“APPLICATION OF BENZYNE CHEMISTRY FOR THE TOTAL SYNTHESIS OF CEPHALOTAXINE, 2-AROYL BENZOFURANS AND SYNTHETIC STUDIES TOWARDS LABELLED NICOTINE”

A SYNOPSIS

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BY

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Synopsis

The thesis entitled "**Application of benzyne chemistry for the total synthesis of Cephalotaxine, 2-aroyl benzofurans and synthetic studies towards labelled Nicotine**" has been divided into three chapters.

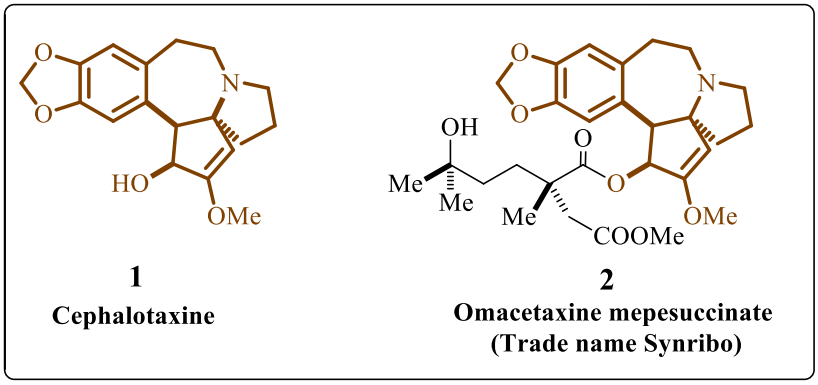
Chapter-I : describes about Formal Total Synthesis of (±)-Cephalotaxine and Congeners *via* Aryne Insertion Reaction.

Chapter-II : describes about Syntheses of 2-Aroyl Benzofurans through Cascade Annulation on Arynes.

Chapter-III : describes about Synthetic Studies towards Deuterated Nicotine.

Chapter-I : Formal Total Synthesis of (±)-Cephalotaxine and Congeners *via* Aryne Insertion Reaction.

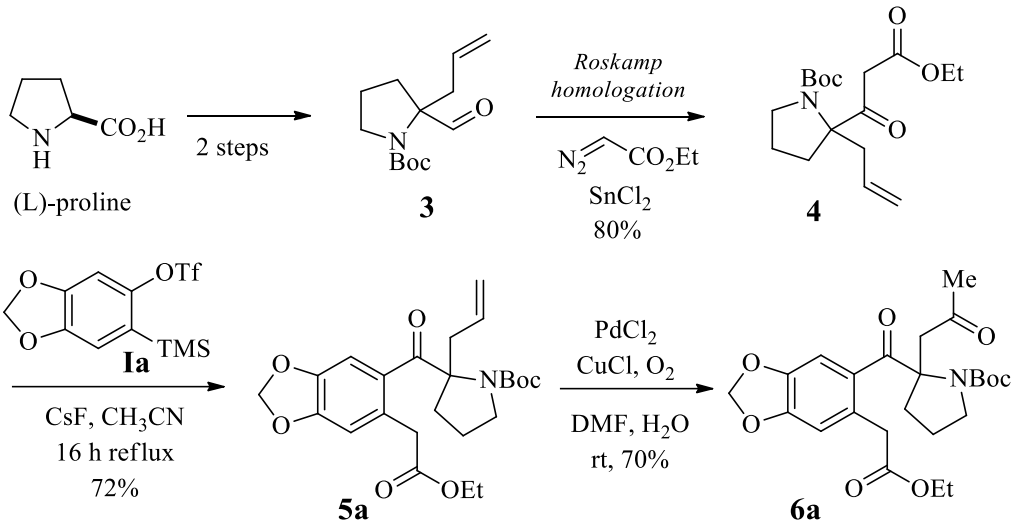
This chapter describes the synthesis of (±)-cephalotaxine **1** was isolated by Paudlar and co-workers from *Cephalotaxus harringtonii*. One of the esters of cephalotaxine namely homoharringtonine (HHT) **2** was approved by Food and Drug Administration (FDA) for treatment of orphan leukemia in 2012 (syn. Omacetaxine mepesuccinate, OmaproTM).



Structures of cepahalotaxine and HHT

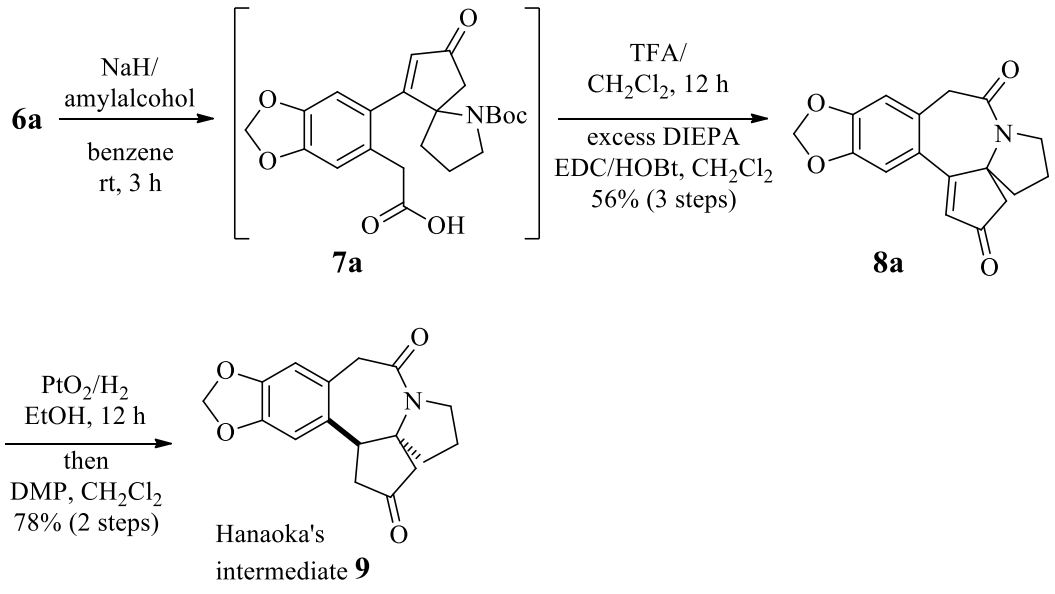
The clinical approval of Omacetaxine mepesuccinate **2** as orphan drug, the biological signifciance and structural complexity of 1-azabicyclo[5.3.0]decane skeleton prompted us to take up the research programme towards the synthesis of cephalotaxine. The formal total synthesis of pentacyclic core alkaloid, (±)-cephalotaxine **1** was achieved in eight steps from known 2-allylpy-rrolidine-2-carboxaldehyde using aryne insertion reaction as a key step in 10% overall yield. The developed novel strategy also enabled to access cephalotaxine congeners with ease.

The synthesis of cephalotaxine started from pyrrolidine-2-carbaldehyde derivative **3** (by known literature method from commercially available L-Proline) was subjected Roskamp homologation to synthesize the *β*-keto ester **4** in 80% yield. Reaction of *β*-ketoester **4** with benzyne generated from methylenedioxy aryne precursor **Ia** in presence of CsF allowed a smooth σ-bond insertion reaction to afford compound **5a** (scheme **2**). The Wacker oxidation of **5a** with catalytic $PdCl_2$ and CuCl in presence of oxygen atmosphere gave the requisite methyl ketone **6a** in 70% yield (scheme 1).



Scheme 1

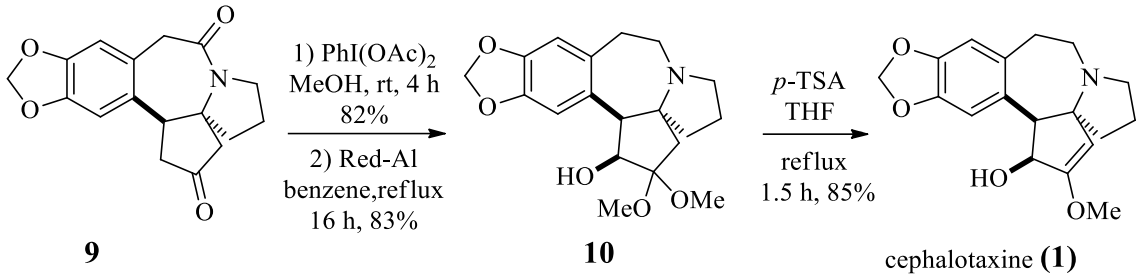
Methyl ketone **6a** was subjected to intramolecular aldol reaction triggered by NaH in amyl alcohol/benzene solvent mixture and subsequent hydrolysis of ester group were executed in one-pot to yield the spiro pyrrolidine **7a**. The crude intermediate **7a** was subjected to TFA in CH_2Cl_2 to remove the Boc-protection at room temperature. Sequential addition of excess DIPEA and EDCl/HOBt in same pot provided pentacyclic frame **8a** in 56% isolated yield (scheme 2).



Scheme 2

Reduction of **8a** using Adam's catalyst (PtO_2) under hydrogen atmosphere provided ketolactam **9** along with slight amounts of over reduced alcohol as an inseparable mixture. This mixture on oxidation with Dess-Martin periodinane allowed us to isolate Hanaoka's intermediate **9** smoothly in 78% yield for two steps (scheme 2).

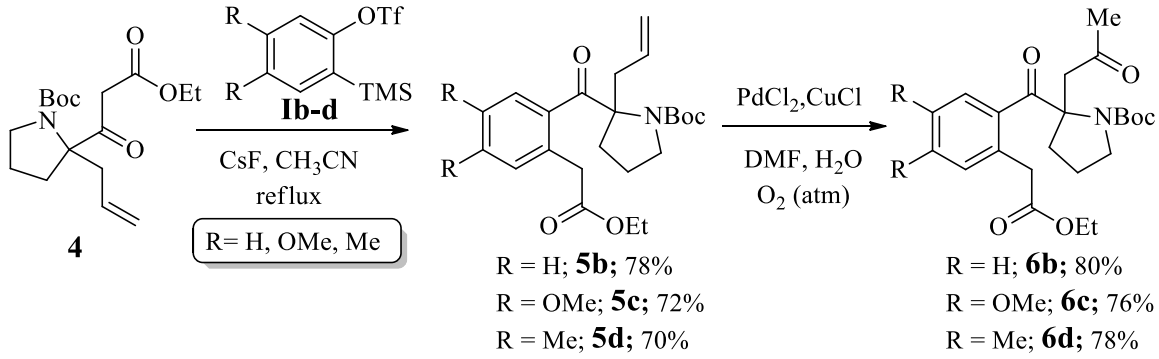
Compound **9** was reacted with BAIB and KOH in MeOH at room temperature furnished hydroxyl acetal, reduction of amide with Red-Al in benzene reflux gave amine **10** in 83% yield. Finally treatment of acetal **10** with *p*-TSA in THF reflux to provide Cephalotaxine **1** in 85% yield (scheme 3).

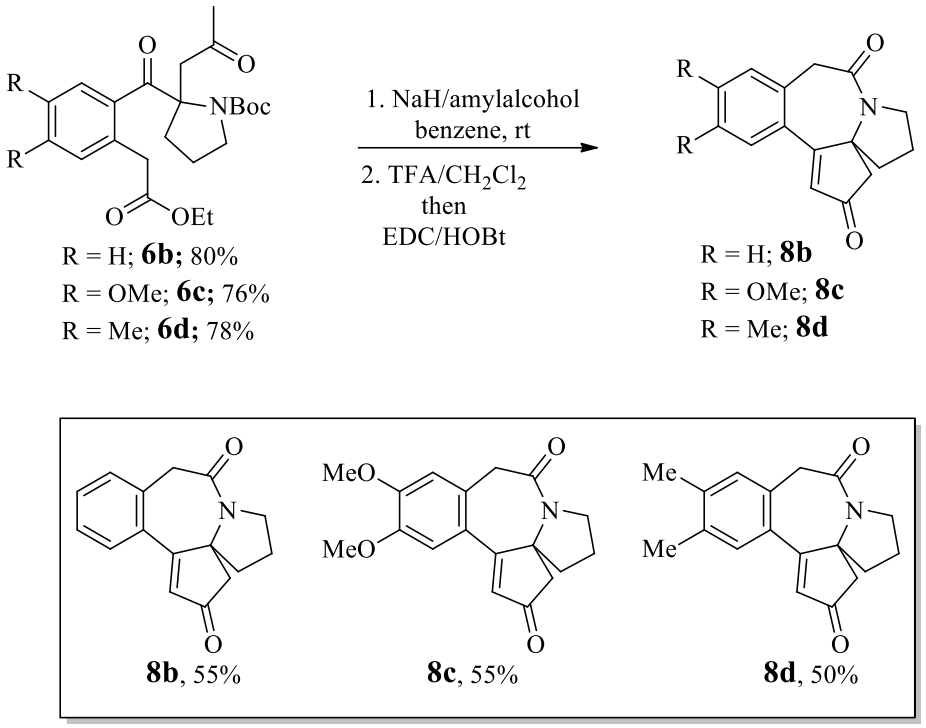


Scheme 3

Synthesis of cephalotaxine congeners

The easy access to multiple grams of compound **4** prompted us to attempt insertion reaction on various arynes viz, benzyne, dimethoxybenzyne and dimethylbenzyne. Following the synthetic route as used for the synthesis of cephalotaxine **1** various aryne precursors **Ib-d** were subjected to smooth aryne insertion reaction with compound **4** afforded **5b-d** followed by Wacker oxidation gave **6b-d** in excellent yields. Subsequent NaH mediated aldol reaction resulted in analogs of cephalotaxine **8b-d** in good yields (Scheme 4).

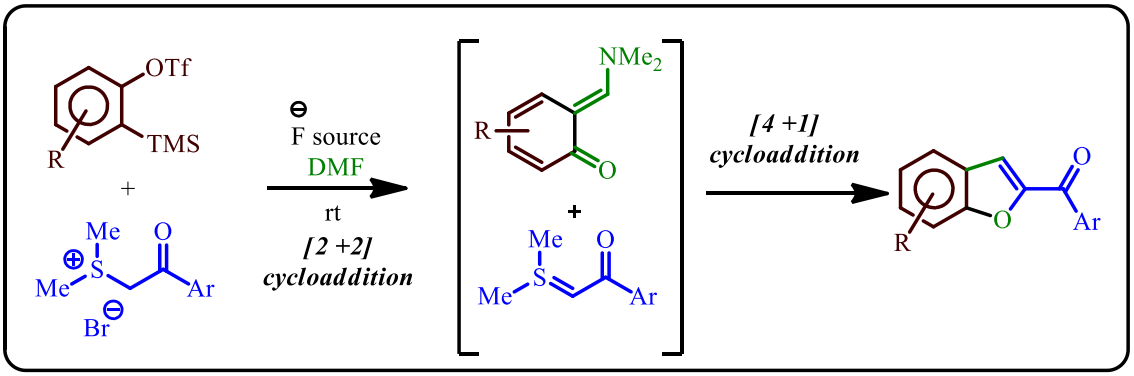




Scheme 4

Chapter-II : Syntheses of 2-aroyl benzofurans through cascade annulation on arynes

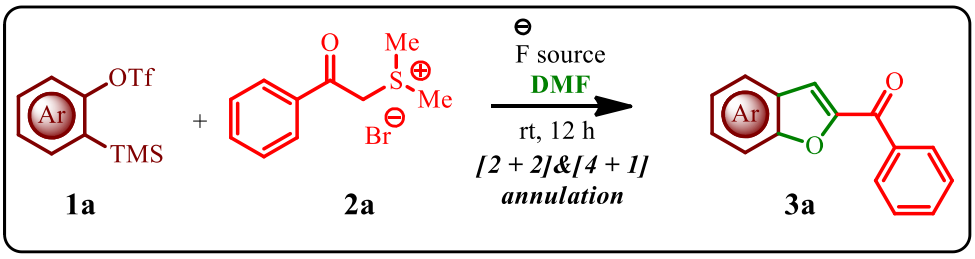
Oxygen containing molecules are an important class of the organic heterocyclic compounds. This chapter highlights the synthesis of benzofuran derivatives through three-component coupling reactions. The highly efficient and expedient route for the syntheses of 2-aroyl benzofurans *via* the cascade [2+2] followed by a [4+1] annulation on arynes has been developed. The overall transformation proceeded through the formation of *ortho*-quinone methide (*o*-QM) by the insertion of transient aryne into *N*,*N*-dimethylformamide and subsequent trapping with sulfur ylide. Sulfur ylides are versatile reagents which can be generated from easily accessible α-halo carbonyls and dialkyl sulfides. Many research groups elegantly demonstrated the utility of these ylides in cycloaddition reactions. The present cascade reaction works well with various sulfur ylides with broad scope and high functional group tolerance (Scheme 1).



- **Mild condition**
- **One-step strategy**
- **Broad substrate scope**
- **High fuctional group tolerance**

Scheme 1 Synthesis of 2-aroyl benzofurans

At first instance, the reaction of Kobayashi's ortho-silyl aryl triflate **1a** in DMF with CsF as a base at room temperature was treated with sulfonium bromide salt **2a**. To our delight, this initial attempt produced the desired product **3a** in 87% yield, thereby confirming the feasibility of our aryne-based approach to 2-aroyl benzofurans. (Scheme 2).

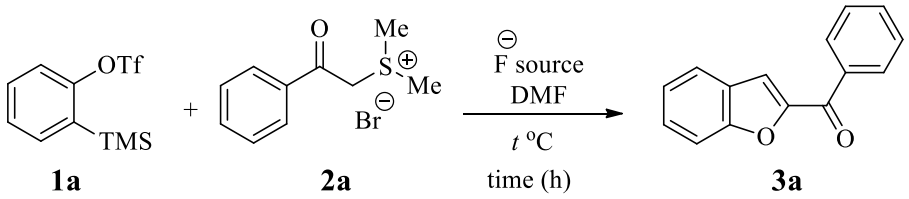


Scheme 2

Next continued by examining alternative sources of fluoride for the in situ formation of benzyne, at various temperatures (Table 1). Increasing the reaction temperature did not show any significant variation on yields. While both TBAF (entrie 4) and KF (entries 5 and 7) promoted formation of the product, but in low yield. The addition of 18-crown-6 to KF and

CsF did not lead to an improvement in the reaction yield. In the case of CsF, decrease in the reaction time was found to have high impact on the efficiency of the reaction (Table 1). Hence, after a brief screening, the optimal conditions to be concluded are **1a** (1.2 mmol), **2a** (1 mmol), and fluoride source (4 mmol) in DMF (0.1 M) at room temperature.

Table 1. Screening for Optimal Reaction Conditions[a]



1a + **2a** → **3a**

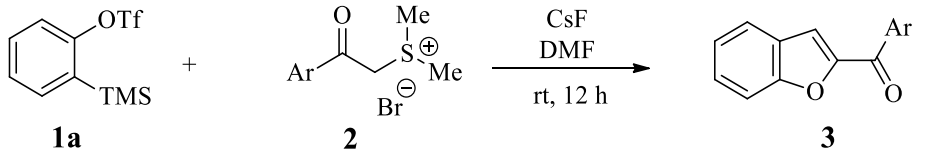
entry	F source	time (h)	*t* (°C)	yield[b]
1	**CsF**	**12**	**rt**	**87**
2	CsF	12	50	87
3	CsF	12	80	88
4[c]	TBAF	12	rt	52
5	KF	12	rt	68
6[c]	CsF/18-*C*-6	12	rt	87
7[c]	KF/18-*C*-6	12	rt	63
8	NaF	1	rt	0
9	CsF	1	rt	30
10	CsF	5	rt	58

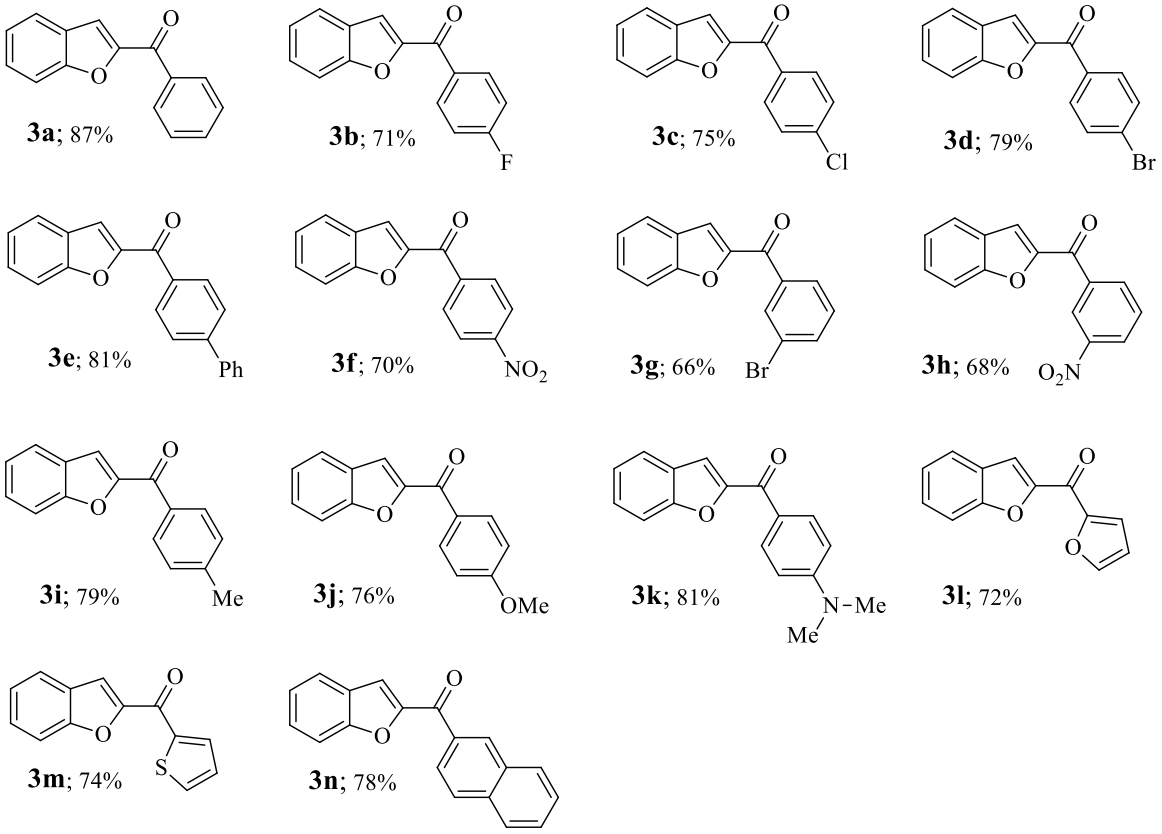
[a]Standard reaction conditions: The reaction was carried out with **1a** (1.2 mmol), **2a** (1 mmol), and fluoride source (4 mmol) in solvent (0.1 M). [b]Yield of the isolated product. [c]18-Crown-6 (0.25 mmol) was used.

With a suitable set of reaction conditions in hand the substrate scope of the reaction was then explored. Firstly, the sulfonium bromide salts were investigated – the results of which are detailed in Table 2. Substrate scope was then examined under the optimized reaction conditions. The reaction was found to be viable for a range of sulfer ylides bearing either

electron-donating or electron-withdrawing undergoing smooth cascade annulation in good to excellent yields (66-87%). However, substituents at *meta*-position gave slightly lower yields. With other sulfonium salts bearing heteroaryl groups also proceeded smoothly with good yields (Table 2).

Table 2. Substrate scope for sulfur ylides[a,b]

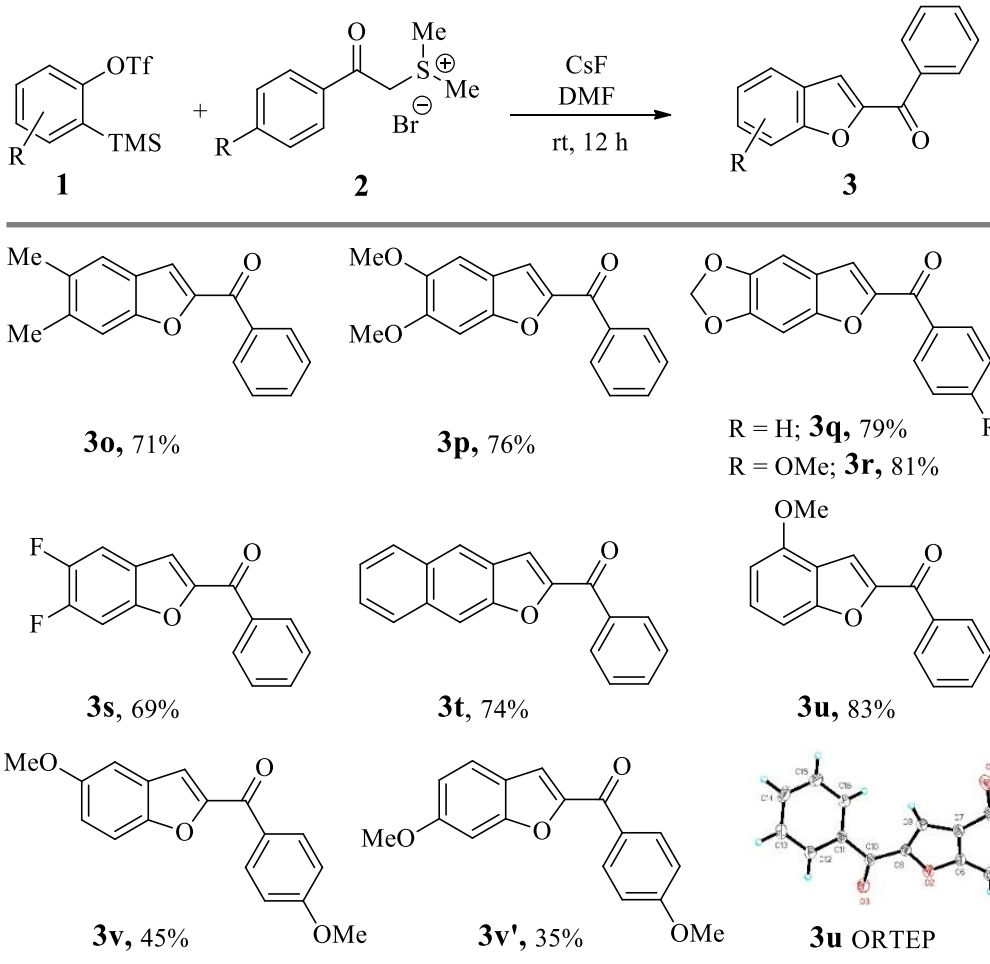




[a]Reation conditions: The reaction was carried out with **1a** (1.2 mmol), **2** (1 mmol), and fluoride source (4 mmol) in DMF (0.1 M). [b]Yields of products isolated after column chromatography

Further investigated the substrate tolerances by examining a series of substituted aryne precursors in combination with sulfonium salt **2** (Table 3). Regardless of electron-donating or withdrawing nature of the substituent on the symmetrical aryne precursors **1a-f**, were found to produce the expected benzofurans in good yield (69−83%). In case of unsymmetrically substituted aryne precursor, 3-methoxy-2-(trimethylsilyl)phenyl triflate **1g** reacted with sulfonium salt **2a** to give **3u** exclusively in 83% yield with complete regiocontrol. However, the annulation of 4-methoxytriflate with **2j** generated a 9 : 7 mixture of isomeric products.

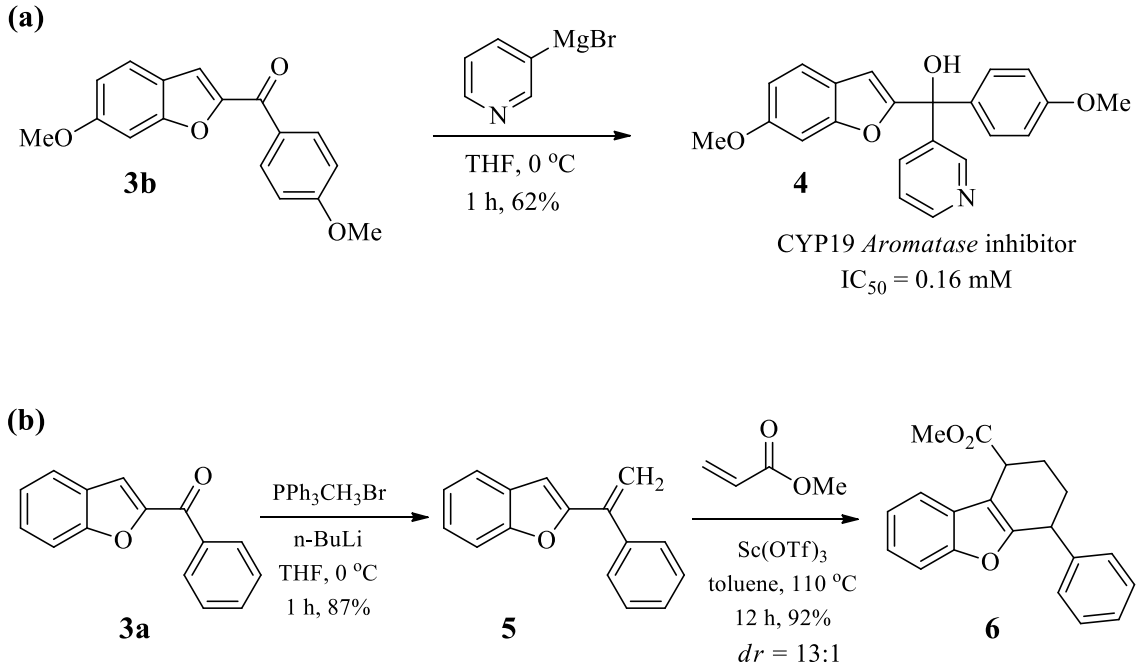
Table 3. Substrate scope for benzyne[a,b]



[a]Reaction conditions: The reaction was carried out with **1** (1.2 mmol), **2** (1 mmol), and fluoride source (4 mmol) in DMF (0.1 M). [b]Yields of products isolated after column chromatography

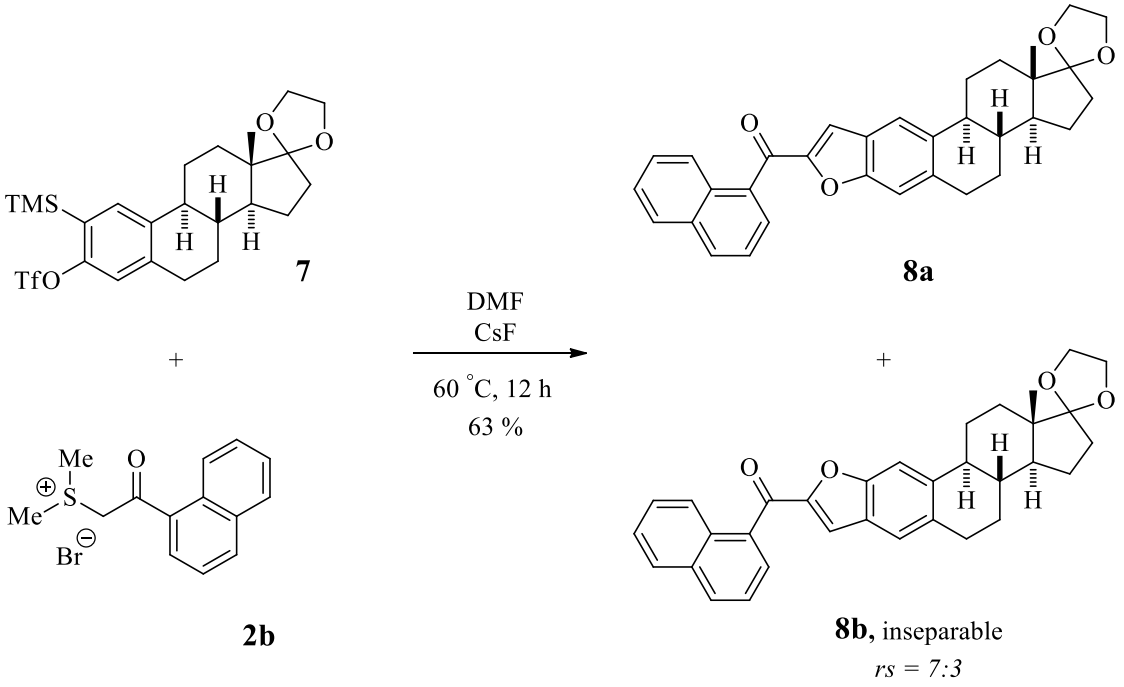
Synthetic utility

To demonstrate the synthetic utility of this method, 2-aroyl benzofuran **3b** was treated with pyridine-3-magnesium bromide to generate potent CYP19 *Aromatase* inhibitor **4** in 62% yield (Scheme 3a). The C_1-Wittig olefination of **3a** afforded 2-vinylbenzofuran **5** in 87% yield. Diels-Alder reaction of compound **5** using methyl acrylate in the presence of $Sc(OTf)_3$ at 110 ^oC gave tetrahydrodbenzofuran **6** in 92 % yield with 13:1 ratio of diastereoselectivity (Scheme 3b).



Scheme 3

The present cascade reaction was employed for late-stage functionalization on the complex bioactive steroid estrone. The sterically crowded aryne precursor **7** synthesized from estrone , was subjected to sulfonium salt **2b** under standard reaction conditions at 60 ^oC to afford the corresponding product as 7:3 ratio of inseparable regiomers **8a** & **8b** (Scheme 4).



Scheme 4

Chapter-III : **Synthetic Studies towards Deuterated Nicotine**

Nicotine **1** is an alkaloid present in tobacco and a wide variety of other plants. It targets and activates nicotinic acetylcholine receptors (nAChRs). Nicotine itself and several analogues (Figure 1) have shown therapeutic benefits for a number of central nervous system disorders such as Alzheimer's, Parkinson's, and Tourette's diseases. Since the first synthesis by Pictet in 1904, numerous syntheses of nicotine and its analogues have been reported.

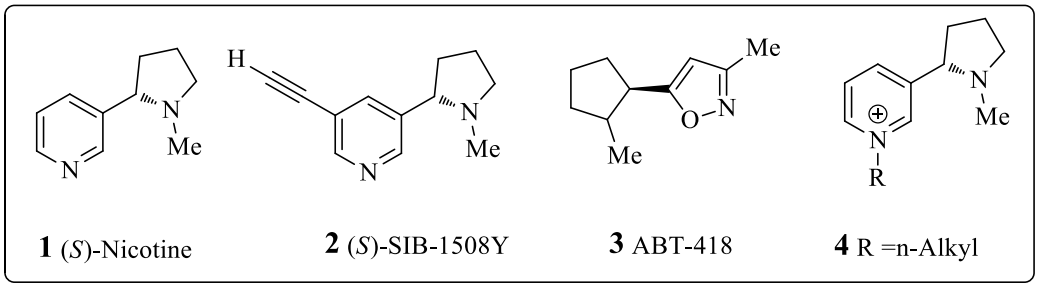
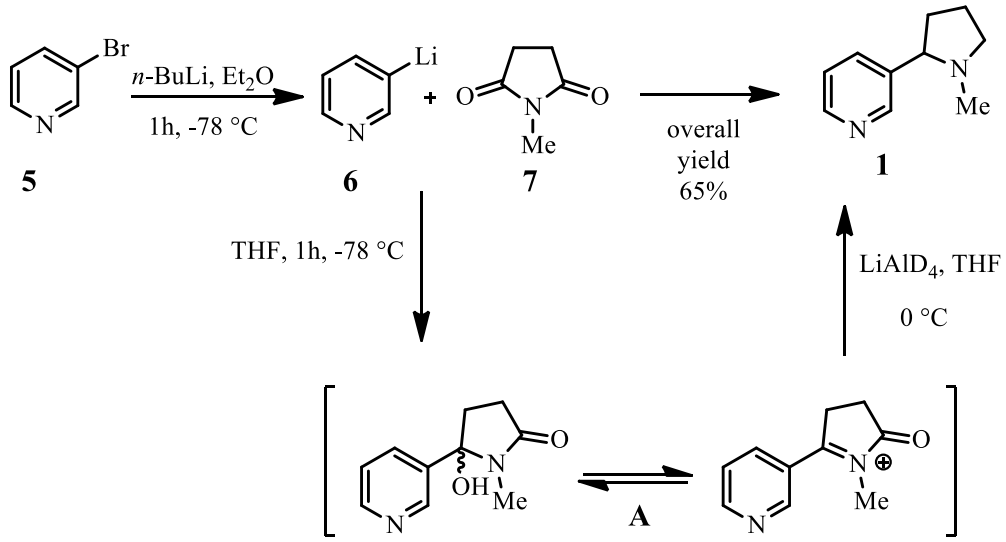


Figure 1 Nicotine and analogues.

In this chapter, a new method for the synthesis of nicotine in one-pot has been developed with 65% overall yield (Scheme 1). The synthesis of nicotine **1** commenced from commercially available 3-bromopyridine **5**, which was treated initially with *n*-butyllithium at –78 °C in diethyl ether. *N*-Methyl succinimide **7** was then added to the resulting lithiated pyridine derivative to afford the amido alcohol intermediate at -78 °C. Without isolating the intermediate, the reaction mixture was further diluted with THF and subjected to reduction with $LiAlH_4$ at room temperature to afford nicotine **1** in 65% overall yield (Scheme 1).



Scheme 1

This method facilitated the synthesis of fully and partially deuterated nicotine compounds (Figure 2). The main interest behind this project is to study the effect of deuterium incorporation on nicotine biochemical potency, because selective incorporation of deuterium in place of hydrogen has the unique effect of retaining the biochemical potency and selectivity to relevant pharmacological targets. In selected cases deuterium incorporation exhibited positive effects on biochemical potency by modifying the metabolic rate to substantially alter their overall therapeutic profile. Following the same synthetic route (Scheme 1), various deuterated nicotine compounds (Figure 2) were also synthesized.

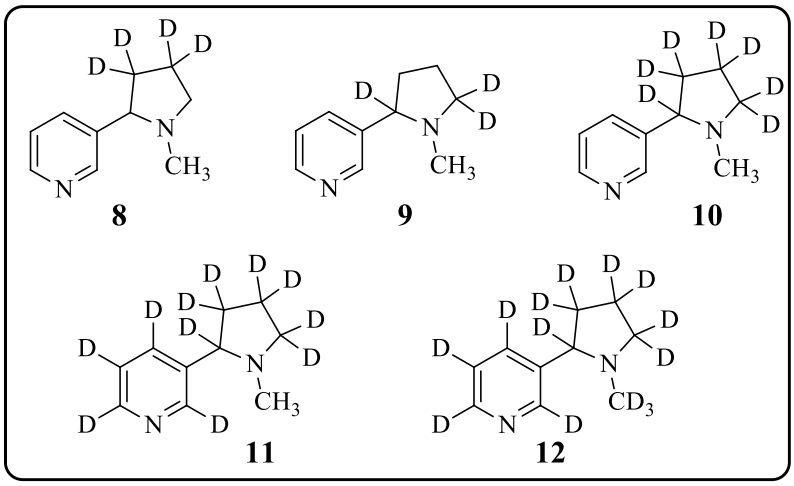
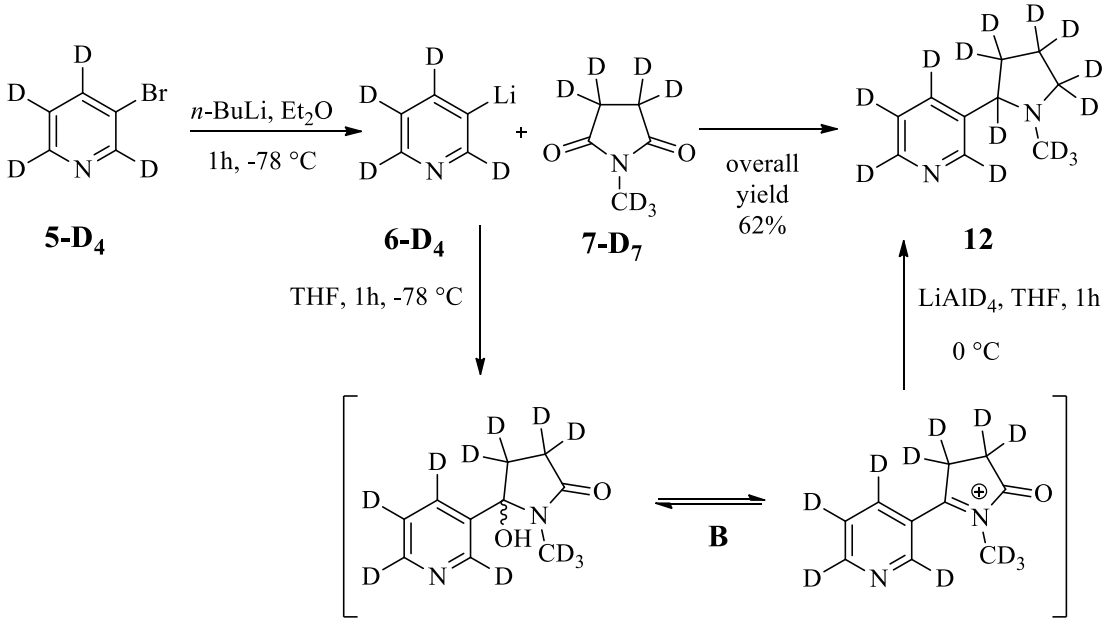


Figure 2 Deuterated nicotine compounds

Synthesis of fully deuterated nicotine strated with 3-Bromopyridine-D_4 **5-D_4** was treated with *n*-butyllithium at –78 °C in diethyl ether, to generate lithiated pyridine **6-D_4** derivative and was added *N*-CD_3 succinimide **7- D_7** to afford the corresponding amido alcohol intermediate **B** at -78 °C. Without isolating the intermediate **B**, the reaction mixture was diluted with THF and subjected to reduction with $LiAlD_4$ at room temperature to afford the deuterated nicotine **12** in 62% overall yield (Scheme 2).



Scheme 2