ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 8985

Received 29th May 2014,
Accepted 17th June 2014

DOI: 10.1039/c4cc04111a

www.rsc.org/chemcomm

Synthesis of *N*-aryl substituted, five- and six-membered azacycles using aluminum-amide complexes†

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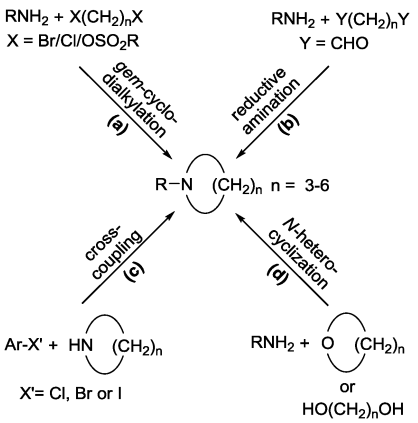
Synthesis of *N*-aryl substituted, five- and six-membered azacycloalkanes, isoindolines and tetrahydroisoquinolines, has been described. In this synthesis, cyclic ethers (*n* = 1, 2) were treated with dimethylaluminum-amide reagents, derived from a range of aryl amines and trimethyl-aluminum, to afford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

N-Substituted azacycles, such as pyrrolidines, piperidines, piperazines, isoindolines and tetrahydroisoquinolines, *etc*, are very important motifs that have a wide range of applications in 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 bonds and are categorized in Scheme 1: (a) dialkylation 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] 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) the cross-coupling reaction of *N*-unsubstituted azacycles and aryl halides[5] with the use of a catalytic or a 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 ethers[6] under drastic, dehydrating conditions in the presence of an oxide catalyst, such as Al_2O_3,[6a] TiO_2[6b] and $AlCl_3$.[6c] Different kinds of N-heterocylizations utilizing diols through a "borrowing hydrogen" (BH) strategy[7] using transition metal catalysts such as ruthenium,[7a–d] iridium[7e–g] and Pt–Sn/γ-Al_2O_3 have also been reported.[7h]

Yet, aforementioned reactions have disadvantages such as the use of toxic and expensive metals, and often require longer reaction times, harsh reaction conditions and a tedious work-up process. Therefore it is highly desirable to develop some alternatives which use cheap and commercially available, or easily accessible starting materials and reagents.



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

So far, many organoaluminum reagents have proven to be remarkable reagents in organic synthesis due to their inherent reactivity, wide range of applicability, low cost and commercial availability.[8] Organoaluminum compounds can easily react 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 the corresponding amine. This reagent has been utilized in the direct conversion of esters or acids to amides,[10,11] carbamates to urea[12] and nitriles to amidines.[13]

As a part of on-going research on solution- and solid-phase synthesis of small organic molecules, we have utilized a dimethylaluminum-amide reagent extensively to introduce further diversity in core scaffolds.[12,14] In these studies, amides and substituted ureas were prepared from resin-bound esters and carbamates, respectively, which we dubbed as "smart cleavage reaction". Recently, we found that a substrate having an oxygen-containing ring undergoes an unwanted side reaction when treated

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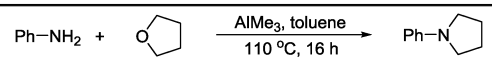
† Electronic supplementary information (ESI) available: General information, the experimental procedure, characterization data and copies of ^1H and ^{13}C NMR spectra of all the products. See DOI: 10.1039/c4cc04111a

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 a 1 mmol scale. [b] Isolated yields based on **1a**.

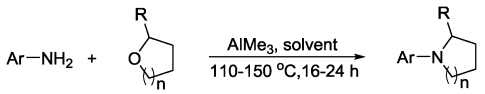
with a dimethylaluminum-amide reagent, and this observation provoked us to investigate the reaction between oxacycloalkanes and this reagent. Herein, we wish to report the $AlMe_3$-mediated synthesis of *N*-aryl substituted azacycles from oxacycles and aromatic amines.

Our investigation began by treating tetrahydrofuran (**2a**, 1 equiv.) with a 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, we used the aluminum-amide reagent as a limiting reagent. When **2a** was used in 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).

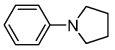
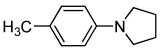
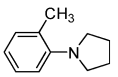
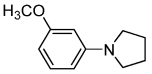
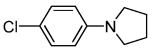
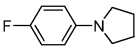
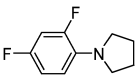
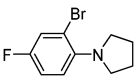
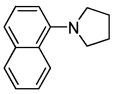
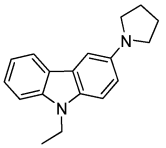
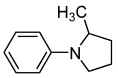
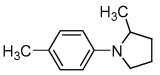
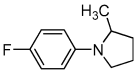
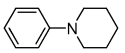
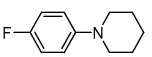
Then the scope of this reaction was examined using a combination of aryl amines **1** and cyclic ethers **2** under optimized reaction conditions (Table 2). In brief, the reaction was tolerant for a variety of aryl amines and cyclic ethers (n = 1, 2) to afford the corresponding products in moderate to 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. Compared to unsubstituted aniline **1a** (Table 2, entry 1) and anilines with an 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 the corresponding products in higher yields (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% yields, respectively (Table 2, entries 9 and 10). Steric hindrances on the cyclic ether can also be tolerated. For example, 2-methyltetrahydrofuran (**2b**) reacted well with anilines to afford the corresponding products in moderate to high yields (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) were required to get the desired products in moderate yields (Table 2, entries 14 and 15). When aliphatic amines (benzylamine and phenethylamine) and hexamethylene oxide were employed, no appreciable reaction occurred at all (data not shown here).

Encouraged by the above results, we then set out to further expand the application of this $AlMe_3$-mediated N-heterocyclization

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



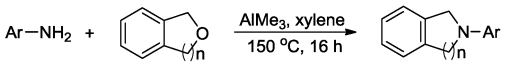
1a-j **2a**: n=1, R=H; **2b**: n=1, R=CH_3; **2c**: n=2, R=H **3a-o**

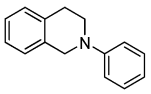
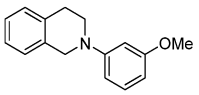
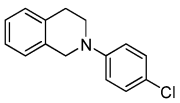
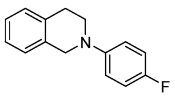
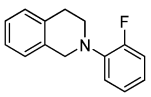
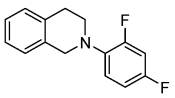
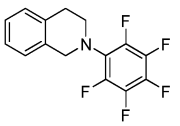
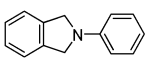
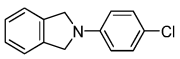
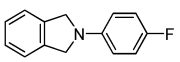
Entry	**1** (Ar)	**2**	Product **3**		Yields[c] (%)
1	Ph (**1a**)	**2a**		**3a**	72
2	4-CH_3Ph (**1b**)	**2a**		**3b**	70
3	2-CH_3Ph (**1c**)	**2a**		**3c**	68
4	3-CH_3OPh (**1d**)	**2a**		**3d**	71
5	4-ClPh (**1e**)	**2a**		**3e**	85
6	4-FPh (**1f**)	**2a**		**3f**	80
7	2,4-F_2Ph (**1g**)	**2a**		**3g**	82
8	2-Br-4-FPh (**1h**)	**2a**		**3h**	79
9	1-Naphthyl (**1i**)	**2a**		**3i**	60
10	9-Ethyl-9*H*-carbazol-3-yl (**1j**)	**2a**		**3j**	40
11	**1a**	**2b**		**3k**	78
12	**1b**	**2b**		**3l**	63
13	**1f**	**2b**		**3m**	90
14[b]	**1a**	**2c**		**3n**	58
15[b]	**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 tetrahydropyrane (**2c**), in xylene, 150 °C, 24 h. [c] Isolated yields based on aromatic amines.

of aromatic amines towards the synthesis of a nitrogen-containing fused heterocyclic ring system (Table 3). The structure containing tetrahydroisoquinoline and isoindoline fragments is found in many biologically active compounds, both synthetic and natural, such as alkaloids and pharmaceutical agents.[15] Since the boiling point of isochroman (**4a**, 228 °C) and *o*-xylene oxide (**4b**, 192 °C) is sufficiently higher than the reaction temperature, these oxacycles were employed as limiting reagents. Aluminum-amide reagents

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



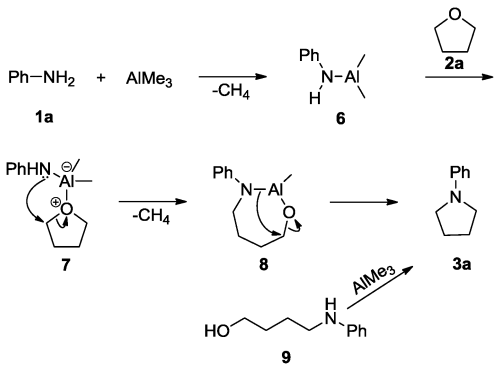
Entry	**1** (Ar)	**4**	Product **5**		Yields[b] (%)
1	**1a**	**4a**		**5a**	65
2	**1d**	**4a**		**5b**	62
3	**1e**	**4a**		**5c**	78
4	**1f**	**4a**		**5d**	85
5	2-FPh (**1k**)	**4a**		**5e**	80
6	**1g**	**4a**		**5f**	83
7	F_5Ph (**1l**)	**4a**		**5g**	83
8	**1a**	**4b**		**5h**	66
9	**1e**	**4b**		**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 °C, 16 h. [b] Isolated yields based on **4a**/**4b**.

were reacted with **4a** to give the corresponding tetrahydroisoquinolines **5a–g** in good yields (Table 3, entries 1–7). Here again, reactivity trends governed by the electronic effect of substituents on aryl amines were similar to those given in Table 2.

$AlMe_3$-mediated N-heterocyclization of aryl amines with **4b** was carried out under similar reaction conditions and this strategy again turned out to be practically useful. Desired *N*-aryl substituted isoindolines **5h–j** were prepared in moderate yields (Table 3, entries 8–10).

A plausible mechanism for the formation of *N*-aryl substituted azacycles from the reaction of oxacycles with aluminum-amide reagents derived from aryl amines and $AlMe_3$ using, **1a** and **2a** as model substrates, is depicted in Scheme 2. **1a** is first reacted with $AlMe_3$ followed 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 the nucleophilic amide attacks at the



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

α-position of activated oxacycle **7** *via* a four-membered transition state to afford the cyclic intermediate **8**, followed by the evolution of methane. Then the 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 **3a** in 30% yield. And we believe that this conversion may support the proposed mechanism depicted in Scheme 2.

In conclusion, we have developed an efficient synthetic route for the preparation of *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 utilizes cheap and commercially available starting materials, it would be one of the alternative methods for the synthesis of *N*-aryl substituted five- and six-membered azacycles.

Financial support of this research by the Basic Science Research Program through the National Research Foundation of Korea (2011-0007322) is gratefully acknowledged.

Notes and references

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

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