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(Bromodimethyl)Sulfonium Bromide Mediated Rapid And Facile Protection Of Amines

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ABSTRACT

A new clean protocol for protection of aryl and aliphatic amines with t-butoxycarbonyl (t-BOC) and benzyloxycarbonyl (Cbz) was developed using catalytic amount of (bromodimethyl) sulfonium bromide. The method is solvent free, mild and rapid protection of amines has been achieved in excellent yields.

KEYWORDS

(Bromodimethyl) sulfonium bromide; Protection; Amine and solvent free reactions.

INTRODUCTION

Protecting groups play a vital role in carrying out reactions selectively at one reactive site in a multi-functional compound. The significance of protecting groups can be judged by the numerous literature reports appearing on new groups as well as many new methods of introduction or removal of them. (Protecting groups)[1]. Efficient protection of amines is a key step in organic synthesis more so because it has become an essential tool in contemporary peptide[2] and organic chemistry[3]. t-butoxycarbonyl(t-BOC) and benzyloxycarbonyl(Cbz) are among the favorite protecting group's for protection of amines.

The acid labile nature of the t-BOC is both a great disadvantage and advantage as it can be used as deprotection method. Cbz on the other hand is stable to basic and most aqueous acidic media, removed photolytically or by hydrogenolysis. While benzyloxycarbonyl chloride(CbzCl) is used for introduction of Cbz group, di-tert-butyldicarbonate, $(Boc)_2O$, is widely used for bringing in t-Boc.

The Cbz protection has been achieved in a variety of base mediated reaction conditions[4]. Very few reports on the protection of amines in an acid medium by Cbz are available[5]. In pursuit of our endeavor to develop novel & environmental friendly, solvent free green methods, we herein report an

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operationally facile, rapid, efficient and high yielding and above all solvent free protocol for Cbz protection of amines using catalytic amounts of bromo dimethylsufonium bromide[6] (Me_2SBr_2) reagent. (Bromodimethyl) sulfonium bromide has attractive features as a catalyst, which includes clean reaction (synthetic) conditions, versatility, mildness, and ease of handling and synthesis of the catalyst itself that have not been fully exploited yet. Our earlier experience with(Bromodimethyl) sulfonium bromide proves it to be a versatile reagent for development of cleaner synthetic methods since reactions have been carried out without solvent as well.

EXPERIMENTAL

General procedure

To a stirred mixture of amine(1mmol) and the protecting group(1mmol) (either CBzCl as 50% solution in toluene or $(Boc)_2O$ as a neat liquid) was added dropwise followed by Me_2SBr_2. The reaction mixture was stirred at room temperature and monitored by TLC. After the completion of the reaction as indicated by the disappearance of the amine, water was added, stirred and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield the product.

Spectral Data for Important compounds

TABLE 1

Benzyl[4-(triflouromethyl)benzyl]carbamate **1d:** M.p.:43°C; IR(ν, cm^{-1}): 3300, 1720; ^{1}HNMR(δ): 7.56 (d, 2H, J=8.29 Hz, Ar), 7.42(d, 2H, J=8.29 Hz, Ar), 7.30(m, 5H, Ar), 5.02(s, 2H, Bn), 4.30(d, 2H, J=6.03, CH_2); E.I. Mass(m/z):332(M+Na).

Benzyl(2-phenylethyl)carbamate **2:** M.p.:55°C; IR(ν, cm^{-1}): 3303, 3033, 1735; ^{1}HNMR(δ): 7.30(m, 10H, Ar), 5.10(s, 2H, Bn), 4.38(d, 2H, J=5.88 Hz, CH_2); E.I. Mass(m/z): 241(M^+); CHN Analysis: Calcd-C:75.30, H:6.66, N:5.49, Found: C:74.01, H:6.62, N:5.43.

Benzyl(1-phenylethyl) carbamate **4:** M.p.:46°C; IR(ν, cm^{-1}): 3327, 3029, 2929, 1688; ^{1}HNMR(δ): 7.34(m, 10H, Ar), 5.03(s, 2H, Bn), 3.40(t, 2H, J=13.03 Hz, CH_2), 2.80(t, 2H, J=6.99 Hz, CH_2); E.I. Mass(m/z): 278(M+Na).

Benzyl morpholine-1-carboxylate **5:** Oil; IR(ν, cm^{-1}): 3440, 2910, 2852, 1697; ^{1}HNMR(δ): 7.30(m, 5H, Ar), 5.10(s, 2H, Bn), 3.60(br, 4H, N-CH_2), 3.40 (t, 4H, J =4.91 Hz, CH_2); E.I. Mass(m/z): 221(M^+).

Benzyl 4-methyl piperidine-1-carboxylate **6:** Oil; IR(ν, cm^{-1}): 3440, 2923, 2853, 1700; ^{1}HNMR(δ): 7.30 (m, 5H, Ar), 5.09(s, 2H, Bn), 4.14(br, 2H, CH_2), 2.68 (br, 2H, CH_2), 1.60(m, 3H, CH & CH_2), 1.10(br, 2H, CH_2), 0.96(d, 3H, J =6.60 Hz, CH_3); E.I. Mass(m/z): 232(M^+).

Benzyl(2-methoxyethyl)-1-carbamate **7b:** Oil; IR(ν, cm^{-1}): 3337, 3033, 2925, 1708; ^{1}HNMR(δ): 7.50 (m, 5H, Ar), 5.02(s, 2H, Bn), 3.40(t, 2H, J=5.29 Hz, CH_2), 3.30(t, 4H, J =5.29 Hz, CH_2), 3.22(s, 3H, OCH_3); E.I. Mass(m/z): 208(M-1), 167(M- OCH_3).

4a-methyl 2-phenyl-7-chloroindeno[1,2-d][1,2,3] oxadiazine-2,4a(4H,5H)-dicarboxylate **11:** M.p.: 122-25°C; IR(ν, cm^{-1}): 3454, 3032, 2951, 1746; ^{1}HNMR(δ): 7.64(d, 1H, J=8 Hz Ar), 7.40-7.20 (m, 2H, Ar), 5.50(d, 1H, J=10.0 Hz, OCH), 5.30(s, 2H, Bn), 5.10 (d, 1H, J=10.0 Hz, OCH), 3.63(s, 3H, OCH_3), 3.42(d, 1H, J=18 Hz, CH), 3.20(d, 1H, J=18 Hz, CH); FAB Mass: 401(M^+); CHN Analysis: Calcd-C:58.80, H:4.43, N:7.22, Found:C:58.56, H:4.41, N:7.14.

TABLE 2

Tert-Butyl(1-phenylethyl)carbamate **3:** M.p.: 65°C; IR(ν, cm^{-1}): 3388, 3031, 2932, 1684; ^{1}HNMR(δ): 7.30(m, 5H, Ar), 5.40(br, 1H, CH), 4.70 (br, 1H, NH), 2.58(s, 3H, CH_3), 1.40(s, 9H, t-Bu); CHN Analysis: Calcd-C:65.30, H:7.70, N:5.90, Found:C:66.64, H:7.74, N:5.96.

Tert-Butyl morpholine-4-carboxylate **8:**M.p.:54^{0}C;

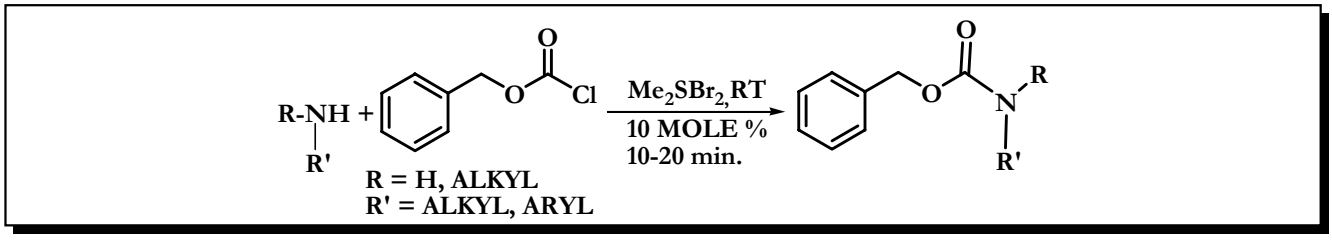

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TABLE 1: Me_2SBr_2 catalysed Cbz protection of amines

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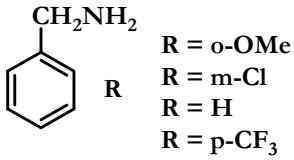
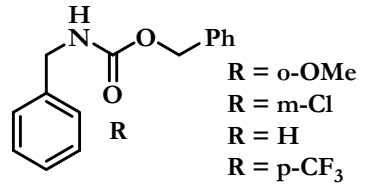
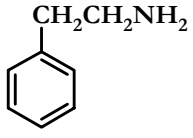
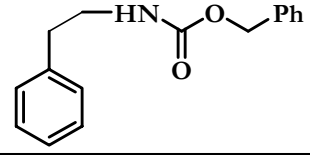
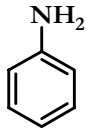
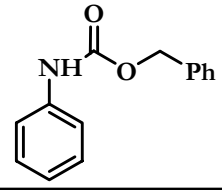
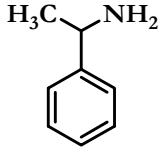
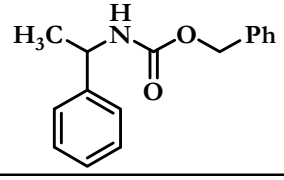
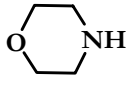
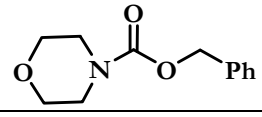
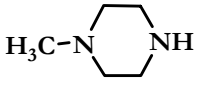
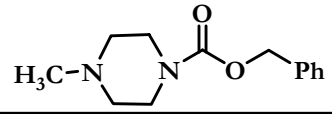
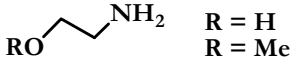
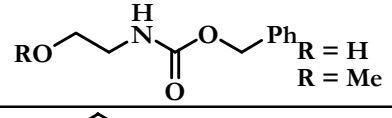
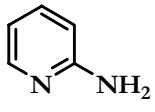
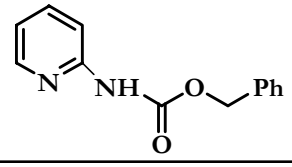
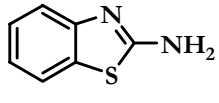
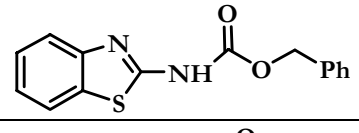
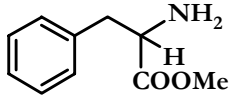
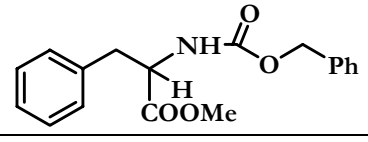
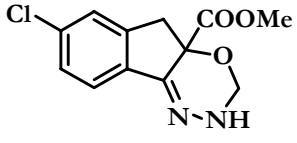
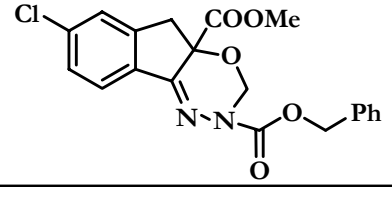
1	 R = o-OMe R = m-Cl R = H R = p-CF_3	 R = o-OMe R = m-Cl R = H R = p-CF_3	89 91 84 85	12 20 10 15
2			83	10
3			74	10
4			90	15
5			72	10
6			76	15
7	 R = H R = Me	 R = H R = Me	87 88	12
8			86	18
9			83	10
10			85	20
11			88	15

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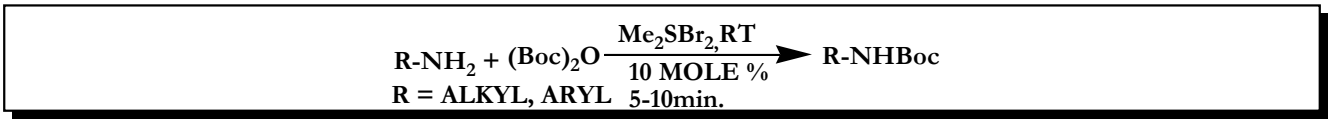
IR(ν, cm^{-1}): 3443, 2929, 2866, 1697; ^{1}HNMR(δ): 3.60 (t, 4H, J=5.28 Hz, N-CH_2), 3.38(t, 4H, J= 5.28 Hz, CH_2), 1.49(s, 9H, t-Bu); CHN Analysis: Calcd-C:56.01, H:8.71, N:7.05, Found:C:56.97, H:8.75, N:7.11.

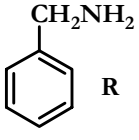
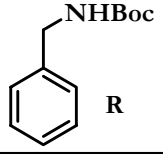
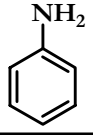
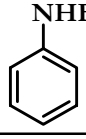
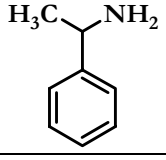
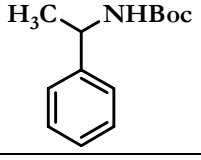
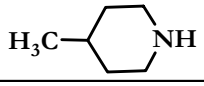
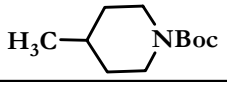
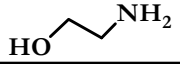
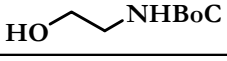
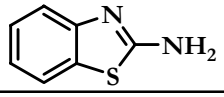
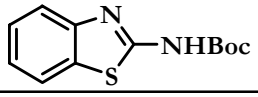
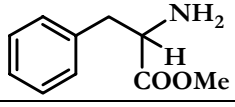
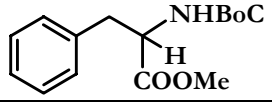
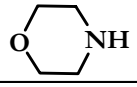
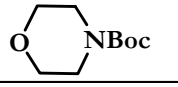
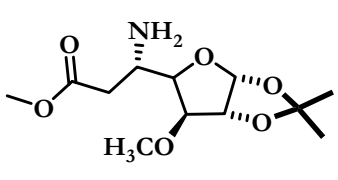
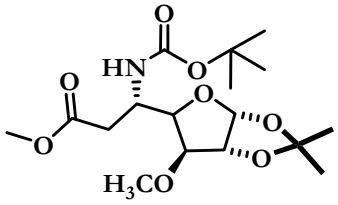
Methyl 3-tert-butyl carbamate-3-[2,2,6-trimethyl-**(6s)** -perhydrofuro[2,3-d][1,3]dioxol-5-yl]propionate **9:** oil; ^{1}HNMR(δ):5.91(d, 1H, J=3 Hz), 5.15(br, 1H, NH), 4.58(d 1H, J=3 Hz, CH_2), 4.30(br, 2H), 3.70(s, 4H), 3.37(s, 3H), 2.65(m, 2H), 1.49(s, 3H), 1.40(s, 9H, t-Bu), 1.32(s, 3H).

RESULTS AND DISCUSSION

Benzylamine and CbzCl(50% solution in toluene) were treated with 10 mol% of Me_2SBr_2 at room temperature to afford the corresponding Cbz protected amine in good yields (TABLE 1) in 10min. Further reactions were carried out to test the generality of the method using a variety of substrates and substitutions. In each case, the reaction proceeded efficiently at ambient temperature and afforded the corresponding Cbz protected amine. Protection is

TABLE 2: Me_2SBr_2 catalysed Boc protection of amines



Entry	Amine	Product	Yield (%)	Time (min.)
1			85	5
2			77	6
3			92	8
4			81	5
5			82	8
6			80	10
7			80	10
8			80	7
9			75	10

equally effective with secondary amines like piperidine, morpholine etc. (entry 5,6). The interesting feature being(is) the facile protection of the amino group of α-amino acid ester(entry 10) as well as β-amino acid esters derived from sugars, which could find applications in peptide chemistry. Additionally, the method is highly chemo selective as only amine gets protected even in the presence of an alcohol(entry 7). All products were characterized by ^{1}HNMR, IR and Mass spectrometry. Reaction rate and conversion yields were dependent on the nature of the amines. In general, primary amines react faster and give better yields when compared with the literature data.

In an additional investigation, the protection of amines was also attempted with $(Boc)_2O$ employing similar conditions in the presence of 10 mol% Me_2SBr_2. The reaction was carried out with di-tert-butyldicarbonate and amine followed by addition of Me_2SBr_2 at room temperature. The protection proceeds smoothly to generate N-Boc amines almost instantaneously and in good yields. All products were characterized by ^{1}HNMR, IR and Mass spectrometry and by comparison with the literature data. Again the reaction protocol was found to be a generally applicable one with a variety of amines protected in a facile manner (TABLE 2). The yields were higher for Boc protection and reaction times are shorter with respect to the Cbz protection. Also the Boc protection was equally effective in the case of amino acid esters (TABLE 2, entry 7) as well as chemoselective (TABLE 2, entry 5). Compared with the other Boc protection methods employed for the protection, like the base catalysed[7], neutral conditions(method)[8], the Yittria-Zirconia[9] mediated or the Lewis acid catalysed[10], the Me_2SBr_2 catalysed protocol has distinct advantages like simplicity, short reaction times, more environmentally friendly cleaner approach.

The role of the catalyst, (bromodimethyl) sulfonium bromide, we feel is somewhat like that of Lewis acid i.e., an electrophilic activation of benzyloxycarbonyl chloride and di-tert-butyldicarbonate.

In conclusion the Me_2SBr_2 catalysed direct protection of amines by both CbZ and Boc groups is an operationally facile, rapid, mild and environmentally friendly clean synthetic method. The protocol is general and applicable to a variety of alkyl, substituted alkyl, aryl, substituted aryl amines and amino acid esters.

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