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A simple one-pot procedure for the iminium salt formation: an efficient route to β-arylethylamines

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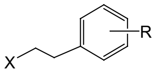
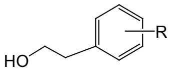
Abstract—A practical and highly efficient process for the preparation of β-arylethylamines **7** was developed. Benzylic organozinc compounds **10** were reacted with the iminium salts **9** generated in situ from the amine salt **8** and paraformaldehyde in one pot and in a polar and aprotic solvent, such as NMP. A variety of the β-arylethylamines were prepared in 43–91% yields.

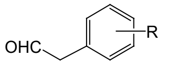
Development of a practical and efficient procedure for the β-arylethylamines **7** has been the focus of several recent studies[1] because they are the common subunit of a large variety of biologically active compounds.[2] The most common syntheses of the β-arylethylamines **7** are the N-alkylation reactions of the amines with the corresponding halides **1**[3] or activated alcohols **2**.[4] The main drawbacks of this approach are that a substantial amount of quaternary amine salt could be produced as well as a styrene by-product formed via E_2 elimination.[2e] Another common method for β-arylethylamines **7** is the reductive amination reaction of the corresponding aldehydes **3**.[5]



1: X = Br, Cl, I



2a: R=2-Br
2b: R=2-i-Pr, 3-Me



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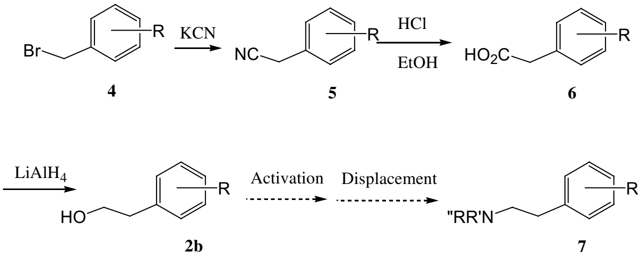
Although these approaches appear straightforward, multiple steps are often required when the precursor halides, alcohols or aldehydes have some degree of structural complexity. For example, both alcohols **2a** and **2b** were obtained from the corresponding benzyl bromide[6] after undergoing multi-step transformations to achieve a one-carbon homologation. Specifically, for the preparation of **2b**, the bromides **4** was reacted with KCN to obtain nitrile **5**, which was hydrolyzed to afford the acid **6**, and reduction of **6** led to **2b**. Conversion of **2b** to the amines **7** would require two additional steps of activation and displacement (Scheme 1). It should also be noted that the reductive amination process would require the preparation of aryl-acetaldehyde precursors, which were often difficult to prepare due to their poor stability.[7]

The most recent advancement for the preparation of the β-arylethylamines **7** was reported by Hartwig and coworkers.[1a,b] They achieved the anti-Markovnikov hydroamination of vinylarenes via the rhodium or ruthenium catalyzed reactions.

The above-mentioned methodologies for the β-arylethylamines **7** all involve introduction of amines to the



Scheme 1.

Keywords: β-Arylethylamines; Iminium salt; Mannich reaction.

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corresponding pre-established two-carbon side unit. On the other hand, direct one-carbon homologation and concurrent introduction of amine functionality from the benzylic organometallic and Mannich reagents could provide an attractive alternate route for the β-arylethylamines **7**. In fact, this approach to β-arylethylamines **7** has not been well recognized.[8] Herein, we would like to report a highly efficient procedure for the preparation of the β-arylethylamines **7** via a one-pot direct α-aminomethylation of the benzylic organozinc reagents **10** with the iminium **9** generated in situ.

The Mannich reaction is one of the most important methods for the α-aminomethylation of acidic CH compounds.[9] In practice, enolizable carbonyl compounds serving as the acidic CH substrate are heated with aqueous formaldehyde and an amine hydrochloride in a protic solvent to produce the β-aminocarbonyl compound. One of the limitations of these reaction conditions is the use of formaldehyde[10] in an aqueous media. Recently, significant improvements have been made in the field,[11] the key success has come from the use of pre-formed Mannich reagents. For example, iminium salts can be prepared by cleavage of aminals with acetyl chloride, iodotrimethylsilane or trifluoroacetic anhydride;[12] by cleavage of aminol ethers with trichloromethylsilane or chlorotrimethylsilane[13] in an aprotic solvent. The availability of these pre-formed Mannich reagents having good electrophilicity in aprotic solvents allowed for the use of more reactive nucleophiles such as enolates, Grignard and organozinc reagents.[8]

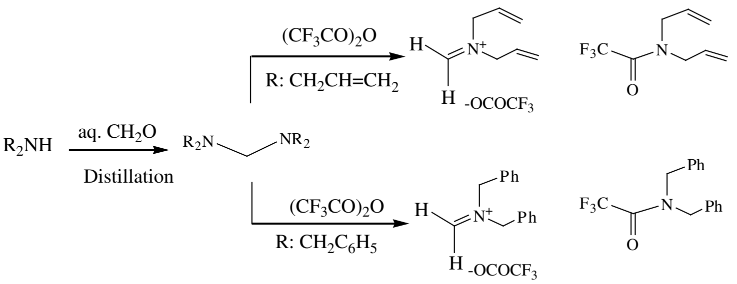
The main disadvantages involved in the synthesis of pre-formed Mannich reagents are that it requires an additional synthetic step to prepare the aminal or aminol ether and the reagents are typically distilled (Scheme 2).[14] In the case when aminal was used,[8] 1 equiv of amine is consumed to form the amide (Scheme 2), wasting 1 equiv of amine. It is undesirable when a valuable amine such as chiral amine is used.

We have now demonstrated that the iminium reagents can be generated efficiently in a single step under the conditions compatible with the organozinc reagents, by simply reacting the amine salt (HCl, CF_3CO_2H) and paraformaldehyde in a polar and aprotic solvent such as NMP. The iminium reagents generated can be used directly to react with organozinc reagents under mild conditions, thus further extending the scope of the application of the Mannich reaction.

A variety of β-arylethylamines **7** were prepared from the reaction of the organozinc reagent **10** and the Mannich reagents **9** generated in situ (Table 1, Scheme 3). The organozinc reagents are readily accessible by direct insertion of zinc[15] to the readily available benzyl bromides, and in fact, many benzylic organozinc reagents are commercially available. The Mannich reagents were typically prepared by heating a mixture of 1 equiv of amine salt (HCl, CF_3CO_2H) and 1.2–2.0 equiv of paraformaldehyde in a polar aprotic solvent, such as NMP at 40–60 °C for >10 h. Several other polar aprotic solvents, such as DMF, DMA, DMSO and CH_3CN could also be used to generate the Mannich reagents. The resulting reaction mixture was used directly without further processing. The Mannich reagents obtained from either chloride or trifluoroacetate salts produced similar results in the subsequent reaction with the organozinc reagents, although when the trifluoroacetate salt was used, the Mannich reagents could be prepared at lower temperatures (∼40 °C). Typically, the reactions between the organozinc reagents and the Mannich reagents were carried out at ambient temperature and reached completion within 10 min to produce the β-arylethylamines **7**. When the bulky amine, 2,2,6,6-tetramethylpiperidine, was used in the reaction (entry 15), a lower yield was obtained, which presumably is caused by the steric hindrance of the amine.

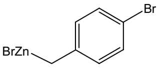
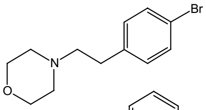
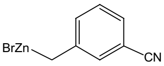
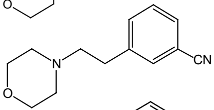
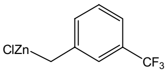
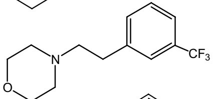
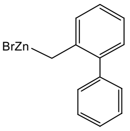
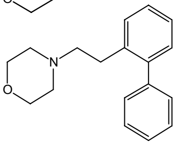
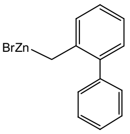
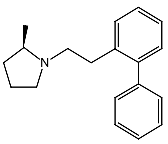
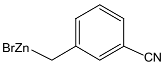
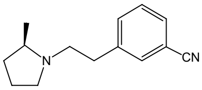
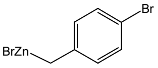
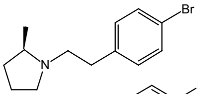
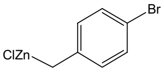
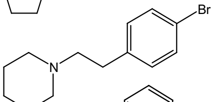
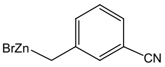
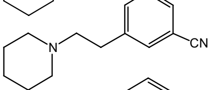
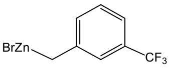
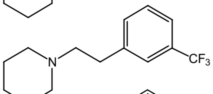
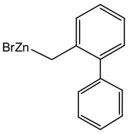
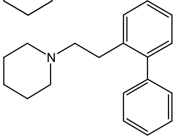
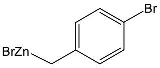
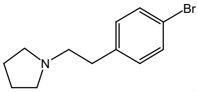
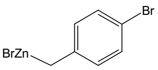
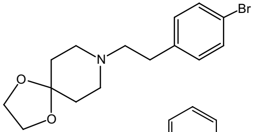
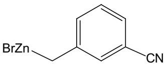
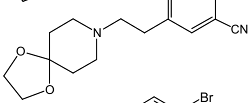
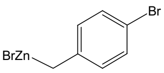
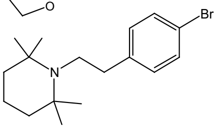
It is noteworthy that when a chiral amine, *R*-2-methylpyrrolidine, was used in the synthesis of β-arylethylamines **7e–g**, no racemization occurred throughout the process. The enantiomeric purities of the products are consistent with the enantiomeric purity of the starting amine, *R*-2-methylpyrrolidine. Chiral HPLC analysis was used to determine the enantiomeric purities of the β-arylethylamines products **7e–g**, while the chiral derivatization using Cbz valine anhydride to prepare the diastereomeric derivatives was used to determine the enantiomeric purity of the starting material, *R*-2-methylpyrrolidine.

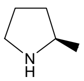
The major by-product formed in the reaction was from hydrolysis of the corresponding benzylic organozinc reagents. All other minor by-products were also neutral species. All the by-products were easily removed from the desired amine product by an acid/base extractive work-up procedure. Thus, analytically pure β-arylethylamines **7** can be obtained without the need of column chromatographic purification. It should be noted that HPLC analysis of the aqueous washes indicated the loss



Scheme 2.

Table 1. Preparation of the terminal amines

Entry	Organozinc reagent	Amine	Product type		Yield[a] (%)
1		**8d**		**7a**	83
2		**8d**		**7b**	87
3		**8d**		**7c**[1a]	91
4		**8d**		**7d**	86
5		**8a**		**7e**	81
6		**8a**		**7f**	73
7		**8a**		**7g**	68
8		**8b**		**7h**	70
9		**8b**		**7i**	70
10		**8b**		**7j**	71
11		**8b**		**7k**	77
12		**8c**		**7l**[2c]	66
13		**8e**		**7m**	65
14		**8e**		**7n**	59
15		**8f**		**7o**	43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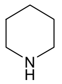
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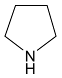
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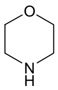
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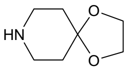
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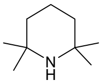
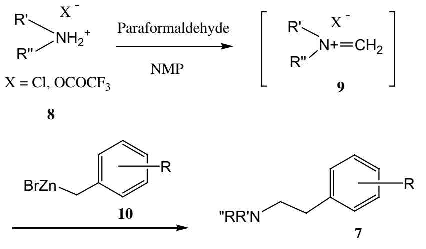

8f

[a] The HPLC assay yields of the reaction mixture were determined using quantitative HPLC analysis by comparison to a know amount of analytical pure reference standards. The yields were not optimized.



Scheme 3.

of product (15–20%) during work-up. Further optimization of the work-up procedure could reduce the product losses.

The good reactivity exhibited by the Mannich reagents generated in situ directly from paraformaldehyde and the amine salts coupled with the simplicity of the isolation and purification procedure provide a viable synthesis for the β-arylethylamines **7**. The reactions were carried out under mild conditions and they are compatible with a variety of functional groups such as bromo, nitrile and acetal, all of which can be further functionalized to obtain structurally more diverse β-arylethylamines **7**.

In conclusion, we have demonstrated a practical and efficient process for the preparation of various β-arylethylamines **7** containing a wide range of substitution patterns under mild reaction conditions from readily accessible benzyl organozinc reagents and easily prepared Mannich reagents. The methodology should be easily applicable to a large number of biologically active compounds contain the subunit of β-arylethylamines. The process is highlighted by the development of a single-step procedure to generate the pre-formed Mannich reagents in situ. It further extends the spectrum of the application of the Mannich reaction.

Supplementary data

The supplementary data is available online with the paper in ScienceDirect. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.027.

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