Pergamon

Tetrahedron Letters 41 (2000) 7115–7119

TETRAHEDRON LETTERS

The direct synthesis of novel enantiomerically pure α-amino acids in protected form via Suzuki cross-coupling

Philip N. Collier,[a] Andrew D. Campbell,[a] Ian Patel[b] and Richard J. K. Taylor[a,*]

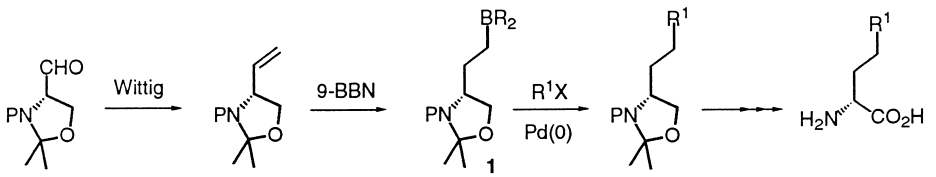
[a]*Department of Chemistry, University of York, Heslington, York YO10 5DD, UK*
[b]*AstraZeneca, Avlon Works, Severn Road, Hallen, Bristol BS10 7ZE, UK*

Received 24 June 2000; accepted 12 July 2000

Abstract

Protected allylglycine has been hydroborated and the intermediate organoborane employed in Suzuki coupling reactions with a number of olefinic, aromatic and heteroaromatic bromides and iodides to produce a range of novel α-amino acids in good, unoptimised yields.

The synthesis of non-proteinogenic α-amino acids continues to be an area of great interest amongst the synthetic community. Such compounds are of interest in their own right and have also been widely employed as building blocks for the preparation of products with interesting biological activities.[1,2] In a recent publication, we described the novel organoborane homoalanine anion equivalent **1** which was simply and effectively transformed into a range of known and novel non-proteinogenic α-amino acids under mild conditions (Scheme 1).[3] Similar transformations were subsequently reported by Sabat and Johnson.[4]



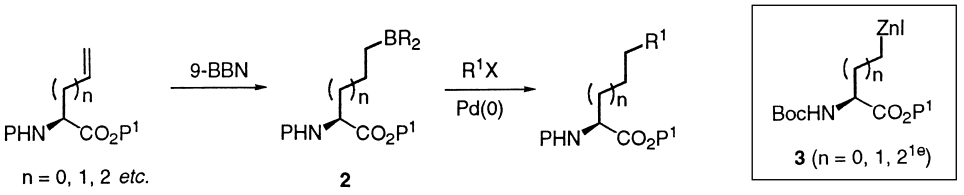
Scheme 1.

The success of the above methodology encouraged us to investigate the viability of the direct utilisation of unsaturated amino acids, in protected form, in a similar hydroboration–Suzuki

* Corresponding author. E-mail: rjkt1@york.ac.uk

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01174-6

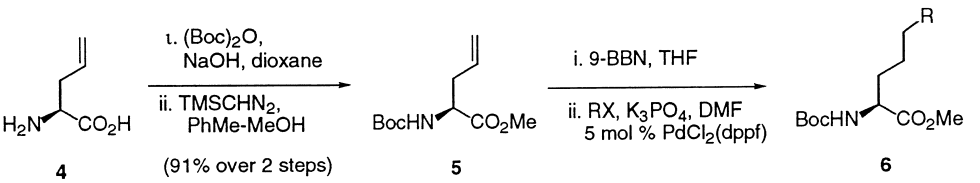
coupling sequence proceeding via organoboron intermediate **2** (Scheme 2). Such an approach would avoid the need for a subsequent oxidative step, minimising the risk of racemisation and extending the range of compatible substituents. This chemistry would be ideally suited to analogue synthesis given the scope of the Suzuki coupling process.[5]



Scheme 2.

A number of amino acid-derived anionic reagents have been developed[1,3,4] but most have the carboxylic acid at a reduced level. The Jackson method using organozinc derivatives **3** is noteworthy, however, in that the acids are simply protected as esters.[1e] Jackson reagents **3** have been employed to prepare a wide range of phenylalanines, homophenylalanines and bishomophenylalanines. We hoped that the organoboron reagents **2** would prove equally valuable from a synthetic viewpoint and would be advantageous in terms of reagent preparation. Herein, we report the successful realisation of this concept for the preparation of novel α-amino acids by the direct hydroboration and Suzuki coupling of protected allyl glycine (Scheme 2, n = 1). We chose to utilise protected allyl glycine in these preliminary studies as its successful hydroboration–oxidation has been recently described.[6]

(L)-Allyl glycine **4** is commercially available or can be readily prepared using literature methods.[6b,7] Boc-protection of **4** followed by esterification with trimethylsilyldiazomethane gave the protected amino ester **5** {$[\alpha]_D$ +18.8 (*c* 1.0, $CHCl_3$); lit.[6b] $[\alpha]_D$ +19.3 (*c* 1.5, $CHCl_3$)} required as substrate for hydroboration–Suzuki coupling studies (Scheme 3).

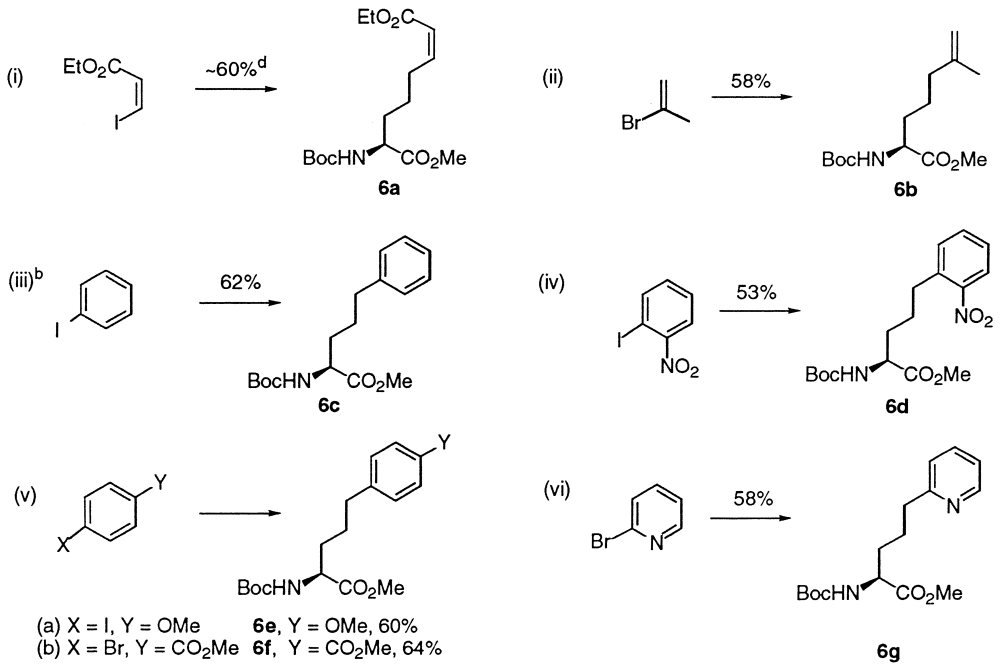


Scheme 3.

The hydroboration of alkene **5** with 9-BBN proceeded smoothly using 2 equivalents of the borane in THF. We next investigated the Suzuki coupling reactions of the organoborane derived from **5** with vinyl and aryl halides. [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) [$PdCl_2$(dppf)][5b] was used as catalyst in view of its success in our earlier studies. The results of the coupling reactions are summarised in Table 1.[8]

The reaction proceeded in good yield with an iodoacrylate (entry i) and the product **6a** retained the *Z*-alkenyl stereochemistry present in the coupling partner (J = 11.6 Hz). Electron rich vinyl bromides were also viable Suzuki coupling partners as illustrated by the reaction with 2-bromopropene producing adduct **6b** (entry ii). Subsequent studies focused on aryl halides and it was

Table 1
Hydroboration–Suzuki cross-coupling of **5** with unsaturated halides[a,b,c]



[a]Yields based on alkene **5**

[b]A representative experimental procedure is given in the references section.[9]

[c][α]$_D$ data as follows: **6b**, +13.1 (*c* 0.5, $CHCl_3$); **6c**, +21.3 (*c* 0.23, $CHCl_3$); **6d**, +15.0 (*c* 0.75, $CHCl_3$); **6e**, +17.5 (*c* 0.8, $CHCl_3$); **6f**, +16.2 (*c* 1.5, $CHCl_3$); **6g**, +14.6 (*c* 1.25, $CHCl_3$).

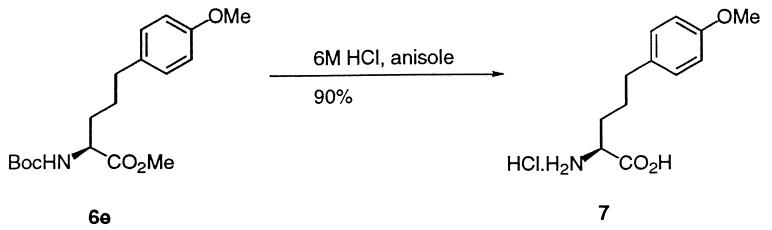
[d]Estimated yield based on NMR analysis; product **6a** was contaminated by an inseparable boron impurity

found that the palladium-catalysed coupling reaction with iodobenzene gave the expected product **6c** in 62% yield (entry iii). Both electron-withdrawing and electron-donating substituted aromatic iodides were successful candidates in the couplings [entries iv and v(a)] producing adducts **6d** and **6e**, respectively; an activated aryl bromide also coupled successfully giving **6f** in 64% yield [entry v(b)]. 2-Bromopyridine also underwent efficient coupling (entry vi) and product **6g** displayed spectroscopic data consistent with those previously reported for the racemic material.[10]

The stereochemical integrity of the hydroboration–Suzuki coupling sequence was confirmed by conversion of anisole derivative **6e** into the known amino acid **7** by hydrolysis with 6 M HCl at 70°C (Scheme 4): the optical rotation of **7** was in good agreement with the published value {[α]$_D$ +31.2 (*c* 0.33, 5 M HCl:DMF, 1:1); lit.[11] [α]$_D$ (enantiomer) –31.8 (*c* 2.0, 5 M HCl:DMF, 1:1)}.

In summary, we have demonstrated that the hydroboration–Suzuki coupling of protected allyl glycine provides a convenient procedure for the preparation of a range of novel, unnatural α-amino acids. We believe that the simplicity of this procedure, coupled to its compatibility with easily oxidised and reduced functional groups,[12] will be of value to the synthetic community. We are currently optimising the results described above and looking at the use of newly discovered[13] catalyst systems to extend the method to encompass coupling to aryl chlorides. We are also extending the hydroboration–Suzuki coupling methodology to vinyl glycine (Scheme 2, n = 0),

higher vinylogues (Scheme 2, n≥2) and to alkynyl analogues. In addition, we are developing a polymer-supported version of this methodology to establish a combinatorial approach to the synthesis of unnatural amino acids.



Scheme 4.

Acknowledgements

We thank AstraZeneca and the University of York for financial assistance (P.N.C.).

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8. All new compounds were fully characterised by high field NMR spectroscopy and by HRMS.
9. Representative procedure (Table 1, entry iii): To alkene **5** (133 mg, 0.58 mmol) in THF (2 ml) at 0°C under N_2 was added 9-BBN (0.5 M in THF, 2.32 ml, 1.16 mmol) and the reaction was warmed to rt and stirred for 2 h until TLC showed consumption of starting material (ca. 90 min). Degassed DMF (1 ml) was added followed by careful addition (H_2 evolution) of aq. K_3PO_4 (3 M, 0.39 ml, 1.2 mmol) followed by quick addition of iodobenzene (124 mg, 0.61 mmol) and finally $PdCl_2$(dppf) (23 mg, 5 mol%) under N_2. The reaction was stirred overnight and the solvent removed in vacuo using an oil pump rotary evaporator. The residue was taken up in ether (15 ml) and saturated $NaHCO_3$ (15 ml). The aqueous layer was re-extracted with ether (20 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude product as a brown oil which was purified by column chromatography on silica gel (light petroleum:ethyl acetate, 4:1) to give **6c** (110 mg, 62%) as a

colourless oil, R_f 0.35 (light petroleum:ethyl acetate, 3:1); $[\alpha]_D$ +21.3 (*c* 0.23, $CHCl_3$); $\nu_{max.}$ ($CHCl_3$)/cm^{-1} 3369, 3025, 1745, 1715; δ_H (270 MHz, $CDCl_3$) 1.44 (9H, s, ^tBu), 1.54–1.91 (4H, m, $2\times CH_2$), 2.55–2.70 (2H, m, CH_2), 3.72 (3H, s, CH_3), 4.28–4.42 (1H, m, CH), 4.99 (1H, d, $J=8.0$, NH), 7.13–7.34 (5H, m, ArH); δ_C (67.9 MHz, $CDCl_3$) 27.7 ($CH_2CH_2CH_2$), 28.9 (CH_3), 32.9 ($CHCH_2$), 35.9 (CH_2C), 52.9 (CH_3), 53.9 (CH), 80.5 ($C(CH_3)_3$), 126.5, 129.0 (×2), 142.3 (Ar), 156.0 ((N)C=O), 174.0 (C=O); *m*/*z* (CI) 325 (MNH_4^+, 1%), 308 (MH^+, 7%); HRMS (CI): found MH^+: 308.1857. $C_{17}H_{26}NO_4$ requires: 308.1862 (1.7 ppm error).

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