N-Boc-*O*-Tosyl Hydroxylamine as a Safe and Efficient Nitrogen Source for the N-Amination of Aryl and Alkyl Amines: Electrophilic Amination

Thankappan Baburaj,[a] Sivalingam Thambidurai*[b]

[a] Anthem Biosciences Pvt. Ltd., Bommasandra Industrial Area, Phase I, 49, Canara Bank Road, Bangalore 560 099, India

[b] Department of Industrial Chemistry, Alagappa University, Karaikudi 630 003, India
Fax +91(4565)225202; E-mail: sthambi01@yahoo.co.in

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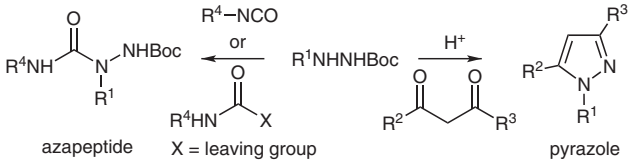
Abstract: β-Boc-protected aryl and alkyl hydrazines, useful intermediates for azapeptides and N-substituted pyrazoles, were synthesized by electrophylic amination methodology, using less energetic *N*-Boc-*O*-tosyl hydroxylamine as an efficient nitrogen source. Also we have demonstrated a two-step, chromatography-free synthesis of *N*-Boc-*O*-tosyl hydroxylamine.

Key words: electrophylic amination, β-Boc-alkylhydrazines, β-Boc-arylhydrazines, *N*-Boc-*O*-tosyl hydroxylamine, azapeptides

Terminal *tert*-butoxycarbonyl (Boc)-protected aryl and alkyl hydrazines are useful intermediates for azapeptides, by reacting it with isocyanates of amino acids or, by activating it as a suitable carbamate derivative, followed by reacting it with amino acids.[1–3] These intermediates are also useful for the synthesis of 1-alkyl or arylpyrazoles by reacting with 1,3-dicarbonyl compounds, after deprotecting with standard reaction conditions[4] (Scheme 1).



Scheme 1 Synthetic applications of β-Boc-hydrazines

To our knowledge direct amination of anilines by electrophylic amination is not well documented, probably because of the poor nucleophilicity of anilines or the inefficiency of available electrophilic aminating agents. Anilines are converted to corresponding *N*-aryl hydrazines mostly by diazotization followed by reducing the resulting diazonium salt by suitable reducing agents[5] such as $SnCl_2$.[6] The tedious workup procedure and isolation of highly polar, water-soluble hydrazines is the major disadvantage of this method. However, N-amination of heterocycles can be achieved by *O*-(diphenylphosphinyl)hydroxylamine,[7] chloramine,[8] or by *O*-arylhydrroxylamines[9] with isolated yields ranging from 45–97%. Oxaziridine derivatives **1**,[10] **2**,[11] and **3**[4] were used as very good reagents for electrophilic amination of alkyl amines and amino acid derivatives. Secondary amines gave good to excellent yields with **1** (Figure 1), whereas in the case of primary amines, the reactive byproduct 4-cyanobenzaldehyde generated from **1** involved in competitive side reaction resulting the formation of unwanted imines as side products, resulting in the loss of isolated yields of required products.[12] In the case of other reagents **2** and **3**, the synthesis of the reagents itself is a multistep synthesis and not efficient in a small scale.

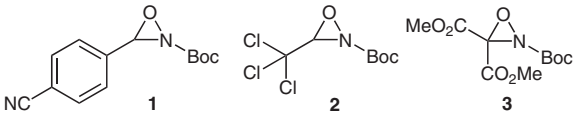


Figure 1 Structures of **1**, **2**, and **3**

In an effort to find a suitable aminating agent, we screened the literature reports, and we could find that most of the derivatives of aminating agent **4** (Figure 2) are not safe to handle because of the unstable or explosive nature, and even some of them can detonate.[13] *N*-Boc-*O*-tosyl hydroxylamine (**5**),[14] has been used as an aminating agent after lithiation (**5a**), as a source of NH-Boc, for the electrophilic amination of Grignard reagents and carbonyl compounds having highly acidic protons.[15] As the synthesis and handling of this protected aminating agent is relatively easy and safe when compared to the hazard involved in the other aminating agents, we felt using **5** for our study towards N-amination.

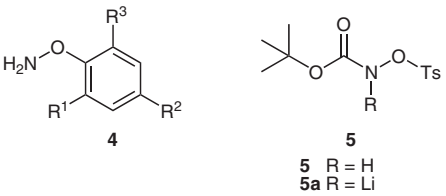


Figure 2 Structures of **4** and **5**

As the initial task towards our study, we have synthesized *N*-Boc hydroxylamine by avoiding *tert*-butyl azidoformate.[14] This hazardous reagent was readily replaced with $(Boc)_2O$ without any difficulty, by treating commercially available cheap aqueous hydroxylamine and $(Boc)_2O$ in the presence of a base.[16] The crude *N*-Boc hydroxylamine obtained was taken as such for tosylation using dichlo-

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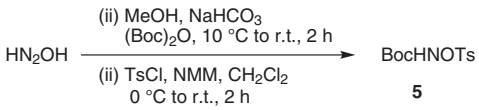
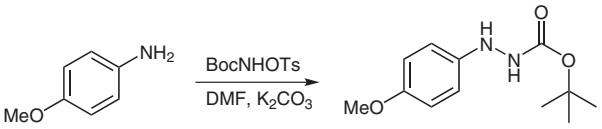
romethane as solvent and *N*-methylmorpholine (NMM) as base at 0 °C, and the residue was purified by recrystallization, to get the pure product **5** as white crystalline solid (Scheme 2).[17] As most of the reported electrophilic aminating agents are potential explosives, we decided to study the safety aspects of **5**, before using it for trials.



Scheme 2 Synthesis of **5**

The differential scanning calorimetry results of **5** showed that the decomposition energy was 215 J/g with an onset temperature of 95 °C, which is much lesser than the decomposition energy of derivatives of **4** (>1200 J/g to ca. 2300 J/g).[18,8a] With this motivating information, we screened the possibility of N-amination of anilines first,[19] and of the various reaction conditions tried, the combination of *p*-anisidine, potassium carbonate and *N*,*N*-dimethylformamide was found to be more efficient (Scheme 3).

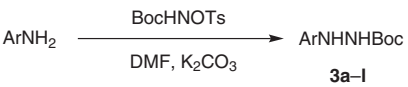


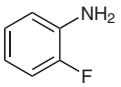
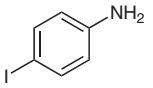
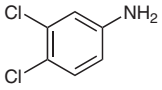
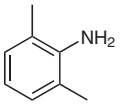
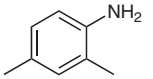
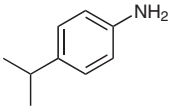
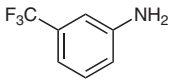
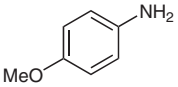
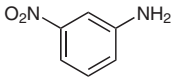
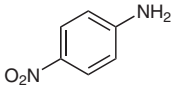
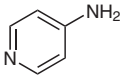
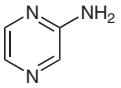
Scheme 3 Electrophilic amination of anilines by **5**

The product was isolated just by adding water into the reaction mixture and by collecting the solid product by filtration.[20] The reactivity of anilines are subject to steric and electronic factors of anilines. In the case of 2,6-dimethylaniline and *p*-nitro aniline the reaction took longer time to complete, and the yields are also slightly lower than other anilines. Heteroaryl amines also afforded the required products with good yields. The presence of a Boc group in **5**, not only facilitated the product formation, but also the isolation of products. The reaction time and yields of various amines studied are reported in Table 1.

To study the reactivity of **5** with aliphatic amines, morpholine was treated with these reaction conditions, and we could observe that the isolated product was contaminated with *N*,*N*-dimethylformamide. When we attempted to remove *N*,*N*-dimethylformamide completely by repeat water wash, we lost sufficient quantity of product. To avoid this, we changed the reaction medium to dichloromethane and aliphatic tertiary amine based bases, of that 4-methylmorpholine was found to be more efficient. Various primary and secondary amines afforded product with excellent yield under these reaction conditions.[21] Benzylamines and heteroarylmethylamines also reacted to give the product in excellent yields (Table 2).

Table 1 Electrophylic Amination of Aryl Amines by **5**

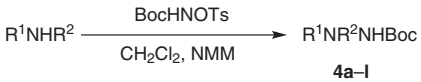


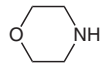
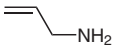
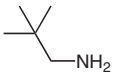
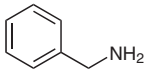
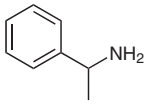
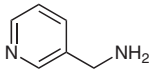
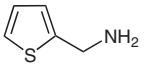
Entry	$ArNH_2$	Product	Time (h)	Yield (%)
1		**3a**	2	84
2		**3b**	2	88
3		**3c**	2	82
4		**3d**	16	68
5		**3e**	3	82
6		**3f**	2	90
7		**3g**	2	85
8		**3h**	2	89
9		**3i**	2	83
10		**3j**	16	72
11		**3k**	2	86
12		**3l**	2	78

In conclusion we demonstrated a very efficient procedure for terminal protected aryl and alkyl hydrazines by electrophilic amination strategy. These protected hydrazines can be used as very good intermediates for aza peptides and other heterocyclic analogues.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Table 2 Electrophylic Amination of Aliphatic Amines by **5**



Entry	R^1NHR^2	Product	Time (h)	Yield (%)
1		**4a**	18	92
2		**4b**	18	88
3		**4c**	18	82
4		**4d**	18	87
5		**4e**	18	85
6		**4f**	18	88
7		**4g**	18	71
8		**4h**	18	86
9		**4i**	18	89
10		**4j**	18	82
11		**4k**	18	87
12		**4l**	18	84

Acknowledgment

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References

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(17) **Typical Procedure for 5**
To a stirred solution of hydroxylamine (25 mL, 40% w/v, 0.3 mol) in MeOH (100 mL) was added $NaHCO_3$ (27.7 g, 0.33 mol) and then $(Boc)_2O$ (72.0 g, 0.33 mol) dropwise over a period of 30 min, by maintaining the reaction temperature at 20–25 °C. After stirring the reaction mixture at 25 °C for 5 h, MeOH was removed under vacuum, and the residue was diluted with H_2O (200 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layer was dried over Na_2SO_4 and concentrated. The crude Boc-hydroxylamine obtained was diluted with CH_2Cl_2 (200 mL), cooled to 0 °C and was added NMM (60.6 g, 0.6 mol) and then tosyl chloride (63 g, 0.33 mol) in CH_2Cl_2 (200 mL), dropwise over a period of 1 h. After stirring at r.t. for 3 h, the reaction mixture was diluted with H_2O (500 mL), and the organic layer was separated, washed with H_2O (250 mL), 5% citric acid solution in H_2O (2 × 100 mL), dried over Na_2SO_4 and concentrated. The resulting residue was crystallized from 20% EtOAc in PE to afford the pure product as white solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 9 H), 2.48 (s, 3 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.61 (s, 1 H), 7.90 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 27.7, 83.8, 129.6, 129.7, 130.7, 146.0, 154.3.
(18) Boyles, D. C.; Curran, T. T.; Parlett, R. V. IV *Org. Process Res. Dev.* **2002**, *6*, 230.
(19) Even though **5** is less energetic compared to other aminating reagents, keeping safety as priority we carried out all reactions and workup at temperatures below 50 °C.
(20) **Typical Procedure for Aryl Amines (Method A)**
To a stirred solution of 4-methoxyaniline (1 g, 8.13 mmol) in DMF (10 ml) was added K_2CO_3 (1.46 g, 10.57 mmol), and the reaction mixture was cooled to ca. 10 °C. To this was added BocNHOTs (2.8 g, 9.76 mmol) and stirred at r.t. for 2 h. Reaction mixture was diluted with H_2O, and the resulting solid was filtered and dried under suction. The dried solid was crystallized from 3% EtOAc in PE to afford the pure product as brown solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 9 H), 3.81 (s, 3 H), 6.68 (br s, 1 H), 6.89 (dd, *J* = 9.0, 2.1 Hz, 2 H), 7.38 (dd, *J* = 9.0, 2.1 Hz, 2 H), 7.44 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.4, 55.5, 81.4, 114.3, 121.8, 130.3, 156.3, 158.5. LC-MS: *m/z* = 239.3 [M + H^+].

(21) **Typical Procedure for Alkyl Amines (Method B)**
To a stirred solution of morpholine (0.5 g, 5.74 mmol) in CH_2Cl_2 (10 mL) was added NMM (0.75 g, 7.46 mmol), and the reaction mixture was cooled to ca. 10 °C and then added BocNHOTs (1.98 g, 6.90 mmol), and the reaction mixture was stirred at r.t. for 18 h. Reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated. The crude obtained was purified by flash column chromatography to get the pure product as yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 9 H), 3.42 (t, *J* = 4.8 Hz, 4 H), 3.70 (t, *J* = 4.8 Hz, 4 H), 6.86 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.3, 43.9, 66.4, 80.4, 159.9. LC-MS: 203.3 [M + H$^+$].