Reactions of amines and formaldehyde/aryl aldehydes in combination or in isolation, with 1-(2-hydroxyphenyl)-1,3-butanedione

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Reaction of 1-(2-hydroxyphenyl)-1,3-butanedione 1 with aliphatic primary amines gives imines through the attack of NH$_2$ at the CO adjacent to the benzene ring. The dione 1 reacts with aryl aldehydes in the presence of a secondary amine to give chalcones while it reacts with Schiff bases of aryl aldehydes and amines to yield imines. It affords 2-methylchromone when boiled in ethanol with a secondary amine. Its reaction with formaldehyde yields a mixture of 3-hydroxymethyl-2-methylchromone and 3-acetylbischromanylmethane. 1 reacts with secondary amines and formaldehyde to give 3-aminomethyl-2-methylchromones.

1,3-Diketones are interesting substrates for a variety of nucleophilic substitution reactions. Though, they contain an acidic hydrogen (COCH$_2$CO), in many base catalysed reactions CO - C cleavage is observed. For example, reaction with aldehydes may take unusual course to give a variety of products. We have earlier reported such observation in the case of 2-hydroxydibenzoylmethane. Such reactions are therefore mechanically interesting. In the present paper, we present our observations in the case of reactions of 1-(2-hydroxyphenyl)-1,3-butanedione with different primary/secondary amines and formaldehyde/aryl aldehyde either separately or in conjugation.

Compound 1 was prepared by the reaction of 2-hydroxyacetophenone with ethyl acetate in the presence of sodium. Compound 1 was unstable towards alkali. When it was stirred at room temperature with 10-20\%aq. NaOH, it underwent cleavage to form salicylic acid 2. In this reaction, nucleophilic OH attacked the carbonyl group adjacent to the phenyl ring. It is reported that 1 reacts with the primary amines to give imine 4, through the nucleophilic attack of NH$_2$ at the carbonyl group adjacent to the phenyl ring. However, we observed that the reaction of 1 with aliphatic primary amines, gave imines 3 (Table I). In the $^1$H NMR spectra of 3, the position of the peak of CH$_3$ at ~2.1 was not changed with respect to that in 1. In the light of the alkaline hydrolysis of 1 to 2, nucleophilic attack of NH$_2$ at the CO adjacent to the benzene ring seems probable.

When 1 was reacted with aromatic aldehydes in the presence of different secondary amines, chalcones 5 were obtained (Table II). It is interesting to note that a similar reaction with 2-hydroxy dibenzoylmethane gave 2-phenylhydroxychromone. Thus in this reaction no -CO-C cleavage was observed.

1,3-Diketones are reported to add across the azomethine group in Schiff bases. When 1 was reacted with the Schiff base of benzaldehyde and benzylamine (6), imine 3a was obtained, and no reaction of PhCHO with 1 was observed. The same imine 3a was obtained when 1 was reacted with a mixture of PhCHO and PhCH$_2$NH$_2$. When 1 was refluxed in ethanol in the presence of a secondary amine, it cyclized to 2-methylchromone 7. Acid catalysed cyclization of 1 to 7 is known. When 1 was refluxed in ethanol with formaldehyde a mixture of 8 and 9 was observed. In the $^1$H NMR of 8, no olefinic proton was seen, but CH$_2$OH appeared at $\delta$ 5.0. In $^1$H NMR of 9, two sets of couple of doublets, each integrating for one proton, were observed at $\delta$ 4.35 and 4.6, due to the geminally coupled H. Moreover, the peak around $\delta$ 8.0 was characteristic of the peri-H in the chromone nucleus. We have earlier reported a similar reaction of 2-hydroxydibenzoylmethane. The possible mechanism of the reaction is shown in Scheme I.

The Mannich reaction of 1,3-diketones is often complex and many a times instead of the desired aminomethyl derivatives, diverse compounds are formed, mainly through the reaction of formaldehyde.
Scheme I
with the substrate\(^{10-13}\). The reaction of 1 with formaldehyde and secondary amines under acidic conditions is reported to give a mixture of different products\(^{13}\). We found, that under the acidic conditions the main product was 7 only. However, when 1 was reacted with different secondary amines and formaldehyde at room temperature under neutral conditions, the Mannich bases \(^{14}\) and 15 were obtained (Tables III and IV).

It is interesting to see that 7 failed to react with secondary amines and formaldehyde to give Mannich bases \(^{14}\) and 15. On the other hand, the reaction of 7 with 1-arylpiperazine in the presence of formaldehyde gave only bispiperazinylmethane. This behaviour of 1 was strikingly different than that of 2-hydroxydibenzoylmethane \(^{6}\). Thus, it may be concluded that 1 underwent normal Mannich reaction at the active -CH\(_2\)- and the product cyclised to 14/15.

### Experimental Section

The mps were taken in open capillaries on a Campbell precision melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 397 spectrophotometer and the values reported in wavenumbers (cm\(^{-1}\)). The \(^1\)H NMR were recorded on a Varian EM-360 (60MHz) and Varian XL-300 (300MHz) spectrometers with TMS as the internal standard and the chemical shifts reported in ppm (\(\delta\) units). Elemental analyses of all compounds were found to be satisfactory.

1-(2-Hydroxyphenyl)-1,3-butanedione 1 was prepared from 2-hydroxyacetophenone and ethyl acetate by the reported procedure\(^{5}\). 1-Arylpiperazines were prepared by the condensation of diethanolamine and anilines as per the reported procedure\(^{14}\).

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### Table II — Characterisation data of 5

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<td>C(_6)H(_5)</td>
<td>58</td>
<td>111-12</td>
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<td>5b</td>
<td>4-MeO-C(_6)H(_4)</td>
<td>34</td>
<td>138-39</td>
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<td>5c</td>
<td>4-NO(_2)-C(_6)H(_4)</td>
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<tr>
<td>5d</td>
<td>3,4-(MeO)(_2)C(_6)H(_3)</td>
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### Table III — Characterisation data of 14

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<td>15f</td>
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1: Yield 65%, m.p. 96-99°C (reported 95°C); IR(KBr): 1680, 1615, 1480, 1420, 1420, 1380, 1330, 1250, 1200, 1120, 1080, 945 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.1 (3H, s, CH\(_3\)); 6.8-7.7 (4H, m, ArH), 11.9 (1H, s, phenolic OH).

Reaction of 1 with \(\text{aq. NaOH}\). Compound 1 (0.3 g) was stirred with \(\text{aq. NaOH}\) (10%) for 2hr. The solution was acidified with conc HCl when 2 separated.

Reaction of 1 with morpholine. Compound 1 (0.3 g, 1.7 mmoles) and morpholine (0.14 g, 1.6 mmoles) were stirred in ethanol (15mL) at r.t for 2hr, ethanol was removed by distillation and the sticky mass was triturated with pet.ether (60-80°C) to obtain 7; yield 0.23 g (85%); m.p. 56-57°C (reported\(^{6}\) 67°C); IR(KBr): 3490, 3260, 1700, 1610, 1510, 1340, 1250, 1050, 950, 880, 760 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.1 (3H, s, CH\(_3\)); 5.0 (2H, s, CH\(_2\)OH), 6.9-7.9 (4H, m, ArH), 7.0-8.2 (4H, m, ArH).

Reaction of 1 with formaldehyde. To formalin (38-42% \(\text{aq. 0.6 mL}\)) in ethanol (20 mL), 1 (0.3 g, 1.7 mmoles) was added and the solution refluxed for 4hr. Ethanol was removed and the residue was separated by column chromatography over silica gel (60-120 mesh) using benzene as the eluent, when 8 separated first, followed by 9.

8: Yield 0.13 g (43%); m.p. 79-80°C; IR(KBr): 3490, 3260, 1700, 1610, 1510, 1340, 1250, 1210, 1050, 950, 880, 760 cm\(^{-1}\); \(^1\)H NMR(CDCl\(_3\)): \(\delta\) 2.1 (3H, s, CH\(_3\)); 5.0 (2H, s, CH\(_2\)OH), 6.9-7.9 (4H, m, ArH), 15.8 (1H, s, CH\(_2\)OH).
9: Yield 0.07 g (14%); m.p. 151-52°C; IR(KBr): 1700, 1640, 1615, 1470, 1400, 1300, 760 cm⁻¹; ¹H NMR (CDCl₃): δ 2.41 (3H, s, CH₃), 2.6 (3H, m, CH₂-CH), 3.19 (2H, m, CH₂-CO), 4.35 (1H, d, CH₃-Hδ), 4.6 (1H, d, CH₃-Hδ).

Reaction of 1 with formaldehyde and secondary amine to obtain 14/15. To a solution of an amine (1.4 mmol) and formaldehyde in ethanol (20 mL), 1 (1.7 mmol) was added and the solution was stirred at r.t. for 2 hr. Ethanol was removed and the residue was crystallized from pet. ether (60-80°C).

Compounds 14 were prepared using paraformaldehyde (3.2 mmol for 1.7 mmol of 1).

Compounds 15 were prepared using 1-arylpiperazines (1.9 mmol), 1 (1.7 mmol) and formalin (38-42% aq. 0.24 mL, 3.2 mmol); and the products were crystallized from chloroform and pet. ether (8:2).

14a: IR(KBr): 2860, 2840, 1640, 1580, 1470, 1400, 1300, 1240, 1120, 920, 860, 760 cm⁻¹; ¹H NMR (CDCl₃): δ 2.5 (7H, m, CH₃, O(CH₂–H); 3.5 (2H, s, CH₂-N), 3.7 (4H, t, -N(CH₂-H). 15a: IR(KBr): 2840, 1650, 1580, 1470, 1240, 1110, 1000, 950, 930, 750 cm⁻¹; ¹H NMR(CDCl₃): 82.55 (3H, s, CH₃), 2.7 (4H, s, N(CH₂-H), 3.09 (4H, s, N(CH₂-H), 3.6 (2H, s, CH₂-N), 7.0-8.2 (9H, m, ArH).

Reaction of 1 with arylaldehyde and morpholine. To an arylaldehyde (2.4 mmol) and morpholine (1.4 mmol) in ethanol (20 mL), 1 (1.6 mmol) was added and the solution stirred at r.t for 2 hr. Ethanol was distilled and the residue purified by coh chromatography over silica gel using benzene as eluent to obtain 5. IR(KBr) of 5a: 1690, 1610, 1300, 1220, 1150, 1110, 1020, 980, 760, 700 cm⁻¹; NMR (CDCl₃): 8 52.1 (3H, s, CH₃), 6.2 (1H CH=), 6.8-8.0 (4H, m, ArH).

References