Efficient solventless technique for Boc-protection of hydrazines and amines

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Abstract
A new efficient technique for Boc introduction into hydrazines and amines is reported. The substrate is stirred in molten di-(*tert*-butyl)dicarbonate without any solvent. The method requires neither DMAP nor other catalyst. The scope of the method is demonstrated using several hydrazines and amines.

Keywords: Boc-protection, solventless technique, hydrazines, amines

Introduction

The protecting group strategy has found many applications in preparative organic chemistry. The *tert*-butoxycarbonyl (Boc) group is one of the most frequently used for protection of NH_2 group in different applications. This is particularly important in peptide and amino acid synthesis. The Boc group is orthogonal to benzyloxycarbonyl (Z), 2,2,2-trichloroethyloxycarbonyl (Troc), p-toluenesulfonyl (Tos) and some other well known and useful protecting groups.[1] Furthermore, two Boc groups at the same nitrogen are also orthogonal.[2] The Boc group is not hydrolyzed under basic conditions, is extremely resistant to many other nucleophiles, and is not susceptible toward catalytic hydrogenolysis. On the other hand, several mild and selective cleavage methods for this group are available. All these factors make the Boc group an excellent tool for many purposes.[1]

There are several reagents that can be used for the introduction of Boc groups, such as Boc_2O, $BocONH_2$, $BocN_3$, 1-(*tert*-butoxycarbonyl)benzotriazole, and BocON=N(CN)Ph.[3] Among them, di-(*tert*-butyl) dicarbonate was found to be the best in most applications, owing to its commercial availability, high stability, and low price. This reagent is mainly used in the presence of a basic catalyst (NaOH, K_2CO_3, DMAP, NaHMDS, Et_3N).[4] The Lewis acids[5] and even Brönsted acids[6] have also been used as catalysts for Boc protection.

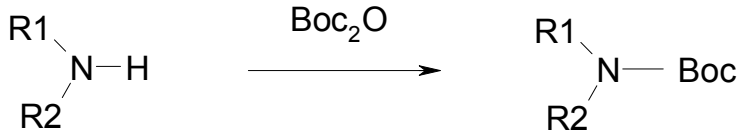
Classical methods for Boc protection suffer from several drawbacks. The tedious work-up is time consuming, and most of the catalysts employed are expensive and cannot be recycled; also, side products appear.[7]

Recently several methods for N-protection of amino groups have been published with the "green chemistry" concept taken into account. Water[6a,8] and ionic liquids[6c] were used as solvents, and finally solventless methods were introduced.[6a,5d] Among the reported techniques there is a procedure where no catalyst is used at all.[7]

Although Boc- protection of amines is well known and occurs relatively smoothly, the protection of hydrazines is a more complicated task, and only a few examples are described. The protection of *Z*-hydrazine was the first example we encountered as a solventless reaction between Boc_2O and an NH_2-group- containing substrate. It should be emphasized that this process cannot be performed under common conditions (acetonitrile, DMAP), due to the formation of mixtures of products which are difficult to separate. On the other hand, Z-hydrazine can be selectively Boc- protected at the NH_2 position in melted (22-24 ºC) Boc_2O.[9] Since the stepwise strategy of the synthesis of substituted hydrazines became very popular during the last decade,[9,10] several Boc- protected hydrazine derivatives are particularly needed. The goal of the present work was to demonstrate the scope of a solventless "green" method for Boc monoprotection of monosubstituted hydrazines and several primary and secondary amines.

Results and Discussion

The various monosubstituted hydrazines and amines were protected according to the Scheme:



a **b**

R_1 or R_2 = H, Alk, Ar or R_1 = H and R_2 = AlkOCONH, ArNH, AlkNH

Scheme 1

Since the reagents are not air- or moisture- sensitive the synthesis can be carried out under very robust conditions. In our experiments, the neat NH_2- compound in any form (liquid or solid) was directly added to the melted Boc_2O. In most cases the reaction was fast, and violent liberation of gas was observed. Usually the conversion was complete in a very short time and a simple recrystallization of the reaction mixture gave pure products in very good yield. Whereas the conversion is complete then the products could be just kept under vacuum and used directly for the next steps of the synthetic sequence (Table 1).

Table 1

Entry	NH compound	Product	Time, min	Temp, ºC	Yield, %
1	Boc-$NHNH_2$	BocNHNHBoc	10	RT	85
2	Z-$NHNH_2$	Z-NHNHBoc	10	50	91
3	Troc$NHNH_2$	TrocNHNHBoc	20	50	72
4	Ph$NHNH_2$	PhNHNHBoc	10	RT	85
5	Ac$NHNH_2$	AcNHNHBoc	50	RT	77
6	2,4-DNPNHNH_2	2,4-DNPNHNHBoc	30 seconds	MW**	mixture
7	Me$NHNH_2$	MeNHNHBoc	10	RT	99 (2 compds.)
8	BuNH_2	BuNHBoc	20 + 10*	RT	97
9	Et_2NH	Et_2NBoc	20 + 10*	RT	89
10	BnMeNH	BnMeNBoc	20 + 10*	RT	96
11	PhNH_2	PhNHBoc	20 + 30*	RT	99
12	PhMeNH	PhMeNBoc	20 + 30*	RT	95
13	Ph_2NH	Ph_2NBoc	24 h	50	Not complete
14	PhAcNH	PhAcNBoc	15	35	99***

* Addition + reaction; ** a conventional MW oven at 360 W was used, and the complex mixture of products was not separated; *** yield after addition of 0.01 equiv. of DMAP.

Sometimes the exothermic solventless reactions are difficult to scale up. Boc- protected hydrazines and amines are thermally stable in the absence of acids. Therefore, the present solventless-, and the non-catalyzed, method could find applications on the industrial scale.

It is obvious that the pKa is a good parameter to evaluate the reactivity of NH compounds under the Boc protection. The pKa values of amines are easy to find in the literature[11] and can be used directly for evaluation since the reaction center is the same for dissociation and protection. The pKa values of monosubstituted hydrazines do not directly describe the reactivity because these are measured at the other nitrogen, and not where the protection is going on. Indeed, the pKa value could be used, but not in the same series with amines. The least acidic hydrazine in the series studied here was the methylhydrazine which reacted very fast even at room temperature. The pKa for this compound is not known, but the acidity could not be much more different than that of hydrazine, having a proposed value of pKa about 37.[12] The methyl group does not have significant electronic and steric effects in order to differentiate the two possible reaction centers. Therefore the protection of this most nucleophilic substrate in our series was not selective, and two products were obtained. The phenyl group in the next weak acid, phenylhydrazine, with the pKa values of 28.8 [13] decreased the reactivity of the PhNH center, which resulted in excellent selctivity. Boc-hydrazine is a substantially stronger acid. The pKa is known only for the nearest analog of Boc-hydrazine - the ethoxycarbonyl derivative (pKa 22.2[13]). The influence of a Boc group on the nucleophilicity of the NH_2 group is relatively weak and excellent results were obtained. There are no pKa data available for Troc- and Z-hydrazines.

Their acidity could be compared with Boc- hydrazine through the influence of the corresponding groups on the acidity of carbamates.[14] According to these data the influence of a Troc group is about 1.5 pKa units stronger than that of a Z group, and 1.7 units stronger than the Boc group. It is also known for hydrazines that the ZNH is about 0.2 pKa units stronger as an acid than BocNH.[12] Acetylhydrazine has pKa 21.8,[11] and is about 0.4 units stronger as an acid than is ethoxycarbonylhydrazine. There are no pKa data available for 2,4-DNP-hydrazine but it could be indirectly evaluated according to the data for corresponding phenyl derivatives.[13] It appeared that the pKa of 2,4-DNPNH is 12.4 units lower than that of corresponding phenyl derivative. Therefore the reactivity of 2,4-DNP-hydrazine should be the lowest in the series and, indeed, this compound demanded strong heating in a microwave oven to react, giving the mixture of compounds. By conventional heating at 75 ºC for several days the reaction was not finished, and also gave a mixture of products. The behavior of the rest of the compounds is in good agreement with the pKa values. Based on the results, it could be proposed that the limit of pKa for monosubstituted hydrazine protected without catalyst could be around 17. According to the increase of acidity, the hydrazines studied could be ordered as follows: Me, Ph, Boc, Z, Troc, Ac, and 2,4-DNP. The reactivity of the corresponding compounds decreased in the same order.
The same procedure as described above was also very effective for amines, affording pure products in high yields. Diphenylamine reacted very slowly under the conditions used, and even after 24 hr at room temperature the reaction was not complete. Acetanilide was not reactive, and the protection took place only after the addition of 0.01 equiv of DMAP. Again, this observation is in a good agreement with the pKa values of these substrates.[11] Primary as well as secondary aliphatic amines are all very weak acids (pKa higher than 30) and therefore reacted very fast (within minutes). Here, the pKa limit of non-catalyzed protection (within a reasonable time) is between 25.0 (Ph_2NH) and 21.5 (PhNHAc).

Conclusions

The method for solventless and non-catalyzed Boc- protection of substituted hydrazines and amines was tested experimentally, and the scope and limitations have been demonstrated. The pKa value of the NH acid is a good parameter for evaluation and prediction of the reactivity of the substrates.

Experimental Section

General Procedures. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50 MHz) spectra were recorded on a Bruker Avance II 200 spectrometer, using $CDCl_3$ as solvent and tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer PC 16 FTIR spectrometer; all are given in cm^{-1}; the material under investigation was mixed in KBr pellets (for solids) or as a liquid film

between KBr wafers (for liquids). Thin layer chromatography was performed on "Alugram® SIL G/ UV 254" silica gel plates provided by Macherey-Nagel. For visualization of the spots, the plates were illuminated under UV-light and treated with phosphomolybdic acid (*ca*. 1% solution in ethanol). All the reactions were carried out in oven- or air- gun- dried round-bottom flasks.

Typical procedure for Boc-protection of hydrazines and amines. To the magnetically stirred molten Boc_2O (1–1.1 equiv), 1 equiv. of NH- containing compound (hydrazines or amines) was added gradually to keep the mixture at room temperature and avoid too violent gas evolution. The reaction was followed by TLC until completion. The product was directly recrystallized from suitable solvent or kept under vacuum until only the product remained.

All products were previously described in the literature and are characterized here by spectroscopic methods. The spectroscopic data and melting points of some representative products are given below.

1b. Mp 75 ºC (lit. 75-77 ºC).[16] FTIR (KBr): 3318 NH, 1738 C=O, 1700 C=O. ^{1}H NMR at 200 MHz ($CDCl_3$): δ 1.47 (s, 9H, Boc), 6.6 (s, 2H, 2 x BocNH); ^{13}C NMR ($CDCl_3$): δ 28.3 (CH_3, Boc), 81.4 (Cq, Boc), 156 (C=O). Mp 122 ºC (lit. 122 ºC).[15]

2b. FTIR (KBr): 3266 NH, 1752 C=O, 1694 C=O. ^{1}H NMR 200 MHz ($CDCl_3$)): δ 1.48 (s, 9H, Boc), 5.16 (s, 2H, CH_2), 6.43 (s, 1H, NH), 6.72 (s, 1H, NH), 7.33 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 28.3 (CH_3, Boc), 67.8 (CH_2), 81.8 (Cq, Boc), 128.2, 128.4, 128.6, 136.0 (Ph), 156 (C=O).

3b. Mp 55-56 ºC (lit. 54-55 ºC).[17] FTIR (KBr): 3300 NH, 1746 C=O, 1716 C=O. ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 9H, Boc), 4.90 (s, 2H, CH_2CCl_3), 6.49 (s, 1H, NH-Troc), 6.94 (s, 1H, NHBoc). ^{13}C NMR ($CDCl_3$): δ= 28.2 (Boc), 75.2 (CH_2), 82.3 (Cq, Boc), 94.9 (CCl_3), 155.3, 155.1 (C=O).

4b. Mp 91 ºC (lit. 91-92 ºC).[15] FTIR (KBr): 3354 NH, 3282 NH, 1726 C=O, 1698 C=O. ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 9H, Boc), 5.92 (br s, 1H, PhNH), 6.71- 6.87 (m, 4H, Ph, BocNH), 7.13-7.21 (m, 2H, Ph). ^{13}C NMR ($CDCl_3$): δ 28.4 (CH_3, Boc), 81.1 (Cq, Boc), 113.3, 120.7, 129.1, 148.8 (Ph), 156.5 (C=O).

5b. Mp 115-117 ºC (lit. 117-117.5 ºC).[18] FTIR (KBr): 3262 NH, 1717 C=O, 1694 C=O. ^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9H, Boc), 2.02 (s, 3H, Ac), 7.23 (s, 1H, NH-Boc), 8.79 (s, 1H, NHAc). ^{13}C NMR ($CDCl_3$): δ 20.6 (Ac), 28.2 (Boc), 81.7 (Cq, Boc), 94.9 (CCl_3), 156.1 (C=O, Boc), 170.1 (C=O, Ac).

7b. Mp 48-50 ºC (lit. 49-51 ºC).[19] After several recrystallizations from hexane a pure analytical sample of MeNHNHBoc was separated. ^{1}H NMR ($CDCl_3$): δ 1.48 (s, 9H, Boc), 2.02 (s, 3H, Ac), 7.23 (s, 1H, NH-Boc), 8.79 (s, 1H, NHAc). ^{13}C NMR ($CDCl_3$): δ 28.3 (Boc), 39.3 (Me), 81.1 (Cq, Boc), 155.8 (C=O, Boc).

8b. Colorless oil.[20] FTIR (liq. film): 3351 NH, 1693 C=O. ^{1}H NMR 200 MHz ($CDCl_3$) δ 0.93 (t, J 7.2 Hz, 3H, CH_3), 1.34 (m, 2H, CH_2), 1.45 (s, 11H, Boc + CH_2), 3.12 (m, 2H, CH_2), 4.83 (br, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.4, 19.6, 31.7, 39.7 (Bu), 27.7 (Boc), 77.8 (Cq, Boc), 155.6 (C=O, Boc).

9b. Colorless oil.[21] FTIR (liq. film): 1693 C=O. ^{1}H NMR 200 MHz ($CDCl_3$): δ 0.75 (t, 6H, 2 x CH_3), 1.08 (s, 9H, Boc), 2.88 (q, 4H, 2 x CH_2). ^{13}C NMR ($CDCl_3$): δ= 13.8 (CH_3), 28.2 (Boc), 40.4 (CH_2), 79.6 (Cq, Boc), 155.3 (C=O, Boc).
10b. Colorless oil.[22] FTIR (liq. film): 1698 C=O. ^{1}H NMR 200 MHz ($CDCl_3$): δ 1.47 (c, 9H, Boc), 2.82 (s, 3H, Me), 4.42 (s, 2H, CH_2), 7.33-7.16 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 28.4 (Boc), 33.8 (N-Me), 52.4 (CH_2), 79.6 (Cq), 127.1, 128.4, 138.0, (Ph), 155.8 (C=O, Boc).
11b. Mp. 131-133. (lit. mp. 132 ºC).[23] FTIR (KBr): 3312 NH, 1688 C=O. ^{1}H NMR 200 MHz ($CDCl_3$): δ= 1.51 (s, 9H, Boc), 6.55 (br s, 1H, NH), 6.99-7.04 (m, 1H, Ph), 7.24-7.36 (m, 4H, Ph). ^{13}C NMR ($CDCl_3$): δ 28.2 (Boc), 80.3 (Cq), 118.3, 122.7, 128.8, 138.3 (Ph), 152.6 (C=O, Boc).
12b. Colorless oil.[24] FTIR (liq. film): 3351 NH, 1694 C=O. ^{1}H NMR 200 MHz ($CDCl_3$): 1.43 (s, 9H, Boc), 3.21 (s, 3H, CH_3), 7.12-7.31 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ= 28.3 (Boc), 37.4 (Me), 80.2 (Cq), 125.5, 125.6, 128.6, 143.8 (Ph), 154.8 (C=O, Boc).
14b. Mp. 58-59 ºC. (lit. 59.5-60 ºC).[25] FTIR (KBr): 1735 C=O, 1705, C=O. ^{1}H NMR 200 MHz ($CDCl_3$): 1.36 (s, 9H, Boc), 2.49 (s, 3H, Ac), 7.03-7.17 (m, 2H, Ph). 7.28-7.41 (m, 3H, Ph). ^{13}C NMR ($CDCl_3$): δ= 26.1 ($COCH_3$), 27.3 (Boc), 82.4 (Cq), 127.2, 128.2, 128.5, 138.7 (Ph), 152.0 (CO, Boc), 171.7 (Ac).

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