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Solid-Phase Synthesis of Heterocycles via Palladium-Catalyzed Annulation

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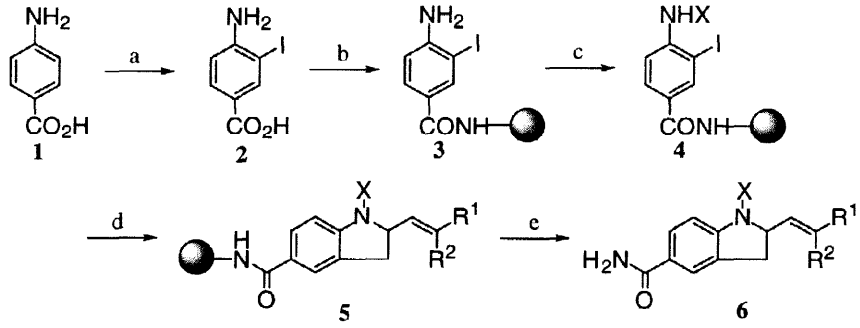
Abstract: Solid-phase linked *o*-iodoanilines (**4**) and *o*-iodophenol (**9**) reacted with 1,3- and 1,4-dienes in the presence of palladium acetate to generate highly substituted indolines, tetrahydroquinolines, hydrobenzofurans and hydrobenzopyrans, which provided an efficient way for making heterocyclic molecule libraries.

Heterocyclic structures are part of many biologically interesting compounds. As core structures, indoline,[2] tetrahydroquinoline,[3] hydrobenzofuran[4] and hydrobenzopyran (chroman)[5] appear frequently in natural and synthetic products possessing various pharmacological properties. Although some methods to form these types of compounds have been developed, e.g. palladium-catalyzed annulation of functionalized aryl halides with 1,2-,[6] 1,3-[7] and 1,4-[8] dienes, and acetylenes,[9] they are rarely used in library synthesis for drug discovery and lead optimization due to the traditional purification. A general method for the solid-phase synthesis of these molecules would be extremely valuable. Herein we report the successful application of palladium-catalyzed annulation to the solid-phase synthesis of highly substituted indolines, tetrahydroquinolines,[10] hydrobenzofurans and chromans.

Scheme 1 shows the synthesis of highly substituted indolines via palladium-catalyzed annulation of solid-phase linked *o*-iodoaniline derivatives (**4**) with 1,3-dienes. Solid-phase linked *o*-iodoaniline (**3**) was prepared by coupling Rink resin[11] and 4-amino-3-iodobenzoic acid (**2**) which was readily obtained from the treatment of 4-aminobenzoic acid (**1**) with iodine and silver sulfate at low temperature.[12]

Scheme 1



Conditions: (a) I_2, Ag_2SO_4, MeOH, -20 °C, 76%; (b) Rink resin, BOP, DIPEA, NMP, rt; (c) XCl (X= RSO_2, RCO), pyridine, CH_2Cl_2, rt; (d) 1,3-diene, $Pd(OAc)_2$, LiCl, DIPEA, DMF, 100 °C; (e) 10% TFA/CH_2Cl_2, rt.

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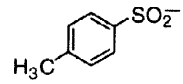
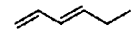
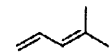
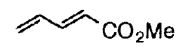
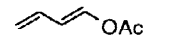
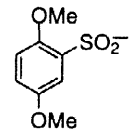
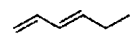
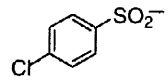
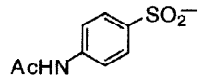
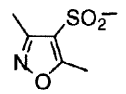
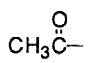
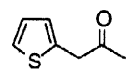
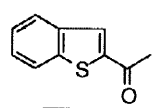
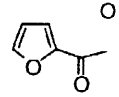
Table 1. Palladium-catalyzed Annulation of Solid Supported *N*-Protected *o*-Iodoanilines with 1,3-Dienes

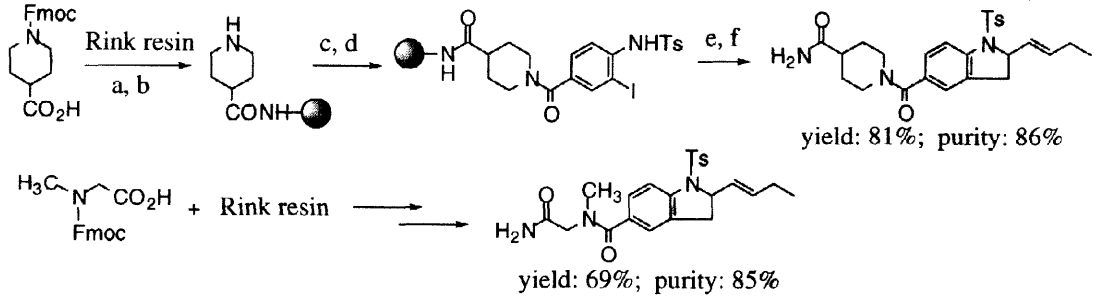
entry	X	1,3-diene	yield (%) of **6**	purity (%) of **6**
1			90	89
2	"		87	90
3	"		91	73
4	"		79	77
5			83	90
6		"	80	74
7		"	90	72
8		"	76[a]	49
9		"	86	67
10		"	85	68
11		"	79	85
12		"	80	77

[a] 22% of unreacted iodide was recovered.

To demonstrate the diversity of the structures formed through this process, we introduced a number of functional groups onto the nitrogen of iodoaniline by treating **3** with sulfonyl chlorides or acid chlorides (Table 1). The annulation reaction was carried out by heating **4** with 1,3-dienes in the presence of 10 mol % of $Pd(OAc)_2$, LiCl, and diisopropylethylamine (DIPEA) as a base in DMF at 100 °C for 2 days. The cleavage of the products from Rink resin was achieved by treating the resin with 10% TFA in methylene chloride for 1 hour. After the removal of solvents, the product (**6**) was checked by HPLC and LC-MS without further purification. The results of palladium-catalyzed annulation are summarized in Table 1.[13] All 1,3-dienes with or without other functional groups (entries 1-4) applied to this process afforded the desired products in good yields with high purities. *p*-Toluenesulfonamide is well known as a good nucleophile in palladium-mediated reactions.[7b] In our solid-phase synthesis of indolines, several arylsulfonamides were employed. Most of them, similar to *p*-toluenesulfonamide, provided good results (entries 5-7), although the isoxazolesulfonamide (entry 8) reacted very slowly. Besides sulfonamides, alkyl and arylcarboxamides were tested in this annulation process, and they all provided satisfactory results (entries 9-12). Interestingly, free aniline **3** was unreactive under our reaction conditions. After the cleavage, most of the starting iodide was recovered.

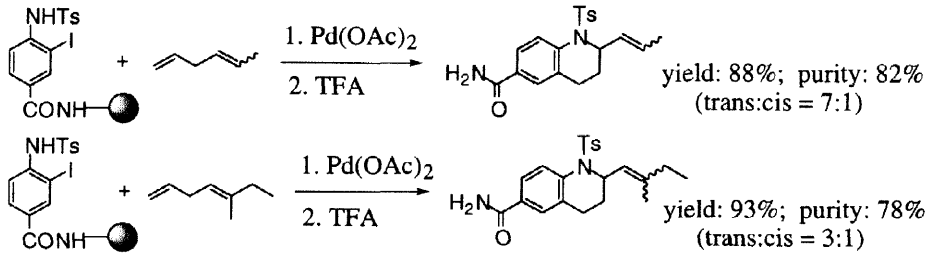
To build libraries of small molecules with an indoline core structure, one can increase the diversity not only by the choices of 1,3-dienes, sulfonyl chlorides and acid chlorides, but also by the introduction of amino acids to the benzene ring in the core structure. We demonstrated a couple of examples as shown in Scheme 2.

Scheme 2



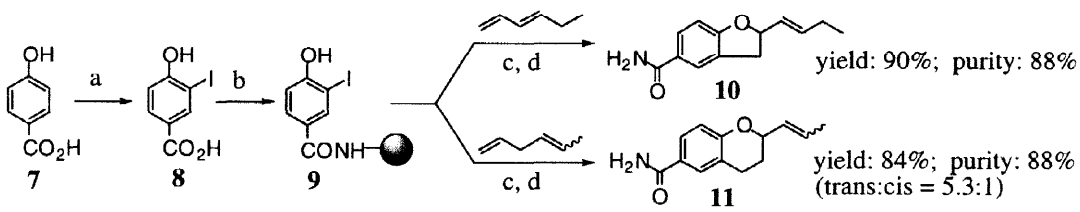
Conditions: (a) BOP, DIPEA, NMP, rt; (b) 25% piperidine in NMP, rt; (c) **2**, BOP, DIPEA, NMP, rt; (d) TsCl, pyridine, CH_2Cl_2, rt; (e) 1,3-hexadiene, $Pd(OAc)_2$, LiCl, DIPEA, DMF, 100 °C; (f) 10% TFA/CH_2Cl_2, rt.

By using 1,4-dienes instead of 1,3-dienes in the above palladium-catalyzed annulation on solid support, 1,2,3,4-tetrahydroquinoline derivatives were readily generated (eqs. 1 and 2). The potential for diversity should be the same as with indolines.



We also extended our investigation of palladium-catalyzed annulation to solid supported *o*-iodophenol (**9**) to form 2,3-dihydrobenzofuran and 2,3-dihydrobenzopyran (chromane) derivatives (**10** and **11**). As shown in Scheme 3, iodination of *p*-hydroxybenzoic acid (**7**) by modifying the literature procedure[14] gave 4-hydroxy-3-iodobenzoic acid (**8**), which was coupled to Rink resin using EDCI and HOBt as the coupling reagent without a base to provide **9**. Under our standard palladium-catalyzed annulation conditions, **9** reacted with 1,3- and 1,4-hexadienes to generate **10** and **11** respectively.

Scheme 3



Condition: (a) NaI, NaOCl, MeOH, -20 °C; (b) Rink resin, EDCI, HOBt, CH_2Cl_2/MeOH, rt; (c) $Pd(OAc)_2$, LiCl, DIPEA, DMF, 100 °C; (d) 10% TFA/CH_2Cl_2, rt.

In conclusion, we have successfully explored the application of palladium-catalyzed annulation to the solid-phase synthesis and provided a valuable process to build large chemical libraries of heterocyclic molecules with core structures of indoline, tetrahydroquinoline, hydrobenzofuran and hydrobenzopyran.

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13. Typical Procedure: 200 mg of resin bound *o*-iodoaniline **3** (0.66 mmol/g) was mixed with 3 equiv. of TsCl and 0.5 ml of pyridine in 1.5 ml of CH_2Cl_2. The mixture was shaken at rt overnight, then filtered and washed with CH_2Cl_2 and MeOH three times. The resin was put into a pressure tube, to which was added 2 ml of DMF, 10 mol % of $Pd(OAc)_2$, 2 equiv. of LiCl, 8 equiv. of DIPEA and 8 equiv. of 1,3-hexadiene respectively. Sealed with a teflon cap, the tube was shaken at 100 °C for 2 days. After cooling to rt, the resin was filtered and washed with DMF, CH_2Cl_2 and MeOH three times. The dried resin was treated with 2 ml of 10% TFA in CH_2Cl_2 for 1 hour, then filtered and washed with CH_2Cl_2. The filtrate was evaporated under reduced pressure to give the product in 90% yield with 89% purity (Table 1, entry 1). The molecular weight (M+H: 371) was confirmed by LC-MS spectroscopy. ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.5 Hz, 3 H), 2.03 (quintet, J = 7.4 Hz, 2 H), 2.38 (s, 3 H), 2.71 (dd, J = 16.6, 3.2 Hz, 1 H), 3.10 (dd, J = 16.3, 10.0 Hz, 1 H), 4.82 (m, 1 H), 5.43 (ddt, J = 15.3, 7.3, 1.5 Hz, 1 H), 5.84 (dt, J = 15.3, 6.3 Hz, 1 H), 6.19 (br s, 2 H), 7.21 (d, J = 8.2 Hz, 2 H), 7.59-7.66 (m, 5 H).
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