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Preparation of Tertiary Amines by the Reaction of Iminium Ions Derived from Unsymmetrical Aminals with Zinc and Magnesium Organometallics

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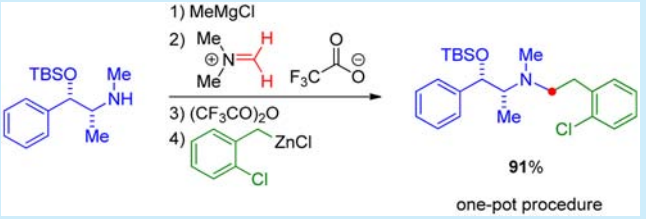
Supporting Information

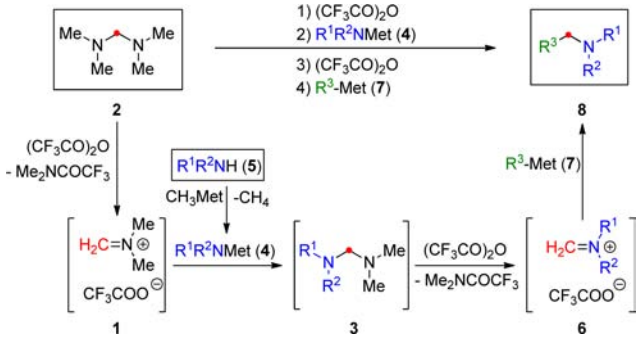
ABSTRACT: We report a convenient one-pot preparation of polyfunctional tertiary amines, including various biorelevant phenethylamines or ephedrine derivatives, via the reaction of new functionalized iminium ions with a variety of zinc and magnesium organometallic reagents. These iminium ions were generated from unsymmetrical aminals, obtained by the *in situ* addition of various amides to Tietze's iminium salt [$Me_2NCH_2^+CF_3COO^-$]. A functionalized aniline, prepared by this method, was converted to a quinolidine via an intramolecular Heck reaction.



Polyfunctional amines are ubiquitous in organic chemistry and numerous preparation methods have been reported.[1,2] In particular, the addition of organometallic reagents to iminium ions[3,4] constitutes a useful synthesis of tertiary amines.[5,6] Potier reported the first preparation of *N,N*-dimethyl(methylene)iminium trifluoroacetate (**1**) from trimethylamine oxide.[7] This synthesis was considerably improved by Tietze, who reported a preparation by the reaction of *N,N,N′,N′*-tetramethylmethanediamine (TMDAM, **2**) with trifluoroacetic anhydride (TFAA).[8,9] We envisioned that the iminium salt (**1**) could be used to prepare new unsymmetrical aminals of type **3** by the reaction of **1** with metallic amides of type **4** (R^1R^2NMet; Met = Li, MgX). The amides **4** were prepared by deprotonation of the corresponding amine R^1R^2NH (**5**) with CH_3Met (Met = Li, MgX). This reaction sequence will provide a route to complex iminium ions of type **6**. Thus, the treatment of the aminals **3** (which are prone to disproportionation under mild acidic conditions)[10] with TFAA under Tietze's conditions will regioselectively provide the iminium salt **6**. It is expected that the acylation of aminals **3** with TFAA occurs selectively on the least sterically hindered nitrogen of the *N,N*-acetal. The resulting functionalized iminium salt **6** may react with various organometallics (R^3-Met (**7**)), leading to polyfunctional tertiary amines of type **8** (Scheme 1). Herein, we report a successful one-pot procedure, which allows the conversion of TMDAM (**2**) directly into a broad variety of tertiary amines of type **8**.

Although a convenient one-pot procedure has been developed (Table 1), the isolation of the unsymmetrical aminals of type **3** postulated in Scheme 1 has been performed in the special case of 9*H*-carbazole[11] (**5a**). Thus, the treatment of a THF solution of **5a** with MeLi (1.1 equiv, 1.6 M in Et_2O, −78 °C, 30 min) provided the corresponding lithium amide, which was added to the iminium trifluoroacetate (**1**), generated

Scheme 1. Preparation of Tertiary Amines of Type 8 by Cleavage of Mixed Aminals of Type 3 and Subsequent Reaction with Organometallic Reagents of Type 7



by the addition of TFAA (1.0 equiv) to TMDAM (**2**; 1.0 equiv, CH_2Cl_2, 0 °C, 15 min). This resulted in the clean formation of the mixed aminal **3a**,[12] which was in this first experiment isolated after a basic workup in 86% yield (NMR analysis showed that no disproportionation has occurred). The reaction of the aminal (**3a**) with TFAA (1.0 equiv, CH_2Cl_2, −78 °C, 15 min) led selectively to a new iminium trifluoroacetate (**6a**) which was treated with the benzylic zinc reagent[13] **7a** in THF furnishing the expected tertiary amine **8a** in 52% yield (45% overall yield in this two-step procedure).[14] To avoid the isolation of the sensitive mixed aminal (**3a**), a convenient one-pot procedure was developed, allowing the isolation of the tertiary amine **8a** in 61% yield (Scheme 2).

This one-pot procedure proved to be general and a range of functionalized amines of type **5** as well as a variety of benzylic

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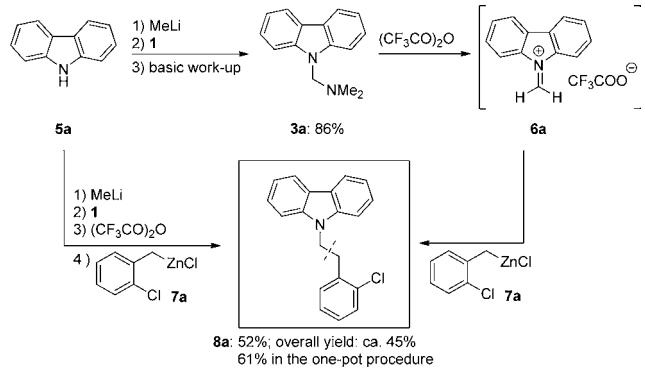
Table 1. Phenethylamines (8), Benzylamines (9), and Homoallylic Amines (10) Obtained by the One-Pot Procedure of Amines of Type 5 with Various Zinc Reagents of Type 7

entry	amine	zinc reagent[a]	product[b],[c]
1	**5b**	**7a**	**8b:** 92%
2	**5c**	**7a**	**8c**: 77%
3	**5d**	**7b**	**8d**: 82%
4	**5e**	**7c**	**8e**: 72%
5	**5f**	**7d**	**8f**: 72%, (68%)[d]
6	**5g**	**7e**	**8g**: 62%
7	**5h**	**7f**	**8h**: 79%
8	**5i**	**7g**	**9a**: 66%
9	**5j**	**7h**	**10a**: 76%

[a]The concentration of the zinc reagent was determined by iodometric titration. [b]Isolated yield of analytically pure product. [c]The reaction was performed on a 1 mmol scale. [d]The reaction was performed on a 10 mmol scale.

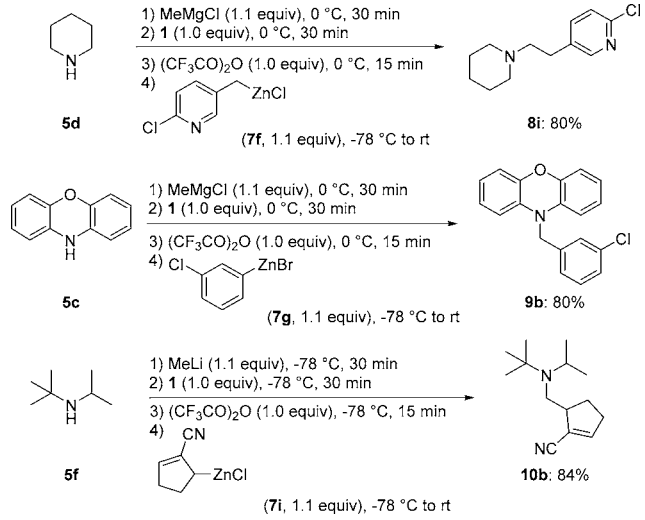
Scheme 2. Preparation of the Mixed Aminal 3a and Subsequent Conversion to the Tertiary Amine 8a



zinc reagents[13] (**7a**–**7e**) were used, leading to various phenethylamines (**8b**–**8g**) in 62–92% overall yield (Table 1, entries 1–6). The preparation of **8f** was successfully performed on gram-scale (72% yield on a 1 mmol scale compared to 68% yield on a 10 mmol scale, entry 5). Phenethylamines are common targets in medicinal chemistry and have found many applications in neuropsychopharmacology.[15]

Interestingly, heterocyclic benzylic zinc reagents[6] such as ((6-chloropyridin-3-yl)methyl)zinc chloride (**7f**) provided an entry to heterocyclic phenethylamines such as **8h** (entry 6) and **8i** (Scheme 3). Other classes of zinc reagents[16] were successfully

Scheme 3. One-Pot Procedure for the Generation of Tertiary Amines of Type 8–10 by Using Benzylic, Aryl, and Allylic Zinc Reagents



used in this homologative synthesis of tertiary amines. Thus, the aminomethylation of the arylzinc bromide (**7g**) with indoline (**5i**) or phenoxazine (**5c**) provided the benzylamines **9a** (entry 8) and **9b** (Scheme 3) in 66–80% yield. Also, functionalized allylic zinc reagents[17] such as cyclohex-2-en-1-ylzinc bromide (**7h**) or the cyano-functionalized[18] (2-cyanocyclopent-2-en-1-yl)zinc chloride (**7i**) were added to iminium ions of type 6, generated from the two amines 1-(3-fluorophenyl)-*N*-methylmethanamine (**5j**) and the sterically hindered aliphatic amine **5f**, furnishing the expected homoallylic amines **10a** (entry 9) and **10b** (Scheme 3) in 76–84% yield.

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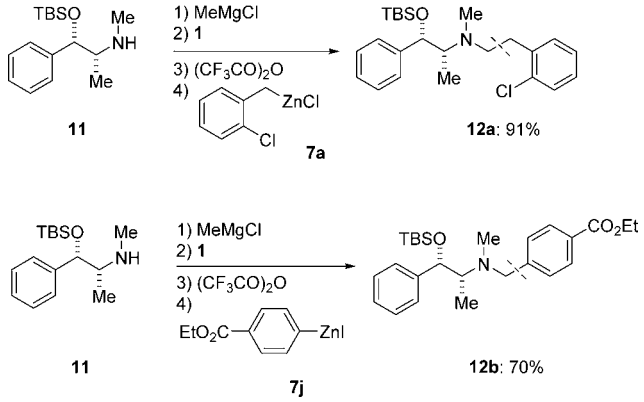
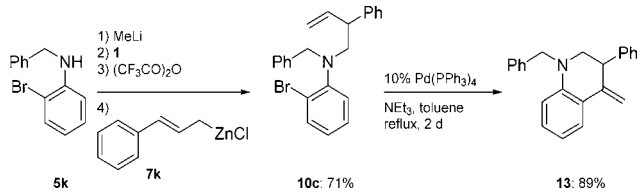
Ephedrine has found several pharmaceutical applications and is especially valuable for the treatment of obesity.[19] Our homologative amination procedure allows conversion of the (+)-ephedrine derivative **11** to the benzylic and phenethylic amines **12a–b** in 70–91% yield (Scheme 4).

Scheme 4. Homologation of the (+)-Ephedrine Derivative 11 into the Corresponding Tertiary Amines of Type 12



The high functional group tolerance of this procedure enabled the synthesis of functionalized precursors suitable for cyclization reactions. This was demonstrated in the homologation of the amine **5k**, which led to an intermediate iminium ion that reacted regioselectively with cinnamylzinc chloride (**7k**) to the polyfunctional aniline **10c** in 71% yield. A subsequent Heck cyclization[20] led selectively to the exomethylene quinolidine (**13**) in 89% yield (Scheme 5).

Scheme 5. Heck Reaction of the Aniline Derivative 10c, Which Was Obtained by the One-Pot Reaction of Aniline (5k) and Cinnamylzinc Chloride (7k)



Finally, aryl and heteroaryl Grignard reagents[21] were used in this one-pot homologative amination, furnishing highly functionalized benzylamines. Thus, piperidine (**5d**) and phenoxazine (**5c**) were converted to the corresponding benzylamines **9c** and **9b** in 76–77% yield, using the Grignard reagents **7l** and **7m** (Table 2, entries 1–2). Also pyridin-3-ylmagnesium bromide (**7n**) provided the corresponding heterocyclic amines (**9d-9e**) in 70–71% yield (entries 3–4). Sterically hindered tertiary amines are often difficult to prepare by conventional methods.[22] Using this one-pot reaction, *tert*-butylisopropylamine (**5f**) reacted with (2,4-dimethoxypyrimidin-5-yl)magnesium bromide (**7o**) furnishing the sterically hindered tertiary amine (**9f**) in 61% yield.

In summary, we have reported a general synthesis of new mixed aminals using Tietze's iminium salt. Their treatment with TFAA provided an entry to new polyfunctional iminium salts, which were trapped by numerous zinc and magnesium organometallics leading to a range of valuable amines using a convenient one-pot procedure. This reaction sequence allowed the preparation of complex amines, including biorelevant phenethylamines and ephedrine derivatives as well as a cyclization precursor, leading to the quinolidine scaffold. Further applications of this method are currently underway in our laboratories.

Table 2. Products of Type 9 Obtained by the One-Pot Procedure of Amines of Type 5 with Various Grignard Reagents of Type 7

entry	amine	Grignard reagent[b]	product[a]
1	**5d**	**7l**	**9c**: 76%
2	**5c**	**7m**	**9b**: 77%
3	**5l**	**7n**	**9d**: 71%
4	**5m**	**7n**	**9e**: 70%
5	**5f**	**7o**	**9f**: 61%

[a]Isolated yield of analytically pure product. [b]The concentration of the Grignard reagent was determined by iodometric titration.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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