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Selective [$^{15}N^{\eta}_{2}$] labelling of an N^{G}-propionylated arginine derivative

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A straightforward convergent synthesis of [$^{15}N^{\eta}_{2}$]-Bz-Arg(N^{η}-propionyl)-OEt*TFA is presented. In this approach, the guanidinylation reagent [$^{15}N_2$]-N(boc)-N′(propionyl)-*S*-methylisothiourea is reacted with the side chain amino group of the title compound's ornithine precursor. The guanidinylation step is promoted by stoichiometric addition of $HgCl_2$ to force completion. This method leads directly to the N^{G}-acylated product and the acyl residue is principally modifiable in the last synthetic step of the guanidinylation reagent.

Keywords: ^{15}N-labelling; arginine; *S*-methylisothiourea

Introduction

For the direct NMR detection and geometrical analysis of intermolecular H-bonding networks of arginines,[1,2] which are crucial for the understanding of many biological and pharmaceutical processes, we required synthetic access to terminally [$^{15}N_2$] labelled N^{G}-acylated arginine derivatives. Owing to the high basicity of their side chain functionality, arginines are often prepared via guanidinylation of the side chain amino group of their corresponding ornithine precursors.[3–5] With this methodology, the arginine side chain can be obtained in protected form, simplifying purification and handling. The guanidinylation of amines is a highly versatile reaction employed in solution chemistry as well as in solid-supported synthesis of peptides[6,7] and nucleic acid derivatives.[8]

Considering the variability of the acyl residue in the target compound as well as commercial availability and cost of labelled starting materials, an approach using [M+2] labelled [$^{15}N_2$]-thiourea was chosen. Thiourea-derived guaninidinylation reagents are well known in literature: For the synthesis of non-labelled compounds, the application of bis(boc)[4,9] and bis(cbz)[9–11] protected *S*-methylisothiourea in guanidine formation has been documented. Mono-acylated *S*-methylisothiourea[12] has been produced from mono-boc-protected acylated *S*-methylisothiourea and has been used in guanidinylation. Boy *et al.* reported in 2007 the direct application of mono-boc-protected acylated *S*-methylisothiourea for guanidinylation of amines.[13]

With regard to isotopically labelled targets, Manning *et al.*[14] used [M+3] labelled [^{13}C, $^{15}N_2$]-thiourea for the production of a stable isotopically labelled [M+7] version of the sodium channel antagonist Lamotrigine. The labelled thiourea was reacted with further labelled compounds in order to obtain the [M+7] labelled target. Zhang[15] reported the use of [M+3] labelled [^{13}C, $^{15}N_2$]-thiourea in the synthesis of stable isotopically labelled 2-methylaminoimidazole ([M+7] and [M+6]). The labelled thiourea was alkylated to obtain [^{13}C, $^{15}N_2$]-*S*-methylisothiourea salts, which were subsequently employed as guanidinylating reagents with a primary amine. Salter *et al.* used bis(boc) protected [^{13}C, $^{15}N_2$]-thiourea as guanidinilyating reagent for a deactivated aniline derivative.[16] $HgCl_2$ was added to assist nucleophilic displacement in this case.

Here, we report the application of mono-boc-protected propionylated [$^{15}N_2$]-*S*-methylisothiourea for the production of [M+2] labelled [$^{15}N^{\eta}_{2}$]-Bz-Arg(N^{η}-propionyl)-OEt*TFA via guanidinylation of its ornithine precursor. This is to the best of our knowledge the first ^{15}N-labelling application of an N(boc)-*N*′(acyl)-*S*-methylisothiourea. The target compound is set free by boc-deprotection with TFA.

Results and discussion

A stable [$^{15}N^{\eta}_{2}$] labelled version of Bz-Arg(N^{η}-propionyl)-OEt*TFA **9** was prepared by the reaction of [$^{15}N_2$]-N(boc)-N′(propionyl)-*S*-methylisothiourea **3** with Bz-Orn-OEt **7** and subsequent boc-deprotection.

The guanidinylation reagent was prepared as depicted in Scheme 1 in three steps from [$^{15}N_2$]-thiourea. This was first methylated with MeI under reflux in acetone,[17] then mono-boc protected with a substoichiometric amount of Boc_2O and finally acylated on the remaining free NH_2-position with propionic acid NHS-ester **4** at r.t. with 0.3 eq. DMAP added to enhance coupling perfomance. The NHS-ester was prepared from the acid chloride and N-hydroxysuccinimide.

The ornithine-derived precursor **7** was obtained according to Scheme 2 after five steps starting from plain Orn*HCl, which was selectively cbz-protected on the side chain[18] and esterified via *in situ* formation of the acid chloride from thionylchloride in the refluxing alcohol.[19] The benzoic amide was introduced in

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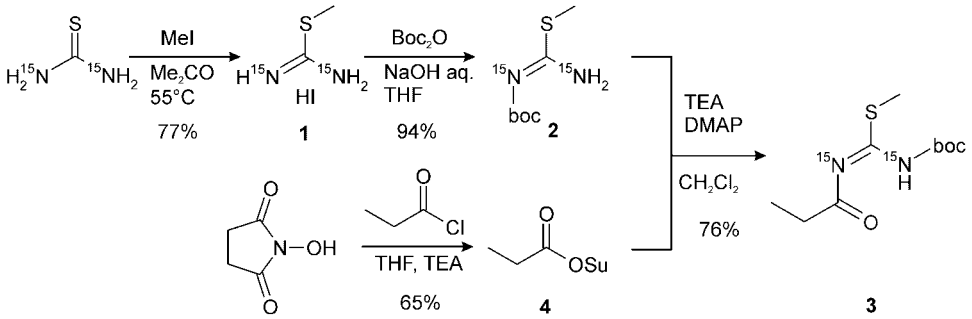
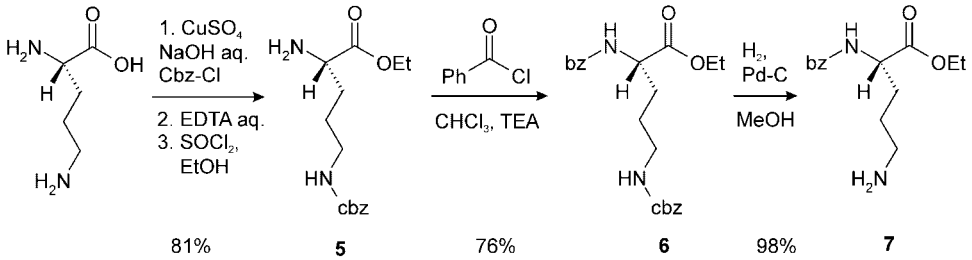
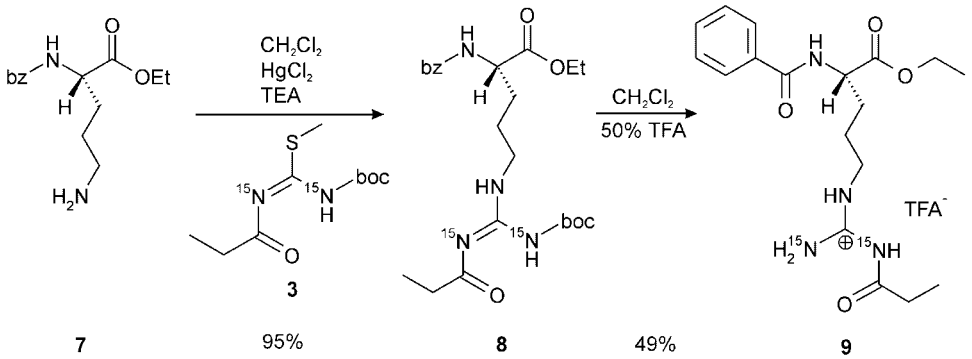


Scheme 1. Synthesis of [$^{15}N_2$]-N(boc)-N′(propionyl)-*S*-methylisothiourea.



Scheme 2. Preparation of Bz-Orn-OEt from plain ornithine.



Scheme 3. Guanidinylation of Bz-Orn-OEt and deprotection.

the N$^{\alpha}$ position by reaction with benzoylchloride.[20] Hydrogenolytic cbz-deprotection yielded the free base on the side chain.

Numerous reports exist about the activation of thiourea-derived guanidinylating reagents by the stoichiometric addition of mercuric chloride as mentioned above,[4,7,16,21,22] which is supposed to drive the reaction by the formation of insoluble mercuric sulfide species. This approach was followed here as well as shown in Scheme 3, since the application of a large excess of either reacting partner was not feasible. Indeed upon addition of 1 eq. of $HgCl_2$ (respective to the thiourea) to a mixture of Bz-Orn-OEt **7** and N(boc)-N′(propionyl)-*S*-methylisothiourea **3** (1.5:1) in dichloromethane, the onset of the reaction is immediately indicated by a grey precipitate and can be followed by thin layer chromatography (TLC). Trials with the unlabelled compound showed that the reaction takes place when $HgCl_2$ is omitted, but does not reach completion as indicated by TLC. Isolation of the product by centrifugation and extraction yielded pure Bz-Arg(N$^{\eta}$-boc,N$^{\eta'}$-propionyl)-OEt **8** after chromatography. Deprotection with 50% TFA in dichloromethane under an argon atmosphere gave the desired compound Bz-Arg(N$^{\eta}$-propionyl)-OEt∗TFA **9** in 47% yield over the last two steps after chromatographic purification over silica gel. NP-chromatography of such a highly polar charged molecule is supposed to be practable only due to the formation of a strongly coordinated ion pair between the guanidinium moiety and the carboxylate in the solvent mixture chloroform/acetonitrile (5:1).

Experimental

All reagents were obtaind from Sigma-Aldrich. Solvents were distilled prior to use. ^{1}H, ^{13}C and ^{15} N NMR spectra were recorded on Bruker Avance AVA 300 and AVA 600 spectrometers.

Abbreviations: Boc, *tert*-butoxycarbonyl-; cbz, carbobenzyloxy-; EDTA, ethylene diamine tetraacetic acid; EtOAc, ethylacetate; DMAP, 4-(dimethylamino)-pyridine; NHS = HOSu, N-hydroxysuccinimide; TEA, triethylamine; TFA, trifluoroacetic acid; TLC, thin layer chromatography; THF, tetrahydrofurane.

[$^{15}N_2$]-*S*-methylisothiourea 1

[$^{15}N_2$]-thiourea (250 mg, 3.2 mmol) was dissolved under stirring in 25 ml of acetone at 50°C. Methyliodide (0.22 ml, 3.5 mmol)

was added in one portion via syringe. The mixture was stirred at 55°C under reflux for 3 h. After cooling to r.t., the reaction mixture was poured into 50 ml of ice-cold diethylether and kept in the ice bath to allow complete precipitation of the product **1**, which was then sucked off on a glass frit, rinsed with cold diethylether and dried under vacuum (540 mg, 77%). M.P. 114°C; ^{1}H NMR (600 MHz, $(CD_3)_2CO$) δ 2.77 (s, 3H, $-SCH_3$), 8.5–9.5 (bs, 4H, NH_2), ^{15}N NMR (60 MHz, $(CD_3)_2CO$) δ 106.37.

[$^{15}N_2$]-mono(boc)-*S*-methylisothiourea 2

[$^{15}N_2$]-*S*-methylisothiourea **1** (540 mg, 2.45 mmol) was dissolved in THF/water (1:1, 5 ml) and 1 M NaOH aq. (2.45 ml, 2.45 mmol) was added under cooling in an ice bath. Boc-anhydride (545 mg, 2.45 mmol) was dissolved in 2.5 ml THF and dropped in. The mixture was stirred overnight at r.t. EtOAc (20 ml) was added and the organic phase was washed once with sat. aq. $NaHCO_3$-solution and brine, respectively. The organic phase was dried over Na_2SO_4 and the solvents evaporated under reduced pressure. The product **2** (440 mg, 94%) was used in the next step immediately without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.50 (s, 9H, boc-CH_3), 2.45 (s, 3H, $-SCH_3$), ^{15}N NMR (60 MHz, $CDCl_3$) δ 44.21, 263.47.

[$^{15}N_2$]-N(boc)-N′(propionyl)-*S*-methylisothiourea 3

[$^{15}N_2$]-mono-boc-*S*-methylisothiourea **2** (440 mg, 2.3 mmol) was dissolved in dichloromethane (10 ml) in presence of TEA (0.66 ml, 4.8 mmol). DMAP (88 mg, 0.72 mmol) and propionyl-OSu **4** (821 mg, 4.8 mmol) were added under stirring. The reaction was run overnight at r.t. After dilution with additional dichloromethane (20 ml), the mixture was washed once with sat. aq. $NaHCO_3$-solution, water and brine, respectively. The organic phase was dried over Na_2SO_4 and the solvents evaporated under reduced pressure. The impure product was purified by column chromatography over silica gel to yield N(boc)-N′(propionyl)-[$^{15}N_2$]-*S*-methylisothiourea **3** as a white powder (450 mg, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (m, 3H), 1.50 (s, 9H, boc-CH_3), 2.39 (s, 3H, –SCH3), 2.46 (m, 2H), ^{15}N NMR (60 MHz, $CDCl_3$) δ 44.21; MS (ESI) 249 ([M+2]+1).

[$^{15}N^{\eta}{}_2$]-Bz-Arg(*N′*-boc,$N^{\eta'}$-propionyl)-OEt 8

Bz-Orn-OEt **7** (273 mg, 1.03 mmol) was dissolved in dichloromethane (5 ml) in presence of TEA (0.19 ml, 2.06 mmol) and N(boc)-N′(propionyl)-[$^{15}N_2$]-*S*-methylisothiourea **3** (0.17 g, 0.7 mmol) was added under stirring. $HgCl_2$ was added in one batch and the precipitate kept in motion by vigorous stirring. After 2.5 h TLC analysis showed completion. The precipitate was separated by centrifugation and rinsed two times with dichloromethane. The combined fractions were washed once with sat. aq. $NaHCO_3$ solution, water and brine, respectively. The organic phase was dried over Na_2SO_4 and the solvents evaporated under reduced pressure. The colourless oily residue was purified by column chromatography over silica gel to yield pure Bz-Arg(N^{η}-boc,$N^{\eta'}$-propionyl)-OEt **8** (302 mg, 95%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (t, 3H, ^{3}J=7.54 Hz, $-CH_2\mathbf{CH_3}$), 1.29 (t, 3H, ^{3}J=7.14 Hz, $-OCH_2\mathbf{CH_3}$), 1.42 (s, 9H, boc), 1.66 (m, 1H), 1.76 (m, 1H), 1.87 (m, 1H), 2.02 (m, 1H), 2.43 (q, 2H, ^{3}J=7.54, $-\mathbf{CH_2}CH_3$), 3.38 (m, 1H), 3.58 (m, 1H), 4.22 (q, 2H, ^{3}J=7.14, $-O\mathbf{CH_2}CH_3$), 4.82 (m, 1H), 7.43 (m, 3H), 7.49 (m, 1H), 7.87 (d, 2H), 9.03 (d, 1H), 12.41 (d, 1H, $^{1}J_{NH}$=90.14 Hz), ^{15}N NMR (60 MHz, $CDCl_3$) δ 133.77 ($^{1}J_{NH}$=90.14 Hz), 162.45; MS (ESI) 465 ([M+2]+1).

[$^{15}N^{\eta}{}_2$]-Bz-Arg(N^{η}-propionyl)-OEt*TFA 9

Bz-Arg(N^{η}-boc,$N^{\eta'}$-propionyl)-OEt **8** (160 mg, 0.34 mmol) was dissolved under stirring in dry dichloromethane/TFA (5 ml, 1:1) under argon and cooling in an ice bath. The mixture was allowed to warm up to r.t. and stirred for 3 h. After evaporation the residue was purified by column chromatography over silica gel in $CHCl_3$/acetonitrile (5:1) to afford the title compound **9** as colourless solid (80 mg, 49%). ^{1}H NMR (600 MHz, CD_2Cl_2/10% $(CD_3)_2SO$) δ 1.08 (t, 3H, ^{3}J=7.52 Hz, $-CH_2\mathbf{CH_3}$), 1.22 (t, 3H, ^{3}J=7.17 Hz, $OCH_2\mathbf{CH_3}$), 1.74 (m, 2H, γ-CH_2), 1.90 (dm, 2H, β-CH_2) 2.45 (q, 2H, ^{3}J=7.52 Hz, $-\mathbf{CH_2}CH_3$), 3.29 (dm, 2H, δ-CH_2), 4.14 (q, 2H, ^{3}J=7.17 Hz - $O\mathbf{CH_2}CH_3$), 4.60 (m, 1H, α-CH), 7.39 (m, 2H, *m*-Bz), 7.47 (m, 1H, *p*-Bz), 7.84 (m, 2H, *o*-Bz), 7.96 (d, 1H, α-NH), 8.42 (d, 1H, $^{1}J_{NH}$=92.13 Hz, η-NH_2), 9.49 (d, 1H, $^{1}J_{NH}$=92.13 Hz, η-NH_2), 10.14 (s, 1H, ε-NH), 13.05 (s, 1H, η-CONH); ^{13}C NMR (150 MHz, CD_2Cl_2/10% $(CD_3)_2SO$) δ 8.3, 14.2, 24.7, 28.9, 30.3 (d), 41.0, 52.5, 61.4, 127.7, 128.5, 131.7, 154.6 (dd), 162.9 (q), 167.8, 172.3, 177.9 (d); ^{15}N NMR (60 MHz, CD_2Cl_2/10% $(CD_3)_2SO$) δ 81.37 (t, NH_2, $^{1}J_{NH}$=92.13 Hz), 132.22 (d, CONH, $^{1}J_{NH}$=89.6 Hz); MS (ESI) 365 ([M+2]).

Propionic acid NHS ester (propionyl-OSu) 4

Propionylchloride (1.87 ml, 21.6 mmol) and TEA (3.27 ml, 23.8 mmol) were dissolved in THF (50 ml). N-hydroxysuccinimide (2.7 g, 23.8 mmol) was added and the reaction mixture stirred at room temperature overnight. After evaporating the THF a low viscous yellow oil remained, which was extracted with brine. The oil crystallized upon removal of THF traces under the oilpump vacuum (2.4 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, ^{3}J=7.49 Hz, CH_3), 2.63 (q, 2H, ^{3}J=7.49 Hz, CH_2), 2.82 (s, 4H, succinimide CH_2).

Orn(cbz)-OH and Orn(cbz)-OEt 5

Ornithine-HCl (7.5 g, 44.5 mmol) was solvated in 0.5 M NaOH aq. (89 ml, 44.5 mmol), $CuSO_4$*5 H_2O (5.55 g, 22.25 mmol) was added and stirring was maintained for 15 min. To the clear blue solution solid K_2CO_3 (6.15 g, 44.5 mmol) was added followed by Cbz-Cl (8.2 ml, 57.9 mmol). The reaction mixture was stirred overnight at r.t., the precipitate sucked off and washed two times with ice-cold MeOH (20 ml each). The precipitate was refluxed in aqueous EDTA (9.94 g, 26.7 mmol) solution for 2 h and stirred at r.t. over night to achieve complete decomplexation. The precipitated crude Orn(cbz)-OH was sucked off and washed carefully with small amounts of ice cold water to yield a pale blue solid that was dried to constant weight in vacuo (9.71 g, 82%).

Orn(cbz)-OH (9.7 g, 36.5 mmol) was solvated in EtOH (5 ml/mmol). After dropwise addition of thionylchloride under cooling in an ice bath, the mixture was refluxed for 1 h and allowed to cool to r.t. The solvent was evaporated to yield **5** as a sticky yellow residue (12.17 g, 99%). ^{1}H NMR (300 MHz, CD_3OD) δ 1.29 (t, 3H, ^{3}J=7.11 Hz, $-OCH_2\mathbf{CH_3}$), 1.61 (m, 2H, γ-CH_2), 1.91 (m, 2H, β-CH_2), 3.16 (t, 2H, δ-CH_2), 4.03 (m, 1H, α-CH), 4.27 (q, 2H, ^{3}J=7.11 Hz, $-O\mathbf{CH_2}CH_3$), 5.06 (s, 2H, bn-CH_2), 7.24–7.38 (m, 5H, bn-Ph).

Bz-Orn(cbz)-OEt 6

Orn(cbz)-OEt **5** (3 g, 9.1 mmol) was dissolved in $CHCl_3$ (5 ml/mmol) and TEA (3.8 ml, 27.3 mmol) was added. After addition of benzoylchloride (1.16 ml, 10 mmol) using a dropping funnel, the mixture was stirred overnight at r.t. The reaction solution was washed two times with sat. aq. $NaHCO_3$ solution, then with water and finally with brine. The organic phase was

dried over $NaSO_4$ and the solvent evaporated to yield crude Bz-Orn(cbz)-OEt, which was subjected to column chromatography over silica gel. The product Bz-Orn(cbz)-OEt **6** was obtained as a colourless solid (2.76 g, 76%). M.P. 95–96°C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, ^3J = 7.11 Hz, –OCH_2**CH_3**), 1.61 (m, 2H, γ-CH_2), 1.81 (m, 1H, β-CH_2), 1.99 (m, 1H, β-CH_2), 3.25 (m, 2H, δ-CH_2), 4.23 (q, 2H, ^3J = 7.11 Hz, –O**CH_2**CH_3), 4.80 (dt, 1H, ^3J = 7.34 Hz, ^3J = 5.38 Hz, α-CH), 4.96 (t, 1H, ε-NH), 5.08 (s, 2H, bn-CH_2), 6.87 (d, 1H, ^3J = 7.34 Hz, α-NH), 7.24–7.38 (m, 5H, bn-Ph), 7.40–7.55 (m, 3H, bz-Ph), 7.81 (m, 2H, bz-Ph).

Bz-Orn-OEt 7

Bz-Orn(cbz)-OEt **6** (1 g, 2.51 mmol) was dissolved in MeOH (p.A., 20 ml) and a spatula tip Pd–C (10% palladium on charcoal) was added. The mixture was stirred under H_2 pressure (20 bar) for 48 h. The catalyst was filtered off and evaporation yielded the faintly yellow product Bz-Orn-OEt **7** (650 mg, 98%). ^{1}H NMR (300 MHz, CD_3OD) δ 1.28 (t, 3H, ^3J = 7.11 Hz, –OCH_2**CH_3**), 1.81 (m, 2H), 1.92 (m, 1H), 2.07 (m, 1H), 2.98 (m, 2H), 4.22 (q, 2H, ^3J = 7.11 Hz, –O**CH_2**CH_3), 4.63 (m, 1H, α-CH), 7.48 (m, 2H), 7.56 (m, 1H), 7.87 (m, 2H).

Conclusion

A straightforward synthesis for [$^{15}N''_2$] labelling of an N^G-propionylated arginine derivative has been presented starting from [$^{15}N_2$]-thiourea. N(boc)-N′(propionyl)-*S*-methylisothiourea has been shown to work as guanidinylating reagent for an N- and C-protected ornithine derivative upon promotion by $HgCl_2$. Since the acyl substituent is incorporated in the guanidinylation reagent in the last step of its synthesis, this methodology is supposed to be applicable for the production of various [$^{15}N''_2$] labelled N^G acylated arginine derivatives by varying the acyl residue introduced in that last step.

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