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A simple and efficient biphasic method for the preparation of 4-nitrophenyl *N*-methyl- and *N*-alkylcarbamates

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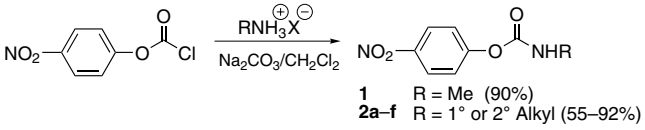
Abstract—Treatment of 4-nitrophenyl chloroformate with alkylammonium hydrochloride salts and solid anhydrous Na_2CO_3 in either CH_2Cl_2 or CH_3CN gave 4-nitrophenyl *N*-methylcarbamate and other *N*-alkylcarbamate analogues in excellent yields. Of particular interest is the observation that 4-nitrophenyl *N*-methylcarbamate, a safer alternative to the highly toxic methyl isocyanate, is obtained in quantitative yield (≥95% pure as determined by ^1H NMR) after simple filtration and solvent evaporation.

N-Methylcarbamates and *N*-methylureas are important classes of biologically active compounds that have found widespread use in a variety of medicinal[1] and agricultural applications.[2] The enhanced conformational flexibilities[3] and potential for H-bonding interactions[4] make ureas and carbamates attractive alternatives to analogous acyl functional groups such as amides, carbonates, or esters.[5] The reagent commonly used for introducing an *N*-methylcarbamoyl moiety is methyl isocyanate.[6] Unfortunately, methyl isocyanate is a highly toxic low boiling liquid, and issues surrounding its safe application have necessitated the development of less toxic and/or more convenient reagents.[7] One such alternative reagent is 4-nitrophenyl *N*-methylcarbamate (**1**).[8] Compound **1** is a solid at ambient temperature (mp = 154–155 °C ($CHCl_3$),[8b] 149 °C (hexane),[8c] 150–151 °C[8d]). It is soluble in most common organic solvents, may be stored indefinitely in a dessicator at room temperature, and is safer and easier to handle than methyl isocyanate. Unfortunately, methods previously published for its preparation suffer from several drawbacks. These drawbacks include low yields, labor-intensive multi-step procedures, and use of toxic reagents.[8] We now report a simple and convenient one-pot biphasic method for preparing 4-ntirophenyl *N*-methylcarbamate and related *N*-alkyl analogues (Scheme 1). The method works well with a variety of primary ammonium salts, gives the *N*-alkylcarbamate products in excellent yields, and is exceptionally simple (Table 1).[9] There was a pronounced solvent effect observed for compound **1**, and yields were 30–40% lower when CH_3CN was used in place of CH_2Cl_2 under



Scheme 1.

Table 1.

Entry	R	Product	Time[a,b]	Yield (%)[b,c]
1	CH_3–	**1**	48 (24 h)	93 (62)
2	$PhCH_2$–	**2a**	7 d (22 h)	92 (81)
3	$CH_3CH_2CH_2$–	**2b**	24 h (8 h)	80 (82)
4	$PhCH_2O$–	**2c**	9 d (67 h)	89 (71)
5	$CH_3O_2CCH_2$–	**2d**	7d (96 h)	55 (70)
6	$CH_3O_2CCH(CH_2Ph)$–	**2e**	5 d (115 h)	87 (67)
7	$CH_3O_2CCH(Ph)$–	**2f**	5 d (5 d)	73 (50)
8	$(CH_3)_3C$–	**2g**	—	No Rxn

[a] Reactions were performed in CH_2Cl_2 or CH_3CN.
[b] Values in parentheses are for reactions in CH_3CN.
[c] Isolated yields.

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Table 2.

Conc.[a]	Solvent	Product	Yield (%)[a–c]
0.2 M	CH_2Cl_2 (CH_3CN)	**1**	60 (25)
0.1 M	CH_2Cl_2 (CH_3CN)	**1**	84 (50)
0.04 M	CH_2Cl_2 (CH_3CN)	**1**	91 (60)

[a] Reactions run on 0.5 mmol scale.
[b] Isolated yields.
[c] Yields in parentheses are for reactions in CH_3CN.

otherwise identical conditions. Use of higher concentrations gave decreased yields of compound **1** in both CH_2Cl_2 and CH_3CN (Table 2). The major byproduct for these reactions was the bis-substitution product 1,3-dimethylurea. The success of the method depends on the low solubility of the primary ammonium salts, which allows for slow release of the nucleophile into the solution. Unlike many biphasic reactions, no phase transfer catalyst is employed. The solubility-controlled release of the nucleophile obviates procedures typically used to obtain time-dependant concentrations of reagents (e.g., syringe–pump addition of the free amine), and allows use of the commercially available hydrochloride salts without previous deprotonation. In the case of compound **1**, crude product was obtained in quantitative yield with $\geqslant$95% purity after simple filtration. Analytically pure material was obtained after flash chromatography.[10]

Procedure for 4-nitrophenyl N-methylcarbamate (**1**):[11] To a flame-dried 500 mL Kjeldahl flask containing dried[12] CH_2Cl_2 (240 mL) were added 4-nitrophenyl chloroformate (2.0 g, 9.9 mmol), anhydrous Na_2CO_3 (2.4 g, 23 mmol), and methylammonium chloride (0.680 g, 10.2 mmol). The resulting suspension was stirred and protected from moisture (N_2 atmosphere or simple capping of flask worked equally well) until 4-nitrophenyl chloroformate was consumed (48–72 h). The reaction rate depended on the rate of stirring, as is generally the case for biphasic reactions, and maximum stir-plate speeds were required to achieve optimal results. Solids were removed via filtration (Celite or Whatman GF/A glass microfibre filter paper) and volatiles were removed under reduced pressure to give **1** as a light yellow solid in quantitative yield. This material was $\geqslant$95% pure (determined by ^{1}H NMR) and could be used for carbamoylation reactions without further purification. Flash[10] chromatography (40% EtOAc/hexanes) gave compound **1** as a white solid (1.8 g, 93%).[13]

In summary, we have developed a simple and efficient, one-pot method for the preparation of 4-nitrophenyl *N*-methylcarbamate and *N*-alkylcarbamate analogues. The method avoids the drawbacks and limitations associated with previously reported methods for 4-nitrophenyl *N*-methylcarbamate, and provides the title compound in quantitative yield and $\geqslant$95% purity. The only workup required is simple filtration followed by solvent evaporation. This method is by far the most simple and efficient method reported for compound **1** to date, and may be applied as a useful alternative[14] for preparing additional 4-nitrophenyl *N*-alkylcarbamates as illustrated by the preparation of compounds **2a**–**f**.

Acknowledgements

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9. All compounds gave clean ^{1}H and ^{13}C NMR spectra and molecular formulas were confirmed by high resolution mass spectrometry (M^+ within $\pm$5 ppm of theory). Char-

acterization data were as follows: (**2a**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.26–8.24 (m, 2H), 7.40–7.32 (m, 7H), 5.51 (br s, 1H), 4.48 (d, $J = 6.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.0, 153.4, 144.9, 137.5, 129.1, 128.2, 127.9, 125.3, 122.2, 115.8, 45.6; MS (ES) m/z 273.0877 ($[M+H]^+$ $[C_{14}H_{13}N_2O_4] = 273.0870$); (**2b**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.24 (d, $J = 9.0$ Hz, 2H), 7.32 (d, $J = 9.0$ Hz, 2H), 5.27 (br s, 1H), 3.29–3.25 (m, 2H), 1.65–1.61 (m, 2H), 0.99 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.1, 153.6, 144.9, 126.3, 125.3, 122.2, 115.8, 43.3, 23.1, 11.4; MS (ES) m/z 247.0701 ($[M+Na]^+$ $[C_{10}H_{12}N_2O_4Na] = 247.0689$); (**2c**): (^{1}H and ^{13}C NMR data were consistent with the literature values);[15] MS (ES) m/z 289.0823 ($[M+H]^+$ $[C_{14}H_{13}N_2O_5] = 289.0819$); (**2d**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.25 (d, $J = 9.3$ Hz, 2H), 7.34 (dd, $J = 7.2$, 2.1 Hz, 2H), 5.75 (br s, 1H), 4.09 (d, $J = 5.4$ Hz, 2H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1, 155.9, 153.4, 145.2, 125.4, 122.3, 115.8, 52.9, 43.0; MS (ES) m/z 255.0619 ($[M+H]^+$ $[C_{10}H_{11}N_2O_6] = 255.0612$); (**2e**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, $J = 5.7$ Hz, 2H), 7.35–7.17 (m, 7H), 5.68 (d, $J = 4.8$ Hz, 1H), 4.74–4.71 (m, 1H), 3.80 (s, 3H), 3.25 (dd, $J = 8.3$, 3.4 Hz, 1H), 3.15 (dd, $J = 8.4$, 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8, 155.6, 153.0, 145.1, 135.3, 129.4, 129.0, 127.7, 126.4, 125.4, 122.2, 115.8, 55.2, 53.0, 38.2; MS (ES) m/z 345.1071 ($[M+H]^+$ $[C_{17}H_{17}N_2O_6] = 345.1081$); (**2f**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.22 (d, $J = 9.5$ Hz, 2H), 7.41–7.39 (m, 5H), 7.30 (d, $J = 9.0$ Hz, 2H), 6.31 (br s, 1H), 5.42 (d, $J = 7.5$ Hz, 1H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 155.7, 152.4, 145.1, 135.9, 129.4, 129.2, 127.4, 125.3, 122.1, 115.7, 58.2, 53.3; MS 331.0925 (ES) m/z ($[M+H]^+$ $[C_{16}H_{15}N_2O_6] = 331.0925$).

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13. Characterization data for compound **1**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.25 (d, $J = 8.5$ Hz, 2H), 7.32 (d, $J = 8.5$ Hz, 2H), 5.08 (br s, 1H), 2.94 (d, $J = 5.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.9, 153.7, 125.1, 121.9, 27.8; mp = 150–152 °C; MS 197.0561 (ES) m/z ($[M+H]^+$ $[C_8H_9N_2O_4] = 197.0557$), Anal. Calcd for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 49.04; H, 4.30; N, 14.27.
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