FACILE SYNTHESIS OF 2-SUBSTITUTED INDOLES FROM o-BROMOANILINE

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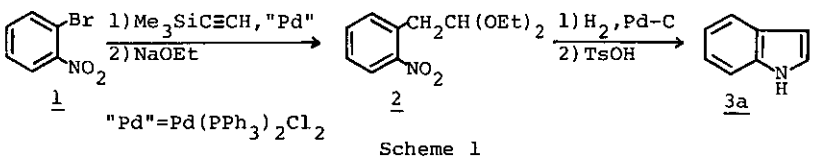
Abstract——— The condensation of ethyl o-bromocarbanilate (4) with trimethylsilylacetylene in the presence of dichlorobis(triphenylphosphine)palladium, followed by treatment with sodium ethoxide in boiling ethanol gave indole (3a) in 72 % overall yield from 4. Similarly, 2-substituted indoles (3b,c) were synthesized from 4 and the corresponding 1-alkynes.

Previously, we reported[1] that the catalytic reduction and subsequent cyclization of o-nitrophenylacetaldehyde diethyl acetal (2), obtained by the condensation of o-bromonitrobenzene (1) and trimethylsilylacetylene followed by the reaction with sodium ethoxide, gave indole (3a). Every steps in this route appeared to have experimental simplicity, but o-halonitrobenzenes did not always undergo the condensation with trimethylsilylacetylene. For example, the reaction of 2,5-dichloro-1-nitrobenzene with trimethylsilylacetylene in the presence of dichlorobis(triphenylphoshpine)palladium resulted in the formation of resinous substance.



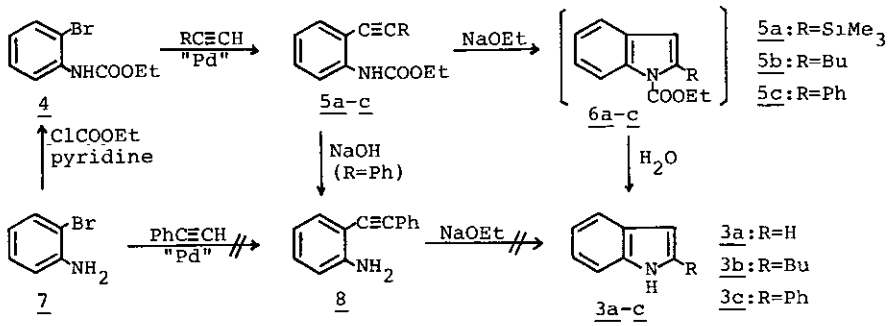
1 2 3a

"Pd"=$Pd(PPh_3)_2Cl_2$

Scheme 1

Thus, further investigation was made to develop a synthetic route for indoles from o-substituted ethynylbenzenes. In the present paper, we describe a facile method for the preparation of indoles (3a-c) from ethyl o-bromocarbanilate (4). The urethane (4), conventionally, reacted with trimethylsilylacetylene in triethylamine in the presence of the palladium catalyst at 100°C for 3 h.[2] The product was refluxed with sodium ethoxide in ethanol to obtain compound 3a in 72 % yield from 4. Similarly, 2-substituted indoles (3b,c) were synthesized from 4 and the corre-

sponding monosubstituted acetylenes as shown in Scheme 2.



Scheme 2

Table Ethyl o-Ethynylcarbanilates (5a-c) and Indoles (3a-c)

	Yield(%)	bp(°C)/mmHg		Yield(%)	mp or bp(°C)/mmHg
5a	77	120-125/4	3a	93	50-51
5b	65	145-150/3	3b	74	155-160/4
5c	77	170-175/3	3c	82	187-188

Thermal cyclization of o-ethynylaniline to indole at 600°C[3] or 170-180°C in the presence of cuprous chloride[4] has been reported. Thus, in order to clarify the cyclization pathway, o-phenylethynylaniline (8), obtained by the alkaline hydrolysis of o-phenylethynylcarbanilate (5c), was refluxed with sodium ethoxide in ethanol, but no cyclization to 2-phenylindole (3c) was observed. Accordingly, the cyclization of 5a-c with sodium ethoxide to indoles (3a-c) was recognized to proceed via formation of 1-ethoxycarbonylindoles (6a-c), followed by hydrolysis of 6a-c during work-up. Furthermore, o-bromoaniline (7), unlike o-bromonitrobenzene (1), did not undergo the cross-coupling reaction with acetylenes, and o-bromoacetanilide became resinous during the reaction with trimethylsilylacetylene in the presence of the palladium catalyst.

On the basis of these facts, it is concluded that the protection of the amino group in o-bromoaniline with ethoxycarbonyl group is essential for not only the cross-coupling reaction, but also the formation of indoles.

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