o-Acylbenzaldehydes in organic synthesis: a brief review

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Abstract
The progress that has been made in organic synthesis via the reactions of o-acylbenzaldehydes is presented in this review, along with the methods for their synthesis and some of their applications.

Keywords: o-Acylbenzaldehydes, o-acetylbenzaldehyde, o-benzoylbenzaldehyde

Introduction

o-Acylbenzaldehydes are very interesting molecules because of their potential to serve as starting materials in organic synthesis. The presence of the two ortho to each other carbonyl groups at the benzene ring allows the formation of novel heterocycles as well as other non-heterocyclic aromatic compounds. Furthermore, aromatic aldehydes have found significant applications in the fragrance, flavour and pharmaceutical industries. However, o-disubstituted benzene derivatives are frequently difficult to prepare and cannot be synthesised by conventional methods. There are several methods for the synthesis of o-acylbenzaldehydes in the literature. The most of them are not general and often involve many steps with low yields. This is probably the reason for the limited number of references in the literature regarding their reactivity. Despite these difficulties a variety of products as isoindoles, phthalimidines, isoindoloquinazolines, indanes, naphthols, olefins have been prepared starting from o-acylbenzaldehydes. The products are usually obtained in good yields by using simple experimental conditions. Several years ago, we prepared o-diacetylbenzaldehydes in high yields, via a general method which includes the reaction of either N-formylhydrazones of o-hydroxyaryl ketones or N-acylhydrazones of salicylic aldehyde with lead tetraacetate (LTA). The purpose of this review is to present all the synthetic approaches for the preparation of o-diacetylbenzaldehydes as well as the progress that has been made in organic synthesis using them as starting materials. The presentation will begin with the methods of synthesis of o-acylbenzaldehydes. The papers dealing with the reactivity of o-acylbenzaldehydes will follow. Finally, some of the applications of o-acylbenzaldehydes and their derivatives will be presented.
It is hoped that this review will demonstrate the synthetic potential of o-acylbenzaldehydes and generate some new ideas in this area.

**Synthesis of o-acylbenzaldehydes**

o-Disubstituted benzene derivatives are frequently difficult to prepare and cannot be synthezised by conventional methods. In the literature, there exist several methods dealing with the synthesis of o-acylbenzaldehydes. However, in most cases they are not general and they usually lead to the synthesis of either o-benzoylelbenzaldehyde 3a (Schemes 1 and 8) or o-acetylbenzaldehyde 3b (Schemes 3-6 and 8).

The oxidation of o-hydroxymethyl-benzhydrol 2a with selenium oxide to afford o-benzoylelbenzaldehyde 3a was the first reported synthesis, in 1968 (Scheme 1).² The product was obtained in 53% yield.² Later, some more o-acylbenzaldehydes 3 were synthezised, according to the same method.³⁻⁶ However, yields are not available. Alternatively, oxidation of 2a with ceric ammonium nitrate led to the formation of 3a in 96% yield.⁷ Dialcohols 2 were usually obtained from the reaction of o-acylbenzoic acids 1 with lithium aluminum hydride.²⁻⁶

![Scheme 1](image)

a: R=Ph

c: R=p-Br-C₆H₄

d: R=p-Cl-C₆H₄

e: R=p-MeO-C₆H₄

A: LiAlH₄/THF /25°C/24h/80% for 3a

B: SeO₂/AcOH/xylene/reflux/20h/53%for 3a

C: SeO₂/AcOH/reflux /4.5h

D: Ce(NH₄)(NO₃)₅/96% for 3a

**Scheme 1**

Furthermore, o-acylbenzaldehydes 3 were synthesized by the oxidation of lactols 6 using selenium oxide as oxidative agent (Scheme 2). Lactols 6 were produced in a rather complicated way and yields for most of the products are not available.

There exist also in the literature⁸⁻¹² a few methods of synthesis especially for o-acetylbenzaldehyde 3b. One of them involves six steps and it is presented in Scheme 3.

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⁷ Reprinted with permission from Green Chem. 2007, 9, 890-897.
Scheme 2

\[
\begin{align*}
A: & \text{BuLi/R}^1\text{CHO/TsOH/THF/25}^\circ\text{C/61\% for 5j} \\
B: & \text{LiAlH}_4/\text{Et}_2\text{O}/5^\circ\text{C/reflux/2h/86\% for 6g} \\
C: & \text{SeO}_2/\text{pyridine/reflux/2-3h/77\% for 3j}
\end{align*}
\]

Scheme 3

\[
\begin{align*}
A: & \text{C}_3\text{H}_5\text{N/reflux/28\%} \\
B: & \text{CH}_3\text{COCH}_3/\text{K}_2\text{CO}_3/\text{CH}_3\text{I/94\%} \\
C: & \text{trimethylorthoformate/ethylene glycol/TsOH/THF/40}^\circ\text{C/3h/74\%} \\
D: & \text{LiAlH}_4/\text{THF/reflux/24h/86\%} \\
E: & \text{C}_3\text{H}_5\text{N}./\text{CrO}_3/\text{HCl/Al}_2\text{O}_3/\text{hexane/CH}_2\text{Cl}_2/25^\circ\text{C/2.5h/87\%} \\
F: & \text{AcOH/CH}_2\text{Cl}_2/\text{hv/40}^\circ\text{C/10h/83\%}
\end{align*}
\]
Treatment of phthalic anhydride 7 with malonic acid 8 yielded o-acetylbenzoic acid 1b in 28% yield. Subsequently, reaction of 1b with methyl iodide led to the formation of o-acetylbenzoic methylester 9 in 94% yield. Treatment of 9 with trimethylorthoformate and ethylene glycol in the presence of p-toluenesulfonic acid gave the ketal 10 in 74% yield, which was further added to a slurry of lithium aluminum hydride to form o-acetyl benzyl alcohol ethylene ketal 11 in 86% yield. Addition of 11 to a mixture of pyridinium chlorochromate absorbed on alumina, in methylene chloride and hexane led to the formation of o-acetyl-benzaldehyde ethylene ketal 12 as a faint yellow liquid in 87% yield. Finally, stirring of 12 in a mixture of acetic acid/water gave o-acetylbenzaldehyde 3b in 83% yield.

o-Acetylbenzaldehyde 3b has been also prepared via permanganate oxidation of 2-acetyl-cis-cinnamic acid 13 in 40% yield, (Scheme 4).8 Acid 13 was synthesized by ozonolysis of 1-methyl-2-naphthol which was prepared according to literature methods.9

\[
\begin{align*}
\text{COMe} & \quad \text{A} \quad \text{COMe} \\
13 \quad \text{CHO} & \quad 3b
\end{align*}
\]

A: Na₂CO₃/MgSO₄/benzene/0-5 °C/ KMnO₄/40%

Scheme 4

It has been also reported that o-acetylbenzaldehyde 3b was obtained as one of the major products of the aqueous ozonolysis of 1-methyl-, 1,2-dimethyl and 1,3-dimethyl-naphthalene 14, in 17%, 65% and 27% yield respectively (Scheme 5).10,11 When the ozonolysis was performed in methanol and n-hexane the yield was decreased to 6-14%.

\[
\begin{align*}
\text{14(a-c)} \quad \text{A} \quad \text{3b}
\end{align*}
\]

a: R¹=Me, R²=R³=H
b: R¹=R²=Me, R³=H
c: R¹=R³=Me, R²=H
A: O₃/H₂O/17-65% or O₃/CH₃OH or hexane/6-14%

Scheme 5
In 1976, it was reported that the photo-oxidation of o-methylacetophenone 15 led to the formation of o-acetylbenzaldehyde 3b (Scheme 6). An analogous report appeared later in the literature about o-benzoylbenzophenones. It has been suggested that the reaction proceeds via the intermediate enole 16 and the cyclic peroxide 17. The photo-oxidation of the ketone 15 in methanol was performed under three sets of conditions: (a) with no additive in yield up to 5%, (b) in the presence of copper(II) sulphate in yield up to 38%, and (c) in the presence of hydrochloric acid in yield up to 9%.

![Scheme 6](image)

A: hv/MeOH/5%
B: hv/MeOH/CuSO₄/38%
C: hv/MeOH/HCl/9%

There is also a reference in the literature about the formation of o-(o'-hydroxyphenyl)benzaldehyde 3k in traces, via the thermal decomposition of phenylanthracene 9,10-photooxide 18, as shown in Scheme 7. It has been proposed that the initially formed isobenzofuran 20 is easily auto-oxidized.

![Scheme 7](image)

A: toluene or dichloromethane/reflux/3h

In 1998, we reported a general, simple and efficient method for the synthesis of o-acylbenzaldehydes (Scheme 8). Formylhydrazones of arylketones bearing a hydroxy group at ortho-position 22 on treatment with lead tetraacetate underwent a rearrangement resulting in an unusual replacement of the phenolic hydroxyl with a formyl group to give o-acylbenzaldehydes.
3, in excellent yields 70-86%. Alternatively, \( \sigma \)-acylbenzaldehydes 3 were obtained by acyl group rearrangement of salicylaldehyde \( N \)-acylhydrazones 24.

\[
\begin{align*}
21 & \xrightarrow{A} 22 \\
23 & \xrightarrow{B} 24 \\
\end{align*}
\]

a: \( R=\text{Ph} \)  
b: \( R=\text{Me} \)  
k: \( R=\sigma \)-HO-C\(_6\)H\(_4\)  
l: \( R=\text{Et} \)  
A: NH\(_2\)NHCHO/n-propanol/reflux/24h/68-85%  
B: NH\(_2\)NHCOR/n-propanol/reflux/24h/95-99%  
C: Pb(OAc)\(_4\)/THF/25\(^\circ\)C/2h/70-86%  
D: Ph[(\text{diacetoxy)iodo}]benzene/CH\(_2\)Cl\(_2\)/25\(^\circ\)C/0.5h/71% for 3b

**Scheme 8**

The first route involves initial conversion of \( \sigma \)-hydroxy ketones 21 to their \( N \)-formylhydrazones 22a,b,k, which upon LTA oxidation, loss of nitrogen and migration of the formyl group, give the corresponding \( \sigma \)-acetylbenzaldehydes 3 in 70-86% yields. The alternative path starts with salicylaldehyde 23 which was condensed with \( N \)-acylhydrazines to give acylhydrazones 24a,k,l, and subsequent LTA treatment results in acyl group migration to give the corresponding \( \sigma \)-acetylbenzaldehydes 3 in 77-82% yields. \( \sigma \)-Acetylbenzaldehyde 3b has been also obtained in 71% yield when salicylic aldehyde acetylhydrazone 24b was oxidized with [(diacetoxy)iodo]benzene instead of lead tetraacetate.\(^\text{16}\)

**Reactivity of \( \sigma \)-acylbenzaldehydes**

The main interest of the researchers on the reactivity of \( \sigma \)-acylbenzaldehydes has been focused on their reactions with nitrogen compounds such as amines, hydrazides and amino acids. The reaction of \( \sigma \)-benzoylbenzaldehyde 3a with ethylenediamine in aqueous ethanolic solution led to
the formation of phthalimidine derivative 25 in 24% yield.\(^2\-^5\) When the condensation of \(o\)-benzoylbenzaldehyde with ethylenediamine was performed under anhydrous conditions the imidazoisoindole derivative 26 was formed in 43% yield.\(^1\,^17\) Furthermore, condensation of 3a with 1,3-propanediamine afforded the analogous pyrimidoisoindole derivative 27 in 73% yield (Scheme 9).\(^2\)

![Diagram](image-url)

A: NH\(_2\)(CH\(_2\))\(_2\)NH\(_2\)/EtOH-H\(_2\)O/reflux/18h/24%
B: NH\(_2\)(CH\(_2\))\(_2\)NH\(_2\)/toluene/reflux/18h/43%
C: NH\(_2\)(CH\(_2\))\(_3\)NH\(_2\)/toluene/reflux/3h/73%

Scheme 9

Furthermore, the reaction of \(o\)-benzoylbenzaldehyde with primary diamine 28 in CD\(_3\)OD led to the intensely fluorescing deuterated isoindoloquinazolines 29 and 30 in 27 and 23% yield respectively (Scheme 10).\(^18\)

![Diagram](image-url)

A: CD\(_3\)OD/N\(_2\)/20\(^\circ\)C/3h/27% for 29 and 23% for 30

Scheme 10

Treatment of \(o\)-acylbenzaldehydes with primary amines in the presence of thiol\(^7\) has been reported to afford 1,2,3-trisubstituted isoindoles 31 as shown in Scheme 11.

Reaction of 3a with aniline led to the formation of phthalimidine 33 in 65% yield (Scheme 12).\(^19\) The same product 33 was obtained via treatment of \(o\)-benzoylbenzaldehyde 3a with
aromatic isocyanates in 54-84% yield (Scheme 12). It was suggested that 2,3-disubstituted phthalimides 33 could be formed via o-benzylbenzylideneaniline intermediate 32 followed by migration of phenyl group.

\[
\begin{align*}
\text{CHO} & \quad \text{COR} \\
\text{3} & \quad \text{A} \\
a: R=\text{Ph} & \quad a: R=\text{Ph}, R^1=\text{Et}, R^2=\text{Bz} \\
e: R=\text{Me} & \quad b: R=\text{Me}, R^1=\text{Et}, R^2=\text{Bz} \\
& \quad c: R=\text{Me}, R^1=\text{C(Me)}_3, R^2=\text{CH(Me)}_2 \\
& \quad d: R=\text{Ph}, R^1=\text{C(Me)}_3, R^2=\text{CH(Me)}_2 \\
A: R^1\text{SH}/R^2\text{NH}_2/23\% & \text{for } 31c \text{ and } 42\% \text{ for } 31d
\end{align*}
\]

**Scheme 11**

\[
\begin{align*}
\text{CHO} & \quad \text{COPh} \\
\text{3a} & \quad \text{A or B} \\
a: R=\text{Ph} \quad (\text{via A}) & b: R=\text{m-MeC}_6\text{H}_4 \quad (\text{via B}) \\
c: R=1\text{-naphthyl} \quad (\text{via B}) & d: R=2\text{-naphthyl} \quad (\text{via B}) \\
A: \text{RNH}_2/\text{benzene/reflux/9h/65}\% & \text{for } 33a \\
B: \text{RN=C=O/200}^\circ\text{C/15-19h/54-84}\%
\end{align*}
\]

**Scheme 12**

In 1991, it was reported that the reaction of o-benzoylelbenzaldehyde 3a with benzylhydrazide dihydrochloride afforded 1-phenyl-2-benzylphthalazinium chloride 34, in 49% yield, which upon treatment with borane in tetrahydrofuran gave benzenedimethaneamine derivative 35. However no yield was reported (Scheme 13).
Treatment of \( \text{o-benzoylbenzaldehyde } 3a \) with \( \beta \)-alanin and malononitrile and subsequent reduction with sodium borohydride gave \( \text{o-benzoylbenzylmalononitrile } 37 \) in 77% yield. Reaction of \( 37 \) with guanidine afforded the pyrimidinetriamine \( 38 \) which was cyclised to pyrimidobenzazepin \( 39 \) upon heating in acetic acid in the presence of trifluoroacetic acid (Scheme 14).\(^{21}\) Furthermore, treatment of \( 37 \) with methanol or ethanol in the presence of the corresponding alkoxide afforded benzazepines \( 40 \). However yields are not available.

![Scheme 13](image1)

A: \( \text{NH}_2\text{NHCH}_2\text{Ph} \cdot 2\text{HCl}/\text{K}_2\text{CO}_3 /\text{THF}/0^\circ\text{C}/55\text{min}/\text{CH}_2\text{Cl}_2/25^\circ\text{C}/35\text{min}/49\%

B: \( \text{BH}_3 / \text{THF} \)

**Scheme 14**

A: \( \text{CH}_2(\text{CN})_2/\beta\text{-alanin}/\text{EtOH}/43\%

B: \( \text{NaBH}_4/\text{MeOH}/-15^\circ\text{C}/77\%

C: \( (\text{NH}_2)_2\text{C}=\text{NH}/\text{EtOH}/46\%

D: \( \text{AcOH}/\text{TFA}/47\%

E: \( \text{ROH} / \text{RO}^- (55\% \text{ for } R=\text{Me}, 38\% \text{ and for } R=\text{Et}) \)
Photooxidation of \( o \)-acetylbenzaldehyde 3b, in methanol with no additive, led to the formation of the lactone 42. In the presence of copper catalyst, the photoreaction of aldehyde 3b led to the formation of the acetal 44 whereas, in the presence of hydrochloric acid the peroxide 45 was obtained as the main product (Scheme 15).\(^{12}\) Further studies on the photochemical reaction of \( o \)-benzoylbenzophenone suggested that the main intermediate is a ketene derivative analogous to 43.\(^{22,23}\)

\[
\begin{align*}
42 & \\
41 & \\
3b & \\
43 & \\
44 & \\
45 & \\
\end{align*}
\]

A: \( \text{hv/MeOH/5\%} \)
B: \( \text{hv/MeOH/CuSO}_4/38\% \)
C: \( \text{hv/MeOH/HCl/9\%} \)

Scheme 15

The reaction of \( o \)-acetylbenzaldehyde 3b with 4-octyne 46 in the presence of niobium(III) reagent \( \text{NbCl}_3(\text{DME}) \) in tetrahydrofuran led to the formation 4-methyl-2,3-di-\( n \)-propyl-1-naphthol 47 in good yield, (Scheme 16).\(^{24}\)

\[
\begin{align*}
3b & \\
\text{NbCl}_3(\text{DME}) & \\
46 & \\
47 & \\
\end{align*}
\]

A: \( \text{THF/0\degree C/1.5h/KOH/MgSO}_4/65\% \)

Scheme 16

Furthermore, the main product of the reaction of \( o \)-acetylbenzaldehyde 3b with \( (\text{CF}_3)_2\text{CCl}_2 \) and triphenylphosphine was the olefin 48 whereas, benzofuran 49 which was isolated in 7% yield was easily converted to 50 at room temperature (Scheme 17) The mechanism of the olefination reaction was studied and it was shown that it takes place not by Wittig- but by a Knoevenagel-type of reaction.\(^{25}\)
**Scheme 17**

Condensation of \( o \)-benzoylbenzaldehyde 3a with nitromethane in the presence of sodium methoxide gave after acidification, 2-nitro-1-phenyl-1-hydroxyindene 51, 2-nitro-3-phenyl-1-hydroxyindene 52, and 2-nitro-1-phenyl-1,3-dihydroxyindan 53 in 39.1, 3.1 and 28.8% yield respectively. Treatment of either 51, 52, or 53 with sulfuric acid in benzene as dehydrating agent gave 1,3-diphenyl-2-nitroindene 54 (Scheme 18).\(^{26}\)

**Scheme 18**

**Applications**

\( o \)-Acylbenzaldehydes have been of interest as fluorescence reagents for high sensitive detection and quantitative measurements of biological compounds bearing primary amino group, as amino
acids and peptides.\textsuperscript{6,7,27} They have been also used for a high specific TLC-fluorescent detection of oxazepam and lorazepam.\textsuperscript{27}

\textit{o}-Acylbenzaldehydes have also proven to be useful precursors to isoindoles,\textsuperscript{2-6} phthalimidines,\textsuperscript{19} isoindoloquinazolines,\textsuperscript{18} naphthols,\textsuperscript{24} indane derivatives,\textsuperscript{26} and olefins.\textsuperscript{36} Recently, \textit{o}-acetylbenzaldehyde has been used to synthesize glycosylporphyrins appropriate for cancer photochemotherapy.\textsuperscript{28-30} Photodynamic therapy is based on the principal that porphyrins become concentrated in tumor cells and upon subsequent irradiation with visible light in the presence of oxygen, specifically destroy the cell.\textsuperscript{31,32} Finally, some organic peroxides as 45 (Scheme 15) derived from \textit{o}-acylbenzaldehydes showed antibacterial activity\textsuperscript{12,33} whereas, the imidazo and pyrimidoisoindole derivatives 26 and 27 (Scheme 9) were found to be psychostimulants at 0.03-50 mg/kg. They were found also to show analgesic, antipyretic, anti-inflammatory and antifungal activity.\textsuperscript{17}

\section*{Conclusions}

Despite the difficulties for their preparation, \textit{o}-acylbenzaldehydes have been shown to be useful starting materials in the synthesis of various compounds such as isoindoles, phthalimidines, isoindoloquinazolines, indanes, naphthols, olefins and promising tools for the future.

\section*{References}