Chapter 2: Utilization of ortho-diacylbenzenes in synthesis of carbo- and heterocycles

2. ortho-Diacylbenzenes in organic synthesis

2.1 Introduction

2.1.1 Review of literature

Scheme 2.1. Structural feature of ortho-diacylbenzenes 1.

ortho-Diacylbenzenes can provide a number of heterocycles via a range of intermolecular as well as intramolecular transformations. Houlihan and co-workers (2002) synthesized 5-(4-chlorophenyl)-3,5-dihydro-2H-imidazo[2,1-a]isoindole (Mazindane) via the reaction of 2-(4-chlorobenzoyl)benzaldehyde (1) with ethylene diamine (2). Mazindane was found to be a pro-drug, oxidized to mazindol on rat striatal membranes and HEK-hDAT cells. Mazindol analogues are potential inhibitors of the cocaine binding site at the dopamine transporter (Scheme 2.2).

Scheme 2.2. Synthesis of mazindane from ortho-aryloxybenzaldehyde 1.

Liu and co-workers (2010) fabricated benzo[5,6][1,3]oxazino[2,3-a]phthalazin-8(13aH)-one (4) by the reaction of salicylhydrazide 3 with ortho-phthalaldehyde 1 (Scheme 2.3), which was proved to be a selective, cell-permeable fluorescent probe for Al^{3+} in living cells.
Scheme 2.3. Condensation of salicylhydrazide 3 with ortho-phthalaldehyde 1.

Schmald et al. (2011) synthesized isoindolinones via N-capping of primary amines or amino acid esters 5 with 2-acylbenzaldehydes 1. In this protocol, natural product pestalone was successfully introduced as a reagent which after capturing primary amines provided N-substituted derivatives of pestalachloride A (Scheme 2.4).3

Scheme 2.4. Synthesis of isoindolinones 6.

Phthalaldehyde 1 and 1,4-cyclohexanediione 7 reacts in the 2:1 molar ratio via crossed aldol condensation in pressurized hot water to produce 6,13-pentacenequinone 8 that was further used as a precursor to parent pentacene 9 (Scheme 2.5). Pentacene serves as a raw material for organic field-effect transistors, solar batteries, liquid crystal displays and organic electroluminescence displays in the area of the ever-expanding organic semiconductor industry.4

Scheme 2.5. Intermolecular cross aldol reaction towards synthesis of 8 and successive reduction to 9.

Langer and associates reported the cyclization of 1,3-bis-silyl enol ethers 10 with orthodiacyl benzenes 1. This protocol allowed a convenient synthesis of a variety of substituted 7H-benzo[7]annulen-7-one 11 (Scheme 2.6).5
Total syntheses of justicidin B \( 14 \) and retrojusticidin B \( 15 \) involving a base induced annulation of ketoaldehyde and phosphonate via a tandem Horner–Emmons–Claisen condensation sequence was developed by D. C. Harrowven et al. (2001) (Scheme 2.7).\(^6\)

Several reports of intramolecular Tischenko reaction involving ortho-diacyl benzenes to attain phthalides, core structure of several natural products having a range of utility as flavoring agents and in treatment of memory loss can be found. Most remarkable among these is the rhodium catalyzed stereoselective synthesis of isobenzofuran derivatives \( 16 \) by Dong and co-workers (Scheme 2.8).\(^7\)

Cheng and co-workers (2010) demonstrated a robust protocol to afford the 3-aryl and alkenyl phthalides via rhodium catalyzed cascade aryl addition/intramolecular esterification of phthalaldehyde with arylboronic acids (Scheme 2.9).\(^8\)
Scheme 2.9. Use of boronic acid derivatives 17 to fabricate 3-aryl/alkenyl phthalides 16.

2.1.2 Statement of the problem

From the structural features of the precursor 1, it is pertinent to note that these precursors have great potential to be used as the synthon of 3-hydroxyindanone or indenone skeletons in stereoselective organocatalytic intramolecular aldol reaction if at least one acyl group possesses an active methylene center (Scheme 2.1). As per our literature survey no such efforts are made yet. In view of these broad utility profiles, we have synthesized several reported as well as new ortho-diacyl benzene substrates. Further they have been utilized in synthesis of functionalized/spirocyclic 3-hydroxyindanones via trans-selective intramolecular aldolization of substrate 1 (Discussed in Part 1 of this chapter) and indeno-fused naphthalenes/quinolines having structural resemblance with C-nor-D-homo-steroids via a quadruple domino approach (Discussed in Part 2 of this chapter). Moreover, transformation of 3-hydroxyindanones (obtained during the experiments performed in Part 1 and 2 of this chapter) via an acid/base-free approach is documented in Part 3 of this chapter. 2-Aryl indenones thus formed were yet again utilized as the synthon of thermal dehydro-Diels–Alder cycloaddition reaction for the first time and is documented in Part 4 of this chapter.

2.2 Experimental section (Synthesis of ortho-diacylbenzene substrates 1)

2.2.1 General Remarks

$^1$H- and $^{13}$C-NMR spectra were recorded at 300 and 75 MHz respectively. Chemical shift (δ) values are given in parts per million (ppm) with reference to tetramethylsilane (TMS) as the internal standard. ‘J’ values are given in Hz. High resolution mass spectra were recorded by ESI method. Organic solvents used were dried by standard methods when necessary. Commercially obtained reagents were used as such without further purification. All these reactions were monitored by TLC with silica gel coated plates. Column chromatography was carried out using silica gel of 100/200 mesh. Mixture of hexane/ethyl acetate in appropriate proportion (determined by TLC analysis) was used as eluent solvent system.
2.2.2 General Reaction Procedures

![Scheme 2.10](image)

**Scheme 2.10.** Preparation of ortho-acyl phenol derivatives C.

2.2.2.1 Preparation of 3-chloro-6-hydroxy-2,4-dimethylbenzaldehyde C(1c)

Paraformaldehyde (7 mmol) was added to a mixture of 4-chloro-3,5-dimethylphenol C'(1c) (1 mmol), anhydrous MgCl₂ (1.5 mmol) and Et₃N (4 mmol) in dry THF (10 ml), and the mixture was heated to reflux for 24 h. Reaction was cooled to room temperature, solvent was evaporated. 50 mL of 5% aqueous HCl was poured to it and extracted with EtOAc (3×20). Combined organic layer was washed with water followed by brine. Solvent was evaporated in vacuo and subjected to column chromatography using mixture of EtOAc and hexane in appropriate proportion as eluent to afford C(1C) in 86% yield.

2.2.2.2 Procedure for the preparation of substrate ortho-diacylbenzenes 1

Substrates 1 were synthesized by modified procedure reported by Kotali et al. according to the Schemes 2.10 and 2.11.

2.2.2.3 Preparation of acyl hydrazine B

At first several different acyl hydrazines B were synthesized. To do this, we started with corresponding carboxylic acid A in solvent EtOH (2mL/mmol), 4 equivalents of thionyl chloride (SOCl₂) was added drop wise at room temperature and stirred for 24 h at room temperature, SOCl₂ and EtOH were evaporated. Water was added to the crude mixture, extracted with dichloromethane (DCM) and dried with anhydrous Na₂SO₄. DCM was evaporated and the residue was dried at high vacuum, provided the ethyl ester of the corresponding carboxylic acid A.
Chapter 2

The ester was added drop wise to hydrazine hydrate (NH$_2$NH$_2$.H$_2$O) (5mmol/1mmol of ethyl carboxylate) and heated at 80 °C for 12 h and allowed to stand for 12 h. If solid appeared it was filtered off and the residue was dried in high vacuum at 80 °C for 12 h. If solid was not obtained, the reaction mixture was freezeed and again brought to the room temperature. Solid thus obtained was filtered off and the residue was dried in high vacuum at 80 °C for 12 h that leads to different acyl hydrazine B corresponding to the starting carboxylic acid A.

2.2.2.4 Preparation of hydrazide D

As per requirement, different acyl hydrazine B was refluxed for 3-8 hours in ethanol with 1 equivalent of different substituted ortho-hydroxyacylbenzene C. After completion of the reaction (monitored by TLC) ethanol was evaporated and the crude was washed with hexane and dried in high vacuum which provided pure hydrazide D.

2.2.2.5 Preparation of ortho-diacylbenzenes 1

The hydrazides D thus obtained dissolved in dry THF (5 mL/mmol of D) in a round bottom flask and the temperature was brought to 0 °C, 1.2 equivalents of Pb(OAc)$_4$ was added to it in 4 to 5 portions. Reaction mixture was stirred for 2-8 h. After completion of the reaction (determined by TLC analysis) it was filtered using a pad of celite, THF was evaporated from the filtrate and the residue was washed several times with EtOAc. Combined EtOAc layer and the dried filtrate part was mixed together and washed several times with water to make it acid free and finally with brine. Combined organic layer was dried over anhydrous Na$_2$SO$_4$, solvent was evaporated and product mixture was subjected to column chromatography using EtOAc/n-hexane mixture as eluent.
Table 2.1. List of ortho-diacylbenzene precursors 1 synthesized and used in this chapter.
2.2.3 Characterization data of the synthesized molecules

5-Bromo-2-propionylbenzaldehyde (1a)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 10.13 (s, 1H), 7.99 (s, 1H), 7.78 (d, $J = 8.1$ Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 1H), 2.99 (q, $J = 7.101$ Hz, 2H), 1.27 (t, $J = 7.05$ Hz, 3H).

2-Propionylbenzaldehyde$^7$ (1b)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 10.15 (s, 1H), 7.89 (d, $J = 5.7$ Hz, 1H), 7.64 (broad, 3H), 2.98 (q, $J = 7.2$ Hz, 2H), 1.28 (t, $J = 7.05$ Hz, 3H).

2-Acetyl-5-bromobenzaldehyde (1d)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 10.13 (s, 1H), 7.92 (s, 1H), 7.73 (d, $J = 8.1$ Hz, 1H), 7.59 (d, $J = 8.1$ Hz, 1H), 2.58 (s, 3H).

2-Acetylbenzaldehyde$^9$(1e)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 10.19 (s, 1H), 7.86 (d, $J = 8.1$ Hz, 1H), 7.68-7.61 (m, 3H), 2.63 (s, 3H).

2-Acetyl-5-nitrobenzaldehyde$^7$ (1f)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 10.43 (s, 1H), 8.92 (s, 1H), 8.74 (d, $J = 8.4$ Hz, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 2.94 (s, 3H).

2-Acetyl-5-methylbenzaldehyde$^7$ (1g)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 10.15 (s, 1H), 7.80 (d, $J = 7.8$ Hz, 1H), 7.45-7.41 (m, 2H), 2.62 (s, 3H), 2.47 (s, 3H).
ortho-Diacetylbenzene\textsuperscript{10} (1h)

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta 7.53 \text{ (broad, 4H), 2.51 (s, 6H).} \]

1-Acetyl-2-propionylbenzene\textsuperscript{11} (1p)

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta 7.63-7.43 \text{ (m, 4H), 2.82 (q, } J = 7.2 \text{ Hz, 2H),} \\
\text{2.53 (s, 3H), 1.23 (t, } J = 7.05 \text{ Hz, 3H).} \]

5’-Bromo-2’-cyclohexanoylbenzaldehyde (1s)

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta 10.01 \text{ (s, 1H), 8.01 (s, 1H), 7.77 (d, } J = 8.1 \text{ Hz, 1H),} \\
\text{7.50 (d, } J = 8.1 \text{ Hz, 1H), 3.02-2.93 (m, 1H), 1.93-1.70 (m, 5H), 1.49-1.22 (m, 5H).} \]

2’-Cyclopentanoylbenzaldehyde (1x)

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta 7.63-7.61 \text{ (m, 1H), 7.53-7.47 (m, 3H), 3.39} \\
\text{(quintet, } J = 7.95 \text{ Hz, 1H), 2.54 (s, 3H), 1.94-1.75 (m, 4H), 1.75-1.59 (m, 4H).} \]

5’-Bromo-2’-cyclopropanoylbenzaldehyde (1za)

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta 10.13 \text{ (s, 1H), 8.04 (s, 1H), 7.81-7.74 (m, 2H),} \\
\text{2.52-2.46 (m, 1H), 1.38-1.33 (m, 2H), 1.20-1.14 (m, 2H).} \]

2’-Benzoylacetoephone\textsuperscript{10} (1zc):

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta 7.89 \text{ (d, } J = 7.5 \text{ Hz, 1H), 7.74 (d, } J = 7.2 \text{ Hz,} \\
\text{2H), 7.63-7.51 (m, 3H), 7.43 (t, } J = 7.2 \text{ Hz, 3H), 2.52 (s, 3H).} \]

2’-Benzoyl-5’-methylacetophenone\textsuperscript{10} (1zd):

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta 7.74 \text{ (d, } J = 7.2 \text{ Hz, 2H), 7.62 (s, 1H), 7.54-} \\
\text{7.49 (m, 1H), 7.42-7.37 (m, 3H), 7.31 (d, } J = 7.8 \text{ Hz, 2H), 2.48 (s, 6H).} \]
2′-(3-Methylbenzoyl)acetophenone (1ze):

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.65-7.58 (m, 2H), 7.43 (d, $J = 7.8$ Hz, 1H), 7.31-7.22 (m, 3H), 6.97-6.81 (m, 2H), 2.36 (s, 6H).

2′-Benzoyl-5′-chloroacetophenone$^{11}$ (1zf):

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.80 (s, 1H), 7.73 (d, $J = 7.2$ Hz, 2H), 7.59-7.52 (m, 2H), 7.44-7.34 (m, 3H), 2.49 (s, 3H).

2′-(4-Chlorobenzoyl)acetophenone$^{12}$ (1zh):

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.61-7.38 (m, 7H), 7.32-7.27 (m, 1H), 2.49 (s, 3H).

2′-(3-Chlorobenzoyl)acetophenone (1zh):

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.91-7.30 (m, 8H), 2.51 (s, 3H).

2′-(2-Chlorobenzoyl)acetophenone (1zi):

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.61-7.38 (m, 7H), 7.32-7.27 (m, 1H), 2.49 (s, 3H).

2′-(4-Methoxybenzoyl)acetophenone$^{13}$ (1zk)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.87 (d, $J = 8.7$ Hz, 1H), 7.73 (d, $J = 9$ Hz, 2H), 7.62-7.53 (m, 2H), 7.39 (d, $J = 8.7$ Hz, 1H), 6.90 (d, $J = 9$ Hz, 2H), 3.84 (s, 3H), 2.51 (s, 1H).
**2’-Pyridoylacetophenone (1zl):**

\[
1^\text{H}-\text{NMR} \ (300 \ MHz, \ \text{CDCl}_3) \ \delta \ 8.73 \ (\text{broad, 2H}), \ 8.17 \ (d, \ J = 7.8 \ Hz, \ 1H), \\
7.95 \ (d, \ J = 6.9 \ Hz, \ 1H), \ 7.70-7.61 \ (m, \ 2H), \ 7.41-7.39 \ (m, \ 2H), \ 2.54 \ (s, \ 3H).
\]

**5’-Chloro-2’-pyridoylacetophenone (1zm):**

\[
1^\text{H}-\text{NMR} \ (300 \ MHz, \ \text{CDCl}_3) \ \delta \ 8.74 \ (\text{broad, 2H}), \ 8.16 \ (d, \ J = 8.1 \ Hz, \ 1H), \\
7.87 \ (s, \ 1H), \ 7.66 \ (d, \ J = 7.8 \ Hz, \ 1H), \ 7.44-7.35 \ (m, \ 2H), \ 2.54 \ (s, \ 3H).
\]

**5’-Methyl-2’-pyridoylacetophenone (1zn):**

\[
1^\text{H}-\text{NMR} \ (300 \ MHz, \ \text{CDCl}_3) \ \delta \ 8.73 \ (\text{broad, 2H}), \ 8.16 \ (d, \ J = 7.8 \ Hz, \ 1H), \\
7.69 \ (s, \ 1H), \ 7.48-7.26 \ (m, \ 3H), \ 2.52 \ (s, \ 3H), \ 2.51 \ (s, \ 3H).
\]
2.3 References


