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.

Tamura et al.¹⁴–¹⁷ demonstrated that a significant amount of the protonated starting material was treated with MSH as the starting materials. When known strong organic bases with high basicities (pKₐ ≈ 18.4–22) were used, the resulting mesitylenesulfonate salts (2d–g) were new compounds, while the N-aminoanion reactions cations paired with different counter anions have been reported.⁹,¹⁰,²¹,²²

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 (pKₐ in MeCN: 18.4)²² is comparable to that of 1g (pKₐ 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 (pKₐ 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, pKₐ in MeCN: 23.6)²² and 7-methyl-1,5,7- triazabicyclo[4.4.0]dec-5-ene (3e, pKₐ 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 'H-NMR spectrum of the crude product, which was obtained by concentrating the reaction mixture, suggests that a significant amount of the protonated starting mater-
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...
To be 39:18:1.3. Although the methylation rate constant of the iminic nitrogen atom sites in 3d, the relative rate constants for the methylation at that of K, consistent with the higher nucleophilicities of 3b and 3d (23.6). These results are in MeCN: 23.9–24.3) to that of 3d, this side reaction is shown in Chart 2. The diimide formed in 1A) can be explained similarly. A plausible mechanism for 3e (pK_aH in MeCN: 25.5), 22) which demonstrates the applicability of this reaction to a weak organic base. The reaction between 3f (1.2 equiv.) and MSH (1 equiv.) at 0°C afforded the N-aminated salt 4f (22–24%) as a precipitate in 82% yield. The long reaction time (3h) was attributed to the low basicity of 3f (pK_aH in MeCN: 12.0).22)

Conclusion
Here, we extended the substrate scope of MSH-mediated EA. The aminated salts of aliphatic tert-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.

References

![Chart 3. Electrophilic N-Amination of 3d Using DPH](chart3.png)

![Chart 4. Electrophilic N-Amination of 3f Using MSH in Et2O](chart4.png)

chromatography26,27) using a NaCl-treated silica gel plate (see Supplementary Materials for details). Then, 4d/Cl was converted to 4d/B(C6F5)4 by treating with LiB(C6F5)4 (Chart 1B). This salt was isolated as a monohydrate in 87% yield. The structure of 4d/B(C6F5)4 was confirmed by single crystal X-ray structure analysis (CCDC 2114892, see Supplementary Materials for details). Thereafter, following the EA procedure for 3d, 3e was reacted with MSH to afford the aminated salt, 4e (Chart 1C). In this case, the precipitate formed in the reaction mixture was contaminated by a small amount of a byproduct, which was tentatively assigned as protonated 3e. Pure 4e was obtained in 66% yield after the recrystallization.

When strongly basic carbanions were reacted with the EA reagents, such as MSH and O-(2,4-dinitrophenyl)-hydroxylamine (DPH), the competing protonation of the nucleophiles occurred as a side reaction.28–30) The proposed mechanism for this side reaction involves the deprotonation of the EA reagents by the nucleophile, followed by the decomposition of the EA reagents to afford diimide. Since 3d, a strong base, could deprotonate MSH, the formation of 3d–H+ (Chart 1A) can be explained similarly. A plausible mechanism for this side reaction is shown in Chart 2. The diimide formed in the reaction mixture could be further disproportionated to N2 and hydrazine. In contrast to 3d, 3b and 3c did not afford any protonated byproduct during their EA reactions (entries 2 and 3 in Table 2), irrespective of their comparable basicities (pK_aH in MeCN: 23.9–24.3) to that of 3d (23.6). These results are consistent with the higher nucleophilicities of 3b and 3c than that of 3d. The relative rate constants for the methylation at the iminic nitrogen atom sites in 3b, 3c, and 3d were reported to be 39:18:1.31) Although the methylation rate constant of 3e was 3.4 times higher than that of 3d, the EA of 3e did not afford a very high yield (66%, Chart 1C). This result is attributed to the high basicity of 3e (pK_aH in MeCN: 25.5),22) which facilitated the deprotonation of MSH.

The EA of 3d was further examined using DPH instead of MSH (Chart 3). The results revealed that 4d/Cl was obtained in 49% yield after purification involving chloride anion exchange, although the reaction required a high heating temperature (approx. 75°C in 1,4-dioxane). This result suggests that a mild EA reagent can partially suppress the side reaction caused by the acid–base equilibrium. However, the reaction selectivity was still unsatisfactory, as indicated by the 1H-NMR signals corresponding to 3d–H+ (approx. 30% integral ratio to that of the desired aminated product) in the crude mixture.

In addition to the strong organic bases, quinoline (3f, Chart 4) was subjected to the MSH-mediated EA in Et2O, to demonstrate the applicability of this reaction to a weak organic base. The reaction between 3f (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 (3h) was attributed to the low basicity of 3f (pK_aH in MeCN: 12.0).22)


19) The MSH-mediated EA of a benzimidazole derivative was reported using Et₂O as the solvent. Although the corresponding N-aminated salt was precipitated, recrystallization was required to obtain the pure product in 43% yield. Vinogradova O. V., Krystalyuk O. V., Rudnev M. I., Pozharskii A. F., Kaz’menok V. V., *Chem. Heterocycl. Compd.*, 30, 1182–1186 (1994).


