Chinese Chemical Letters Vol. 13, No. 8, pp 705 – 707, 2002
http://www.imm.ac.cn/journal/ccl/html

Soluble Polymer-supported Synthesis of Indoles *via* Palladium-mediat -ed Heteroannulation of Terminal Alkynes with *o*-Iodoanilines

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Abstract: A soluble polymer-supported synthesis of indoles *via* palladium-mediated hetero-annulation of terminal alkynes with *o*-iodoanilines has been described. The protocol provides a useful tool for constructing combinatorial indole libraries.

Keywords: Indole, polyethylene glycol(PEG), liquid-phase.

Recently, the liquid-phase synthesis of small organic molecules has been a subject of intense research activity[1] since it profits from both the advantageous features of homogeneous solution chemistry and of solid-phase methods. Substituted indoles offer a high degree of structure diversity and have proven to be very important in medicinal chemistry. There have been a few solid-phase methods for the generation of indole-based combinatorial libraries[2]. As we know, however, so far little work has been done to construct indole derivatives using PEG as support on the liquid- phase.

In connection with our research on the PEG as soluble support in liquid-phase synthesis[3], we wish to report here the first synthesis of indoles on PEG 4000 *via* palladium-mediated heteroannulation of terminal alkynes with o-iodoaniline derivatives.

As shown in **Scheme 1,** ethyl 4-aminobenzoate **2** was treated with I_2/Ag_2SO_4[4], followed by hydrolysis, to give 4-amino-3-iodobenzoic acid **4** . **4** was attached to the PEG 4000 support by reaction with the modified PEG support **1** in the presence of K_2CO_3 in DMF at 65°C for 16 h. According to the Yamanaka s procedure for solution-phase synthesis of indole[5], the polymer-supported 4-amino-3-iodobenzoat **5** was mesylated by $MeSO_2Cl$, and then reacted with a terminal alkyne in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI in DMF and Et_3N at 80°C for 12 h to afford indole **7**. Under the same conditions, if the amino group of **5** was not mesylated *prior to* coupling with a terminal alkyne, a internal alkyne **8**, instead of 2-substituted indole **7,** was isolated. The aryl iodide **6** is coupled with a terminal alkyne to form the sp^2-sp coupling product, which then undergoes an intramolecular cyclization to form indole ring **7**. In this process, activation of the amine is required[5]. Therefore, when the amine is activated by a strong electron-withdrawing group, sulfonyl, the sp^2-sp coupling and the indole cyclization can occur in one pot under relatively mild conditions[5].

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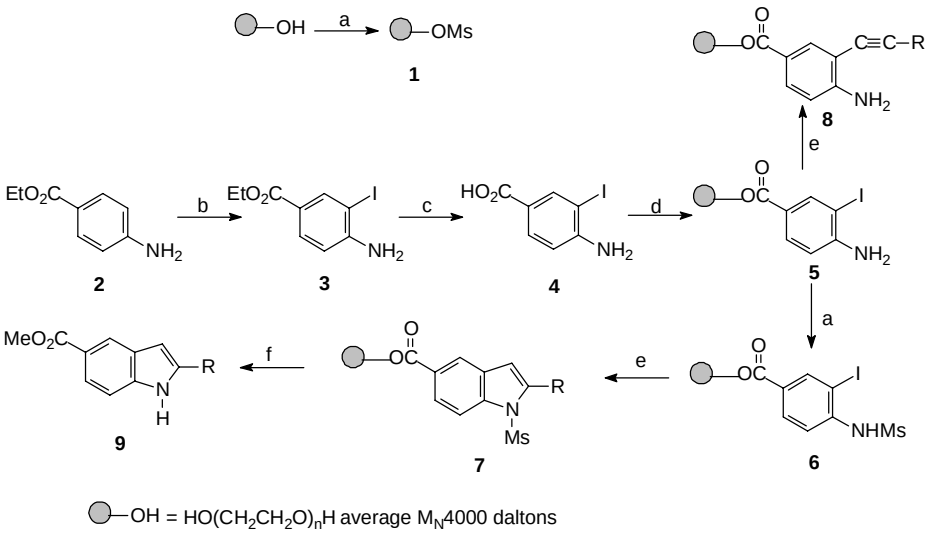
The cleavage of the indoles from the polymer was studied so that a N-unsubstituted indole would directly yield. It was found that transesterification of compounds **7** with methanol in the presence of CH_3ONa at reflux resulted in 2-substituted indole **9** in excellent yield and purity (**Table 1**). It is important that the yields and purity for this protocol are actually much better than those for solid-phase synthesis[2]. The purity is enough for primary biological screening without further purification.

Scheme 1



Reagents and Conditions: a) $MeSO_2Cl$, $(C_8H_{17})_3N$, CH_2Cl_2, RT; b) I_2, Ag_2SO_4, EtOH; c) i) 4 mol/L NaOH, EtOH, ii) 5 Mol/L HCl; d) PEG-OMs, K_2CO_3, DMF, 65°C; e) RC≡CH, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 80°C; f) CH_3ONa, CH_3OH.

Table 1 Soluble polymer-supported synthesis of indoles[i]

Entry	R	M^+	Yield[ii](%)	Purity[iii](%)
1	n-C_4H_9	231	87.4	99.2
2	n-C_5H_{11}	245	83.7	98.5
3	n-C_6H_{13}	259	81.9	97.8
4	Ph	251	86.5	98.7

i. The reaction was carried out with 1.5 g PEG bound molecule **6**, 5% mmol $PaCl_2(PPh_3)_2$, 10% mmol CuI, 1.5 mmol corresponding terminal alkyne and 6 mmol Et_3N in 6 mL DMF at 80°C for 12 h under nitrogen; ii. Yield of **9**, based on the loading level of polymer **6** and all the products are characterized by ^{1}H-NMR, MS and FT-IR; iii. Determined by GC-MS analysis.

In conclusion, we have developed a facile and efficient method for increasing diversity of combinatorial indole libraries. Further work is in progress to extend this method of liquid-phase synthesis to the preparation of 2,3-disubstituted indoles.

Acknowledgments

We are greatly indebted for the financial support from the National Natural Science Foundation of China (No. 29972037) and Foundation for University Key Teacher by the Ministry of Education.

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Received 16 November, 2001