Preparation of α-Hydroxy Ketones from Aromatic Aldehydes

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Received date: September 17, 2011

Abstract

Benzoin condensation of some aromatic aldehydes was investigated by catalytic effect of cyanide ion in alcoholic solvents. Some aldehydes including 4-methylbenzaldehyde, 4-chlorobenzaldehyde, 2-furylcarbaldehyde and 4-pyridinecarbaldehyde were converted to their relative α-hydroxy ketones. 2-Pyridinecarbaldehyde yielded an endiol tautommer of its relative α-hydroxy ketone, and 4-nitrobenzaldehyde was converted to unexpected esters in the same conditions.

Keywords: Aromatic aldehydes, Benzoin, Cyanide, α-Hydroxy ketones

1. Introduction

α-Hydroxy ketone is a functional group entity of many biologically active natural products such as sugars and antibiotics. Furthermore, α-Hydroxy ketones are useful synthones in organic synthesis, with widely studied chemistry. Various methods have been developed for the synthesis of α-hydroxy ketones including oxidation of enol phosphates, selective oxidation of vicinal diols, acyloin condensation of diesters, reduction of 1,2-diketones with TiI₄, oxidation of diarylalkynes with DMSO/FeBr₃, reductive coupling of aromatic aldehydes by TiCl₄/Et₃N, Fridel-Crafts reaction of reactive aromatic rings with oxalychloride, the reaction of organolithium or Grignard compounds with 1,4-dialkylpiperazine-2,3-diones, microwave assisted conversion of α-bromo aromatic ketones, and ultrasonic activated condensation of benzaldehydes in ionic liquids.

Benzoin condensation of benzaldehyde is a classic route for preparation of benzoin. In spite of the development of various new methods for preparation of symmetric or asymmetric α-diketons and α-hydroxyketons, there was not an exhaustive report on the extension of benzoin condensation to
other aromatic aldehydes. In this work, we have investigated the classic benzoin condensation of different aromatic aldehydes.

2. Results and Discussion

Alcoholic solutions of aromatic aldehydes were refluxed in the presence of catalytic amounts of NaCN or KCN. Some aldehydes, including 4-methylbenzaldehyde, 4-chlorobenzaldehyde, 2-furylcarbaldehyde, 2-pyridinecarbaldehyde and 4-pyridinecarbaldehyde converted to their relative benzoin (or pyridoin) derivatives. The products were obtained in reasonable times with relatively good yields. More details are shown in Table 1.

Based on IR and ¹H NMR spectral data, the products were often characterized as α-hydroxy ketones. The IR spectra of entries 1-3 showing ν C=O at 1667-1646 cm⁻¹. Due to the conjugation of carbonyl with aromatic rings, a shift of ν C=O to the lower wave numbers usually occurs in benzoin derivatives. This is not the case for entry 4, which shows ν C=O at 1721 cm⁻¹. This behavior may be attributed to the weakening of resonance between the two electron poor conjugated groups: the carbonyl and the pyridyl ring. The IR spectra of entries 1-4 also show ν OH at 3446, 3446, 3420 and 3123 cm⁻¹, respectively. The decrease of ν OH in these compounds seems to be in accordance with the increase of hydrogen bonding in this series. The ¹H NMR spectra of entries 1-4 show a signal for hydroxyl proton around δ 4.6-6 ppm.

Entry 5 was an exception to this general trend. The ¹H NMR spectrum shows four signals at aromatic region with equal integrations, which indicates a symmetric structure. On the other hand, a signal for two protons is appeared at δ 13.13 ppm, which is in the usual range of enolic protons. Furthermore, the ν C=O and the expected signal for carbonyl group are absent in the IR and ¹³C NMR spectra. Based on these spectral data, the product of entry 5 was recognized as an endiol. In fact, endiol is a tautomeric form of desired pyridoin, which is stabilized by hydrogen bonding between hydroxyl groups and their neighboring nitrogen atoms (Scheme 1).

![Scheme 1](image)

Scheme 1. Tautomeric forms of 2-pyridoin

In contrast to the above mentioned desirable results, some unexpected results were obtained from other aromatic aldehydes. It seems that electronic and steric properties affecting the reactivity of aromatic aldehydes in benzoin condensation. For example, p-dimethylamino benzaldehyde, possessing a strong
Table 1. synthesis of α-hydroxyketones from aromatic aldehydes

<table>
<thead>
<tr>
<th>entry</th>
<th>aromatic aldehyde</th>
<th>solvent</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-methylbenzaldehyde</td>
<td>2-butanol</td>
<td><img src="https://via.placeholder.com/150" alt="image" /> 180 82</td>
</tr>
<tr>
<td>2</td>
<td>4-chlorobenzaldehyde</td>
<td>Ethanol</td>
<td><img src="https://via.placeholder.com/150" alt="image" /> 90 68</td>
</tr>
<tr>
<td>3</td>
<td>2-furylcarbaldehyde</td>
<td>Ethanol</td>
<td><img src="https://via.placeholder.com/150" alt="image" /> 90 56</td>
</tr>
<tr>
<td>4</td>
<td>4-pyridylcarbaldehyde</td>
<td>Ethanol</td>
<td><img src="https://via.placeholder.com/150" alt="image" /> 120 75</td>
</tr>
<tr>
<td>5</td>
<td>2-pyridylcarbaldehyde</td>
<td>Ethanol</td>
<td><img src="https://via.placeholder.com/150" alt="image" /> 45 94</td>
</tr>
</tbody>
</table>

electron donating substituent, was unreactive in this transformation. On the other hand, \( p \)-nitro benzaldehyde, having a strong electron withdrawing substituent, was converted to a mixture of products. From the mixture, two esters were separated by column chromatography: ethyl-4-nitrobenzoate and diethoxy(4-nitrophenyl)methyl-4-nitrobenzoate.

Formation of esters gives evidence of the instability of the desired product in these conditions. Presumably, 4-nitrobenzaldehyde regularly converts to its relative α-hydroxy ketone in the applied conditions. The so formed benzoin derivative simply oxidizes to its benzil derivative under air. Cyanide catalyzed cleavage of benzil and some related α-diketones in alcoholic solvents was previously reported. Based on this report, cyanide ion catalyses the cleavage of benzil to benzaldehyde and an ester of benzoic acid (Scheme 2). This procedure rationalizes the formation of ethyl-4-nitrobenzoate in the reaction of 4-nitrobenzaldehyde with cyanide ion in ethanol.
Scheme 2. Cyanide catalyzed cleavage of benzoin in alcohol.

A similar mechanism may be considered to explain the formation of diethoxy(4-nitrophenyl)methyl-4-nitrobenzoate (Scheme 3). This procedure requires three air oxidation steps: the oxidation of benzoin to benzil, oxidation of a portion of 4-nitrobenaldehyde to 4-nitrobenzoic acid which provides the required acidic media, and oxidation of benzilic hydrogen in intermediate (1).

Scheme 3. Proposed mechanism for formation of diethoxy(4-nitrophenyl)methyl-4-nitrobenzoate

Condensation of 3-pyridincarbaldehyde, terphetalaldehyde and cinamaldehyde also led to gummy mixtures. All efforts for separation of products from mixtures were unsuccessful. Finally, there
were no reaction with 2-substituted benzaldehydes including 2-hydroxybenzaldehyde, 2,4-dimethoxybenzaldehyde, 2,4-dichlorobenzaldehyde and 2,6-dichlorobenzaldehyde.

3. Experimental

3.1. Material and measurements

All chemicals are commercially available and used as received. Melting points were determined on a Bransted Electrotermal apparatus and are uncorrected. FTIR spectra were measured on a Perkin-Elmer Spectrum RX1 spectrometer. $^1$C NMR and $^1$H NMR spectra were recorded on a Bruker Avance-300 MHz spectrometer employing tetramethylsilane as an internal reference. Mass spectra were recorded on a Finigan-MAT8430 70 eV spectrometer.

3.2. Typical procedure

A solution of sodium cyanide (2 mmol, 0.098 g) in H$_2$O (2 ml), was added to a stirred solution of a benzaldehyde derivative (10 mmol) in proper solvent (10 ml) (Table 1). The mixture was then refluxed. The progress of reaction was monitored by TLC using hexane/ethyleacetate (80:20) as eluent. The solvent was then removed by evaporation under reduced pressure. The residue was washed with water and diethyl ether.

3.2.1. 2-Hydroxy-1,2-di-p-tolylethanone

White crystals, Yield: 82%, mp: 85-87 °C; FT-IR (KBr, Cm$^{-1}$): 3446 (O-H), 1667 (C=O), 1171 (C-O); $^1$H NMR (DMSO-d$_6$, ppm): $\delta$ 2.21 (s, 3H, CH$_3$), 2.29 (s, 3H, CH$_3$), 5.86 (d, 1H, CH), 6.0 (d, 1H, OH), 7.1 (d, 2H, Ph), 7.24 (q, 4H, Ph), 7.87 (d, 2H, Ph).

3.2.2. 1,2-bis(4-chlorophenyl)-2-hydroxyethanone

Yellow crystals, Yield: 68 %, mp: 195-197 °C; FT-IR (KBr, Cm$^{-1}$): 3446 (O-H), 1654.76 (C=O), 1209 (C-O); $^1$H NMR (DMSO-d$_6$, ppm): $\delta$ 4.6 (broad s, 2H, CH and OH), 7.41 (d, 2H, Ph), 7.69 (d, 2H, Ph), 7.87 (d, 2H, Ph), 7.95 (d, 2H, Ph).

3.2.3. 1,2-di(furan-2-yl)-2-hydroxyethanone

Yellow crystals, Yield: 56%, mp: 125-126 °C; FT-IR (KBr, Cm$^{-1}$): 3420 (OH), 1646 (C=O), 1025(C-O); $^1$H NMR (DMSO-d$_6$, ppm): $\delta$ 5.78 (d, 1H, OH), 5.89 (d, 1H, CH), 6.83 (d, 2H, furyl), 7.52 (d, 1H, furyl), 7.63 (d, 1H, furyl), 7.99 (d, 1H, furyl), 8.24 (d, 1H, furyl).

3.2.4. 2-hydroxy-1,2-di(pyridin-4-yl)ethanone

Orange solid, Yield: 75 %, mp : 206-208 °C; FT-IR (KBr, cm$^{-1}$): 3123 (OH), 1721 (C=O), 1603 (C= Npyridyl); $^1$H NMR (DMSO-d$_6$, ppm): 5.6 (broad s, 2H, CH and OH), 7.22 (d, 2H, Py), 7.8 (d, 2H, Py), 8.4 (d, 2H, Py), 8.76 (d, 2H, Py).
3.2.5. 1,2-di(pyridin-2-y)ethane-1,2-diol
Orange crystals, Yield: 94 %, mp: 155-157 °C; FT-IR(KBr, Cm⁻¹): 3447 (OH), 1591 and 1560 (C=Npyridyl), 1495(C=C); ¹H NMR (DMSO-d₆, ppm): δ 7.39 (t, 2H, py), 7.8 (d, 2H, py), 8.00 (t, 2H, py), 8.6 (d, 2H, py), 13.13 (S, 2H, OH); ¹³C NMR (DMSO-d₆, ppm): δ 119.04, 122.07, 135.00, 138.52, 146.25, 155.45.3.2.6. Ethyl 4-nitrobenzoate
Yellow crystals, Yield: 32 %, mp: 55-57 °C; FT-IR (KBr, Cm⁻¹): 1718(C=O), 1276 (NO₂), 1103 (C-O); ¹H NMR (DMSO-d₆, ppm): δ 1.35 (t, 3H, CH₃), 4.36 (q, 2H, CH₂), 8.17 (dd, 2H, Ph), 8.34 (dd, 2H, Ph).
3.2.7. Diethoxy(4-nitrophenyl)methyl 4-nitrobenzoate
Pale yellow crystals, Yield: 24%, mp: 182-183 °C; FT-IR (KBr, Cm⁻¹): 1712 (C=O), 1272 (NO₂), 1102 (C-O); ¹H NMR (DMSO-d₆, ppm): δ 1.35 (m, 6H, CH₃), 4.35 (q, 4H, CH₂), 8.12 (s, 4H, Ph), 8.17 and 8.2 (d, 2H, Ph), 8.39 (d, 2H, Ph); Mass (m/e, %): 390 (1) (M⁺), 314 (4), 297 (6), 269 (6), 243 (6), 241 (6), 213 (6), 195 (4), 149 (100) (base peak), 103 (50), 65 (48).

4. Conclusion
Cyanide catalyzed condensation of aromatic aldehydes is mainly affected by the steric and electronic nature of the substrate. While aromatic aldehydes with low steric repulsion and low electronic effects on the reaction center, showed a straight conversion to their relative benzoin (pyridoin) derivatives, electron rich or strically hindered aromatic aldehydes were unreactive, and electron poor ones were converted to the complicated mixture of products.

Acknowledgement
Financial support from Islamic Azad University, Saveh branch is gratefully acknowledged.

References and Notes