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Authors Van Hieu Tran, Wan Pyo Hong and Hee-Kwon Kim

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ORCID® IDs Hee-Kwon Kim - <https://orcid.org/0000-0001-7612-7049>

Facile Metal-Free Direct Transformation of *N*-Allyl- and *tert*-Butyl-Protected Arylamines to Azacycles Using Phosphoryl Chloride and TBD

Van Hieu Tran^{1,2}, Wan Pyo Hong³, and Hee-Kwon Kim^{*1,2}

¹Department of Nuclear Medicine, Molecular Imaging & Therapeutic Medicine Research Center, Jeonbuk National University Medical School and Hospital, Jeonju, 54907, Republic of Korea, ²Research Institute of Clinical Medicine of Jeonbuk National University, Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju, 54907, Republic of Korea, and ³Department of Advanced Materials and Chemical Engineering, Daegu Catholic University, 13-13, Hayang-ro, Hayang-eup, Gyeongsan-si, Gyeongbuk, 38430, Republic of Korea

Email: Hee-Kwon Kim* - hkkim717@jbnu.ac.kr

* Corresponding author

Abstract

A novel synthetic approach to the preparation of *N*-aryl substituted azacycles from *N*-allyl and *N-tert*-butyl protected arylamines is described. In this preparation, a metal free reagent system utilizing POCl₃ and TBD proved to be an important contributor for reactions of *N*-allyl- and *tert*-butyl-protected arylamines with cyclic ethers to generate the target azacycles. This protocol provides a practical approach to high yield, direct synthesis of *N*-aryl substituted five-membered and six-membered azacycles from *N*-allyl arylamines and *N-tert*-butyl arylamines.

Keywords

Azacycles; *N*-allyl arylamines; *N-tert*-butyl arylamines; Direct Transformation; Cyclic ethers.

Introduction

N-Substituted azacycles are widely used in organic chemistry and material science as important building block motifs [1-6]. Additionally, these structures are frequently found in a wide range of biologically active compounds and FDA approved drugs [7-11].

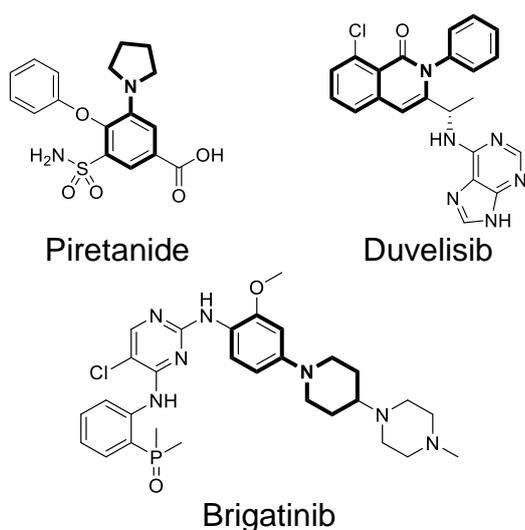


Figure 1. FDA-approved novel drugs containing *N*-substituted azacycles

Due to their ubiquitous nature, synthetic studies of *N*-substituted azacycles have attracted considerable interest in organic chemistry and drug discovery. Various synthetic methods have been developed for preparation of *N*-substituted aryl azacycles: reduction of *N*-alkyl substituted lactams to the corresponding azacycles or reductive amination of dicarbonyl derivatives [12-14], formation of the C–N linkage by cross-coupling reactions between *N*-heterocyclic compounds and aryl halides [15-16], and cyclization of aryl amines with diols or dihalides [17-20]. Intramolecular protocols have also been developed to prepare *N*-substituted azacycles: intramolecular C(sp³)-N coupling of *N,N*-dialkyl secondary amines, intermolecular C(sp³)-H amination of alkyl bromide derivatives, and Mitsunobu cyclodehydration for formation of azacycles from α,ω -aminoalcohols [21-23].

In addition, reactions of various arylamines with cyclic ethers using metal-based reagents including activated alumina, aluminum oxide, aluminum chloride, titanium (IV) chloride, and trimethylaluminum were discovered to produce *N*-substituted azacycles [24-27]. Several nonmetal reagent protocols have also been developed: $B(C_6F_5)_3$ and *p*TSA•H₂O were reported as key reagents for preparation of *N*-substituted azacycles from primary arylamines and cyclic ethers *via* ring-opening of cyclic ethers followed by cyclization [29]. $BF_3 \cdot Et_2O$ was also employed as an active Lewis acid to assist in ring-opening of tetrahydrofuran for synthesis of *N*-aryl-substituted pyrrolidines [30]. Hydrogen iodide has also been used for synthesis of *N*-substituted azacycles [31]. However, most of the reported protocols require harsh reaction conditions such as high temperature, making it difficult to expand the scope of this reaction [32]. Moreover, most of the previously reported methods employed primary arylamines (highly reactive free arylamines) as starting materials for production of *N*-substituted azacycles. However, primary free amines are generally protected with a protecting group, and protected forms of amines (secondary amines) are frequently employed in multistep organic syntheses to prevent production of unwanted side products [33-40].

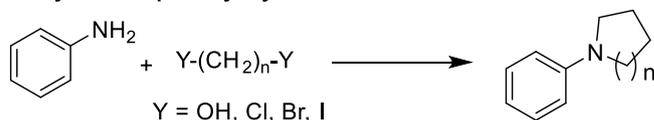
The allyl group is a commonly used protecting group for amines in organic and pharmaceutical syntheses as various simple methods to prepare *N*-allylamines have been developed. They are generally synthesized by reaction of the primary amine with allylbromide in the presence of base; several metal complexes or ion liquids have been used as efficient reagents, and microwave irradiation methods have also been employed for this purpose.

While direct transformation of *N*-allylamine derivatives to other useful structures would constitute an attractive strategy, to our knowledge, direct synthesis of *N*-substituted aryl azacycles from *N*-allyl protected amine derivatives have not been reported due to the low reactivity of *N*-allyl protected amines (secondary amines). Herein, we describe a novel, practical, metal-free, direct preparation of *N*-aryl substituted azacycles from *N*-allyl arylamine

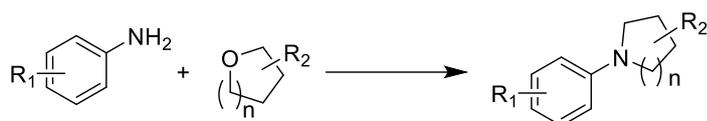
derivatives. In addition, this method was applied to direct conversion of *N-tert*-butyl protected arylamines to azacycles.

Previous studies:

- *N,N*-dialkylation of primary arylamine with diols or dihalides



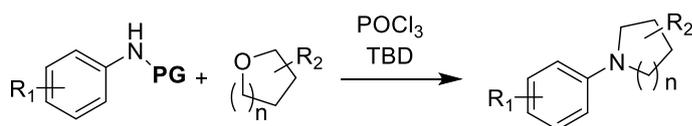
- *N*-hetero-cyclization of primary arylamines and ethers



metal-based reagents = Al_2O_3 , AlCl_3 , AlMe_3 , TiCl_4 , TiO_2

non-metal reagents = $\text{B}(\text{C}_6\text{F}_5)_3$, $\text{pTSA}\cdot\text{H}_2\text{O}$, HF

This work: *N*-hetero-cyclization of protected arylamines



PG (protecting group) = allyl, *tert*-butyl

Scheme 1: Synthesis of *N*-substituted azacycles.

Results and Discussion

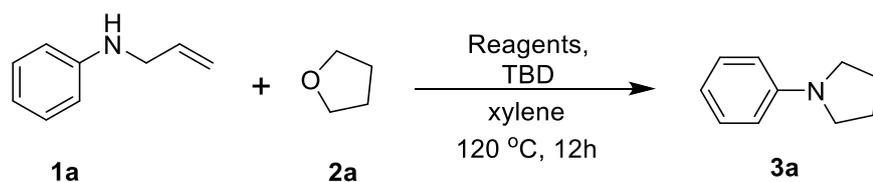
In most previously reported methods, preparation of *N*-substituted azacycles was achieved by employment of primary arylamines. Thus, synthesis of *N*-substituted azacycles from *N*-allyl protected arylamines (secondary amines) and cyclic ethers would require two separate steps: de-allylation of *N*-allyl arylamine to provide the free primary amine and then reaction of the primary amine with a cyclic ether to form the azacycle. Direct preparation of azacycles from *N*-allyl protected arylamines (secondary amines) would provide several benefits including fewer reaction steps and reductions of cost and waste.

In this study, several types of reaction conditions were investigated to achieve direct conversion of an *N*-allyl protected arylamine to *N*-substituted azacycle. Initially, new combination reagent/base systems for synthesis of *N*-substituted azacycles from *N*-allyl

arylamines and cyclic ethers were investigated. The reaction was conducted in the presence of TBD as a base at 120 °C for 12 h, and *N*-allylaniline was used as a model substrate.

First, a variety of Lewis acids (metal-based reagents) including FeCl₃, InCl₂, and SnCl₄ was examined to find usable conditions. However, none of these reagents led to the desired product. AlMe₃, which has previously been employed for synthesis of azacycles from primary amines [28] was also examined and was found to provide the corresponding azacycle in poor yield (8%). Employment of CaBr₂ and CaI₂ likewise did not produce the target product. Other metal-free reagents including BF₃·OEt₂, PCl₃, and PCl₅ were investigated for the reaction, however, it provided similar negative results. It was reported that phosphoramidates can be employed as useful intermediates in preparation of several types of cyclic structures [41-45].

Table 1. Screening of reaction conditions for conversion of *N*-allyl aniline to azacycle ^a

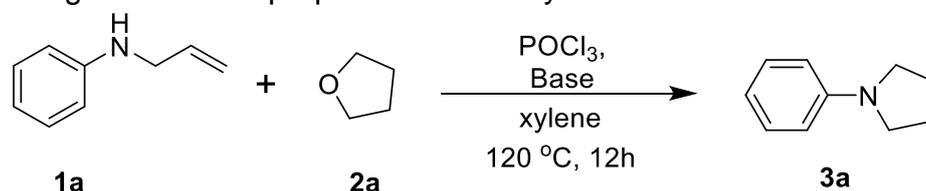


Entry	Reagents or Lewis acid	Time	Temp.	Yield ^b (%)
1	FeCl ₃	12	120 °C	NR ^[c]
2	InCl ₂	12	120 °C	NR ^[c]
3	SnCl ₄	12	120 °C	NR ^[c]
4	AlMe ₃	12	120 °C	8
5	CaBr ₂	12	120 °C	NR ^[c]
6	CaI ₂	12	120 °C	NR ^[c]
7	BF ₃ ·OEt ₂	12	120 °C	NR ^[c]
8	PCl ₃	12	120 °C	NR ^[c]
9	PCl ₅	12	120 °C	NR ^[c]
10	POCl ₃	12	120 °C	95
11	None	12	120 °C	NR ^[c]

^a Reaction conditions: compound 1a (2.0 mmol), THF 2a (50 mmol), TBD (3.0 mmol), 12 h. ^b Isolated yield after purification by flash column chromatography. ^c No reaction.

Thus, phosphorus oxychloride (POCl₃) was tested in the reaction of *N*-allyl protected aniline to yield the *N*-aryl substituted azacycle, and the POCl₃-mediated reaction delivered the desired product in high yield (95%). The initial reagent screening led to the promising discovery that POCl₃ was an efficient reagent for direct conversion of *N*-allyl protected aniline to *N*-aryl pyrrolidine.

Table 2. Screening of bases for preparation of azacycle^a

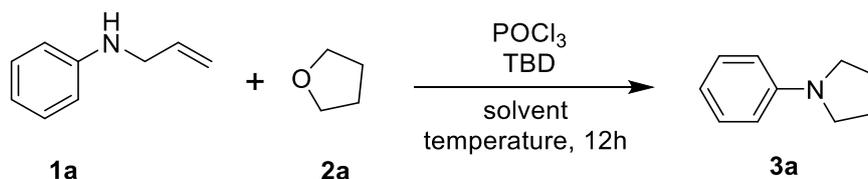


Entry	Reagents	Base	Temp.	Yield ^b (%)
1	POCl ₃	NaOH	120 °C	7
2	POCl ₃	NaHCO ₃	120 °C	2
3	POCl ₃	K ₂ CO ₃	120 °C	3
4	POCl ₃	CsCO ₃	120 °C	9
5	POCl ₃	Et ₃ N	120 °C	12
6	POCl ₃	DIEA	120 °C	14
7	POCl ₃	DBN	120 °C	58
8	POCl ₃	TBD	120 °C	95
9	POCl ₃	DMAP	120 °C	NR ^[c]
10	POCl ₃	None	120 °C	NR ^[c]

^a Reaction conditions: compound 1a (2.0 mmol), THF 2a (50 mmol), POCl₃ (2.8 mmol), Base (3.0 mmol), 12 h. ^b Isolated yield after purification by flash column chromatography. ^c No reaction.

Next, several kinds of bases were examined to find a suitable combined reagent system to prepare *N*-substituted azacycles. As shown in Table 2, introduction of NaOH, NaHCO₃, K₂CO₃, and Cs₂CO₃ into the reactions did not afford positive results (synthetic yields were less than 10%). Liquid organic bases were also assessed for synthesis of azacycles. Employment of trimethylamine (Et₃N) and *N,N*-diisopropylethylamine (DIEA) also led to low yields of azacycle. In addition, cyclic bases such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) were investigated. When DBN was used as the base, conversion of *N*-allyl protected arylamine to pyrrolidine was enhanced to 58%, which was still unsatisfactory. The reaction in the presence of TBD yielded the corresponding azacycle with a significantly increased yield (95%).

Table 3. Screening of solvents for preparation of azacycle^a

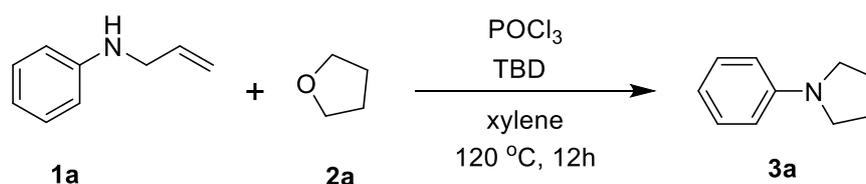


Entry	Reagents	Solvent	Temp.	Yield ^b (%)
1	POCl ₃	MeCN	reflux	NR ^c
2	POCl ₃	DCE	reflux	NR ^c
3	POCl ₃	DMF	120 °C	NR ^c
4	POCl ₃	DMSO	120 °C	NR ^c
5	POCl ₃	Toluene	120 °C	36
6	POCl ₃	PhCF ₃	reflux	39
7	POCl ₃	Xylene	120 °C	95

^a Reaction conditions: compound **1a** (2.0 mmol), THF **2a** (50 mmol), POCl₃ (2.8 mmol), TBD (3.0 mmol), solvent (2 mL), 12 h. ^b Isolated yield after purification by flash column chromatography. ^c No reaction.

The effect of reaction solvent on preparation of azacycles was investigated (Table 3). Utilization of MeCN, DMF, or DCE solvent led to none of the azacycle, while toluene and PhCF₃ gave modest synthetic yields (36% for toluene and 39% for PhCF₃). However, when xylene was used as solvent, the target cyclic amine was produced in high yield, suggesting that xylene was a better solvent for synthesis of azacycles.

Table 4. Screening of amount of reagents for preparation of azacycle^a



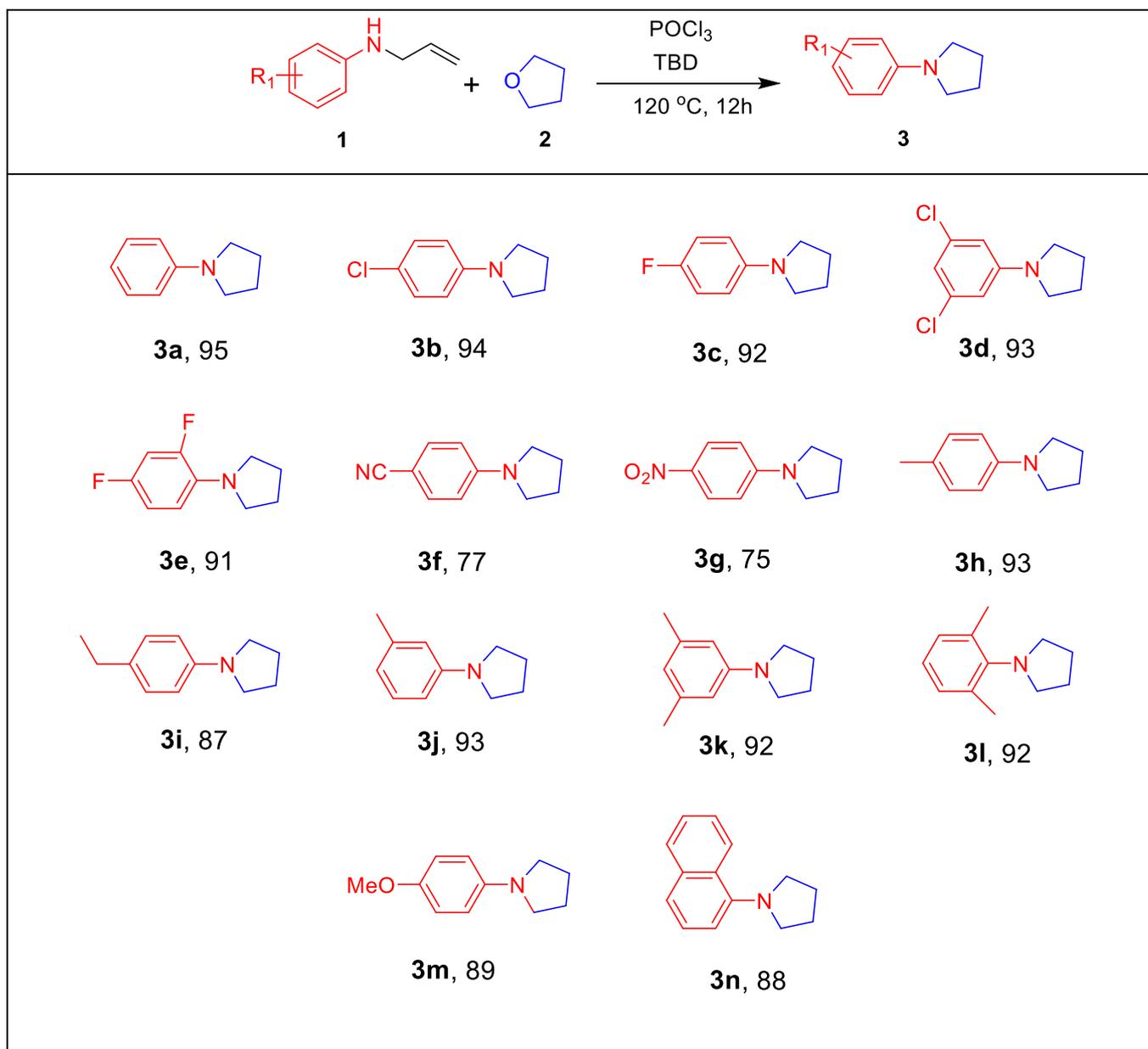
Entry	<i>N</i> -allyl-Amine (equiv.)	THF (equiv.)	POCl_3 (equiv.)	TBD (equiv.)	Yield ^b (%)
1	1	40	1.4	1.5	95
2	1	30	1.4	1.5	95
3	1	25	1.4	1.5	95
4	1	20	1.4	1.5	90
5	1	15	1.4	1.5	83
6	1	10	1.4	1.5	55
7	1	5	1.4	1.5	16
8	1	25	3	1.5	69
9	1	25	2	1.5	95
10	1	25	1	1.5	78
11	1	25	0.5	1.5	42
12	1	25	0.1	1.5	8
13	1	25	1.4	3	95
14	1	25	1.4	2	70
15	1	25	1.4	1	53
16	1	25	1.4	0	NR ^c

^a Reaction conditions: compound **1a** (2.0 mmol), 12 h, $120\text{ }^\circ\text{C}$. ^b Isolated yield after purification by flash column chromatography. ^c No reaction.

Next, the amounts of cyclic ether and base used for the reaction were investigated to find optimal reaction conditions (Table 4). *N*-Allyl protected aniline was treated with a series of tetrahydrofuran (THF) equivalents. The yield of azacycle increased as amount of THF was increased until reaching a plateau at 25 equiv. (55% for 10 equiv., 83% for 15 equiv., 90% for 20 equiv., and 95% for 25 equiv. of THF). Next, the effect of POCl₃ and TBD amounts on the reaction was examined. As shown in Table 4, several different amounts of POCl₃ (3.0, 2.0, 1.4, 1.0, 0.5, and 0.1 equiv. of POCl₃) and TBD (3.0, 2.0, 1.5, and 1.0 equiv. of TBD) were tested in reactions of *N*-allyl protected aniline with THF. The results indicated that employment of 1.4 equiv. of POCl₃ and 1.5 equiv. of TBD provided a high synthetic yield of azacycle (95%). However, greater amounts of POCl₃ or TBD in the reaction did not lead to a significant increase in synthetic yield. Reactions were carried out at several temperatures, and the target product was successfully obtained *via* reactions at 120 °C (see Table S1 in Supporting Information).

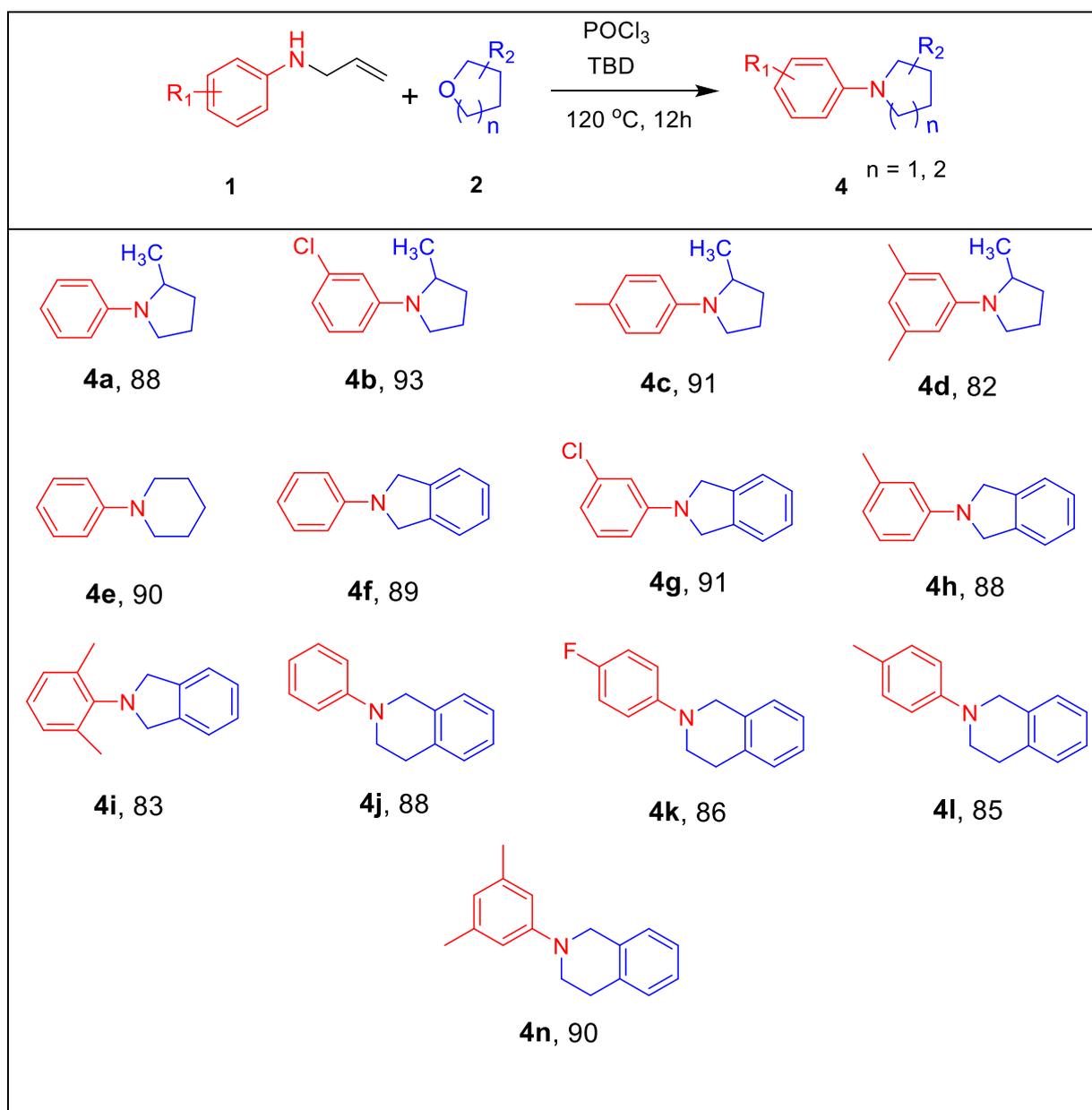
After determining optimized reaction conditions, the scope of this method for preparation of *N*-aryl substituted azacycles was investigated with a variety of *N*-allyl protected arylamines and cyclic ethers. First, different *N*-allyl protected arylamines were employed for the reaction with THF to give *N*-aryl substituted pyrrolidines. All desired products were successfully prepared in high yields *via* this novel synthetic method (Scheme 2). In this study, various substituents on the aromatic ring of *N*-allyl arylamines were examined, and reaction yields were not significantly influenced by electronic properties or position of substituents on the aromatic ring: Generation of target *N*-aryl-substituted azacycles in high yield was achieved with *N*-allyl protected arylamines bearing electron-withdrawing substituents (chloro-, fluoro-, nitrile-, and nitro-) and electron-donating substituents (methyl-, ethyl-, and methoxy-) (Scheme 2, **3b-3m**). *N*-Allyl protected arylamines containing two electron-withdrawing groups were tolerated in this

protocol: synthetic yields were 91% for two chloro groups and 90% for two fluoro groups (Scheme 2, **3d** and **3e**).



Scheme 2: Scope of synthesis of azacycloalkanes from various *N*-allyl arylamines. Reaction conditions: compound **1** (1.0 mmol), THF **2** (50 mmol), POCl₃ (2.8 mmol), TBD (3.0 mmol), 12 h, 120 °C. All yields are isolated yields after purification by flash column chromatography.

Moreover, while reactions of 2,6-disubstituted anilines with tetrahydrofuran were not previously successful due to the steric effect, *N*-allyl 2,6-dimethylaniline readily reacted with tetrahydrofuran under our reaction conditions to yield the target product **3i** in good yield.



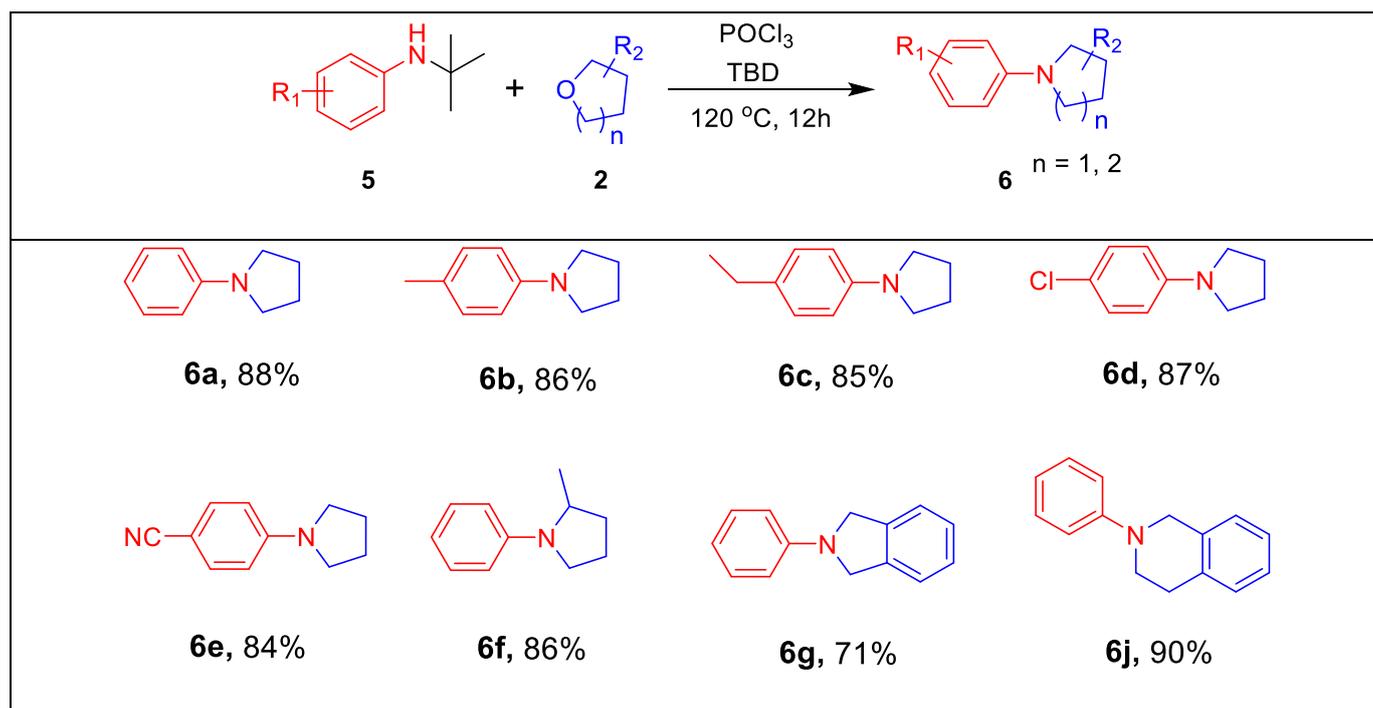
Scheme 3: Scope of synthesis of azacycloalkanes from various cyclic ethers. Reaction conditions: compound **1** (2.0 mmol), cyclic ether **2** (50 mmol), POCl_3 (2.8 mmol), TBD (3.0 mmol), 12 h, $120\text{ }^\circ\text{C}$. All yields are isolated yields after purification by flash column

chromatography.

A variety of cyclic ethers was also surveyed to evaluate the scope of this protocol. Reactions of 2-methyltetrahydrofuran with several *N*-allyl protected arylamines were performed (Scheme 3). 2-Methyltetrahydrofuran has greater steric hindrance than tetrahydrofuran; however, the target *N*-aryl substituted azacycles were prepared in high yields from reactions of *N*-allyl protected arylamines bearing either electron-withdrawing or electron-donating groups (Scheme 3, **4b-4d**).

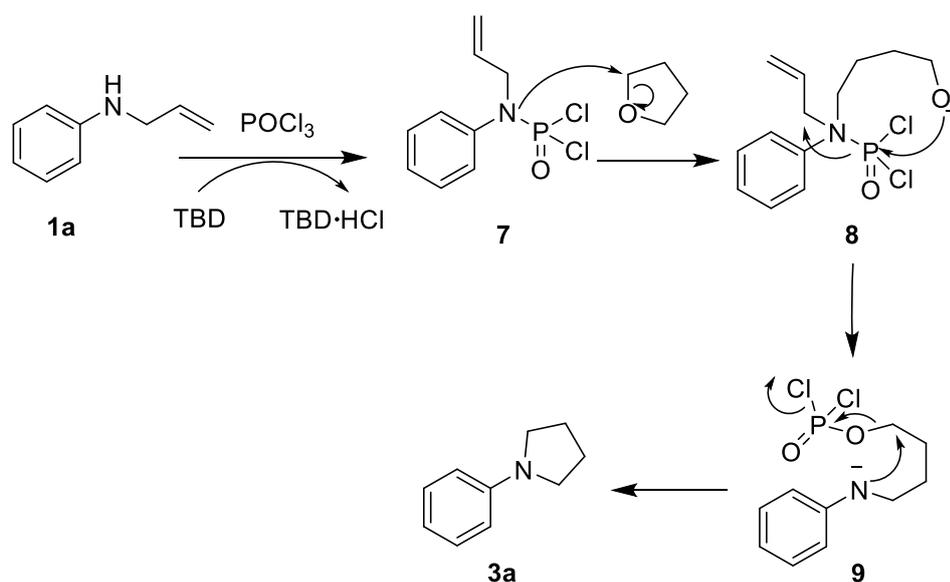
It has been reported that reactions of six-membered cyclic ethers such as tetrahydropyran with arylamines (primary amines) yielded *N*-aryl substituted azacycles in low yields. However, tetrahydropyran was successfully treated with *N*-allyl protected aniline (secondary amine) *via* our synthetic method, which resulted in high yield production of the target piperidine **4e**. Several nitrogen-containing fused heterocyclic ring structures such as tetrahydroisoquinoline and isoindoline are found as important units in biologically active natural products and pharmaceuticals, which are commonly used in various medical and biological studies [46-49]. Thus, the discovery of efficient reactions of *N*-allyl protected arylamines with benzene fused cyclic ethers to give *N*-aryl substituted benzene-fused azacycles is valuable. Utilization of this POCl₃/TBD mediated protocol was further expanded to direct preparation of various nitrogen-containing fused heterocyclic ring compounds from *N*-allyl protected arylamines. *N*-Allyl protected arylanilines readily reacted with phthalan or isochroman to produce the desired azacycles **4f** and **4j** in good yields. Of note, the yields of nitrogen-containing fused heterocyclic ring compounds from *N*-allyl protected arylamines were not affected by different substituents on the aryl amine, which suggests that electronic effects of substituent are not an important factor for substrate reactivity. Treatment of *N*-allyl protected arylamines bearing electron-withdrawing or electron-donating groups with phthalan or isochroman readily yielded the target isoindolines and tetrahydroisoquinolines in high yields (Scheme 4, **4g-4i** and **4k-4m**).

The scope of this method was extended to the reaction of *N-tert*-butyl arylamines to produce azacycles since the *tert*-butyl group has been widely used for protection of amines. Several *N-tert*-butyl arylamines were successfully employed in reactions with several types of cyclic ethers to give the corresponding azacycles. In particular, *N-tert*-butyl arylamines containing either electron-donating or electron-withdrawing groups were treated with tetrahydrofuran, phthalan, or isochroman under the same reaction conditions using POCl₃ and TBD, and the desired azacycles were synthesized in high yields. These results indicate that successful direct conversion of *N-tert*-butyl arylamines to *N*-aryl substituted azacycles can be achieved using the novel POCl₃/TBD mediated reaction system.



Scheme 4: Scope of synthesis of azacycloalkanes from *N-tert*-butyl arylamines. Reaction conditions: compound **5** (2.0 mmol), cyclic ether **2** (50 mmol), POCl₃ (2.8 mmol), TBD (3.0 mmol), 12 h, 120 °C. All yields are isolated yield after purification by flash column chromatography.

To obtain mechanistic insight into this transformation, we carried out control experiments. Use of POCl_3 alone did not yield the target intermediate (phosphoramidic dichloride **7**). Likewise, no product was observed when only TBD was employed for the reaction. However, the reaction in the presence of both POCl_3 and TBD successfully produced phosphoramidic dichloride **7**. Next, THF was added to the prepared phosphoramidic dichloride **7**, which successfully generated the desired product. Thus, based on the results from this study, a possible reaction pathway is proposed, as shown in Scheme 5. Treatment of POCl_3 and TBD with *N*-allylic arylamine **1a** produces phosphoramidic dichloride **7**. Next, reaction of phosphoramidic dichloride **7** with THF followed by intramolecular phosphoryl transfer generates intermediate **9**. Finally, nucleophilic displacement of the phosphonate by nitrogen generates the target product, 1-phenylpyrrolidine **3a**.



Scheme 5: Proposed reaction pathway for azacycle from *N*-allylic arylamine

Conclusion

In conclusion, a novel facile method for reaction of *N*-allyl and *N*-*tert*-butyl protected arylamines with cyclic ethers to give *N*-aryl-substituted azacycles has been reported.

In this study, POCl₃ and TBD were used as crucial reagents to convert *N*-allyl/*N*-*tert*-butyl protected arylamines to the corresponding azacycles. Practical utilization of this method was demonstrated from successful direct synthesis of *N*-aryl-substituted five- and six-membered azacycles from reactions of various *N*-allylic and *N*-*tert*-butyl arylamines with a variety of cyclic ethers. Moreover, this synthetic method uses inexpensive and commercially available reagents, and reaction operation is simple. With excellent results from a wide array of substrates, this novel synthetic method provides an approach to direct generation of various azacycles from *N*-allylic and *N*-*tert*-butyl arylamines.

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Supporting Information

Screening of reaction conditions, experimental procedures, compound characterisation data, and ¹H and ¹³C NMR spectra.

Supporting Information File 1:

File Name: Text

File Format: Text

Title: Screening of reaction conditions, experimental procedures, compound characterisation data, and ¹H and ¹³C NMR spectra.

Supporting Information File 2:

File Name: Text

File Format: Text

Title: Text

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