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Heck Reaction on Solid Support: Synthesis of Indole Analogs

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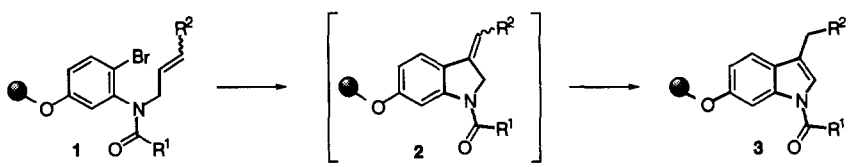
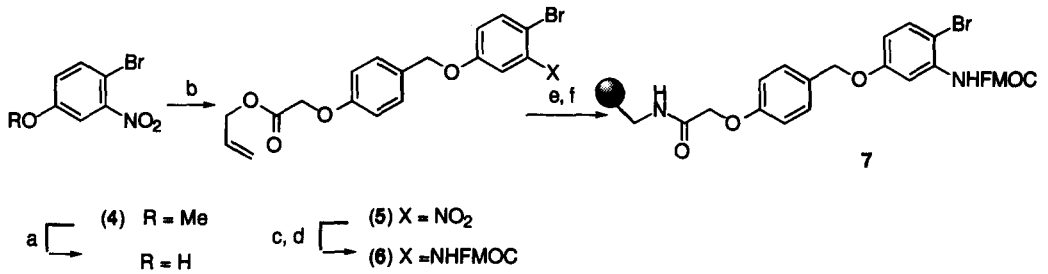
Abstract: The intramolecular Heck reaction of polymer bound arylhalides such as **1** affords indole analogs **11** in high yield. The precursor is readily assembled from acid chlorides and allylic bromides and offers an approach to diverse libraries of indole analogs. Copyright © 1996 Elsevier Science Ltd

Since the disclosure of the benzodiazepine libraries by Ellman's group in 1992,[1] there have been a number of reports on solid phase syntheses of heterocyclic compounds.[2] The success of these endeavors has provided the impetus for expanding the repertoire of chemical reactions that are compatible with solid phase synthesis. The results of such studies impacts pharmaceutical research both in the area of new lead discovery and in rapid structure-activity relationship studies through the combinatorial chemistry approach. Herein, we wish to report a novel synthesis of indole based libraries via an intramolecular Heck reaction on solid support.

The Heck reaction[3] has been applied to solid phase synthesis in an intermolecular[4] reaction for the synthesis of cinnamoyl derivatives and in an intramolecular macrocyclization[5] reaction. During the course of our recent study on indole based libraries, we postulated that an intramolecular Heck reaction of substrate **1** would proceed via a 5-*exo*-trig transition state to afford the intermediate **2** which should undergo an *exo* to *endo* double bond migration to provide the indole derivative **3** as the stable product. This would therefore provide a novel and versatile approach to diverse indole analogs on solid support.

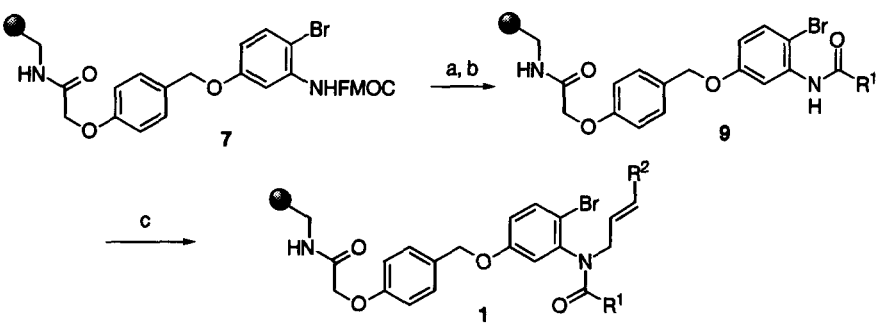


The polymer-bound starting material **7** was assembled as shown in Scheme 1. Commercially available 4-bromo-3-nitroanisole (**4**) was demethylated with BBr_3 in CH_2Cl_2, and the resulting phenol coupled to the acid labile linker, 4-(bromomethyl)-phenoxyacetic acid allyl ester[1] to afford **5** in 91% yield. The nitro group was reduced with $Na_2S_2O_4$ to afford the primary amine which was protected as its FMOC derivative to afford compound **6.** Removal of the allyl ester[1] provided the carboxylic acid which was then coupled to the solid support (TentaGel S-NH_2[6]) to provide the polymer-bound derivative **7.**



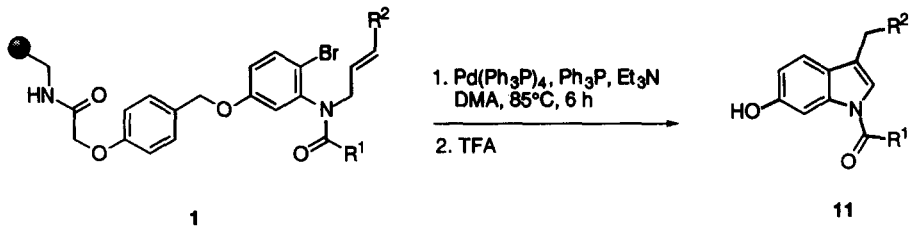
Scheme 1: a) BBr_3 (2.5 eq), CH_2Cl_2, -78 to 22°C, 18 h, (70%); b) allyl 2-(4-bromomethyl)-phenoxyacetate (1 eq), K_2CO_3(2.2 eq), DMF, 22°C, 3 h, (91%); c) $Na_2S_2O_4$ (8 eq), THF/H_2O (1:1), 22°C, 4 h, (64%); d) FMOCCl, (1.05 eq), pyridine (1.2 eq), CH_2Cl_2, 22°C, 1 h, (96%); e) $Pd(Ph_3P)_4$ (0.02 eq), Bu_3SnH (1.1 eq), CH_2Cl_2, 22°C, 40 min, (71%); f) TentaGel S-NH_2 (0.27 mmol/g), DIC (4.4 eq), HOBT (4.4 eq), DMF, 22°C, 2 d.

Solid-phase acylation and alkylation of **7** was initiated by removal of the FMOC protecting group followed by acylation of the resulting free amine with the acid chloride **8** to afford the anilide **9**. Alkylation of the anilide **9** with the allylic bromide **10** in the presence of lithium benzyloxazolidinone completed the introduction of the functional groups R^1 and R^2, providing the Heck reaction precursor **1** (Scheme 2)[7]. The alkylation reactions were regularly repeated to ensure complete alkylation.



Scheme 2: a) 20% piperidine in DMF, 22°C, 30 min; b) R^1COCl (**8**), pyridine, CH_2Cl_2, 22°C, 2 h; c) *n*-BuLi, 4-benzyl-2-oxazolidinone, $R^2CHCHCH_2Br$ (**10**), THF-DMF, -78 to 22°C, 6 h, repeat.

Compound **1** was then subjected to Heck reaction conditions (Scheme 3). Thus, a catalytic amount of $Pd(Ph_3P)_4$ with Ph_3P and Et_3N were added to the suspension of the resin in anhydrous N,N-dimethylacetamide (DMA), and the reaction was agitated at 85°C under N_2 for 5 h to assure complete conversion as monitored by reversed phase HPLC. An inert atmosphere is essential since Pd(0) is oxidized in air at elevated temperatures resulting in reductive debromination of **1**. Cleavage of the final product from the resin was carried out in TFA without the addition of a scavenger. The desired indole analogs **11** were obtained in 65-94% crude yields based on the loading level of polymer bound starting material **7** (Table 1). All compounds provided satisfactory NMR and LC/MS spectra.[8]



1 11

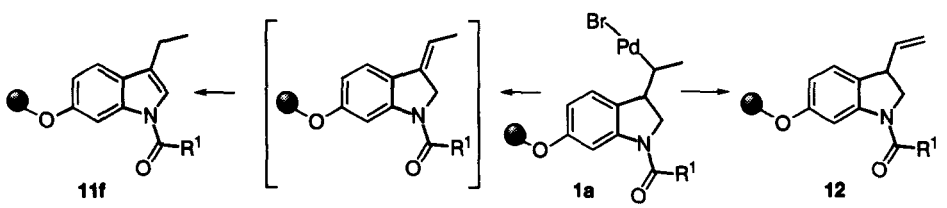
Scheme 3

Table 1. Heck Reaction-Mediated Synthesis of Indole Analogs

No.	R^1	R^2	Yield (%)[a]	Purity[b]
11a	Et	H	90	88
11b	Et	Ph	94	93
11c	i-Pr	Me	92	91
11d	Ph	H	70	48
11e	Ph	Ph	65	55
11f/12	Ph	Me	90	25[c]
11g	3-MeO-Ph	H	90	89
11h	3-MeO-Ph	Ph	83	75

[a] Yields reported are crude yields based on polymer loading. [b] Purity was determined by HPLC (Dynamax, 60A, C-18, 20-80% CH_3CN in H_2O containing 0.1% TFA). [c] The major product (55%) is the indoline analog **12.** All compounds were characterized by ^1H NMR and LC/MS. Analytically pure compounds provide satisfactory HRMS analysis.

The mechanism for the conversion of **1** to the product **11** appears to be a general pathway providing uniquely the desired indoles **11a-h** (Table 1) except for analog **11f.** In this case, the indoline product **12** was observed as the major product. This is easily understood given that the reductive β-elimination of palladium in the Heck intermediate **1a** is sterically less hindered and more entropically favored towards the elimination of a terminal hydrogen resulting in the exocyclic double bond-containing product **12** (Scheme 4).



11f 1a 12

Scheme 4

In summary, we have demonstrated the feasibility of indole based library synthesis via an intramolecular Heck reaction on solid support. Given the large pool of commercialIly available acid chlorides and allylic alkylating agents and the mild reaction conditions, this methodology is readily amenable to automation thereby providing access to a large number of substituted indoles.

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7. General Procedure for Indole Synthesis: Resin bound **7** was suspended in 20% piperidine in DMF and vortexed for 30 min. The resin was washed with DMF and CH_2Cl_2, and treated with the acid chloride **8** (5 eq) and pyridine (7 eq) in CH_2Cl_2 at 22°C for 2 h. After washing with DMF, i-PrOH and CH_2Cl_2, the resin bound **9** was slurried in DMF and a solution of lithium benzyloxazolidinone (15 eq) in THF was added. The reaction was vortexed at 22°C for 1 h followed by the addition of the allylic halide **10** (30 eq). After vortexing for 6 h, the alkylation procedure was repeated. The resin was rinsed with DMF, i-PrOH and CH_2Cl_2. To the resin bound **1** was added $Pd(Ph_3P)_4$ (0.5 eq), Ph_3P (2 eq), Et_3N (13 eq) and DMA. The reaction tube was evacuated then sealed under N_2 and heated to 85-90°C for 5 h. This procedure was repeated. The resin was then washed with DMF, a solution of $Et_2NCS_2Na\text{-}3H_2O$ in DMF (0.2 M), DMF, i-PrOH, CH_2Cl_2. Cleavage with 95% TFA in H_2O for 3 h afforded, after concentration, the indole analogs **11**. An analytical sample was purified by flash chromatography (SiO_2, 10-30% EtOAc-hexane gradient elution).
8. For **11d:** ^1H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, J = 2.4 Hz, 1H), 7.73 (d, J = 7.0 Hz, 2H), 7.52 - 7.63 (m, 3H), 7.37 (d, J = 8.2 Hz, 1H), 6.91 - 6.94 (m, 2H), 6.49 (br s, 1H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.9, 154.0, 137.6, 136.9, 133.4, 131.4, 130.9 (2), 126.7 (2), 124.8, 117.1, 116.2, 114.3, 102.4, 9.8; IR (neat) ν_{max} 3244, 2970, 1650, 1395, 1346, 1202; HRMS (EI) calc. for $C_{16}H_{13}NO_2$ m/z 251.0946, found 251.0941.

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