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A Simple, Efficient, Catalyst-Free and Solvent-Less Microwave-Assisted Process for *N*-Cbz Protection of Several Amines

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ABSTRACT. A simple, green and chemo-selective method for the *N*-benzyloxycarbonylation of amines, *β*-amino alcohols, *α*-amino esters and sulfonamides has been developed under microwave irradiation. Good to excellent yields of the *N*-benzyloxy-carbamates compounds were obtained in short times without any side products.

Key words: Amine, Benzyl chloroformate (Cbz-Cl), Protection, Microwave-assisted, Solvent-free

INTRODUCTION

The presence of amine functionality in a large variety of biologically active compounds makes protection/cleavage of the amino group frequently necessary in synthetic organic and medicinal chemistry.[1]

More than 350 protecting groups for amines are described in literature, the amines can be protecting in many forms such as imines, enamines, carbamates and sulfonyl derivatives.[2]

The benzyloxycarbonyl motif is very useful for the protection of the amine function in poly-functional molecules.[3] This is due to its stability in acidic/basic conditions, orthogonality vis-a-vis other protecting groups and its easy removal by catalytic hydrogenation without any secondary reaction.[4]

Many protocols are available in various works present the protection of amines derivatives with the Cbz group. Among these methods: the use of *β*-cyclodextrin in aqueous medium,[5] lithium hexamethydisilazane (LiHMDS) as base in THF-HMPA,[6] tetrabutylammonium bromide (TBAB),[7] silica-sulfuric acid as a catalyst under solvent-free conditions,[8] $La(NO_3)\cdot 6H_2O$,[9] the use of molecular iodine[10] using ionic liquid tetrapropylammonium L-prolinate ([TPA] [L-Pro]) as a reaction medium,[11] in micellar media,[12] the use of PEG-600 as a recyclable catalyst,[13] reaction on a solid surface[14] and Amberlyst-15 under solvent-free conditions.[15] However, most of the reported methods suffer from various drawbacks such as the use of organic solvents and highly basic conditions, relatively high reaction temperatures and tedious work-up procedures.

In the last few years, the application of microwave (MW) in organic transformations has become more and more scientist's interest.[16] Introduced in 1986 by Gedye[17] and Guigere,[18] MW irradiation offers a cleaner and easier pathway compared to conventional methods, it has several advantages such as high temperature homogeneity, instantaneous and rapid heating, allowing the progress of reactions without solvent with a maximal efficiency.[19]

In continuation of our work toward the development of new, greener and useful methods in the field of the chemistry of protecting groups,[20–22] we report herein the successful use of microwave irradiation for the selective benzyloxycabonylation of various amine derivatives.

EXPERIMENTAL

Instruments and Materials

All reagents and solvents were of commercial quality and used without further purification. All reactions were carried out in a SAMSUNG microwave oven type M1610N, 230–50 Hz, and 2450 Hz MW at 50 °C. All reaction were monitored by TLC on Silica gel Merck 60 F254 (Art. 5554) percolated aluminum plates and were developed by spraying with Ninhydrine solution. Melting points were determined in open capillary tubes on an electrothermal apparatus and uncorrected. Mass spectra were recorded on a SHIMADZU QP 1100 Ex mass spectrometer. IR spectra were recorded on a Perkin-Elmer FT-600 spectrometer. Proton nuclear magnetic resonance were determined 250 or 400 MHz Brücker spectrometer using $CDCl_3$ as a solvent and TMS as an internal standard. Chemical shifts are reported in δ units (ppm). All coupling constants (J) are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and combination these signals.

Typical experimental procedure of *N*-benzyloxycarbonylation protection on amines derivatives promoted by microwave irradiation

Benzylcholoroformate Cbz-Cl (1 mmol) was added to amine (1 mmol) and the mixture was subjected to the microwave irradiation (100W) for the appropriate time (tables **2**, **3**, **4** and **5**). After completion of the reaction (monitored by TLC) dichloromethane: methanol (98/2), the reaction mixture was treating with *n*-hexane (15–20 mL) and was allowed to stand at room temperature overnight. The solid products were collected by filtration, washed with *n*-hexane and dried to give the *N*-Cbz derivatives in good to excellent yields. During the reaction, the formation of hydrogen chloride (gas) was observed, confirming the protection of all amines structures proposal.

***N*-Carbobenzyloxyaniline (1a)**

White solid; Yield 98%; m.p. 68-69 ºC; R_f 0.86 (DCM-MeOH 98/2); MSEI (m/z) 228 $[M+1]^+$; IR (KBr): υ max/cm^{-1} 3272.62 (N-H), 2953.42 (C-H), 1690.64 (C=O), 1564.89 (C=C), 1445.21 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (s, 2H, CH_2-Ph), 6.76 (s, 1H, NH), 7.30-7.42 (m, 10H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.1, 118.8, 123.6, 128.4, 128.5, 128.6, 128.7, 129.0, 129.2, 136.1, 137.9, 153.4.

***N*-Carbobenzyloxybenzylamine (2a)**

White solid; Yield 97%; m.p. 72-75 ºC; R_f 0.86 (DCM-MeOH 98/2); IR (KBr): υ max/cm^{-1} 3324.29 (N-H), 3032.90 (C-H), 1687.61 (C=O), 1543.36 (C=C), 1453 (C-N); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.45 (s, 2H, CH_2-NH), 5.25 (s, 2H, CH_2-Ph), 7.40-7.70 (m, 10H, H-Ar); ^{13}C NMR (60 MHz, $CDCl_3$) δ 45.1, 66.8, 126.9, 126.7, 127.1, 127.6, 128.5, 128.9, 136.1, 137.9, 152.6.

***N*-Carbobenzyloxy-4-methoxyaniline (4a)**

Brown pale solid; Yield 94%; m.p. 84.5-90.8 ºC; R_f 0.50 (DCM-MeOH 98/2); MSEI(m/z) 258.1 $[M+1]^+$; IR (KBr): υ max/cm^{-1} 3307.42 (N-H), 3010.20 (C-H), 1699.57 (C=O), 1513.29 (C=C), 1454.04 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H, CH_3-O), 5.19 (s, 2H, CH_2-Ph), 6.64 (s, 1H, NH), 6.83-6.88 (2d, J = 8.0 Hz, 2H, H-Ar), 7.26–7.42 (m, 7H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 66.9, 114.3, 120.7, 128.3, 128.4, 128.6, 130.8, 136.2, 153.8.

***N*-Carbobenzyloxy-2-methoxyaniline (5a)**

Oil; Yield 94%; R_f 0.55 (DCM-MeOH 98/2); IR (KBr): ν/cm^{-1} 3425.99 (N-H), 2838.60 (C-H), 1732.91 (C=O), 1580.21 (C=C), 1435.61 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H, CH_3-O), 5.22 (s, 2H, CH_2-Ph), 6.85–6.87 (2d, J = 6.0 Hz, 1H, H-Ar), 6.97-7.02 (m, 2H, H-Ar), 7.26–7.45 (m, 6H, H-Ar), 8.1 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 67.0, 110.1, 118.4, 121.3, 122.9, 127.7, 128.4, 128.7, 136.4, 147.8, 153.4.

***N*-Carbobenzyloxyurea (9a)**

White crystal; Yield 87%; m.p. 135-138 ºC; R_f 0.54 (DCM-MeOH 98/2); MSEI (m/z) 193.0 $[M-1]^+$; IR (KBr): υ max/cm^{-1} 3418.05 (N-H), 3334.74 (N-H), 3273.46 (N-H), 3035.46 (C-H), 1693.39 (C=O), 1403.46 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (br s, 2H, NH_2), 5.10 (s, 2H, CH_2-Ph), 7.20–7.36 (m, 5H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.1, 128.3, 128.7, 136.4, 156.9.

***N*-Carbobenzyloxydiphenylamine (10a)**

Pale yellow solid; Yield 85%; m.p. 101.8–108.9 ºC; R_f 0.85 (DCM-MeOH 98/2); MSEI (m/z) 304.2 $[M+1]^+$; IR (KBr): υ max/cm^{-1} 2969.09 (C-H), 1707.50 (C=O), 1591.89 (C=C), 1455 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (s, 2H, CH_2-Ph), 7.19–7.31 (m, 15H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.6, 126.3, 127.1, 127.8, 128.1, 128.5, 129.1, 136.5, 142.7, 154.8.

***N*-Carbobenzyloxymorpholine (12a)**

White solid; Yield 88%; m.p. 47–49 °C; R_f 0.40 (DCM-MeOH 98/2); IR (KBr): υ max/cm^{-1} 2978 (C-H), 1703.01 (C=O), 1545.20 (C=C), 1427.97 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (t, J = 4.9 Hz, 4H, $2CH_2$-O), 3.65 (br s, 4H, $2CH_2$-N), 5.14 (s, 2H, CH_2-Ph), 7.26–7.37 (m, 5H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.1, 66.5, 67.2, 128.0, 128.1, 128.5, 136.4, 155.2.

***N*-Carbobenzyloxyphenylpiperazine (13a)**

White solid; yield 86%; m.p. 71-73 °C; R_f 0.55 (DCM-MeOH 98/2); MSEI (m/z) 297.2 $[M+1]^+$; IR (KBr): υ max/cm^{-1} 2964.81 (C-H), 1703.01 (C=O), 1591.89 (C=C), 1455.51 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (br s, 4H, $2CH_2$-N-CO), 3.66 (t, J = 5.2 Hz, 4H, $2CH_2$-N-Ph), 5.2 (s, 2H, CH_2-Ph), 6.89–7.39 (m, 10H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.0, 49.6, 67.4, 116.9, 120.6, 128.1, 128.2, 128.7, 129.4, 151.3, 155.4.

***N*-Carbobenzyloxypropylamine (16a)**

White crystal; Yield 93%; m.p. 36.5–40.1 ºC; R_f 0.56 (DCM-MeOH 98/2); MSEI (m/z) 194.1 $[M+1]^+$; IR (KBr): υ max/cm^{-1} 3322.01 (N-H), 2934.67 (C-H), 1687.92 (C=O), 1541.03 (C=C), 1457.73 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.6 Hz, 3H, CH_3), 1.48 (m, 2H, CH_2-CH_3), 3.13 (q, J = 6.8 Hz, 2H, CH_2-NH), 4.73 (br s, 1H, NH), 5.1 (s, 2H, CH_2-Ph), 7.21-7.36 (m, 5H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 23.4, 43.01, 66.8, 128.2, 128.7, 136.9, 156.6.

***N*-Carbobenzyloxycyclohexylamine (18a)**

White solid; Yield 91%; m.p. 64–67 ºC; R_f 0.50 (DCM-MeOH 98/2); MSEI (m/z) 233 $[M]^+$; IR (KBr): υ max/cm^{-1} 3319.88 (N-H), 2931.08 (C-H), 1686.93 (C=O), 1541.63 (C=C), 1311.19 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ

1.08–1.95 (m, 10H, CH_2), 3.49–3.52 (m, 1H, CH-NH), 4.61 (br s, 1H, NH), 5.09 (s, 2H, CH_2-Ph), 7.25–7.40 (m, 5H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 25.7, 33.6, 50.1, 66.6, 128.2, 128.3, 128.7, 136.9, 155.7.

(*S*)-*N*-Carbobenzyloxyphenylalaninol (1b)

White solid; Yield 85%; m.p. 49–52 ºC; R_f 0.40 (DCM-MeOH 98/2); IR (KBr): υ max/cm^{-1} 3352.64 (N-H, O-H), 2931.69 (C-H), 1699.70 (C=O), 1539 (C=C), 1475.25 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (br s, 1H, O-H), 2.76 (d, J = 12.0 Hz, 2H, *C-CH_2-Ph), 3.47 (dd, J_1 = 8.0 Hz, J_2 = 12.0 Hz, 2H, CH_2-OH), 3.86 (br s, 1H, *C-H), 4.99 (s, 1H, N-H), 5.02 (s, 2H, O-CH_2-Ph), 7.10–7.30 (m, 10H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.4, 54.2, 64.0, 66.9, 126.7, 128.2, 128.3, 128.6, 128.7, 129.4, 136.4, 137.7, 156.6.

(*S*)-*N*-Carbobenzyloxyvalinol (2b)

White solid; Yield 83%; m.p. 53.7–55.1 ºC; R_f 0.33 (DCM-MeOH 98/2); MSEI (m/z) 259.7 [M+Na]$^+$; IR (KBr): υ max/cm^{-1} 3307 (N-H, O-H), 2958.69 (C-H), 1684.39 (C=O), 1544.88 (C=C), 1469.84 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94–0.98 (2d, J_1 = 6.8 Hz, J_2 = 10.8 Hz, 6H, 2CH_3), 1.84–1.89 (m, 1H, CH-*i*-pro), 2.18 (br s, 1H, O-H), 3.50–3.51 (m, 1H, *CH), 3.64–3.70 (m, 2H, CH_2-OH), 5.11 (s, 2H, CH_2-Ph), 7.26–7.36 (m, 5H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 19.7, 29.4, 58.8, 64.1, 67.1, 128.2, 128.3, 128.7, 136.6, 157.3.

(*S*)-*N*-Carbobenzyloxyphenylalaninemethylester (2c)

White solid; Yield 85%; m.p. 86–88 ºC; R_f 0.59 (DCM-MeOH 98/2); MSEI (m/z) 312 [M+1]$^+$; IR (KBr): υ max/cm^{-1} 3340.94 (N-H), 3064.45 (C-H), 1723.98 (C=O), 1521.84 (C=C), 1498.66 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.04 (2dd, J_1 = 6.0 Hz, J_2 = 12.0 Hz, 2H, CH_2-C*), 3.71 (s, 3H, CH_3-O), 4.62–4.68 (m, 1H, *C-H), 5.04 (s, 1H, CH_2-Ph), 5.19–5.21 (m, 1H, NH), 7.07–7.36 (m, 10H, H-Ar); ^{13}C NMR (400 MHz, $CDCl_3$) δ 38.4, 52.4, 55.0, 67.1, 127.3, 128.2, 128.3, 128.7, 128.7, 129.4, 135.8, 136.4, 155.7, 177.1.

(S)-*N*-Carbobenzyloxyprolineethylester (3c)

Oil; Yield 80%; R_f 0.59 (DCM-MeOH 98/2); MSEI (m/z) 278.1 [M+1]$^+$; IR (KBr): υ max/cm^{-1} 2981.16 (C-H), 1745.10 (C=O), 1708.99 (C=O), 1542.42 (C=C), 1416.79 (C-N); ^{1}H NMR (400 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 1.13 (t, 3H, J = 7.2 Hz, CH_3-CH_2), 1.26 (t, 3H, J = 7.2 Hz, CH_3-CH_2), 1.88–2.23 (m, 4H, CH_2-CH_2-C*), 3.49–3.63 (m, 2H, CH_2-N), 4.00–4.09 (m, 1H, CH_2-CH_3), 4.19 (q, J = 7.1 Hz, 1H, CH_2-CH_3), 4.32 (dd, 1H, J_1 = 8.6 Hz J_2 = 3.2 Hz, *CH), 5.13–5.15 (m, 2H, CH_2-Ar), 7.29–7.35 (m, 5H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$ mixture of rotamers) δ 14.1, 14.2, 23.6, 24.3, 30.0, 31.0, 46.5, 47.0, 59.1, 59.4, 61.1, 61.2, 67.0, 127.8, 127.9, 128.4, 128.5, 136.7, 136.9, 154.4, 156.0, 172.7, 172.9.

(*S*)-*N*-Carbobenzyloxyleucineethylester (4c)

Oil. Yield 82%. R_f 0.57 (DCM-MeOH 98/2). MSEI (m/z) 294.1 [M+1]$^+$; IR (KBr): υ max/cm^{-1} 3342.19 (N-H), 2958.52 (C-H), 1722.51 (C=O), 1530.75 (C=C), 1370.25 (C-N). ^{1}H NMR (400 MHz, CDCl3) δ : 0.92 (d, J = 6.4 Hz, 6H, 2CH_3), 1.26 (t, J = 7.2 Hz, 3H, CH_3-CH_2), 1.48–1.55 (m, 1H, CH-*i*-pro), 1.60–1.76 (m, 2H, CH_2-C*), 4.21 (q, J = 7.2, 2H, CH_2-CH_3), 4.35–4.41 (m, 1H, *CH), 5.11 (s, 2H, CH_2-Ph), 5.20–5.21 (m, 1H, NH), 7.30–7.40 (m, 5H, H-Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 22.0, 22.9, 24.9, 42.0, 52.7, 61.4, 67.0, 128.1, 128.2, 128.6, 136.5, 156.1, 173.2.

(*S*)-Benzyl-*N*-(1-hydroxy-3-methylbutan-2-yl) sulfamoylcarbamate (2d)[23,24]

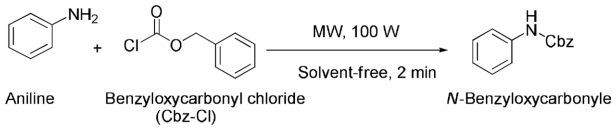
White solid; Yield 80%; m.p. 135°C; R_f 0.37 (DCM/MeOH: 98/2); MSEI (m/z) 339.05 [M+Na]$^+$; IR (KBr): υ max/cm^{-1} 3523 (O-H), 3277 (N-H), 1717 (C=O), 1463.74 (C-N), 1160.30 and 1330.15 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (2d, J = 8.4 Hz, 6H, 2CH_3), 1.83–1.88 (m, 1H, CH), 3.23–3.27 (m, 1H, *CH), 3.52–3.62 (2dd, J_1 = 6.5 Hz, J_2 = 4.0 Hz, *Jgem* =11.7 Hz, 2H, CH_2-OH), 5.16 (s, 2H, O-CH_2), 5.49 (d, J = 7.6 Hz, 1H, NH-*CH), 7.34–7.39 (m, 5H, H-Ar), 8.01 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 18.0, 24.2, 55.0, 64.7, 68.6, 128.6, 128.7, 129.4, 134.5, 151.9.

(*S*)-Benzyl-*N*-(1-hydroxy-4-methylpentan-2-yl) sulfamoylcarbamate (3d)[23,24]

White solid; Yield 82%; m.p. 121 ºC; R_f 0.34 (DCM/MeOH: 98/2); MSEI (m/z) 353.17 [M+Na]$^+$; IR (KBr): υ max/cm^{-1} 3538.42 (O-H), 3290.02 (N-H), 1695.12 (C=O), 1455.63 (C-N), 1175.56 and 1345.20 (SO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (2d, J = 5.4 Hz, 6H, 2CH_3), 1.24–1.37 (m, 2H, CH_2), 1.67–1.70 (m, 1H, *CH), 3.41–3.63 (2dd, J_1 = 5.4 Hz, J_2 = 3.3 Hz, *Jgem* = 11.3 Hz, 2H, CH_2-OH), 3.48–3.51 (m, 1H, *CH), 5.15 (s, 2H, CH_2-Ph), 5.48 (d, J = 8.0 Hz, 1H, NH-*CH), 7.35–7.42 (m, 5H, H-Ar), 8.06 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.8, 24.3, 40.9, 55.0, 64.7, 68.6, 128.7, 128.8, 128.9, 134.7, 151.8.

RESULTS AND DISCUSSION

For model reaction, 1 mmol of aniline was reacted with 1 mmol of benzyl chloroformate (Cbz-Cl) in dichloromethane as a solvent, under microwave irradiation with the absence of any catalyst, the expected *N*-carbobenzyloxyaniline was obtained in 85% yield within just 6 minutes. In order to further investigate the efficiency of our method and to study the effect of MW irradiation on our reaction, we repeat the reaction in the absence of solvent; the result was a better product yield within shorter reaction time (*Scheme* 1). The yield is optimal in solvent-free conditions.



***Scheme* 1.** Microwave-assisted protection of aniline.

***Table* 1.** Influence of irradiation[a]

Entry	Irradiation/W	Time (min)
1	100	2
2	200	2
3	300	/
4	450	/
5	600	/

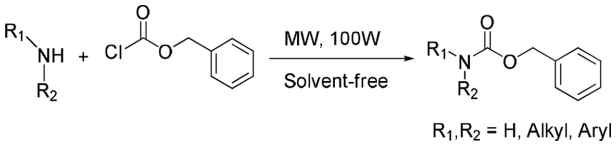
[a]Reaction conditions: aniline, 1 mmol; Cbz-Cl, 1 mmol; no use of catalyst; solvent free; yield, 98%

To find the optimum value of microwave irradiation for the Cbz protection of amines, we have tested the solvent-less reaction of aniline (1 mmol) with Cbz chloride (1 mmol) under various irradiation values. The best results were obtained at 100 and 200 Watts (*Table* 1). Excellent yields were obtained after 2 minutes.

To investigate the influence of solvent, we decided to carry out the reaction using CH_3CN, THF, CH_2Cl_2, AcOEt, methanol and water as reaction media but no significant improvement of the yield was observed even after half an hour of reaction time.

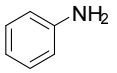
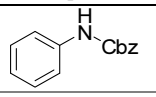
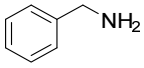
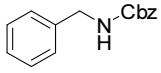
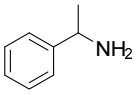
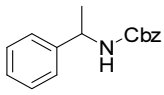
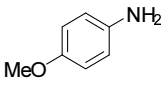
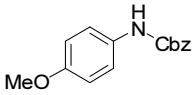
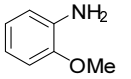
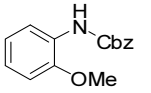
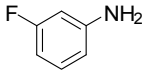
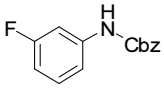
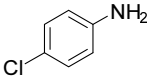
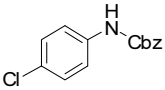
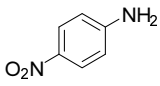
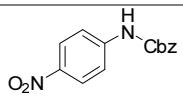
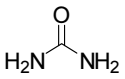
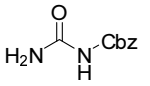
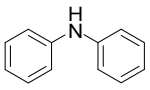
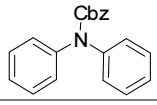
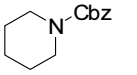
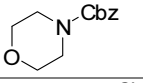
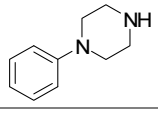
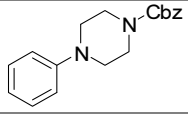
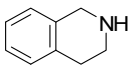
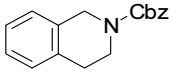
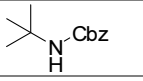
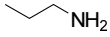
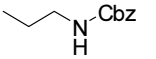
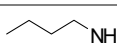
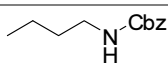
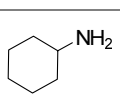
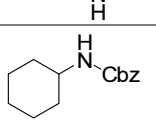
After the optimization of the reaction conditions and encouraged by the experimental results, we extended the *N*-Cbz protection to a series of structurally diverse amines under microwave irradiation at 100W (*Scheme* 2) (*Table* 2, entries **1a**–**18a**).

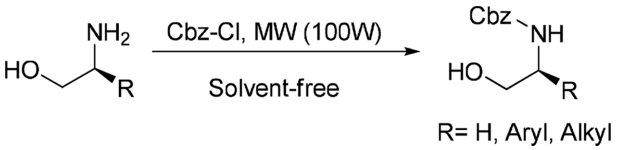
As can be seen from *Table* 2, the protection of primary and secondary, aliphatic and aromatic amines afford their corresponding *N*-Cbz protected derivatives within 2-5 min in 82–98% yield. The thin-layer chromatography (TLC) analysis of the crude mixture revealed the formation of a new product less polar than the starting amine. Purification of the crude product by crystallization in *n*-hexane gave the *N*-Cbz carbamates in good to excellent yields (*Table* 2). From aromatic amines, the nature of the substituents, the electron-donating or withdrawing groups such as OMe, NO_2, F, Cl, do not have a significant influence on the time



***Scheme* 2.** Microwave-assisted protection of various structurally amines.

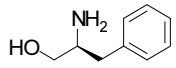
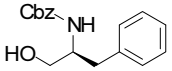
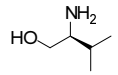
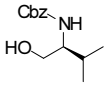
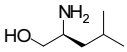
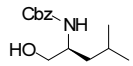
***Table* 2.** *N*-Benzyloxycarbonylation of amines under microwave irradiation

Entry	Amine	Compound	Time (min)	Yield (%)
1a			2	98
2a			2	97
3a			2	90
4a			2	94
5a			2	94
6a			3	90
7a			3	91
8a			5	88
9a			3	87
10a			4	85
11a			4	82
12a			4	88
13a			4	86
14a			4	84
15a			3	87
16a			2	93
17a			2	92
18a			2	91



***Scheme* 3.** Microwave-assisted protection of *β*-amino alcohols.

***Table* 3.** *N*-Benzyloxycarbonylation of *β*-amino alcohol under microwave irradiation

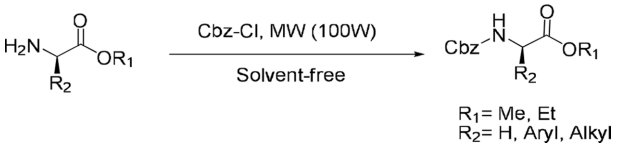
Entry	Amine	Compound	Time (min)	Yield (%)
1b			3	85
2b			4	83
3b			4	80
4b			4	81

and the yields of the reaction. Surprisingly, only the mono *N*-Cbz derivative was observed for urea substrate (entry **9a**) derivative without formation of the bis *N*-Cbz derivative, in spite of the symmetry of the substrate. We think that the reactivity of the second nitrogen, we believe that the benzyloxycarbonylation of the first nitrogen affects the second and so makes it unreactive.

In order to exploit the chemo-selectivity of this method, we attempted the *N*-benzyloxycarbonylation of *β*-amino alcohols (*Scheme* 3), alaninol, valinol, leucinol and phenylalaninol (*Table* 3, entries **1b**–**4b**). In all cases, only the *N*-Cbz protected compounds were obtained, without any competitive formation of *O*-Cbz compounds, this protocol showed an excellent chemo-selectivity.

To explore the limits of this procedure, a range of *α*-amino esters were reacted with Cbz-Cl under the same reaction conditions (*Table* 4, entries **1c**–**4c**). The reactions were completed (as monitored by TLC) after 3-4 minutes. In all cases, the amino esters were converted into their corresponding *N*-Cbz derivatives in good yields.

In particular, the NMR spectroscopy of the entry **3c** shows a doubling of some signals due to the existence of two major



***Scheme* 4.** Microwave-assisted benzyloxycarbonylation of *α*-amino esters.

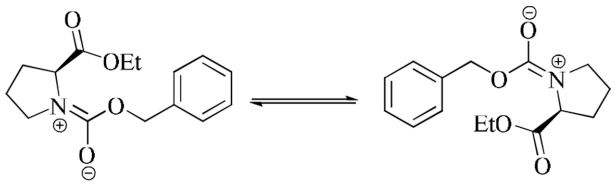
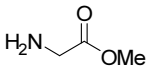
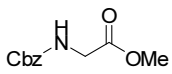
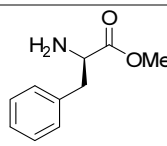
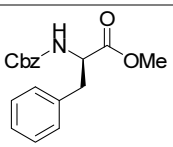
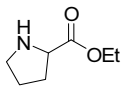
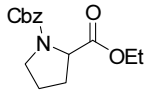
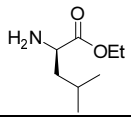
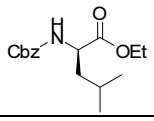
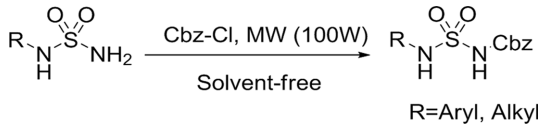


***Figure* 1.** The two major rotamers of proline amino ester.

***Table* 4.** *N*-Benzyloxycarbonylation of *α*-amino esters under microwave irradiation

Entry	Amine	Compound	Time (min)	Yield (%)
1c			3	85
2c			3	85
3c			4	80
4c			4	82



***Scheme* 5.** Microwave-assisted benzyloxycarbonylation of sulfonamides.

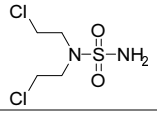
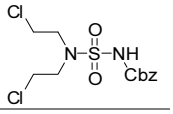
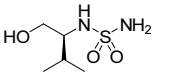
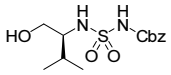
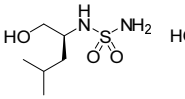
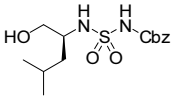
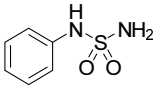
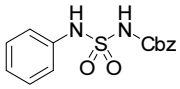
rotamers in agreement with literature for the Fmoc group.[25] (*Fig.* 1).

To increase the scope of this reaction, we prolonged this study to sulfonamides (*Scheme* 5) and were tested to verify the region-selectivity. The results showed that the benzyloxycarbonylation occurred at the primary amine and no bis *N*-Cbz formation was observed. All *N*-protected sulfonamides were obtained in good yields (*Table* 5, entries **1d**–**4d**).

All *N*-Cbz products structures were characterized by the different spectral methods (^{1}H, ^{13}C NMR, IR and MS). In the ^{1}H NMR, The resulting carbamates are confirmed by the appearance of a singlet between 4.5 and 5.2 ppm corresponding to methylene protons (OCH_2).

In the ^{13}C NMR, the benzylic carbon of the Cbz group appeared at 68 ppm. In infrared spectra, the presence of absorption band at 1678–1700 cm^{-1} (CO carbamate) approves all the protected structures.

***Table* 5.** *N*-Benzyloxycarbonylation of sulfonamides under microwave irradiation

Entry	Amine	Compound	Time (min)	Yield (%)
1d			7	81
2d			6	80
3d			6	82
4d			5	83

The fragmentation in mass spectrometry in different mode of ionization on (ESI) shows loss of the benzyl group (91%) and shows the molecular peak with a relative intensity.

CONCLUSION

In conclusion, we have described an efficient and mild approach for the microwave-assisted benzyloxycarbonylation of amine functionality in various chemical scaffolds. The main advantages of our method include the absence of any solvent and catalyst in the reaction, easy work up, no side reaction, facile isolation of products, excellent yields. Further work is ongoing to explore the use of alternative energy sources in protecting groups. We believe that our process will find its use in the peptides chemistry.

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