Synthesis of N-Aminated Salts of Aliphatic tert-Amines, (Trialkyl)-amidines, and (Pentaalkyl)guanidines by Electrophilic Amination in an Ethereal Solvent

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The electrophilic amination of nitrogen-based nucleophiles, including strong organic bases, was conducted in an Et2O solvent using O-(mesitylenesulfonyl)hydroxylamine. Aliphatic tert-amines and N,N,N’-(trialkyl)amidines rapidly formed precipitates of the corresponding aminated salts in high yields. The amination of the highly basic and sterically hindered N,N,N’-N”,N”-(pentaalkyl)guanidines was achieved under modified conditions, although the yields were moderate because of a competing side reaction caused by the acid–base equilibrium.

Key words: electrophilic amination; strong organic base; O-(mesitylenesulfonyl)hydroxylamine

Introduction

The electrophilic amination (EA) of nucleophilic nitrogen atoms yields molecules containing a N–N bond. In particular, the EA of aliphatic tert-amines and iminic compounds, such as pyridines, is an important transformation reaction. This is because the resulting N-aminated products are useful precursors of amine imide derivatives, i.e., nitrogen ylides, which exhibit unique reactivities and properties.1–5 Thus far, various reagents and routes for EA reactions are being developed6–9 to overcome the drawbacks associated with the traditional acid–base equilibrium.

MSH (12,13) is a commonly used EA reagent, whose utility was immediately before use). O-(mesitylenesulfonyl)hydroxylamine (MSH)12,13 is a commonly used EA reagent, whose utility was established by Tamura et al.14–17 MSH offers the advantages of high reactivity and sufficient solubility in common organic solvents. Typically, the EA of tert-amines with MSH is conducted by mixing equimolar amounts of these compounds in CH2Cl2 at 0 °C.15,16,18 Subsequently, the precipitate is filtered to afford a crude N-aminoammonium salt. Occasionally, the addition of Et2O to the reaction mixture was required to facilitate the precipitation. Thereafter, the crude solid is recrystallized to obtain pure N-aminoammonium mesitylenesulfonate.

Herein, we report a facile procedure for the EA of aliphatic tert-amines with MSH using Et2O as the solvent. The precipitation of the corresponding N-aminoammonium salts occurred rapidly, owing to their low solubility in Et2O. Further, we describe previously unknown MSH-mediated EA reactions involving strong, nitrogen-containing organic bases.

Results and Discussion

The EA of N-methylpyrrolidine (1a), N-methylpiperidine (1b), and quinuclidine (1c) (1.05 equivalent (equiv) each) was conducted using freshly recrystallized MSH13 (1 equiv) in Et2O at 0 °C (Table 1, entries 1–3). After filtration, compounds 2a–c were obtained in excellent yields (97–100%) and high purity. With Et2O as the solvent, the experimental procedure was simplified and the yields of 2a–c were improved by 8–15%, compared with the reported yields in CH2Cl2 (88, 85, and 91%, respectively, after recrystallization).18 Following this practical procedure, we conducted the EA reactions of N-methylmorpholine (1d), N-ethylpiperidine (1e), trimethylamine (1f), and triethylamine (1g) to obtain the corresponding N-aminoammonium salts (2d–g) in 89–99% yields (Table 1, entries 4–7). The resulting mesitylenesulfonate salts (2d–g) are new compounds, while the N-aminoammonium cations paired with different counter anions have been reported.9,10,20,21

Thereafter, we focused on the EA of the iminic nitrogen atoms, whose basicity was enhanced by the conjugation with a dialkylamino group (Table 2). p-(Pyrrolidino)-pyridine (3a, entry 1), whose basicity (pK\text{aH} in MeCN: 18.4)22 is comparable to that of 1g (pK\text{aH} in MeCN: 18.8),22 afforded the aminated salt, 4a, in 92% yield, under the reaction conditions listed in Table 1. N,N,N’- (Trialkyl)amidines, such as 1,5-diazabicyclo[4.3.0]non-5-ene (3b, entry 2) and 1,8-diazabicyclo[5.4.0]undec-7-ene (3c, entry 3), are well-known strong organic bases with high basicities (pK\text{aH} in MeCN = 23.9 and 24.3 for 3b and 3c, respectively).22 However, minimal attention has been paid to the EA of strong organic bases. To the best of our knowledge, only two reports have described the EA of N,N,N’-(trialkyl)amidines: chloramine-mediated EA for 3b23 or a series of 5-membered cyclic amidines.24 Our EA procedure using MSH in Et2O effortlessly afforded 4b and 4c from 3b and 3c, respectively, in 95–97% yields (Table 2, entries 2–3).

Next, we investigated the unprecedented EA reactions of N,N,N’,N”,N”- (pentaalkyl)guanidines25 (Chart 1). Barton’s base (3d, pK\text{aH} in MeCN: 23.6)27 and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (3e, pK\text{aH} in MeCN: 25.5),22 both of which were commercially sourced, were selected as the starting materials. When 3d was treated with MSH under the standard EA conditions, no precipitation occurred, unlike the case in the reactions described in Tables 1 and 2. The 1H-NMR spectrum of the crude product, which was obtained by concentrating the reaction mixture, suggests that a significant amount of the protonated starting mate-

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rial (3d–H⁺) was formed along with the desired aminated salt (approx. 1 : 1 ratio). The EA of 3d was conducted at –78 °C to achieve improved selectivity (Chart 1A). However, a similar product ratio was achieved. After purification, the aminated salt (4d/Cl⁻) and the protonated salt (3d–H⁺/Cl⁻) were obtained in 31 and 32% yields, respectively. These compounds were isolated as chloride salts because anion exchange was necessary during the purification process, where 4d/Cl⁻ and 3d–H⁺/Cl⁻ were separated by preparative thin layer ion-pair.

Table 1. Electrophilic Amination of Aliphatic tert-Amines Using MSH in Et₂O

| Entry | tert-Amine (1) | N-Aminoammonium salt (2) | Yield (%) |
|-------|----------------|--------------------------|-----------|
| 1     | N Me           | MesSO₃, N NH₂             | 97        |
| 2     | N Me           | MesSO₃, N NH₂             | 100       |
| 3     | N Me           | MesSO₃, N NH₂             | 99        |
| 4     | N Me           | MesSO₃, N NH₂             | 95        |
| 5     | N Me           | MesSO₃, N NH₂             | 99        |
| 6     | N Me           | MesSO₃, N NH₂             | 89        |
| 7     | N Me           | MesSO₃, N NH₂             | 96        |

Table 2. Electrophilic Amination of Iminic Nitrogen Atoms Conjugated with a Dialkylamino Group Using MSH in Et₂O

| Entry | Nucleophile (3) | Aminated salt (4) | Yield (%) |
|-------|----------------|-------------------|-----------|
| 1     |                | 3a                | 92        |
| 2     |                | 3b                | 95        |
| 3     |                | 3c                | 97        |

Chart 1. (A) Electrophilic Amination of 3d Using MSH; (B) Anion Exchange of 4d/Cl⁻; (C) Electrophilic Amination of 3e Using MSH

Chart 2. Plausible Reaction Mechanism for the Formation of 3d–H⁺
to be 39 : 18 : 1.31). Although the methylation rate constant of the iminic nitrogen atom sites in that of 3d. The relative rate constants for the methylation at K3b and K3c in MeCN: 23.9–24.3) to that of 3d and hydrazine. In contrast to the reaction mixture could be further disproportionated to N2+ (1.2 equiv.) and MSH (1 equiv.) at 0°C afforded the N-aminated salt 4f (22–34%) as a precipitate in 82% yield. The long reaction time (3 h) was attributed to the low basicity of 3f (pKαH in MeCN: 12.0).22)

Conclusion
Here, we extended the substrate scope of MSH-mediated EA. The aminated salts of aliphatic tertiary-amines and N,N,N′-(trialkyl)amidines were rapidly precipitated in Et2O. The EA reactions of the sterically hindered N,N,N′,N″-(pentaalkyl)-guanidines were more challenging because of the competing protonation side reaction. Nevertheless, we successfully isolated the corresponding aminated guanidinium salts in moderate yields. The N-aminated salts synthesized in this study will be useful for preparation of new amine imide derivatives.

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Conflict of Interest
The authors declare no conflict of interest.

Supplementary Materials
The online version of this article contains supplementary materials.

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