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Palladium-Catalysed Synthesis of Heterocondensed Pyrroles

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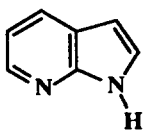
Abstract: The palladium-catalysed preparation of some heterocondensed pyrroles from ortho nitrogen containing hetaryl iodides and derivatives of propargyl alcohol is described.

A considerable variety of analogues of natural amino acids have been synthesised[1] and investigated in biological systems, both as the free amino acids and in peptide sequence. The response of an enzyme, receptor or membrane to an analogue is very often unpredictable and challenging in interpretation.

One might anticipate that interchange between sp^2 carbon and sp^2 nitrogen should have little effect on biological activity, since the alteration in geometry is quite small; yet, 7-azaindole (1) has been found to inhibit the growth of *E. coli* [2] and to exert a mild block on tryptophan biosynthesis from indole. The possibility that 1 shows antagonist activity because of the basicity of the pyridine nitrogen led us to consider thieno and pyrimidino analogues of both indole and tryptophan as mimics which might show interesting and useful effects at various stages in tryptophan metabolism.



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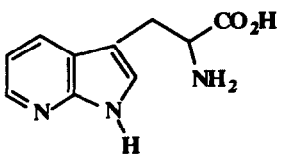

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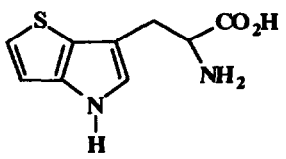

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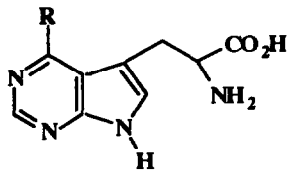
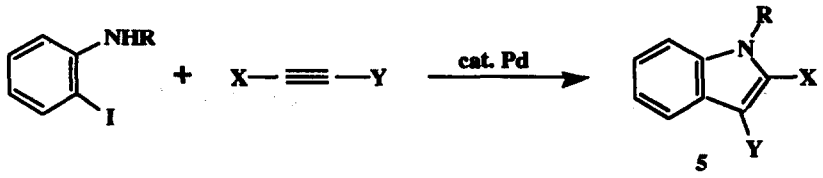


4 R = H, OH

Thus, we have become interested in the preparation of tryptophan analogues of the types shown in 2-4 [3]. Of these analogues, only 2 has been extensively studied with respect to biological properties.[4] The usual preparative route to tryptophan analogues of this kind is based on classical amino acid synthesis, starting from heterocondensed pyrroles.[3,5] Total yields are often low, especially if the heteroaromatic part has to be constructed first.

Larock et. al. recently published an elegant method for the preparation of indoles (eq.1),[6] which utilises catalytic amounts of palladium.[7] Regioselectivity is exellent, with the sterically more demanding substituent of the acetylene ending up adjacent to nitrogen in indole 5. Thus, when X= $SiMe_3$, 5 is a precursor to 2-unsubstituted indoles via desilylation.



(1)

5

R = H, Me, Ac, Ts

X = $SiMe_3$, alkyl, aryl

Y = alkyl, aryl

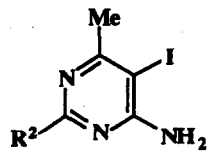
We have investigated the application of this procedure to the preparation of heterocondensed pyrroles. The aryl iodides used are depicted in the chart below. We initially selected the readily available hetaryl iodides **6**[8] (N-substituted because of the expected instability of 2-iodo-3-amino-thiophene[9]), since similar thienyl halides proved to be useful in palladium-catalysed dithienopyridine syntheses, previously developed by us.[10] The pyrimidines **7** and pyridines **8** were easily prepared according to literature procedures[11]. As models of acetylenic coupling partners we chose propargyl alcohols **10** (eq. 2).[12]

Chart

6

a : R^1 = Ac

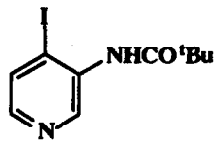
b : R^1 = ^{t}Boc



7

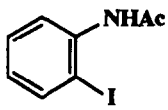
a : R^2 = H

b : R^2 = Me



8a

8b



9

A preliminary experiment, using conditions indicated by Larock et al.,[6] with aryl iodide **6b** and acetylene **10a**, resulted in a complex reaction mixture, partly consisting of acetylenic coupling product **12a** (eq. 2, table ; Ar = 2- thienyl, R = ^{t}Boc). The structure of **12a** was ascertained by comparing spectroscopic data with those of an independently prepared authentic sample.[13] It is worth mentioning that 2-iodoaniline (as already shown by Larock et. al.[6]) gave the desired ring-closed product with **10a**. However, with this acetylene, neither 2-iodo-acetanilide **9** nor the N-substituted aryl iodides **6a, b** and **8a** gave any synthetically useful results with regard to **11** (eq. 2). Furthermore, when substituting the hydroxyl in **10a** for other groups, complex mixtures were also obtained.

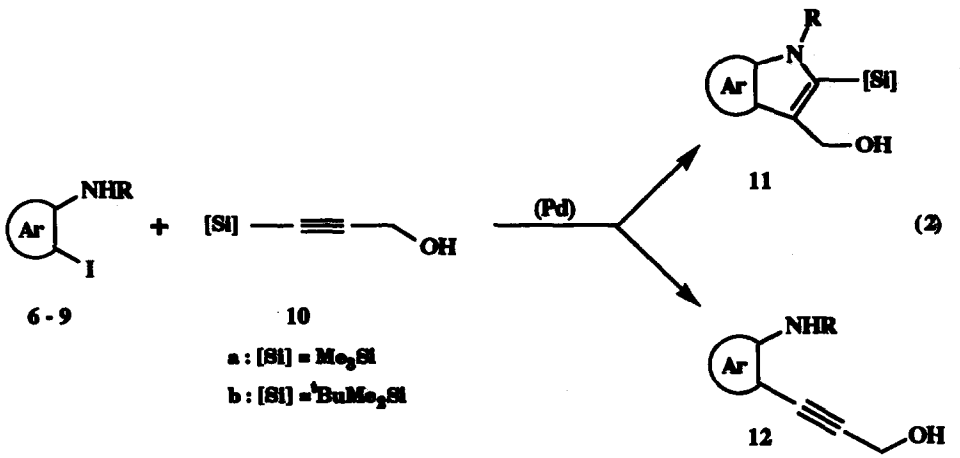


Table. Pd-Catalysed Reactions of Aryl Iodides **6 - 9** with Propargyl Alcohols[a]

aryl iodide	acetylene	conditions[a]	time (h)	product[b]		isolated yield (%)
6a	**10b**	A	22	thieno[3,2-b]pyrrole	**11a**	22
6b	**10b**	B	3	thieno[3,2-b]pyrrole	**11b**	67
6b	**10a**	C	5	(Ar= 2-thienyl; R=^{t}Boc)	**12a**	28
7a	**10a**	D	19	pyrrolo[2,3-d]pyrimidine	**11c**	44
7a	**10b**	D	27	pyrrolo[2,3-d]pyrimidine	**11d**	16
7b	**10a**	D	19	pyrrolo[2,3-d]pyrimidine	**11e**	51
7b	**10b**	D	32	pyrrolo[2,3-d]pyrimidine	**11f**	21
8a	**10b**	A	24	pyrrolo[2,3-c]pyridine	**11g**	20
8b	**10b**	A	24	pyrrolo[3,2-c]pyridine	**11h**	40
9	**10b**	E	3	indole	**11i**	45

[a] cf. equation 2. All reactions were run in DMF with aryl iodide **6 - 9**(0.5 - 2.5 mmol), $Pd(OAc)_2$ (5 mol%), n-Bu_4NCl (1 equiv.) and acetylene **10** (2 equiv.) at 90 - 100°C under nitrogen. A: KOAc (5 equiv.); B: Na_2CO_3 (5 equiv.); C: Na_2CO_3 (5 equiv.) and PPh_3 (5 mol%); D: triethyl amine (5 equiv.) and PPh_3 (5 mol%); E: KOAC (5 equiv.) and PPh_3 (5 mol%)

[b] All products gave appropriate ^{1}H-NMR, ^{13}C-NMR, IR, MS and elemental or high resolution MS analyses. The regiochemistry was confirmed by NOE experiments in three cases (**11g, 11h, 11i**)

By turning to the TBDMS-substituted acetylene **10b** these problemes were overcome and annulated compounds **11** could be isolated from reactions of **6**, **8** and **9** (table). On the other hand, the use of **10a** proved advantageous with pyrimidines **7** (N-unsubstituted).

We are currently investigating the application of this simple palladium-catalysed coupling/annulation reaction for the direct synthesis of tryptophan analogues.

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References and Notes

1. Roberts, D.C.; Vellaccio, F. in *The Peptides* ; Gross, E.; Meienhofer, J. Eds.; Academic Press, 1983; pp. 342-449.
2. Pardee, A.B.; Prestidge, L.S. *Biochim. Biophys. Acta* **1958**, *27*, 330-344.
3. a) Humphries, A.J.; Keener, R.L.; Yano, K.; Skelton, F.S.; Freiter, E.; Snyder, H.R. *J. Org. Chem.* **1972**, *37*, 3626 - 3629. b) Burroughs Wellcome &Co., Brit. Pat. 981,458, Jan. 27, **1965**; cf. *CA* **1965**, *63*, P 4309 d. c) Azimov, V.A.; Uritskaya, M. Ya.; Yakhontov, L.N. *Khim. Farm. Zh.* **1968**, *2*, 16 - 19 d) Robinson, M.M.; Robinson, B.L. *J. Am.. Chem. Soc.* **1965**, *77*, 457 - 460
4. For a few examples, see: a) Bottomley, P.J.; Van Baalen, C.; Tabita, F.R. *Arch. Biochem. Biophys.* **1980**, 204 - 213. b) Yabe, Y.; Miura, C.; Horikoshi, H.; Baba, Y. *Chem. Pharm. Bull.* **1976**, *24*, 3149 - 3157. c) Widholm, I.M. *Biochim. Biophys. Acta* **1972**, *279*, 48 - 57 and **1972**, *261*, 44 - 51 and 52 - 58
5. For reviews concerning preparations of thienopyrroles and pyrrolopyrimidines, see: a) Garcia, F.; Galvez, C. *Synthesis* **1985**, 143 - 156. b) Armanath, V.; Madhav, R. *Synthesis* **1974**, 837 - 859. c) For preparations of pyrrolopyridines, see: Mahadevan, I.; Rasmussen, M. *J. Heterocyclic Chem.* **1992**, *29*, 359 - 367 and references cited there.
6. Larock, R.C.; Yum, E.K. *J. Am. Chem. Soc.* **1991**, *113*, 6689 - 6690.
7. For other indole syntheses employing palladium catalysts, see for example: a) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988**, *27*, 2225 - 2249. b) Kasahara, A.; Izumi, T.; Kikuchi, T.; Xiao-Ping, L. *J. Heterocyclic Chem.* **1987**, *24*, 1555 - 1556. c) Kasahara, A.; Izumi, T.; Murakami, S.; Yanai, H.; Takatori, M. *Bull. Chem. Soc. Japan* **1986**, *59*, 927 - 928. d) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915 - 3918. e) Hegedus, L.S. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1113 - 1126. f) Satoh, M.; Miyaura, N.; Suzuki, A. *Synthesis* **1987**, 373 - 377
8. a) **6a** was prepared according to Campaigne, E.; Monroe, P. A. *J. Am. Chem. Soc.* **1954**, *76*, 2447 - 2450. b) **6b** was obtained through iodination of t-butyl-N-(3-thienyl)carbamate according to the procedure for the corresponding bromination: Brunett, E.W.; McCarthy, W.C. *J. Pharm.Sci.* **1968**, *57*, 2003 - 2005.
9. Compare the very unstable 2-aminothiophene which is stabilised through conversion to its hydrochloride salt: a) Binder, D.; Habison, G.; Noe, C.R. *Synthesis* **1977**, 255 - 256. b) Eck, D.L.; Stacy, G.W. *J. Heterocyclic Chem.* **1969**, *6*, 147 - 151. c) Regarding the instability of 3-aminothiophene, see ref. 8a).
10. Yang, Y.; Hörnfeldt, A.-B.; Gronowitz, S. *Chemica Scripta* **1988**, *28*, 275 - 279
11. a) For **7a**, **b** see: Zeuner, F; Niclas, H.-J. *J. Prakt. Chem.* **1989**, *331*, 324 - 330 and ref. 11.b). b) Niclas, H.-J.; Zeuner, F.; Gruendemann, E.; Zoelch, L. *J. Prakt. Chem.* **1987**, *329*, 400 - 408. c) For **8** see: Estel, L.; Marsais, F.; Quéguiner, G. *J. Org. Chem.* **1988**, *53*, 2740 - 2744
12. These were prepared from the anion of the THP derivative of propargyl alcohol and TMS-Cl or TBDMS-Cl.
13. Compound **12a** (eq.2; Ar = 2-thienyl, R = ^{t}Boc) was independently synthesised using a method described for similar compounds: Neenan, T.X.; Whitesides, G.M. *J. Org. Chem.* **1988**, *53*, 2489 - 2496.

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