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Efficient peptide coupling method of conjugated carboxylic acids with methyl ester amino acids hydrochloride. Application to the synthesis of Fa-Met, an important enzymatic substrate

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Dedicated to the memory of A. Mingot deceased on September 19, 2004

Abstract—Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate reagent (BOP) serves as an efficient and versatile coupling reagent for the coupling of conjugated carboxylic acid with methyl ester amino acids hydrochloride allowing the synthesis of various substituted amino acid derivatives in high chemical yields of up to 90%. The usefulness of this method is illustrated in the synthesis of Fa-Met, an important enzymatic substrate.

Substituted furan-amino acid derivatives have been reported to possess biological and pharmacological activities.[1] Two major methods of synthesis have been described to date. The first method involves the reaction of 2-furylacryloylchloride with appropriate amino acids leading to the expected compounds in moderate yields.[2] In our hands, formation of numerous by-products have been also noticed and the purity of the products obtained is less than 80% due to difficulties of purification. The second interesting method introduced by Blumberg and Vallee in 1975 involves the synthesis of *N*-hydroxysuccinimide esters of aliphatic and aromatic amino acids. Nevertheless, in this case the authors mentioned that the products are obtained in low yields.[3] Thus, the synthesis of such compounds remains an interesting challenge and in this context, peptide coupling reactions, which have been significantly advanced in accord with the development of new peptide coupling reagents in organic syntheses could constitute an interesting alternative.[4,5]

In this letter, we report an efficient and general method for the synthesis of various substituted amino acid derivatives and its application to the total synthesis of Fa-Met, an important enzymatic substrate.

For our optimization studies, we chose to focus on the coupling of 3-(2-furyl)acrylic acid with methionine methyl ester hydrochloride, as our test reaction, under various experimental conditions (Table 1).

The standard coupling method using a dicyclohexylcarbodiimide (DCC)/additive method produces generally peptides in good yields but in this case no conversion was observed whatever the applied experimental conditions (entries 1–5). Similar negative results were encountered using more sophisticated coupling reagents such as *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluoro phosphate (HBtU).[6] Introduced in 1975 by Castro et al., benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate reagent (BOP)[7] and its parent derivatives have been widely applied in organic synthesis.[8] BOP is a nonhygroscopic crystalline compound easily prepared in large quantities and which led to the expected coupling product **3** in 75% isolated yield at room temperature in CH_2Cl_2 in the presence of 3 equiv of diisopropylethylamine (Table 1,

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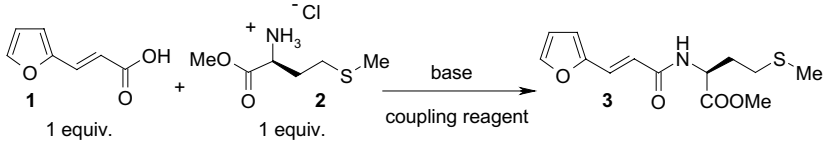
Table 1. Coupling of 3-(2-furyl)acrylic acid **1** with methionine methyl ester hydrochloride **2** under various experimental conditions



Entry[a]	Coupling agent	Base[b]	Solvent	Yield (%)
1	DCC/DMAP	—	CH_2Cl_2	<2
2	DCC	$EtN(i\text{-}Pr)_2$	CH_2Cl_2	<2
3	DCC/HOBt	—	CH_2Cl_2	<2
4	DCC/HOAt	—	CH_2Cl_2	<5
5	DCC/HOAt	—	DMF	<5
6	HBtU	—	CH_2Cl_2	<5
7	HBtU	—	DMF	<5
8	**BOP**	**$EtN(i\text{-}Pr)_2$**	**CH_2Cl_2**	**75**
9	BOP	—	CH_2Cl_2	27

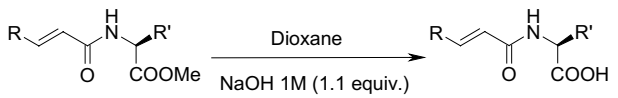
[a] Reactions performed at room temperature.
[b] Reactions performed using 3 equiv of $EtN(i\text{-}Pr)_2$.

entry 8).[9] This method was then successfully applied to the coupling of conjugated carboxylic acids with numerous methyl ester amino acids hydrochloride as illustrated in Table 2.

In all cases, adducts **3** and **5**–**12** were obtained in excellent yields varying from 31% to 90% depending on the nature of the considered amino acid derivatives. It is noteworthy that replacement of 3-(2-furyl)acrylic acid by *trans*-cinnamic acid led to the formation of the expected coupling products in yields above 80% (Table 2, entries 8 and 9). Moreover, no detectable racemization of the amino acid moiety has been noticed whatever the considered substrate.[10]

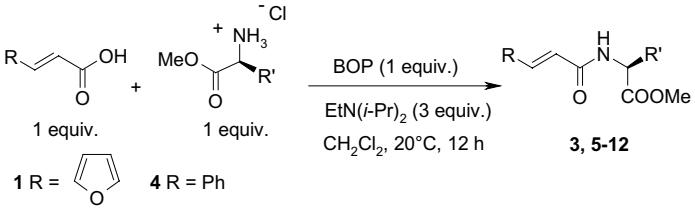
As previously mentioned, substituted amino acid derivatives possess biological activities and their synthesis could be envisioned through removal of the methyl ester moiety. This reaction was easily performed by hydrolysis of compounds **5**–**13** with a 1 M NaOH solution in dioxane for 12 h at room temperature. In all cases, the products were obtained in excellent isolated yields varying from 80% to 92% (Table 3).[11]

Table 3. Synthesis of substituted amino acid derivatives **13**–**20**



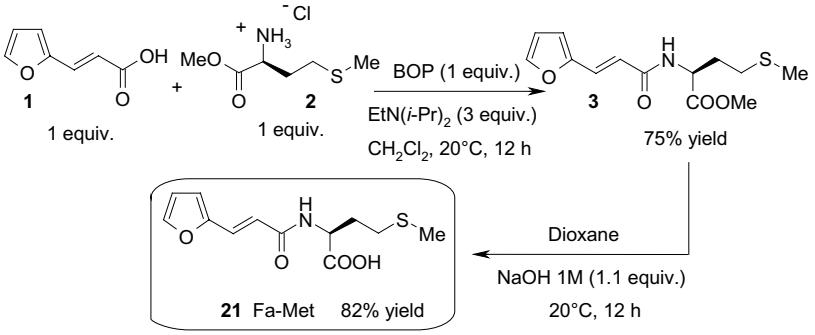
Entry	Compound	Product	Isolated yield (%)
1	**5**	**13**	84
2	**6**	**14**	89
3	**7**	**15**	80
4	**8**	**16**	80
5	**9**	**17**	88
6	**10**	**18**	81
7	**11**	**19**	92
8	**12**	**20**	89

Table 2. Synthesis of substituted amino acid methyl ester derivatives **3**, **5**–**12**



Entry	Acid derivative	R′	Product	Yield (%)[a]
1	**1**	$MeSCH_2CH_2$	**3**	75
2	**1**	H	**5**	69
3	**1**	*i*-Pr	**6**	73
4	**1**	*i*-Bu	**7**	89
5	**1**	MeO_2CCH_2	**8**	90
6	**1**	$PhCH_2$	**9**	59
7	**1**	*p*-$HOPhCH_2$	**10**	31
8	**4**	$MeSCH_2CH_2$	**11**	86
9	**4**	*i*-Pr	**12**	83

[a] Isolated yield.



Scheme 1. Synthesis of Fa-Met **21**.

Efficiency of this methodology is illustrated in Scheme 1 dealing with the synthesis of Fa-Met **21** in 62% overall yield, an important synthetic substrate for enzymatic studies allowing, due to its structure, the determination of acylases activities.[12]

In summary, we have determined that BOP serves as an efficient and versatile coupling peptide reagent for coupling of conjugated carboxylic acid with methyl ester amino acids hydrochloride allowing the synthesis of various substituted amino acid derivatives. Usefulness of this method has been illustrated in the synthesis of Fa-Met **21** and further applications will be reported in due course.

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9. General procedure (Table 2, entry 1): In a 50 mL two necked round flask were placed at room temperature under argon methionine methyl ester hydrochloride (630 mg, 3.8×10^{-3} mol) and 3-(2-furyl)acrylic acid (531 mg, 3.85×10^{-3} mol) in anhydrous CH_2Cl_2 (30 mL). The mixture was placed under stirring and cooled to 0 °C. Diisopropylethylamine (1.49 g, 1.41×10^{-2} mol) was slowly added, followed by the addition of the coupling reagent (BOP) (1.8 g, 4.23×10^{-3} mol) dissolved in 5 mL of anhydrous CH_2Cl_2. The reaction was stirred for 12 h at 20 °C. Ethyl acetate (50 mL) was added to the reaction mixture and the organic layer was successively washed with a 1 N HCl solution (2×35 mL), a 20% $NaHCO_3$ solution (2×30 mL) and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by chromatography on a silica gel column using EtOAc/petroleum ether as eluent (1:1) affording the expected coupling product **3** in 75% yield.
Compound **3**, white solid; mp: 103 °C; ^{1}H NMR ($CDCl_3$): δ = 7.39–6.34 (m, 6H), 4.86–4.79 (m, 1H), 3.73 (s, 3H), 2.54–2.49 (m, 2H), 2.22–1.95 (m, 5H). ^{13}C ($CDCl_3$): δ = 172.50, 165.60, 151.06, 144.07, 128.47, 117.62, 114.01, 112.06, 52.44, 51.61, 31.69, 29.91, 15.33.
Compound **5**, white solid; mp: 134 °C; ^{1}H NMR ($CDCl_3$): δ = 7.47–7.28 (m, 2H), 6.58–6.37 (m, 3H), 6.20 (s, 1H), 4.19 (d, 2H), 3.80 (s, 3H). ^{13}C ($CDCl_3$): δ = 170.89, 166.23, 151.51, 144.58, 129.07, 117.79, 114.59, 112.57, 52.84, 41.88.
Compound **6**, white solid; mp: 146 °C; ^{1}H NMR ($CDCl_3$): δ = 7.61–6.23 (m, 6H), 4.74–4.70 (m, 1H), 3.77 (s, 3H), 2.25–2.21 (m, 1H), 0.99–0.94 (m, 6H). ^{13}C ($CDCl_3$): δ = 173.03, 166.05, 151.62, 144.48, 128.89, 118.33, 114.36, 112.53, 57.58, 52.56, 31.95, 19.32, 18.27.
Compound **7**, white solid; mp: 100 °C; ^{1}H NMR ($CDCl_3$): δ = 7.41–7.36 (m, 2H), 6.55–6.36 (m, 4H), 4.90–4.75 (m, 1H), 3.73 (s, 3H), 1.72–1.58 (m, 3H), 0.95–0.90 (m, 6H). ^{13}C ($CDCl_3$): δ = 174.25, 166.17, 151.61, 144.46, 128.88, 118.19, 114.34, 112.50, 52.71, 51.27, 42.03, 25.26, 23.20, 22.30.

Compound **8**, white solid; mp: 152 °C; ^{1}H NMR ($CDCl_3$): δ = 7.40–6.37 (m, 6H), 5.03–4.95 (m, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.06–2.89 (m, 2H). ^{13}C ($CDCl_3$): δ = 171.99, 171.69, 166.17, 151.49, 144.64, 129.12, 117.93, 114.62, 112.56, 53.21, 52.42, 49.10, 36.55.

Compound **9**, white solid; mp: 109 °C; ^{1}H NMR ($CDCl_3$): δ = 7.45–7.04 (m, 7H), 6.58–6.24 (m, 3H), 6.19 (s, 1H), 3.76 (s, 3H), 3.23–2.85 (m, 3H). ^{13}C ($CDCl_3$): δ = 172.47, 165.72, 151.53, 144.58, 136.21, 129.72, 129.00, 127.55, 117.98, 114.61, 112.59, 53.74, 52.79, 38.31.

Compound **10**, white solid; mp: 90 °C; ^{1}H NMR ($CDCl_3$): δ = 7.46–6.29 (m, 10H), 6.14–6.11 (d, 1H), 5.01 (m, 1H), 3.76 (s, 3H), 3.21–3.05 (m, 2H). ^{13}C ($CDCl_3$): δ = 172.59, 165.84, 155.53, 155.05, 151.47, 147.34, 144.64, 130.81, 129.18, 127.81, 117.88, 115.97, 114.74, 112.62, 53.89, 52.83, 37.60.

Compound **11**, white solid; mp: 137 °C; ^{1}H NMR ($CDCl_3$): δ = 7.66–6.48 (m, 5H), 4.91–4.88 (m, 1H), 3.76 (s, 3H), 2.59–2.54 (m, 2H), 2.30–2.02 (m, 6H). ^{13}C ($CDCl_3$): δ = 173.16, 166.28, 142.31, 135.00, 130.23, 129.19, 128.29, 120.35, 53.00, 52.11, 32.11, 30.43, 15.84.

Compound **12**, white solid; mp: 130 °C; ^{1}H NMR (DMSO): δ = 7.69–7.38 (m, 6H), 6.53–6.47 (d, 1H), 6.21 (s, 1H), 4.78–4.73 (m, 1H), 3.78 (s, 3H), 2.30–2.21 (m, 1H), 1.02–0.96 (m, 6H). ^{13}C (DMSO): δ = 173.09, 166.11, 142.20, 135.09, 130.20, 129.22, 128.27, 120.57, 57.56, 52.62, 31.97, 19.36, 18.30.

10. No detectable racemization was noticed by comparison of optical rotations of our products with authentic samples purchased from Sigma.
11. General procedure (Table 3, entry 1): In a 25 mL two necked round flask was placed compound **5** (75 mg, 3.8×10^{-4} mol) at room temperature under argon in anhydrous dioxane (5 mL). NaOH (0.38 mL, 1 M) solution was added and the mixture stirred at room temperature for 12 h. HCl (0.38 mL, 1 M) solution was then added and stirring was maintained for 2 h. The reaction mixture was concentrated in vacuo and the crude residue was purified by chromatography on a silica gel column using EtOAc/MeOH as eluent (1:0–1:1) affording the expected product **13** in 84% yield as a white solid. Compound **13**, white solid; mp: 245 °C; ^{1}H NMR (D_2O): δ = 7.61–7.30 (m, 2H), 6.76–6.46 (m, 3H), 3.87 (s, 2H). ^{13}C (D_2O): δ = 177.14, 168.82, 151.11, 145.50, 128.59, 117.60, 115.16, 112.81, 43.80.

Compound **14**, white solid; mp: 210 °C; ^{1}H NMR (D_2O): δ = 7.60–6.51 (m, 5H), 4.23 (d, J = 6.0 Hz, 1H), 3.75–3.55 (m, 1H), 2.30–2.10 (m, 1H), 0.98–0.93 (m, 6H). ^{13}C (D_2O): δ = 178.93, 168.60, 151.15, 145.37, 128.56, 117.65, 115.09, 112.81, 61.24, 30.92, 19.25, 17.65.

Compound **15**, white solid; mp: 215 °C; ^{1}H NMR (DMSO): δ = 8.14–6.5 (m, 6H), 4.35–4.27 (m, 1H), 3.75 (s, 1H), 1.61–1.45 (m, 3H), 0.86–0.84 (m, 6H). ^{13}C (DMSO): δ = 165.08, 152.03, 145.41, 126.54, 121.20, 114.06, 113.15, 53.14, 42.62, 25.36, 24.06, 22.70.

Compound **16**, white solid; mp: 230 °C; ^{1}H NMR (D_2O): δ = 7.63–6.47 (m, 6H), 4.68–4.63 (m, 1H), 2.90–2.73 (m, 2H). ^{13}C (D_2O): δ = 177.67, 177.06, 168.43, 151.13, 145.45, 128.78, 117.50, 115.23, 112.83, 52.28, 38.36.

Compound **17**, White solid; mp: 206 °C; ^{1}H NMR (DMSO): δ = 7.97–6.51 (m, 10H), 4.35–4.31 (m, 1H), 3.44 (s, 2H), 3.08–2.74 (m, 2H). ^{13}C (DMSO): δ = 164.18, 155.67, 151.37, 144.66, 130.25, 129.43, 125.65, 120.69, 114.87, 113.30, 112.48, 56.07, 47.24.

Compound **18**, white solid; mp: 212 °C; ^{1}H NMR (DMSO): δ = 7.51 (m, 3 H), 7.26–6.19 (m, 9H), 5.06 (m, 1H), 3.36–3.11 (m, 2H). ^{13}C (DMSO): δ = 177.01, 165.09, 154.70, 150.31, 145.02, 129.15, 128.80, 121.52, 120.48, 112.10, 111.03, 55.15, 37.20.

Compound **19**, white solid; mp: 220 °C; ^{1}H NMR (DMSO): δ = 8.07–6.90 (m, 7H), 4.48–4.27 (m, 1H), 3.52–3.12 (m, 6H), 2.01 (s, 3H). ^{13}C (DMSO): δ = 165.18, 157.63, 139.02, 135.99, 129.73, 128.37, 123.89, 54.38, 48.71, 33.61, 15.55.

Compound **20**, white solid; mp: 206 °C; ^{1}H NMR (DMSO): δ = 7.75–6.95 (m, 7H), 4.09–4.05 (m, 1H), 3.65–3.20 (m, 1H), 2.20–2.08 (m, 1H), 0.85–0.82 (m, 6H). ^{13}C (DMSO): δ = 173.34, 164.37, 140.57, 136.30, 128.90, 128.88, 128.41, 113.41, 58.07, 31.09, 20.03, 18.03.

Compound **21**, white solid; mp: 182 °C; ^{1}H NMR ($CDCl_3$): δ = 11.0 (s, 1H), 7.60–7.21 (m, 3H), 6.49–6.24 (m, 3H), 4.59 (s, 1H), 2.50–1.95 (m, 7H). ^{13}C ($CDCl_3$): δ = 177.57, 166.93, 151.21, 144.03, 128.17, 118.24, 113.94, 112.04, 53.46, 31.35, 30.52, 15.24.

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