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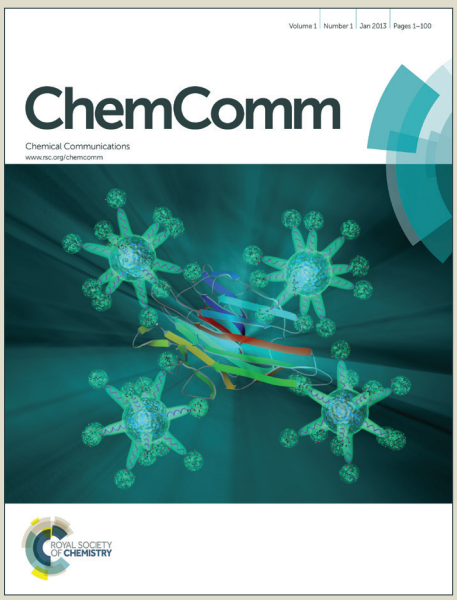

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Synthesis of *N*-Aryl Substituted, Five- and Six-membered Azacycles using Aluminum-amide Complexes†

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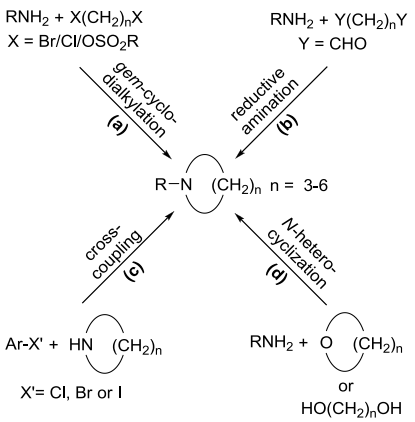
Synthesis of *N*-aryl substituted, five- and six-membered azacycloalkanes, isoindole and tetrahydroisoquinolines has been described. In this synthesis, cyclic ethers (n = 1,2) were treated with dimethylaluminum-amide reagents, derived from a range of aryl amines and trimethylaluminum, to afford the corresponding azacycles in good yields.

N-Substituted azacycles, such as pyrrolidine, piperidine, piperazine, isoindoline and tetrahydroisoquinoline, etc, are very important motifs that have wide range of applications in the field of pharmaceutical, agrochemical and material industries.[1] In addition, their structural subunits exist in many natural products such as vitamins, hormones, antigens, alkaloids, herbicides, dyes and many more compounds.[2] In recognition of their widespread importance, many synthetic methods have emerged over the years for the formation of C-N bond and are categorized in Scheme 1: (a) dialkyation of primary amines with dihalides under different reaction conditions,[3] such as KI in ethanol,[3a,b] $NaHCO_3$ in sodium dodecyl sulphate-water,[3c] $(i\text{-Pr})_2NEt$[3d] and under microwave irradiation in water,[3e] and aqueous K_2CO_3;[3f-h] (b) reductive amination of dicarbonyl compounds[4] using $KHFe(CO)_4$,[4a,b] n-Bu_2SnClH-HMPA,[4c] and $NaBH_4$;[4d] (c) cross-coupling reaction of *N*-unsubstituted azacycles and aryl halides[5] with the use of catalytic or stoichiometric system derived from iron,[5a-c] cobalt,[5d] nickel,[5e] copper[5f] and palladium;[5g] (d) *N*-heterocylization of primary amines with diols or cyclic ether[6] under drastic, dehydrating conditions in the presence of oxide catalyst, such as Al_2O_3,[6a] TiO_2[6b] and $AlCl_3$.[6c] Different kind of *N*-heterocylization utilizing diols through a "borrowing hydrogen" (BH) strategy[7] have also been reported using transition metal catalysts such as ruthenium,[7a-d] iridium[7e-g] and Pt-Sn/γ-Al_2O_3.[7h]

Yet, aforementioned reactions have disadvantages such as the use of toxic, expensive metals; often require longer reaction time, harsh reaction condition and tedious work up process. Therefore it is highly desirable to develop some alternatives which use cheap and commercially available, or easily accessible starting material and reagent.

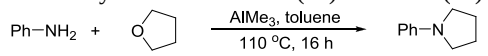


Scheme 1. Literature survey for the synthesis of *N*-substituted azacycles.

So far, many organoaluminum reagents have proven as remarkable reagents in organic synthesis due to their inherent reactivity, wide range of applicability, low cost and commercial availability.[8] Organoaluminum compounds can easily reacts with various heteroatoms in organic molecules, particularly with oxygen and nitrogen, to generate 1:1 complexes.[9] One widely used reagent of note is dimethylaluminum amide, derived from the reaction between trimethylaluminum and corresponding amine. This reagent has been utilized in the direct conversion of ester or acid to amide,[10,11] carbamate to urea[12] and nitrile to amidine.[13]

As a part of on-going research on solution- and solid-phase synthesis of small organic molecules, we have utilized dimethylaluminum-amide reagent extensively to introduce further diversity on to core scaffolds.[12,14] In these studies, amides and substituted ureas were prepared from resin-bound esters and carbamates respectively, as we dubbed as "smart cleavage reaction". Recently, we found that a substrate having an oxygen-containing ring undergoes unwanted side reaction when treated with dimethylaluminum-amide reagent, and this observation provoked us to investigate the reaction between the oxacycloalkanes with this reagent. Herein, we wish to report the $AlMe_3$-mediated synthesis of *N*-aryl substituted azacycles from oxacycles and aromatic amines.

Table 1. Optimization of reaction conditions for the $AlMe_3$-mediated *N*-heterocyclization of aniline (**1a**) with THF (**2a**).[a]



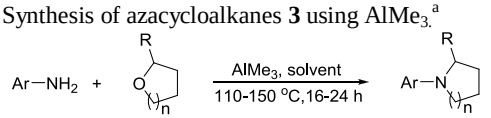
1a **2a** **3a**

Entry	**1a**:$AlMe_3$:**2a**	Yield (%)[b]
1	1:1.2:1	20
2	1:1.2:5	40
3	1:1.2:10	72
4	1:0:10	0

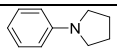
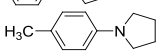
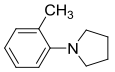
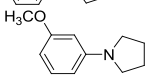
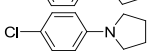
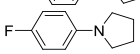
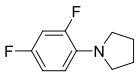
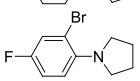
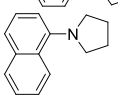
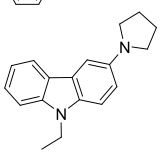
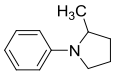
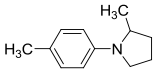
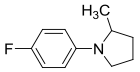
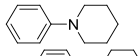
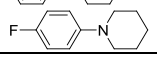
[a]All reactions were carried out on 1 mmol scale. [b]Isolated yields based on **1a**.

Our investigation began by treating tetrahydrofuran (**2a**, 1 equiv.) with dimethylaluminum-amide reagent prepared from $AlMe_3$‡ (1.2 equiv.) and aniline (**1a**, 1 equiv.) in toluene at 110 °C for 16 h. However, to our disappointment the yield of *N*-phenylpyrrolidine (**3a**) was not satisfactory (20%, Table 1, entry 1). Since **2a** is quite volatile considering the reaction temperature, then we used aluminum amide reagent as a limiting reagent. When **2a** was used five- and ten-fold excess, the yield was increased to 40% and 72%, respectively (Table 1, entries 2 and 3). In the absence of $AlMe_3$, product formation was not observed (Table 1, entry 4).

Table 2. Synthesis of azacycloalkanes **3** using $AlMe_3$.[a]



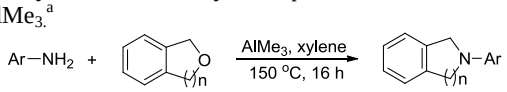
1a-j **2a**: n=1, R=H; **2b**: n=1, R=CH_3; **2c**: n=2, R=H **3a-o**

Entry	Ar	**2**	Product **3**		Yields[c] (%)[c]
1	Ph (**1a**)	**2a**		**3a**	72
2	4-CH_3Ph (**1b**)	**2a**		**3b**	70
3	2-CH_3Ph (**1c**)	**2a**		**3c**	68
4	3-CH_3OPh (**1d**)	**2a**		**3d**	71
5	4-ClPh (**1e**)	**2a**		**3e**	85
6	4-FPh (**1f**)	**2a**		**3f**	80
7	2,4-F_2Ph (**1g**)	**2a**		**3g**	82
8	2-Br-4-FPh (**1h**)	**2a**		**3h**	79
9	1-naphthyl (**1i**)	**2a**		**3i**	60
10	9-ethyl-9H-carbazol-3-yl (**1j**)	**2a**		**3j**	40
11	**1a**	**2b**		**3k**	78
12	**1b**	**2b**		**3l**	63
13	**1f**	**2b**		**3m**	90
14	**1a**	**2c**		**3n**	58
15	**1f**	**2c**		**3o**	60

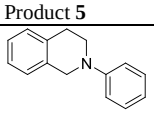
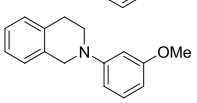
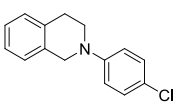
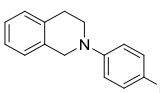
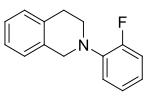
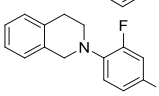
[a]Reaction conditions: aromatic amine **1**:$AlMe_3$:cyclic ether **2** (1:1.2:10 mmol); For THF (**2a**)/2-methylTHF (**2b**), in toluene, 110 °C, 16 h. [b]For tetrahydopyrane (**2c**), in xylene, 150 °C, 24 h. [c]Isolated yields based on aromatic amines.

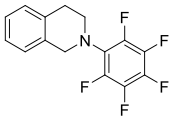
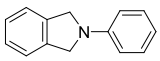
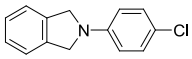
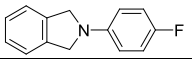
Then the scope of this reaction was examined using a combination of aryl amines **1** and cyclic ethers **2** under optimized reaction conditions (Table 2). In brief, the reaction was tolerant for a variety of aryl amines and cyclic ethers (n = 1,2) to afford the corresponding products in moderate to high yields. As shown in table 2, the reactivity of the aryl amine is found to be relevant to the electronic effect of the substituent on the aryl ring. Compare to unsubstituted aniline **1a** (Table 2, entry 1) and anilines with electron-donating substituent **1b-d** (Table 2, entries 2-4), those with electron-withdrawing substituent(s) **1e-h** reacted with **2a** faster, as monitored by TLC, and gave corresponding products in higher yield (Table 2, entries 5-8). This reactivity trend was similar when other cyclic ethers were employed as substrates (vide infra). Naphthylamine (**1i**) and 9-ethyl-9*H*-carbazol-3-amine (**1j**) also reacted with **2a** and gave the corresponding products in 60 and 40% yield respectively (Table 2, entries 9 and 10). Steric hindrances on the cyclic ether can also be tolerated. For exmaples, 2-methyltetrahydrofuran (**2b**) reacted well with anilines to afford the corresponding products in moderate to high yield (Table 2, entries 11-13). When tetrahydropyrane (**2c**) was employed, the reactions were somewhat sluggish and thus elevated reaction temperature (150 °C) and prolonged reaction time (24 h) was required to get the desired products in moderate yield (Table 2, entries 14 and 15). When aliphatic amines (benzylamine and phenethylamine) and hexamethylene oxide were employed, no appreciable reaction have been proceeded at all (data not shown here).

Table 3. Synthesis of tetrahydroisoquinolines and isoindolines **5** using $AlMe_3$.[a]



1a,d-g,k,l **4a**: n=2; **4b**: n=1 **5a-j**

Entry	Ar	**4**	Product **5**		Yields (%)[b]
1	**1a**	**4a**		**5a**	65
2	**1d**	**4a**		**5b**	62
3	**1e**	**4a**		**5c**	78
4	**1f**	**4a**		**5d**	85
5	2-FPh (**1k**)	**4a**		**5e**	80
6	**1g**	**4a**		**5f**	83

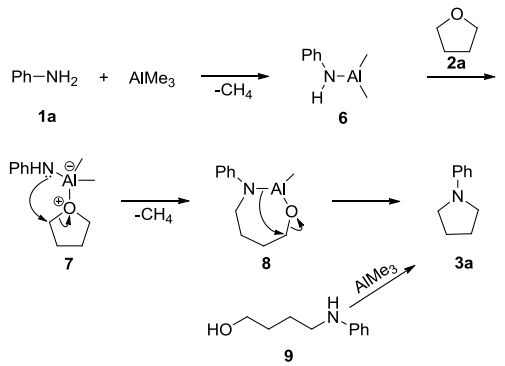
7	F_5Ph (**1l**)	**4a**		**5g**	83
8	**1a**	**4b**		**5h**	66
9	**1e**	**4b**		**5i**	75
10	**1f**	**4b**		**5j**	77

[a]Reaction conditions: aromatic amine **1**:$AlMe_3$:cyclic ether **4** (2:1.5:1 mmol); in xylene, 150 ℃, 16 h. [b]Isolated yields based on **4a**/**4b**.

Encouraged by above results, then we set out to further expand the application of this $AlMe_3$-mediated *N*-heterocyclization of aromatic amines towards the synthesis of nitrogen-containing fused heterocyclic ring system (Table 3). The structure containing tetrahydroisoquinoline and isoindoline fragments are found in many biologically active compounds, both synthetic and natural, such as alkaloids and pharmaceutical agents.[15] Since the boiling point of the isochroman (**4a**, 228 °C) and o-xylene oxide (**4b**, 192 °C) is sufficiently higher than the reaction temperature, these oxacycles were employed as limiting reagent. Aluminum amide reagents were reacted with **4a** to give corresponding tetrahydroisoquinolines **5a-g** in good yield (Table 3, entries 1-7). Here again, reactivity trends governed by the electronic effect of substituent's on aryl amines were similar with those observed in Table 2.

$AlMe_3$-mediated *N*-heterocyclization of aryl amines with **4b** have been carried out under similar reaction condition and this strategy again turned out to be practically useful. Desired *N*-aryl substituted 2,3-dihydro-1*H*-isoindoles **5h-j** were prepared in moderate yield (Table 3, entries 8-10).

The plausible mechanism for the formation of *N*-aryl substituted azacyles from the reaction of oxacyles with aluminum amide reagents derived from aryl amines and $AlMe_3$ is depicted in Scheme 2 using **1a** and **2a** as model substrates. **1a** is first reacted with $AlMe_3$ by the evolution of methane to afford dimethylaluminum-amide **6**, and this is coordinated with **2a** to form a Lewis acid-base complex **7**.Then nucleophilic amide attacks at the α-position of activated oxacycle **7** via four membered transition states to afford the cyclic intermediate **8**, followed by the evolution of methane. Then amide migrates again to the carbon connected to oxygen to afford the desired azacycle **3a**. In a separate experiment, 4-(phenylamino)butan-1-ol **9** was prepared[16] and treated with $AlMe_3$ in toluene at 140 °C for 16 h to afford the **3a** in 30% yield. And we believe that this conversion may support the proposed mechanism depicted in Scheme 2.



Scheme 2. Plausible mechanism for $AlMe_3$-mediated *N*-heterocyclization.

In conclusion, we have developed an efficient synthetic route for *N*-aryl substituted azacycles directly from its oxacycles and dimethylaluminum-amide reagents derived from aromatic amines and $AlMe_3$. Since this procedure is simple and utilized cheap and commercially available starting material, this would be one of the alternative methods for the synthesis of *N*-aryl substituted five- and six-memberd azacycles.

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Notes and references

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† Electronic Supplementary Information (ESI) available: General information, experimental procedure, characterization data and copies of ^1H and ^{13}C NMR spectra for all the products. See DOI: 10.1039/c000000x/

‡ **Caution:** Trimethylaluminum is moisture sensitive and pyrophoric, and should be handled with great care. See ESI† for more detail.

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