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Graphical Abstract

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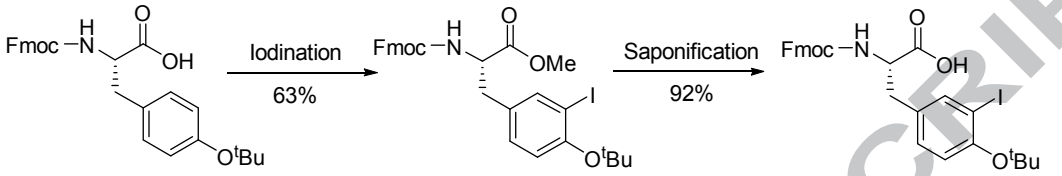
Andrew M. Steer,[a] , Hannah L. Bolt,[a] William D. G. Brittain[a] and Steven L. Cobb[a]*



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ABSTRACT

Herein the synthesis of an Fmoc/O^{t}Bu orthogonally protected iodotyrosine derivative is reported. This has been achieved *via* a simple two-step process in an overall 58% yield from commercially available Fmoc-Tyr(^{t}Bu)-OH. The Fmoc/O^{t}Bu orthogonally protected iodotyrosine was also shown to be amenable to Suzuki-Miyaura cross-coupling to deliver a novel bi-aryl tyrosine derivative.

Introduction

Halogenated aromatic amino acids represent an important class of building blocks which have been utilised for a myriad of applications. Iodo-, bromo- and chloro-aromatic amino acids have been exploited in cross-coupling reactions (e.g. Negishi,[1, 2] Suzuki-Miyaura[3-5] and Sonogashira[6] cross-couplings) to afford a wide range of unnatural amino acids. The halide functionality has also been used to introduce fluorine tags into biomolecules[7, 8] and as key components in natural product synthesis.[9, 10]

Iodotyrosines have been widely utilised in natural product synthesis[11-13] and the formation of unnatural bi-aryl amino acids.[14, 15] Butyloxycarbonyl (Boc) protected iodotyrosines **1** and **2** have previously been synthesised and used to incorporate boronic acid moieties into peptides (Fig. 1).[12, 16] Carboxybenzyl (Cbz) protected iodotyrosines **3** have also been previously accessed.[17, 18] While these can be used in solution phase synthesis the aforementioned combination of protecting groups are not compatible with fluorenylmethyloxycarbonyl (Fmoc) based solid phase peptide (SPPS) synthesis. For example, **1** and **2** could only be incorporated at the *N*-terminus of an Fmoc SPPS-synthesised peptide sequence and in the case of **2** additional steps would be required to remove the methyl ether after peptide cleavage from the solid support.

The ideal building block for Fmoc SPPS would be Fmoc- and O^{t}Bu-protected iodotyrosine **4,** but to the best of our knowledge a synthesis of this amino acid has not yet been reported. Given this we wished to develop a method to access orthogonally protected iodotyrosine (**4**).

Results and Discussion

To access our desired target **4** we initially applied the iodination conditions previously reported by González and co-workers.[19, 20] Applying their bis(pyridine)iodinium tetrafluoroborate (IPy_2BF_4) mediated reaction conditions to Fmoc-Tyr(^{t}Bu)-OH **5** did lead to iodination, but with concomitant removal of the ^{t}Bu group to yield compound **6** in 66% yield (Scheme 1).

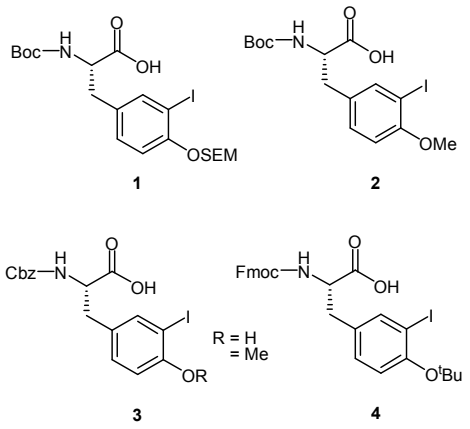

Figure 1. Previously reported *N*-protected iodotyrosines **1-3** and the Fmoc iodotyrosine target of this work, compound **4**.

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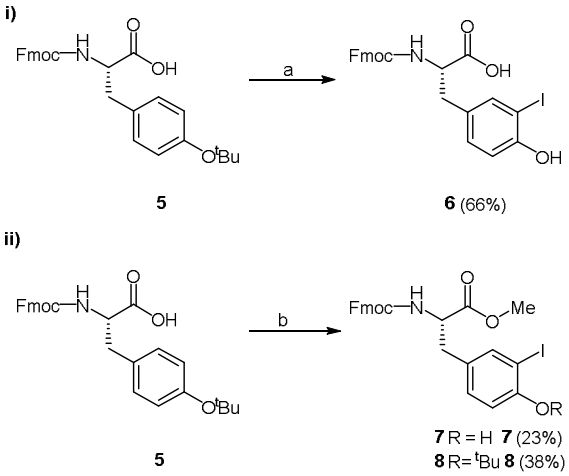
The conditions employed by González and co-workers utilised CH_2Cl_2:TFA (10:1) as the reaction solvent and thus the observed loss of the ^{t}Bu ether was not surprising. In order to combat this, less acidic reaction conditions were sought. This led us to explore the combination of iodine and silver sulfate in methanol which had been previously reported to deliver a range of iodotyrosines in excellent yields but not the desired target **4**.[21]



Scheme 1. i) Iodoination following previously reported conditions by González and co-workers. (Conditions a: **5** (1.0 equiv.), IPy_2BF_4 (1.5 equiv.), CH_2Cl_2:TFA (10:1), 15 min, rt) and **ii)** Iodination using silver sulfate in methanol (Conditions b: **5** (1.0 equiv.), I_2 (1.2 equiv.), Ag_2SO_4 (1.2 equiv.), MeOH, 1.5 h, rt)

We found that the reaction of Fmoc-Tyr(^{t}Bu)-OH **5** with iodine (1.2 equiv.) and Ag_2SO_4 (1.2 equiv.) proceeded to give a mixture of the methyl ester of the desired compound **8** in 38% isolated yield and an unwanted ^{t}Bu ether deprotected compound **7** in 23% yield. Using 2D NMR techniques on compounds **7** and **8** it was confirmed that iodination had occurred at the 3 position of the aromatic ring. This was corroborated through the attainment of a crystal structure of compound **7** (Fig. 2). The formation of **8** had shown that iodination without the loss of the acid sensitive ^{t}Bu protecting group was possible.

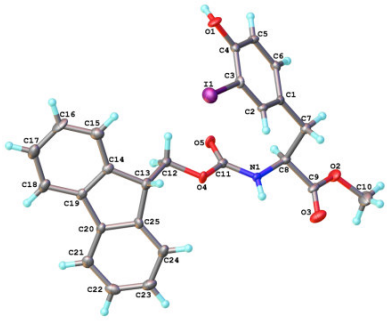
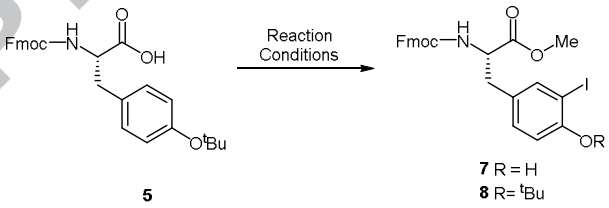


Figure 2. Crystal structure of compound **7** used to confirm that iodination had occurred at the 3 position of the aromatic ring.

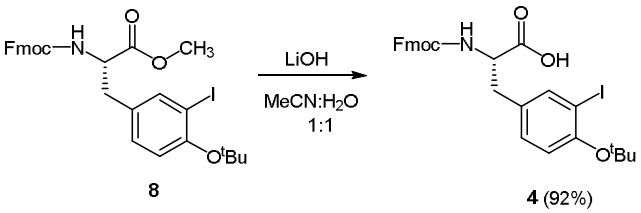
Hydrolysis of the methyl ester **8** to the desired free carboxylic acid **4** was readily achieved through standard lithium hydroxide mediated conditions in 92% yield. It is also worth noting that methyl ester protection would be required in solution phase Suzuki-Miyaura cross-couplings due to reaction compatibility issues with free carboxylic acids.

Table 1. Optimisation of the reaction conditions



Entry	Reaction Conditions	Temp (^{o}C)	Time (h)	Solvent	7 (%)[b]	8 (%)[b]
1	200 mg scale (**5**) (1 equiv.), Ag_2SO_4 (1.2 equiv.), I_2 (1.2 equiv.)	rt	1.5	MeOH	23	38
2	200 mg scale (**5**) (1 equiv.), Ag_2SO_4 (1.2 equiv.), I_2 (1.2 equiv.)	50	2	MeOH	34	63
3	200 mg scale (**5**) (1 equiv.), Ag_2SO_4 (0.5 equiv.), I_2 (1.2 equiv.)	rt	1.5	MeOH	29	26
4	200 mg scale (**5**) (1 equiv.), Ag_2SO_4 (1.2 equiv.), I_2 (1.2 equiv.)	rt	1.5	MeCN	-	-
5[a]	200 mg scale (**5**) (1 equiv.), Ag_2SO_4 (1.2 equiv.), I_2 (1.2 equiv.)	50	2	MeCN	-	-
6	200 mg scale (**5**) (1 equiv.), Ag_2CO_3 (1.2 equiv.), I_2 (1.2 equiv.)	rt	1.5	MeOH	-	-
7	200 mg scale (**5**) (1 equiv.), $AgNO_3$ (1.2 equiv.), I_2 (1.2 equiv.)	rt	1.5	MeOH	51	-

[a]Reaction was conducted under an inert atmosphere
[b]Isolated yield.

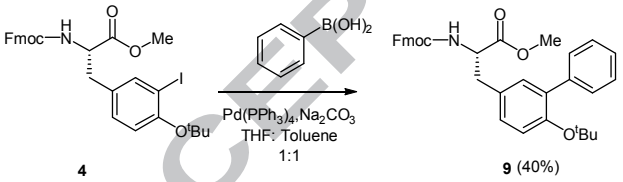


8 **4** (92%)

Scheme 2. Hydrolysis of methyl ester **8** to the free carboxylic acid **4**. Conditions: **8** (1 equiv.), 0.1 M LiOH (2 equiv.), THF:H_2O (1:1), stir 0 °C 30 min. Stir 30 min at 0 °C upon addition of a further equivalent of 0.1 M LiOH.

Reaction optimization was then conducted in the hope that the product ratio could be improved further to favour compound **8**. Increasing the temperature of the reaction to 50 °C increased the yield of **8** to 63% (Table 1, entry 2). The use of substoichiometic silver was also probed. Reducing the amount of silver sulfate to 0.5 equiv. led to a decrease in the yield of compound **8** (26%) with an overall drop in yield across the reaction (Table 1, entry 3). It was hoped that it would also be possible to suppress methyl ester formation to directly give target **4**. Unfortunately when the reaction solvent was changed to acetonitrile, no reaction was observed and the starting material was recovered (Table 1, entries 4 and 5). Finally the identity of the silver salt was altered. Silver carbonate led to no reaction (Table 1, entry 6). Silver nitrate did cause the reaction to proceed but only the undesired compound **7** was isolated in 51% yield (Table 1, entry 7). With this it was concluded that the optimal conditions were silver sulfate (1.2 equiv.) in methanol at 50 °C.

With the optimized reaction conditions in hand, we wished to see if compound **8** could undergo Suzuki-Miyaura cross-coupling. Previous studies by Hutton and Skaff have demonstrated that iodotyrosines with OBn and OMe protected phenol oxygens are amenable to Suzuki-Miyaura cross-coupling.[21] To confirm that a O^{t}Bu protecting group is also compatible in this type of reaction, **8** was reacted with phenylboronic acid using tetrakis(triphenylphosphine)palladium as the catalyst (5 mol%) in the presence of sodium carbonate. The reaction proceeded to give the desired bi-aryl species **9** in 40% yield. This was a pleasing result considering the steric bulk of the *ortho* ^{t}Bu ether.



4 **9** (40%)

Scheme 3. Suzuki-Miyaura cross-coupling of iodotyrosine **4** to give bi-aryl compound **9**. Conditions: **4** (1 equiv.), phenylboronic acid (2 equiv.), Na_2CO_3 (2 M, 2 equiv.), $Pd(PPh_3)_4$ (5 mol%), THF:toluene (1:1), 80 °C, 19 h

Conclusion

In summary, we have demonstrated that an Fmoc SPPS compatible iodotyrosine with an intact ^{t}Bu ether group can be synthesized *via* the iodination of Fmoc-Tyr-(^{t}Bu)-OH **5** under silver-mediated conditions. Following reaction optimisation an isolated 63% yield of compound **8** was obtained. Hydrolysis of this material occurred in 92% yield to give the desired target compound **4**. Therefore, an overall 58% yield of iodotyrosine **4** was obtained in two steps from the commercially available Fmoc-Tyr(^{t}Bu)-OH **5**. In addition **4** was shown to be amenable to Suzuki-Miyaura cross-coupling to give a novel bi-aryl amino acid **9** in 40% yield. We envisage that both the modified amino acids **4** and **8** will be useful building blocks in the synthesis of peptide natural products.

Acknowledgments

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Supplementary Material

For synthetic procedures for compounds (**4**, **7**, **8** and **9**), copies of ^{1}H and ^{13}C NMR for compounds (**4**, **7**, **8** and **9**) and crystallographic data for compound **7** see supporting information.

Crystallographic data for the structure **7** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 973408. Copies of the data can be obtained, free of charge, on

application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk

Research Highlights

- Synthesis of an orthogonally protected iodotyrosine which can be directly used in Fmoc SPPS
- Iodination reaction conditions optimised
- Synthesised iodotyrosine shown to be amenable to Suzuki-Miyaura cross-coupling