Carbamoyl Azides of α-N-Protected Amino Acids: A Fast and Simple One-Pot Synthesis

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Abstract: A fast and simple one-pot synthesis of carbamoyl azides of α-N-protected amino acids is reported. The procedure involves the reaction between sodium azide and the mixed anhydride obtained from an α-N-protected amino acid and isobutyl chloroformate, in the presence of KH_2PO_4. The reaction rate was influenced by the nature of both the α-N-protection and the amino acid side chain. Surprisingly, *tert*-butyloxycarbonyl (α-*N*-Boc) and benzyloxycarbonyl (α-*N*-Cbz) protected proline afforded the corresponding isocyanates instead of the expected carbamoyl azides.

Key words: α-N-protected amino acids, sodium azide, carbamoyl azide, mixed anhydride, Curtius rearrangement

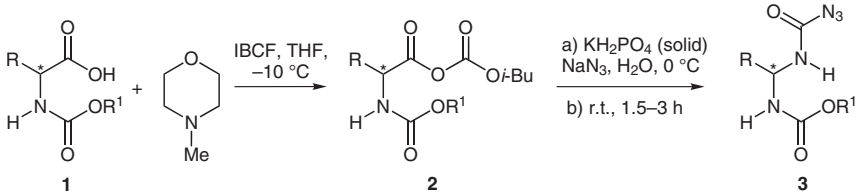
Carbamoyl azides are an important class of compounds having a wide range of applications in organic synthesis.[1] Some are used as intermediates in the synthesis of heterocyclic,[2] pharmaceutical[3] and non-crosslinked foam[4] compounds. Carbamoyl azides are generally prepared by reacting the corresponding carbonyl halides with inorganic azides,[2d,5] by nitrosation of semicarbazides,[2b,3b,6] and by the addition of hydrazoic acid[3c,4,7] or organometallic polyazides[8] to isocyanates. All these procedures suffer limitations associated with the availability of precursors and hazards in handling reagents (triphosgene in the synthesis of carbamoyl halides from amines and hydrazoic acid). Carbamoyl azides have also been obtained starting from carboxaldehydes[9] and carboxylic acids[10] but, to our knowledge, the use of α-N-protected amino acids as precursors does not appear to have any precedent in the literature. In this paper we report an efficient extension of the mixed anhydride method to the one-pot synthesis of α-N-protected carbamoyl azides.

The simple and convenient synthesis of α-N-protected carbamoyl azides **3**, reported here, was accomplished in a two-step, one-pot reaction sequence (Scheme 1; Table 1). The first step of the process consisted of the preparation of the mixed anhydride **2**, which was obtained by reacting the *N*-methylmorpholinium salt of an α-N-protected amino acid **1** with isobutyl chloroformate (IBCF), in tetrahydrofuran at –10 °C. After a few minutes (second step), solid potassium dihydrogenphosphate (6 equiv) was added in one portion at 0 °C to the resulting well-stirred mixture, followed by slow addition of an aqueous solution of sodium azide (3 equiv). The resulting mixture was then stirred at room temperature for 1.5–3 hours to afford, after work-up, the carbamoyl azide **3** in a spectroscopically pure form without any further purification in 80–90% overall yield.

From a mechanistic point of view, the reaction of the mixed anhydride **2** with sodium azide, gives rise to the azide **4** (Scheme 2) which, in contrast to the isolable Fmoc-amino acid azides reported by Babu et al.,[11] proved to be unstable and led to the corresponding isocyanate **5** by the Curtius rearrangement. Compound **5**, in the presence of excess sodium azide, yields the corresponding carbamoyl azide **3**.

It was essential for the success of our synthetic method to carry out the second step of the reaction in the presence of KH_2PO_4, which allowed the pH of the mixture to be kept constant at around 7. In fact, in preliminary experiments carried out using **1e** as a model substrate, without the addition of KH_2PO_4, the pH of the final reaction mixture was approximately 9 and the ESI-MS analysis evidenced the presence of the carbamoyl azide **3e** accompanied by the corresponding urea **8e** (Scheme 3) in a ratio of 65:35.

In fact, the hydroxide ion formed by the hydrolysis of sodium azide and produced in the course of the reaction (Scheme 3), reacted with the isocyanate **5e** and/or the carbamoyl azide **3e** yielding the ethyl 1-amino-3-methylbutylcarbamate (**7e**) via the corresponding carbamic acid **6e**. At this point, compound **7e** was capable of reacting with



Scheme 1

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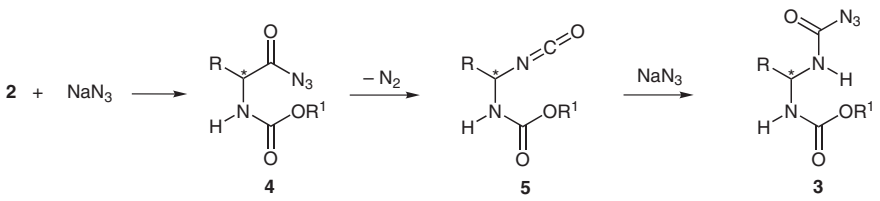


Scheme 2

3e and/or **5e**, giving the urea **8e**. The presence of KH_2PO_4 was therefore critical because, upon neutralizing the hydroxide ion, the KH_2PO_4/K_2HPO_4 couple was produced, which effectively buffered the reaction mixture at about pH 7. Following the protocol described above, the ESI-MS analysis of the intact reaction mixtures obtained 30 minutes after the end of the addition of sodium azide, showed the presence of the corresponding isocyanate **5** along with a variable amount of the carbamoyl azide **3**. This appears to be a clear indication that the Curtius rearrangement of the acyl azide **4** into the corresponding isocyanate **5** (Scheme 2) occurs rapidly, the rate determining step of the reaction leading to **3** being the addition of the azide ion to **5**. With the aid of ESI-MS analysis, we observed that the rate of this reaction was influenced by the nature of both the α-N-protection and the amino acid side chain. In detail, the reaction, probably due to steric hindrance, was found to proceed slower with *tert*-butyloxycarbonyl (α-*N*-Boc) and benzyloxycarbonyl (α-*N*-Cbz) derivatives as well as in the case of valine and phenylglycine derivatives when bulky substituents in the α-position of the starting amino acid were present. All these substrates required longer reaction times (3 h instead of 1.5 h) for complete conversion into the carbamoyl azide **3**.

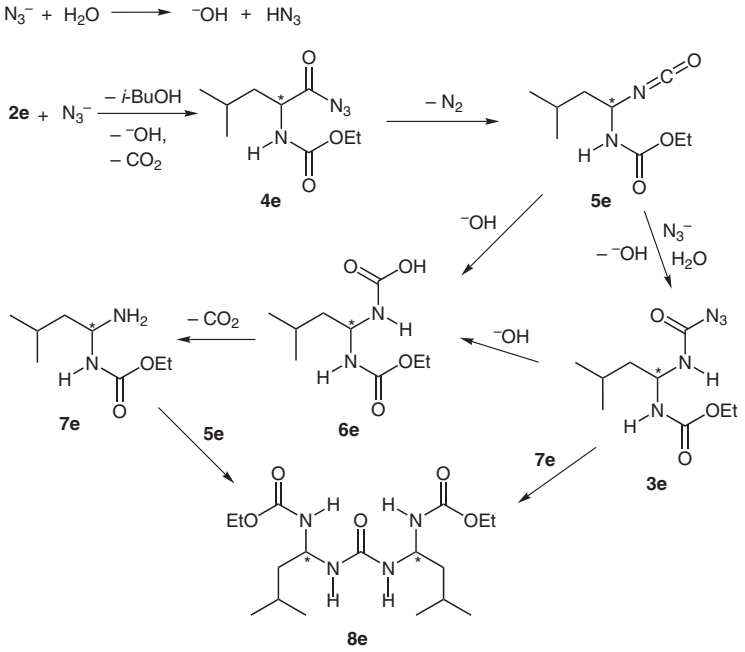
Surprisingly, when *N*-Boc-protected (**1p**) and *N*-Cbz-protected (**1q**) proline were treated according to our protocol, ESI-MS analysis of the intact reaction mixture obtained after 1.5 hours of stirring at room temperature, revealed only the presence of the corresponding isocyanates **5p** and **5q**, which were finally isolated after suitable workup, in 97% and 94% yields, respectively. Prolonged stirring (24 h) at room temperature after the addition of aqueous sodium azide yielded small amounts (10–15%) of the carbamoyl derivatives **3p** and **3q**.

Carbamoyl azides **3** were found to be fairly stable crystalline solids that could be stored at –20 °C for up to two weeks; however, storage at room temperature for more than 24 hours led to their decomposition. Furthermore, solutions of **3** in aprotic solvents were more stable than in the solid form.

The results obtained and some properties of **3** are reported on Table 2. Data pertinent to the synthesized carbamoyl azides **3** are collected in Table 3.

With the exception of the carbamoyl azides of leucine (**3d–g**), phenylglycine (**3h** and **3i**) and *N*-Boc-valine (**3b**), the ^1H and ^{13}C NMR spectra of **3** appeared complex (Table 3), due to the restricted rotation around the carbamate C–N bond.[12]

The EI-MS spectra of the carbamoyl azides **3** (Table 3) exhibited the following common features (Scheme 4): (i) absence of the molecular ion, (ii) loss of hydrazoic acid



Scheme 3

Table 1 R-Group Assignments for All Compounds

	R	R^1
a	*i*-Pr	Et
b	*i*-Pr	*t*-Bu
c	*i*-Pr	Bn
d	*i*-Bu	Me
e	*i*-Bu	Et
f	*i*-Bu	*t*-Bu
g	*i*-Bu	Bn
h	Ph	Et
i	Ph	*t*-Bu
j	Bn	Me
k	Bn	Et
l	Bn	Bn
m	$MeS(CH_2)_2$	Et
n	1*H*-indole-3-CH_2	Me
o	1*H*-indole-3-CH_2	Et

Table 2 Yields and Selected Properties of Carbamoyl Azides **3**

Product[a]	Yield (%)[b]	Mp (°C)	$[\alpha]_D^{20}$ (*c*, solvent)
3a	97	127–129 (dec)	–11.8 (1.1, $CHCl_3$)
3b	86	132–134 (dec)	+33.2 (1.1, THF)
3c	92	147–148; 151 (dec)	+49.5 (1.0, THF)
3d	85	79–80; 110 (dec)	–18.5 (1.1, THF)
3e	90	99–101; 117 (dec)	+9.8 (1.0, $CHCl_3$)
3f	90	109–110; 116 (dec)	+19.9 (1.0, THF)
3g	91	130 (dec)	+29.9 (1.0, THF)
3h	88	136–137; 140 (dec)	+7.8 (1.0, THF)
3i	86	116–118 (dec)	–10.7 (1.1, THF)
3j	90	144 (dec)	+10.8 (1.0, EtOAc)
3k	91	146 (dec)	–7.8 (1.0, THF)
3l	89	138–139; 141 (dec)	+10.6 (1.0, EtOAc)
3m	89	77–79; 83 (dec)	–17.0 (1.0, THF)
3n	93	65–67; 89 (dec)	–6.7 (1.1, EtOAc)
3o	95	115 (dec)	–8.3 (1.0, EtOAc)

[a] Satisfactory elemental analyses obtained: C ± 0.15, H ± 0.10, N ± 0.14.
[b] Reported yields refer to pure isolated products.

(HN_3; *m*/*z* = 43), (iii) loss of carbamoyl azide (NH_2CON_3; *m*/*z* = 86) and/or the corresponding radical ($NHCON_3$; *m*/*z* = 85), and (iv) loss of the amino acid chain radical.

Table 3 Spectroscopic Data of Carbamoyl Azides **3**

Product	IR (KBr) (cm^{-1})	^{1}H NMR [δ (ppm), *J* (Hz)]	^{13}C NMR [δ (ppm)]	EI-MS: *m*/*z* (%)	ESI-MS:[a] *m*/*z*
3a	3312 (br), 2981, 2255, 2137, 1698, 1517, 1230, 1042, 711	0.91–1.03 [m, 6 H, $(CH_3)_2CH$], 1.25 (t, *J* = 7.1, 3 H, CH_3CH_2), 1.78–2.05 [m, 1 H, $(CH_3)_2CH$], 4.03–4.25 (m, 2 H, OCH_2), 4.70–4.93 and 5.03–5.20 (2 × m, 1 H, *CH), 5.36 and 5.74 (2 × br d, *J* = 8.5 and 7.1, 1 H, $NHCO_2Et$), 6.08 and 6.31 (2 × br s, 1 H, $NHCON_3$)[b]	14.4, 17.2 and 17.8, 18.6, 31.6 and 33.6, 61.1 and 61.5, 65.3 and 68.1, 155.9, 156.1 (br)[b]	186 (100), 144 (18), 143 (98), 98 (16), 86 (33), 71 (75), 56 (69), 43 (77)	252 $[M + Na]^+ \rightarrow$ 224, 178
3b	3337 (br), 1983, 2254, 2136, 1699, 1545, 1510, 1234, 684	0.82 and 0.84 [2 × d, *J* = 6.8, 6.6, 6 H, $(CH_3)_2CH$], 1.37 [s, 9 H, $(CH_3)_3C$], 1.79 [hept, *J* = 6.6, 1 H, $(CH_3)_2CH$], 4.76 (app q, *J* = 8.3, 1 H, *CH), 7.08 (br d, *J* = 8.1, 1 H, $NHCO_2tBu$), 8.14 (br d, *J* = 8.3, 1 H, $NHCON_3$)[c]	18.4, 28.2, 31.7, 64.2, 78.0, 154.6, 154.8 (br)[c]	214 (3), 171 (5), 158 (22), 141 (4), 114 (8), 71 (8), 59 (15), 57 (100)	280 $[M + Na]^+ \rightarrow$ 224, 196, 152
3c	3312 (br), 2964, 2254, 2136, 1699, 1514, 1232, 1032, 705	0.78–0.96 [m, 6 H, $(CH_3)_2CH$], 1.71–1.98 [m, 1 H, $(CH_3)_2CH$], 4.78–5.13 (m, 3 H, *CH and OCH_2), 7.25–7.43 (m, 5 H, H_{arom}), 7.64 (br d, *J* = 7.3, 1 H, $NHCO_2Bn$), 8.28 (br d, *J* = 8.1, 1 H, $NHCON_3$)[c]	17.8 and 18.1, 18.3 and 18.4, 31.6 and 32.8, 64.7 and 69.0, 65.4 and 65.9, 127.8, 128.0, 128.4, 136.6 and 137.0, 154.9, 155.4 (br)[c]	248 (2), 205 (5), 162 (8), 107 (20), 91 (100), 43 (9)	314 $[M + Na]^+ \rightarrow$ 286, 178
3d	3321 (br), 2960, 2252, 2138, 1704, 1521, 1245, 1038, 660	0.94 [dd, *J* = 6.4, 2.3, 6 H, $(CH_3)_2CH$], 1.45–1.87 (m, 3 H, $CHCH_2$), 3.68 (s, 3 H, OCH_3), 5.04–5.29 (m, 1 H, *CH), 5.96 (br d, *J* = 7.2, 1 H, $NHCO_2Me$), 6.48 (br d, *J* = 7.8, 1 H, $NHCON_3$)[b]	22.1, 24.7, 45.2, 58.7, 61.9, 155.9, 156.2 (br)[b]	186 (1), 172 (14), 144 (12), 129 (100), 101 (13), 88 (9), 59 (21), 43 (19)	252 $[M + Na]^+ \rightarrow$ 224, 192

Table 3 Spectroscopic Data of Carbamoyl Azides **3** (continued)

Product	IR (KBr) (cm^{-1})	^{1}H NMR [δ (ppm), *J* (Hz)]	^{13}C NMR [δ (ppm)]	EI-MS: *m*/*z* (%)	ESI-MS:[a] *m*/*z*
3e	3315 (br), 2170, 2135, 1702, 1556, 1516, 1295, 1228, 1039, 708	0.94 [dd, *J* = 6.2, 2.0, 6 H, $(CH_3)_2CH$], 1.28 (t, *J* = 7.3, 3 H, CH_3CH_2), 1.54–1.82 (m, 3 H, $CHCH_2$), 4.12 (q, *J* = 7.3, 2 H, OCH_2), 5.04–5.32 (m, 1 H, *CH), 6.02 (br d, *J* = 8.6, 1 H, $NHCO_2Et$), 6.67 (br d, *J* = 8.5, 1 H, $NHCON_3$)[b]	14.4, 22.1, 24.7, 42.6, 58.6, 61.0, 155.9, 156.0 (br)[b]	200 (1), 186 (88), 158 (14), 155 (8), 143 (73), 115 (9), 86 (14), 71 (25), 43 (100)	266 $[M + Na]^+ \rightarrow$ 238, 192
3f	3346 (br), 2960, 2247, 2136, 1701, 1548, 1502, 1223, 1155, 680	0.84 [dd, *J* = 6.1, 1.7, 6 H, $(CH_3)_2CH$], 1.37 [s, 9 H, $(CH_3)_3C$], 1.30–1.66 (m, 3 H, $CHCH_2$), 5.09 (app qt, *J* = 7.6, 1 H, *CH), 7.17 (br d, *J* = 7.1, 1 H, $NHCO_2tBu$), 8.19 (br d, *J* = 8.1, 1 H, $NHCON_3$)[c]	22.1, 24.1, 28.1, 42.9, 57.6, 78.0, 154.3, 154.5 (br)[c]	228 (1), 214 (7), 186 (1), 171 (5), 158 (46), 155 (9), 130 (7), 114 (33), 86 (89), 57 (100)	294 $[M + Na]^+ \rightarrow$ 238, 210, 166
3g	3317 (br), 2960, 2250, 2137, 1697, 1152, 1514, 1228, 1040, 697	0.85 [dd, *J* = 6.0, 1.7, 6 H, $(CH_3)_2CH$], 1.38–1.66 (m, 3 H, $CHCH_2$), 5.02 (s, 2 H, OCH_2), 5.08–5.26 (m, 1 H, *CH), 7.26–7.45 (m, 5 H, H_{arom}), 7.71 (br d, *J* = 8.1, 1 H, $NHCO_2Bn$), 8.33 (br d, *J* = 7.6, 1 H, $NHCON_3$)[c]	22.1, 24.0, 42.7, 57.9, 65.3, 127.8, 127.9, 128.3, 136.9, 154.6, 154.9 (br)[c]	262 (1), 248 (2), 220 (1), 219 (3), 158 (2), 155 (3), 107 (26), 91 (100), 43 (16)	328 $[M + Na]^+ \rightarrow$ 300, 192
3h	3296 (br), 2248, 2143, 1706, 1515, 1227, 1042, 694	1.16 (t, *J* = 7.1, 3 H, CH_3), 4.02 (q, *J* = 6.9, 2 H, OCH_2), 6.23 (app t, *J* = 8.1, 1 H, *CH), 7.18–7.59 (m, 5 H, H_{arom}), 8.22 (br d, *J* = 8.1, 1 H, $NHCO_2Et$), 8.84 (br d, *J* = 7.8, 1 H, $NHCON_3$)[c]	14.6, 60.1, 61.4, 126.4, 128.0, 128.3, 139.0, 155.0, 155.3 (br)[c]	220 (1), 178 (27), 177 (5), 133 (85), 132 (80), 105 (46), 104 (100), 91 (32), 77 (80), 51 (41), 43 (55)	286 $[M + Na]^+ \rightarrow$ 258, 212
3i	3333 (br), 2981, 2249, 2139, 1699, 1543, 1508, 1232, 1172, 695	1.40 [s, 9 H, $(CH_3)_3C$], 6.21 (app t, *J* = 8.1, 1 H, *CH), 7.24–7.50 (m, 5 H, H_{arom}), 7.92 (br d, *J* = 7.6, 1 H, $NHCO_2tBu$), 8.77 (br d, *J* = 8.1, 1 H, $NHCON_3$)[c]	28.1, 61.1, 78.6, 126.4, 127.9, 128.3, 139.3, 154.3, 154.8 (br)[c]	248 (1), 206 (13), 192 (5), 175 (6), 150 (7), 132 (19), 104 (15), 77 (17), 57 (100)	314 $[M + Na]^+ \rightarrow$ 258, 230, 186
3j	3309 (br), 2254, 2143, 1704, 1551, 1507, 1226, 1053, 704	2.83–3.08 (m, 2 H, $PhCH_2$), 3.49 and 3.56 (2 × s, 3 H, OCH_3), 5.11–5.43 (m, 1 H, *CH), 7.16–7.38 (m, 5 H, H_{arom}), 7.66 and 7.74 (2 × br d, *J* = 7.2 and 7.7, 1 H, $NHCO_2Me$), 8.26 and 8.49 (2 × br d, *J* = 7.8 and 7.7, 1 H, $NHCON_3$)[c]	39.9 and 40.2, 51.3 and 51.7, 61.0 and 64.6, 126.4 and 126.9, 128.2 and 128.3, 129.2 and 129.4, 136.3 and 137.1, 154.7, 155.5 (br)[c]	220 (1), 178 (5), 177 (30), 172 (24), 129 (100), 91 (36), 59 (18), 43 (36)	286 $[M + Na]^+ \rightarrow$ 258, 226
3k	3304 (br), 2253, 2140, 1699, 1552, 1511, 1229, 1055, 1037, 702	1.13 (app q, *J* = 7.3, 3 H, CH_3), 2.82–3.12 (m, 2 H, $PhCH_2$), 3.85–4.08 (m, 2 H, OCH_2), 5.10–5.38 (m, 1 H, *CH), 7.12–7.37 (m, 5 H, H_{arom}), 7.71 and 7.78 (2 × br d, *J* = 7.1 and 7.8, 1 H, $NHCO_2Et$), 8.25 and 8.48 (2 × br d, *J* = 7.8 and 7.8, 1 H, $NHCON_3$)[c]	14.5, 39.7 and 40.1, 59.8 and 60.2, 60.9 and 64.6, 126.5 and 126.8, 128.2 and 128.4, 129.2 and 129.4, 136.3 and 137.1, 154.6, 155.1 (br)[c]	234 (1), 192 (7), 191 (54), 143 (42), 119 (45), 118 (100), 117 (41), 91 (81), 43 (21)	300 $[M + Na]^+ \rightarrow$ 272, 226
3l	3315 (br), 2264, 2135, 1699, 1549, 1510, 1227, 1023	2.83–3.18 (m, 2 H, $PhCH_2$), 5.00 and 5.06 (2 × s, 2 H, OCH_2), 5.21–5.43 (m, 1 H, *CH), 7.22–7.39 (m, 10 H, H_{arom}), 7.95 and 7.99 (2 × br d, *J* = 8.1 and 8.3, 1 H, $NHCO_2Bn$), 8.42 and 8.56 (2 × br d, *J* = 7.5 and 7.6, 1 H, $NHCON_3$)[c]	39.8 and 40.4, 61.0 and 64.6, 65.3 and 65.8, 126.5 and 126.9, 127.7, 127.8 and 127.9, 128.2, 128.3, 129.3 and 129.4, 136.0, 136.3 and 136.9, 154.7, 155.4 (br)[c]	254 (1), 253 (6), 248 (1), 209 (5), 205 (3), 118 (4), 117 (3), 91 (100), 65 (10), 43 (12)	362 $[M + Na]^+ \rightarrow$ 334, 226
3m	3303 (br), 2983, 2250, 2138, 1700, 1518, 1243, 1227, 1055, 709	1.18 (app q, *J* = 7.1, 3 H, CH_3CH_2), 1.76–1.98 (m, 2 H, *$CHCH_2$), 2.03 and 2.04 (2 × s, 3 H, SCH_3), 2.35–2.58 (m, 2 H, SCH_2), 3.90–4.15 (m, 2 H, OCH_2), 5.07–5.34 (m, 1 H, *CH), 7.58 and 7.73 (2 × br d, *J* = 7.0 and 7.1, 1 H, $NHCO_2Et$), 8.22 and 8.34 (2 × br d, *J* = 7.8 and 7.8, 1 H, $NHCON_3$)[c]	14.4 and 14.6, 28.8 and 29.0, 33.3 and 34.5, 58.5 and 62.7, 59.8 and 60.5, 154.7, 155.2 (br)[c]	218 (1), 186 (8), 176 (6), 175 (20), 172 (11), 128 (57), 61 (100), 56 (79), 43 (41)	284 $[M + Na]^+ \rightarrow$ 256, 210

Table 3 Spectroscopic Data of Carbamoyl Azides **3** (continued)

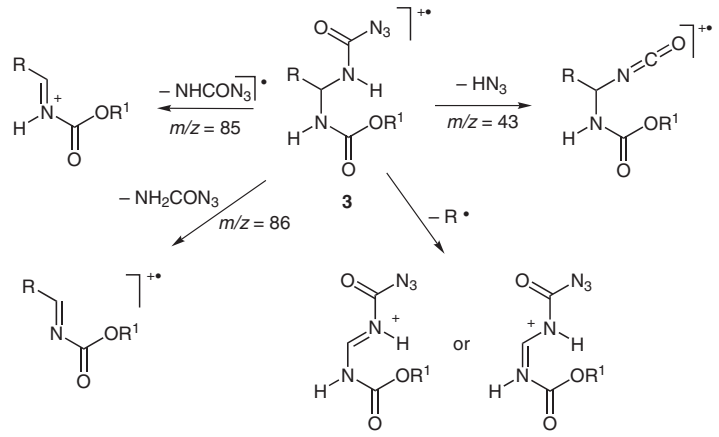
Product	IR (KBr) (cm^{-1})	^{1}H NMR [δ (ppm), *J* (Hz)]	^{13}C NMR [δ (ppm)]	EI-MS: *m*/*z* (%)	ESI-MS:[a] *m*/*z*
3n	3405 (br), 3331 (br), 2250, 2139, 1717, 1515, 1233, 1045, 744	3.05–3.22 (m, 2 H, *CHCH_2), 3.56 and 3.62 (2 × s, 3 H, OCH_3), 5.40–5.68 (m, 1 H, *CH), 5.80 and 6.26 (2 × br d, *J* = 8.0 and 8.2, 1 H, N*H*CO_2Me), 6.84–7.62 (m, 6 H, H_{arom} and $NHCON_3$), 8.53 (br s, 1 H, NH_{arom})[b]	29.9, 52.3 and 52.4, 60.5 and 63.2, 108.3 and 109.3, 111.5, 118.3, 119.7 and 119.9, 122.2 and 122.3, 123.4, 129.3, 136.3, 155.8, 156.2 (br)[b]	259 (1), 216 (100), 184 (43), 157 (33), 156 (32), 130 (86), 103 (19), 77 (18), 43 (64)	325 $[M + Na]^+ \rightarrow$ 297, 265
3o	3404 (br), 3321 (br), 2979, 2174, 2138, 1695, 1519, 1239, 1054, 741	1.05–1.30 (m, 3 H, CH_3), 2.98–3.34 (m, 2 H, *CHCH_2), 3.90–4.21 (m, 2 H, OCH_2), 5.28–5.61 (m, 1 H, *CH), 5.82 and 6.25 (2 × br d, *J* = 8.1 and 8.3, 1 H, $NHCO_2Et$), 6.81–7.75 (m, 6 H, H_{arom} and $NHCON_3$), 8.56 (br s, 1 H, NH_{arom})[b]	14.3, 29.9, 60.0 and 63.1, 61.2, 108.1 and 109.3, 111.4, 118.3, 119.5 and 119.6, 122.0 and 122.1, 123.3, 127.1, 136.2, 155.7, 156.0 (br)[b]	273 (1), 231 (9), 230 (57), 202 (14), 184 (16), 158 (25), 157 (62), 156 (31), 130 (100), 103 (9), 77 (8), 43 (55)	339 $[M + Na]^+ \rightarrow$ 311, 265

[a] Positively ionized molecule $[M + Na]^+$ and fragments obtained with MS^2 experiments are reported.
[b] Solvent: $CDCl_3$.
[c] Solvent: DMSO-d_6.

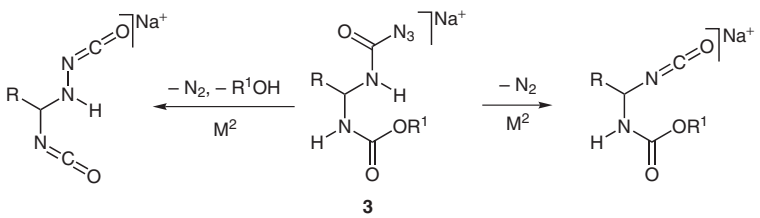
The ESI-MS spectra of carbamoyl azides **3** (Table 3) evidenced only the sodium-cationized molecule $[M + Na]^+$ in the positive ion mode. With the exception of *N*-Boc derivatives **3b**, **3f** and **3i**, the MS^2 spectra of $[M + Na]^+$ for **3** were characterized by the presence of an intense ion (base peak), due to the loss of N_2, and a less intense, abundant peak (10–80% relative intensity) derived from the elimination of N_2 and the alcohol fragment present in the carbamate moiety (Scheme 5).

In contrast, the MS^2 spectra of $[M + Na]^+$ for *N*-Boc derivatives **3b**, **3f** and **3i** evidenced three fragment ions corresponding to the loss of isobutene, N_2 and CO_2 as indicated in Scheme 6.

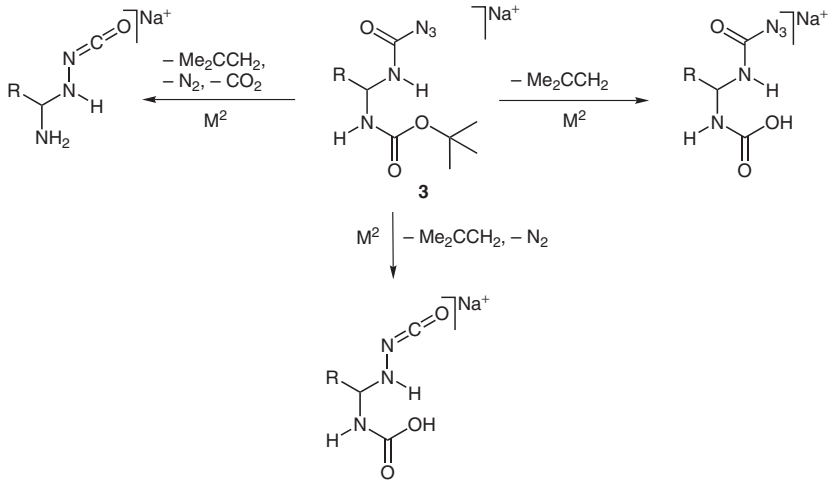
In summary, we have developed a simple, one-pot synthesis of carbamoyl azides starting from α-N-protected amino acids. These intermediates are suitable building blocks for the synthesis of carbamates, asymmetric ureas and peptidyl ureas because their reactivity may be compared to those of the corresponding isocyanates. Moreover, the final reaction mixture obtained with our procedure can be used in further transformations without additional purification.



Scheme 4



Scheme 5



Scheme 6

Caution! Carbamoyl azides are sensitive to thermal and mechanical shock in the solid state and should be handled with due care.

Direct inlet mass spectra (DI-MS) were obtained with a Fisons TRIO 2000 gas chromatograph-mass spectrometer, working in the positive ion 70 eV electron impact mode. Spectra were recorded in the range 35–450 u. Temperatures between 60 °C and 120 °C were found suitable to vaporize all the compounds into the ion source. The reactions were monitored by ESI-MS in the positive ion mode with a Finnigan LXQ (linear trap). The intact reaction mixture was diluted with MeCN and the obtained solution was directly infused into the ion source with the aid of a syringe pump. IR spectra were obtained with a Nicolet FT-IR Magna 550 spectrophotometer using the KBr technique for solids and recorded in the range 4000–400 cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-F 200 spectrometer at 200 and 50 MHz, respectively, using $CDCl_3$ at room temperature or DMSO-d_6 at 40 °C as solvents. NMR peak locations are reported as δ values (ppm) from TMS. Some ^1H multiplets are characterized by the term 'app' (apparent): this refers only to their appearance and may be an oversimplification. Optical rotations were determined at 20 °C (concentration in g/100 mL of solvent) using a POLAX-D polarimeter purchased from ATAGO (Japan). Elemental analyses were performed with a Carlo Erba (Model 1106) elemental analyzer. Melting points were determined with an automatic Mettler (Model FP61) melting point apparatus and are not corrected. All N-protected amino acids **1** were prepared by reported procedures.[13] All solvents and reagents were purchased from Aldrich Chemical Company and used without further purification.

Carbamoyl Azides 3; General Procedure

NMM (0.30 mL, 2.73 mmol) was slowly added into a stirred solution of α-N-protected amino acid **1** (2.50 mmol) in THF (15 mL). After 5 min, the reaction mixture was cooled down to –10 °C and isobutyl chloroformate (0.36 mL, 2.72 mmol) was added dropwise. Stirring was continued for 20 min at –10 °C then the mixture was warmed to 0 °C and KH_2PO_4 (2.05 g, 15.00 mmol) was added, followed by the slow addition of a solution of NaN_3 (0.49 g, 7.50 mmol) in H_2O (3 mL). The mixture was allowed to warm to r.t. and additionally stirred for 1.5 h (3 h in the case of α-*N*-Boc and α-*N*-Cbz derivatives, as well as for valine **1a** and phenylglycine **1h**). The organic phase was separated and THF was removed under reduced pressure; the residue was dissolved in EtOAc (35 mL) and the solution was washed with H_2O (15 mL), a potassium phosphate buffer solution (pH ~7; KH_2PO_4/K_2HPO_4, 20 mL), 10% HCl (10 mL), sat. brine (15 mL), and finally dried over Na_2SO_4. After filtration and evaporation of the solvent in vacuo, the residue consisted of the carbamoyl azide **3** in analytically pure form (Table 2 and Table 3).

Isocyanates of *N*-Boc-proline (5p) and *N*-Cbz-proline (5q); General Procedure

NMM (0.30 mL, 2.73 mmol) was slowly added into a stirred solution of α-N-protected proline **1p** or **1q** (2.50 mmol) in THF (15 mL). After 5 min, the reaction mixture was cooled down to –10 °C and isobutyl chloroformate (0.36 mL, 2.72 mmol) was added. Stirring was continued for 20 min at –10 °C then the mixture was warmed to 0 °C and KH_2PO_4 (1.03 g, 7.50 mmol) was added, followed by the slow addition of a solution of NaN_3 (0.25 g, 3.75 mmol) in H_2O (2 mL). The mixture was allowed to warm to r.t. and additionally stirred for 1.5 h. The organic phase was separated and THF was removed under reduced pressure; the residue was dissolved in EtOAc (30 mL) and the solution was washed with H_2O (10 mL), a potassium phosphate buffer solution (pH ~7; KH_2PO_4/K_2HPO_4, 20 mL), 10% HCl (10 mL), sat. brine (15 mL), and finally dried over Na_2SO_4. After filtration and evaporation of the solvent in vacuo, the residue consisted of the isocyanate **5** in analytically pure form.

1-*tert*-Butylcarbonyl-2-isocyanatopyrrolidine (5p)

Yield: 97%; oil; $[\alpha]_D^{20}$ –62.3 (*c* 1.0, $CHCl_3$).

IR (KBr): 2978, 2934, 2883, 2246, 2139, 1699, 1384, 1215, 1170, 757 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.45 [app d, *J* = 7.5 Hz, 9 H, $(CH_3)_3C$], 1.80–2.37 (m, 4 H, CH_2CH_2), 3.31–3.61 (m, 2 H, N-CH_2), 4.08–4.32 (m, 1 H, *CH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.5 and 24.2, 28.1 and 28.3, 29.8 and 30.8, 46.3 and 46.6, 60.5 and 60.8, 80.1 and 80.3, 153.4 and 154.2, 180.3 and 180.6.

EI-MS: *m/z* (%) = 212 (1) [M^+], 170 (19), 139 (23), 114 (65), 70 (89), 57 (100).

Anal. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.51; H, 7.68; N, 13.12.

1-Benzyloxycarbonyl-2-isocyanatopyrrolidine (5q)

Yield: 94%; oil; $[\alpha]_D^{20}$ –77.9 (*c* 1.0, $CHCl_3$).

IR (KBr): 2979, 2958, 2884, 2246, 2142, 1709, 1414, 1354, 1173, 1122, 770, 699 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.81–2.36 (m, 4 H, CH_2CH_2), 3.40–3.73 (m, 2 H, N-CH_2), 4.25–4.43 (m, 1 H, *CH), 5.01–5.28 (m, 2 H, OCH_2), 7.23–7.50 (m, 5 H, H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.4 and 24.2, 29.8 and 30.9, 46.5 and 46.9, 60.5 and 60.9, 67.1, 127.8, 128.3, 136.4, 153.2 and 154.1, 179.9 and 180.2.

EI-MS: *m/z* (%) = 246 (1) [M$^+$], 204 (6), 203 (10), 160 (8), 146 (8), 91 (100).

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.50; H, 5.66; N, 11.27.

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