Tetrahedron Letters, Vol. 34, No. 40, pp. 6471-6474, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A Novel Approach to Bz-Substituted Tryptophans via Pd-catalysed Coupling / Annulation.

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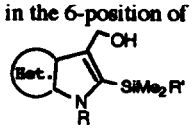
Abstract: The Pd-catalysed preparation of bz-substituted tryptophans and their derivatives, starting from 2-iodoanilines and γ,δ-acetylenic amino acid derivatives, is reported.

We have recently described the Pd-catalysed preparation of heterocondensed pyrroles 1[1]. Herein we report on the synthesis of some tryptophans, carrying substituents in the benzene ring, by use of the same methodology[2] (eq. 1). Earlier methods consist, for instance, of (i) electrophilic substitution in cyclic tautomers of tryptophan[3], or direct nitration in the 6-position of tryptophan[4], (ii) the Fischer indolisation



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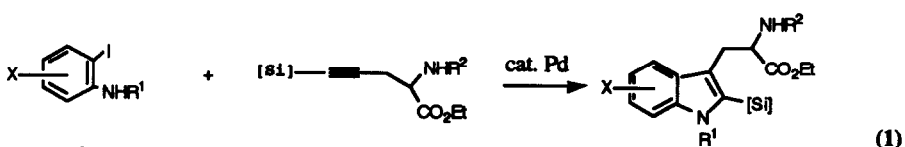


2 3 4 (1)

a: X=H, R^1=Ac
b: X=H, R^1=H
c: X=4-NO_2, R^1=H
d: X=4-Br, R^1=H
e: X=4-Cl, R^1=H
f: X=4-F, R^1=H
g: X=4-NH_2, R^1=H
h: X=5-NO_2, R^1=H

a: [Si]=TMS, R^2=Ac
b: [Si]=TBDMS, R^2=Ac
c: [Si]=TBDMS, R^2=^{t}Boc

starting from suitably substituted arylhydrazones leading directly to tryptophan derivatives[5], or (iii) the construction of tryptophans from indoles, either through organic synthesis[6] or enzymatically[7]. In our strategy (eq. 1) the tryptophan derivatives are built in a convergent manner from easily prepared building blocks **2**[8] and **3**[9,10]. Some results are given in Table 1.

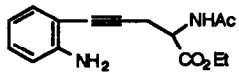
Table 1. Pd-catalysed Reactions of 2-iodoanilines **2** and acetylenic amino acid esters **3**.[a]

Entry	2-iodoanilines	acetylenic amino acid ester	base / time (h)	isolated yield of **4** (%)[b] [Si]=TBDMS
1	2a	3b	KOAc / 22	27 X=H, R^1=R^2=Ac
2	2b	3b	KOAC / 22	38 X=R^1=H, R^2=Ac
3	2b	3c	Et_3N / 23	62 X=R^1=H, R^2=^{t}Boc
4	2c	3c	Et_3N / 24	53 X=5-NO_2, R^1=H, R^2=^{t}Boc
5	2e	3c	Et_3N / 20	48 X=5-Cl, R^1=H, R^2=^{t}Boc
6	2f	3c	Et_3N / 22	47 X=5-F, R^1=H, R^2=^{t}Boc
7	2h	3c	Et_3N / 24	46 X=6-NO_2, R^1=H, R^2=^{t}Boc

[a] All reactions were run in DMF with **2** (0.5 mmol), $Pd(OAc)_2$ (5 mol%), PPh_3 (5 mol%), n-Bu_4NCl (1 equiv.) and acetylenes **3** (2 equiv.) at 90-100°C under nitrogen. The regiochemical outcome[11] was confirmed by NOE experiments of the product in one case (entry 7).

[b] All products gave appropriate ^{1}H-NMR, IR, MS, HR-MS. ^{13}C-NMR spectra were also obtained in some cases.

We have previously shown the necessity of utilising TBDMS-substituted propargyl alcohol when performing this reaction with N-substituted aryl iodides, in the preparation of compounds such as **1**[1]. When aromatics with a free NH_2 group were reacted, the TMS-analogue was preferred[1,2]. Unexpectedly the reaction of **2b** (free NH_2) with the TMS-containing acetylene **3a** yielded 40 % of **5** (^{1}H-NMR, ^{13}C-NMR, IR, MS, HR-MS, compare ref. 1). Preliminary results implied advantages of utilising free anilines



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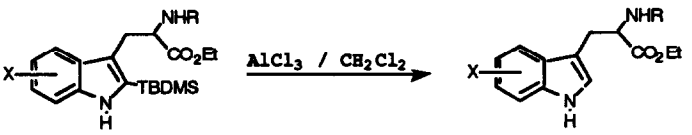
over N-substituted ones (entries 1 and 2, Table 1) and triethylamine as the base (entry 3, Na_2CO_3 resulted in inferior yields). 2-Iodo-4-bromoaniline **2d** gave a complex reaction mixture with **3c**, irrespective of whether Na_2CO_3 or Et_3N was employed as base, or whether PPh_3 was added or not. No reaction between **2g** and **3c**, in the presence of Et_3N / PPh_3, could be observed (TLC).

When the products **4** of the coupling / annulation reaction were desilylated, the ^{t}Boc substituent was concomitantly cleaved off[12,13] (Table 2).

Table 2. Desilylation of **4**.[a]



4 **10**

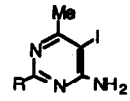
4	isolated yield (%) of **10**[c]		
X=H, R=Ac[b]	30	X=H, R=Ac	**10a**
X=5-NO_2, R=^{t}Boc	56	X=5-NO_2, R=H	**10b**
X=5-Cl, R=^{t}Boc	64	X=5-Cl, R=H	**10c**
X=5-F, R=^{t}Boc	28	X=5-F, R=H	**10d**
X=6-NO_2, R=^{t}Boc	13	X=6-NO_2, R=H	**10e**

[a]Compounds **4** (0.1 mmol) in 5 ml CH_2Cl_2 were added slowly to $AlCl_3$ (10 equiv.) in 1.5 ml CH_2Cl_2 at 0°C. The mixture was stirred at this temperature for 3 h, then hydrolysed with $NaHCO_3$ (sat.). The products **10** were purified by chromatography.

[b]Attempts to desilylate with n-Bu_4NF / CF_3CH_2OH in THF failed.

[c]The ^{1}H-NMR spectrum of **10a** was identical with published data[14]. For compounds **10b-e**, appropriate analytical data (^{1}H-NMR, IR, MS, HR-MS) were obtained.

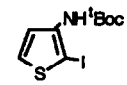
So far, the reactions of **6-9** with **3a-c** under various conditions resulted in considerably lower yields (0-30 %) compared to those indicated in Table 1. The thiophene **9** belongs to the group of substrates from which no detectable amounts of tryptophan analogues were produced, dehalogenated **9** being recovered instead.



6
a: R=H
b: R=Me

7
a: R=H
b: R=CO^{t}Bu

8



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In summary, we have shown this coupling / annulation-desilylation sequence to be applicable to the preparation of bz-substituted tryptophans and their derivatives. We hope, after proper elaboration, that yields will be improved, especially regarding the heterocondensed analogues.

Acknowledgement. Grants from the Swedish Natural Research Council to S.G. and U.A. are gratefully acknowledged.

References and Notes

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8. Prepared by iodination with ICl of the 4- or 5-substituted anilines, cf. *Beilstein*, *12*, 746e.
9. The acetylenic amino acid esters **3** were prepared by alkylation[10] of the benzylidene derivative of glycine with TMS- or TBDMS-substituted propargylbromides in good yields. The free amines, obtained after chromatography[10], were N-acylated with AcCl or ^{t}Boc$_2$O, yielding **3a-c** (76-84 %) which showed appropriate spectroscopic data (^{1}H-NMR, and IR, MS or ^{13}C-NMR).
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11. The sterically more demanding silyl group ends up adjacent to nitrogen in **4** (see ref. 1 and 2).
12. $AlCl_3$ has been used to cleave benzyl esters[13], and the ^{t}Boc group in our cases is probably removed by the Lewis acid in a similar way.
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(Received in UK 16 June 1993; accepted 5 August 1993)