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Solid-Phase Synthesis of Indoles Using the Palladium-Catalysed Coupling of Alkynes with Iodoaniline Derivatives.

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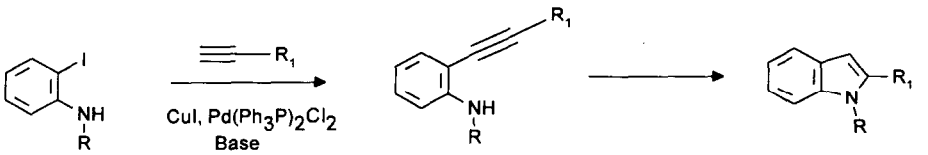
Abstract: The solid-phase synthesis of indoles using Pd(0) catalysed coupling of alkynes with iodaniline derivatives is described. The reaction gives indoles in high yields with a wide range of alkynes. © 1997 Elsevier Science Ltd.

Solid-phase organic synthesis is being widely used for the generation of libraries of small organic molecules.[2] The application of palladium catalysis for the C-C bond formation is particularly attractive owing to the mild reaction conditions and high reaction yields. Therefore palladium-catalysed carbon-carbon bond formation via Stille, Suzuki, and Heck reactions have recently gained a high popularity in solid phase reactions.[3] Herein, we report our preliminary studies on the solid-phase synthesis of five-member heterocycles *via* coupling of an aromatic iodide derivative with alkynes catalysed by a Pd(0)/Cu(I) system. In particular, we have focused on the synthesis of indoles and benzofurans.[4] The indole nucleus is a fundamental constituent of a number of biologically active natural, as well as synthetic products, and a considerable effort has been devoted in recent years to the use of palladium catalysis for their synthesis in solution.[5] This approach is very attractive for solid phase applications because it offers high versatility and the possibility of obtaining 2-substituted or 2,3-disubstituted derivatives according to the reactant alkynes, the catalytic species, and the reaction conditions. The reaction with monosubstituted alkynes proceeds via an intermediate alkyne which then cyclises *in situ*, presumably with the assistance of palladium and/or copper species (scheme 1).[5]

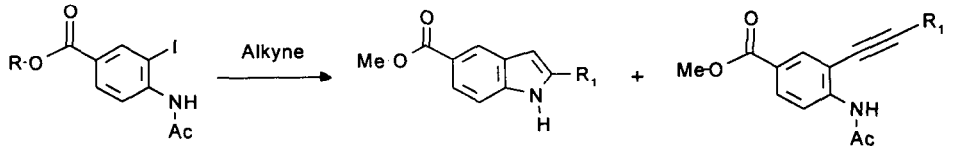


Scheme 1.

The efficiency of the cyclization step depends upon the nature of the R group (scheme 1), the base, and the reaction conditions.[6] Sometimes, in order to obtain complete conversions the cyclization step is performed separately under different conditions.[5, 6, 7] Since our early report on the one-pot synthesis of 2-unsubstituted benzofurans by the use of palladium-catalysed coupling of trimethylsilylacetylene,[8] the same strategy has also been widely applied to the synthesis of indoles.[5] In the same work we disclosed the ability of tetramethylguanidine (TMG) to promote the coupling/cyclisation steps in one-pot, and we wish now to report the application of TMG to the synthesis of indoles in solution and in solid-phase. TMG offers the advantage of effecting the reaction in very high yields under mild and homogeneous conditions.

In the initial model experiments in solution, the anthranilic acid derivative **1**[9] was treated with a series of monosubstituted alkynes in a solvent/base system in the presence of $Pd(Ph_3P)_2Cl_2$ and CuI for 18h. Table 1 summarises the ratios of alkyne/indole found in the experimental conditions. Entry 1 is given as reference.

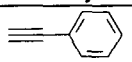
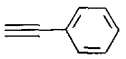
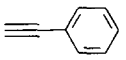
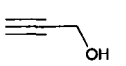
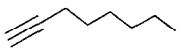
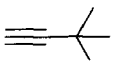
Table 1. Ratio of alkyne/indole in solution.



1a, R = Me
1b, R = H

2

3

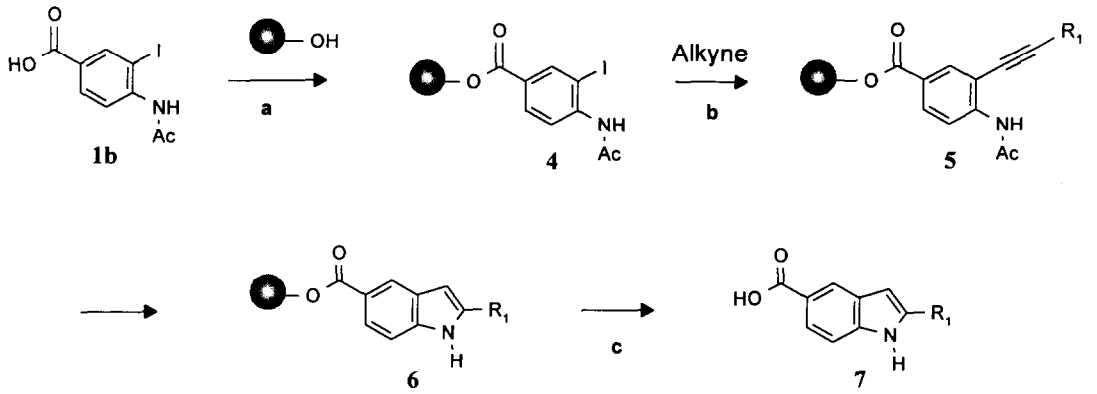
Entry	Alkyne	Base/Solvent	T(°C)	Conversion (%)[a]	Ratio **2/3** (Y%)[b]
1		Et_3N	60	> 99%	0:100 (93%)
2		TMG/Dioxane	60	> 99%	45:55 (95%)
3		TMG/Dioxane	80	> 99%	100:0 (95%)
4		TMG/Dioxane	80	> 99%	100:0 (64%)[c]
5		TMG/Dioxane	80	> 99%	100:0 (84%)
6		TMG/Dioxane	80	> 99%	0:100 (84%)

[a] Based upon the disappearance of **1**. [b] Isolated total yields. [c] N, O acyl migration.

The use of TMG as a cosolvent allowed a complete conversion to 2-phenyl, 2-alkyl, and 2-hydroxymethyl deacetylated indoles **2** at 80 °C (entries 3-5), except for the bulky t-butyl substituent, that suppressed the cyclization step (entry 6). These experimental conditions were transferred to the solid-phase.

Commercially available TentaGel-S™ resin in the OH form was coupled with 3-iodo-4-acetamidobenzoic acid (**1b**) under standard Mitsunobu conditions to provide resin **4** (scheme 2). The resin linked **4** was coupled with the alkyne using the conditions described above to yield the polymer bound alkyne **5**, which cyclises *in situ* to indole **6**. The indole **6** was then cleaved from the resin in NaOH 1M/*i*-PrOH providing the indole carboxylic acids **7**, or in NaOMe/MeOH to give the corresponding methyl esters. The purity and yields of the cleaved indoles were determined by quantitative HPLC analysis by comparison with standards, and their identity by ^1H NMR and MS.

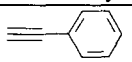
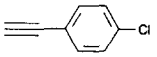
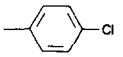
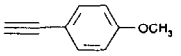
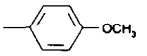
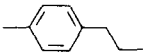
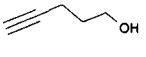
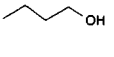
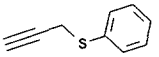
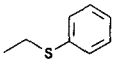
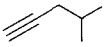
Scheme 2.



a: PPh_3, DEAD, THF, 4h, RT.; b: $Pd(PPh_3)_2Cl_2$, CuI, TMG, Dioxane, 90°C, 18h; c: NaOH 0.03 M/*i*-PrOH, 50°C, 5h.

The purity of **7** was routinely found to be > 80%, and the overall yields based upon loading of the iodide (0.2 mmol/g resin) ranged 50-80%. The only by-product observed arises from an incomplete cyclisation of **5** to **6**.[10] Therefore numerous alkynes were investigated to determine the scope and limitation of the reaction in solid-phase, especially with reference to the ratio **7/8**.[10] Table 2 summarises the results obtained.

Table 2. Indole synthesis in solid phase.

Entry	Alkyne	Ratio **7/8**	R_1	Assay %[a)]	Conversion (Yield)[b)]
1		97:3		83	>99 (72%)
2		> 99:1		81	>99 (52%)
3		> 99:1		85	>99 (48%)
4		> 99:1		87	>99 (55%)
5		99:1		90	>99 (95%)
6		> 99:1		78	>99 (81%)
7		92:8		94	>99 (82%)

[a)] Normalised HPLC area. [b)] Yields were evaluated by quantitative HPLC against standards.

A wide range of functionalities were tolerated in the reaction, and the non cyclised alkynes **8** were almost undetectable in most cases (table 2, entries 1, 2, 3, 4, and 6). Only small amounts of **8** (entry 7) were detected with more hindered alkynes.

In conclusion, we have showed that the synthesis of indoles by palladium-catalysed coupling of alkynes with iodoaniline derivatives can be effectively used on solid support with satisfactory yields and high purity. The mild reaction conditions are viewed as being well suited for automated combinatorial chemistry methodologies. Further work is in progress to extend this method of solid-phase synthesis to the preparation of 2,3 disubstituted indoles.

References and notes.

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4. See accompanying paper.
5. For recent examples of palladium catalysed synthesis of indoles, see Ezquerra, J.; Pedregal, C.; Lamas, J. M.; Barluenga, J.; Perez, M.; Garcia-Martin, M. A.; Gonzalez, J. M. *J. Org. Chem.* **1996**, *61*, 5804, and references herein.
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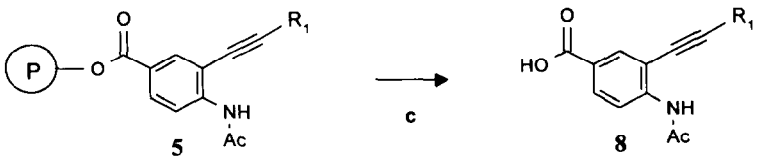
8. Candiani, I.; DeBernardinis, S.; Cabri, W.; Marchi, M.; Bedeschi, A.; Penco, S. *Synlett* **1993**, *3*, 269.
9. 3-iodo-4-acetamidobenzoic acid, methyl ester (**1a**): to a solution of *p*-aminobenzoic acid (5g) in 560 mL acetic acid/CH_2Cl_2, BTMA-ICl_2 (13g) was added. The reaction mixture was stirred overnight, and the solid was collected by filtration, washed, and dried. The crude iodo derivative (6.5g) was used in the next step. The solid was dissolved in acetic acid (80mL) and acetic anydride (4.7mL) was added. The mixture was strirred overnight, concentrated *in vacuo*, filtered, washed with water, and dried to afford 6.2g of the acid (**1b**). The acetylated product was then methylated with diazomethane. **1a** and **1b** gave satisfactory analysis.
10. Upon cleavage of the resin in the conditions described, **5** affords the acetylenic derivative **8** (scheme shown below). The amount of **8** is therefore a direct measure of the efficiency of the cyclisation step.



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