Azidomethyl 4-Nitrophenyl Carbonate – A Reagent for the One-Step Introduction of the Azidomethyloxycarbonyl (Azoc) Protecting Group

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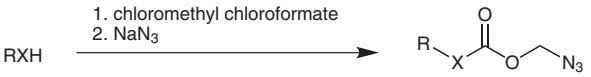
Abstract: Presented here is the three-step synthesis of azidomethyl 4-nitrophenyl carbonate in 58% overall yield. This carbonate allows for the high-yielding (≥90%) introduction of the phosphine-labile azidomethyloxycarbonyl (Azoc) protecting group in one step. The reagent protects a range of amines, including amino acids. For non-ionic substrates, pure carbamates are obtained after extractive work-up.

Key words: Azoc, amine, amino acids, protecting group

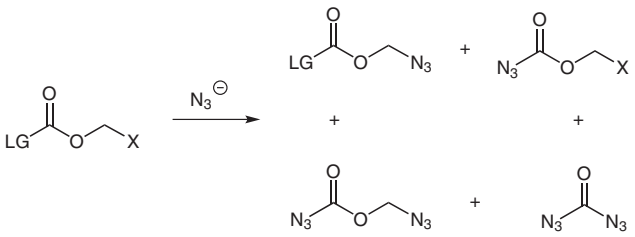
Protecting groups are indispensable tools for the synthesis of complex target molecules. Ideal protecting groups should be (i) easy to introduce in high yield, (ii) stable toward a wide range of reaction conditions, (iii) easily removed in high yield, and (iv) orthogonal to as many other protecting groups as possible.[1] The ever-increasing number of protecting groups makes the latter criterion increasingly difficult to meet. Recently, Pothukanuri and Winssinger introduced the azidomethyloxycarbonyl (Azoc) group as a new protecting group for amines and alcohols.[2] This group can be removed by treatment with phosphines. It has been succesfully employed for the synthesis of peptides, carbohydrates, peptide nucleic acids (PNAs), and triazoles.[2–4] The Azoc group satisfactorily fulfills criteria (ii)–(iv), but thus far, the introduction of Azoc moieties required a two-step process (Scheme 1)[2,3] with overall yields of 34–86% that often involves two chromatographic purifications.



Scheme 1 Two-step introduction of the Azoc group; X = NH, O[2,3]

Here we present the synthesis of azidomethyl 4-nitrophenyl carbonate (**1**), a reagent for the one-step introduction of the Azoc group, together with a convenient methodology for protecting amines using this reagent (Table 1).

The choice of the leaving group affects the stability of a given Azoc reagent. To be nonexplosive, organic azides should fulfill the criteria that the number of nitrogen atoms must not exceed that of carbons and that $(N_C + N_O)/N_N \geq 3$,[5] where N_C, N_O, and N_N are the number of carbon atoms, oxygen atoms, and nitrogen atoms, respectively. Based on this equation, leaving groups like HOAt [$(N_C + N_O)/N_N = 1.4$], HOBt [$(N_C + N_O)/N_N = 1.8$], and NHS [$(N_C + N_O)/N_N = 2.8$] were excluded. Instead, 4-nitrophenol [$(N_C + N_O)/N_N = 3.3$] and pentafluorophenol [$(N_C + N_O + N_F)/N_N = 5.3$] were identified as leaving-group options. A second criterion helped to select the former among these two options. This was the desire to suppress the formation of potentially unstable, toxic and explosive side products like azidomethyl azidoformate [$(N_C + N_O)/N_N = 0.7$] and carbonyl diazide (Scheme 2).



Scheme 2 Product and possible side products of the azide introduction reaction of routes to an Azoc reagent; LG = leaving group, X = halogen

The pK_a values as a simple measure of leaving group capability are 7.16 for 4-nitrophenol and 5.30 for pentafluorophenol, making carbonates of 4-nitrophenol the more stable of the two, less likely to undergo exchange reactions producing azidocarbonates. Additionally, formation of chloromethyl 4-nitrophenyl carbonate (**3**), iodomethyl 4-nitrophenyl carbonate (**4**), and substitution reactions with iodo compound **4** were described in the literature, particularly the patent literature, making a successful synthesis of **1** likely.[6]

Preparation of **1** (Scheme 3) started from commercially available chloromethyl chloroformate (**2**), which gave nitrophenolate **3** in 89% yield.[6b] Treatment of **3** with sodium azide in DMF, acetonitrile, or toluene/15-crown-5, respectively, showed products of addition-elimination reactions at the carbonyl group and decomposition of **3**, without formation of the desired product **1**. But iodide **4** was accessible in 90% yield through a Finkelstein reaction.[6b] Despite its better leaving group, compound **4** reacted similarly to chloride **3** when treated with sodium azide. Only when the iodide leaving group of **4** was activated by addition of Ag^+ ions did the methylene carbon reach the

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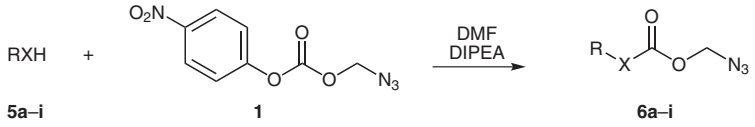
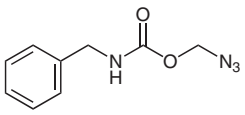
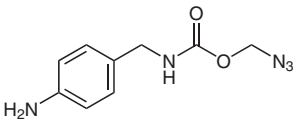
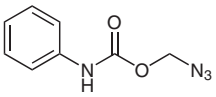
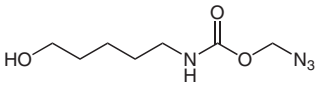
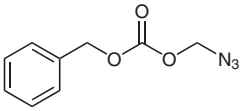
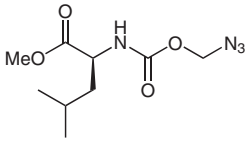
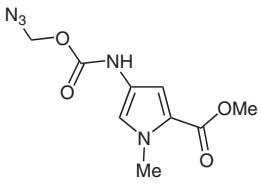
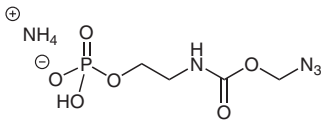
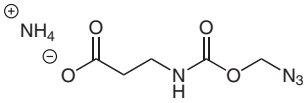
level of reactivity required to compete successfully with that of the carbonate carbon.

Literature reports exist on the substitution of the iodine in **4** in the presence of $AgCO_3$ as base and with silver salts of nucleophiles.[6b–6d] We tested silver azide[7,8] and conditions described by Gediya et al.,[6c] as well as those described by Gallop et al.[6d] We observed formation of the desired azidomethyl 4-nitrophenyl carbonate **1** in 20%[9] yield under the former conditions that involve acetone as solvent, and in 72% yield under the latter conditions that involve toluene as solvent.[10]

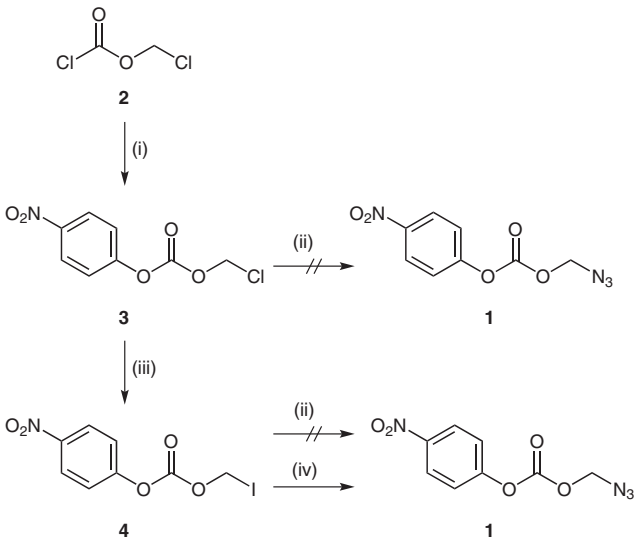
Table 1 Azoc Protection According to General Procedure[11,a]



5a–i **1** **6a–i**

Compd	Product	Temp (°C)	Time	Yield (%)
6a		0	5 min	>99
6b		0	5 min	>99
6c		20	24 h	[b]
6d		0	5 min	98
6e		20	24 h	[c]
6f		0	20 min	93
6g[d]		20	1 h	90[e]
6h		20	30 min	99[f]
6i		20	5 min	91[g]

[a] X = NH, O
[b] No conversion observed after 24 h at 20 °C or after 6 h at 60 °C.
[c] No conversion observed after 24 h.
[d] Starting material **5g** (hydrochloride) was synthesized according to ref. 12.
[e] Yield after flash chromatography, see footnote 11 for details.
[f] Different protocol, see footnote 13.
[g] Different procedure, see footnote 14.



Scheme 3 *Reagents and conditions*: (i) 4-nitrophenol, CH_2Cl_2, pyridine, 0 °C, 2 h, 89%;[6b] (ii) NaN_3 in DMF or MeCN or toluene/15-crown-5, r.t.; (iii) NaI, $NaHCO_3$, acetone, 16 h, 40 °C, 90%;[6b] (iv) AgN_3, toluene, MS 4 Å, r.t., 3 h, 72%.

With azidomethyl 4-nitrophenyl carbonate (**1**) in hand, we then optimized the conditions for the protection of amines. With diisopropyl ethyl amine as base and DMF as solvent, quantitative conversions were observed. Diluting the reaction mixture with ethyl acetate, followed by washing with aqueous carbonate, water, and brine gave carbamates of amines with nonionic residues in near-quantitative yield (Table 1).[11]

Neither anilinic amine (**5b**), aniline itself (**5c**), nor benzyl alcohol (**5e**) showed any reactivity under the chosen conditions, allowing for chemoselective protection of amino groups in richly functionalized substrates. The more electron-rich aminopyrrole **5g**[12] was successfully protected, though. Also, the protection of ionic substrates, such as phosphate **5h**[13] or β-alanine (**5i**)[14] was successful, and pure products were obtained after elution from ion-exchange columns. The one-step protocol avoids the de-esterification step (88–95% yield) of the known syntheses.[2]

In conclusion, we report the three step syntheses of azidomethyl 4-nitrophenyl carbonate (**1**) in 58% overall yield. Compound **1** was employed for chemoselective one-step Azoc protection of amines in yields of 90–99%, including protection of polar amines like phosphate **5h** and amino acid **5i**. It is hoped that these results will lead to a more widespread use of the Azoc protecting group. Phosphine-labile protecting groups and linkers are attractive for their orthogonality to other functionalities and their compatibility with complex substrates, including nucleic acids.[15]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are spectroscopic data of compounds **1**, **6b**,**d**,**g**–**i**, and the complete author list of reference 15.

Acknowledgment

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References and Notes

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(6) See, for example: (a) Gangwar, S.; Pauletti, G. M.; Siahaan, T. J.; Stella, V. J.; Borchardt, R. T. *J. Org. Chem.* **1997**, *62*, 1356. (b) Goebel, T.; Humbert-Droz, E.; Schwarzenbach, M. WO 200029378, **2000**; *Chem. Abstr.* **2000**, *132*, 347496. (c) Gediya, L. K.; Khandelwal, A.; Patel, J.; Belosay, A.; Sabnis, G.; Mehta, J.; Purushottamachar, P.; Njar, V. C. O. *J. Med. Chem.* **2008**, *51*, 3895. (d) Gallop, M. A.; Cundy, K. C.; Zhou, C. X.; Yao, F.; Xiang, J.-N.; Ollman, I. R.; Qiu, F. G. US 20060229361 A1, **2006**; *Chem. Abstr.* **2006**, *145*, 418708.
(7) **CAUTION**: Silver azide is an explosive. Safety equipment such as leather gloves, face shield, protective shield, and ear plugs is recommended. Further safety notes for work with metal and organic azides can be found in ref. 5c.
(8) Remaining silver azide may be quenched through oxidation with aq KI_3 solution under sulfide catalysis (iodine–azide reaction): Silver azide containing salts and contaminated filters were added to a stirred aq solution of KI_3 (500 mL, 0.2 M) and Na_2S (50 mg) resulting in immediate development of N_2. This slurry was stirred overnight.
(9) Calculated from signals in ^{1}H NMR spectrum of crude.
(10) **Azidomethyl 4-Nitrophenyl Carbonate (1)**
$AgNO_3$ (4.60 g, 27.1 mmol, 1.25 equiv) was dissolved in H_2O (20 mL) and added to a stirred solution of NaN_3 (1.76 g, 27.1 mmol, 1.25 equiv) in H_2O (20 mL). AgN_3 (4.06 g, 27.1 mmol, 1.25 equiv) immediately formed as a white microcrystalline precipitate. The supernatant was aspired with a syringe, and the precipitate was washed with H_2O (3 × 30 mL), acetone (3 × 30 mL), and toluene (3 × 30 mL). The AgN_3 was suspended in toluene (50 mL), MS 4 Å (6.0 g) were added, and the resulting slurry was stirred 15 min under argon. Iodomethyl 4-nitrophenyl carbonate[6b] (**4**, 7.00 g, 21.67 mmol, 1.0 equiv) was added in one portion. Complete conversion was detected by TLC [R_f = 0.52 (CH_2Cl_2–PE = 3:2)] after 3 h of stirring in the dark. Silver salts (compare ref. 8) were filtered off, and the filtrate was diluted with CH_2Cl_2 (200 mL) and washed with H_2O (50 mL), Na_2CO_3 solution (2 × 50 mL, 2 M), H_2O (50 mL), and sat. NaCl solution (50 mL). The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting yellow oil was purified by flash column chromatography, eluting with CH_2Cl_2–PE (3:4) → CH_2Cl_2–PE (1:1). The title compound was obtained as a slight yellowish oil that slowly crystallized (3 d) at –18 °C, but rapidly crystallized after addition of a seed crystal (3.72

g, 15.6 mmol, 72%). Yellowish powder, mp 35 °C. IR (neat): 3119, 2962, 2559, 2369, 2105, 1967, 1766, 1617, 1594, 1523, 1491, 1347, 1198 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.32 (s, 2 H, CH_2N_3), 7.40–7.46 (m, 2 H, ArH), 8.28–8.34 (m, 2 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 78.96 (CH_2), 121.74 (CH), 125.45 (CH), 145.72, 152.29, 155.04. MS (EI, 70 eV): *m/z* (%) = 238 (2) $[M]^+$, 196 (12), 166 (36), 139 (40), 122 (42), 56 (100), 28 (71). HRMS (EI): *m/z* calcd for $C_8H_6N_4O_5$: 238.0338 $[M]^+$; found: 238.0319 $[M]^+$. Anal. Calcd for $C_8H_6N_4O_5$: C, 40.35; H, 2.54; N, 23.53. Found: C, 40.25; H, 2.69; N, 23.26.

(11) **General Procedure for Azoc Protection with Azidomethyl 4-Nitrophenyl Carbonate (1) and Analytical Data of Compounds 6b,d,g**

Azidomethyl 4-nitrophenyl carbonate (**1**, 300 mg, 1.26 mmol, 1.0 equiv) was dissolved in anhyd DMF (3 mL) and cooled to 0 °C. Either of compounds **5a–g** (1.26 mmol) was dissolved in anhyd DMF (2 mL) in an separate flask and treated with DIPEA (1.39 mmol, 236 µL, 1.1 equiv). The resulting solution was added dropwise, within 2 min, to the solution of **1**. The reaction was monitored via TLC (CH_2Cl_2–PE = 3:2). After complete conversion, the reaction mixture was diluted with EtOAc (200 mL) and washed with Na_2CO_3 solution (8 × 50 mL, 2 M). The combined aqueous solutions were re-extracted with EtOAc (30 mL). The extract was washed once with H_2O (10 mL). The combined organic phases were washed with sat. NaCl solution (2 × 50 mL), dried over Na_2SO_4, filtered, concentrated in vacuo and dried at $<10^{-3}$ mbar for at least 3 h. Analytical data of compounds **6a** and **6f** were found to be identical to those in ref. 2.

Azidomethyl 4-Aminobenzylcarbamate (6b)

Orange oil which slowly crystallized at –18 °C (2 weeks) to give an orange solid with mp 26–28 °C. IR (neat): 3423, 3328, 2154, 2098, 1723, 1697, 1617, 1539, 1512 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.68 (s, 2 H, NH_2), 4.27 (d, ^3J = 5.9 Hz, 2 H, CH_2Ar), 5.05–5.20 (m, 3 H, CH_2N_3, NH), 6.62–6.68 (m, 2 H, ArH), 7.08 (d, ^3J = 8.3 Hz, 2 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.89 ($ArCH_2$), 75.32 (CH_2N_3), 115.25, 127.59, 128.72, 129.04, 146.08, 155.18. ESI-HRMS: *m/z* calcd for $C_9H_{11}N_5O_2Na$: 244.0805 $[M + Na]^+$; found: 244.0802 $[M + Na]^+$.

Azidomethyl 5-Hydroxypentylcarbamate (6d)

Colorless oil. IR (neat): 3329, 2937, 2864, 2140, 2100, 1705, 1532 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36–1.48 (m, 2 H, H-3), 1.51–1.65 (m, 5 H, H-2, H-4, OH), 3.24 (q, ^3J = 6.7 Hz, 2 H, CH_2NH), 3.65 (t, ^3J = 6.4 Hz, 2 H, CH_2OH), 5.02 (s, 1 H, NH), 5.13 (s, 2 H, CH_2N_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.87 (C-3), 29.51, 32.13, 41.02 (C-1), 62.55 (C-5), 75.22 (CH_2N_3), 155.36 (C=O). ESI-HRMS: *m/z* calcd for $C_7H_{14}N_4O_3Na$: 225.0958 $[M + Na]^+$; found: 225.0964 $[M + Na]^+$.

Methyl 4-[(Azidomethoxy)carbonylamino]-*N*-methylpyrrole-2-carboxylate (6g)

Compound **6g** was purified via flash column chromatography using a gradient of CH_2Cl_2 → CH_2Cl_2–MeOH (99:1).

Orange brownish powder; mp 136–138 °C. IR (neat): 3509, 3310, 2958, 2163, 2141, 2112, 1967, 1717, 1679, 1586, 1565 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 3.72 (s, 3 H, Me), 3.82 (s, 3 H, Me), 5.27 (s, 2 H, CH_2N_3), 6.69 (d, ^4J = 1.9 Hz, 1 H, ArH), 7.14 (d, ^4J = 1.9 Hz, 1 H, ArH), 9.80 (s, 1 H, NH). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 36.09, 50.88, 74.88, 107.56, 118.99, 119.47, 121.92, 152.38, 160.54. ESI-HRMS: *m/z* calcd for $C_9H_{11}N_5O_4Na$: 276.0703 $[M + Na]^+$; found: 276.0716 $[M + Na]^+$.

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(13) **Ammonium 2-[(Azidomethoxy)carbonylamino]ethyl Hydrogenphosphate (6h)**

Azidomethyl 4-nitrophenyl carbonate (**1**, 300 mg, 1.26 mmol, 1.0 equiv) and 2-aminoethyl dihydrogen phosphate (177.7 mg, 1.26 mmol, 1.0 equiv) were added to a flask and suspended in DMF (4 mL). DIPEA (4.16 mmol, 707 µL, 3.3 equiv) and H_2O (3 mL) were added. The resulted suspension was sonicated for 2 min and then stirred at 20 °C. After 20 min, a clear solution formed. A complete conversion was detected after 30 min via TLC (CH_2Cl_2–PE = 3:2). The reaction mixture was diluted with H_2O (200 mL) and poured on a DEAE-cellulose column [100 g, 20 cm, HCO_3^- form, Express-Ion exchanger D, Whatman (Maidstone, UK)]. The column was washed with H_2O (200 mL) and 100 mM NH_4HCO_3 solution (500 mL). The product-containing fractions were combined and the resulting solution concentrated to 20 mL, followed by lyophilization to dryness. The title compound **6h** was obtained as a colorless solid (321 mg, 1.25 mmol, 99%). IR (neat): 3210, 2889, 2103, 1705, 1532, 1455 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ = 3.28 (t, ^3J = 5.3 Hz, 2 H), 3.75–3.83 (m, 2 H), 5.06 (s, 2 H, CH_2N_3). ^{13}C NMR (75 MHz, D_2O): δ = 41.25 (d, $^3J_{P-C2}$ = 7.8 Hz, C-2), 63.59 (d, $^2J_{P-C1}$ = 5.2 Hz, C-1), 75.71 (CH_2N_3), 157.35 (C=O). ^{31}P NMR (121.5 MHz, D_2O): δ = 1.10. ESI-HRMS: *m/z* calcd for $C_4H_8N_4O_6P$: 239.0187 $[M]^-$; found: 239.0175 $[M]^-$.

(14) **Ammonium 3-[(Azidomethoxy)carbonylamino]-propanoate (6i)**

A sample of β-alanine (112.2 mg, 1.26 mmol) was treated as described in ref. 13 but in the presence of a smaller amount of DIPEA (471 µL, 2.77 mmol, 2.2 equiv). The column purification used a higher concentration of NH_4HCO_3 (250 mM) for elution from the DEAE-cellulose. The title compound was obtained as colorless oil (236.2 mg, 1.15 mmol, 91%). IR (neat): 3231, 2965, 2103, 1967, 1701, 1524, 1447, 1409, 1219 cm^{-1}. ^1H NMR (300 MHz, D_2O): δ = 2.44 (t, ^3J = 6.6 Hz, 2 H), 3.31 (t, ^3J = 6.6 Hz, 2 H), 5.06 (s, 2 H, CH_2N_3). ^{13}C NMR (75 MHz, D_2O): δ = 34.95, 36.79, 75.62 (CH_2N_3), 157.14, 177.60. ESI-HRMS: *m/z* calcd for $C_5H_7N_4O_4$: 187.0473 $[M]^-$; found: 187.0468 $[M]^-$.

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