

An efficient and operationally convenient general synthesis of tertiary amines by direct alkylation of secondary amines with alkyl halides in the presence of Huenig's base

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Dedicated to Professor Eusebio Juaristi on the occasion of his 55th birthday

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Abstract

A general method for the direct formation of tertiary amines via direct N-alkylation of secondary amines by alkyl halides in acetonitrile in the presence of Hunig's base is reported. In contrast to methods previously reported in the literature, this procedure is highly functional group tolerant and employs operationally convenient conditions in the absence of transition metal catalysts or solid supports and without formation of the undesired quaternary ammonium salt.

Keywords: Tertiary amines, alkylation, Huenig's base, operationally convenient conditions

Introduction

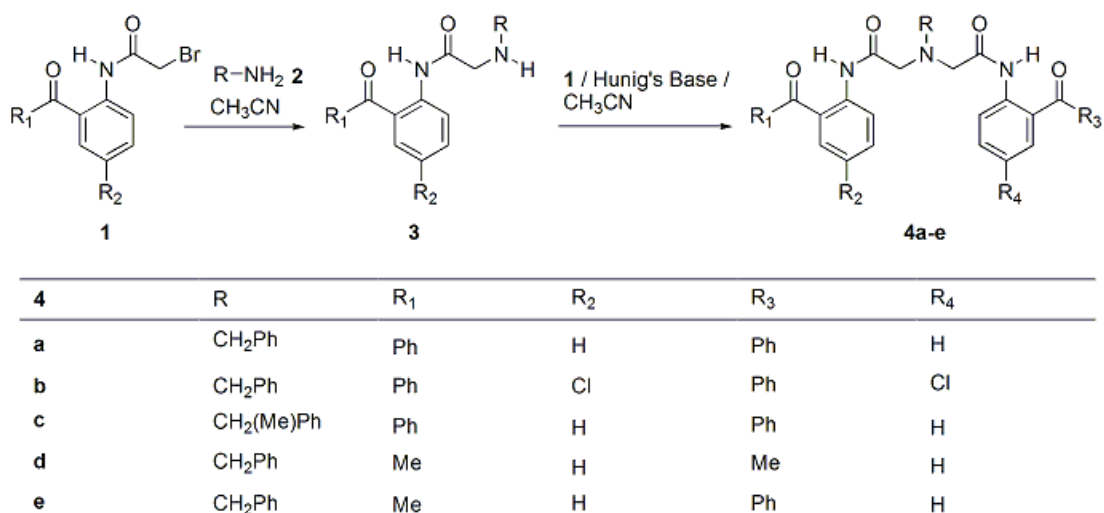
Amines are one of the most common structural features of naturally occurring biologically active compounds and are widely used throughout the chemical industry as basic intermediates to prepare fine chemicals, pharmaceuticals, and agrochemicals.¹ Due to their unique biological properties, amines have played an important role in chemotherapeutic approaches to a variety of diseases.² As a result, the development of new synthetic routes to these compounds has stimulated constant interest and has been the focus of many research groups over the years. From a methodological standpoint the direct alkylation of secondary amines with alkyl halides is the most straight-forward method for the synthesis of tertiary amines.³ However, this method on a practical basis has been somewhat limited since direct N-alkylation of secondary amines often results in the formation of the quaternary ammonium salts and a mixture of the desired tertiary amine and the starting secondary amine.³⁻⁵ In an attempt to address some of these issues, Varma et al., recently reported a method for the direct formation of unfunctionalized tertiary amines via N-alkylation of primary or secondary amines by alkyl halides in aqueous media using microwave irradiation.⁴ This method, while relatively environmentally friendly, requires the use of

specialized microwave equipment and the use of strong inorganic bases, which in the presence of base sensitive functional groups, can lead to undesired results as well as hydrolysis of the corresponding alkyl halide. Another procedure presented in the literature describes the N-alkylation of secondary amines via their metal amides with alkyl halides in the presence of excess triethylamine.⁵ This method, while useful is potentially problematic in that the use of metal hydrides presents a problem for the direct synthesis of highly functionalized tertiary amines, particularly if the secondary amine or alkyl halide contains acidic functional groups.

Several alternative methods to direct alkylation have also been reported. Among these methods is the use of solid phase supports.⁶ While these methods are apparently useful for constructing libraries of secondary and tertiary amines they are obviously not practical for large scale preparations. Other alternative and generalized methods include reductive amination⁷, reductive and catalytic alkylation⁸, Mannich and Petasis reactions⁹, and metal induced amination of alkenes and alkynes.¹⁰ These methods, while useful suffer from specific limitations including low catalytic efficiency, a relatively narrow range of usable substrates and limited functional group tolerance.

Results and Discussion

In the course of one of our research projects we needed an expedient and preparative scale method for preparing tertiary amines of the general formula **4a-e** shown in Scheme 1. The synthetic route we envisioned for preparation of these compounds included a two step alkylation of primary amine **2** with alkyl halide **1** through intermediate secondary amine **3**. We found that the first step could be efficiently conducted in acetonitrile at room temperature using 3.0 mol eq. excess of primary amine **2**. Under these conditions secondary amines **3** were cleanly obtained in greater than 95% chemical yields. In contrast, the second step, alkylation of amines **3** with alkyl halides **1**, was found to be quite problematic. Thus, attempts to apply the literature methods for the direct synthesis of tertiary amines utilizing our highly functionalized alkyl halides and secondary amines were unsuccessful. Reported procedures using aqueous media and microwave irradiation as well as metal amides were found to be incompatible with our substrates do to the rapid hydrolysis of alkyl halides **1** under strongly basic conditions and due to the presence of the highly acidic N-H protons of the amide moieties. Unfortunately, these methods also led to the formation of the undesired quaternary ammonium salt as observed by the formation of a highly insoluble yellow precipitate as the major reaction product.



Scheme 1. Synthesis of tertiary amines **4a-e**.

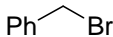
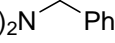
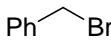
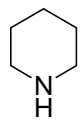
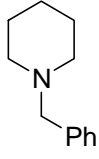
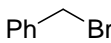
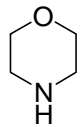
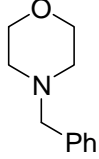
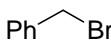

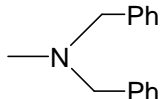
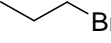
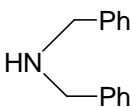
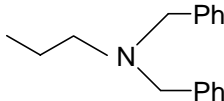
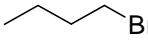
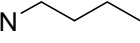
Based on these less than desirable results, a series of reaction conditions were attempted in order to facilitate the direct alkylation. A variety of bases were screened including potassium carbonate, sodium hydroxide, and potassium hydroxide. Different solvents were also evaluated including methylene chloride, acetonitrile, and biphasic systems that incorporated the use of tetrabutylammonium bromide as a phase transfer catalyst. Unfortunately, all of the reaction conditions examined led to the formation of various byproducts, including the unwanted quaternary ammonium salt, but very little of the desired tertiary amine product.

Eventually, after additional repeated attempts our persistence finally led to success. Unexpectedly we found that in the presence of 1.5 mol equivalents of *N,N*-diisopropylethylamine (Hunig's base) the reaction proceeded cleanly to tertiary amine **4a** in almost quantitative yield. Following these remarkable results this procedure was repeated using various secondary amines **3** and alkyl halides **1** containing benzophenone and/or highly C-H acidic acetophenone moieties. In all attempted cases the reactions were complete, according to TLC, in approximately 24 hours in acetonitrile at 60 – 70 °C using ratios of secondary amine, alkyl halide, and Hunig's base at 1.0, 1.1, and 1.5, respectively. According to crude ¹H NMR the yield of the desired tertiary amine products was more than 90%. Tertiary amines **4a-e** were obtained in analytically pure form via column chromatography on silica gel.

As a result of these findings we also decided to explore the versatility and generality of this method for preparing a variety of unfunctionalized tertiary amines. Since alkyl halides **1** (Scheme 1) are highly complex polyfunctional alkyl halides we envisioned that this method would also be applicable to prepare less functionalized amines and would be superior and more convenient to use than existing literature procedures. For representative examples we chose direct benzylation of symmetrical acyclic (entry 1), cyclic (entry 2), heterocyclic (entry 3), and unsymmetrical substituted derivatives (entry 4) all of which were reacted using our standard conditions at room temperature to give the target tertiary amines in high chemical yields as

shown in Table 1. In addition, we also demonstrated the applicability of this method for the alkylation of secondary amines bearing benzyl and *n*-alkyl substituents with normal alkyl halides (entries 5 and 6) to yield the target tertiary amines in high chemical yields without the formation of the undesired quaternary ammonium salt.

Table 1. Tertiary amines synthesized via direct N-alkylation of secondary amines with alkyl halides in the presence of Hunig's base ^a

Entry	Alkyl Halide	Amine	Product Amine	Yields ^b (%)	Time ^c
1		(<i>n</i> -Butyl) ₂ NH	(<i>n</i> -Butyl) ₂ N 	> 90	3 hrs
2				91	2 hrs
3				> 90	2 hrs
4				> 90	3 hrs
5				> 90	3 hrs
6		(<i>n</i> -Hexyl) ₂ NH	(<i>n</i> -Hexyl) ₂ N 	> 90	24 hrs ^d

^a General Reaction Conditions: 1.0 eq. secondary amine, 1.1 eq. alkyl halide, 1.5 eq. Hunig's base, acetonitrile, rt.

^b Yields corresponding to the content of the target product in the crude reaction mixture, as estimated by ¹H NMR. Compounds were obtained in analytically pure form via column chromatography.

^c Reaction progress was monitored by TLC.

^d Reaction progress was monitored by ¹H NMR.

The unique role of Hunig's base in preventing the quaternization is not clear. However, we can assume that this non-nucleophilic strong base forms a salt with the released hydrogen halide allowing the reaction to proceed under mild kinetically controlled conditions. In which case, the reaction of the secondary amine with the starting alkyl halide is faster than the reaction of the tertiary amine product with the starting alkyl halide.

In summary, we have demonstrated an efficient and general synthesis of tertiary amines by direct N-alkylation of secondary amines with alkyl halides in the presence of Huenig's base. The reaction is applicable to aliphatic halides and aliphatic amines and is suitable for use in the presence of other functional groups without the need for protecting them. Short reaction times, high product yields, scalability, absence of quaternary ammonium salt formation and operationally convenient conditions are some of the advantages that render this method favorable over other previously reported methods.

Experimental Section

General Procedures. Secondary amine (0.500 g, 1 mol eq.), *N,N*-diisopropylethylamine (1.5 mol eq.), alkyl halide (1.1 mol eq.) and 10 mL acetonitrile were placed in a round bottom flask and stirred at room temperature under nitrogen. After completion of the reaction (monitored by TLC) the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in 5 mL of CH₂Cl₂ and washed with 5 mL of distilled water. The aqueous layer was washed with 3 x 5 mL fractions of CH₂Cl₂. The collected organic fractions were dried over MgSO₄ and the solvent was removed under reduced pressure to yield the crude product.

Compound characterization. ¹H NMR spectra acquired on a Varian 300 NMR spectrometer (300 MHz) at 295K in CDCl₃ containing TMS as internal standard. ¹H NMR spectra for the reported compounds were consistent with literature data.^{3a,3d,11a-e}

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