Synthesis of N-alkyl-C$^\alpha\alpha$-dimethylglycine derivatives

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Abstract
The application of trialkyloxonium tetrafluoroborates for N-alkylation of the nonnatural amino acid C$^\alpha\alpha$-dimethylglycine is described. Several methyl esters of dimethylglycine protected with different amine protecting groups were subject to N-ethylation or N-methylation with triethyloxonium tetrafluoroborate or trimethyloxonium tetrafluoroborate, respectively. The corresponding N-alkyl-C$^\alpha\alpha$-dimethylglycine derivatives were obtained in good to high yields. Removal of the methyl ester rendered amino acid derivatives ready for application in peptide synthesis.

Keywords: Amino acids, nonnatural amino acids, alkylation, N-alkyl-C$^\alpha\alpha$-dimethylglycines

Introduction
Non-proteinogenic amino acids are an important class of organic compounds with a large application spectrum in medicinal chemistry, since they can have intrinsic biological activity or can be found in peptides with antibiotic, antiviral, antitumor, anti-inflammatory or immunosuppressive activities. Among non-proteinogenic amino acids are N-alkylamino acids and C$^\alpha\alpha$-dialkylamino acids, both of which can be found in many biologically important peptides.$^{1-3}$

N-Alkylamino acids are constituents of naturally occurring peptides and proteins.$^{1-3}$ The alkyl group attached to the amine function causes changes in volume and conformation of peptides; those changes result in reduced flexibility, increased lipophilicity and prevention of degradation by proteolytic enzymes.$^4$ For example, histones, the molecules that wrap DNA, may be N-methylated, with consequent induction or suppression of transcription.$^5$ Besides, N-alkylamino acids are found in peptides that show antibiotic, anticancer or antiviral activity.$^5$ The increase in lipophilicity they cause in peptides is also an attractive feature of this class of molecules for Medicinal Chemistry.
Many methods of synthesis of N-alkylamino acids have been developed, most of them are N-methylations. Belsito et al. proposed the ethylation of several 4-nitrobenzenesulfonyl (Nosyl) protected amino acids using triethylxonium tetrafluoroborate (Et$_3$OBF$_4$) as alkylating agent and N,N-diisopropylethylamine (DIPEA) as base to give N-ethylamino acid derivatives in high yields. Subsequently, these authors proposed the use of trimethylxonium tetrafluoroborate (Me$_3$OBF$_4$) to obtain the corresponding N-methylated amino acid derivatives. A combination of this alkylation procedure and dehydration methodologies gave new non-proteinogenic amino acids namely, N-(4-nitrophenylsulfonyl), N-ethyl-α,β-dehydroamino acids. The application of this N-alkylation procedure to several methyl esters of β,β-dibromo and β-bromo, β-substituted dehydroamino acids protected with standard amine protecting groups was subsequently reported. The N-ethyl, β-bromo dehydroamino acid derivatives were obtained in fair to high yields and some were used as substrates in Suzuki cross coupling reactions to give N-ethyl, β,β-disubstituted dehydroalanine derivatives. By substituting N,N-diisopropylethylamine for potassium tert-butoxide the method was applied to obtain in high yields N-ethyl β-halogenated dehydroamino acid derivatives and also non-halogenated N-ethyl dehydroamino acid derivatives.

C$^{α,α}$-Dialkylglycines, such as dimethylglycine, also known as 2-methylalanine (Aib), diethylglycine (Deg) and isovaline (Iva) are the main feature of peptaibols, a family of naturally occurring antibiotic peptides isolated from soil fungi which exhibit a broad range of activities against Gram-negative and Gram-positive bacteria and fungi. Owing to their non-proteinogenic nature, the introduction of these amino acids in peptides results in more defined conformations and increased resistance to proteolytic enzymes.

The restricted rotation around peptide bonds of C$^{α,α}$-dialkylglycines is also responsible for a series of practical difficulties, which render the synthesis of peptide analogues bearing these amino acids a real synthetic challenge. This difficulty can only be overcome by taking advantage of synthetic methodologies not usually used in peptide chemistry, such as the methodology based on the Ugi reaction, which we have been developing over the last decade. Several studies on the biological activity of N-methyl, C$^{α,α}$-dimethylglycine, (Me-Aib) have been reported. Me-Aib has been widely used as a specific model substrate for system A amino acid transport, which is expressed strongly in transformed and malignant cells. Sodium ion-dependent transport of Me-Aib has been used to indicate System A activity since it concentrates in cells only via System A transport and has a very low metabolism. Me-Aib has been labelled with carbon-11 for PET studies on System A amino acid transport in vivo, and $^{11}$C-Me-Aib has been shown to be metabolically stable in humans. Me-Aib has also been reported to reduce hepatic collagen content of rats in a model of CCl$_4$-induced liver injury, and in vitro studies indicated that Me-Aib directly reduced collagen synthesis. Due to the interest in biological applications of Me-Aib a few methods for their synthesis have been reported. However, no reports on the synthesis and application of the corresponding N-ethylated derivative can be found in the literature.
Herein, we explore $N$-ethylation of several $N$-protected derivatives of $C^{\alpha,\alpha}$-dimethylglycine using the triethyloxonium tetrafluoroborate/potassium tert-butoxide methodology. The same procedure but using trimethyloxonium tetrafluoroborate as alkylating agent is also described to give $N$-methylated derivatives of $C^{\alpha,\alpha}$-dimethylglycine.

**Results and Discussion**

The methyl ester of $C^{\alpha,\alpha}$-dimethylglycine $N$-protected with the tert-butoxycarbonyl group was prepared (compounds 1a, Scheme 1). This $C^{\alpha,\alpha}$-dimethylglycine derivative was subject to treatment with 2.5 equiv. of triethyloxonium tetrafluoroborate using 3.5 equiv. of potassium tert-butoxide as base. In these conditions the reaction was complete in approximately 30 minutes allowing, the isolation of the $N$-ethyl $C^{\alpha,\alpha}$-dimethylglycine derivative in 93% yield (compound 2a, Scheme 1, Table 1). Thus, other $C^{\alpha,\alpha}$-dimethylglycine methyl ester derivatives with different types of amine protecting groups, namely, the benzyloxycarbonyl (Z), the 4-nitrobenzenesulfonyl (Nosyl), the 4-toluenesulfonyl (Tos), the benzoyl (Bz) and the acetyl (Ac) group were prepared (compounds 1b-f, Scheme 1) and subject to $N$-ethylation in the same conditions. The corresponding $N$-ethyl-$C^{\alpha,\alpha}$-dimethylglycine derivatives were obtained in yields ranging from 73% to 94% (compounds 2b-f, Scheme 1, Table 1).

![Scheme 1](image-url)

**Table 1.** Results obtained in the $N$-alkylation of the methyl esters of $N$-protected $C^{\alpha,\alpha}$-dimethylglycines

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boc-Aib-OMe, 1a</td>
<td>Boc-(N(Et))-Aib-OMe, 2a</td>
<td>93</td>
</tr>
<tr>
<td>Z-Aib-OMe, 1b</td>
<td>Z-(N(Et))-Aib-OMe, 2b</td>
<td>78</td>
</tr>
<tr>
<td>Nosyl-Aib-OMe, 1c</td>
<td>Nosyl-(N(Et))-Aib-OMe, 2c</td>
<td>84</td>
</tr>
<tr>
<td>Tos-Aib-OMe, 1d</td>
<td>Tos-(N(Et))-Aib-OMe, 2d</td>
<td>94</td>
</tr>
<tr>
<td>Bz-Aib-OMe, 1e</td>
<td>Bz-(N(Et))-Aib-OMe, 2e</td>
<td>73</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac-Aib-OMe, 1f</td>
<td>Ac-N(Et)-Aib-OMe, 2f</td>
<td>89</td>
</tr>
<tr>
<td>Boc-Aib-OMe, 1a</td>
<td>Boc-N(Me)-Aib-OMe, 3a</td>
<td>89</td>
</tr>
<tr>
<td>Z-Aib-OMe, 1b</td>
<td>Z-N(Me)-Aib-OMe, 3b</td>
<td>97</td>
</tr>
<tr>
<td>Nosyl-Aib-OMe, 1c</td>
<td>Nosyl-N(Me)-Aib-OMe, 3c</td>
<td>76</td>
</tr>
<tr>
<td>Tos-Aib-OMe, 1d</td>
<td>Tos-N(Me)-Aib-OMe, 3d</td>
<td>75</td>
</tr>
<tr>
<td>Bz-Aib-OMe, 1e</td>
<td>Bz-N(Me)-Aib-OMe, 3e</td>
<td>94</td>
</tr>
</tbody>
</table>

Recently, De Marco et al.\(^8\) proposed the use of trimethyloxonium tetrafluoroborate (Me$_3$OBF$_4$) together with N,N-diisopropylethylamine as base, for N-methylation of N-(4-nitrobenzenesulfonyl)amino acid derivatives. Thus, we decided to apply this alkylating agent, combined with potassium tert-butoxide as base, for the preparation of N-protected, N-methyl C\(^{\alpha,\alpha}\)-dimethylglycine derivatives. Thus compounds 1a-1e were reacted with 2.5 equiv. of trimethyloxonium tetrafluoroborate in the presence of 3.5 equiv. of potassium tert-butoxide. Again, in all cases, the N-methyl C\(^{\alpha,\alpha}\)-dimethylglycine derivatives were obtained in yields ranging from 75% to 97% (compounds 3a-e, Scheme 1, Table 1).

By removal of the Nosyl protecting group from N-Nosyl, N-ethyl amino acid methyl esters and reprotection of the amino function with the 9-fluorenylmethoxycarbonyl group (Fmoc), Liguori demonstrated the compatibility of this N-ethylation procedure with standard Fmoc chemistry.\(^7\) Conversion of the methyl esters of N-ethyl dehydroamino acids to the corresponding acids by treatment with a mixture of an aqueous solution of NaOH and dioxane and coupling with an amino acid was previously carried out by us.\(^13\) To test if this cleavage method could be extended to the methyl esters of N-alkyl, C\(^{\alpha,\alpha}\)-dimethylglycine derivatives, compounds 2a and 2c were treated with a mixture of an aqueous solution of NaOH and dioxane, giving the corresponding N-protected, N-ethyl C\(^{\alpha,\alpha}\)-dimethylglycine in 54% and 76% respectively (compounds 4a and 4c).

Conclusions

Atrialkylloxonium tetrafluoroborate / potassium tert-butoxide alkylation procedure was applied for N-alkylation of several methyl esters of C\(^{\alpha,\alpha}\)-dimethylglycines, N-protected with several types of amine protecting groups. All N-alkyl, C\(^{\alpha,\alpha}\)-dimethylglycine derivatives could be obtained in high yields. Some of these N-alkylated methyl ester derivatives were converted to their corresponding carboxylic acid derivatives.

This method constitutes a high yielding procedure for synthesis of both N-methylated or N-ethylated C\(^{\alpha,\alpha}\)-dimethylglycine derivatives. N-Methylated C\(^{\alpha,\alpha}\)-dimethylglycine derivatives have found interesting biological applications, however, no reports on the synthesis of the corresponding N-ethylated derivatives have been described. Thus, we believe the synthesis of N-ethyl, C\(^{\alpha,\alpha}\)-dimethylglycines opens perspectives for the use of these nonnatural amino acids in...
biological and pharmacological applications. Also, these residues when incorporated into peptides, due to the presence of the N-ethyl and the Cαα-dimethyl moieties, can yield peptides with more defined conformations, increased resistance to proteolytic enzymes and increased lipophilicity.

Experimental Section

General. Melting points were determined with a Gallenkamp apparatus and are uncorrected. 1H and 13C NMR spectra were recorded with a Varian Unity Plus spectrometer at 300 and 75.4 MHz, respectively, or with a Bruker Avance II+ operating at 400 and 100.6 MHz, respectively. 1H-1H spin-spin decoupling, DEPT (θ 45º), HMQC and HMBC were used to attribute some signals. The stereochemistry of the dehydroamino acids derivatives was determined by NOE difference experiments. Chemical shifts are given in ppm and coupling constants (J) in Hz. HRMS data were obtained by the mass spectrometry service of the University of Vigo, Spain. Elemental analysis was performed with a LECO CHNS 932 elemental analyzer. The reactions were monitored by thin layer chromatography (TLC). Petroleum ether refers to fractions with the boiling range 40-60 °C. Solvents were used without purification except for dichloromethane, which was dried according to standard procedures.

Synthesis of the methyl esters of N-protected, Cαα-dimethylglycines.

Boc-Aib-OMe (1a). HCl·H-Aib-OMe (1151 mg, 7.500 mmol) was dissolved in dichloromethane (0.1 mol dm−3) followed by addition of 2.2 eq. of triethylamine and 1 eq. of tert-butylpyrocarbonate with vigorous stirring and cooling in an ice bath. The reaction mixture was stirred at room temperature for 4 hours. The solvent was then evaporated at reduced pressure. The extract was partitioned between 150 cm3 of ethyl acetate and 30 cm3 of KHSO4 (1 mol dm−3), and washed with KHSO4 (1 mol dm−3), NaHCO3 (1 mol dm−3) and brine (2 times, 30 cm3 each). After drying over MgSO4 the extract was taken to dryness at reduced pressure to give compound 1a (1309 mg, 82%) as a white solid. mp 67-69 °C (from ethyl acetate/petroleum ether). 1H NMR (400 MHz, CDCl3): δ 1.43 (s, 9H, CH3 Boc), 1.49 [s, 6H, C(CH3)2], 3.73 (s, 3H, OCH3), 5.03 (br. s, 1H, NH) ppm. 13C NMR (100.6 MHz, CDCl3): δ 25.4 [C(CH3)2], 28.3 [C(CH3)3], 52.4 (OCH3), 56.1 (αC), 79.7 [C(CH3)3], 154.6 (C=O), 175.3 (C=O) ppm. C10H19NO4 (217.26): calcd. C 55.28, H 8.81, N 6.45; found C 55.03, H 8.68, N, 6.68.

Z-Aib-OMe (1b). Thionyl chloride (1.25 cm3, 5.0 mmol) was added to methanol (10 cm3) followed by Z-Aib-OH (1185 mg, 5.000 mmol). The reaction mixture was stirred at 40 °C for 3 hours. The solvent was then evaporated at reduced pressure. The extract was partitioned between 100 cm3 of ethyl acetate and 30 cm3 of NaHCO3 (1 mol dm−3), and washed with NaHCO3 (1 mol dm−3) and brine (2 times, 30 cm3 each). After drying over MgSO4 the extract was taken to dryness at reduced pressure to give compound 1b (1078 mg, 86%) as a white solid. mp 63-64 °C. (from diethyl ether/petroleum ether). 1H NMR (400 MHz, CDCl3): δ 1.55 [s, 6H, C(CH3)2], 3.73 (s, 3H, OCH3), 5.09 (s, 2H, CH2 Z), 5.41 (br. s, 1H, NH), 7.34-7.37 (m, 5H, ArH) ppm. 13C
NMR (100.6 MHz, CDCl₃):  δ 25.1 [C(CH₃)₂], 52.6 (OCH₃), 56.5 (αC), 66.5 (CH₂), 128.0 (CH), 128.1 (CH), 128.5 (CH), 136.4 (C), 154.9 (C=O), 175.0 (C=O) ppm. C₁₃H₁₇NO₄ (251.28): calcd. C 62.14, H 6.82, N 5.57; found C 62.30, H 6.80, N 5.70.

**Nosyl-Aib-OMe (1c).** The procedure described for the synthesis of compound 1a was followed using 4-nitrobenzenesulfonyl chloride as reactant to afford 1c (1880 mg, 83%) as a white solid. mp 111-113 °C. (from ethyl acetate/petroleum ether). ¹H NMR (300 MHz, CDCl₃):  δ 1.48 [s, 6H, C(CH₃)₂], 3.70 (s, 3H, OCH₃), 5.80 (s, 1H, NH), 8.08 (d, J 8.8 Hz, 2H, ArH), 8.34 (d, J 8.8 Hz, 2H, ArH) ppm. ¹³C NMR (100.6 MHz, CDCl₃):  δ 25.8 [C(CH₃)₂], 53.0 (OCH₃), 59.6 (αC), 124.2 (CH), 128.2 (CH), 148.2 (C), 156.2 (C), 174.1 (C=O) ppm C₁₁H₁₄N₂O₄S (302.30): calcd. C 43.70, H 4.67, N 9.32, S 10.84.

**Tos-Aib-OMe (1d).** The procedure described for the synthesis of compound 1a was followed using 4-toluenesulfonyl chloride as reactant to afford 1d (1789 mg, 88%) as a white solid. mp 107-108 °C. (from ethyl acetate/petroleum ether). ¹H NMR (400 MHz, CDCl₃):  δ 1.44 [s, 6H, C(CH₃)₂], 2.41 (s, 3H, CH₃ Tos), 3.64 (s, 3H, OCH₃), 5.43 (br. s, 1H, NH), 7.28 (d, J 8.4 Hz, 2H, ArH), 7.76 (d, J 8.4 Hz, 2H, ArH) ppm. ¹³C NMR (100.6 MHz, CDCl₃):  δ 21.5 (CH₃ Tos), 25.7 [C(CH₃)₂], 52.7 (OCH₃), 58.9 (αC), 127.1 (CH), 129.5 (CH), 139.3 (C), 143.2 (C), 174.5 (C=O) ppm. C₁₂H₁₇NO₄S (271.33): calcd. C 53.12, H 6.32, N 5.16; found C 53.34, H 6.30, N 5.25.

**Bz-Aib-OMe (1e).** The procedure described for the synthesis of compound 1a was followed using benzoyl chloride as reactant to afford 1e (1095 mg, 66%) as a white solid. mp 114-115 °C. (from ethyl acetate/petroleum ether). ¹H NMR (300 MHz, CDCl₃):  δ 1.70 [s, 6H, C(CH₃)₂], 3.80 (s, 3H, OCH₃), 6.80 (s, 1H, NH), 7.43-7.46 (m, 3H, ArH), 7.78-7.80 (m, 2H, ArH) ppm. ¹³C NMR (100.6 MHz, CDCl₃):  δ 24.7 [C(CH₃)₂], 52.7 (OCH₃), 56.9 (αC), 126.9 (CH), 128.5 (CH), 131.5 (CH), 134.5 (C), 165.5 (C=O), 175.3 (C=O) ppm. C₁₂H₁₅NO₃ (221.25): calcd. C 65.14, H 6.83, N 6.33; found C 65.01, H 6.67, N 6.44.

**Ac-Aib-OMe (1f).** The procedure described for the synthesis of compound 1a was followed using acetyl chloride as reactant to afford 1f (503 mg, 42%) as a white solid. mp 96-97.5 °C. (from diethyl ether/petroleum ether). ¹H NMR (300 MHz, CDCl₃):  δ 1.52 [s, 6H, C(CH₃)₂], 1.96 (s, 3H, CH₃ Ac), 3.72 (s, 3H, OCH₃), 6.27 (s, 1H, NH) ppm. ¹³C NMR (75.4 MHz, CDCl₃):  δ 24.7 [C(CH₃)₂], 41.14 (CH₃ Ac), 52.6 (OCH₃), 56.3 (αC), 169.6 (C=O), 175.1 (C=O) ppm. C₇H₁₃NO₃ (159.18): calcd. C 52.82, H 8.23, N 8.80; found C 52.88, H 8.02, N 8.96.

**Synthesis of the methyl esters of N-protected, N-alkyl Cαα-dimethylglycines.**

**General procedure for the synthesis of the methyl esters of N-protected, N-alkyl Cαα-dimethylglycines.** The methyl ester of N-protected, Cαα-dimethylglycine was dissolved in dry dichloromethane (0.05 mol dm⁻³) followed by addition of 3.5 eq. of potassium tert-butoxide and 2.2 eq. of trialkyloxonium tetrafluoroborate under inert atmosphere. The reaction mixture was stirred at room temperature for 30 min. Then dichloromethane (50 cm³) was added. The organic phase was washed with KH₂SO₄ (1 mol dm⁻³), NaHCO₃ (1 mol dm⁻³) and brine (3 x 20 cm³ each) and was dried over MgSO₄. Evaporation at reduced pressure afforded the corresponding N-protected, N-alkyl Cαα-dimethylglycine derivative.
Boc-N(Et)-Aib-OMe (2a). The general procedure described above was followed using Boc-Aib-OMe (1a) (434 mg, 2.00 mmol) and triethylxonium tetrafluoroborate as reactants to afford 2a (457 mg, 93%) as an orange oil that failed to crystallize. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.14 (t, \(J = 7.2\) Hz, 3H, \(CH_2CH_3\)), 1.42 (s, 9H, \(CH_3\) Boc), 1.46 [s, 6H, C(CH\(_3\))\(_2\)], 3.36 (q, \(J = 7.2\) Hz, 2H, \(CH_2CH_3\)), 3.78 (s, 3H, OCH\(_3\)) ppm. \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)): \(\delta\) 15.7 (CH\(_2CH_3\)), 24.9 \([C(CH_3)_2]\), 28.3 \([C(CH_3)_3]\), 38.0 \((CH_2CH_3\)), 52.0 \((OCH_3\)), 60.6 \((\alpha C\)) 80.1 \([C(CH_3)_3]\), 154.7 \((C=O\)) 175.7 \((C=O\)) ppm. HRMS (ESI): calcd. for \(C_{12}H_{21}NO_4\) 246.1705; found 246.1700.

Z-N(Et)-Aib-OMe (2b). The general procedure described above was followed using Z-Aib-OMe (1b) (502 mg, 2.00 mmol) and triethylxonium tetrafluoroborate as reactants to afford 2b (456 mg, 78%) as a light brown oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.19 (t, \(J = 6.8\) Hz, 3H, \(CH_2CH_3\)), 1.50 [s, 6H, C(CH\(_3\))\(_2\)], 3.45 (q, \(J = 7.2\) Hz, 2H, \(CH_2CH_3\)), 3.61 (br. s, 3H, OCH\(_3\)), 5.13 (s, 2H, \(CH_2\) Z), 7.28-7.35 (m, 5H, ArH) ppm. \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)): \(\delta\) 15.8 \((CH_2CH_3\)), 24.7 \([C(CH_3)_2]\), 38.1 \((CH_2CH_3\)), 52.1 \((OCH_3\)), 61.1 \((\alpha C\)), 67.0 \((CH_2Z\)), 127.8 \((CH\)) 128.3 \((CH\)) 128.34 \((CH\)) 135.5 \((C=O\)) 175.2 \((C=O\)) ppm. HRMS (ESI): calcd. for \(C_{16}H_{22}NO_4\) 280.1549; found 280.1543.

Nosyl-N(Et)-Aib-OMe (2c). The general procedure described above was followed using Nosyl-Aib-OMe (1c) (907 mg, 3.00 mmol) and triethylxonium tetrafluoroborate as reactants to afford 2c (834 mg, 84%) as light yellow solid. mp 100-102 °C. (from ethyl acetate/petroleum ether). \(^1\)H NMR (300 MHz, CDCl\(_3\)): (rotamers) \(\delta\) 1.23 (t, \(J = 7.2\) Hz, 3H, \(CH_2CH_3\)), 1.61, 1.63 [s, 6H, C(CH\(_3\))\(_2\)], 3.32 (q, \(J = 7.2\) Hz, 2H, \(CH_2CH_3\)), 3.72, 3.78 (s, 3H, OCH\(_3\)) 8.20 (d, \(J = 8.8\) Hz, 2H, ArH), 8.35 (d, \(J = 8.8\) Hz, 2H, ArH) ppm. \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)): (rotamers) \(\delta\) 16.3 \((CH_2CH_3\)), 25.8, 26.4 \([C(CH_3)_2]\), 40.7 \((CH_2CH_3\)), 52.8, 53.11 \((OCH_3\)), 59.6, 64.5 \((\alpha C\)) 124.0 \((CH\)) 124.2 \((CH\)) 128.2 \((CH\)) 129.2 \((CH\)) 147.0 \((C\)) 149.9 \((C\)) 174.8 \((C=O\)) ppm. \(C_{13}H_{18}N_2O_6S\) (330.36): calcd. C 47.26, H 5.49, N 8.48, S 9.71; found C 46.83, H 5.62, N 8.46, S 9.56.

Tos-N(Et)-Aib-OMe (2d). The general procedure described above was followed using Tos-Aib-OMe (1d) (542 mg, 2.00 mmol) and triethylxonium tetrafluoroborate as reactants to afford 2d (562 mg, 94%) as a white solid. mp 59-60 °C. (from ethyl acetate/petroleum ether). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.14 (t, \(J = 7.2\) Hz, 3H, \(CH_2CH_3\)), 1.61 [s, 6H, C(CH\(_3\))\(_2\)], 2.42 (s, 3H, CH\(_3\) Tos), 3.27 (q, \(J = 7.2\) Hz, 2H, \(CH_2CH_3\)), 3.78 (s, 3H, OCH\(_3\)) 7.29 (d, \(J = 8.4\) Hz, 2H, ArH), 7.85 (d, \(J = 8.4\) Hz, 2H, ArH) ppm. \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)): \(\delta\) 16.3 \((CH_2CH_3\)), 21.5 \((CH_3\) Tos\)), 26.1 \([C(CH_3)_2]\), 40.1 \((CH_2CH_3\)), 52.5 \((OCH_3\)), 63.6 \((\alpha C\)) 127.9 \((CH\)) 129.3 \((CH\)) 138.3 \((C\)) 143.2 \((C\)) 175.2 \((C=O\)) ppm. \(C_{14}H_{21}NO_4S\) (299.39): calcd. C 56.16, H 7.07, N 4.68; found C 56.45, H 7.01, N 4.77.

Bz-N(Et)-Aib-OMe (2e). The general procedure described above was followed using Bz-Aib-OMe (1e) (221 mg, 1.00 mmol) and triethylxonium tetrafluoroborate as reactants to afford 2e (190 mg, 73%) as a colourless oil that solidified on standing. mp 116-117 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.13 (t, \(J = 7.2\) Hz, 3H, \(CH_2CH_3\)), 1.61 [s, 6H, C(CH\(_3\))\(_2\)], 3.39 (q, \(J = 7.2\) Hz, 2H, \(CH_2CH_3\)), 3.74 (s, 3H, OCH\(_3\)) 7.36-7.40 (m, 5H, ArH) ppm. \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)): \(\delta\) 17.0 \((CH_2CH_3\)), \([C(CH_3)_2]\), 40.4 \((CH_2CH_3\)), 52.3 \((OCH_3\)), 61.1 \((\alpha C\)) 126.0 \((CH\)) 128.3 \((CH\)).
Ac-N(Et)-Aib-OMe (2f). The general procedure described above was followed using Ac-Aib-OMe (1f) (318 mg, 2.00 mmol) and triethyloxonium tetrafluoroborate as reactants to afford 2f (332 mg, 89%) of a light brown oil. 1H NMR (400 MHz, CDCl3): δ 1.26 (t, J 6.8 Hz, 3H, CH2CH3), 1.48 [s, 6H, C(CH3)2], 2.13 (s, 3H, CH3 Ac), 3.46 (q, J 6.8 Hz, 2H, CH2CH3), 3.69 (s, 3H, OCH3) ppm. 13C NMR (100.6 MHz, CDCl3): δ 16.4 (CH2CH3), 22.2 (CH3 Ac), 24.1 [C(CH3)2], 39.4 (CH2CH3), 52.5 (OCH3), 60.7 (αC), 170.4 (C=O), 174.9 (C=O) ppm. HRMS (ESI): calcd. for C13H19NO3 254.1368; found 254.1363.

Boc-N(Me)-Aib-OMe (3a). The general procedure described above was followed using Boc-Aib-OMe (1a) (72 mg, 0.33 mmol) and trimethylxonium tetrafluoroborate as reactants to afford 3a (68 mg, 89%) as a light yellow oil. 1H NMR (300 MHz, CDCl3): δ 1.44 (s, 15H, CH3 Boc + C(CH3)2), 2.91 (s, 3H, NCH3), 3.71 (s, 3H, OCH3) ppm. 13C NMR (75.4 MHz, CDCl3): δ 23.8 [C(CH3)2], 29.5 [C(CH3)2], 52.0 (OCH3), 60.3 (αC), 155.2 (C=O), 175.6 (C=O) ppm. HRMS (ESI): calcd. for C14H22NNaO4 254.1368; found 254.1363.

Z-N(Me)-Aib-OMe (3b). The general procedure described above was followed using Z-Aib-OMe (1b) (176 mg, 0.700 mmol) and trimethylxonium tetrafluoroborate as reactants to afford 3b (145 mg, 97%) as a light yellow oil. 1H NMR (400 MHz, CDCl3): δ 1.46 [s, 6H, C(CH3)2], 2.98 (s, 3H, NCH3), 3.66 (br. s, 3H, OCH3), 5.11 (s, 2H, CH2 Z), 7.33-7.36 (m, 5H, ArH) ppm. 13C NMR (100.6 MHz, CDCl3): δ 23.8 [C(CH3)2], 29.7 (NCH3), 52.1 (OCH3), 60.8 (αC), 67.3 (CH2), 128.0 (CH), 128.4 (CH), 136.5 (C), 155.9 (C=O), 175.1 (C=O) ppm. HRMS (ESI): calcd. for C14H22NNaO4 288.1212; found 288.1206.

Nosyl-N(Me)-Aib-OMe (3e). The general procedure described above was followed using Nosyl-Aib-OMe (1c) (302 mg, 1.00 mmol) and trimethylxonium tetrafluoroborate as reactants to afford 3e (239 mg, 76%) as a light brown solid. mp 116-118 °C. (from ethyl acetate/petroleum ether). 1H NMR (300 MHz, CDCl3): δ 1.58 [s, 6H, C(CH3)2], 2.79 (s, 3H, NCH3), 3.80 (s, 3H, OCH3), 8.17 (d, J 7.2 Hz, 2H, ArH), 8.36 (d, J 7.2 Hz, 2H, ArH) ppm. 13C NMR (75.4 MHz, CDCl3): δ 25.0 [C(CH3)2], 31.0 (NCH3), 52.8 (OCH3), 63.7 (αC), 124.1 (CH), 129.1 (CH), 146.0 (C), 150.0 (C), 174.5 (C=O) ppm. C12H16N2O5S (316.33): calcd. C 45.6, H 5.10, N 8.86, S 10.14; found C 45.51, H 5.18, N 8.89, S 10.11.

Tos-N(Me)-Aib-OMe (3d). The general procedure described above was followed using Tos-Aib-OMe (1d) (189 mg, 0.700 mmol) and trimethylxonium tetrafluoroborate as reactants to afford 3d (131 mg, 75%) as a colorless oil. 1H NMR (400 MHz, CDCl3): δ 1.54 [s, 6H, C(CH3)2], 2.43 (s, 3H, CH3 Tos), 2.71 (s, 3H, NCH3), 3.81 (s, 3H, OCH3), 7.30 (d, J 8.4 Hz, 2H, ArH), 7.84 (d, J 8.4 Hz, 2H, ArH) ppm. 13C NMR (75.4 MHz, CDCl3): δ 21.5 (CH3 Tos), 24.7 [C(CH3)2], 30.7 (NCH3), 52.6 (OCH3), 62.9 (αC), 127.9 (CH), 129.4 (CH), 137.1 (C), 143.5 (C), 175.0 (C=O) ppm. HRMS (ESI): calcd. for C13H19NO4S 308.0933; found 308.0927.

Bz-N(Me)-Aib-OMe (3e). The general procedure described above was followed using Bz-Aib-OMe (1e) (155 mg, 0.700 mmol) and trimethylxonium tetrafluoroborate as reactants to afford 3e (155 mg, 94%) as a light yellow oil that solidified on standing. mp 95-96 °C. 1H NMR (300
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