



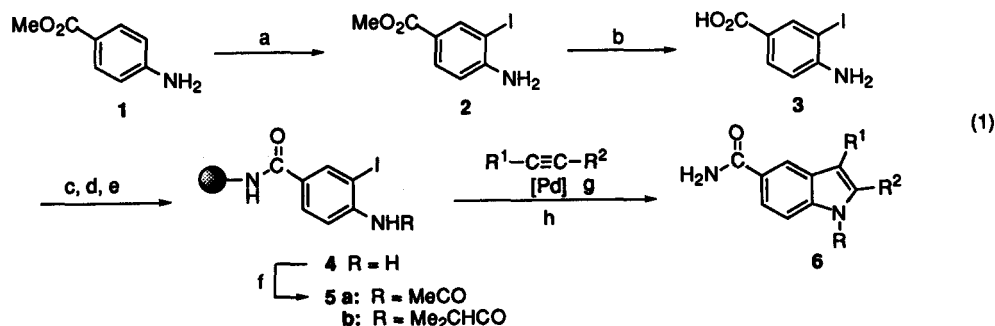
Synthesis of Trisubstituted Indoles on the Solid Phase via Palladium-Mediated Heteroannulation of Internal Alkynes

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Abstract: Palladium-mediated heteroannulation of internal alkynes with resin-bound *o*-iodoaniline derivatives **4** or **5a** provided diverse trisubstituted indoles **6** in good yields. The facile reaction of trimethylsilylalkynes afforded resin-bound precursors useful for obtaining other 2-substituted indole derivatives, such as **12**.
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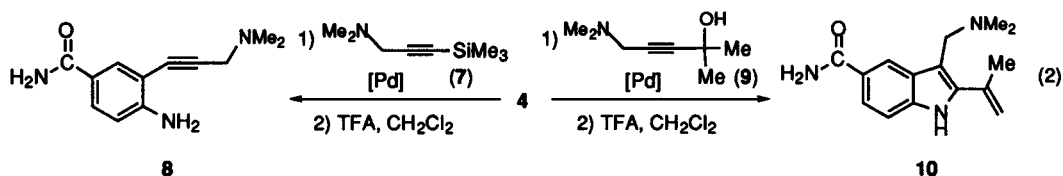
The generation of chemical libraries containing diverse, small organic molecules has attracted widespread attention.¹ Significant advances to this field can be brought about through the development of general resin-based methods for the construction of biologically interesting molecules via combinatorial or parallel synthesis. Heterocycles such as 1,4-benzodiazepine, hydantoin, and thiazolidine have proven to be worthwhile templates for chemical libraries.^{1b} In this vein, we recently developed a solid-phase method for the assembly of indole and benzofuran derivatives based on a palladium-mediated Heck-type cyclization.² Since the indole nucleus is present in a wide variety of biologically active compounds, and can serve as a template for orienting diverse substituents in space, we have adapted another organometallic method to the solid-phase synthesis of multiply substituted indoles. This palladium-mediated addition of acetylenes to resin-bound *o*-iodoanilines is powerful carbon-carbon bond-forming strategy that supplements the growing collection of organometallic reactions, such as Suzuki, Stille, and Heck couplings, which have been effectively transported to a solid-phase environment.³



Reagents and conditions: (a) I₂, Ag₂SO₄, 18 h, 54%; (b) Me₃SiOK, Et₂O, 3 d, 91%; (c) Fmoc-Cl, Na₂CO₃, dioxane-H₂O, 0 °C, 1 h; (d) NH₂ (Rink amide AM resin), DCC, HOBT, DMF, 26 h; (e) Piperidine, DMF; (f) MeCOCl or Me₂CHCOCl, pyridine, CH₂Cl₂, 2 h; (g) See footnote a in Table; (h) TFA, CH₂Cl₂, 1 h.

Larock⁴ developed a useful route to indole derivatives via palladium-mediated heteroannulation of internal alkynes with *o*-iodoanilines, which has been successfully employed by other researchers.⁵ Given the ready availability of various internal alkynes, we sought to adapt this elegant method to the solid-phase synthesis of diverse 2,3-disubstituted indoles. To test the chemistry on a solid support, we first established a resin-bound *o*-iodoaniline precursor. Thus, methyl 4-aminobenzoate (**1**) was treated with I_2/Ag_2SO_4 ⁶ to furnish mono-iodinated product **2**, hydrolysis ($KOSiMe_3$)⁷ of which gave acid **3**. This was protected with 9-fluorenylmethoxycarbonyl chloride (Fmoc-Cl) and loaded onto Rink amide AM resin (deprotected with 20% piperidine in DMF) by using dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt). Deprotection of the Fmoc group with piperidine afforded resin-bound precursor **4**, which was confirmed by resin cleavage with 30% CF_3CO_2H (TFA) in CH_2Cl_2 . Direct coupling of **3** to the resin without Fmoc protection also worked well under the same conditions, and no dimerization was observed.

The resin-bound *o*-iodoaniline **4** was tested for palladium-mediated reaction with an alkyne. Treatment of **4** with excess of 4-octyne, a catalytic amount of palladium(II) acetate (10 mol %), Ph_3P (20 mol %), LiCl, and K_2CO_3 in DMF at 80 °C was followed by resin cleavage with 30% TFA in CH_2Cl_2 .⁸ Analysis of the cleaved product by 1H NMR, MS, and HPLC showed that the desired 2,3-disubstituted indole predominated (Table, entry 1), indicating that palladium-mediated heteroannulation of internal alkyne occurred smoothly on solid support under the reaction conditions. This method was then applied to a variety of commercially available internal alkynes to afford indole derivatives in good to excellent yields (Table). With most of the unsymmetrical alkynes, the predominant product was the 2,3-disubstituted indole having the more sterically demanding group (e.g., *t*-Bu, Me_3Si) at the 2-position. The high regioselectivity presumably derives from insertion of the intermediate arylpalladium species [generated from oxidative addition of the aryl iodide to $Pd(0)$] into the alkyne from the less hindered side.⁴ The final product arises from indole ring closure via displacement of Pd in the resulting vinylpalladium intermediate with the aryl amine. The alkyne is able to carry alkyl, aryl, silyl, halo, hydroxyl, methoxy, amino, and ester groups. Tetrabutylammonium chloride was more effective and more reproducible than LiCl for the annulation of silylalkynes. With an electron-deficient alkyne we obtained a lower yield of indole (entry 6), and with alkynes **7** and **9** we obtained unusual products **8** and **10**. An acetylenic coupling product similar to **8** was also observed in solution-phase chemistry.^{5a,b} Vinyl-substituted indole **10** was presumably formed via dehydration of tertiary alcohol in the normal heteroannulated product under the acidic resin-cleavage conditions (TFA/ CH_2Cl_2).



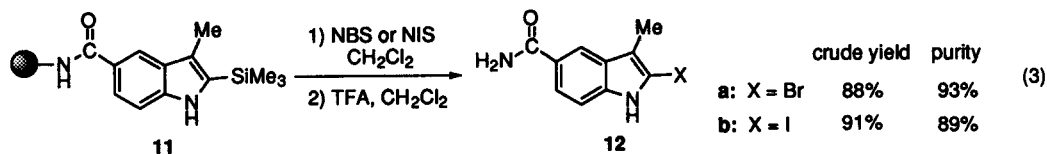
The facile heteroannulation of trimethylsilylalkynes with **4** provided useful resin-bound precursors to 2-unsubstituted and other 2-substituted indole derivatives via desilylation or other silyl function transformation. Protonolysis of a 2-trimethylsilylindole can be effected with $AlCl_3/CH_2Cl_2$,⁴ $HCl/MeOH$,^{5c} or TFA/water.⁹ During our mild resin cleavage with 30% TFA in CH_2Cl_2 over 1 h, the 2-trimethylsilyl substituent in the indole products was concomitantly removed to give 2-unsubstituted indoles (Table, entries 3, 5, 7-9, 12, 14). Thus,

Table. Pd-Mediated Synthesis of Indole on Solid Phase (4 or 5 → 6)^a

Entry	R	R ¹	R ²	Procedure	Time (h)	Yield (%) ^b	Purity (%) ^c
1	H	Pr	Pr	A	22	91	82
2	H	Me	<i>t</i> -Bu	A	15	87	84
3	H	Me	Me ₃ Si ^d	B	6	77 ^e	-
4	H	Me	Ph	A	20	86	72
5	H	Ph	Me ₃ Si ^d	B	6	56 ^{e,f}	-
6	H	CO ₂ Et	Ph	A	20	38 ^e	-
7	H	HOCH ₂ CH ₂	Me ₃ Si ^d	B	16	95	89
8	H	ClCH ₂ CH ₂	Me ₃ Si ^d	B	16	88	76
9	H	<i>m</i> -MeOC ₆ H ₄ CH ₂ CH ₂	Me ₃ Si ^d	B	16	90	92
10	H			A	22	63 ^e	-
11	Ac	Pr	Pr	C	16	95	84
12	Ac	Me	Me ₃ Si ^d	B	7	93	94
13	Me ₂ CHCO ^g	Me	<i>t</i> -Bu	A	120	75	53 ^h
14	Me ₂ CHCO	Me	Me ₃ Si ^d	B	120	100	53 ^h

^a Conditions for the Pd-mediated heteroannulation of alkynes with resin 4 or 5: alkyne (10-15 equiv), LiCl (1 equiv, procedure A) or Bu₄N⁺Cl⁻ (1 equiv, procedure B and C), base (5 equiv, procedure A: K₂CO₃; procedure B: Na₂CO₃; procedure C: KOAc), PPh₃ (0.2 equiv), Pd(OAc)₂ (0.1 equiv), DMF, 80 °C. ^b Crude yield unless noted otherwise (based on the loading level of resin 4). All products gave satisfactory analytical data. ^c Determined by reversed-phase HPLC. ^d Me₃Si group in the product was lost during resin cleavage with TFA/CH₂Cl₂, so R² = H in 6. ^e Purified by preparative TLC. ^f The regioisomer, 2-phenylindole derivative, was also isolated in 27% yield. ^g Me₂CHCO group was lost in the product, so R = H in 6. ^h About 20% of unreacted *o*-iodoanilide was observed by HPLC.

conversion of the trimethylsilyl group to bromo or iodo groups was accomplished on the solid phase with *N*-bromo- (NBS)⁴ or *N*-iodosuccinimide (NIS) in CH₂Cl₂ (11 → 12). The resin-bound 2-haloindoles could be converted to diverse 2-substituted indole derivatives via standard organometallic coupling reactions.



To achieve the diversity at N-1 of the indole, the resin-bound *o*-iodoaniline 4 was acylated with acetyl chloride or isobutyl chloride to give the anilides 5a and 5b, respectively. Heteroannulation of alkynes with 5a occurred smoothly to provide N-Ac indole derivatives (Table, entries 11 and 12). However, with a more bulky acyl group, 5b underwent reaction with alkynes much slowly and gave less clean products (entries 13 and 14). About 20% of unreacted *o*-iodoanilide was observed by HPLC in both entries even after 5 days at 80 °C. The N-COCHMe₂ group was found to stay only in entry 14, where product was 2-unsubstituted indole derivative

after TFA cleavage. With the product having a substituent at 2-position, the Me_2CHCO group was lost and the free NH indole derivative was obtained instead (entry 13). An attempt to prepare resin-bound *N*-benzyl-*o*-iodoaniline via reductive alkylation of **4** with benzaldehyde in the presence of sodium triacetoxyborohydride failed. If **4** were to be alkylated with benzyl bromide and base, *N,N*-dialkylation would be difficult to avoid since an excess of reagents are normally used for solid-phase reactions. Successful *N*-alkylation on the solid phase was achieved after indole ring formation. Thus, treatment of a resin-bound 2,3-dipropylindole (Table, entry 1) with benzyl bromide and NaH in DMF gave, after TFA cleavage, the *N*-benzylindole in 80% isolated yield.

In conclusion, we have described a facile solid-phase synthesis of trisubstituted indoles via palladium-mediated heteroannulation of internal alkynes. The heteroannulation of trimethylsilylalkynes affords useful resin-bound precursors to 2-unsubstituted or other 2-substituted indole derivatives. Given the ready availability of internal alkynes, this method should be valuable for the generation of indole-based combinatorial libraries.

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- Typical procedure: A suspension of resin **4** (124 mg, 0.06 mmol) in DMF (2 mL) was treated with 4-octyne (66 mg, 0.6 mmol), LiCl (2.6 mg, 0.06 mmol), K_2CO_3 (42 mg, 0.3 mmol), PPh_3 (3.2 mg, 0.012 mmol) and $\text{Pd}(\text{OAc})_2$ (1.4 mg, 0.006 mmol). After being stirred at 80 °C for 22 h, the black mixture was filtered, washed sequentially with DMF, MeOH, CH_2Cl_2 , and Et_2O , and dried *in vacuo*. One-half of the resin (62 mg) was treated with 30% TFA in CH_2Cl_2 for 40 min. ^1H NMR showed only one major product with 82% purity by HPLC, but a certain amount of TFA (present as a potassium salt) was observed by ^{13}C NMR. To remove any possible salt, the cleaved product was dissolved in EtOAc (20 mL) and the solution was washed with saturated NaHCO_3 (5 mL), then brine (5 mL), and dried (Na_2SO_4). Concentration *in vacuo* gave 6.7 mg (91% yield) of the 2,3-dipropylindole derivative (Table, entry 1). Alternatively, when the resin was washed with water-DMF (1:1) to remove K_2CO_3 before TFA cleavage, no significant amount of TFA salt was observed in the cleaved product.
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