A SYNTHESIS OF 3,4-DISUBSTITUTED INDOLES

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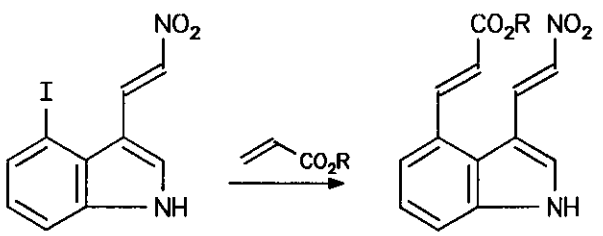
Abstract - 3,4-Disubstituted indoles are prepared through palladium-catalyzed coupling.

A wide variety of alkaloids contain a 3,4-disubstituted indole nucleus.[1] Since a large number of these alkaloids exhibit interesting biological activities, numerous different synthetic approaches have appeared in the literature describing the preparation of indoles with this substitution pattern. One of the recent methods disclosed by Somei *et al.*[2] makes advantage of thallation/iodination of 3-carbonyl substituted indole, followed by a Heck reaction.[3] The relatively harsh conditions of the Heck coupling, however, pose limitations on the scope of this method. For instance, in our hands the palladium catalyzed reaction of **1a** with methyl or ethyl acrylate gave low and poorly reproducible yields (20-30 %)[4] if the indole nucleus was unprotected.

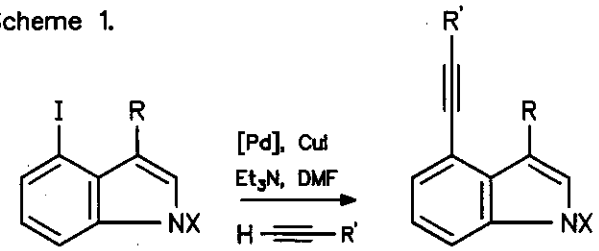


1a

Searching for a more efficient method, we were surprised to realize that no report has appeared in the literature about the Cu(I) - Pd(0) catalyzed coupling[5] of terminal acetylenes with the indole skeleton at C(4).

We were satisfied to establish that this reaction can be efficiently used for the substitution of 4-iodo-indoles (Scheme 1). The results, together with some analytical data,[6] are depicted in the Table.

Scheme 1.



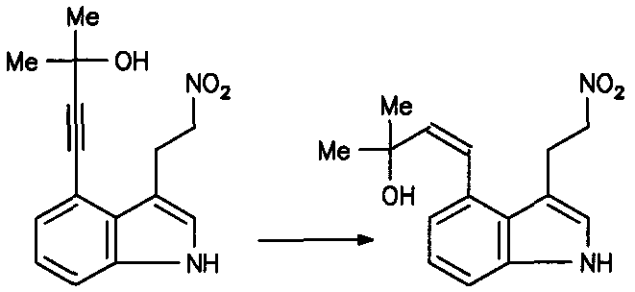
1	R	X	2	R'	3
a	/E/−CH=CHNO$_2$	H	a	TMS	
b	/E/−CH=CHNO$_2$	Ts	b	Bu^n	
c	(CH$_2$)$_2$NO$_2$	H	c	CH$_2$OH	
d	(CH$_2$)$_2$NO$_2$	Me	d	C(OH)Me$_2$	
			e	CH(OEt)$_2$	

In the experiments we checked four different 4-iodoindoles with various electron densities in the aromatic ring (**1a-d**), three different palladium catalyst systems ([Ph$_3$P]$_4$P, [Ph$_3$]$_2$PdCl$_2$, as well as [Ph$_3$P]$_4$Pd generated *in situ* from Pd/C and triphenyl phosphine),[7] and five different acetylenes (**2a-e**). The reactions were uniformly run on a scale of 1 mmol in DMF (*ca.* 20-30 mg/ml indole concentration) under argon atmosphere in the presence of 2 equivalents of triethylamine as base. Usually 2-5 equivalents of acetylene (**2**), 0.2 equivalents of cuprous iodide, and 0.05 equivalents of the palladium catalyst were used. The reactions were run at room temperature, except those with the catalyst generated *in situ* (Runs 13,15,18), where heating at 100 ^{o}C was necessary. In most of the cases fair to good yields of the chromatographically purified products have been achieved (See Table). The yields were similar in the case of the two pre-formed catalysts, and they were always superior to the *in situ* generated ones.

TABLE

Run	Startg. Cpd.	Acetylene		Method[8]	Product	Yield[9]	Tlc[10]		mp[11]	Ms[12]		^{13}C Nmr[13]	
	1	2	R'		3	%	Eluent	R_f	°C	main peak (%)	M+· (%)	$C_{(1')} \equiv C_{(2')}$	
1	a	a	TMS	A	aa	71	30K/1M	0.20	241-4	238(100)	284(42)	98.9	103.9
2	a	a		B	aa	58							
3	a	b	Bu^n	A	ab	73	30K/1M	0.33	150-2	222(100)	268(75)	79.4	95.1
4	a	b		B	ab	68							
5	a	c	CH_2OH	A	ac	48	1H/1E	0.21	211-4	196(100)	242(85)	82.5	94.1
6	a	c		B	ac	48							
7	b	a	TMS	A	ba	67	1H/1K	0.21	125-7	392(35)	439(100)	101.5	101.9[14]
8	b	a		B	ba	63							
9	c	a		B	ca	84	1H/1K	0.13	94-6	73(82)	286(100)	97.1	104.8*
10	c	c	CH_2OH	B	cc	44	20K/1M	0.16		154(45)	244(100)	83.2	91.7
11	c	d	Me_2COH	A	cd	91	20K/1M	0.29	109-12	167(90)	272(100)	81.3	96.4*
12	c	d		B	cd	94							
13	c	d		C	cd	83							
14	d	a	TMS	A	da	57	2H/1K	0.29	62-6	73(45)	300(100)	96.9	104.6*
15	d	a		C	da	45							
16	d	c	CH_2OH	A	dc	75	30K/1M	0.37	98-102	168(40)	258(100)	84.3	89.7*
17	d	c		B	dc	73							
18	d	c		C	dc	14							
19	d	e	$CH(OEt)_2$	A	de	73	B	0.16	oil	285(95)	330(100)	84.6	87.3*

Scheme 2.



3cd **4**

Compound (**3cd**) described above can be partially saturated over Lindlar catalyst to **4**,[6] which has already been transformed to secoagroclavine[2e,f] (Scheme 2). Unfortunately, the yield of the reaction was invariably 25-30% under a variety of conditions.

Further studies on the synthetic potential of these compounds are in progress. [15,16]

REFERENCES and NOTES

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2. **a.** S. Hamabuchi, H. Hamada, A. Hironaka,and M. Somei, *Heterocycles*, **1991**, *32*, 443.
   b. M. Somei, F. Yamada, H Yamada,and T. Kawasaki, *Heterocycles*, **1989**, *29*, 643.
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   h. R. A. Hollins, L. A. Colnago, V. M. Salim,and M. C. Seidl, *J Heterocycl.Chem.*, **1979**, *16*, 993.
3. For a recent review see: V. N. Kalinin, *Synthesis*, **1992**, 413, and references cited therein.
4. Reaction conditions: 1 equiv. of indole iodide, 2 equiv. of acrylic ester, 0.1-0.2 equiv. of palladium(II)chloride, 1.02 equiv. of tetrabutyl ammonium hydrogen sulfate, excess of triethylamine in DMF (50-100 mg of indole/ml of solvent), argon atmosphere, 110-120 ^{o}C.

5. For leading references see: **a**. J. Suffert, *Tetrahedron Lett.*, **1991**, *31*, 7437.

b. K. C. Nicolau, G. Skokotas, S. Furuya, H. Suemune,and D. C. Nicolau, *Angewandte Chem. Int. Ed. in English*, **1990**, *29*, 1064.

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6. All new compounds were characterized with ir, ^{1}Hnmr, ^{13}Cnmr, and ms spectra.

7. M. A. De la Rosa, E. Velarde,and A. Guzmán, *Synth. Communications*, **1990**, *20*, 2059.

8. Method **A**: $(Ph_3P)_4Pd$ catalyst; Method **B**: $(Ph_3P)_2PdCl_2$ catalyst; Method **C**: *in situ* generated $(Ph_3P)_4Pd$ catalyst.

9. Refers to chromatographically purified products.

10. Abbreviations: **K**: chloroform, **M**: methanol, **H**: hexane, **E**: ethyl acetate, **B**: benzene.

11. Not corrected.

12. EI(70 eV) mass spectra, except **ba**, where FAB ionization was used in nitrobenzyl alcohol matrix (MH^+ is given in the Table). The spectra were recorded on an MS-902 type spectrometer.

13. The spectra were recorded on a Varian VXR-300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) in DMSO-d_6, unless marked with *, where the solvent was $CDCl_3$ (internal standard: TMS).

14. We were unable to prepare completely pure **3ba**, due to its lability. The values given in the Table are interchangeable.

15. One of the referees called our attention to the fact that M. Somei *et al*. gave an oral presentation at the "22nd Congress of Heterocyclic Chemistry" (Sendai, October 7-9, 1991) disclosing a similar method for the preparation of some of the compounds described here.

16. Technical assistance of É. Papp-Borsos is acknowledged here.

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