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Conjugate Addition of Benzyl Cyanide to a Quinone Monoacetal and Aromatization of the Adduct

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Much of Michael type addition to quinone moiety have been known, but synthetic utility of these 1, 4–addition may be limited by a lack of regioselectivity and further transformation.[1] Quinone monoacetal which has recently been synthesized would be a good substitute for a quinone in a Michael reaction. Recently, oxidation of quinone monomethyl ether with $Tl(NO_3)_3$, DDQ or $FeCl_3$ in dry methanol[2] or regioselective hydrolysis of bisacetals[3] have made quinone monoacetal readily available and attractive as synthetic intermediate.[4] A few example of 1,4–addition of active methylene compounds(pK*a*; 8–13) to quinone monoacetals have recently appeared,[5] but no example of conjugate addition of benzyl cyanide (pK*a*; –17) to quinone monoacetal has been reported, which would be a good synthetic reaction.

We thought that conjugate addition of benzyl cyanide to quinonemonoacetal would be a key step in a regiospecific approach to synthesis of anthracyclinone antibiotics, Adriamycin (**1**).[6]

We envisioned the conjugate addition of a masked acyl anion[7] to a quinone monoacetal (Figure 1). Nitrile enolates add conjugatively to enones.[8] In view of the numerous methods for the oxidative conversion of nitriles to ketones,[9] we felt that addition of nitrile enolate to quinone monoacetal followed by oxidation might provide a simple entry to the desired benzoylated methoxyphenol.

In a model study, We studied addition of benzyl cyanide to 3,4,4–trimethoxycyclohexa–2,5–diene–1–one (**2**) which was prepared from 3,4–dimethoxybenzaldehyde by Baeyer–Villiger oxidation and hydrolysis followed by $Tl(NO_3)_3$ oxidation in 65 % overall yield.[10] Addition of benzyl cyanide to the above quinone monoacetal (**2**) was effected with a catalytic amount (0.1 eq) of sodium ethoxide at room temperature to afford the Michael adduct(**3**) (Figure 2).

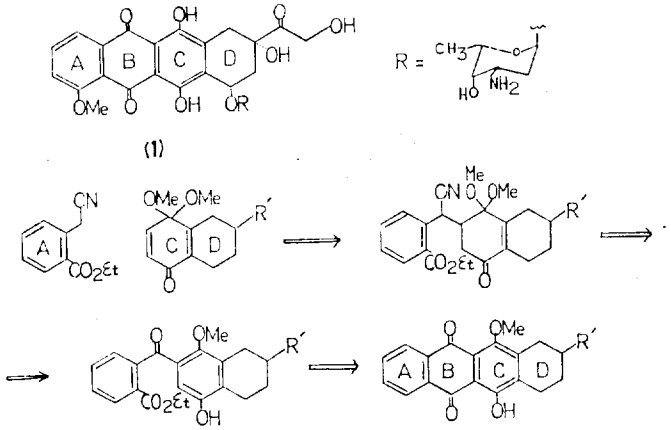

Figure 1.

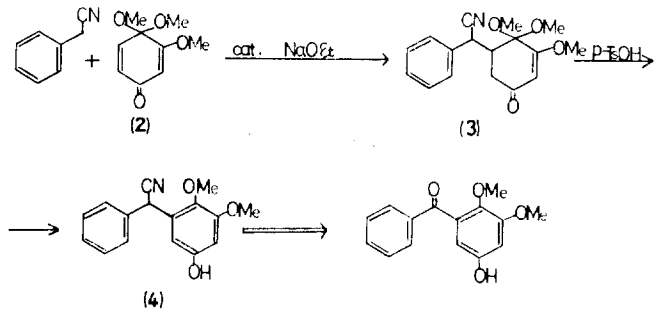

Figure 2.

In our hands, nitrile enolate prepared from benzyl cyanide by NaH in THF, or LDA in THF and HMPA did not add to quinone monoacetal (**2**). Stirring of the adduct (**3**) in refluxing benzene with *p*–TsOH gave the aromatized product (**4**).

A typical experimental procedure is as follows.

Benzyl cyanide (0.210g) was added to a solution of sodium ethoxide (0.012g, 0.1eq) in 1 m*l* EtOH, and 0.330g of quinone monoacetal (**2**) in 1 m*l* EtOH was added dropwise. The reaction mixture was stirred for 24 hrs at room temperature, and then EtOH was evaporated, and the residue was extracted

with ether, which was dried over Na_2SO_4 and concentrated in vacuo to afford 0.380 g of 6-(cyanophenylmethyl)-1,1,2-trimethoxycyclohex-2-ene-4-one (3) (72%).. IR ($CHCl_3$) 1610, 1665, 2245 cm^{-1} NMR($CDCl_3$) δ 2.35 (*m*, 1H,-CH), 2.70 (*m*, 2H,-CH_2) 3.37-3.85 (*m*, 9H, -OCH_3), 4.12, 4.36 (2*d*, 1H, -CHCN, 1:2 ratio; for δ 4.12, J=4Hz, 1/3H, for δ 4.36, J=1Hz, 2/3H), 5.18, 5.52 (2s, 1H, -Vinyl H, 1:2 ratio; forδ 5.18, 1/3H, for δ 5.5 2/3H), 7.38 (*s*, 5H, C_6H_5).

To a stirred solution of 0.147 g *p*-TsOH dissolved in 5 m*l* dry benzene was added 0.234 g of 1, 4-adduct in 5 m*l* dry benzene.

The mixture was heated for 30 min followed by the extraction with ether, which was dried over $MgSO_4$ and concentrated to give an oil (0.170 g).

Separation by chromatography (benzene: ether=1:1) afford ed0.145 g of 3-(cyanophenylmethyl)-4,5-dimethoxyphenol (4) (70 %). IR($CHCl_3$) 2230, 3320 cm^{-1}, NMR($CDCl_3$) δ 3.78 (*s*, 3H, -OCH_3), 3.96 (*s*, 3H, -OCH_3) 4.32 (*bs*, 1H, -OH), 5.28 (s, 1H, CHCN), 6.28-6.62 (*m*, 2H, aromatic H), 7.45 (*m*, 5H,-C_6 H_5).

Application of the conjugate aryloylation sequence to the synthesis of anthracyclinones is in progress.[11]

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(10) Spectral data of 3, 4, 4-trimethoxycyclohexa-2, 5-diene-1-1-one (**2**); IR (CHCl) 3010, 2960, 1665, 1640, 1607cm^{-1}, NMR($CDCl_3$) δ 3.34 (*s*, 6H,-OCH_3), 3.83 (s, 3H,-OCH_3), 5.65 (*d*, 1H, C-2 vinyl H), 6.30 (*dd*, 1H, C-6 vinyl H), 6.78 (*d*, 1H, C-5 vinyl H).

(11) Ethyl 2-cyanomethylbenzoate was prepared from ethyl 2-methylbenzoate by NBS allylic bromation (NBS, CCl_4, reflux, 5hrs.) followed by phase transfer catalyzed cyanation with KCN (CH_3CN, catalytic amount of 18-crown-6, 25°C, 24hrs). 1, 4-Addition of ethyl 2-cyanomethylbenzoate to quinone monoacetal is now under rasearch.