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Facile Substitution of Resin-Bound Indoles via the Mannich Reaction[1]

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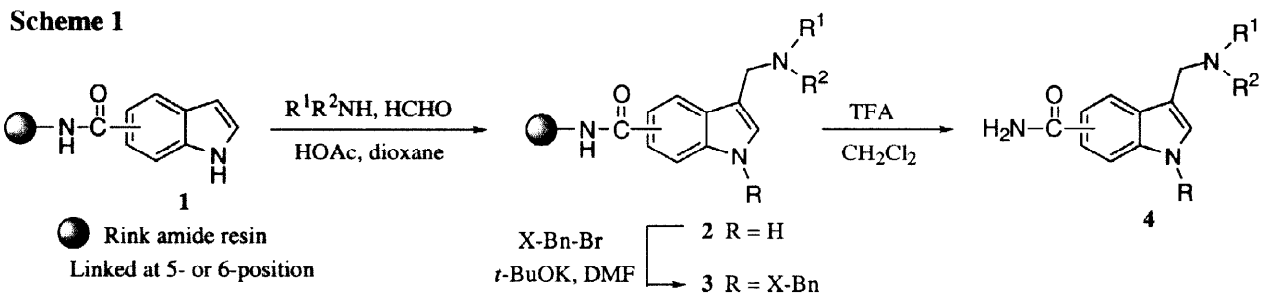
Abstract: Mannich reaction of resin-bound indoles **1** provided 3-aminomethylindoles **4**. Palladium-mediated heteroannulation of terminal alkynes with resin-bound *o*-iodosulfonanilide **7**, followed by Mannich reaction, afforded 2-substituted-3-aminomethylindoles **11**. Nucleophilic substitution of resin-bound 3-dimethylaminomethylindole **12** with KCN or ethyl 2-nitroacetate gave 3-substituted indoles **13** and **14**, respectively. High yields and purities were realized for **4**, **11**, **13**, and **14**.

Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. Thus, the development of strategies for the generation of heterocyclic libraries on solid supports has sparked a great deal of interest.[2] For example, several useful solid-phase approaches to the construction of indoles have been reported.[3] The Mannich reaction is an important process for carbon-carbon bond formation, which has seen wide application for the preparation of diverse aminoalkyl derivatives (so-called "Mannich bases").[4] In fact, 3-aminomethylindoles are particularly interesting on account of their biological activity and use in the total synthesis of ergot alkaloids.[5] Herein, we report the successful application of the Mannich reaction for the solid-phase synthesis of 3-aminomethylindoles and their utility for nucleophilic substitution reactions. We also report an efficient solid-phase synthesis of difficultly accessible 2-substituted-3-aminomethylindoles from a resin-bound *o*-iodosulfonanilide via tandem sequence involving palladium-mediated heteroannulation of a terminal alkyne and Mannich condensation.[6]

Scheme 1



Commercially available indole 5- or 6-carboxylic acid was coupled to the Rink amide resin (deprotected with 20% piperidine in DMF) by using DCC and HOBt to yield resin-bound indoles **1**. Mannich reaction of **1** with formaldehyde (1.5 mol equiv) and a secondary amine (1.5 mol equiv) in the presence of HOAc occurred smoothly on the solid support at 23 °C to give, after resin cleavage (30% TFA in CH_2Cl_2), 3-aminomethylindoles **4** (R = H) in excellent yields and high purity (Table 1). The reactions generally worked better in 1,4-

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dioxane-HOAc (4:1) than in HOAc, which is a common solvent used for Mannich reactions in the solution phase. A primary amine, e.g., $BnNH_2$, also gave satisfactory results under our conditions. It is noteworthy that indole 1,3-di-Mannich bases were produced by using a large excess of formaldehyde and the amine. When the Mannich reaction was followed by an alkylation, with *t*-BuOK as a base (**2** --> **3**), we were able to obtain 1-substituted-3-aminomethylindoles **4** (R = X-Bn) after resin cleavage (Table 1).

Table 1. Mannich Reaction Products **4**[a]

linkage position	R	R^1R^2NH	Yield[b] (%)	Purity[c] (%)	linkage position	R	R^1R^2NH	Yield[b] (%)	Purity[c] (%)
5-	H	pyrrolidine	93	100	6-	H	pyrrolidine	95	86
5-	H	piperidine	90	93	6-	H	Et_2NH	95	89
5-	H	Me_2NH	95	88	6-	Bn	piperidine	93	84[d]
5-	H	Bn(Me)NH	95	83	5-	4-FBn	pyrrolidine	100	88[d]
5-	H	$BnNH_2$	90	78	6-	4-MeBn	piperidine	100	82[d]

[a] Conditions for the Mannich reactions with resins **1**: amine (1.5 mol equiv), HCHO (1.5 mol equiv), HOAc/1,4-dioxane (1:4), 1.5 h. For the alkylations: X-Bn-Br (3 mol equiv), *t*-BuOK (3 mol equiv), DMF, 3 h; NaH and K_2CO_3 gave less clean alkylation. For the resin cleavage: 30% TFA in CH_2Cl_2, 1 h; the cleaved products were triturated with ether.

[b] Crude yields (based on the loading level of resin **1**). All products gave satisfactory analytical data.

[c] Determined by reverse-phase HPLC unless noted otherwise (linear gradient, 1:9 to 9:1, MeCN/water with 0.1% TFA).

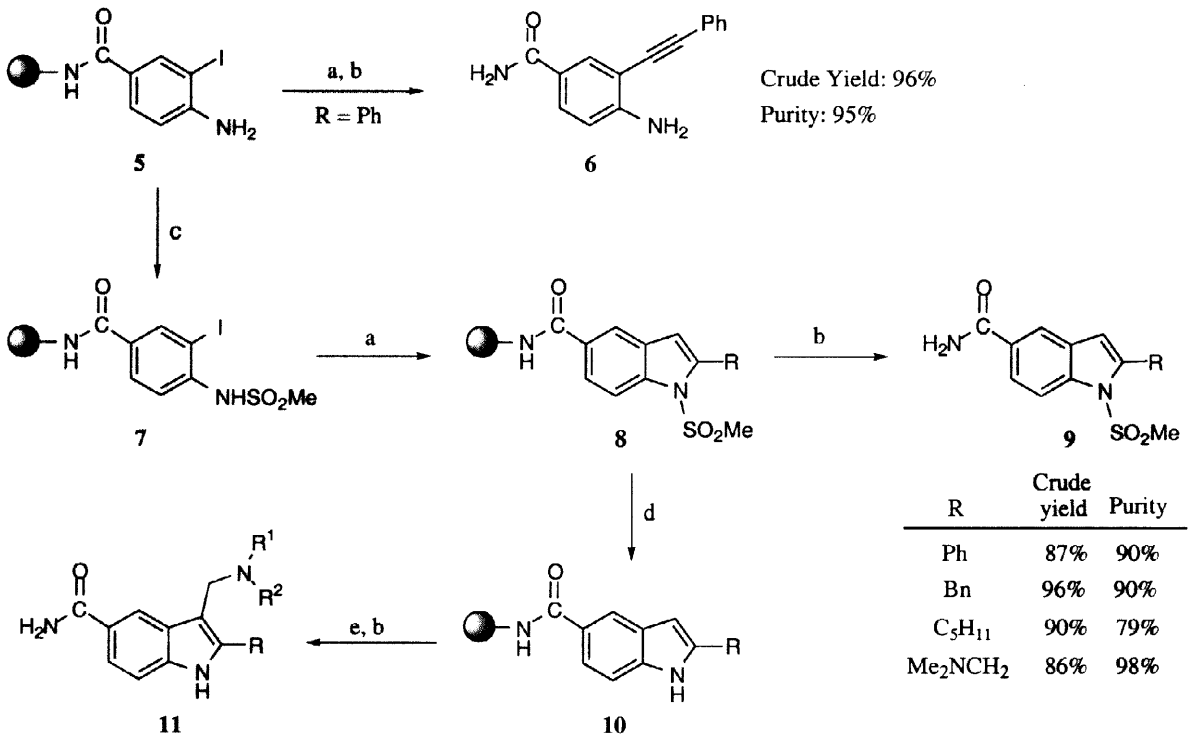
[d] Determined by ^1H NMR.

We then sought to apply our solid-phase reaction conditions to 2-substituted indoles to obtain the corresponding 3-aminomethyl adducts. First, the resin-bound 2-substituted indoles had to be established. Common approaches to 2-substituted indoles include the Fischer indole synthesis[7] and group-directed 2-lithiation of indoles.[8] Although we recently developed a facile solid-phase synthesis of 2,3-disubstituted indoles via palladium-mediated heteroannulation of internal alkynes with a resin-bound *o*-iodoaniline **5**,[3b] attempts to extend this method to 2-substituted indoles via heteroannulation of terminal alkynes (e.g., phenylacetylene) failed, as the sp^2-sp coupling product, **6**, was formed instead (100% yield, 35% purity; Scheme 2). Modified conditions, involving $Pd(PPh_3)_2Cl_2$ as a catalyst in the presence of CuI (Scheme 2, reaction a), afforded much cleaner **6** (96% yield; 95% purity). Again, no indole was formed, suggesting that the organopalladium intermediate[9] is not reactive enough to cyclize to the indole. To activate the intermediate, we introduced a methanesulfonyl group onto the aniline nitrogen, as noted by Yamanaka et al.[10] for solution-phase indole synthesis. Thus, resin **5** was derivatized with MsCl and pyridine to give **7**. Under the same conditions that converted **5** into **6** (Scheme 2, reaction a), palladium-mediated heteroannulation of terminal alkynes (R = Ph, Bn, pentyl, Me_2NCH_2) with **7** now proceeded smoothly and, following resin cleavage, furnished 2-substituted indoles **9** with good yields and purities (Scheme 2). Remarkably, the yields for this solid-phase indole synthesis are actually much better than those for the solution-phase synthesis (31-71%).[10] The methanesulfonyl group in **8** was easily removed by treating the resins with 2% KOH in MeOH-DMF to furnish **10**.

Resin-bound 2-substituted indoles **10** were then subjected to the Mannich reaction under the conditions used for **1**. The reactions were complete in 1.5 h at 23 °C to afford, after resin cleavage, 2-substituted-3-

aminomethylindoles **11** with good yields and purities (Table 2). In contrast to the reactions of 2-unsubstituted indoles **1**, no 1,3-di-Mannich bases were observed, even in the presence of 8 mol equiv of HCHO and amine. An attempt to effect the Mannich reaction with **8** (R = Ph) failed, presumably because of deactivation of the indole ring by the strong electron-withdrawing group at N-1.

Scheme 2



R	Crude yield	Purity
Ph	87%	90%
Bn	96%	90%
C_5H_{11}	90%	79%
Me_2NCH_2	86%	98%

Reagents and conditions: (a) HC≡C–R (10 mol equiv), $Pd(PPh_3)_2Cl_2$ (0.1 mol equiv), CuI (0.2 mol equiv), Et_3N-DMF (1:5), 80 °C, 5-16 h. (b) 30% TFA in CH_2Cl_2, 1 h. (c) $MeSO_2Cl$, pyridine, CH_2Cl_2, 28 h. (d) 2% KOH in MeOH-DMF (1:2), 23-40 °C, 1-3 h. (e) R^1R^2NH (2-8 mol equiv), HCHO (2-8 mol equiv), HOAc/1,4-dioxane (1:4), 1.5 h.

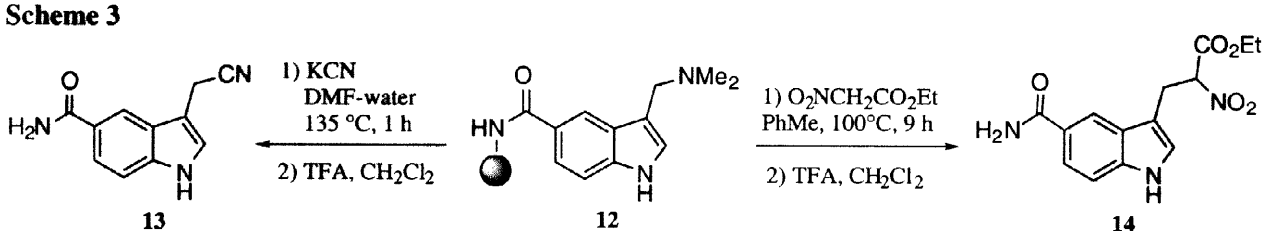
Table 2. Mannich Reaction Products **11**

R	R^1R^2NH	Yield (%)[a]	Purity (%)[b]	R	R^1R^2NH	Yield (%)[a]	Purity (%)[b]
Ph	pyrrolidine	90	80	Bn	Bn(Me)NH	76	93
Ph	piperidine	85	86	C_5H_{11}	pyrrolidine	91	94
Ph	Et_2NH	86	93	C_5H_{11}	piperidine	94	89
Bn	pyrrolidine	84	97	C_5H_{11}	Pr_2NH	81	90
Bn	Me_2NH	95	92	Me_2NCH_2	pyrrolidine	71	98

[a] Crude yields for 4 steps, based on the loading level of resin **7**. All products gave satisfactory analytical data.
[b] Determined by reverse-phase HPLC.

Substitutions of a Mannich base of indole (e.g., 3-dimethylaminomethylindole) with nucleophiles can provide a variety of 3-substituted indoles, which can be important synthetic intermediates for the synthesis of ergot alkaloids.[10] To test such substitution reactions on the solid support, we treated resin-bound 3-dimethylaminomethylindole **12** with KCN (3 equiv) or ethyl 2-nitroacetate (5 equiv). The nucleophilic substitutions occurred smoothly under standard conditions to give, after resin cleavage, indoles **13** and **14**, respectively.

Scheme 3



13 Crude yield: 95%; purity: 94%

12

14 Crude yield: 95%; purity: 80%

In conclusion, we have developed a facile solid-phase synthesis of 3-aminomethylindoles via a Mannich reaction and an efficient solid-phase synthesis of 2-substituted-3-aminomethylindoles via palladium-mediated heteroannulation of terminal alkynes followed by a Mannich reaction. We have also illustrated the successful nuleophilic substitution of resin-bound 3-dimethylaminomethylindole for the synthesis of 3-substituted indoles. These methods should prove quite valuable for the generation of biologically interesting indole-based chemical libraries and for the solid-phase assembly of indole alkaloids.

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References and Notes

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