

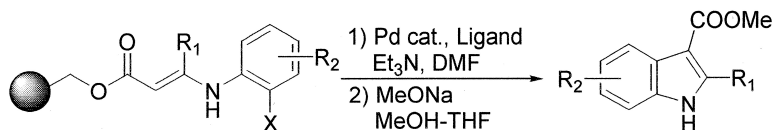
Report

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Palladium-Catalyzed Synthesis of Indole 3-Carboxylates on a Solid Polymer Support

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The synthesis of heterocyclic compounds is a major focus of solid-phase synthesis, and various methods for the preparation of heterocyclic compounds have been transferred to the solid phase.¹ Among the various heterocyclic compounds, indole scaffolds are biologically very attractive and have appeared frequently in the medicinal chemistry literature showing their importance.² Several solid-phase indole syntheses have already been reported;³ however, a considerable effort is to be expected to provide additional efficient solid-phase methodologies for the synthesis of diverse indole derivatives. Hutchins and Chapman have reported the Fischer indolization of polymer-bound ketone with phenylhydrazine; however, this reaction seems to have some limitations due to its nature. Namely, electron-deficient para-substituted hydrazine cannot cyclize to yield indoles, and meta-substituted phenylhydrazines usually yield a mixture of 4- and 6-substituted indoles.^{3a} On the other hand, the intramolecular Heck reaction has been successfully applied to the solid-phase synthesis of 3-substituted indoles using polymer-bound aryl halides.⁴ Previously, indole 3-carboxylates have been synthesized via an intramolecular palladium-catalyzed condensation of halophenylaminoesters,⁵ and we report here that the methodology can be successfully applied to the solid-phase indole synthesis.

The substrates for the palladium-catalyzed cyclization, β -(2-halophenyl)amino substituted α,β -unsaturated esters, were synthesized by the following two methods.

In method A, acid-catalyzed condensation of the polymer-bound β -keto ester **1**⁶ with 2-haloanilines was performed. ATR FT-IR was used to monitor the progression of the reaction using a very small portion of the sample beads by checking the disappearance of the peaks of the ketone (1717 cm^{-1}) and ester (1742 cm^{-1}) on one hand and the appearance of a peak at 1611 cm^{-1} on the other, which corresponds to the absorption by the double bond of the enaminoester.

In method B, palladium(II) chloride catalyzed oxidative amination reaction⁷ of REM resin **3**⁸ with 2-haloanilines was performed. The progression of the reaction was also monitored by the disappearance of a peak at 1723 cm^{-1} and the appearance of a peak at 1623 cm^{-1} in ATR FT-IR. Many oxidative transformations have been achieved using the palladium(II) catalyst in the presence of oxidizing agents in solution-phase chemistry,⁹ but to the best of our knowledge,

Scheme 1

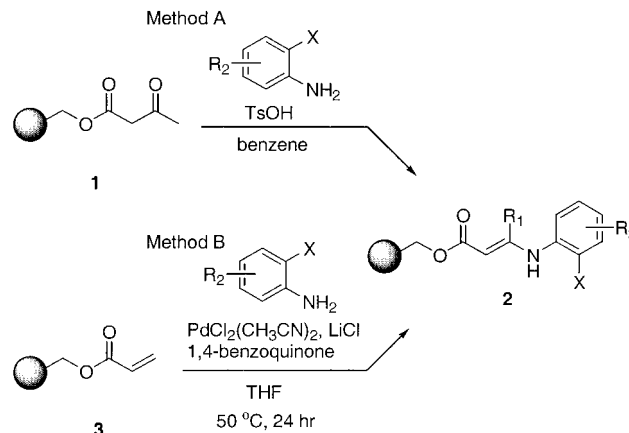


Table 1. Immobilized β -(2-Halophenyl)amino-Substituted α,β -Unsaturated Esters

2	X	R1	R2	method	loading (mmol/g)
a	I	Me	H	A	0.78
b	Br	Me	H	A	0.86
c	Br	Me	4-Me	A	0.93
d	Br	Me	5-CF ₃	A	0.77
e	I	H	H	B	0.98
f	Br	H	H	B	1.06
g	Br	H	4-Me	B	0.68
h	Br	H	4-CF ₃	B	0.81
i	Br	H	5-NO ₂	B	0.82
j	Br	H	5-CF ₃	B	0.88

there is no precedent in the application of this kind of reaction to solid-phase chemistry that has been reported so far. Loading of **2** was estimated by an elemental analysis of the polymer beads for nitrogen, and the measured values indicated smooth and reasonable progress of the transformation (Scheme 1, Table 1).

Next, the palladium-catalyzed cyclization was investigated using polymer-bound enaminoester **2** (Scheme 2). When **2a** was heated at 110 °C for 15 h in the presence of 15 mol % Pd(OAc)₂ and triethylamine₂ in DMF, followed by transesterification of the polymer-bound indole carboxylate using MeONa in MeOH–THF, methylindole 3-carboxylate **4a** was obtained with a yield of 27% based on the loading of **2a** after SiO₂ column chromatography. When P(2-Tol)₃ was added in the above reaction, the yield of isolated **4a** increased from 27% to 63%. Similarly, the β -2-bromophenylamino derivative **2b** was subjected to the same reaction conditions, but the yield was not satisfactory. Here, the use of Pd₂(dba)₃ instead of Pd(OAc)₂ produced a significant improvement. The optimized reaction protocol was applied to **2c–j**, and the results are summarized in Table 2. Good results were generally obtained for 2-unsubstituted indole carboxylates, although in the cases of 2-methyl-substituted indoles, further optimization seems necessary. However, the purities of crude materials were very high in all cases (>90% by HPLC analysis). The low yields are considered to be due to the instability of the polymer-bound enaminoesters (**2c,d,g**), and further careful optimization is underway.

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Scheme 2



Table 2. Palladium-Catalyzed Intramolecular Cyclization Reactions

4	X	R ₁	R ₂	Pd catalyst	ligand	yield (%)
a	I	Me	H	Pd(OAc) ₂	none	27
a	I	Me	H	Pd(OAc) ₂	P(2-Tol) ₃	63
a	Br	Me	H	Pd(OAc) ₂	P(2-Tol) ₃	35
a	Br	Me	H	Pd ₂ (dba) ₃	P(2-Tol) ₃	53
b	Br	Me	5-Me	Pd ₂ (dba) ₃	P(2-Tol) ₃	43
c	Br	Me	6-CF ₃	Pd ₂ (dba) ₃	P(2-Tol) ₃	32
d	I	H	H	Pd ₂ (dba) ₃	none	74
d	I	H	H	Pd ₂ (dba) ₃	P(2-Tol) ₃	78
d	Br	H	H	Pd ₂ (dba) ₃	P(2-Tol) ₃	69
e	Br	H	5-Me	Pd ₂ (dba) ₃	P(2-Tol) ₃	57
f	Br	H	5-CF ₃	Pd ₂ (dba) ₃	P(2-Tol) ₃	65
g	Br	H	6-NO ₂	Pd ₂ (dba) ₃	P(2-Tol) ₃	39
h	Br	H	6-CF ₃	Pd ₂ (dba) ₃	P(2-Tol) ₃	66

In summary, palladium-catalyzed cyclization of the β -(2-halophenyl)amino-substituted α,β -unsaturated esters was found to be effective for the solid-phase synthesis of indole 3-carboxylates with various functional groups on the benzene ring. The palladium-catalyzed oxidative amination route, in particular, is considered to provide a useful strategy for the formation of enamoester. In addition, the application of the reaction toward further diverse synthesis of other heterocyclic systems is to be expected.

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Supporting Information Available. Typical preparation procedures of compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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