.[8,9] Similarly, after 60 h in refluxing acetonitrile, 7 gave a 42% yield of 8.[8]


5 6 7 8

For the preparation of carbocyclic rings, tosylate 9[10] from kojic acid[6] was converted into olefins 10, 12 and 14 by malonate displacement, alkylation and deprotection with boron tribromide in 40-70% overall yield.[8] Pyrolysis of 10 in refluxing benzene for 12 h followed by acetylation (acetic anhydride/pyridine) afforded adduct 11 in 70% yield.[8] Acetylation of the pyrolysis product facilitated isolation of 11. Compound 12 gave adduct 13 (65%, 110°C, 48 h). Adducts 6, 11 and 13 have been assigned the depicted relative stereochemistry from geometric limitations and by analogy with other betaine additions.[4]


9 10 11 12 13

Olefin 14 failed to afford the expected adduct under a variety of conditions. To decrease the entropy loss upon cyclization compound 15 was prepared from 9 and isochroman (6 steps, 51% yield). Pyrolysis of 15 slowly led to complete decomposition. However, treatment of 15 with methanesulfonic acid (1.7 equiv.) in refluxing methanol for 12 h provided ketal 16 in 87% yield.[8,11] The stereochemical assignment of 16 is based on analogy with intermolecular betaine reactions[3a,3b] since neither transition state is sterically hindered; conformation will be provided by an x-ray analysis.



We have shown that heterocycles undergo the perezone type cycloaddition with facility. We are currently examining the reactions of thiapyrones and the application of species such as 13 and 16 to the synthesis of manicoline A and colchicine respectively.[12]

Footnotes and References

1. Sánchez, I. H.; Yáñez, R.; Enríquez, R.; Joseph-Nathan, P. J. Org. Chem. 1981, 46, 2818-2819.
2. Büchi, G.; Chu, P.-S. J. Am. Chem. Soc. 1981, 103, 2718-2721 and refs therein.
3. a. Katritzky, A. R.; Cutter, A. T.; Dennis, N.; Sabongi, G. J.; Rahimi-Rastgoo, S.; Fischer, G. W.; Fletcher, I. J. J. Chem. Soc. Perkin Trans I 1980, 1176-1184 and ref therein.
   b. Henrickson, J. B.; Farina, J. S. J. Org. Chem. 1980, 45, 3359-3361.
4. Sammes, P. G.; Street, L. J. J. Chem. Soc. Chem. Commun. 1982, 1056-1057.
5. A related study with quinones will be submitted, Frazier, J. D. and Garst, M. E.

6. We are grateful to Pfizer Chemicals and Dr. Glenn Andrews for a generous gift of kojic acid.
7. Successive treatment of comenic acid with acetic anhydride, thionyl chloride, a secondary amine and methanolic carbonate gave the amide 5 or 7 in 60% overall yield. Allyl comenate failed to undergo cyclization.
8. All new compounds have been characterized by IR, NMR, ^{13}C NMR and high resolution MS.
9. Compound 6 is typical of these adducts: IR (film) 1760, 1720-1680 cm^{-1}; NMR 2.20 (s, 3H), 2.90 (s, 3H), 3.00-3.90 (m, 5H), 4.95 (dd, J = 7.5, 1 Hz, 1H), 7.05 ppm (s, 1H); ^{13}C NMR 222.9 (s), 189.1 (s), 167.7 (s), 145.1 (s), 135.1 (d), 86.4 (s), 84.8 (d), 54.1 (t), 42.8 (q), 31.6 (t), 29.8 (t), 20.1 ppm (q).
10. Thomas, A. F. J. Chem. Soc. 1962, 439-442.
11. For related base catalyzed condensation see: Volkmann, R. A.; Weeks, P. D.; Kuhla, D. E.; Whipple, E. B.; Chmurny, G. N. J. Org. Chem. 1977, 42, 3976-3978 and refs therein.
12. We are grateful to the Cancer Research Coordinating Committee for support of this work.

(Received in USA 6 December 1982)