Propylphosphonic Anhydride (T3P®)-Mediated One-Pot Rearrangement of Carboxylic Acids to Carbamates

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Abstract: A simple one-pot conversion of carboxylic acids to carbamates is achieved by propylphosphonic anhydride (T3P[®]) in combination with azidotrimethylsilane and an alcohol via the Curtius rearrangement. Besides diverse primary to tertiary alcohols, the reaction tolerated a wide scope of aromatic, heterocyclic, and aliphatic carboxylic acids which underwent rearrangement in excellent yields.

Key words: propylphosphonic anhydride, Curtius rearrangement, carbamates, peptide coupling agents, azidotrimethylsilane

The Curtius rearrangement,^{1,2} is a thermal decomposition of acyl azides into amines via isocyanate intermediates, which has been widely used for the transformation of carboxylic acids into isocyanates, carbamates, and ureas. A number of methods describing it are multistep in nature and have focused on a stepwise approach wherein the first step of the synthesis involves the isolation of acyl azides from carboxylic acid derivatives such as acyl chlorides,³ mixed anhydrides,⁴ and hydrazides.⁵ The isocyanates that are subsequently formed by molecular rearrangement under thermal conditions can be trapped by a variety of nucleophiles to provide the amino derivatives. The acid chloride method is incompatible with acid-sensitive functionalities and has disadvantages such as the preparation and storage of the acid chloride itself. Preparation of acid azides via mixed anhydrides has been used to advantage, but this method employs chloroformates which are inconvenient to handle. One-pot transformations of carboxylic acids into carbamates have become more accepted as they avoid the isolation of unstable acyl azides. Several reported protocols involve the use of diphenylphosphoryl azide (DPPA)⁶ for the one-pot Curtius reaction. Conversely, toxicity considerations limit its usage and the high boiling point of DPPA creates additional difficulties during workup and purification.

Peptide coupling agents are versatile reagents for the activation of carboxylic acids. Conversion of carboxylic acids into acyl azides and ureidopeptides has recently been described using propylphosphonic anhydride (T3P[®]) in the presence of sodium azide under ultrasonication.⁷ Interestingly, T3P[®] has not been exploited for the synthesis of

SYNTHESIS 2011, No. 9, pp 1477–1483 Advanced online publication: 22.03.2011 DOI: 10.1055/s-0030-1259964; Art ID: Z17611SS © Georg Thieme Verlag Stuttgart · New York carbamates from carboxylic acids. Here, we report a general and one-pot procedure for the conversion of carboxylic acids to carbamates in high yields using T3P^{®8} and azidotrimethylsilane in the presence of an alcohol.

Our initial objective was to develop an efficient one-pot procedure for the synthesis of carbamates from carboxylic acids through the Curtius rearrangement by employing T3P[®] under the reaction conditions reported for ureidopeptides.⁷ Accordingly, the transformation of 4-bromobenzoic acid into *tert*-butyl 4-bromophenylcarbamate (1) was evaluated (Table 1). A solution of 4-bromobenzoic acid in tetrahydrofuran was treated with T3P[®] (1.1 equiv) in the presence of sodium azide (1.1 equiv), triethylamine (1.5 equiv), and *tert*-butyl alcohol (entry 1). The heterogeneous reaction mixture became a viscous mass after sonication at 45 °C for one hour. As there was no reaction (entry 1), the mixture was then refluxed for two hours under conventional heating, however, as it then became too gelatinous, dilution with tetrahydrofuran was necessary for smooth stirring; no reaction was observed under these conditions (entry 2). Interestingly, when a mixture of tetrahydrofuran-dimethyl sulfoxide (1:1) was used, carbamate 1 was obtained in 17% yield (entry 3). However, there was no significant reaction when dimethyl sulfoxide was used as the sole solvent (entry 4). Further improvement could be achieved by using a soluble source of azide namely azidotrimethylsilane⁹ affording **1** in 82% yield in tetrahydrofuran at room temperature (entry 5). Finally the optimization of the temperature led to 1 in 98% yield in tetrahydrofuran in a shorter period (entry 6). The solvent proved influential, as low conversions were observed with solvents other than N,N-dimethylformamide and tetrahydrofuran (entries 7-10).

In order to explore the scope of carboxylic acids tolerated by this process, diverse carboxylic acids were subjected to the Curtius rearrangement under the optimal reaction conditions (Table 1, entry 6). The reaction proceeded well with all substrates to give access to the corresponding *tert*butyl carbamates **1–13** in excellent yields (Table 2). Electron-withdrawing or electron-donating functionalities on the substrate had no influence on the yield, but they did influence the rate of reaction. While electron-rich systems took approximately one hour to go to completion, carboxylic acids bearing electron-withdrawing groups required two to three hours for optimum rearrangement. From Table 2, we can conclude that besides various aromatic,

Table 1 Screening Optimal Conditions

Br	ОН	T3P (1.1 equiv) azide t-BuOH (1.2 equiv) Et ₃ N (1.5 equiv) solvent	Br		,Ot-Bu
Entry	Azide ^a	Solvent	Time (h)	Temp ^b (°C)	Yield (%) of 1
1	NaN ₃	THF	1	45	_c,d
2	NaN ₃	THF	2	70	d
3	NaN ₃	THF-DMSO (1:1)	4	70	17
4	NaN ₃	DMSO	3	90	28
5	TMSN ₃	THF	3	25	82
6	TMSN ₃	THF	0.5	70	98
7	TMSN ₃	MeNO ₂	3	70	68
8	TMSN ₃	DMF	0.5	90	97
9	TMSN ₃	toluene	3	90	86
10	TMSN ₃	DMSO	0.5	90	65

^a Amount used: 1.1 equiv.

^b Heating bath temperature.

^c Reaction was performed under ultrasonication.

^d No reaction.

heteroaromatic, and aliphatic carboxylic acids, the reaction tolerated a wide scope of functional groups and substituents, such as halo, methoxy, alkyl, nitro, cyano, and trifluoromethyl, to provide the corresponding *tert*-butyl carbamates in excellent yields. It is noteworthy that under our new reaction conditions, the Curtius rearrangement of a chiral enantioenriched α -substituted carboxylic acid proceeded with retention of configuration to afford carbamate **12** in 94% yield with almost no loss of enantiomeric excess (98% ee) during the process (Table 2, entry 12).¹⁰

Next, we investigated the scope of various alcohols tolerated by the Curtius rearrangement mediated by T3P[®]. Thus, 4-carboxybenzaldehyde was treated with various alcohols (Table 3) under the standard reaction conditions. As evident from Table 3, primary alcohols including benzyl alcohol and allyl alcohol gave excellent yields of the corresponding carbamates 14, 15, 19, 20, 22. This indicates the versatility of this method in producing benzyloxycarbonyl (Cbz) and Alloc-protected amines from carboxylic acids. In addition, secondary alcohols, both cyclic and acyclic, gave the respective carbamates 16–18 in high yields. Phenol, on the other hand, under these conditions did not yield the desired product (entry 8), probably due to its poor nucleophilicity. Symmetrical urea was the sole product isolated from the reaction besides unreacted phenol.

Among the widely used protecting groups for amines, the Cbz group is extensively used as it can be easily removed T3P. TMSN:

t-BuOH, Et₃N

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Ot-Bu

		1-13	
Entry	RCO ₂ H	Product	Yield ^a (%)
1	Br	1	98
2	MeO	2	95
3	Соон	3	97
4	F COOH	4	96
5	O ₂ N COOH MeO	5	96
6	N S COOH	6	93
7	Me ^{-S} N COOH	7	92
8	MeO O COOH	8	93
9	соон	9	94
10	F F	10	91
11	СООН	11	86
12	Соон	12	94 ^b
13	соон	13	85

^a Reaction conditions: T3P[®] (1.1 equiv), TMSN₃ (1.1 equiv), *t*-BuOH (1.2 equiv), Et₃N (1.5 equiv), THF, reflux.

^b 98% ee.

by smooth orthogonal catalytic hydrogenation and its stability to basic and most aqueous acidic conditions. Consequently, the one-pot synthesis of carbamates from carboxylic acids was further surveyed by reacting various

Table 3	Scope of T3P [®] -Mediated Curtius	Rearrangement: Synthe-
sis of Div	erse Carbamates from 4-Carboxyb	enzaldehyde

онс⁄	COOH -	T3P, TMSN ₃	онс	
Entry	ROH		Product	Yield ^a (%)
1	HO		14	95
2	HO	~ `	15	96
3	ОН		16	94
4	OH		17	94
5	HO	N Tot	18	91
6	HO	SiMea	19	94
7	HNCC	OOMe	20	88
8	HO		21	0
9	но		22	96



^a Reaction conditions: $T3P^{\textcircled{o}}$ (1.1 equiv), $TMSN_3$ (1.1 equiv), ROH (1.2 equiv), Et_3N (1.5 equiv), THF, reflux, 2–3 h.

carboxylic acids with benzyl alcohol under the standard reaction conditions (Table 4). As summarized in Table 4, the reaction proceeded well with most of the substrates affording subsequent Cbz-protected amines **23–30** in excellent yields.

In summary, a practical and new method for the direct conversion of carboxylic acids to carbamates has been developed. Besides diverse primary to tertiary alcohols, the reaction tolerated a wide range of aromatic, heterocyclic and aliphatic carboxylic acids which underwent rearrangement in excellent yields. As T3P[®] offers several advantages over traditional reagents in terms of higher yields, low epimerization tendency, nontoxic nature, ease of isolation of products due to water soluble byproducts, and shorter reaction periods, this process should make it a versatile transformation with potential large-scale application.

^a Reaction conditions: $T3P^{\circledast}$ (1.1 equiv), $TMSN_3$ (1.1 equiv), BnOH (1.2 equiv), Et_3N (1.5 equiv), THF, reflux, 1–3 h.

¹H and ¹³C NMR spectra were recorded on 400 MHz and 100 MHz Bruker spectrometer, respectively and elemental analysis was performed on a Thermo Finnigan FLASH EA 1112 CHN analyzer. Melting points were recorded (uncorrected) on Buchi Melting Point B-545 instrument. IR spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR spectrophotometer.

Carbamates 1–30; General Procedure

The appropriate alcohol (0.012 mol) was added to a stirred soln of carboxylic acid (0.01 mol), $T3P^{\oplus}$ (0.011 mol), $TMSN_3$ (0.011 mol), and Et₃N (0.015 mol) in THF (10 mL) at r.t. The resulting mixture was stirred at reflux for 1–3 h under N₂. When the reaction was completed (TLC), the volatiles were removed under reduced pressure and the residue was diluted with H₂O (25 mL). The product was extracted with EtOAc (2 × 20 mL) and the combined organic phases were washed with sat. NaHCO₃ soln (10 mL) and brine. The organic phase was dried (Na₂SO₄) and evaporated under reduced pressure. The resulting material was passed through a small plug of silica (5% EtOAc–hexanes) to afford the desired carbamate in excellent yield.

tert-Butyl 4-Bromophenylcarbamate (1)¹¹

White solid; yield: 98%; mp 101 °C.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.17 \text{ min}; m/z = 174.0 [M + 2 - \text{Boc}]^+.$

tert-Butyl 3,5-Dimethyl-4-methoxyphenylcarbamate (2)

White solid; yield: 95%; mp 142 °C.

IR (KBr): 3295, 1722, 1609, 1547, 1147, 995 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 1.44 (s, 9 H), 2.49 (s, 6 H), 3.56 (s, 3 H), 7.07 (s, 2 H), 9.08 (br s, 1 H).

¹³C NMR (100 MHz, DMSO- d_6): δ = 15.9, 28.1, 59.3, 118.4, 130.0, 134.8, 151.4, 152.8.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.0$ min; m/z = 196.2 [M – 55]⁺.

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.97; H, 8.46; N, 5.52.

tert-Butyl 4-Methylnaphthalen-1-ylcarbamate (3)

White solid; yield: 97%; mp 84 °C.

IR (KBr): 3269, 1686, 1531, 1504, 1238, 750 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): $\delta = 1.47$ (s, 9 H), 2.60 (s, 3 H), 7.30 (d, J = 7.5 Hz, 1 H), 7.39 (d, J = 7.5 Hz, 1 H), 7.56–7.50 (m, 2 H), 8.03–7.97 (m, 2 H), 9.10 (br s, 1 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 18.7, 28.1, 78.6, 121.3, 123.3, 124.2, 125.2, 125.7, 126.0, 128.4, 130.6, 132.3, 132.4, 154.1.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.16$ min; m/z = 202.2 [M – 55]⁺.

Anal. Calcd for C₁₆H₁₉NO₂: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.72; H, 7.47; N, 5.39.

tert-Butyl 4-Cyano-2-fluorophenylcarbamate (4)

White solid; yield: 96%; mp 110 °C.

IR (KBr): 3295, 1727, 1523, 1239, 1154, 684 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): $\delta = 1.46$ (s, 9 H), 7.61 (d, J = 8.5 Hz, 1 H), 7.82–7.79 (dd, J = 10.9, 1.8 Hz, 1 H), 7.98 (t, J = 8.2 Hz, 1 H), 9.55 (br s, 1 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 27.8, 80.4, 105.1 (d, *J*_{CF} = 10.0 Hz), 117.9 (d, *J*_{CF} = 21.5 Hz), 119.3 (d, *J*_{CF} = 21.5 Hz), 122.4 (d, *J*_{CF} = 2.8 Hz), 129.2 (d, *J*_{CF} = 2.8 Hz), 132.0 (d, *J*_{CF} = 10.2 Hz), 151.5 (d, *J*_{CF} = 231 Hz), 152.4.

¹⁹F NMR (376.5 MHz, DMSO- d_6): $\delta = -122.8$ (s, 1 F).

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 3.81 \text{ min}; m/z = 237.2 \text{ [M + H]}^+.$

Anal. Calcd for $C_{12}H_{13}FN_2O_2;\,C,\,61.01;\,H,\,5.55;\,N,\,11.86.$ Found: C, 61.07; H, 5.58; N, 11.81.

tert-Butyl 4-Methoxy-3-nitrophenylcarbamate (5) White solid; yield: 96%; mp 159 °C.

IR (KBr): 3348, 1719, 1586, 1540, 1231, 1148 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): $\delta = 1.48$ (s, 9 H), 3.86 (s, 3 H), 7.11–7.08 (dd, J = 9.0, 2.0 Hz, 1 H), 7.52 (d, J = 2.0 Hz, 1 H), 7.89 (d, J = 9.0 Hz, 1 H), 10.04 (br s, 1 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 27.9, 56.1, 80.2, 101.8, 109.1, 127.0, 132.4, 146.1, 152.3, 154.2.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 3.89 \text{ min}; m/z = 269.2 [M + H]^+.$

Anal. Calcd for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44. Found: C, 53.80; H, 6.06; N, 10.41.

tert-Butyl 2-(Pyridin-4-yl)thiazol-4-ylcarbamate (6)¹² Off-white solid; yield: 93%; mp 192 °C.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 3.65 \text{ min}; m/z = 278.2 \text{ [M + H]}^+.$

tert-Butyl 5-Chloro-2-(methylsulfanyl)pyrimidin-4-ylcarbamate (7)

White solid; yield: 92%; mp 77 °C.

IR (KBr): 3222, 1706, 1567, 1547, 1471, 1138 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 1.45 (s, 9 H), 2.48 (s, 3 H), 8.55 (s, 1 H), 9.80 (br s, 1 H).

¹³C NMR (100 MHz, DMSO- d_6): δ = 13.9, 27.7, 80.8, 116.0, 150.3, 154.6, 156.8, 168.9.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 3.86 \text{ min}; m/z = 276.0 \text{ [M + H]}^+.$

Anal. Calcd for $C_{10}H_{14}CIN_3O_2S$: C, 43.56; H, 5.12; N, 15.24. Found: C, 43.62; H, 5.17; N, 15.20.

tert-Butyl 5-Methoxybenzofuran-2-ylcarbamate (8) White solid; yield: 93%; mp 117 °C.

IR (KBr): 3340, 1732, 1612, 1521, 1456, 775 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 1.47 (s, 9 H), 3.73 (s, 3 H), 6.30 (s, 1 H), 6.68–6.65 (dd, *J* = 8.8, 2.6 Hz, 1 H), 6.97 (d, *J* = 2.6 Hz, 1 H), 7.27 (d, *J* = 8.8 Hz, 1 H), 10.54 (br s, 1 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 27.9, 55.4, 80.3, 87.7, 102.9, 109.5, 110.3, 130.0, 144.0, 150.7, 151.3, 155.7.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.08 \text{ min}; m/z = 164.2 [M - 100]^+.$

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.92; H, 6.54; N, 5.29.

tert-Butyl 5-Methylthiophen-2-ylcarbamate (9)¹³

White solid; yield: 94%; mp 103 °C.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 3.75 \text{ min}; m/z = 114.2 [M - 100]^+.$

tert-Butyl {2-[4-(Trifluoromethyl)phenyl]ethenyl}carbamate (10)

White solid; yield: 91%; mp 127 °C.

IR (KBr): 3334, 1697, 1651, 1524, 1498, 1326, 1100, 944 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 1.44 (s, 9 H), 6.02 (d, J = 14.6 Hz, 1 H), 7.33–7.27 (dd, J = 14.2, 10.6 Hz, 1 H), 7.46 (d, J = 8.3 Hz, 2 H), 7.55 (d, J = 8.3 Hz, 2 H), 9.72 (d, J = 9.4 Hz, 1 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 27.9, 79.7, 107.2, 123.1, 125.4 (m), 125.6, 125.8, 128.2 (d), 141.4, 152.8.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.38 \text{ min}; m/z = 188.2 \text{ [M} - 100]^+.$

Anal. Calcd for $C_{14}H_{16}F_3NO_2$: C, 58.53; H, 5.61; N, 4.88. Found: C, 58.57; H, 5.65; N, 4.83.

tert-Butyl Tetrahydro-2*H*-pyran-4-ylcarbamate (11) White solid; yield: 86%; mp 93 °C.

IR (KBr): 3357, 1679, 1515, 1232, 1143 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 1.39–1.32 (m, 11 H), 1.65– 1.62 (m, 2 H), 3.30–3.24 (m, 2 H), 3.41–3.40 (m, 1 H), 3.80–3.76 (m, 2 H), 6.81 (d, *J* = 7.2 Hz, 1 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 28.2, 32.7, 46.3, 65.9, 77.4, 154.7.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 3.76$ min; product not ionized.

Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.73; H, 9.57; N, 6.91.

tert-Butyl (1R)-1-Phenylethylcarbamate (12)¹⁴

White solid; yield: 94%; mp 72 °C.

 $[\alpha]_{\rm D}$ +34.4 (*c* 0.1, MeOH).

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 3.85$ min; m/z = 122.2 [M – 100]⁺.

tert-Butyl Pent-4-ynylcarbamate (13)15

Colorless liquid; yield: 85%.

IR (liquid film): 1695, 1509, 1247, 1166, 755 cm⁻¹.

Benzyl (4-Formylphenyl)carbamate (14)¹⁶ White solid; yield: 95%; mp 187 °C.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 3.78 \text{ min}; m/z = 256.2 [M + H]^+.$

Prop-2-enyl 4-Formylphenylcarbamate (15)¹⁷ White solid; yield: 96%; mp 119 °C.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 3.27 \text{ min}; m/z = 206.2 [M + H]^+.$

Isopropyl 4-Formylphenylcarbamate (16)

White solid; yield: 94%; mp 110 °C.

IR (KBr): 3328, 1724, 1673, 1579, 1523, 1210 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 1.26–1.25 (d, 6 H), 4.94–4.88 (m, 1 H), 7.66 (d, J = 8.6 Hz, 2 H), 7.81 (d, J = 8.6 Hz, 2 H), 9.83 (s, 1 H), 10.09 (br s, 1 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 21.8, 68.0, 117.6, 130.5, 130.8, 145.1, 152.8, 191.3.

LC-MS (MeOH=0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 3.40$ min; m/z = 208.2 [M + H]⁺.

Anal. Calcd for C₁₁H₁₃NO₃: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.82; H, 6.37; N, 6.71.

Cyclohexyl 4-Formylphenylcarbamate (17)

White solid; yield: 94%; mp 123 °C.

IR (KBr): 3321, 1721, 1589, 1532, 1212 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 1.37–1.36 (m, 1 H), 1.45–1.39 (m, 4 H), 1.53–1.50 (m, 1 H), 1.72–1.69 (m, 2 H), 1.91–1.88 (m, 2 H), 4.68–4.62 (m, 1 H), 7.66 (d, *J* = 8.6 Hz, 2 H), 7.81 (d, *J* = 8.6 Hz, 2 H), 9.83 (s, 1 H), 10.10 (br s, 1 H).

¹³C NMR (100 MHz, DMSO- d_6): δ = 23.4, 24.9, 31.5, 72.9, 117.6, 130.5, 130.9, 145.2, 152.8, 191.4.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.03 \text{ min}; m/z = 248.2 \text{ [M + H]}^+.$

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.06; H, 6.98; N, 5.61.

tert-Butyl 4-{[(4-Formylphenyl)carbamoyl]oxy}piperidine-1carboxylate (18)

White solid; yield: 91%; mp 162 °C.

IR (KBr): 1721, 1667, 1601, 1524, 1213, 1054 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 1.38 (s, 9 H), 1.54–1.48 (m, 2 H), 1.91–1.87 (m, 2 H), 3.71–3.67 (m, 2 H), 4.87–4.81 (m, 2 H), 5.73 (m, 1 H), 7.67 (d, *J* = 8.6 Hz, 2 H), 7.81 (d, *J* = 8.6 Hz, 2 H), 9.83 (s, 1 H), 10.16 (br s, 1 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 28.0, 30.5, 70.4, 78.6, 117.6, 130.6, 130.8, 144.9, 152.5, 153.8, 191.3.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.01 \text{ min}; m/z = 347.2 \text{ [M - H]}^+.$

Anal. Calcd for $C_{18}H_{24}N_2O_5{:}$ C, 62.05; H, 6.94; N, 8.04. Found: C, 62.10; H, 6.99; N, 8.00.

2-(Trimethylsilyl)ethyl 4-Formylphenylcarbamate (19)

White solid; yield: 94%; mp 82 °C. IR (KBr): 3311, 1730, 1662, 1579, 1528, 1208 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 0.04 (s, 9 H), 1.04–0.99 (m, 2 H), 4.22–4.18 (m, 2 H), 7.66 (d, *J* = 8.6 Hz, 2 H), 7.81 (d, *J* = 8.6 Hz, 2 H), 9.80 (s, 1 H), 10.08 (br s, 1 H).

¹³C NMR (100 MHz, DMSO- d_6): δ = -1.4, 17.2, 62.7, 117.6, 130.5, 130.9, 145.1, 153.4, 191.4.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.24$ min; m/z = 264.2 [M – H]⁺.

Anal. Calcd for C₁₃H₁₉NO₃Si: C, 58.84; H, 7.22; N, 5.28. Found: C, 58.87; H, 7.27; N, 5.23.

Methyl 2-[(*tert*-Butoxycarbonyl)amino]-3-{[(4-formylphenyl)carbamoyl]oxy}propanoate (20) White solid; yield: 88%; mp 114 °C.

IR (KBr): 3345, 1707, 1588, 1518, 1159 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 1.37 (s, 9 H), 3.66 (s, 3 H), 4.26–4.21 (m, 1 H), 4.46–4.38 (m, 2 H), 7.40 (d, *J* = 7.7 Hz, 1 H), 7.67 (d, *J* = 8.2 Hz, 2 H), 7.83 (d, *J* = 8.4 Hz, 2 H), 9.84 (s, 1 H), 10.22 (br s, 1 H).

¹³C NMR (100 MHz, DMSO- d_6): δ = 28.0, 52.1, 52.8, 63.3, 78.6, 117.8, 130.7, 130.8, 144.7, 152.8, 155.3, 170.2, 191.4.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 3.60 \text{ min}; m/z = 267.2 \text{ [M} - 100]^+.$

Anal. Calcd for $C_{17}H_{22}N_2O_7\!\!:$ C, 55.73; H, 6.05; N, 7.65. Found: C, 55.80; H, 6.09; N, 7.62.

Prop-2-ynyl 4-Formylphenylcarbamate (22)

White solid; yield: 96%; mp 167 °C.

IR (KBr): 1728, 1670, 1597, 1533, 1215, 1057 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 3.59 (s, 1 H), 4.80 (s, 2 H), 7.66 (d, *J* = 8.6 Hz, 2 H), 7.84 (d, *J* = 8.6 Hz, 2 H), 9.85 (s, 1 H), 10.37 (br s, 1 H).

¹³C NMR (100 MHz, DMSO- d_6): δ = 52.3, 77.8, 78.5, 117.8, 130.9, 144.5, 152.4, 191.4.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 2.96 \text{ min}; m/z = 204.2 \text{ [M + H]}^+.$

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.07; H, 4.51; N, 6.82.

Benzyl 4-Bromophenylcarbamate (23)¹⁸

White solid; yield: 95%; mp 113 °C.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.23$ min; product not ionized.

Benzyl 4-Methylnaphthalen-1-ylcarbamate (24) Semi-solid; yield: 96%.

IR (KBr): 1691, 1533, 1090, 750 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 2.61 (s, 3 H), 5.17 (s, 2 H), 7.58–7.32 (m, 9 H), 8.06–7.99 (m, 2 H), 9.56 (br s, 1 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 18.8, 65.7, 121.4, 123.2, 124.3, 125.5, 125.9, 126.1, 127.8, 128.4, 131.1, 131.9, 132.4, 136.8, 154.9.

LC-MS (0.1% TFA in H₂O, 0.1% TFA–MeCN, 2.0 mL/min, Xbridge C8): $t_{\rm R} = 5.13$ min; m/z = 292.2 [M + H]⁺.

Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.39; H, 5.93; N, 4.78.

Benzyl 4-{[(*tert*-Butoxycarbonyl)amino]methyl}phenylcarbamate (25)¹⁹

White solid; yield: 94%; mp 107 °C.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.00$ min; product not ionized.

Benzyl 4-Chloropyridin-2-ylcarbamate (26) White solid; yield: 94%; mp 187 °C.

IR (KBr): 1718, 1572, 1529, 1409, 1210 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 5.18 (s, 2 H), 7.19–7.17 (dd, *J* = 5.4, 1.7 Hz, 1 H), 7.43–7.31 (m, 5 H), 7.91 (d, *J* = 1.7 Hz, 1 H), 8.23 (d, *J* = 5.4 Hz, 1 H), 10.60 (br s, 1 H).

¹³C NMR (100 MHz, DMSO- d_6): δ = 66.1, 111.6, 118.6, 127.9, 128.0, 128.4, 136.2, 143.9, 149.4, 153.3, 153.4.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.18 \text{ min}; m/z = 264.2 \text{ [M + H]}^+.$

Anal. Calcd for $C_{13}H_{11}CIN_2O_2$: C, 59.44; H, 4.22; N, 10.66. Found: C, 59.49; H, 4.26; N, 10.61.

Benzyl 5-Bromothiophen-2-ylcarbamate (27)

White solid; yield: 91%; mp 53 °C.

IR (KBr): 1688, 1564, 1495, 1240, 1056 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 5.16 (s, 2 H), 6.32 (d, J = 4.0 Hz, 1 H), 6.91 (d, J = 4.0 Hz, 1 H), 7.40–7.34 (m, 5 H), 11.0 (br s, 1 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 66.7, 101.2, 110.0, 127.5, 128.1, 128.2, 128.4, 136.0, 141.6, 153.2.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.15 \text{ min}; m/z = 314.2 \text{ [M + 2]}^+.$

Anal. Calcd for $C_{12}H_{10}BrNO_2S$: C, 46.17; H, 3.23; N, 4.49. Found: C, 46.24; H, 3.27; N, 4.43.

Benzyl [2-(4-tert-Butylphenyl)ethenyl]carbamate (28)

White solid; yield: 90%; mp 119 °C.

IR (KBr): 1691, 1657, 1501, 1221, 1055, 689 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): $\delta = 1.24$ (s, 9 H), 5.12 (s, 2 H), 5.99 (d, J = 14.4 Hz, 1 H), 7.12–7.06 (dd, J = 14.4, 10.2 Hz, 1 H), 7.19 (d, J = 8.4 Hz, 2 H), 7.26 (d, J = 8.4 Hz, 2 H), 7.39–7.32 (m, 5 H), 9.83 (d, J = 10.2 Hz, 1 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 31.0, 34.0, 66.0, 109.7, 124.4, 124.5, 125.3, 128.0, 128.4, 133.7, 136.4, 148.2, 153.7.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.63 \text{ min}; m/z = 310.2 \text{ [M + H]}^+.$

Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.71; H, 7.53; N, 4.49.

Benzyl (1-Phenylcyclopropyl)carbamate (29)

White solid; yield: 84%; mp 103 °C.

IR (KBr): 1701, 1399, 1337, 1087, 693 cm⁻¹.

¹H NMR (400 MHz, DMSO- d_6): δ = 1.14 (br s, 4 H), 4.99 (s, 2 H), 7.30–12 (m, 5 H), 7.36–7.32 (m, 4 H), 8.14 (br s, 1 H).



¹³C NMR (100 MHz, DMSO-*d*₆): δ = 18.0, 34.5, 34.5, 65.1, 124.6, 125.5, 127.7, 128.0, 128.3, 137.1, 143.7, 156.0.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 3.91 \text{ min}; m/z = 268.2 \text{ [M + H]}^+.$

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.43; H, 6.46; N, 5.20.

tert-Butyl 4-{[(Benzyloxy)carbonyl]amino}piperidine-1-carboxylate (30)²⁰

White solid; yield: 90%; mp 88 °C.

LC-MS (MeOH–0.1% HCO₂H, 1.0 mL/min, Atlantis dC18): $t_{\rm R} = 4.02 \text{ min}; m/z = 235.2 [M - 100]^+.$

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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