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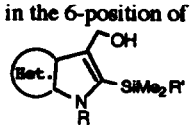
*Abstract*: The Pd-catalysed preparation of bz-substituted tryptophans and their derivatives, starting from 2-iodoanilines and γ,δ-acetylenic amino acid derivatives, is reported.

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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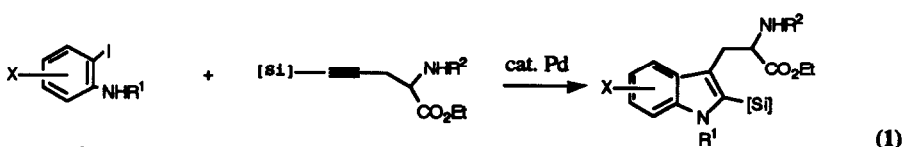



2 3 4 (1)

**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.

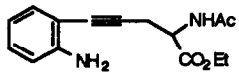
**Table 1.** Pd-catalysed Reactions of 2-iodoanilines **2** and acetylenic amino acid esters **3**.[a]

| 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

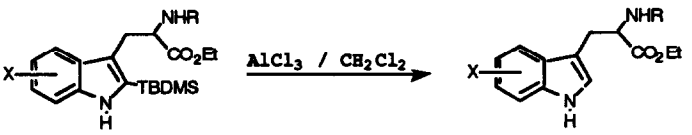



**5**

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**

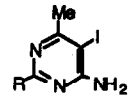
| **4** | isolated yield (%) of **10**[c] | | |
|---|---|---|---|
| X=H, R=Ac[b] | 30 | X=H, R=Ac | **10a** |
| X=5-$NO_2$, R=$^t$Boc | 56 | X=5-$NO_2$, R=H | **10b** |
| X=5-Cl, R=$^t$Boc | 64 | X=5-Cl, R=H | **10c** |
| X=5-F, R=$^t$Boc | 28 | X=5-F, R=H | **10d** |
| X=6-$NO_2$, R=$^t$Boc | 13 | X=6-$NO_2$,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

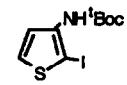
So far, the reactions of **6-9** with **3a-c** under various conditions resulted in considerably lower yields (0-30 %) compared to those indicated in Table 1. The thiophene **9** belongs to the group of substrates from which no detectable amounts of tryptophan analogues were produced, dehalogenated **9**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




**6**
**a:** R=H
**b:** R=Me


**7**
**a:** R=H
**b:** R=CO t Bu


**8**




**9**

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.

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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 $^tBoc_2O$, 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)