Approaches to the Mitomycins: Oxidation of 2,5-Dimethoxy-4-methylacetophenone with Thallium Trinitrate.

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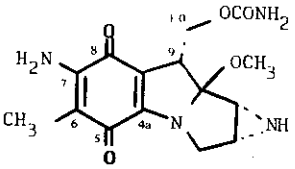
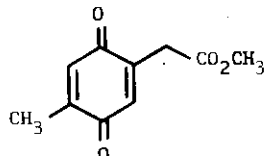
Summary: Multiple reactivity of the title acetophenone with TTN is described. Hithertofore undescribed solvent effects are reported.

The mitomycin antibiotics (1) have been the subject of a wide variety of synthetic endeavors.[1] One of many possible retro-synthetic schemes suggests that a quinone such as (2), containing carbons 4a through 10 of the natural product, would be a useful synthon. We wish to describe a facile synthesis of (2) using thallium trinitrate

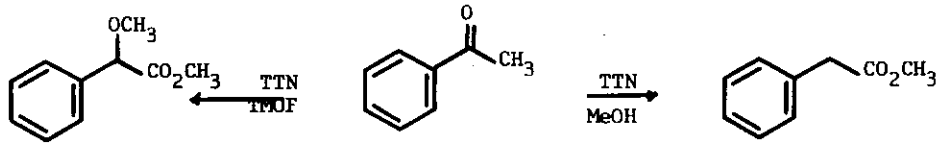


(1)

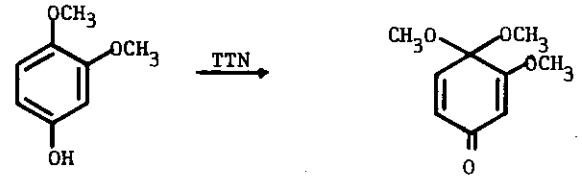


(2)

(TTN) chemistry. It is well-known that TTN in methanol or supported on montmorillonite clay[2,3] causes the rearrangement of acetophenone (3) to methyl phenylacetate (4). If the solvent for TTN is changed to trimethyl orthoformate, then (3) is converted to the methoxylated ester (5)[4]. Furthermore, it is also well-known that TTN is a powerful oxidizing agent which will convert p-substituted phenols to quinone ketals, for example (6)→(7).[5] Thus, when acetophenone (8) was subjected to TTN-methanol, we observed the occurrence of both classes of TTN reactivity simultaneously and were able to isolate synthon (2) in approximately 90% yield. Although (2) is a very unstable solid, it was characterized by elemental analysis and by its characteristic nmr spectrum which revealed quinone protons clearly coupled to the benzylic protons of the methyl and methylene substituents. Two carbonyl peaks for ester and quinone in the ir were also confirmatory. Careful preparative tlc revealed the presence of three minor products of the TTN-methanol reaction, all found in less than 2% yield. One product was identified as the methoxylated quinone (9), by its characteristic nmr and ir spectra, its combustion analysis, and its independent preparation via argentic oxide oxidation[6] of the related hydroquinone ether (10) (vide infra). A second minor product was dimethoxycresol (11). This product of *ipso* thallation followed by deacetylation and thallium replacement could be obtained as the exclusive product of reaction of TTN with acetophenone (8) when t-butanol replaced methanol as solvent. We have no explanation for this unusual solvent effect. A third minor product was the methyl ester (12), which was the rearrangement product expected if subsequent



(5) (3) (4)

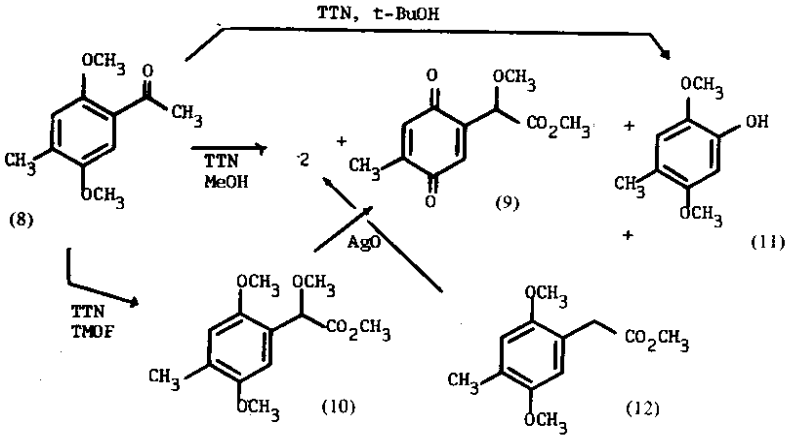


(6) (7)

After completion of this research and the submission of this article, a paper describing results in substantial agreement with ours appeared: K. Maruyama and T. Kozuka, *Bull. Soc. Chem. Japan*, 51, 3586 (1978).

oxidative demethylation had not occurred. Argentic oxide served to convert (12) to (2) in good yield. It seems clear that water must be present in the reaction mixture for the TTN oxidation of hydroquinone dimethyl ether to quinone to occur. When the TTN reaction of (8) is carried out in trimethyl orthoformate, a solvent which acts as its own dessicant, the major product obtained is the hydroquinone dimethyl ether (10).

The potential synthon (2), when reacted with other synthons containing the remaining carbons and the N_4 required for a mitomycin synthesis, did not yield any characterizable products.



Experimental[7]

5-Methyl-2-acetyl-1, 4-dimethoxybenzene (8)

In 90 ml of dry benzene was dissolved 20 g (0.132 mol) of toluhydroquinone dimethyl ether. This solution was added dropwise with stirring in a nitrogen atmosphere over a period of 20 min. into a precooled (O^oC) mixture of 60.4 g (0.132 mol. 35 ml) of titanium tetrachloride, 12.5 g (0.16 mol, 11 ml) of acetyl chloride and 10 ml of benzene. After 10 additional min. the reaction was quenched with 0.1 N HCl. The benzene layer was separated and the aqueous layer extracted with ether. The organic layers were then washed with 5% hydrogen chloride, sodium bicarbonate, water and brine, then dried over sodium sulfate. Solvent removal and one recrystallization (95% ethanol) yielded 13.2 g (51%) of white crystals of (4). mp 77.0^o. ir ($CHCl_3$) 3.40, 6.00, 6.20, 6.71, 6.85, 7.18, 8.00, 9.63, 11.10 μ Nmr ($CDCl_3$) δ 2.28, (s, 3H), 2.64, (s, 3H, $COCH_3$), 3.85 (s, 3H), 3.89 (s, 3H), 6.85 (s, 3H), 7.36 (s, 1H).

Methyl-4-methyl-3, 6-dioxo-1, 4-cyclohexadiene-1-acetate (2).

To a stirred solution of 3.0 g (7.7 mmol) of TTN, in 9 ml of methanol and 3 ml of perchloric acid was added 0.7 g (3.6 mmol) of 4. After 20 min. starting material was consumed (tlc, chloroform) and the reaction mixture was filtered through glass wool to remove the thallium nitrate (TN) precipitate. Water (20 ml) was added and the filtrate was extracted with a total of 300 ml of ether which was washed twice with water and brine and dried over sodium sulfate. The solvents were removed and 0.67 g (96%) of (2) as an unstable solid was recovered and stored in ether solution in the refrigerator. ir ($CHCl_3$) 5.79, 6.06, 6.22, 7.50 8.77, 11.05 μ. Nmr ($CDCl_3$) δ 2.09 (d, 3H, J=1.5Hz), 3.49, (d, 2H, J=1.5Hz), 3.79 (s, 3H), 6.74 (m, 2H).

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.80; H, 5.16. Found: C, 61.65; H, 5.09.

Although quinone (2) was not stable to silica gel chromatography, three other products were isolable in low yield if an acetonitrile-treated silic gel preparative plate was used, with ethyl acetate as eluant. These compounds were :

Methyl-2-methoxy-2-(4-methyl-2, 5-benzoquinone)-acetate (9).

R_f = 0.7, oil ir ($CHCl_3$) 5.76, 6.06, 6.23, 7.48, 7.92, 9.02, 11.02 μ. Nmr ($CDCl_3$) δ 1.94 (d, 3H, J=1.5Hz), 3.56 (s, 3H), 3.80 (s,3H), 4.90 (d, 1H, J=1.5 Hz), 6.69 (q, 1H, J=1.5Hz), 6.92 (d, 1H, J=1.5Hz).

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.90; H, 5.40. Found: C, 59.10; H, 5.47.

Methyl-2-(4-methyl-2, 5-dimethoxyphenyl)-acetate (12).

R_f = 0.8, mp 72° ir ($CHCl_3$) 3.45, 5.80, 7.13, 9.60 μ. Nmr ($CDCl_3$) δ 2.24 (s, 3H), 3.63 (s, 2H), 3.72, (3, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 6.75 (s, 2H).

Anal. Calcd. for $C_{12}H_{16}O_4$: m/e 224.1150 Found 224.1049.

2,5-Dimethoxy-p-cresol (11).

R_f = 0.9, mp 112°, ir ($CHCl_3$) 2.80 br. 3.40, 6.80, 8.45, 9.20, 9.90, 10.90 μ. Nmr ($CDCl_3$) δ 2.31 (s, 3H), 3.88 (s, 3H), 3.90 (br, s, 1H, ex), 3.96 (s, 3H), 6.96 (br, s, 1H), 7.45 (br, s, 1H).

2,5-Dimethoxy-p-cresol (11).

The procedure for this experiment was the same as for the preparation of (2) except that 17 ml of t-butanol was substituted for methanol and 0.35 g (1.8 mmol) of (4), 1.5 g (3.85 mmol) of TTN and 3 ml of perchloric acid were used. After solvent removal 0.287 g (95%) of (11) was isolated. Melting point and spectral data recorded above.

Methyl-2-methoxy-2-(4-methyl-2, 5-dimethoxyphenyl)-acetate (10).

To a solution of 4.0 g (10.3 mmol) of TTN in 10 ml of trimethylorthoformate was added 0.35 g (1.8 mmol) of (8). The solution was stirred at room temperature for 40 min. filtered, added to 20 ml of water and extracted with a total of 300 ml of ether which was in turn washed with water and brine. This solution was dried over sodium sulfate and appeared as five spots on tlc having two major components. After a silica dry column (8 in length, 1.25 in diameter, $CHCl_3$) separation, the first major fraction isolated from the column was 0.07 g (15%) of (11). From the third band was isolated 0.18 g (39.4%) of (10), mp 64°, ir ($CHCl_3$) 3.48, 5.79, 6.08, 6.25, 7.18, 8.50 9.70, 9.90 μ. Nmr ($CDCl_3$) δ 2.27 (br, s, 3H), 3.48 (s, 3H), 3.82 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 5.36 (s, 1H), 6.92 (br, s, 1H) 7.05 (br, s, 1H).

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.41; H, 7.08. Found: C, 61.29; H, 7.09.

Acknowledgements

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7. Analyses were performed by Spang Laboratories, Ann Arbor, Michigan. NMR spectra were determined with Varian A-60A, XL 100 and a Perkin-Elmer R12B Spectrometers with chemical shifts expressed in 6 units. For funds used to purchase the Perkin-Elmer R12B, we acknowledge Biomedical Sciences Support Grant RR 07150 from DHEW.