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A New Reagent for Incorporating the 2-(1-Adamantyl)-2-propyloxycarbonyl Protecting Group into Amines

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ABSTRACT: *A new reagent to incorporate the 2-(1-adamantyl)-2-propyloxycarbonyl (Ad-POC) protecting group into amines, 2-(1-adamantyl)-2-propyl p-nitrophenylcarbonate, was prepared in two steps from the commercially available 1-adamantylcarbonyl chloride. The Ad-POC group was introduced into a variety of amines and amino acid derivatives.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:192–195, 2000

INTRODUCTION

Carbamate protecting groups such as benzoyloxycarbonyl (CBz) [1], *t*-butyloxycarbonyl (t-BOC) [2], and 2-(*p*-biphenyl)-2-propyloxycarbonyl (B-POC) [3] are commonly employed in synthetic schemes to protect amines. Kalbacher and Voelter [4,5] introduced the 2-(1-adamantyl)-2-propyloxycarbonyl (Ad-POC) protecting group as an alternative to the aforementioned carbamates. The Ad-POC protecting group possesses several advantages over these carbamate protecting groups. The CBz derivatives of methionine can produce unwanted alkylation of the sulfur atom during the removal of the protecting group. The Ad-POC protected derivatives of methionine do not appear to undergo these alkylation reactions. In contrast to B-POC derivatives of amino acids, which undergo slow autocatalyzed decomposition [6], Ad-POC-protected amino acids are stable for several months at room temperature. In addition, the Ad-POC group can be removed 10^3 times faster than the *t*-BOC group [4]. Typically, the Ad-POC group can be cleaved within 2–3 minutes at room temperature in the presence of 3% trifluoroacetic acid.

Kalbacher and Voelter described two different reagents for introducing the Ad-POC group. The first reagent, 2-(1-adamantyl)-2-propyl phenylcarbonate, was used to protect a variety of amino acids. One drawback of the phenylcarbonate reagent was contamination of a number of Ad-POC protected amino acids with phenol and diphenyl carbonate despite several recrystallizations. The second reagent, 2-(1-adamantyl)-2-propyl carbonyl fluoride, a compound obtained from the reaction of 2-(1-adamantyl)-2-propanol with fluoroformyl chloride, circumvented the contamination problem. The toxicity of fluoroformyl chloride, however, limits the utility of this method.

In our laboratory, we were unable to obtain the Ad-POC derivative of *N*-methylaniline from the phenylcarbonate reagent. Considering the potential problems associated with the carbonyl fluoride reagent, we chose to develop a new reagent to introduce the Ad-POC protecting group, 2-(1-adamantyl)-2-propyl *p*-nitrophenyl carbonate (**1**). A two-step synthesis produces multigram quantities of **1** from the commercially available 1-adamantylcarbonyl chloride (Scheme 1). Compound **1** is also very stable with no decomposition being observed over a period of several months when stored at 0°C.

DMF solutions of primary aliphatic and secondary amines or amino acid derivatives when treated with **1** in the presence of sodium carbonate yield the

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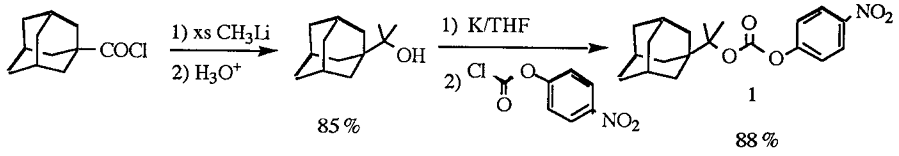
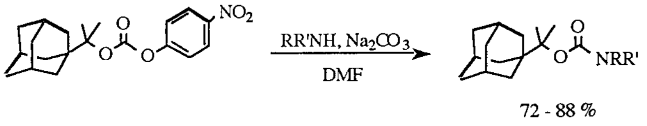


SCHEME 1

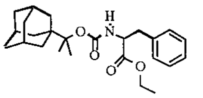
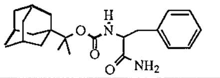
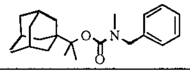
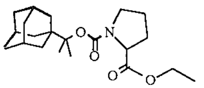
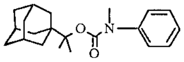
anticipated Ad-POC protected compounds (equation 1).



(1)

As evidenced in Table 1, we obtained the desired compounds in very good yields that are comparable to those obtained in previously described methods. All compounds were isolated in pure form after column chromatography. We believe that compound **1** is an excellent alternative for the reagents described by Kalbacher and Voelter to prepare Ad-POC protected amines.

TABLE 1 Ad-POC Derivatives Prepared from the Reaction of 2-(1-Adamantyl)-2-propyl *p*-nitrophenyl Carbonate with Amines and Amino Acid Derivatives

Ad-POC Derivative	Percent Yield
	82
	85
	88
	86
	72

EXPERIMENTAL

Capillary melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic spectra were recorded on a Varian Unityplus 300 MHz spectrometer. Proton spectra were recorded at 300 MHz and are referenced to tetramethylsilane ($\delta = 0.00$ ppm). Carbon spectra were recorded at 75.46 MHz and are referenced to tetramethylsilane ($\delta = 0.00$ ppm). Tetrahydrofuran (THF) was dried by being refluxed and distilled from $LiA1H_4$. DMF was distilled from barium oxide and stored over sodium hydroxide pellets.

2-(1-Adamantyl)-2-propanol

To a 1 L three-necked round-bottomed flask equipped with a magnetic stirrer, addition funnel, and condenser was added under an argon atmosphere 200 mL anhydrous diethyl ether and 54 mL (0.076 mole) of 1.4 M methyllithium solution in diethyl ether 1-Adamantylcarbonyl chloride (5.02 g, 0.025 mole) was dissolved in 100 mL of anhydrous diethyl ether and added dropwise to the methyllithium solution. After the addition was complete, the reaction mixture was refluxed for 30 minutes, cooled to room temperature, and the reaction was quenched by the slow dropwise addition of water.

The ether layer was separated, washed with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a light yellow oil. The yellow oil was dissolved in a minimum amount of hexanes, and placed on a silica gel column. Trace quantities of ketone were separated using hexanes as eluent. The eluent was changed to a 10% (v/v) ether-hexanes solution; 4.19 g(85.3% yield) of 2-(1-adamantyl)-2-propanol ($R_f = 0.3$) was obtained after removal of the solvent under reduced pressure; m.p. = 77–80°C (literature value = 78–80°C [7]). ^{1}H-NMR: ($CDCl_3$) δ 1.08 (singlet, 6H, -CH_3), 1.75 (singlet, 6H, -CH_2), 1.76 (singlet, 6H, -CH_2), 2.00 (singlet, 3H, -CH), 4.80 (broad singlet, 1H, -OH). ^{13}C NMR: ($CDCl_3$) δ 24.1 (-CH_3), 28.5 (Ad C-3), 36.2 (-CH_2), 37.0 (-CH_2), 38.7 (Ad C-1), 74.8 (C–O).

Potassium 2-(1-Adamantyl)-2-propoxide

To a 250 mL round-bottomed flask equipped with a magnetic stirrer, condenser, and argon atmosphere was added 2.01 g (0.0104 mole) 2-(1-adamantyl)-2-

propanol, 80 mL anhydrous THF, and 0.62 g (0.016 mole) potassium metal. The reaction mixture was allowed to reflux overnight. After the mixture had been cooled to room temperature, the excess potassium metal was removed by filtration through glass wool. The reaction mixture was assumed to contain 0.014 mole of potassium 2-(1-adamantyl-2-propoxide).

2-(1-Adamantyl)-2-propyl p-Nitrophenyl Carbonate (**1**)

To a 250 mL round-bottomed flask cooled in an ice bath and equipped with a magnetic stirrer, an addition funnel, and an argon atmosphere was added 2.08 g (0.0104 mole) of 4-nitrophenyl chloroformate in 60 mL of anhydrous THF. A solution of 0.0104 mole of potassium 2-(1-adamantyl)-2-propoxide in anhydrous THF was added dropwise. After the addition was complete, the THF was removed under reduced pressure, and the resulting semi-solid was mixed with 150 mL diethyl ether. The ether solution was washed with 50 mL of 5% sodium bicarbonate solution, 50 mL of a saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a light yellow oil. The yellow oil was dissolved in a minimum amount of 10% (v/v) ether-hexanes solution, placed on a silica gel column, and eluted with 10% (v/v) ether-hexanes solution. After removal of the solvent under reduced pressure, 3.30 g (88.4% yield) of 2-(1-adamantyl)-2-propyl *p*-nitrophenyl carbonate (R_f = 0.5) was obtained. The product was recrystallized from hexanes; m.p. = 101–103°C. ^{1}H-NMR: ($CDCl_3$) δ 1.48 (singlet, 6H, -CH_3), 1.62 (singlet, 6H, -CH_2), 1.68 (singlet, 6H, -CH_2), 2.10 (singlet, 3H, -CH), 7.29 (doublet, 2H, Ar-H), 8.24 (doublet, 2H, Ar-H). ^{13}C NMR: ($CDCl_3$) δ 19.2 (-CH_3), 28.4 (Ad C-3), 35.9 (-CH_2), 36.9 (-CH_2), 39.7 (Ad C-1), 91.9 (C-O), 122.1 (o-C), 125.1 (m-C), 145.0 (C), 150.7 (p-C), 155.9 (C=O). Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.96; H, 7.34; N, 4.08. Found C, 69.78; H, 7.12; N, 4.21.

General Procedure for Preparing Ad-POC Derivatives

To a 50 mL round-bottomed flask equipped with magnetic stirrer, condenser, and drying tube was added 0.0017–0.0023 mole of 2-(1-adamantyl)-2-propyl *p*-nitrophenyl carbonate, 0.0017–0.0023 mole of the amine, 1.0 g (0.0094 mole) anhydrous sodium carbonate, and 10 mL anhydrous DMF. The mixture was heated to 100°C and allowed to stir overnight. The DMF was removed under vacuum (1 mmHg), and the resulting yellow semi-solid was mixed with 100 mL of diethyl ether. The ether solution was washed with 50 mL of a 1M sodium hydroxide solution, then with 50 mL of a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure to give an oil.

2-(1-Adamantyl)-2-propyl N-(S)-1-Ethoxycarbonyl-2-phenylethylcarbamate

Treatment of 0.39 g (0.0020 mole) of ethyl L-phenylalaninate with 0.79 g (0.0020 mole) of **1** resulted in a light yellow oil, which was dissolved in a minimum amount of 20% (v/v) ether-hexanes, placed on a silica gel column, and eluted with 20% (v/) ether hexanes. The solvent was removed under reduced pressure to give 0.74 g (82% yield) 2-(1-adamantyl)-2-propyl N-(S)-1-ethoxycarbonyl-2-phenylethyl carbamate (R_f = 0.3) as a white solid; m.p. = 57–60°C. ^{1}H-NMR: ($CDCl_3$) δ 1.21 (triplet, 3H, -CH_3), 1.42 (doublet, 6H, -CH_3), 1.62 (singlet, 6H, -CH_2), 1.68 (singlet, 6H, -CH_2), 2.00 (broad singlet, 3H, -CH), 2.89 (broad singlet, 1H, -NH), 3.21 (multiplet, 2H, -C$\underline{H}_2$C=O), 4.27 (quartet, 2H, -C$\underline{H}_2CH_3$), 4.57, and 5.01 (multiplet, 1H, -CH), 7.16 (multiplet, 2H, ArH), 7.23 (multiplet, 3H, Ar-H). ^{13}C NMR: ($CDCl_3$)δ 14.1 (-CH_3), 19.7 (-CH_3), 28.5 (Ad C-3), 36.1 (-CH_2), 37.1 (-CH_2), 39.5 (Ar-C$\underline{H}_2$), 40.0 (Ad C-1), 54.5 (CH), 54.5 (OC$\underline{H}_2$−), 86.4 (C-O), 126.9 (p-C), 128.4 (o-C), 129.4 (m-C), 136.1 (C), 155.3 (-N-$\underline{C}$=O), 172.0 (-O-$\underline{C}$=O). Anal. Calcd. for $C_{25}H_{35}NO_4$: C, 72.60; H, 8.53; N, 3.38. Found: C, 72.54; H, 8.45; N, 3.52.

2-(1-Adamantyl)-2-propyl N-(S)-1-Carbamoyl-2-phenylethylcarbamate

Treatment of 0.39 g (0.0023 mole) of L-phenylalaminamide with 0.82 g (0.0023 mole) of *1* resulted in a light yellow oil which was dissolved in a minimum amount of 10% (v/v) ether-hexanes, placed on a silica gel column, and eluted with 10% (v/v) ether hexanes. The solvent was removed under reduced pressure to give 0.75 g (86% yield) 2-(1-adamantyl)-2-propyl *N*-(*S*)-1-carbamoyl-2-phenylethyl carbamate (R_f = 0.2) as a white solid; m.p. = 88–90°C. ^{1}H-NMR: ($CDCl_3$)δ 1.42 (doublet, 6H, -CH_3), 1.64 (multiplet, 12H, -CH_2), 2.82 (broad singlet, 1H, -NH), 3.01 (multiplet, 3H, -CH), 3.16 (broad singlet, 2H, -C$\underline{H}_2$C=O), 4.40 and 5.10 (multiplet, 1H, -CH), 5.72 and 6.01 (multiplet, 2H, -NH_2). ^{13}C NMR: ($CDCl_3$) δ 19.7 (-CH_3), 28.5 (Ad C-3), 35.8 (-CH_2), 37.0 (-CH_2), 38.5 (Ar-C$\underline{H}_2$), 39.5 (Ad C-1), 53.2 (CH), 86.4 (C–O), 126.9 (p-C), 128.6(*o*-C), 129.3 (*m*-C), 136.7 (C), 155.8 (-N–$\underline{C}$=O), 173.8 (-O–

$\underline{\text{C}}$ = O). Anal. Calcd. for $C_{23}H_{32}N_2O_3$: C, 71.84; H, 8.38; N, 7.29. Found: C, 72.05; H, 8.52; N, 7.18.

2-(1-Adamantyl)-2-propyl N-Methyl-N-Benzylcarbamate

Treatment of 0.21 g (0.0017 mole) of *N*- methyl benzylamine with 0.60 g (0.0017 mole) of **1** resulted in a light yellow oil, which was dissolved in a minimum amount of 20% (v/v) ether-hexanes, placed on a silica gel column, and eluted with 20% (v/v) ether hexanes. The solvent was removed under reduced pressure to give 0.49 g (86% yield) 2-(1-adamantyl)-2-propyl *N*-methyl-*N*-benzylcarbamate (R_f = 0.3) as a white solid; m.p. = 61–68°C. ^{1}H-NMR: ($CDCl_3$) δ 1.45 (singlet, 6H, -CH_3), 1.49 (singlet, 6H, -CH_2), 1.82 (multiplet, 6H, -CH_2), 2.00 (broad singlet, 3H, -CH), 3.82 (broad singlet, 3H, -CH_3), 4.42 (broad singlet, 2H, -NCH_2−), 7.25 (multiplet, 5H, Ar-H). ^{13}C NMR: ($CDCl_3$) δ 19.8 (-CH_3), 28.5 (Ad C-3), 34.3 (-NCH_3), 36.1 (-CH_2), 37.0 (-CH_2), 39.8 (Ad C-1), 52.4 (Ar-CH_2), 86.6 (C-O), 127.6 (*o*-C), 128.1 (m-C), 128.4 (*p*-C), 138.1 (C), 155.9 (C = O). Anal. Calcd. for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15; N, 4.10. Found: C, 77.11; H, 8.95; N, 4.01.

2-(1-Adamantyl)-2-propyl N-Methyl-N-Phenylcarbamate

Treatment of 0.21 g (0.0017 mole) of *N*-methylaniline with 0.60 g (0.0017 mole) of **1** resulted in a light yellow oil, which was dissolved in a minimum amount of 20% (v/v) ether-hexanes, placed on a silica gel column, and eluted with 20% (v/v) ether hexanes. The solvent was removed under reduced pressure to give 0.49 g (86% yield) 2-(1-adamantyl)-2-propyl *N*-methyl-*N*-phenylcarbamate (R_f = 0.3) as a white solid; m.p. = 65–68°C. ^{1}H-NMR: ($CDCl_3$) δ 1.45 (singlet, 6H, -CH_3), 1.49 (singlet, 6H, -CH_2), 1.82 (multiplet, 6H, -CH_2), 2.00 (broad singlet, 3H, -CH), 3.82 (broad singlet, 3H, -CH_3), 4.42 (broad singlet, 2H, -NCH_2−), 7.25 (multiplet, 5H, Ar-H). ^{13}C NMR: ($CDCl_3$) δ 19.8 (-CH_3), 28.5 (Ad C-3), 34.3 (-NCH_3), 36.1 (-CH_2), 37.0 (-CH_2), 39.8 (Ad C-1), 52.4 (Ar-CH_2), 86.6 (C-O), 127.6 (*o*-C), 128.1 (m-C), 128.4 (*p*-C), 138.1 (C), 155.9 (C = O). Anal. Calcd. for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found C, 77.18; H, 9.02; N, 4.35.

2-(1-Adamantyl)-2-propyl N-(S)-2-Ethoxycarbonylpyrrolidinylcarbamate

Treatment of 0.32 g (0.0019 mole) of ethyl L-prolinate with 0.76 g (0.0019 mole) of **1** resulted in a light yellow oil, which was dissolved in a minimum amount of 30% (v/v) ether-hexanes, placed on a silica gel column, and eluted with 30% (v/v) ether hexanes. The solvent was removed under reduced pressure to give 0.66 g (86% yield) 2-(1-adamantyl)-2-propyl *N*-(*S*)-2-ethoxycarbonylpyrrolidinylcarbamate (R_f = 0.3) as a white solid; m.p. = 60–62°C. ^{1}H-NMR: ($CDCl_3$) δ 1.22 (triplet, 3H, -CH_3), 1.43 (doublet, 6H, -CH_3), 1.64 (multiplet, 12H, -CH_2), 2.01 (broad singlet, 3H, -CH), 3.42 (multiplet, 2H, -CH_2), 3.60 (multiplet, 2H, -CH_2N), 4.20 (multiplet, 1H, -CH), 4.38 (quartet, 2H, -CH_2O). ^{13}C NMR: ($CDCl_3$) δ 14.1 (-CH_3), 19.8 (-CH_2), 23.1 (-CH_2-$\underline{\text{C}}H_2$-CH_2), 28.4 (Ad C-3), 31.1 (-CH-$\underline{\text{C}}H_2$-CH_2) 35.6 (-CH_2), 36.9 (-CH_2), 39.9 (Ad C-1), 46.5 (N-$\underline{\text{C}}H_2$), 59.0 ($\underline{\text{C}}H_2$-O), 70.0 (N-$\underline{\text{C}}$H −), 86.9 (C-O), 143.9 (C), 154.1 (N–$\underline{\text{C}}$ = O), 173.1 (O–$\underline{\text{C}}$ = O). Anal. Calcd. for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.30; H, 9.08; N, 3.76.

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