SYNTHETIC APPROACH TOWARD MITOMYCINS. NEW FACILE SYNTHESIS OF 3*H*-PYRROLO[1,2-*a*]INDOL-5,8-DIONES

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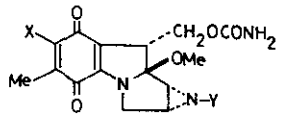
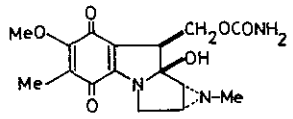
Since the first success on the isolation of mitomycin A (1), B (2), C (3), and porfiromycin (4) at the late 1950's, these unique quinones with complex functionality have attracted much attention of chemists.[1] Especially mitomycin C was shown to have the strongest and broadest activity against tumors and has been used in practice in cancer chemotherapy.[2] Development of a rapid entry to the general ring system is still urgent subject allowing for structural modification for the mitomycin skelton. We recently developed a new and efficient route, which contains simultaneous double ring cyclization and leads to a shortening of reaction processes.



1: X=OMe, Y=H
3: X=NH_2, Y=H
4: X=NH_2, Y=Me



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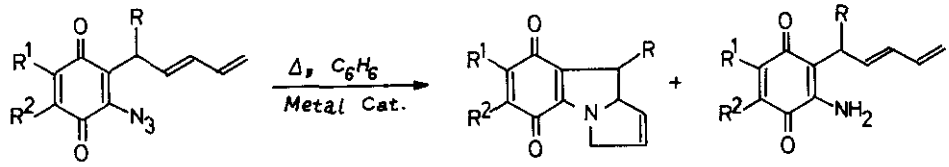
2-(2,4-Pentadienyl)-3-azido-1,4-quinones (5), which were easily prepared via either 2,4-pentadienylation of the corresponding quinones[3] or Lewis acid catalyzed Claisen rearrangement of the corresponding 2,4-pentadienyl aryl ether, were heated under the presence of metal catalyst to afford the title compounds (6) and aminoquinones (7). Among various kinds of transition metal catalysts, Cu and $Cu(acac)_2$ afforded the best results and 6 (R=H, R^1=OMe, R^2=Me) was isolated in 58% yield. The quinones 5b (R^1=OMe, R^2=Me) with bezyloxymethyl group at the dienyl side chain also gave the desired pyrrolizidinoquinone 6b in a fair yield. This is the key compound for the total synthesis of mitomycins. Detail of the reactions and further results toward the total synthesis will be discussed.



5a R = H
5b R = CH_2OBn

6a, b

7a, b

[1] W.A.Remers, "The Chemistry of Antitumor Antibiotics", vol. 1, p. 221, Wiley, New York (1979).

[2] S.K.Carter and S.T.Crooke, eds., "Mitomycin C", Academic Press, New York (1979).

[3] Y.Naruta, Y.Arita, N.Nagai, H.Uno, and K.Maruyama, Chem. Lett., 1982, 1859.