o-Acylbenzaldehydes in organic synthesis: a brief review

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(received 21 Mar 03; accepted 28 Apr 03; published on the web 29 Apr 03)

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

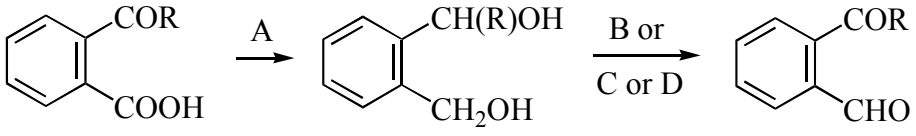
o-Acylbenzaldehydes are very interesting molecules because of their potential to serve as starting materials in organic synthesis. The presence of the two *ortho* to each other carbonyl groups at the benzene ring allows the formation of novel heterocycles as well as other non-heterocyclic aromatic compounds. Furthermore, aromatic aldehydes have found significant applications in the fragrance, flavour and pharmaceutical industries.[1] However, *o*-disubstituted benzene derivatives are frequently difficult to prepare and cannot be synthezised by conventional methods. There are several methods for the synthesis of *o*-acylbenzaldehydes in the literature.[2-16] 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*-diacylbenzaldehydes 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).[15]
The purpose of this review is to present all the synthetic approaches for the preparation of *o*-diacylbenzaldehydes 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*-benzoylbenzaldehyde **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*-benzoylbenzaldehyde **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]



1 **2** **3**

a: R=Ph

c: R=*p*-Br-C_6H_4

d: R=*p*-Cl-C_6H_4

e: R=*p*-MeO-C_6H_4

A: $LiAlH_4$/THF /25°C/24h/80% for **3a**

B: SeO_2/AcOH/xylene/reflux/20h/53%for **3a**

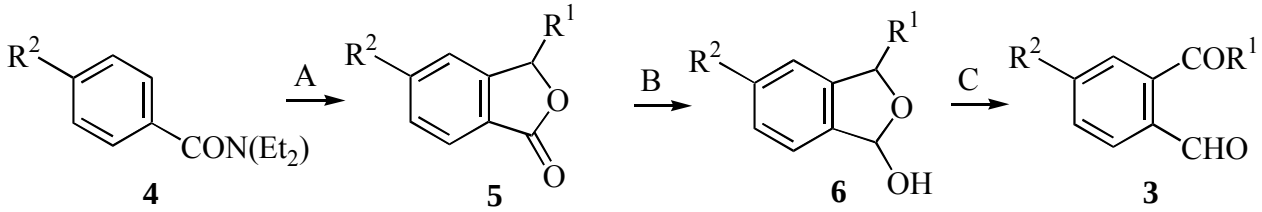
C: SeO_2/AcOH/reflux /4.5h

D: $Ce(NH_4)(NO_3)_5$/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 literature[8-12] a few methods of synthesis especially for *o*-acetylbenzaldehyde **3b**. One of them involves six steps and it is presented in Scheme 3.



4 **5** **6** **3**

f: R^1=Ph R^2=Me_2N

g: R^1=naphthyl R^2=H

h: R^1=naphthyl R^2=Ph

i: R^1=naphthyl R^2=Me_2N

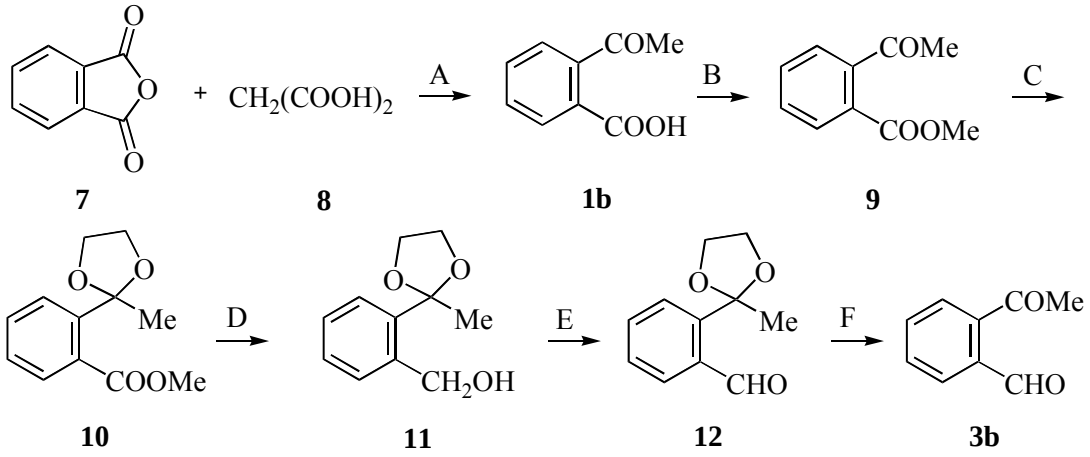
j: R^1=4-stilbenyl R^2=H

A: BuLi/R^1CHO/TsOH/THF/25^{o}C/61% for **5j**

B: $LiAlH_4$/Et_2O/5^{o}C/reflux/2h/86% for **6g**

C: SeO_2/pyridine/reflux /2-3h/77% for **3j**

Scheme 2



7 **8** **1b** **9**

10 **11** **12** **3b**

A: C_5H_5N /reflux /28%

B: CH_3COCH_3/K_2CO_3/CH_3I/94%

C: trimethylorthoformate/ethylene glycol/TsOH/THF/ 40^{o}C/3h/74%

D: $LiAlH_4$/THF/reflux/24h/86%

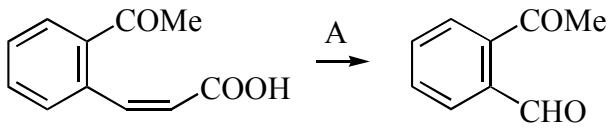
E: C_5H_5N**.**CrO_3/HCl/Al_2O_3/hexane/CH_2Cl_2/25^{o}C/2.5h/87%

F: AcOH/CH_2Cl_2/hv/40^{o}C/10h/83%

Scheme 3

Treatment of pthalic 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]

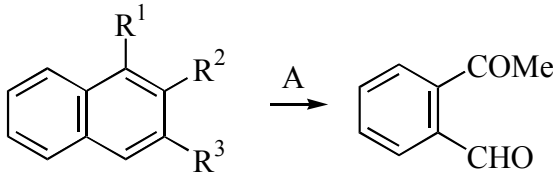


13 **3b**

A: $Na_2CO_3/MgSO_4$/benzene/0-5 ^oC/ $KMnO_4$/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%.



14(a-c) **3b**

a: R^1=Me, R^2=R^3=H

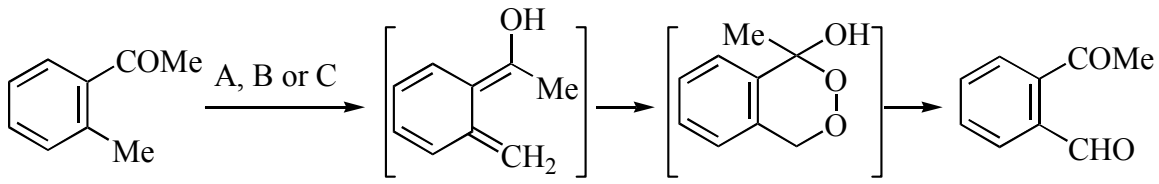
b: R^1=R^2=Me, R^3=H

c: R^1=R^3=Me, R^2=H

A: O_3/H_2O/17-65% or O_3/CH_3OH 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).[12] An analogous report appeared later in the literature about *o*-benzoylbenzophenones.[13] 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%.



15 **16** **17** **3b**

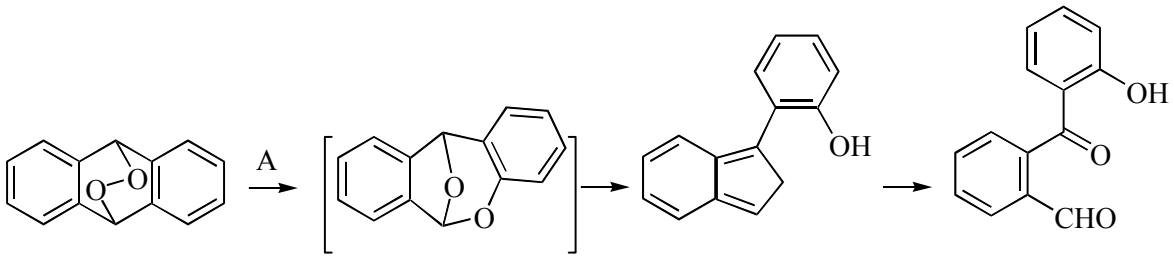
A: hv/MeOH/5%

B: hv/MeOH/$CuSO_4$/38%

C: hv/MeOH/HCl/9%

Scheme 6

There is also a reference[14] 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.



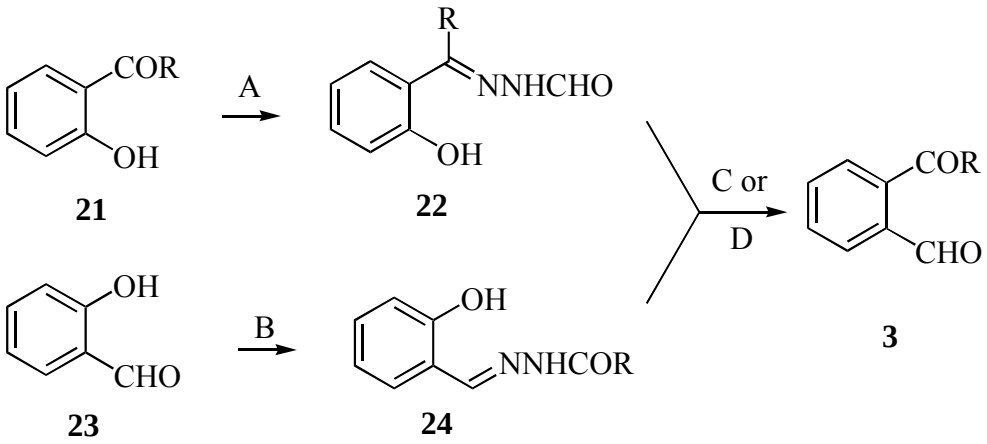
18 **19** **20** **3k**

A: toluene or dichloromethane/reflux/3h

Scheme 7

In 1998, we reported a general, simple and efficient method for the synthesis of *o*-acylbenzaldehydes (Scheme 8).[15] 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, *o*-acylbenzaldehydes **3** were obtained by acyl group rearrangement of salicylaldehyde *N*-acylhydrazones **24**.



a: R=Ph

b: R=Me

k: R=*o*-HO-C_6H_4

l: R=Et

A: NH_2NHCHO/n-propanol/reflux/24h/68-85%

B: NH_2NHCOR/n-propanol/reflux/24h/95-99%

C: $Pb(OAc)_4$/THF/25^oC/2h/70-86%

D: $Ph[I(OAc)_2]/CH_2Cl_2$/25^oC/0.5h/71% for **3b**

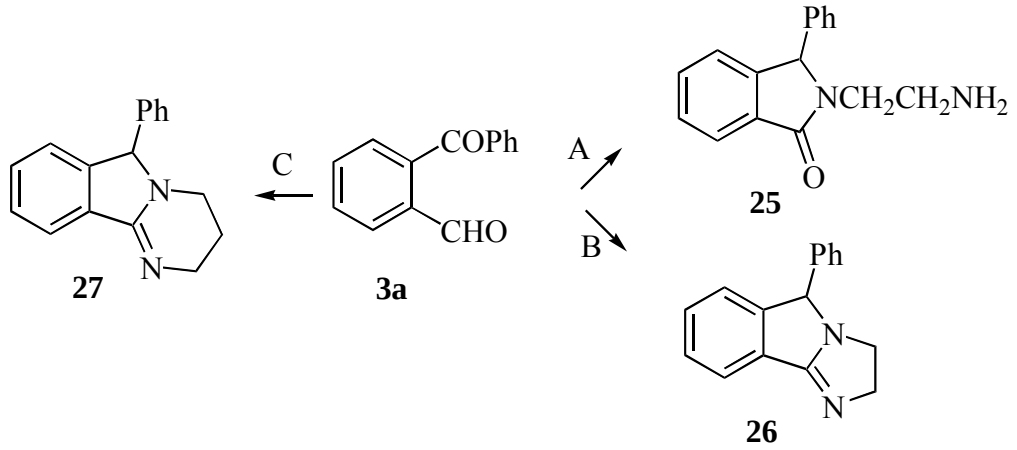
Scheme 8

The first route involves initial conversion of *o*-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 *o*-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 *o*-acetylbenzaldehydes **3** in 77-82% yields. *o*-Acetylbenzaldehyde **3b** has been also obtained in 71% yield when salicylic aldehyde acetylhydrazone **24b** was oxidized with [(diacetoxy)iodo]benzene instead of lead tetraacetate.[16]

Reactivity of *o*-acylbenzaldehydes

The main interest of the researchers on the reactivity of o-acylbenzaldehydes has been focused on their reactions with nitrogen compounds such as amines, hydrazides and amino acids. The reaction of *o*-benzoylbenzaldehyde **3a** with ethylenediamine in aqueous ethanolic solution led to

the formation of pthalimidine derivative **25** in 24% yield.[2-5] When the condesation 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]



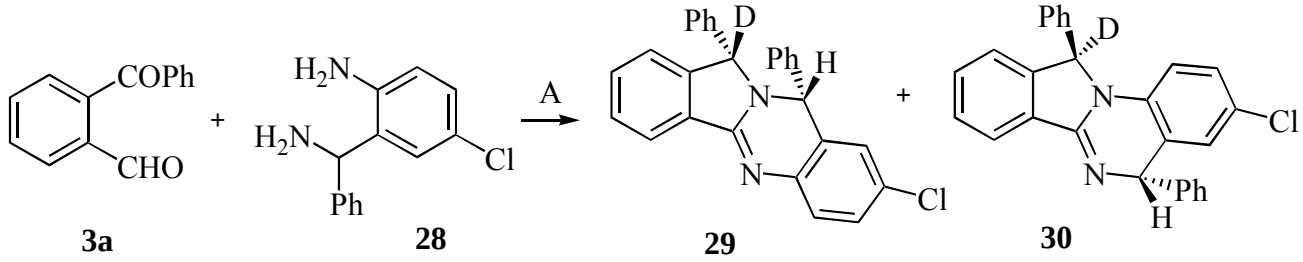
A: $NH_2(CH_2)_2NH_2$/EtOH-H_2O/reflux/18h/24%

B: $NH_2(CH_2)_2NH_2$/ toluene/reflux/18h/43%

C: $NH_2(CH_2)_3NH_2$/toluene/reflux/3h/73%

Scheme 9

Furtermore, the reaction of *o*-benzoylbenzaldehyde with primary diamine **28** in CD_3OD led to the intensely fluorescing deuterated isoindoloquinazolines **29** and **30** in 27 and 23% yield respectively (Scheme 10).[18]



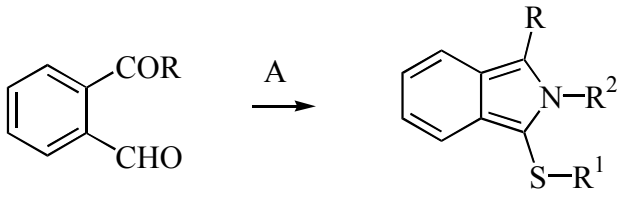
A: $CD_3OD/N_2/20^oC$/3h/27% for **29** and 23% for **30**

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).[19] It was suggested that 2,3-disustituted phthalimidines **33** could be formed *via o*-benzylbenzylideneaniline intermediate **32** followed by migration of phenyl group.



3 **31**

a: R=Ph a: R=Ph, R^1=Et, R^2=Bz

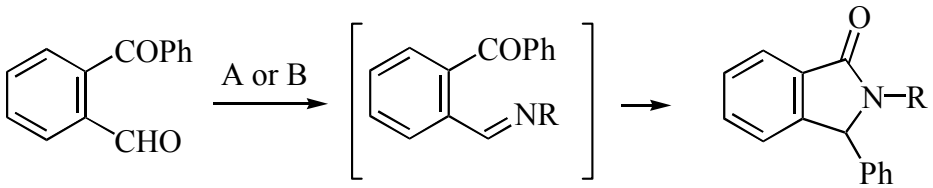
e: R=Me b: R=Me, R^1=Et, R^2=Bz

c: R= Me, R^1=$C(Me)_3$, R^2=$CH(Me)_2$

d: R= Ph, R^1=$C(Me)_3$, R^2=$CH(Me)_2$

A: R^1SH/R^2NH_2/23% for **31c** and 42% for **31d**

Scheme 11



3a **32(a-d)** **33(a-d)**

a: R=Ph (*via* A)

b: R= *m*-MeC_6H_4(*via* B)

c: R=1-naphthyl (*via* B)

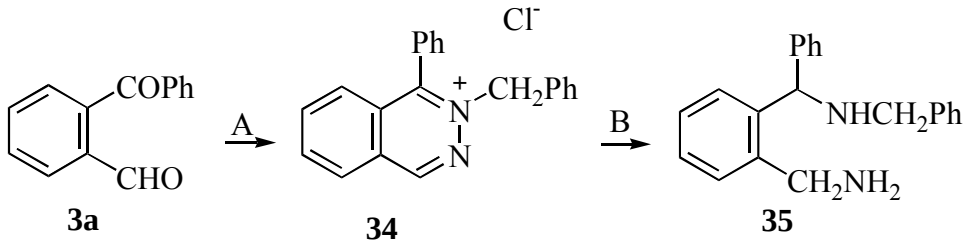
d: R=2-naphthyl (*via* B)

A: RNH_2/benzene/reflux/9h/65% for **33a**

B: RN=C=O/200^oC/15-19h/54-84%

Scheme 12

In 1991, it was reported that the reaction of *o*-benzoylbenzaldehyde **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).[20]



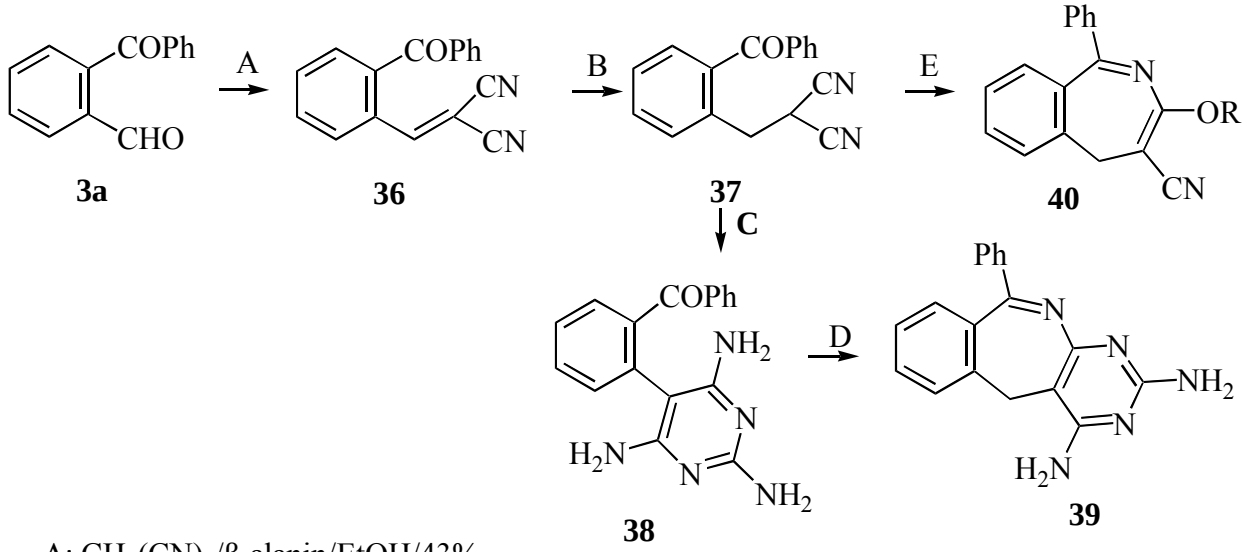
3a **34** **35**

A: $NH_2NHCH_2Ph \cdot 2HCl/K_2CO_3$ /THF/0°C/55min/CH_2Cl_2/25°C/35min/49%

B: BH_3 / THF

Scheme 13

Treatment of *o*-benzoylbenzaldehyde **3a** with β-alanin and malononitrile and subsequent reduction with sodium borohydride gave *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.



3a **36** **37** **40** **38** **39**

A: $CH_2(CN)_2$/ß-alanin/EtOH/43%

B: $NaBH_4$/MeOH/-15°C/77%

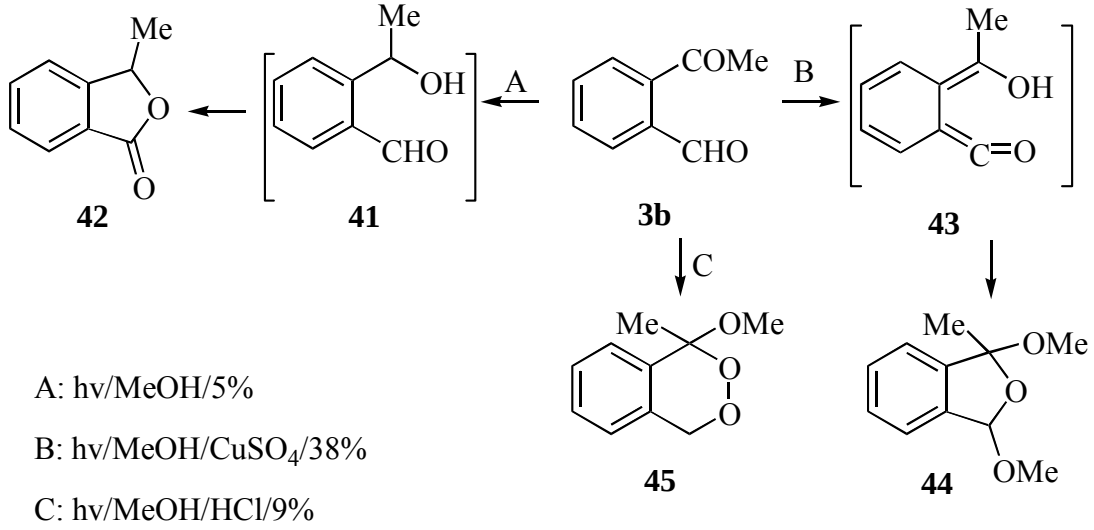
C: $(NH_2)_2C$=NH/EtOH/46%

D: AcOH/TFA/47%

E: ROH / RO^- (55% for R=Me, 38% and for R=Et)

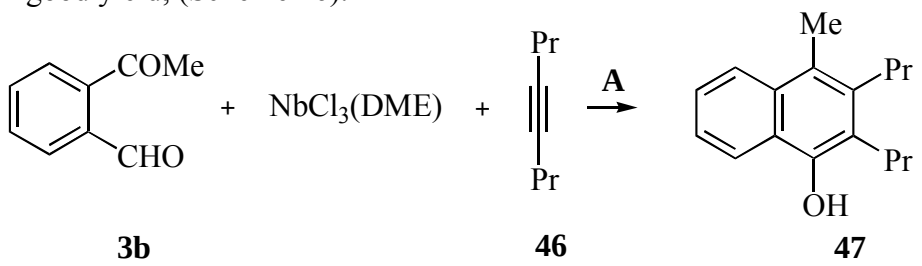
Scheme 14

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]



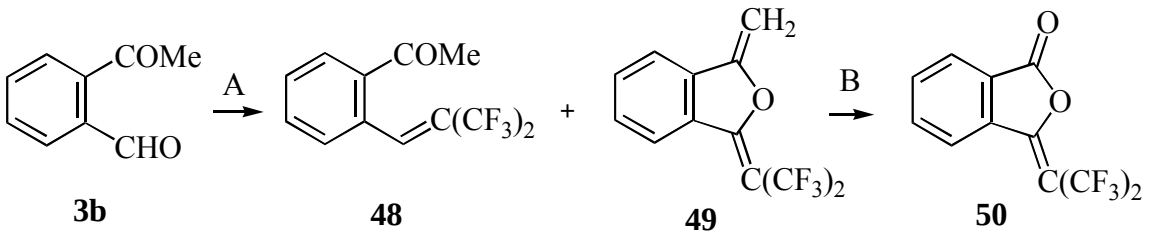
Scheme 15

The reaction of *o*-acetylbenzaldehyde **3b** with 4-octyne **46** in the presence of niobium(III) reagent $NbCl_3$(DME) in tetrahydrofuran led to the formation 4-methyl-2,3-di-*n*-propyl-1-naphthol **47** in good yield, (Scheme 16).[24]



Scheme 16

Furthermore, the main product of the reaction of *o*-acetylbenzaldehyde **3b** with $(CF_3)_2CCl_2$ 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]



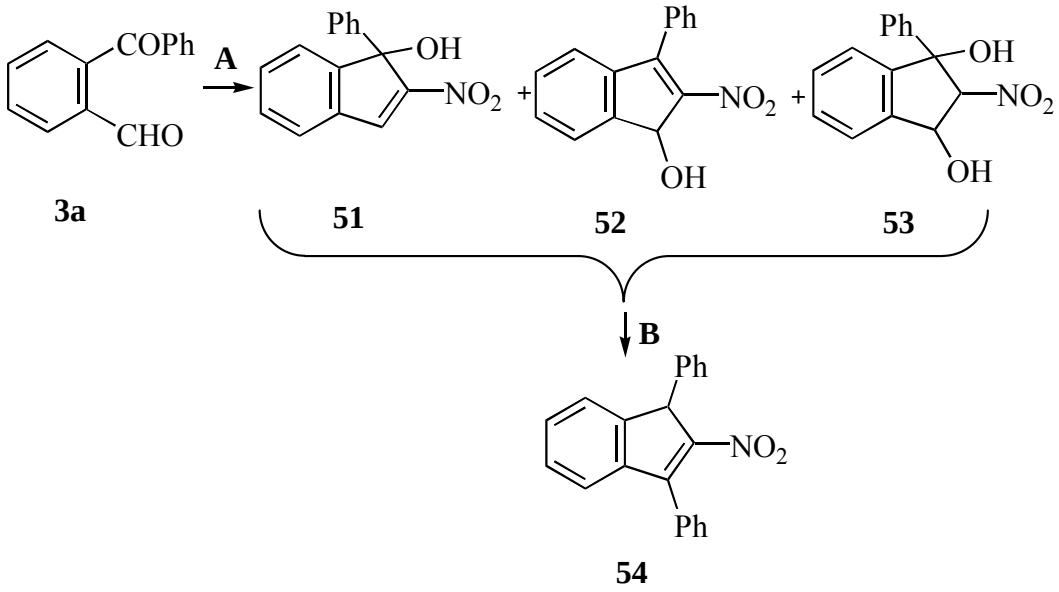
3b **48** **49** **50**

A: $(CF_3)_2CCl_2/P(C_6H_5)_3/CH_2Cl_2/-50^oC$/24% for **47** and 7% for **48**

B: CH_2Cl_2/30%

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]



3a **51** **52** **53** **54**

A: $MeNO_2$/MeONa/MeOH/0.5h/H_2SO_4/30min/39.1 for **50**/3.1% for **51**/28.8% for **52**

B: C_6H_6/H_2SO_4/reflux/1.5h/73%

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.[6,7,27] They have been also used for a high specific TLC-fluorescent detection of oxazepam and lorazepam.[27]

o-Acylbenzaldehydes have also proven to be useful precursors to isoindoles,[2-6] phthalimidines,[19] isoindoloquinazolines,[18] naphthols,[24] indane derivatives, [26] and olefins.[36] Recently, *o*-acetylbenzaldehyde has been used to synthesize glycosylporphyrins appropriate for cancer photochemotherapy.[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.[31,32] Finally, some organic peroxides as **45** (Scheme 15) derived from *o*-acylbenzaldehydes showed antibacterial activity[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.[17]

Conclusions

Despite the difficulties for their preparation, *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.

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