Intramolecular Organocatalytic Morita-Baylis-Hillman Reaction

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Certificate of Examination

This is to certify that the dissertation titled *"Intramolecular Organocatalytic Morita-Baylis-Hillman Reaction"* submitted by Mr. Siddhant Wagulde (Reg. No. MS12056) for the partial fulfilment of BS-MS dual degree programme of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

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Dated: April 21, 2017

Declaration

The work presented in this dissertation has been carried out by me under the guidance of **Dr. S. S. V. Ramasastry** at the Indian Institute of Science Education and Research Mohali.

This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussion. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

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Dated: April 21, 2017

In my capacity as the supervisor of the candidate's project work, I certify that the above statements by the candidate are true to the best of my knowledge.

Dr. S. S. V. Ramasastry
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List of Figures

Figure 1. The biological activity range of benzofuran derivatives.

Figure 2. Pyranones and derivatives.

List of Tables

Table 1. Scope of Nucleophile for 1,3-dicarbonyls.

Table 2. Screening of different catalysts and solvent combinations for **2c**.

Table 3. Screening of different Palladium catalysts and solvents for **2c**.

Table 4. Optimization of MBH conditions for **4a**.

List of Schemes

Scheme 1. Acid Catalyzed Ring Transformation of Benzofurans to Tri- and Tetrasubstituted Furans.

Scheme 2. Lewis Acid Catalyzed Regiospecific Cross-Dehydrative Coupling Reaction of 2-Furylcarbinols with β-Keto Amides or 4-Hydroxycoumarins.

Scheme 3. Lewis Acid Catalyzed Regiospecific Cross-Dehydrative Coupling Reaction of 2-benzofuryldiphenylmethanol with 1,3-dicarbonyls.

Scheme 4. Synthesis of 2-benzofuryldiphenylmethanol.

Scheme 5. Lewis Acid Catalyzed Regiospecific Cross-Dehydrative Coupling Reaction of 2-benzofuryldiphenylmethanol with 1,3-dicarbonyls.

Scheme 6. General approach for the synthesis of **1c.**

Scheme 7. Substrate-Controlled Regioselective Arylations of 2-Indolylmethanols with Indoles.

Scheme 8. Cascade Michael addition–cycloacetalisation strategy on acyloxypyran-3-one system.

Scheme 9. Reaction of 1,3-acetone dicarboxylic acid with enone systems to give cyclohexanone derivatives.

Scheme 10. Reaction of 1,3-acetone dicarboxylic acid with acyloxy-pyran-3-one.

Scheme 11. Synthesis of acyloxypyran-3-one **2.1c**.

Scheme 12. General approach for the synthesis of **2c.**

Scheme 13. MBH reaction of β,β- disubstituted enones.

Scheme 14. MBH reaction of substituted dienones.

Scheme 15. General approach for the synthesis of **3.**

Scheme 16. Synthesis of cyclopenta[*b*]annulated arenes **4.**

Scheme 17. General approach for the synthesis of **4.**

Notations and Abbreviations

NMR	Nuclear magnetic resonance
IR	Infra-red
TLC	Thin layer chromatography
δ	Chemical shift in ppm
ppm	Parts per million
EtOAc	Ethyl acetate
s	Singlet
d	Doublet
t	Triplet
q	Quartet
m	Multiplet
dd	Doublet of doublet
dt	Doublet of triplet
td	Triplet of doublet
ddd	Doublet of doublet of doublet
M. P.	Melting point

Contents

I. List of Figures I

II. List of Tables II

III. List of Schemes III

IV. Notations and Abbreviations IV

1. Abstract 1

1. Lewis acid catalyzed directly dehydrative carbon–carbon bond formation reaction of 2-benzofuryldiphenylmethanol with 1,3-dicarbonyls.

    1a. Introduction. 2

    1b. Results and discussions. 4

    1c. Experimental methods. 7

    1d. Summary 10

    1e. Bibliography 10

2. An unprecedented utilization of 1,3-acetonedicarboxylic acid as a 1,3-bis-pro-nucleophile with acyloxy-pyran-3-one for the synthesis of bicyclic compounds.

    2a. Introduction. 11

    2b. Results and discussions. 13

    2c. Experimental methods. 16

    2d. Summary 19

    2e. Bibliography 19

3. The synthesis of starting material 2-((2*E*,4*E*)-5-phenylpenta-2,4-dienoyl) benzaldehyde and optimized condition for the IMBH adducts.

    3a. Introduction. 22

    3b. Results and discussions. 23

3c. Experimental methods. 25
3d. Summary 27
3e. Bibliography 27

Abstract

The thesis has been divided into three chapters:

- **Chapter 1:** Lewis acid catalyzed directly dehydrative carbon–carbon bond formation reaction of 2-benzofuryldiphenylmethanol with 1,3-dicarbonyls, is investigated.
- **Chapter 2:** An unprecedented utilization of 1,3-acetonedicarboxylic acid as a 1,3-bis-pro-nucleophile with acyloxy-pyran-3-one for the synthesis of bicyclic compounds, is studied.
- **Chapter 3:** The synthesis of starting material 2-((2*E*,4*E*)-5-phenylpenta-2,4-dienoyl)benzaldehyde and optimized condition for the IMBH adducts, is presented.

Chapter 1

Introduction

Benzofurans are very fascinating heterocycles, which have attracted lot of interest due to their variety of biological and pharmacological activities.[1,2] Recent studies revealed that benzofuran analogs show a broad range of pharmacological activities like antihyperglycemic[3], anti-breast cancer agents[4], antiparasitic agents[5], antimicrobial agents[6], antitumor and kinase inhibitor[7], multidrug resistance-reversing activity, analgesic activities[8,9], (Fig. 1) etc.

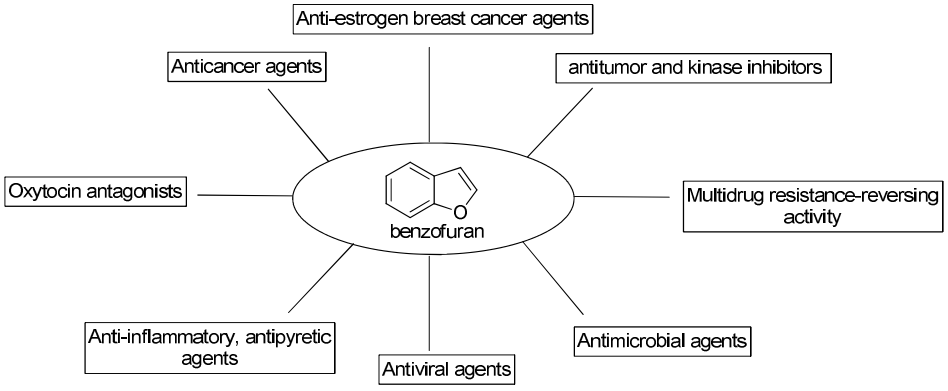
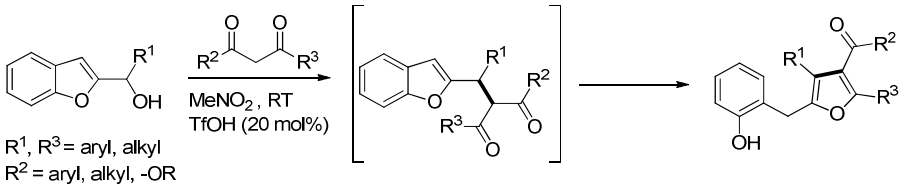
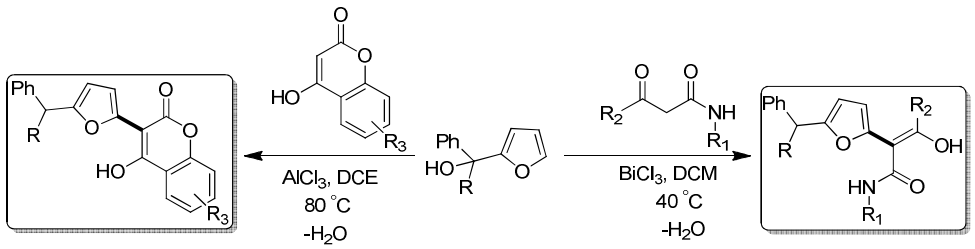


Fig. 1. The biological activity range of benzofuran derivatives.

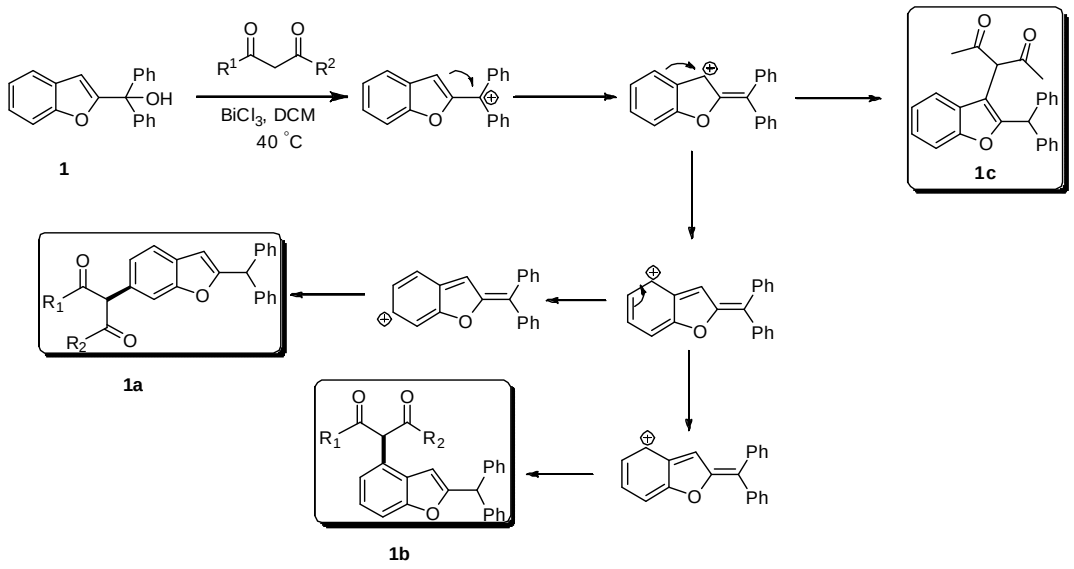


Scheme 1. Acid Catalyzed Ring Transformation of Benzofurans to Tri- and Tetrasubstituted Furans.

In 2013, our group reported an acid catalyzed ring transformation of benzofurans to tri- and tetrasubstituted furans (Scheme 1).[10] Also, in literature, Lewis acid catalyzed direct dehydrative carbon–carbon bond formation reaction of 2-furylcarbinols with β-keto amides was investigated (Scheme 2).[11] So, we extended this approach to benzofuran system.



Scheme 2. Lewis Acid Catalyzed Regiospecific Cross-Dehydrative Coupling Reaction of 2-Furylcarbinols with β-Keto Amides or 4-Hydroxycoumarins.

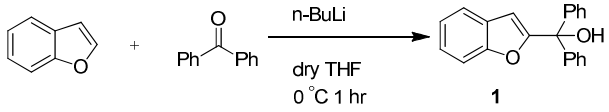


Scheme 3. Lewis Acid Catalyzed Regiospecific Cross-Dehydrative Coupling Reaction of 2-benzofuryldiphenylmethanol with 1,3-dicarbonyls.

We hypothesized that, the carbocation generated in presence of Lewis acid will migrate to the benzene ring as depicted in Scheme 3. Hence, formation of products **1a** or **1b** is possible.

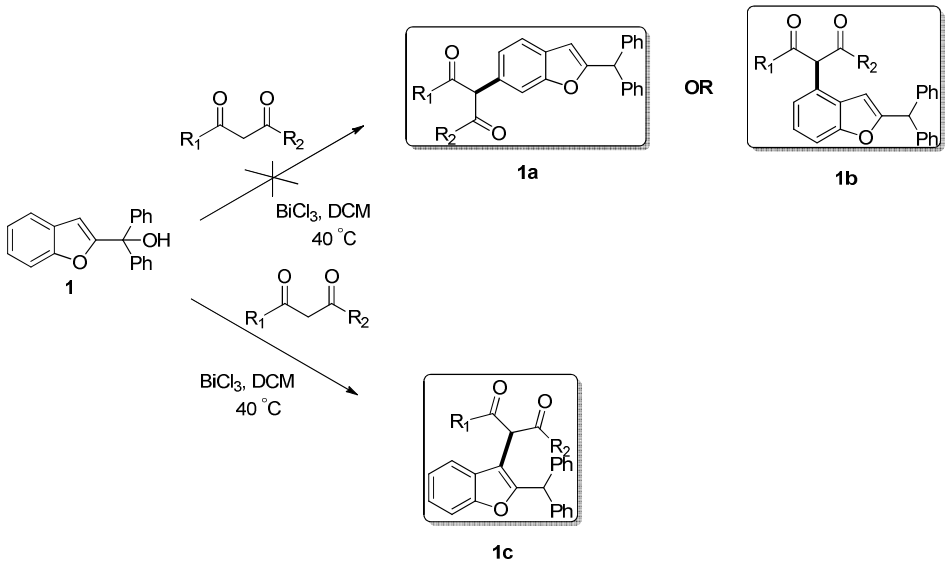
Results and Discussions

At the outset, the 2-benzofuryldiphenylmethanol **1** was synthesized from via n-butyllithium mediated direct alkylation.



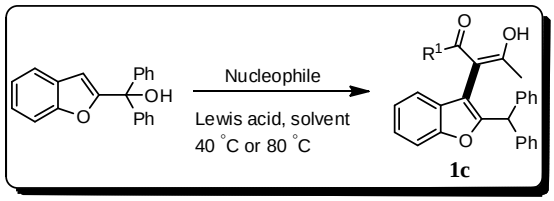
Scheme 4. Synthesis of 2-benzofuryldiphenylmethanol

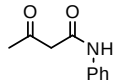
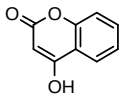
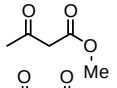
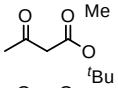
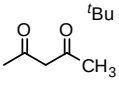
Later, the reactions of **1** with different 1,3-dicarbonyls were initiated. Interestingly, none of the expected products **1a** or **1b** were observed, instead the reaction delivered **1c.**



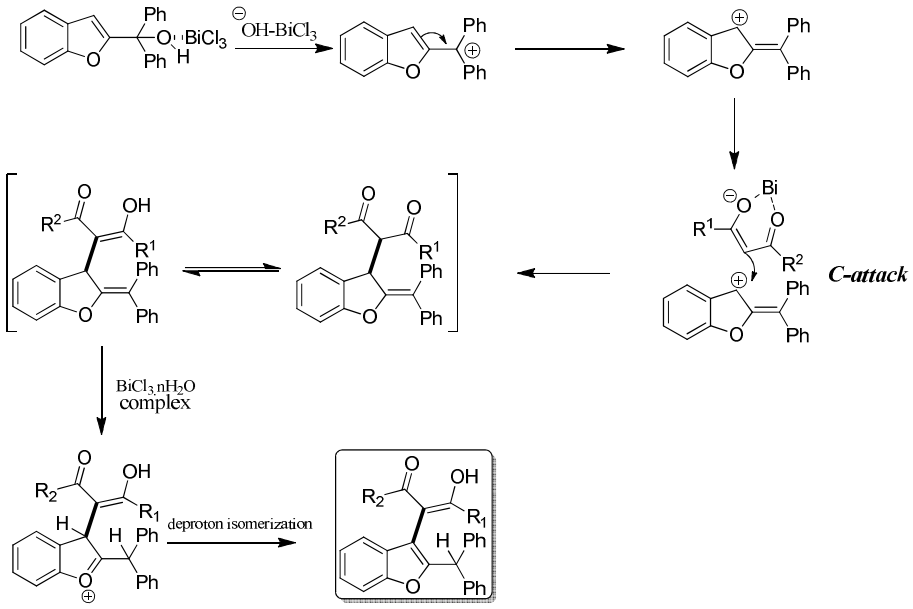
Scheme 5. Lewis Acid Catalyzed Regiospecific Cross-Dehydrative Coupling Reaction of 2-benzofuryldiphenylmethanol with 1,3-dicarbonyls

Table 1. Scope of Nucleophile for 1,3-dicarbonyls.



S. No	Nucleophile	Lewis Acid	Solvent	Temp	Time	Result
1		$BiCl_3$	DCM	40 °C	6h	1c
2		$AlCl_3$	DCE	80 °C	24h	-
3		$BiCl_3$	DCM	40 °C	6h	1c
4		$BiCl_3$	DCM	40 °C	6h	1c
5		$BiCl_3$	DCM	40 °C	6h	1c

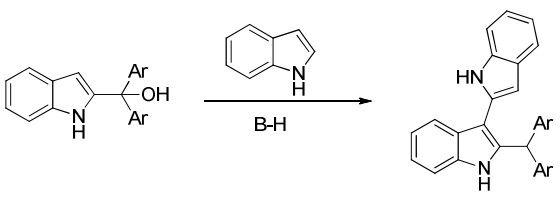
The formation of **1c** was characterized by ^{1}H and ^{13}C NMR.



Scheme 6. General approach for the synthesis of **1c.**

The literature report on, Lewis acid catalyzed regiospecific cross-dehydrative coupling reaction of 2-Furylcarbinols with β-Keto Amides or 4-Hydroxycoumarins (Scheme 2) assisted us in confirming the formation of **1c** and also to propose a plausible mechanism by which it is formed (Scheme 6).

Unfortunately, while this study was in progress, similar results were recently published on indole system so we stopped pursuing this project further (Scheme 7).[12]



Scheme 7. Substrate-Controlled Regioselective Arylations of 2-Indolylmethanols with Indoles.

Experimental methods

General experimental methods: All the starting compounds and catalysts employed in this study were procured from Sigma-Aldrich and were used without further purification. For thin layer chromatography (TLC), silica aluminium foils with fluorescent indicator 254 nm (from Aldrich) were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), and acetic acid (10 mL) in ethanol (900 mL) followed by heating. Column chromatography was performed using SD Fine silica gel 100-200 mesh (approximately 15–20 g per 1 g of the crude product). Dry THF was obtained by distillation over sodium and stored over sodium wire. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker Biospin Advance III FT-NMR spectrometer. NMR shifts are reported as delta (δ) units in parts per million (ppm) and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are utilized to describe peak patterns when appropriate: br=broad, s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet. Proton chemical shifts are given in δ relative to tetramethylsilane (δ 0.00 ppm) in $CDCl_3$ or in $(CD_3)_2SO$ (δ 2.50 ppm) or in $(CD_3)_2CO$ (δ 2.05 ppm). Carbon chemical shifts are internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.1 ppm) or in $(CD_3)_2SO$ (δ 39.5 ppm) or in $(CD_3)_2CO$ at δ 29.9 and 206.7.

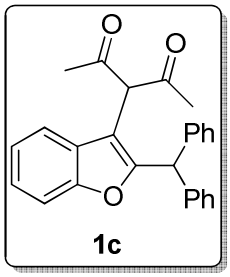
General Procedure: Synthesis of 2-benzofuryldiphenylmethanol 1.

An oven dried 50 mL RB flask was charged with Benzofuran (1.0 mmol), 5 mL dry THF and placed at 0 °C. *n*-BuLi (1.6 *M* in hexanes, 1.1 mmol) was added drop wise at same temperature and stirred for 15 minutes. Benzophenone (1.1 mmol) dissolved in 1 mL of dry THF, was added dropwise over 2 mins and stirred at room temperature for 1 hour. The reaction mixture was quenched with saturated aq. ammonium chloride solution and extracted using ethyl acetate. The organic extracts were combined dried over anhydrous sodium sulphate and concentrated. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate as eluent to afford 2-benzofuryldiphenylmethanol **1**.

General Procedure: Synthesis of substituted benzofuran 1c.

An oven dried 5 mL glass vial was charged with **1** (20 mg, 0.066 mmol) DCM (1 mL) and $BiCl_3$ (0.0066 mmol) and appropriate nucleophile (0.0726 mmol) were introduced at room temperature (rt) stirring continued at rt until **1** disappeared as monitored by TLC. All the volatiles were removed under reduced pressure. The crude product was directly purified by silica gel flash chromatography using hexane/ethyl acetate as eluent, to afford **1c** as yellow liquid.

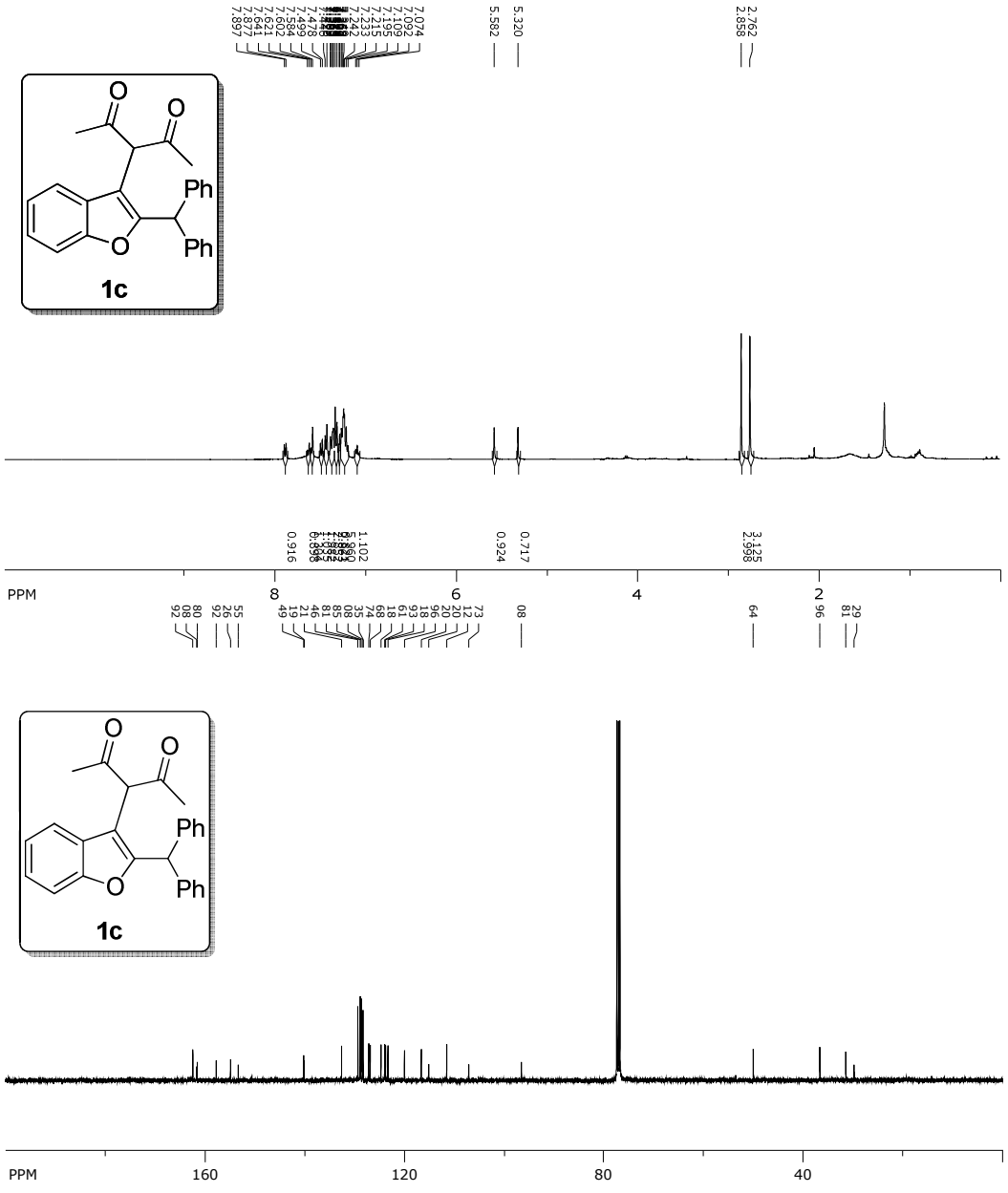
Spectroscopic data of 1c



1c

This compound was prepared by following the general procedure: synthesis of substituted benzofuran **1c** and isolated as yellow liquid. R_f = 0.2 (Hexane/EtOAc = 5/1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.88 (d, *J* = 8 Hz, 1H), 7.63 (d, *J* = 8 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.49 (d, *J* = 8 Hz, 1H), 7.43 (d, *J* = 8 Hz, 2H), 7.37 (d, *J* = 13.6 Hz, 3H), 7.32 (d, *J* = 7.6 Hz, 3H), 7.28 (s, 1H)), 7.23 (m, 7H)), 7.10 (d, *J* = 6.8 Hz, 1H)), 5.58 (s, 1H)), 5.32 (s, 1H)), 2.85 (s, 1H), 2.76 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 162.5, 161.7, 161.6, 157.8, 154.9, 153.3, 140.2, 140.1, 132.6, 129.3, 128.9, 128.7, 128.3, 128.2, 127.2, 126.8, 124.7, 123.9, 123.8, 123.3, 119.9, 116.6, 115.1, 111.5, 107.1, 96.5, 49.9, 36.6, 31.4, 29.7.

NMR Spectra



Summary

The reaction of 2-benzofuryldiphenylmethanol with 1,3-dicarbonyls yielded **1c**, but similar results were already published on indole system so we stopped exploring further.

Bibliography

1. Hayta, S.A.; Arisoy, M.; Arpaci, O.T.; Yildiz, I.; Aki, E.; Ozkan, S.; Kaynak, F.; *Eur. J. Med. Chem.* **2008**, *43*, 2568-2578.
2. Kamal, M.; Shakya, A.K.; Jawaid, T. *Int. J. Med. Pharm. Sci.*, **2011**, *1*, 1-15.
3. Cottineau, B.; Toto, P.; Marot, C.; Pipaud, A.; Chenault, J. *Bioorg. Med. Chem. Lett.*, **2002**, *12*, 2105-2108.
4. (a) Miert, S.V.; Dyck, S.V.; Schmidt, T.J.; Brun, R.; Vlietinck, A.; Lemiere, G.; Pieters, L. *Bioorg. Med. Chem.*, **2005**, *13*, 661-669. (b) Zhang, G.N.; Zhong, L.Y.; Bligh, S.W.A.; Guo, Y.L.; Zhang, C.F.; Zhang, M.; Wang, Z.T.; Xu, L.S. *Phytochemistry*., **2005**, *66*, 1113-1120.
5. Thѐvenin, M.; Thoret, S.; Grellier, P.; Dubois, J. *Bioorg. Med. Chem.*, **2013**, *21*, 4885-4892.
6. Koca, M.; Servi, S.; Kirilmis, C.; Ahmedzade, M.; Kazaz, C.; Özbek, B.; Ötük, G. *Eur. J. Med. Chem.*, **2005**, *40*, 1351-1358.
7. Xie, F.; Zhu, H.; Zhang, H.; Lang, Q.; Tang, L.; Huang, Q.; Yu, L. *Eur. J. Med. Chem.*, **2015**, *89*, 310-319.
8. Xie, Y. S.; Kumar, D.; Bodduri, V.D.V.; Tarani, P.S.; Zhao, B. X.; Miao, J. Y.; Jang, K.; Shin, D. S. *Tetrahedron Lett.*, **2014**, *55*, 2796-2800.
9. Khanam, H.; Shamsuzzaman. *Eur. J. Med. Chem.*, **2014**, 1-22.
10. Dhiman, S.; Ramasastry, S. S. V. *J. Org. Chem.* **2013**, *78*, 10427−10436.
11. Miao, M.; Luo, Y.; Li, H.; Xu, X.; Chen, Z.; Xu, J.; Ren, H. *J. Org. Chem.*, **2016**, *81*, 5228–5235.
12. He, Y. Y.; Sun, X. X.; Li, G. H.; Mei, G. J.; Shi, F. *J. Org. Chem.* **2017**, *82*, 2462−2471.

Chapter 2

Introduction

Pyran-3-ones are often used as substrates for the synthesis of racemic monosaccharides[2], pyrones (e.g. maltol)[3] and potential antibacterials.[4] In carbohydrate chemistry, these compounds are also denoted as 2,3-dideoxy-2-enopyranos-4-uloses[5] or hex-2-eno-pyranosid-4-uloses.[6] Hexenuloses have been used in the synthesis of infrequent sugars, antibiotic sugars and branched–chain sugars.[6,7] Maltol (3-hydroxy-2-methyl-4H-pyran-4-one) and associated compounds have been of great attention as flavoring additives in foods.[3,8] Pyran-3-ones have also been used in the synthesis of a variety of other biologically active compounds[9] like **2.3**, a pheromone of the olive fruit fly[10] and esters of phorbol **2.4**, which have antitumor or anti-HIV activity.[11]

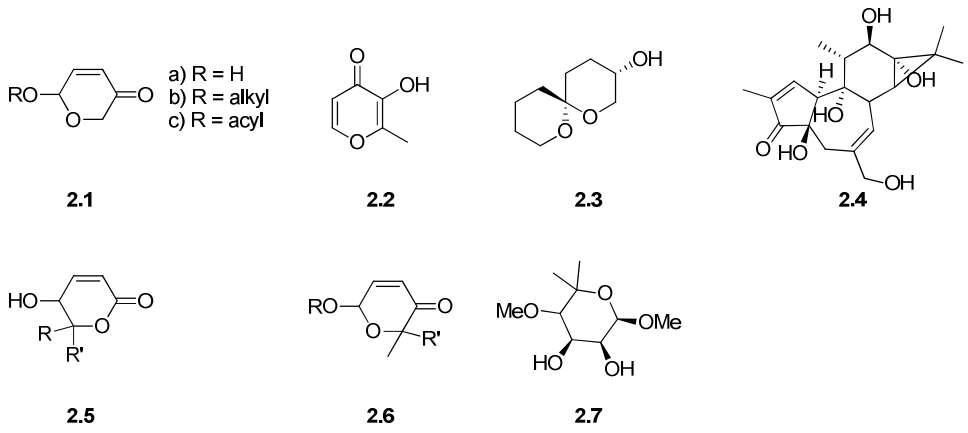
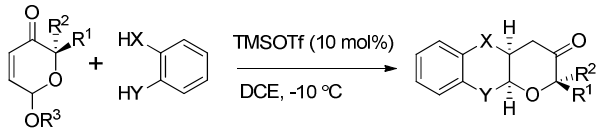


Fig. 2. Pyranones and derivatives.

Many pyranones, such as, for example, the 6-hydroxy-pyran-2-ones **2.5** and 6-hydroxy-pyran-3-ones **2.6**, show antimicrobial and anticoccidial activities[4] by coupling **2.1**,

or its derivatives, to a monosaccharide by a glycosidic linkage, countless disaccharides can be synthesized.[12]

Racemic acyloxypyran-3-ones can be readily synthesized from furfuryl alcohols.[14] Optically active hydroxy- **2.1a**, alkoxy- **2.1b**, and acyloxy-pyran-3-ones **2.1c** are striking chiral synthons in natural products chemistry, due to their multifunctional nature and numerous possibilities for enantioselective transformations like cycloadditions,[16,17] enolate and acetal chemistry, and conjugate addition reactions.[17,18] Another example of the adaptability of pyranones as synthons is the extension of the pyranone ring to a seven-membered ring *via* cycloaddition involving a pyrylium zwitterion.[19] Pyran-3-ones have been explored as chiral dienophiles and Michael acceptors.

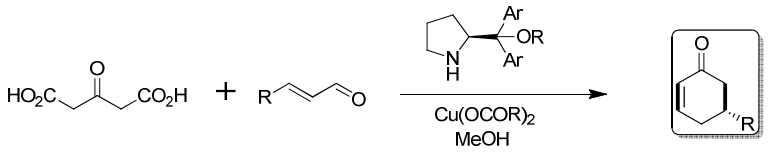


X = Y = O/N/OR

R^1, R^2 = alkyl, aryl; R^3 = alkyl, aryl, acyl, etc.

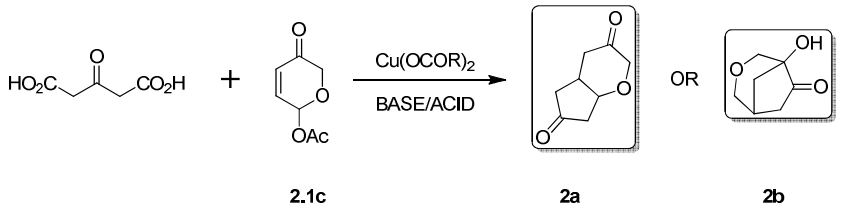
Scheme 7. Cascade Michael addition–cycloacetalisation strategy on acyloxypyran-3-one system.

Our group has reported a cascade Michael addition–cycloacetalisation strategy on acyloxypyran-3-one system[20] (Scheme 7) and in literature, it is known that 1,3-acetone dicarboxylic acid can be used as a 1,3-bis-pro-nucleophile with enone systems to give cyclohexanone derivatives.[21]



Scheme 8. Reaction of 1,3-acetone dicarboxylic acid with enone systems to give cyclohexanone derivatives.

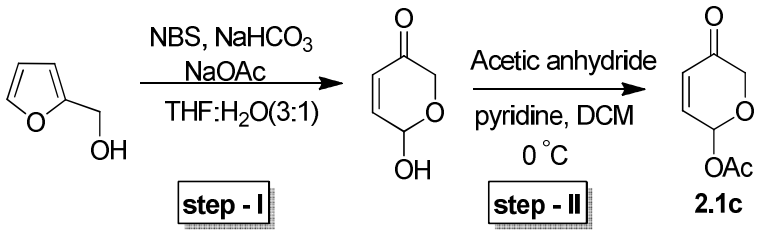
With this background, we made an attempt to use acyloxy-pyran-3-one **2.1c** as a Michael acceptor and 1,3-acetonedicarboxylic acid as a 1,3-bis-pro-nucleophile for the synthesis of bicyclic compounds.



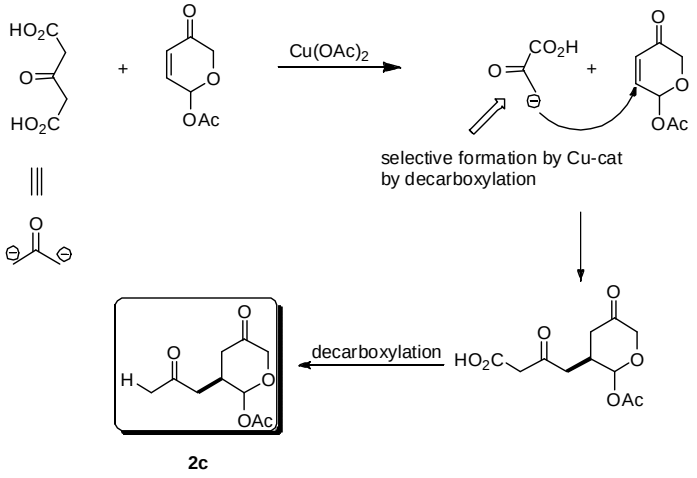
Scheme 9. Reaction of 1,3-acetone dicarboxylic acid with acyloxy-pyran-3-one.

Results and Discussions

At the outset, acyloxypyran-3-one **2.1c** was synthesized from furfuryl alcohol in two steps. Firstly, hydroxypyran-3-one was synthesized from furfuryl alcohol by Achmatowicz rearrangement and then acyloxypyran-3-one **2.1c** was obtained by Acetylation in presence of acetic anhydride and pyridine.



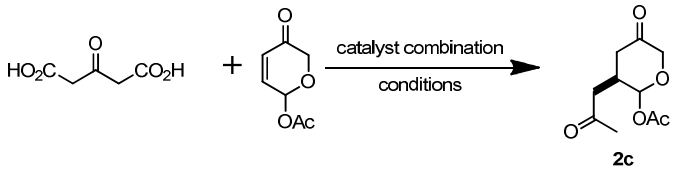
Scheme 10. Synthesis of acyloxypyran-3-one **2.1c**



Scheme 11. General approach for the synthesis of **2c.**

Further, we commenced the screening of various catalyst and solvent combinations with 1,3- acetone dicarboxylic acid and **2.1c** with the intention to obtain **2a** or **2b.** Reactions with different catalyst combinations like copper acetate and a nucleophilic base, copper acetate and a Lewis acid, copper acetate and a non-nucleophilic base, just copper acetate and other copper catalysts.

Table 2. Screening of different catalysts and solvent combinations for **2c**.



2c

S.No	Catalyst combinations		Solvent	Temp (°C)	Time (h)	2c
1	$Co(acac)_2$		dry THF	rt	24	not formed
2	CuI		dry THF	rt	24	not formed
3	$Cu(OAc)_2$		dry THF	rt	24	trace
4	**$Cu(OAc)_2$**	**Et_3N**	**DCE**	**80**	**8**	**formed (single spot)**
5	$Cu(OTf)_2$		DCE	80	24	formed
6	$Bi(OTf)_3$		DCE	80	24	formed
7	$Cu(OAc)_2$	$BiCl_3$	DCM	40	24	formed (single spot)
8	$Cu(OAc)_2$	$AlCl_3$	DCM	40	24	formed
9	Thiourea	AcOH	Toluene	100	24	not formed
10	$Cu(OAc)_2$	pyrrolidine	DCE	80	24	not formed
11	$Cu(OAc)_2$	NaOMe	MeOH	rt	24	formed
12	$Cu(OAc)_2$ (6.25 mol%)	proline (25 mol%)	dry THF	rt	8	formed
13	$Cu(OAc)_2$	$Ph_3C^{\oplus}\,BF_3^{\ominus}$	dry THF	rt	15	formed
14	$Cu(OAc)_2$	tripentafluorophenyl borane	dry THF	rt	15	formed
15	$Cu(OAc)_2$ (6.25 mol%)		MeOH	rt	24	formed

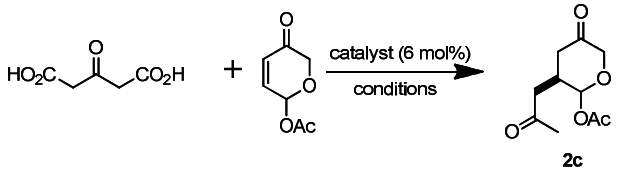
Note: 6 mol% of catalysts are used in cases where it is not specified.

16	**$Cu(OAc)_2$**	**Et_3N**	**$CHCl_3$**	**50**	**8**	**formed (single spot)**
17	$Cu(OAc)_2$	n-BuLi	Toluene	rt	24	not formed
18	$Cu(OAc)_2$	DBU	Toluene	rt	24	formed (single spot)
19	$Cu(OAc)_2$	Proline	Toluene	rt	24	formed
20	$Cu(OAc)_2$	Pyridine	Toluene	rt	24	trace
21	$Cu(OAc)_2$	L-proline (0.3eq)	Acetone:DMSO (3:1)	0	24	formed
22	$Cu(OAc)_2$	MgI_2 (1.4eq)	piperidine (1.5eq)	rt	24	formed
23	$Cu(OAc)_2$	$InCl_3$	CH_3NO_2	rt	7	trace
24	$Cu(OAc)_2$	$Sc(OTf)_3$	CH_3NO_2	rt	7	formed
25	$Cu(OAc)_2$	$NaHCO_3$	dry THF	rt	10	trace
26	$Cu(OAc)_2$	K_2CO_3	dry THF	rt	10	trace
27	$Cu(OAc)_2$	DBU	dry THF	rt	10	formed
28		$NaHCO_3$	H_2O	0	15	trace
29	$Cu(OAc)_2$	DBU	CH_3CN	70	6	trace
30	$Cu(OAc)_2$		DCM	rt	48	formed

Note: 6 mol% of catalysts are used in cases where it is not specified.

Many reactions were tried to obtain **2a** or **2b**, but all turned out to be unsuccessful. We then moved on to Palladium catalysts to promote the formation of **2a**. So, now instead of using catalyst combinations, just a single palladium catalyst was employed with appropriate solvent, (Table 3).

Table 3. Screening of different Palladium catalysts and solvents for **2c**.



2c

S.No	Catalyst	Solvent	Temperature (°C)	Time (h)	2c
31	$Pd(PPh_3)_4$	Toluene	rt	17	formed
32	$Pd(PPh_3)_4$	THF	rt	17	formed
33	$Pd(OAc)_2$	Toluene	rt	20	formed
34	$Bis(PPh_3)Pd(II)Cl_2$	Toluene	rt	20	formed
35	$1,1\text{-}Bis(Ph_2P\text{-}Fe(Cp)_2Pd(II)Cl_2$	Toluene	rt	20	formed
36	$Pd_2(dba)_3$	Toluene	rt	20	formed
37	$PdCl_2$	Toluene	rt	20	formed
38	$Pd(PPh_3)_4$	Xylene	rt	20	formed
39	$Pd(PPh_3)_4$	DCM	rt	20	formed

Note: 6 mol% of catalysts are used in cases where it is not specified.

But in this case also we observed **2c**. So, we decided to conclude this project, since we were unable to acquire the desired compounds. So, we decided to stop pursuing it further and thus concluded our studies on this project.

Experimental methods

General experimental methods: All the starting compounds and catalysts employed in this study were procured from Sigma-Aldrich and were used without further purification. For thin layer chromatography (TLC), silica aluminium foils with fluorescent indicator 254 nm (from Aldrich) were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), and acetic acid (10 mL) in ethanol (900 mL) followed by heating. Column chromatography was

performed using SD Fine silica gel 100-200 mesh (approximately 15–20 g per 1 g of the crude product). ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker Biospin Avance III FT-NMR spectrometer. NMR shifts are reported as delta (δ) units in parts per million (ppm) and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are utilized to describe peak patterns when appropriate: br=broad, s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet. Proton chemical shifts are given in δ relative to tetramethylsilane (δ 0.00 ppm) in $CDCl_3$ or in $(CD_3)_2SO$ (δ 2.50 ppm) or in $(CD_3)_2CO$ (δ 2.05 ppm). Carbon chemical shifts are internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.1 ppm) or in $(CD_3)_2SO$ (δ 39.5 ppm) or in $(CD_3)_2CO$ at δ 29.9 and 206.7.

General Procedure: Synthesis of the acyloxypyran-3-one 2.1c. (Scheme 10)

Acyloxypyran-3-one **2.1c** was prepared as in Scheme 10. Commercially available furfuryl alcohol was converted to hydroxypyran-3-one via a Achmatowicz rearrangement. Direct acetylation with an acetic anhydride in presence of pyridine generated the acyloxypyran-3-one **2.1c**.

Representative procedure for the synthesis of hydroxypyran-3-one: (step I) An oven dried 50 mL RB flask was charged with furfuryl alcohol (1 equiv., 2 mmol) in THF/H2O (3:1, 10 mL), $NaHCO_3$ (2 equiv., 4 mmol), NaOAc.3H2O (1 equiv., 2 mmol) and NBS (1 equiv, 2 mmol) at 0 ºC. The mixture was stirred at the same temperature until completion as indicated by TLC. After completion, the reaction was quenched with saturated NaHCO3 solution, extracted by ethyl acetate. The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography with hexane/ethyl acetate as eluent to yield hydroxypyran-3-one, as a yellow oil.

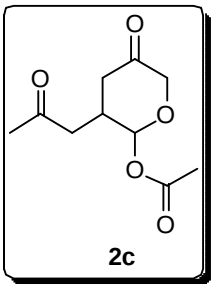
Representative procedure for the synthesis of acyloxypyran-3-one 2.1c: (step II) An oven dried 50 mL RB flask was charged with hydroxypyran-3-one (1 equiv., 0.876mmol) in 5 mL of CH2Cl2 was added acetic anhydride (1.2 equiv., 1.05 mmol, 1.2 eq.) and pyridine (1 equiv., 0.876 mmol). The reaction mixture was stirred at room temperature for 1 night. The solvent was evaporated at room temperature. The residual brown oil was filtered over silica with hexane/ether (1:2). The filtrate was concentrated and the resulting

crude product was purified by flash chromatography over silica hexane/ethyl acetate as eluent to yield **2.1c**.

General Procedure for the Synthesis of 2c. (Scheme 11)

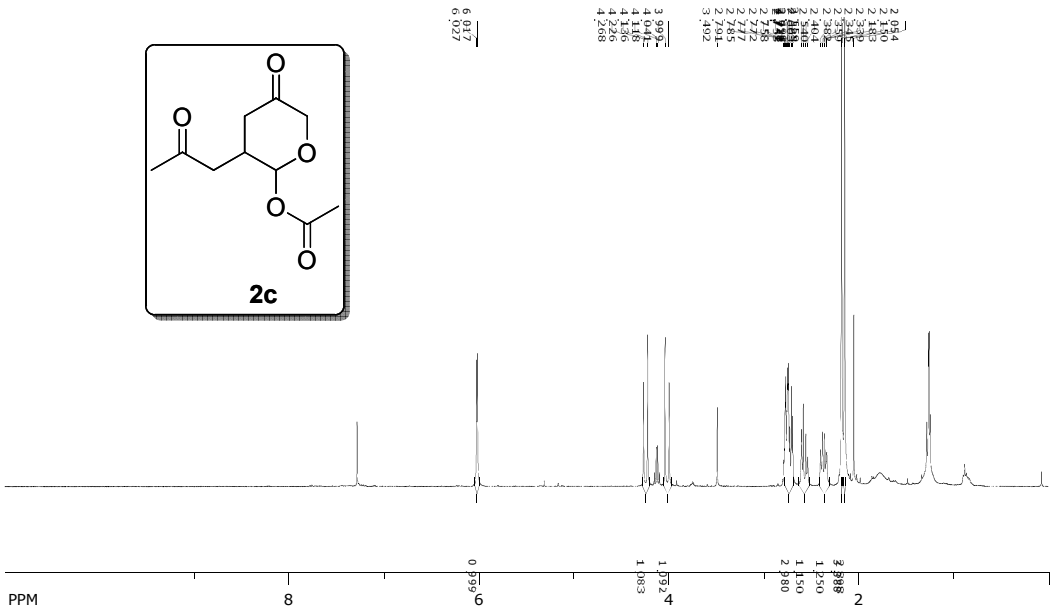
An oven dried 5 mL glass vial was charged with **2.1c** (30 mg, 0.192 mmol) in appropriate solvent (1 mL) and 1,3 acetone dicarboxylic acid (0.126 mmol) and appropriate catalyst (6 mol%) were introduced at room temperature (rt), stirring continued at rt until **2.1c** disappeared as monitored by TLC. All the volatiles were removed under reduced pressure. The crude product was directly purified by silica gel flash chromatography using hexane/ethyl acetate as eluent, to afford **2c** as yellow liquid.

Spectroscopic data of 2c



This compound was prepared by following the general procedure for synthesis of **2c** and isolated as yellow oil. R_f = 0.3 (Hexane/EtOAc = 5/1). **^{1}H NMR (400 MHz, $CDCl_3$):** δ 6.02 (d, *J* = 4.0 Hz, 1H), 4.24 (d, *J* = 16.8 Hz, 1), 4.02 (d, *J* = 16.8 Hz, 1H), 2.77 – 2.69 (m, 3H), 2.57 (q, 1H), 2.37 (q, 1H), 2.18 (s, 3H), 2.15 (s, 3H).

NMR Spectra



Summary

The reaction of acyloxypyran-3-one **2.1c** with 1,3-acetone dicarboxylic acid delivered **2c**.

Bibliography

1. (a) Achmatowicz, O.Jr., Jr.; Bukowski, P.; Szechner, B.; Zwierzchowsk a, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973. (b) Achmatowicz, O., Jr.; Bukowski, P. *Can. J. Chem.* **1975**, *53*, 2524. (c) Achmatowicz, O.Jr.; Szechner, B. *Carbohyd. Res.* **1976**, *50*, 23.
2. (a) Torii, S.; Tanaka, H.; Anoda, T.; Simizu, Y. *Chem. Lett.* **1976**, 495. (b) Weeks, P.D.; Brennan,T.M.; Brannegan, D.P.; Kuhla, D.E.; Elliot, M.L.; Watson, H.A.; Wlodecki, B.; Breitenbach, R. *J. Org. Chem.* **1980**, *45*, 1109.

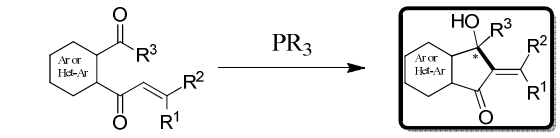
3. (a) Laliberté, R.; Médawar, G.; Lefebvre, Y. *J. Med. Chem.* **1973**, *16*, 1084. (b) Georgiadis, M. P. *J. Med. Chem.* **1976**, *19*, 346.
4. Grynkiewicz, G.; Barszcak, B; Zamojski, A. *Synthesis* **1979**, 364.
5. Holder, N. *Chem. Rev*. **1982**, *82*, 287.
6. Achmatowicz, O.Jr.; Grynkiewicz, G.; Szechner, B. *Tetrahedron* **1976**, *32*, 1051.
7. Pittet, A. O.; Rittersbacher, P.; Muralidhara, R. *J. Agr. Food Chem.* **1970**, *18*.
8. (a) Srivastava, R. M.; Carthy, B. J.; FraserReid, F. *Tetrahedron Lett.* **1974**, 21 75. (b) Prasad, J.S.; Clive, D.L.; da Silva, G.V.J. *J. Org. Chem.* **1986**, *51*, 2717. (c) Maier, M. E.; Schöffling, B.*Tetrahedron Lett.* **1991**, *32*, 53. (d) Georgiadis, M. In *Trends in Medicinal Chemistry* 88; Elsevier, **1989**, 197-215. (e) Ali, A.; Saxton, J.E. *Tetrahedron Lett.* **1989**, *30*, 3197. (f) Martin, S.F.; Pacofski, G.J.; Gist, R.P.; Lee, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 7634. (g) Taniguchi, T.; Nakamura, K.; Ogasawara, K. *Synthesis* **1997**, 509. (h) Matsumura, Y.; Shirai, K.; Maki, T.; Itakura, Y.; Kodera, Y. *Tetrahedron Lett*. **1998**, *39*, 2339. (i) Chen, X.T.; Gutteridge, C.E.; Bhattacharya, S.K.; Zhou, B.; Pettus, T.R.R.; Hascall, T.; Danishefsky, S.J. *Angew. Chem. Int. Ed. Engl*. **1998**, *37*, 185
9. Deshong, P.; Waltermire, R.E.; Ammon, H.L. *J. Am. Chem. Soc.* **1988**, *110*, 1901.
10. Wender, P.A.; Rice, K.D. Schnute, M.E. *J. Am. Chem. Soc.* **1997**, *119*, 7897.
11. Grynkiewicz, G.; Zamojski, A. *Synth. Commun.* **1978**, *8*, 491.
12. (a) Ferrier, R.J.; Prasad, N. *J. Chem. Soc. C.* **1969**, 570. (b) FraserReid, B. *Acc. Chem. Res.* **1985**, *18*,347. (c) Holder, N.L. *Chem. Rev*. **1982**, *82*, 287.
13. (a) Achmatowicz Jr., O.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron***1971**, *27*, 1973. (b) Lefebvre, Y. *Tetrahedron Lett*. **1972**, 133. (c) Constantinou-Kokotou, V.; Kokotos, G.; Georgiadis, M.P. *Liebigs Ann. Chem.* **1991**, 151.
14. (a) Koga, K.; Yamada, S. I.; Yoh, M.; Mizoguchi, T. *Carbohyd. Res.* **1974**, *36*, C9. (b) Kobayashi, Y.; Kusakabe, M.; Kitano, Y.; Sato, F. *J. Org. Chem.* **1988**, *53*, 1587. (c) Kusakabe, M.; Kitano, Y.;Kobayashi, Y.; Sato, F. *J. Org. Chem.* **1989**, *54*, 2058. (d) Ireland, R.E.; Wipf, P.; Miltz, W.; Vanasse, B. *J. Org. Chem.* **1990**, *55*, 1423. (e) Llera, J.-M.; Trujillo, M.; Blanco, M.-E.; Alcudia, F. *Tetrahedron: Asymm.* **1994**, *5*, 709. (f) Nelson, A.; Warren, S. *Tetrahedron Lett.* **1998**, *39*, 1633.

15. (a) Jones, G. *Tetrahedron Lett.* **1974**, 2231. (b) Grynkiewicz, G.; Achmatowicz, O .Jr.;Barton, H. *Rocz.Ann. Soc. Chim. Pol.* **1977**, *51*, 1663. (c) Panfil, I.; Chmielewski, M. *Tetrahedron* **1985**, *41*, 4713. (d)Trost, B.M.; King, S.A.; Nanninga, T.N. *Chem. Lett.* **1987**, 15. (e) Williams, D.R.; Benbow, J.W.; McNutt,J.G.; Allen, E.E. *J. Org. Chem.* **1995**, *60*, 833.
16. Knol, J.; Jansen, J.F.G.A.; Bolhuis, F. van; Feringa, B.L. *Tetrahedron Lett.* **1991**, *32*, 7465.
17. (a) Paulsen, H.; Koebernick, W. *Carbohyd. Res.* **1977**, *56*, 53. (b) Prévost, N.; Rouessac, F. *Tetrahedron Lett.* **1997**, *38*, 4215.
18. Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3359.
19. Martin, S. F.; Guinn, D. E. *J. Org. Chem.* **1987**, *52*, 5588.
20. Bankar, S. K.; Shirke, R. P.; Ramasastry, S. S. V. *Adv. Synth. Catal.* **2015**, *357*, 3284 – 3296.
21. Quintard, A.; Rodriguez, J. *Chem. Commun.*, **2015**, *51*, 9523—9526.

Chapter 3

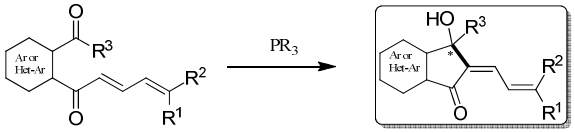
Introduction

Morita-Baylis-Hillman reaction is one of the most facile C-C bond forming reactions.[1] The adaptability of MBH reaction is due to its atom-economy, organocatalytic nature, and ease of transformation of the MBH adducts into other synthetically targeted products.[2] MBH reactions are profusely utilized in the synthesis of several pharmaceutical and biologically active natural products.[1,2] Despite various ameliorations in MBH chemistry, some problems are still unexplored. One of them is the recognition of enantioselective inter- or intramolecular MBH reaction of activated dienes. Among them, the dienones are readily available or are easily accessible by simple synthetic routes. But, to our surprise, there is no significant research on MBH reactions involving dienones.



R^1,R^2 = alkyl, aryl, heteroaryl
R^3 = H, alkyl, aryl

Scheme 12. MBH reaction of β,β- disubstituted enones.



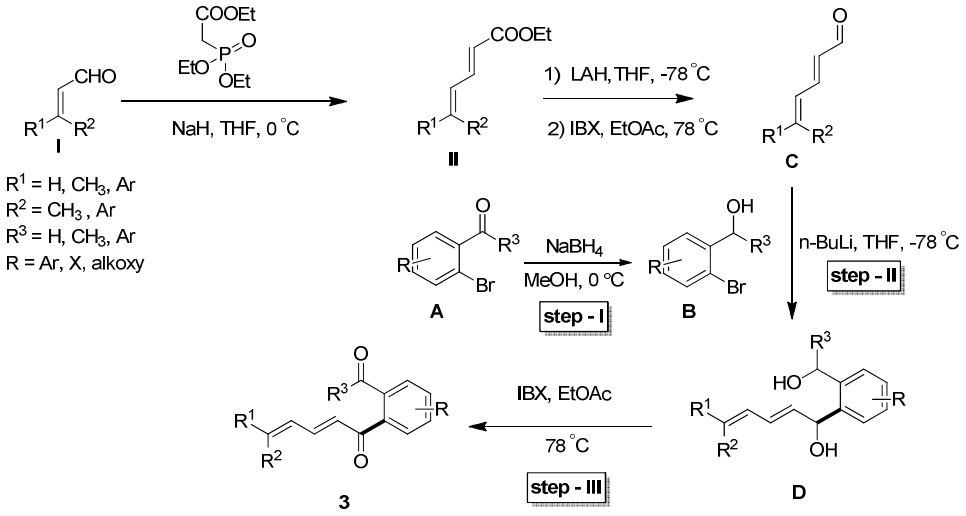
R^1,R^2 = alkyl, aryl, heteroaryl
R^3 = H, alkyl, aryl

Scheme 13. MBH reaction of substituted dienones.

With the background of the earlier report on MBH reaction of β,β- disubstituted enones by our group (Scheme 12),[2] we commenced our study of intramolecular Morita-Baylis-Hillman reaction of dienone systems (as in Scheme 13).

Results and Discussions

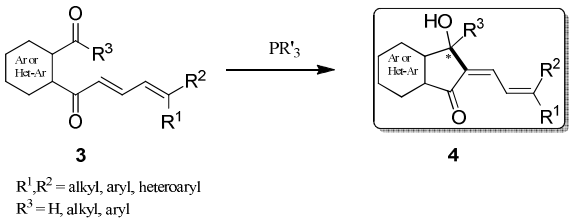
In the beginning, **3** were synthesized from the corresponding dienals and bromobenzyl alcohols (Scheme 14). To synthesize dienals **C**, we started with substituted enals **I**. **I** was converted to **II** *via* Wittig reaction with triethylphosphonoacetate. **II** was further subjected to LAH reduction followed by IBX oxidation to yield dienals **C.**



Scheme 14. General approach for the synthesis of **3.**

Bromobenzyl alcohols were accessible *via* $NaBH_4$ reduction of **A.** Diols **D** were synthesized by n-butyllithium mediated direct alkylation. Final dienones **3** were then obtained by IBX oxidation of diols **D.**

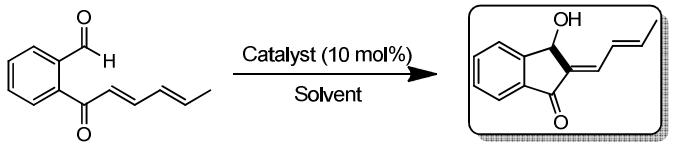
Finally, we wanted to synthesize **4** from **3** (Scheme 15) so we initiated the optimization for **4.**



3 4

Scheme 15. Synthesis of cyclopenta[b]annulated arenes **4**

Table 4. Optimization of MBH conditions for **4a.**



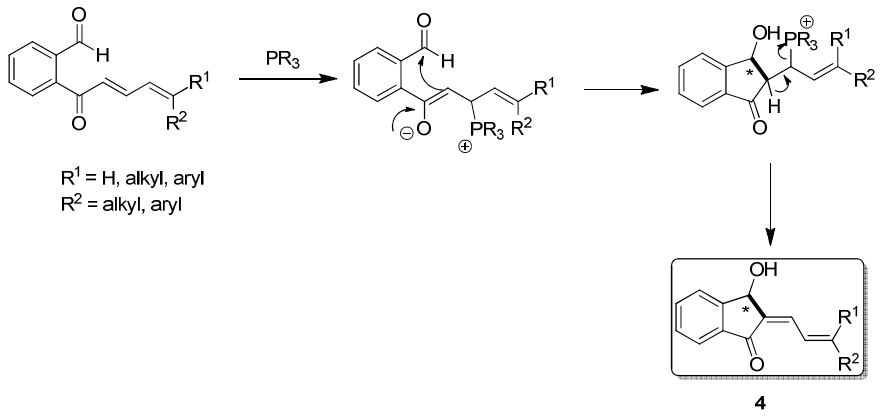
3a **4a**

S.No	Catalyst (10 mol%)	Solvent	Temp (°C)	Time (min)	Yield (%)
1	PPh_3	Toluene	40	1800	no reaction
2	PCy_3	Toluene	rt	20	91
3	PCy_3	DCE	rt	20	90
4	**PMe_3**	**Toluene**	**rt**	**15**	**95**
5	PMe_3	DCM	rt	15	92
6[a]	DBU	DCM	rt	15	86
7[a]	DABCO	DCM	40	15	81
8	PPh_2Et	Toluene	rt	15	89
9	PPh_2Et	DCM	40	15	88
10[a]	DMAP	Toluene	rt	20	85

a = yields based on starting material recovery.

Using **3a** as a model substrate, we started optimizing the conditions by using various nucleophilic bases and solvents with the motive of obtaining cyclopenta[b]annulated arene **4a** (Table 4) with short reaction time and excellent yield. To our delight, PMe_3 in Toluene

yielded **4a** with 95% yield in 15 minutes. The expected mechanism by which the reaction delivered **4a** is depicted in Scheme 16.



Scheme 16. General approach for the synthesis of **4**.

Experimental methods

General experimental methods: All the starting compounds and catalysts employed in this study were procured from Sigma-Aldrich and were used without further purification. For thin layer chromatography (TLC), silica aluminium foils with fluorescent indicator 254 nm (from Aldrich) were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), and acetic acid (10 mL) in ethanol (900 mL) followed by heating. Column chromatography was performed using SD Fine silica gel 100-200 mesh (approximately 15–20 g per 1 g of the crude product). Dry THF was obtained by distillation over sodium and stored over sodium wire. IR spectra were recorded on a Perkin–Elmer FT IR spectrometer as thin films or KBr pellet, as indicated, with ν_{max} in inverse centimetres.

Procedure A: Synthesis of the dienones.

All these dienones were prepared as in Scheme 14. For example, commercially available 2-bromobenzaldehydes **A** (when R^3 = H and R = H) were converted to 2-bromo benzyl alcohols **B** via a straightforward sodium borohydride reduction. Direct *n*-butyllithium mediated metal-halogen exchange followed by alkylation with an appropriate dienal **C** generated the diols **D**. IBX oxidation of the diols **D** led to the formation of the dienone-aldehydes **3**, Scheme 14.

Representative procedure for step-I (Scheme 14): An oven dried 25 mL RB flask was charged with 2-bromo benzaldehyde **A** (2.0 mmol), 10 mL dry MeOH and placed at 0 ^{o}C. Sodium borohydride (2.1 mmol) was added portion wise under nitrogen atmosphere and stirred at room temperature until **A** disappeared (monitored by TLC) and quenched by saturated aqueous ammonium chloride. Methanol was removed under vacuum and extracted using ethyl acetate. Organic extracts were combined and dried over anhydrous sodium sulphate and concentrated to afford crude 2-bromo alcohol **B** and proceeded to the next step without further purification.

Representative procedure for step-II (Scheme 14):[34] An oven dried 25 mL long neck RB flask was charged with 2-bromo alcohol **A** (1.0 mmol), 5 mL dry THF and placed at –78 ^{o}C. *n*-BuLi (1.6 *M* in hexanes, 2.2 mmol) was added drop wise at same temperature and stirred for 2 hours. A dienal **C** (1.3 mmol) dissolved in 1 mL of dry THF, was added dropwise over 2 mins and stirred at room temperature for 30 mins. The reaction mixture was quenched with saturated aq. ammonium chloride solution and extracted using ethyl acetate. The organic extracts were combined dried over anhydrous sodium sulphate and concentrated. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate as eluent to afford diol **D**.

Representative procedure for step-III (Scheme 14): Diol **D** (1 mmol) was dissolved in ethyl acetate (10 mL), and IBX (1.5 mmol) was added. The resulting suspension was immersed in an oil bath set to 75 °C and stirred until alcohol **D** disappeared as monitored by TLC. The reaction was cooled to room temperature and filtered through Buchner funnel. The filter cake was washed with 3× 2 mL of ethyl acetate. Organic extracts were combined and worked up using saturated sodium bicarbonate solution to remove excess iodobenzoic

acid. The extract was dried over anhydrous sodium sulphate and concentrated under vacuum. The crude product was purified by silica gel column chromatography using hexane/ethyl acetate as eluent to afford the enone **3**.

Procedure B: Screening of reaction parameters (Table 4).

An oven dried 5 mL glass vial was charged with **3a** (25 mg, 0.125 mmol). An appropriate solvent (1 mL) and a catalyst (0.0125 mmol) were introduced at room temperature (rt) under nitrogen atmosphere and stirring continued at rt until **3a** disappeared as monitored by TLC. All the volatiles were removed under reduced pressure. The crude product was directly purified by silica gel flash chromatography using hexane/ethyl acetate as eluent, to afford **4a** as pale yellow solid.

Summary

The synthesis of starting material 2-((2*E*,4*E*)-5-phenylpenta-2,4-dienoyl)benzaldehyde (dienones) and optimized condition for the IMBH adducts, is described.

Bibliography

1. a) Morita, K.; Suzuki, Z.; Hirose, H. Bull. Chem. Soc. Jpn. 1968, *41*, 2815; b) Baylis, A. B.;Hillman, M.E.D.; German Patent 2155113, **1972** [Chem. Abstr. **1972**, 77, 34174q]; c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811; d) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed*. **2007**, *46*, 4614; *Angew. Chem.* **2007**, *119*, 4698; e) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511; f) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1; g) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447; h) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005; i) Mansilla, J.; Sa., J. M. *Molecules* **2010**, *15*, 709; j) Basavaiah, D.; Veeraraghavaiah, G. *Chem. Soc. Rev.* **2012**, *41*, 68; k) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659; l) Chandra Bharadwaj, K. *RSC Adv.* **2015**, *5*, 75923.
2. Satpathi, B.; Ramasastry, S. S. V. *Angew.Chem. Int.Ed.* **2016**, *55*,1777 –1781.

3. a) Chen, C. Y.; Wang, Y. D. *Chem. Nat. Compd.* **2011**, *47*, 215–217; b) Yi-Chen, C.; Hung-Chun, Y.; Yu-Ting, Y.; Chung-Yi, C.; *Chem. Nat. Compd.* **2011**, 47, 220–222;

   c) Lin, R. J.; Cheng, M. J.; Huang, J. C.; Lo, W.L.; Y. T.; Yeh, Y. T.; Yen, C. M.; Lu, C. M.; Chen, C. Y. *J. Nat. Prod.***2009**, *72*, 1816–1824; d) Chen, C. Y.; Yang, W. L.; Hsui, Y. R.; *Nat. Prod. Res.* **2010**, *24*, 423–427; e) Tang, C.; Li, Z.; Wang, Y.; Xu, J.; Kong, L.; Yao, H.; Wu, X. *Tetrahedron Lett.* **2011**, *52*, 3275–3278; f) Lee, C. H.; Kuo, C. N.; Chen, H. L.; Chen, C. Y.; *Nat. Prod. Res.* **2013**, *27*, 988–991; g) Kanokmedhakul, S.; Kanokmedhakul, K.; Nambuddee, K.; Kongsaeree, P.; *J. Nat. Prod.* **2004**, 67, 968–972; h) Subehan, S.; Kadota, S.; Tezuka, Y.; Planta Med. **2008**, *74*, 1474–1480.
4. Flanagan, S. R.; Harrowven, D. C.; Bradely, M. *Tetrahedron* **2002**, *58*, 5989.