# A Facile Synthesis of Amides from 9-Fluorenylmethyl Carbamates and Acid Derivatives

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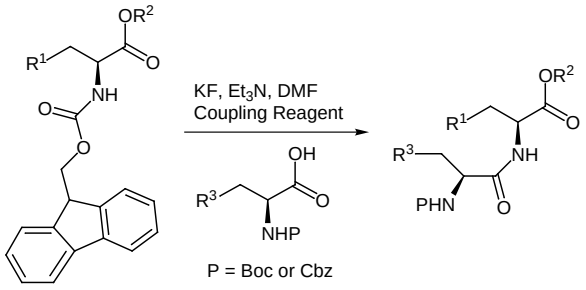
**Abstract:** A mild and convenient one-pot procedure for the synthesis of amides from 9-fluorenylmethyl carbamates and acids using potassium fluoride, triethylamine and various coupling reagents in DMF at room temperature is described. The scope of this procedure was also tested in the coupling of a variety of 9-fluorenylmethyloxycarbonyl-protected amines with active moieties such as anhydrides, acyl imidazolides, activated esters, tosyl chlorides, and acyl halides.

**Key words:** 9-fluorenylmethyl carbamates, peptide synthesis, potassium fluoride, BOP-Cl, amides, acids, protecting groups

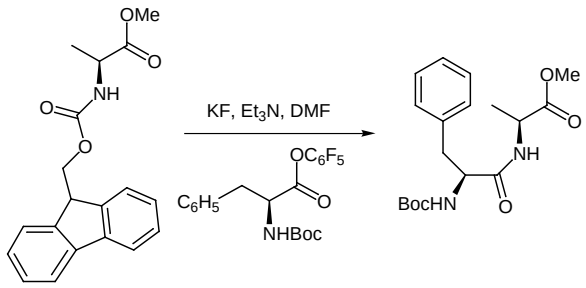
Among the plethora of protecting groups used in peptide synthesis, a number of 9-fluorenylmethyl carbamates, which are deprotected by a variety of amine bases such as piperidine, have been extensively used in solid phase synthesis.[1] Although these carbamates have been successfully utilized as protecting groups for amino acids on the solid support, they have not been generally accepted in solution phase amide formation and peptide synthesis. The main reasons for their lesser usefulness in solution are the side reactions[2,3] and the purification of the resulting free amine product. Therefore, fluoride ion has attracted special interest as an effective alternative to the piperidine reagent for the cleavage of 9-fluorenylmethyloxycarbonyl (Fmoc) group in solid phase peptide synthesis.[3–5] However, the application of fluoride ion to the solution synthesis of peptides or amides has not been reported in the literature.

For the coupling of two peptide fragments three separate reaction steps are generally used, namely: (1) cleavage of the amino protecting group of the first fragment; (2) activation of the carboxylic acid of the second fragment; and (3) coupling of these two resulting fragments. In some cases, the second and third step can proceed in one-pot by activating the carboxylic acid functionality in situ using various coupling reagents. The convenience of combining these three separate steps into one has stimulated our interest in the development of a mild and efficient method to prepare peptides from Fmoc-protected amines using a direct transacylation, without necessitating the removal of the amino protecting group in an initial separate step. This method as shown in Scheme 1 would expand the application of Fmoc protecting group in the solution peptide chemistry and offer an efficient synthesis of peptides and amides.




**Scheme 1**

Our previous results on the selective removal of the Fmoc group[6] by potassium fluoride/18-crown-6 suggested that potassium fluoride/coupling reagent would provide an efficient reagent system for the one-pot solution synthesis of amides and peptides from fluorenylmethyl carbamates and acids. We first examined the reaction of 9-fluorenylmethyl carbamates with potassium fluoride, triethylamine and stable activated esters such as the pentafluorophenyl (OPfp) ester[7–9] (Scheme 2).




**Scheme 2**

In contrast to our selective Fmoc deprotection method, it was found that the 18-crown-6 was not necessary to drive the reaction to completion when the activated carbonyl moiety was present. As the pentafluorophenyl ester can be regarded as a stable activated carbonyl compound, it was anticipated that other molecules containing activated functionalities would react in the same manner with Fmoc-protected compounds, thus affording different amides. The results of such reactions are summarized in Table 1. Various types of stable activated carbonyl moieties were reactive in this process, such as anhydrides,

**Table 1** Results Obtained from the Reaction of 9-Fluorenylmethyl Carbamates with Potassium Fluoride, Triethylamine and Various Active Moieties

| Entry | 9-Fluorenylmethyl Carbamate | Carbonyl Compound | Product | Yield (%) |
|---|---|---|---|---|
| 1 | *N*-Fmoc-L-Phe-OMe | acetic anhydride | *N*-Ac-L-Phe-OMe (**1**) | 87 |
| 2 | *N*-Fmoc-L-Phe-OMe | acetyl bromide | *N*-Ac-L-Phe-OMe (**1**) | 85 |
| 3 | *N*-Fmoc-L-Phe-OMe | 1-acetylimidazole | *N*-Ac-L-Phe-OMe (**1**) | 77 |
| 4 | *N*-Fmoc-L-Phe-OMe | tosyl chloride (Ts-Cl) | *N*-Ts-L-Phe-OMe (**2**) | 78 |
| 5 | *N*-Fmoc-L-Ala-OMe | benzoyl chloride (Bz-Cl) | *N*-Bz-L-Ala-OMe (**3**) | 94 |
| 6 | *N*-Fmoc-L-Ala-OMe | *N*-Boc-L-Phe-OPfp | *N*-Boc-L-Phe-L-Ala-OMe (**4**) | 93 |
| 7 | *N*-Fmoc-L-Ala-OMe | *N*-Boc-L-Phe-OSu | *N*-Boc-L-Phe-L-Ala-OMe (**4**) | 95 |

acyl imidazolides, acyl halides and *N*-hydroxysuccinimide (OSu) ester,[9] all leading to a mild and efficient one-pot transformation of the 9-fluorenylmethyl carbamates into the amides or dipeptides in good to excellent yields. Table 1 illustrates that not only electrophilic carbonyl compounds but also tosyl chloride could be used successfully. However, when less reactive electrophiles such as esters, tosylates and alkyl halides were used, the desired products were not obtained. These groups were stable under the experimental procedure.

Next, a series of experiments was designed to determine the most efficient coupling reagent and conditions to perform the direct coupling method and to synthesize the dipeptide from *N*-Fmoc-L-Ala-OMe and *N*-Boc-L-Phe-OH. The results showed (Table 2) that when less reactive coupling reagent such as 1,3-diisopropylcarbodiimide (DIC) or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) was used as the activating agent, the reaction time was longer and the yield was lower. Use of 1,3-diisopropylcarbodiimide (DIC) in the presence *N*-hydroxybenzotriazole (HOBT) was found to improve the efficiency of coupling. Experiments also showed dramatic improvements in rates and yields when 1.2 equivalents of coupling reagent was mixed with the amino acid in DMF, left to preactivate for 3 minutes, then mixed with the reaction mixture, and coupled. This observation was consistent with the general belief that the preactivation protocol provides increased activity and efficiency over that obtained with the direct coupling method.[10] In summary, these initial experiments (Table 2) showed the *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl)[11] and 2-(1*H*-benzotriazol-1yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU)[12] were effective in the formation of *N*- Boc-L-Phe-L-Ala-OMe.

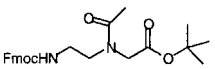
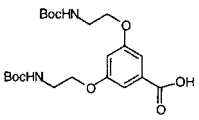
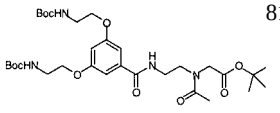
Since the BOP-Cl is a very powerful peptide-coupling reagent, especially for those couplings involving protected secondary amino acid residues, we decide to investigate the scope of this one-pot formation of peptide using BOP-Cl as the activating agent. Table 3 and Table 4 show results obtained when the KF/BOP-Cl/$Et_3N$ method was employed to prepare the amides from various Fmoc-protected fragments and carboxylic acids. The Fmoc-protected fragments used included various Fmoc-protected α-amino acid derivatives and a Fmoc-protected amine. The carboxylic acids, employed in these reactions contained two different protecting groups on the amino nitrogen (Boc and Cbz). These fragments were easily prepared following standard procedures.[9] As shown in the Table 3, the ester groups, the Boc and Cbz groups, the sulfide bond and the *tert*-butyl ether bond were preserved under these conditions. In the present study racemization was not detected after comparison of the optical rotations of the pure products with those reported in the literature.

In order to further demonstrate that the KF/BOP-Cl/$Et_3N$ method could be used for the facile production of oligopeptides, a tetrapeptide **15** and pentapeptide **17** were synthesized as shown in Schemes 3 and 4. Coupling of the $N^{\alpha}$-Fmoc-$N^{\varepsilon}$-Boc-L-lysine with L-glycine methyl ester hydrochloride salt, using HBTU activation, afforded dipeptide **12** in 92% yield. Direct transacylation of the Fmoc-protected dipeptide **12** proceeded in 84% yield by treatment with Cbz-L-alanine and the KF/BOP-Cl/$Et_3N$

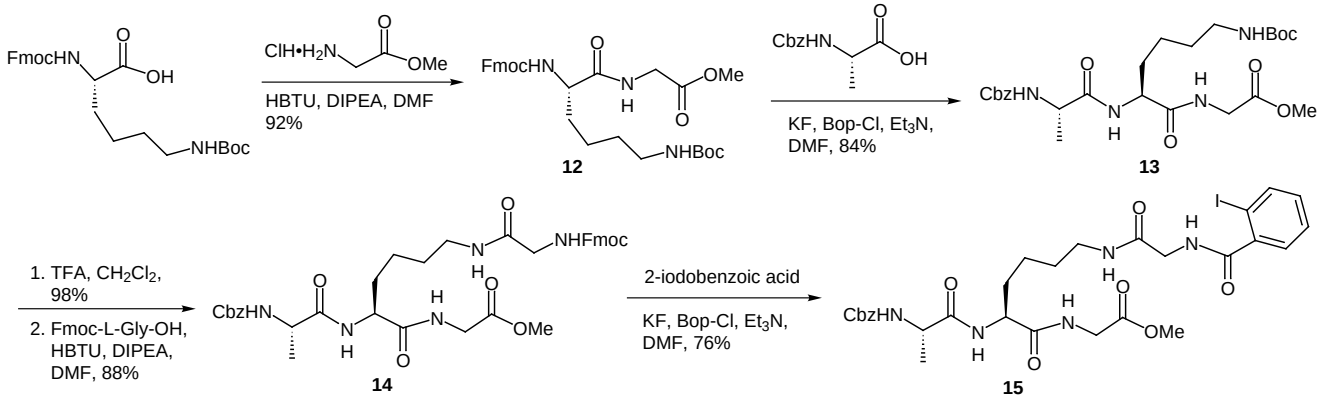
**Table 2** Results Obtained from the Reaction of *N*-Fmoc-L-Ala-OMe with Potassium Fluoride, Triethylamine, *N*-Boc-L-Phe-OH and Various Coupling Reagents to form *N*-Boc-L-Ala-OMe

| Entry | Coupling Reagent | Time (h) | Yield (%) |
|---|---|---|---|
| 1 | 1,3-Diisopropylcarbodiimide (DIC) | 10 | 38 |
| 2 | DIC/*N*-Hydroxybenzotriazole (HOBT) | 8 | 71 |
| 3 | *N*,*N*-Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) | 6.5 | 86 |
| 4 | Benzotriazol-1-yl-oxytris(dimethylamino)phosphonium Hexafluorophosphate (BOP) | 9 | 72 |
| 5 | Isobutyl chloroformate | 7 | 83 |
| 6 | 2-(1*H*-Benzotriazol-1yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) | 6 | 91 |
| 7 | 1,1'-Carbonyldiimidazole (CDI) | 11 | 74 |
| 8 | 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) | 12 | 21 |

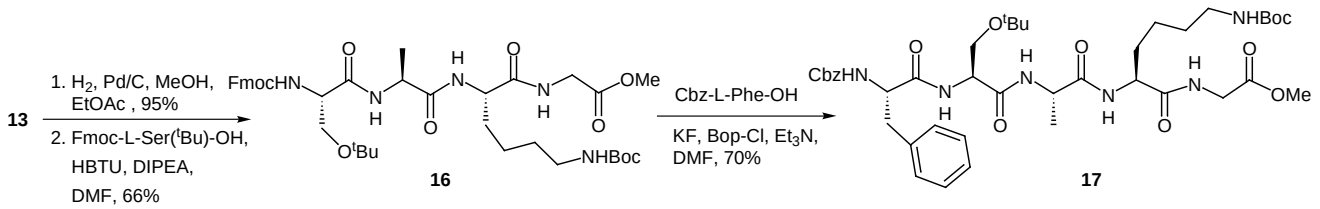
**Table 3** One-Pot Conversion of Fluorenylmethyl Carbamates into the Dipeptides Using the KF/BOP-Cl/$Et_3N$ Reagent System

| Entry | Fluorenylmethyl Carbamate | Acid | Time (h) | Product | Yield (%) | mp (°C) | $[\alpha]_D^{25}$ (c , solvent) [Lit.] |
|---|---|---|---|---|---|---|---|
| 1 | N-Fmoc-L-Ala-OMe | N-Boc-L-Phe-OH | 6.5 | N-Boc-L-Phe-L-Ala-OMe (**4**) | 86 | 104.0−104.5 | +18.5 (0.5, MeOH) [+18.5 (0.5, MeOH)][13] |
| 2 | N-Fmoc-L-Leu-OMe | N-Cbz-L-Phe-OH | 6 | N-Cbz-L-Phe-L-Leu-OMe (**5**) | 75 | 104.5−105.0 | −24.9 (0.49, MeOH) [−24.2 (3.1, MeOH)][14] |
| 3 | N-Fmoc-L-Lys(Boc)-OEt | N-Cbz-L-Met-OH | 8 | N-Cbz-L-Met-L-Lys(Boc)-OEt (**6**) | 84 | 99.5−100.0 | −12.8 (0.48, MeOH) |
| 4 | N-Fmoc-L-Ile-OEt | N-Cbz-L-Ala-OH | 5 | N-Cbz-L-Ala-L-Ile-OEt (**7**) | 84 | 57.5−58.0 | −31.5 (0.51, MeOH) |
| 5 | N-Fmoc-L-Phe-OMe | N-Boc-L-Val-OH | 7 | N-Boc-L-Val-L-Phe-OMe (**8**) | 81 | 98.5−99.0 | −25.0 (0.5, EtOH) [−26.0 (0.5, EtOH)][15] |
| 6 | N-Fmoc-L-Pro-OMe | N-Boc-L-Ala-OH | 9 | N-Boc-L-Ala-L-Pro-OMe (**9**) | 83 | oil | −82.7 (0.59, MeOH) |
| 7 | N-Fmoc-L-Ser(t-But)-OEt | N-Boc-L-Phe-OH | 5 | N-Boc-L-Phe-L-Ser(t-But)-OEt (**10**) | 84 | 110.0−111.0 | 6.0 (0.52, MeOH) |
| 8 |  |  | 6 |  (**11**) | 81 | oil | – |

reagent system giving the tripeptide **13**. Removal of the Boc group of tripeptide **13** with trifluoroacetic acid furnished the corresponding salt in 98% yield. The crude salt was then coupled with Fmoc-L-glycine, using the HBTU reagent in the presence of diisopropylethylamine (DIPEA) to yield the tetrapeptide **14** in 88% yield. Direct acylation of the Fmoc-protected tetrapeptide with 2-iodo-




**Scheme 3**




**Scheme 4**

**Table 4** Spectral Data of Amides **1**–**11**

| Product | $^1$H NMR ($CDCl_3$/TMS) δ, *J* (Hz) | $^{13}$C NMR ($CDCl_3$/TMS) δ, *J* (Hz) | IR (KBr/film) ν ($cm^{-1}$) | HRMS (*m/z*) | |
|---|---|---|---|---|---|
| | | | | Calcd | Found |
| **1** | 1.98 (s, 3 H, $COCH_3$), 3.12 (m, 2 H, $CH_2$), 3.73 (s, 3 H, $OCH_3$), 4.89 (m, 1 H, CH), 5.98 (br d, 1 H, NH, *J* = 6.34), 7.05–7.38 (m, 5 H, $C_6H_5$) | 23.07, 37.81, 52.27, 53.08, 127.09, 128.54, 129.19, 135.80, 169.58, 172.07 | 3340, 3073, 2961, 1754, 1657, 1541 | 221.1052 | 221.1049 |
| **2** | 2.40 (s, 3 H, $CH_3$), 3.02 (d, 2 H, $CH_2$, *J* = 6.0), 3.49 (s, 3 H, $OCH_3$), 4.20 (m, 1 H, CH), 5.12 (br d, 1 H, NH, *J* = 9.1), 7.00–7.70 (m, 9 H, $C_6H_5$) | 21.46, 39.32, 52.30, 56.60, 127.13, 128.52, 129.35, 129.55, 134.93, 136.62, 143.54, 171.22 | 3289, 3035, 2958, 2882, 1748, 1599, 1497 | 333.1035 | 333.1029 |
| **3** | 1.52 (d, 3 H, $CH_3$, *J* = 7.18), 3.79 (s, 3 H, $OCH_3$), 4.81 (m, 1 H, CH), 6.85 (br d, 1 H, NH, *J* = 6.12), 7.30–7.90 (m, 5 H, $C_6H_5$) | 18.55, 48.42, 52.53, 127.00, 128.51, 130.00, 131.68, 133.21, 133.82, 166.79, 173.67 | 3293, 3066, 3031, 2987, 2956, 1750, 1638, 1543 | 207.0895 | 207.0892 |
| **4** | 1.34 (d, 3 H, $CH_3$, *J* = 7.08), 1.40 (s, 9 H, 3 $CH_3$), 3.06 (d, 2 H, $CH_2$, *J* = 6.64), 3.71 (s, 3 H, $OCH_3$), 4.39 (br s, 1 H, CH), 4.52 (m, 1 H, CH), 5.11 (br d, 1 H, NH, *J* = 7.46), 6.61 (br d, 1 H, NH, *J* = 6.86), 7.10–7.35 (m, 5 H, $C_6H_5$)[16] | 18.14, 28.14, 38.31, 47.97, 52.31, 55.47, 80.07, 126.79, 128.48, 129.28, 136.50, 155.29, 170.86, 172.80 | 3336, 2981, 2954, 1754, 1696, 1661, 1524 | 350.1842 | 350.1847 |
| **5** | 0.82–0.92 (m, 6 H, 2 $CH_3$), 1.40–1.60 (m, 3 H, CH and $CH_2$), 3.07 (d, 2 H, $CH_2$, *J* = 6.69), 3.68 (s, 3 H, $OCH_3$), 4.45–4.61 (m, 2 H, 2 CH), 5.07 (s, 2 H, $CH_2$), 5.47 (br d, 1 H, NH, *J* = 8.13), 6.44 (br d, 1 H, NH, *J* = 7.97), 7.13–7.40 (m, 10 H, 2 $C_6H_5$)[17] | 21.82, 22.61, 24.61, 38.35, 41.31, 50.70, 52.20, 55.90, 66.97, 126.91, 127.91, 128.11, 128.45, 128.53, 129.31, 136.03, 136.20, 155.85, 170.63, 172.79 | 3291, 3091, 2960, 1750, 1696, 1657, 1551 | 426.2155 | 426.2163 |
| **6** | 1.27 (t, 3 H, $CH_3$, *J* = 7.08), 1.43 (s, 9 H, 3 $CH_3$), 1.23–2.17 (m, 8 H, 4 $CH_2$), 2.15 (s, 3 H, $CH_3$), 2.58 (t, 2 H, $CH_2$, *J* = 7.17), 3.06 (m, 2 H, $CH_2$), 4.18 (q, 2 H, $CH_2$, *J* = 7.09), 4.40–4.55 (m, 2 H, 2 CH), 4.88 (br s 1 H, NH), 5.11 (s, 2 H, $CH_2$), 5.83 (br d, 1 H, NH, *J* = 7.76), 6.93 (br d, 1 H, NH, *J* = 7.74), 7.33 (s, 5 H, $C_6H_5$) | 14.05, 14.98, 22.29, 28.32, 29.23, 29.77, 31.58, 39.95, 52.03, 53.54, 61.39, 66.92, 79.03, 127.95, 128.06, 128.41, 128.63, 136.08, 156.03, 171.13, 171.83 | 3334, 2961, 2865, 1740, 1692, 1651, 1534 | 539.2665 | 539.2656 |
| **7** | 0.89 (t, 6 H, 2$CH_3$, *J* = 6.99), 1.15–1.42 (m, 2 H, $CH_2$), 1.27 (t, 3 H, $CH_3$, *J* = 7.10), 1.37 (d, 3 H, $CH_3$, *J* = 7.10), 1.79–1.98 (m, 1 H, CH), 4.18 (m, 2 H, $CH_2$), 4.35 (dd, 1 H, CH, *J* = 7.42, 7.42), 4.55 (m 1 H, CH), 5.11 (s, 2 H, $CH_2$), 5.61 (br d, 1 H, NH, *J* = 7.62), 6.78 (br d, 1 H, NH, *J* = 8.32), 7.25–7.41 (s, 5 H, $C_6H_5$) | 11.53, 14.11, 15.29, 18.52, 25.00, 37.76, 50.33, 56.38, 61.16, 66.85, 127.92, 128.05, 128.42, 136.14, 155.84, 171.61, 172.10 | 3326, 3068, 2985, 2938, 2880, 2767, 1732, 1694, 1657, 1536 | 364.1998 | 364.2004 |
| **8** | 0.88 (m, 6 H, 2 $CH_3$), 1.44 (s, 9 H, 3 $CH_3$), 2.00–2.15 (m, 1 H, CH), 3.11 (d, 2 H, CH, *J* = 5.20), 3.70 (s, 3 H, $OCH_3$), 3.92 (m, 1 H, CH), 4.87 (m, 1 H, CH), 5.06 (br d, 1 H, NH, *J* = 8.18), 6.41 (br d, 1 H, NH, *J* = 7.49), 7.09–7.32 (m, 5 H, $C_6H_5$)[18] | 17.61, 19.09, 28.23, 30.80, 37.90, 52.23, 53.06, 59.81, 79.80, 127.09, 128.55, 129.17, 135.65, 155.67, 171.25, 171.66 | 3343, 2977, 1744, 1669, 1528 | 378.2155 | 378.2150 |
| **9** | 1.35 (d, 3 H, $CH_3$, *J* = 6.99), 1.43 (s, 9 H, 3 $CH_3$), 1.83–2.73 (m, 4 H, 2 $CH_2$), 3.41–3.92 (m, 2 H, $CH_2$), 3.72 (s, 3 H, $OCH_3$), 4.34–4.71 (m, 2 H, 2 CH), 5.39 (br d, 1 H, NH, *J* = 8.06) | 18.18, 24.83, 28.29, 28.84, 46.68, 47.68, 52.15, 58.64, 79.49, 155.18, 171.70, 172.35 | 3347, 2983, 1752, 1717, 1657, 1516, 1457 | 300.1685 | 300.1696 |

**Table 4** (continued)

| Product | $^1$H NMR ($CDCl_3$/TMS) δ, *J* (Hz) | $^{13}$C NMR ($CDCl_3$/TMS) δ, *J* (Hz) | IR (KBr/film) ν ($cm^{-1}$) | HRMS (*m/z*) | |
|---|---|---|---|---|---|
| | | | | Calcd | Found |
| **10** | 1.10 (s, 9 H, 3 $CH_3$), 1.26 (t, 3 H, $CH_3$, *J* = 7.14), 1.40 (s, 9 H, 3 $CH_3$), 3.10 (m, 2 H, $CH_2$), 3.40−3.80 (m, 2 H, $CH_2$), 4.19 (q, 2 H, $CH_2$, *J* = 7.15), 4.41 (br s, 1 H, CH), 4.55−4.69 (m, 1 H, CH), 5.08 (br s, 1 H, NH), 6.61 (br d, 1 H, NH, *J* = 7.70), 7.21−7.33 (m, 5 H, $C_6H_5$) | 14.14, 27.19, 28.20, 38.59, 52.92, 55.47, 61.32, 61.80, 73.27, 79.93, 126.80, 128.51, 129.37, 136.57, 155.14, 169.91, 170.96 | 3369, 3274, 2977, 1740, 1719, 1698, 1651, 1526 | 436.2573 | 436.2577 |
| **11** | 1.45 (s, 18 H, 6 $CH_3$), 1.48 (d, 9 H, 3 $CH_3$, *J* = 3.82), 2.04 (d, 3 H, $CH_3$, *J* = 2.64), 3.53 (m, 8 H, 4 $CH_2$), 4.04 (m, 6 H, 3 $CH_2$), 5.27 (m, 2 H, 2 NH), 6.56 (m, 1 $H_{arom}$), 6.97 (m, 2 $H_{arom}$) , 7.64 and 7.99 (br s, 1 H, NH) | 20.90, 21.25, 27.78, 28.19, 37.53, 39.04, 39.64, 47.24, 49.50, 52.05, 67.11, 79.30, 82.37, 82.90, 104.86, 105.41, 135.96, 136.25, 155.76, 159.63, 166.90, 168.30, 170.20, 171.39, 172.87 | 3349, 2983, 2942, 1717, 1655, 1597, 1536, 1469 | 638.3527 | 638.3528 |

benzoic acid was accomplished by employing the KF/BOP-Cl/$Et_3N$ method in 76% yield.

As shown in Scheme 4, the tripeptide **13** could also be extended to the pentapeptide **17** from the Cbz-protected site. Cleavage of the Cbz protecting group of tripeptide **13** by catalytic hydrogenation using 10% Pd/C as a catalyst afforded the crude amine in 95% yield. The resulting amine was then coupled with Fmoc-*O*-*tert*-butyl-L-serine using the HBTU/DIPEA activation conditions to give the tetrapeptide **16** in 66% yield. Following procedure similar to that described in the synthesis of dipeptides (Table 3), the Fmoc-protected tetrapeptide **16** was coupled with Cbz-L-phenylalanine to afford the fully protected pentapeptide **17** in 70% yield. As shown in Schemes 3 and 4, the KF/BOP-Cl/$Et_3N$ reagent system can prove to be of value in the synthesis of peptides and also in the direct acylation of carboxylic acids with Fmoc-protected amines.

In conclusion, we have successfully formed peptide bonds using KF in conjunction with triethylamine and a coupling reagent such as BOP-Cl or HBTU. Using this protocol, the three separate reaction steps required for amide bond formation were combined into a single, easy and effective procedure. The advantages of this methodology are the short reaction time, simple and mild reaction conditions, easy workup, good yields and no racemization. This method can be applied widely in solution peptide synthesis and should stimulate the wider use of the Fmoc protecting group.

All solvents were reagent grade and distilled before use. Analytical TLC was performed on Merck silica gel (60 F 254) plates (0.25 mm). Visualization was effected with ultraviolet light or any of the following reagents: ninhydrin, phosphomolybdic acid and anisaldehyde. Chromatography was carried out on Merck silica gel 60 (particle size 240−400 mesh). Melting points were determined with a Mel-Temp II melting point apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DRX-200 spectrometer. Chemical shifts were measured in parts per million (δ) relative to TMS or $CHCl_3$ as the internal standard. Coupling constants (*J*) are in Hertz (Hz). Multiplicities are designated as singlet (s), broad singlet (br s), broad doublet (br d), doublet (d), triplet (t), quartet (q), and multiplet (m). IR spectra were obtained on a Bio-Rad FTS 155 spectrometer. Absorptions are reported in wave numbers ($cm^{-1}$), and their intensities are designated as broad (br), medium (m) or strong (s). The spectra taken were referenced to the 1601 $cm^{-1}$ band of polystyrene, and only the most prominent or characteristic absorptions are noted. Optical rotations (in degrees) were recorded on a Perkin-Elmer Model 343 polarimeter at the sodium D line. Concentration were reported in g/100 mL. HRMS were obtained on JEOL SX-102A, using either ammonia Chemical Ionization (CI) or electron impact (EI).

**Conversion of 9-Fluorenylmethyl Carbamates into Amides; General Procedures**

A. *Procedure Used for Experiments Listed in Table 1*: 9-Fluorenylmethyl carbamate (0.6 mmol) was dissolved in DMF (3 mL) at r.t. under argon, and treated with KF (139 mg, 2.4 mmol) followed by $Et_3N$ (0.161 mL, 1.26 mmol). After the carbamate had dissolved, the stable activated compound was added and the mixture was then stirred at r.t. until the reaction was complete. The reaction was monitored by TLC using MeOH/$CH_2Cl_2$ (20:80) or EtOAc/hexane (30:70) as eluting system. After dilution with EtOAc (35 mL), the mixture was washed with 5% aq HCl (2 × 10 mL) and 5% aq $NaHCO_3$ solution (2 × 10 mL). The aqueous layers were combined and extracted with EtOAc (2 × 10 mL). The organic layers were combined and washed with brine (2 mL). The organic layer was dried ($Na_2SO_4$), filtered, and concentrated. The resulting crude products were purified by column chromatography and eluted with a EtOAc/hexane system to afford the pure products.

B. *Procedure Used for Experiments Listed in Tables 2 and 3*. In the direct coupling runs, the experiments were performed in the same way as described in A, except that the acid was preactivated according to the following procedure to increase the coupling efficiency. The acid (0.72 mmol) was dissolved in DMF (3 mL), activated by the addition of coupling reagent (0.72 mmol) and $Et_3N$ (0.192 mL, 1.5 mmol), and added directly to the reaction mixture after 3 min. The mixture was then stirred at r.t. until the reaction was complete and worked up as above.

**Methyl, Ethyl or the Pentafluorophenyl Esters; Fmoc-isoleucine Ethyl Ester; Typical Procedure**

Fmoc-isoleucine (0.60 g, 1.7 mmol) was dissolved in EtOH (8.5 mL) in a flame-dried flask equipped with a magnetic stirrer. To this stirred solution was added 1,3-diisopropylcarbodiimide (DIC) (0.32 mL, 2.1 mmol) and 4-dimethylaminopyridine (DMAP) (21 mg, 0.17 mmol) under argon. The mixture was stirred for 1 h, and then concentrated under reduced pressure. The resulting crude material was dissolved in $CH_2Cl_2$ (10 mL). After collecting the precipitated urea, the filtrate was concentrated. The resulting crude product was purified by column chromatography eluting with EtOAc/hexane (10:90). Fmoc-isoleucine ethyl ester (0.589 g, 91%) was obtained as a white solid.

**$N^{\alpha}$-Fmoc-$N^{\varepsilon}$-Boc-L-Lysine-glycine-OMe (12)**

$N^{\alpha}$-Fmoc-$N^{\varepsilon}$-Boc-L-Lysine-OH (1.0 g, 2.13 mmol) was dissolved in DMF (10.6 mL) under argon, and treated with HBTU (888 mg, 2.34 mmol) followed by diisopropylethylamine (DIPEA) (0.74 mL, 4.47 mmol). The mixture was stirred at r.t. for 5 min. Then glycine methyl ester hydrochloride salt (281 mg, 2.24 mmol) and DIPEA (0.39 mL, 2.34 mmol) were added and the solution was kept at r.t. for 15 min. After dilution with EtOAc (150 mL), the organic layer was washed with 5% aq HCl (30 mL), 5% aq $NaHCO_3$ solution (20 mL), and brine (10 mL). The EtOAc layer was dried ($Na_2SO_4$), filtered, and concentrated. The crude product was purified by column chromatography eluting with EtOAc/hexane (60:40). The fully protected dipeptide **12** (1.06 g, 92%) was obtained as a white solid; $[\alpha]_D^{26}$ −13.4 (*c* = 0.53, MeOH).

IR (KBr): ν = 3316 (br), 2977 (m), 2940 (m), 1690 (s), 1527 $cm^{-1}$ (s).

$^1$H NMR ($CDCl_3$): δ = 1.17−2.15 (m, 15 H, 3 $CH_2$ and 3 $CH_3$), 3.09 (d, 2 H, $CH_2$, *J* = 5.86 Hz), 3.70 (s, 3 H, $CH_3$), 4.01 (br s, 2 H, $CH_2$), 4.19 (m, 2 H, 2 CH), 4.39 (d, 2 H, $CH_2$, *J* = 6.74 Hz), 4.74 (br s, 1 H, CH), 5.70 (br d, 1 H, NH, *J* = 7.2 Hz), 6.88 (br s, 1 H, NH), 7.17−7.82 (m, 8 Harom).

$^{13}$C NMR ($CDCl_3$): δ = 22.12, 28.17, 29.31, 31.79, 39.66, 40.84, 46.88, 52.08, 54.42, 66.82, 78.91, 119.71, 124.82, 126.83, 127.46, 141.03, 143.53, 155.99, 169.86, 171.94.

HRMS: *m*/*z* calcd for $C_{29}H_{38}N_3O_7$ (M + H): 540.2710, found: 540.2710.

**Cbz-L-Alanine-$N^{\varepsilon}$-Boc-L-lysine-glycine-OMe (13)**

According to the general procedure used for experiments listed in Tables 2 and 3, the tripeptide **13** was prepared starting from **12** (1.03 g, 1.91 mmol), Cbz-L-alanine (511 mg, 2.29 mmol), DIPEA (444 mg, 7.64 mmol), BOP-Cl (590 mg, 2.29 mmol), KF (0.67 mg, 4.78 mmol), and DMF (19 mL). Flash chromatography of the crude product (EtOAc/hexane, 8:2) afforded a solid; yield: 834 mg (84%); $[\alpha]_D^{26}$ −26.5 (*c* = 0.51, MeOH).

IR (KBr): ν = 3304 (br), 2978 (m), 2934 (m), 1685 (s), 1653 (s), 1539 $cm^{-1}$ (s).

$^1$H NMR ($CDCl_3$): δ = 1.19−2.28 (m, 18 H, 3 $CH_2$ and 4 $CH_3$), 3.62 (d, 2 H, $CH_2$, *J* = 5.92 Hz), 3.72 (s, 3 H, $CH_3$), 3.99 (d, 2 H, $CH_2$), 4.28 (m, 1 H, CH), 4.50 (m, 1 H, CH), 5.09 (br s, 1 H, NH), 5.30 (s, 2 H, $CH_2$), 5.74 (br s, 1 H, NH), 6.92−7.24 (br s, 2 H, 2 NH), 7.43 (m, 5 H, $C_6H_5$).

$^{13}$C NMR ($CDCl_3$): δ = 18.42, 22.26, 28.25, 29.19, 31.63, 39.91, 40.89, 50.59, 52.11, 52.65, 66.81, 78.90, 127.86, 127.98, 128.34, 136.05, 156.05, 170.07, 171.87, 172.78.

HRMS calcd for $C_{25}H_{39}N_4O_8$ (M+H): 523.2768, found: 523.2766.

**Cbz-L-Alanine-$N^{\varepsilon}$-(Fmoc-glycine)-L-lysine-glycine-OMe (14)**

To a stirred solution of tripeptide **13** (283 mg, 0.54 mmol) in anhyd $CH_2Cl_2$ (4.32 mL) at 0°C under $N_2$ was added anhyd trifluoroacetic acid (TFA, 1.08 mL). The mixture was stirred at r.t. for 10 min, after which the solvent was removed under reduced pressure. The residual TFA and $H_2O$ were removed by coevaporating with anhyd toluene (3 × 10 mL) and hexane (2 × 10 mL). After concentrating the solution, the crude material was triturated and washed by decantation with hexane (2 × 1 mL). The resulting amine salt (285 mg, 98%) was used in the next step. Fmoc-Glycine-OH (61 mg, 0.205 mmol) was dissolved in DMF (0.94 mL), and treated with HBTU (78 mg, 0.205 mmol), followed by addition of DIPEA (0.065 mL, 0.391 mmol). After stirring for 5 min, the mixture was treated with the previously prepared amine TFA salt (0.10 g, 0.186 mmol) and DIPEA (0.034 mL, 0.205 mmol). After the addition, the reaction was kept at r.t. until the amine had been consumed (TLC). The reaction was diluted with EtOAc (30 mL) and washed with 5% aq HCl (10 mL), 5% aq $NaHCO_3$ solution (10 mL), and brine (3 mL). The organic layer was dried ($Na_2SO_4$), filtered, and concentrated. The crude product was purified by column chromatography eluting with MeOH/$CH_2Cl_2$ (5:95). Compound **14** (115 mg, 88%) was obtained as a white solid; $[\alpha]_D^{26}$ −19.5 (*c* = 0.48, MeOH).

IR (KBr): ν = 3297 (br), 3069 (m), 2947 (m), 2864 (m), 1692 (s), 1642 (s), 1536 (s).

$^1$H NMR ($CDCl_3$): δ = 1.21−2.18 (m, 9 H, 3 $CH_2$ and $CH_3$), 3.12−3.29 (m, 2 H, $CH_2$), 3.69 (s, 3 H, $CH_3$), 3.80 (br s, 2 H, $CH_2$), 3.97 (d, 2 H, $CH_2$, *J* = 5.22 Hz), 4.13−4.33 (m, 2 H, 2 CH), 4.39−4.42 (m, 3 H, CH and $CH_2$), 5.16 (s, 2 H, $CH_2$), 5.84 (br s, 1 H, NH), 6.00 (br s, 1 H, NH), 6.55 (br s, 1 H, NH), 7.20−7.78 (m, 15 H, 2 NH and $C_6H_5$).

$^{13}$C NMR ($CDCl_3$): δ = 17.21, 21.12, 27.50, 30.45, 42.98, 45.88, 49.69, 50.72, 51.35, 65.13, 118.72, 124.01, 125.90, 126.50, 126.75, 127.21, 135.45, 139.87, 142.68, 154.95, 155.53, 168.14, 168.96, 171.07, 171.63.

HRMS: *m*/*z* calcd for $C_{37}H_{44}N_5O_9$ (M + H): 702.3139, found: 702.3135.

**Cbz-L-Alanine-$N^{\varepsilon}$-(2-iodobenzoyl-glycine)-L-lysine-glycine-OMe (15)**

According to the general procedure used for experiments listed in Tables 2 and 3, the tetrapeptide **15** was prepared starting from **14** (50 mg, 0.071 mmol), 2-iodobenzoic acid (21 mg, 0.085 mmol), KF (17 mg, 0.284 mmol), BOP-Cl (22 mg, 0.085 mmol), DIPEA (0.025 mL, 0.0178 mmol), and DMF (0.70 mL). Flash chromatography (MeOH/$CH_2Cl_2$, 5:95) furnished **15** as a solid; yield: 38 mg (76%); $[\alpha]_D^{25}$ −18.9 (*c* = 0.52, MeOH).

IR (KBr): ν = 3297 (br), 3068 (m), 2942 (m), 2864 (m), 1651 (s), 1540 (s), 1456 $cm^{-1}$ (m).

$^1$H NMR ($CDCl_3$): δ = 1.21−1.98 (m, 9 H, 3 $CH_2$ and $CH_3$), 3.10−3.51 (m, 2 H, $CH_2$), 3.67 (s, 3 H, $CH_3$), 3.98 (d, 2 H, $CH_2$, *J* = 4.82 Hz), 4.17−4.45 (m, 6 H, 2 $CH_2$ and 2 CH), 4.82−5.13 (m, 3 H, $CH_2$ and NH), 5.74 (br s, 1 H, NH), 6.95−7.43 (m, 11 H, $C_6H_5$ and 3 NH), 7.84 (d, 1 H, $C_6H_5$, *J* = 7.92 Hz).

$^{13}$C NMR ($CDCl_3$): δ = 16.52, 20.79, 27.09, 30.09, 41.23, 48.92, 50.10, 50.76, 64.23, 91.33, 108.01, 117.23, 122.84, 125.37, 126.28, 126.76, 129.28, 135.15, 137.68, 140.51, 141.13, 154.31, 166.96, 167.76, 168.43, 170.61, 171.05, 205.01.

HRMS: *m*/*z* calcd for $C_{29}H_{37}IN_5O_8$ (M + H): 710.1689, found: 710.1683.

**Fmoc-*O*-(*t*-Butyl)-L-serine-L-alanine-$N^{\varepsilon}$-Boc-L-lysine-glycine-OMe (16)**

Tripeptide **13** (423 mg, 0.81 mmol), obtained from the previous reaction sequence, was dissolved in MeOH/EtOAc (1:1, 4 mL). To the resulting solution was added 10% Pd/C (63 mg) and the mixture was stirred under an atmosphere of $H_2$ (30 psi). After 15 h, the solution was filtered through Celite. The Celite was washed with MeOH (50 mL), dried ($Na_2SO_4$), and the filtrate was concentrated. The crude product (300 mg, 95%) was used directly in the next

step. Fmoc-*O*-(*t*-butyl)-L-serine-OH (311 mg, 0.81 mmol) was dissolved in DMF (3.9 mL), and treated with HBTU (322 mg, 0.85 mmol), followed by the addition of DIPEA (0.27 mL, 1.62 mmol). After stirring for 5 min, the mixture was treated with the previously prepared amine (0.30 g, 0.77 mmol) and kept at r.t. until the amine had been consumed (TLC). The reaction was diluted with EtOAc (100 mL) and washed with 5% aq HCl (20 mL), 5% aq $NaHCO_3$ solution (20 mL), and brine (5 mL). The organic layer was dried ($Na_2SO_4$), filtered, and concentrated. The crude product was purified by column chromatography eluting with EtOAc/hexane (1:9). Compound **16** (387 mg, 66%) was obtained as a white solid; $[\alpha]_D^{26}$ −22.6 (*c* = 0.58, MeOH).

IR (KBr): ν = 3291 (br), 3070 (m), 2977 (m), 1692 (br), 1636 (s), 1532 $cm^{-1}$ (br).

$^1H$ NMR ($CDCl_3$): δ = 0.79−2.26 (m, 27 H, 3 $CH_2$ and 7 $CH_3$), 3.06 (d, 2 H, $CH_2$, *J* = 5.90 Hz), 3.4−3.87 (m, 5 H, $CH_3$ and $CH_2$), 4.01 (m, 2 H, $CH_2$), 4.24 (m, 2 H, 2 CH), 4.45 (m, 4 H, 2 CH and $CH_2$), 4.73 (br s, 1 H, NH), 6.82 (br s, 1 H, NH), 7.09 (br s, 2 H, 2 NH), 7.18−7.90 (m, 9 H, NH and $C_6H_5$).

$^{13}C$ NMR ($CDCl_3$): δ = 17.92, 22.29, 27.09, 28.15, 29.18, 31.27, 39.84, 40.83, 46.81, 49.32, 51.98, 52.71, 54.94, 61.45, 66.96, 73.98, 78.77, 119.72, 124.78, 126.80, 127.48, 141.00, 143.46, 155.87, 156.22, 169.93, 170.52, 171.55, 171.89.

HRMS: *m*/*z* calcd for $C_{39}H_{56}N_5O_{10}$ (M + H): 754.4027, found: 754.4022

**Cbz-L-phenylalanine-*O*-(*t*-butyl)-L-serine-L-alanine-N$^{\varepsilon}$-Boc-L-lysine-glycine-OMe (17)**

According to the general procedure used for experiments listed in Tables 2 and 3, compound **16** (50 mg, 0.066 mmol) was treated with Cbz-L-phenylalanine (24 mg, 0.079 mmol), KF (15 mg, 0.264 mmol), BPOP-Cl (20 mg, 0.079 mmol), DIPEA (0.023 mL, 0.0165 mmol) and DMF (0.66 mL) to afford 40 mg (74%) of pentapeptide **17** as a solid, after flash chromatography ($MeOH/CH_2Cl_2$, 5:95); $[\alpha]_D^{25}$ −16.3 (*c* = 0.45, MeOH).

IR (KBr): ν = 3290 (br), 2974 (m), 1715 (br), 1664 (s), 1500 $cm^{-1}$ (br).

$^1H$ NMR ($CDCl_3$): δ = 1.01−2.09 (m, 27 H, 7 $CH_3$ and 3 $CH_2$), 2.89−3.21 (m, 4 H, 2 $CH_2$), 3.45−3.91 (m, 5 H, $CH_3$ and $CH_2$), 3.91−4.08 (m, 2 H, $CH_2$), 4.11−4.52 (m, 4 H, 4 CH), 4.85 (br s, 1 H, NH), 5.52 (s, 2 H, $CH_2$), 5.75 (br s, 1 H, NH), 6.85−7.40 (m, 14 H, 4 NH and 2 $C_6H_5$).

$^{13}C$ NMR ($CDCl_3$): δ = 16.52, 19.17, 20.58, 25.26, 26.38, 27.34, 29.95, 36.36, 46.40, 49.72, 50.39, 54.24, 59.79, 63.43, 71.10, 75.48, 123.35, 124.29, 125.46, 125.72, 126.07, 126.23, 126.94, 127.33, 135.00, 135.40, 136.12, 153.69, 153.99, 167.35, 168.17, 169.72, 170.08.

HRMS: *m*/*z* calcd for $C_{41}H_{61}N_6O_{11}$ (M + H): 813.4398, found: 813.4399.

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