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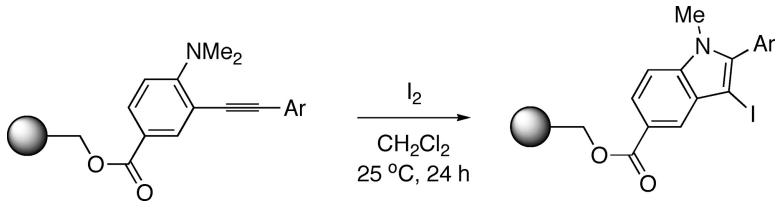

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Solid-Phase Synthesis of 1,2,3-Trisubstituted Indoles and 2,3-Disubstituted Benzofurans via Iodocyclization

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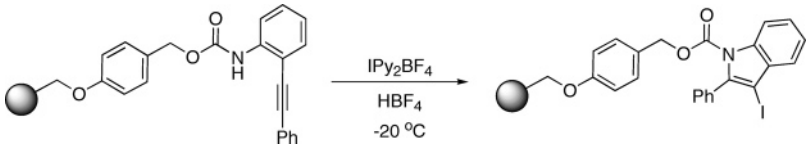
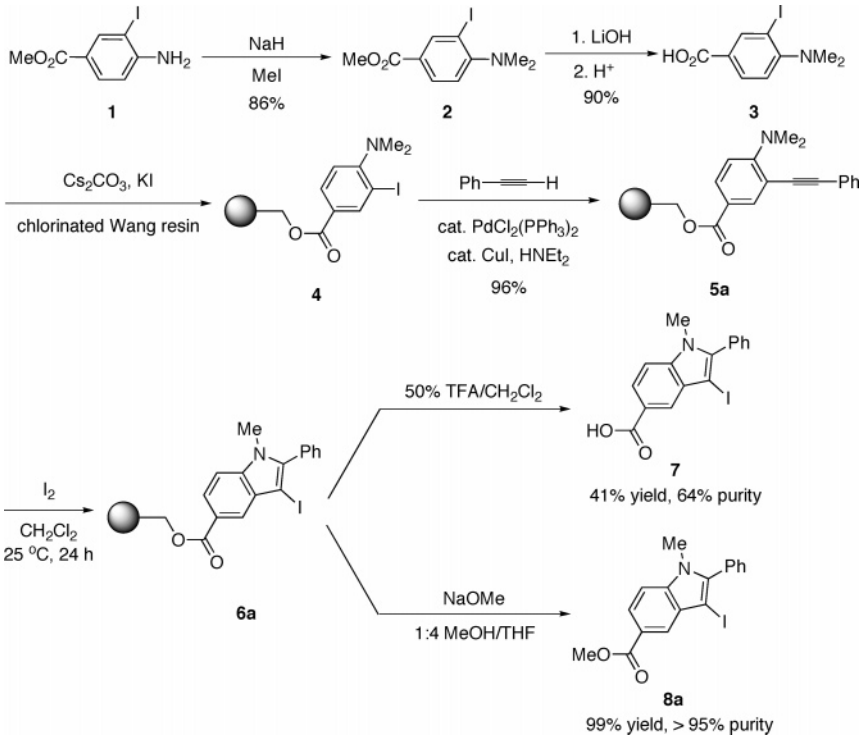
Introduction. The combinatorial synthesis of diversified heterocyclic compounds that are subsequently screened for biological activity is a promising strategy for developing new pharmaceutical lead structures.[1] Among the various possible libraries of low molecular weight compounds, nitrogen-containing heterocycles, which are recognized as pharmacophores, are particularly attractive.[2] One particular molecular scaffold of interest is the indole scaffold, since indoles are known to exhibit a broad range of biological activity and are found in numerous natural products.[3] Consequently, there is a great demand for their evaluation as potential drug candidates. With recent advances in solid-phase synthesis, many combinatorial approaches for generating indole libraries have been described, with each method providing synthetic access to indole products bearing different substitution patterns.[4] To the best of our knowledge, the only solid-phase synthesis of 3-iodoindoles via iodocyclization was reported by Barluenga, who included only one example of an indole (Scheme 1).[5] That reaction was carried out at low temperature by using expensive IPy_2BF_4 and the strong acid HBF_4 on an alkynyl carbamate, and the yield was low.

The emergence of solid-phase organic synthesis has encouraged the transfer of solution-phase reactions to the solid phase. Many useful reactions have now been optimized for solid-phase conditions, even though the transfer of standard solution-phase reactions to the solid-phase can often be problematic.[6] Recently, we disclosed the solution-phase synthesis of 3-iodoindoles by the iodocyclization of *N*,*N*-dimethyl-2-(1-alkynyl)anilines.[7] This strategy provides an ideal starting point for the synthesis of diverse indoles on solid-phase. Furthermore, the ability to introduce various additional substituents into the resulting indoles using known Pd chemistry would further expand the scope of this solid-phase indole synthesis, since Pd chemistry on a solid phase has been well-developed.[8] We now report the successful transfer of our solution-phase synthesis of 3-iodoindoles via

Scheme 1



Scheme 2



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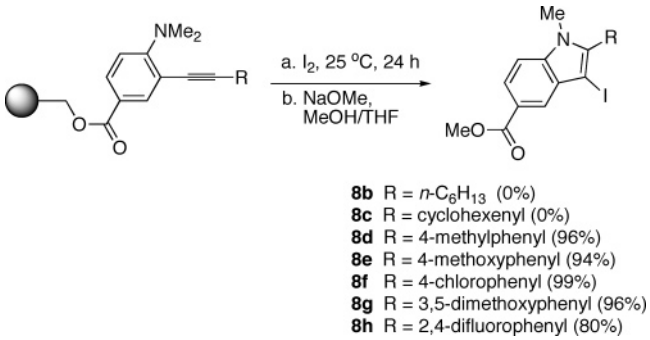
Scheme 3



8b R = *n*-C_6H_{13} (0%)
8c R = cyclohexenyl (0%)
8d R = 4-methylphenyl (96%)
8e R = 4-methoxyphenyl (94%)
8f R = 4-chlorophenyl (99%)
8g R = 3,5-dimethoxyphenyl (96%)
8h R = 2,4-difluorophenyl (80%)

iodocyclization to the solid phase. 3-Iodobenzofurans can also be synthesized on the basis of a similar strategy.

Results and Discussion. Our general reaction sequence for the solid-phase synthesis of the 3-iodoindoles is outlined in Scheme 2. Methylation of the amino group of **1** using NaH and MeI, followed by saponification with LiOH in THF/H_2O, afforded the carboxylic acid **3**. The benzoic acid **3** was anchored to commercially available Wang chlorinated resin (3.0 equiv of Cs_2CO_3, 0.5 equiv of KI, 1.5 equiv of acid per Cl residue, DMF, 80 °C), providing resin **4** with a loading of 0.67 mmol/g.[9] The Sonogashira reaction of **4** under standard reaction conditions [catalyst $PdCl_2(PPh_3)_2$, catatalyst CuI, $HNEt_2$] afforded the immobilized alkynylaniline **5a** in excellent yield and purity.[10] The resin-bound anilines **4** and **5a** have been verified by cleaving a small sample of the resin with 50% TFA/CH_2Cl_2 (1 h, room temperature); however, in later work, aniline **4** and all Sonogashira products have been verified by NaOMe cleavage. The cyclization of **5a** to the polymer-bound 3-iodoindole **6a** was carried out in CH_2Cl_2 using a 3-fold excess of I_2 at room temperature for 24 h. The resulting polymer-bound indole **6a** was cleaved from the resin using 50% TFA/CH_2Cl_2 (1 h, room temperature). To our disappointment, the desired 3-iodoindole **7** was isolated in only a 40% yield with poor purity. We reasoned that the 3-iodoindole might be unstable under the strongly acidic conditions used to cleave the indole from the solid support. Thus, pure 3-iodo-1-methyl-2-phenylindole was subjected to 50% TFA/CH_2Cl_2 for 1 h at room temperature. A complex mixture was obtained. We were gratified to see that when the polymer-bond indole **6a** was cleaved from the resin by basic transesterification with excess NaOMe in a 1:4 mixture of MeOH/THF, the corresponding methyl indole-5-carboxylate **8a** was obtained in a 99% yield with excellent purity.

With an effective set of reaction conditions for the solid-phase iodocyclization established, the conversion of a range of alkynylanilines into the desired 3-iodoindoles and subsequent cleavage of the products from the resin was examined (Scheme 3). Of the polymer-bound alkynylanilines examined, the R substituents that did not work were *n*-hexyl and 1-cyclohexenyl, even though they worked very well in the corresponding solution-phase chemistry.[7] The starting materials were consumed, but none of the desired products were obtained after cleavage. This is undoubtedly due to the heterogeneous nature of the reaction when carried out on the solid phase. When the R group is an aryl group, the cyclization proceeds smoothly in 24 h at room temperature. The effect of various aryl substituents on the cyclization has been examined. The desired 3-iodoindoles were obtained in 80−99% yields and >95% purities independent of the nature of the substituent on the phenyl moiety. The slightly lower yield obtained when the 2,4-difluorophenyl group is employed might be due to either a steric effect or inductive electron withdrawal from the triple bond. In each case, cleavage of a small sample of the resin by basic transesterification with excess NaOMe in a 1:4 mixture of MeOH/THF led to the crude product, whose purity was estimated by ^1H NMR spectroscopy and GC/MS analysis. The crude products were then further purified by flash chromatography to give the final isolated yields of products reported, on the basis of the loading of the polymer-bound alkynylaniline.

One advantage of our iodocyclization process is that the iodo-containing products present on the solid support can be further elaborated through various palladium-mediated coupling reactions. For example, the Sonagashira coupling[10] and Suzuki coupling[11] of **6a** afforded the corresponding coupling products **9** and **10** in 91% and 80% yields,

Scheme 4

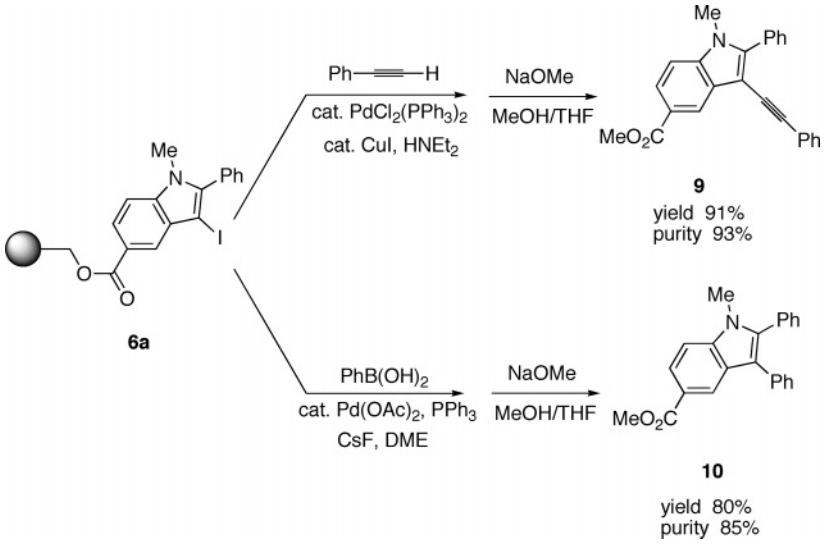
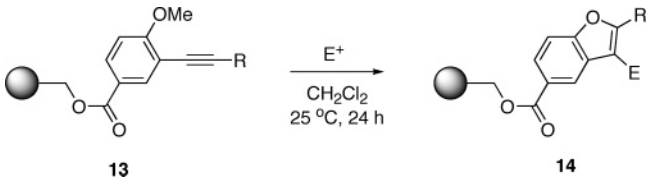
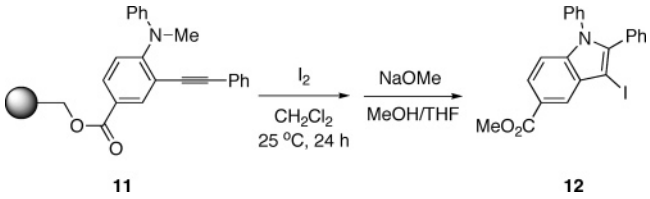


Table 1

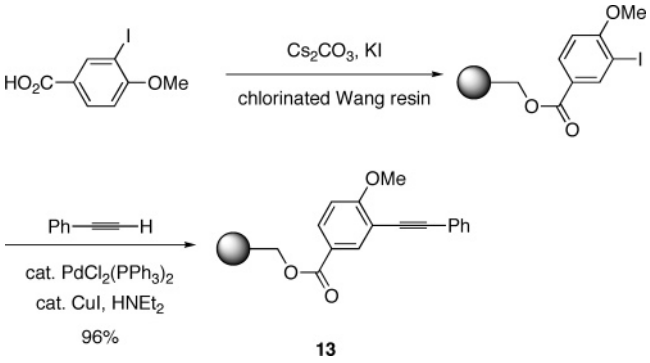


entry	14	R	electrophile	yield (%)	purity (%)
1	**14a**	Ph	I_2	46	81
2	**14a**	Ph	ICl	52	>95
3	**14b**	Ph	*p*-$NO_2C_6H_4SCl$	44	82
4	**14c**	*p*-Tol	ICl	72	>95

Scheme 5



Scheme 6



respectively, as determined by transesterification and isolation of the corresponding methyl esters (Scheme 4).

The ability to introduce diverse substituents on the 1-position of the indole would further expand the scope of this solid-phase indole chemistry. Toward this end, resin **11** was prepared and subjected to our standard cyclization conditions. The reaction afforded exclusively 3-iodo-1-phenylindole **12** in an 82% yield and 92% purity as determined by transesterification and isolation (Scheme 5).

We have also investigated the synthesis of 3-iodobenzofurans on a solid phase using a similar strategy. The resin **13** was prepared by using a procedure that was similar to that used for resin **5a** (Scheme 6). When using our standard cyclization conditions (4.0 equiv of I_2 in CH_2Cl_2 for 24 h), the desired 3-iodobenzofuran **14** can be obtained in a fair yield and good purity, as determined by transesterification and isolation (Table 1, entry 1). When the stronger electrophile ICl was employed, the yield was improved to 52% and the purity to >95% (entry 2). Interestingly, *p*-$NO_2C_6H_4SCl$ can also be employed as an electrophile, affording the benzofuran product **14b** in a 44% yield and good purity (entry 3), even though this electrophile failed to afford any cyclization product in the previous solid-phase synthesis of indoles. When R is a slightly more electron-rich 4-methylphenyl group, the yield using ICl increased to 72% (entry 4).

Conclusions. In summary, we have developed an efficient method for the synthesis of 3-iodoindoles on a solid support which provides excellent yields and purities under very mild reaction conditions. The 3-iodoindoles bound to polystyrene are versatile building blocks for the preparation of various 3-substituted indoles through palladium-mediated coupling reactions. This approach allows one to introduce diverse substituents into the indole N-1, C-2, C-3, and C-5 positions. Hence, our protocol can be applied to the combinatorial library synthesis of a diverse collection of structurally novel indoles. We will report on the application of this methodology for the synthesis of additional libraries in due course. Polymer-bound 3-iodobenzofurans can also be prepared using a similar strategy.

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Supporting Information Available. General experimental procedures and spectral data for the compounds listed in Table 1 and Schemes 2−4. This material is available free of charge via the Internet at http://pubs.acs.org.

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