

# Immobilized $\alpha$ -diazophosphonoacetate as a versatile key precursor for palladium catalyzed indole synthesis on a polymer support

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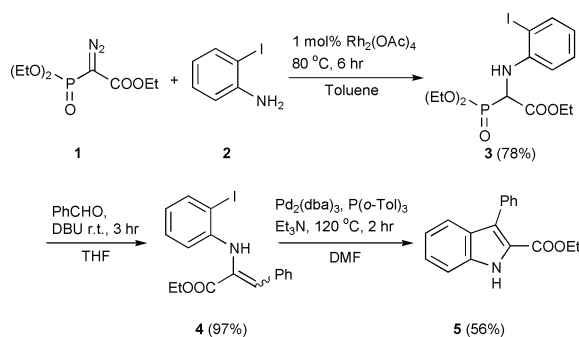
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**Rh(II)-catalyzed N–H insertion reaction of immobilized  $\alpha$ -diazophosphonoacetate with 2-haloanilines followed by Horner–Emmons reaction gave immobilized enaminoesters, which were efficiently cyclized to indoles via intramolecular palladium catalyzed reaction on a polymer support.**

The insertion reactions of carbene and carbenoid species have been widely used as one of the important methods in recent organic chemistry.<sup>1</sup> Moody and coworkers reported the N–H insertion reaction of rhodium carbenoids, which allow functionalization of amides, carbamates and anilines effectively.<sup>2</sup> Rhodium carbenoid insertion reactions have already been used for the construction of several heterocyclic compounds and cyclopropane derivatives in solid phase chemistry,<sup>3,4</sup> however the N–H insertion reaction of  $\alpha$ -diazophosphonoacetate on a polymer support has not been reported to our knowledge. In this communication we present the rhodium catalyzed reaction of immobilized  $\alpha$ -diazophosphonoacetate with anilines and its application to a new indole synthesis.<sup>5</sup>

First, we started with a solution phase investigation for our indole synthesis. Triethyl  $\alpha$ -diazophosphonoacetate **1** was reacted with iodoaniline in the presence of  $\text{Rh}_2(\text{OAc})_4$  and the rhodium-catalyzed N–H insertion reaction proceeded smoothly to give the desired  $\alpha$ -anilinophosphonoacetate **3** in 78% yield (Scheme 1). Subsequent Horner–Emmons reaction<sup>7</sup> of **3** with benzaldehyde gave  $\alpha$ -(2-iodophenyl)amino substituted  $\alpha,\beta$ -unsaturated ester **4** in almost quantitative yield. Compound **4** was found to be a single isomer but its geometry has not yet been determined. The palladium-catalyzed intramolecular cyclization<sup>8</sup> of the enaminoester **4** was carried out to give ethyl 3-phenyl-2-indolecarboxylate **5** in 56% yield. Based on these results in the solution phase, we next investigated the solid phase application of the rhodium-catalyzed N–H insertion reaction.

Polymer-bound diethylphosphonoacetate **6** was easily synthesized from hydroxymethyl polystyrene resin. The condensation of hydroxymethyl polystyrene resin (1% DVB) with diethylphosphonoacetic acid was carried out using the mixed anhydride method.<sup>9</sup> Diazo transfer to the phosphonoacetate **6**

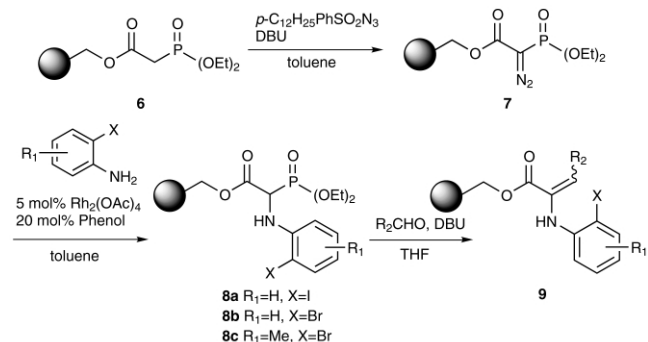


Scheme 1

was achieved by the treatment of **6** with dodecylbenzenesulfonyl azide using DBU as a base in toluene (Scheme 2). The resulting polymer-bound  $\alpha$ -diazophosphonoacetate showed characteristic absorptions at 2124 and 1702  $\text{cm}^{-1}$  in ATR FT-IR indicating the existence of the diazo and ester functionalities, respectively. The loading of resin **7** was estimated by elemental analysis of the polymer beads for nitrogen as 1.1–1.2  $\text{mmol g}^{-1}$  for each batch and the measured values indicated the smooth and reasonable progress of the transformation.

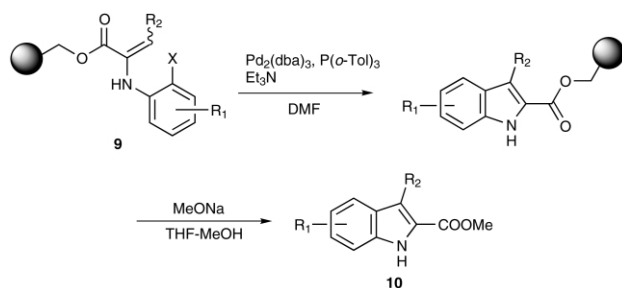
Next, we investigated the reaction conditions of rhodium-catalyzed N–H insertion of resin **7**.<sup>10</sup> When the reaction of **7** with 2-iodoaniline (5 equiv.) in the presence of 5 mol% rhodium acetate was carried out at 80 °C in toluene, a long reaction time (40 h) was found to be required upon monitoring the complete disappearance of the diazo absorption at 2124  $\text{cm}^{-1}$  in ATR FT-IR. When 20 mol% phenol was used as an additive for the reaction, a significant rate acceleration was observed. The role of phenol in the reaction rate enhancement is not clear, however a previous report also suggested a similar additive effect.<sup>2c</sup> Similarly, other anilines gave N–H insertion products using the reaction conditions with retention of the high loading level. The solid phase Horner–Emmons reaction of **8** with aromatic aldehyde (3 equiv.) using DBU (3 equiv.) as a base proceeded smoothly without any problems and a broad range of aryl and heteroaryl aldehydes were found to be amenable for the reaction. The progress of the reaction was conveniently monitored by ATR FT-IR which showed that the ester absorption of **8** at 1737  $\text{cm}^{-1}$  disappeared and was replaced by a new absorption for the enaminoester at 1702  $\text{cm}^{-1}$ . Polymer-bound  $\alpha$ -anilinophosphonoacetates were found to be useful precursors for the preparation of immobilized  $\alpha$ -anilino- $\alpha,\beta$ -unsaturated esters; acid catalyzed condensation of  $\alpha$ -keto esters with aniline on a polymer support as an alternative approach has not previously been investigated.

Finally, palladium-catalyzed intramolecular cyclization was carried out using similar reaction conditions as for the solution phase procedure. When **9a** was heated at 110 °C for 12 h in the presence of 15 mol%  $\text{Pd}_2(\text{dba})_3$ ,  $\text{P}(o\text{-Tol})_3$  and triethylamine in DMF followed by the transesterification of polymer-bound indole carboxylate using MeONa in MeOH–THF, methyl 3-phenyl-2-indolecarboxylate **10a** was obtained in 48% yield after  $\text{SiO}_2$  column chromatography based on the loading of **9a**



Scheme 2

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Scheme 3

Table 1 Palladium catalyzed cyclization of haloarylamino esters 9

9	X	Loading/mmol g <sup>-1</sup>	10	R <sub>1</sub>	R <sub>2</sub>	Yield (%)
a	I	1.00	a	H	Ph	48
b	Br	1.04	a	H	Ph	52
c	I	0.94	b	H	4-MeOC <sub>6</sub> H <sub>4</sub>	40
d	Br	0.90	c	H	2-Pyridyl	54
e	I	0.93	d	H	2-Thienyl	31
f	Br	0.92	e	4-Me	Ph	62

(Scheme 3). In a similar fashion, palladium catalyzed reactions for the other substrates were also carried out to give 3-arylindole-2-carboxylates **10b–e** in the yields summarized in Table 1.

In summary, we have demonstrated the first solid phase application of rhodium catalyzed N–H insertion into immobilized carbenoids generated from immobilized  $\alpha$ -diazo-phosphonoacetate and a new and efficient method for the synthesis of 3-arylindole-2-carboxylates was developed. Further applications of this strategy toward diverse synthesis of other heterocyclic systems are currently under investigation.

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- 10 *Typical experimental procedure*: a mixture of resin **7** (1.5 g, 1.8 mmol), 2-iodoaniline (1.97 g, 9.0 mmol), phenol (35 mg, 0.36 mmol), Rh<sub>2</sub>(OAc)<sub>4</sub> (40 mg, 0.09 mmol) and toluene (15 ml) was heated at 80 °C for 12 h under argon atmosphere. The resin was washed with toluene (15 ml  $\times$  3), DMF (15 ml  $\times$  3), THF (15 ml  $\times$  3), CH<sub>2</sub>Cl<sub>2</sub> (15 ml  $\times$  3), MeOH (15 ml  $\times$  3) and the resin was dried under reduced pressure at 40 °C. The loading of **8a** was estimated by elemental analysis for nitrogen as 0.94 mmol g<sup>-1</sup>. DBU (0.11 ml, 0.76 mmol) was added to a suspension of resin **8a** (270 mg, 0.25 mmol) in THF (3 ml) and agitated for 5 min then benzaldehyde (0.077 ml, 0.76 mmol) was added and agitated for 12 h at rt. The resin was washed with THF (3 ml  $\times$  3), DMF (3 ml  $\times$  3), THF (3 ml  $\times$  3), CH<sub>2</sub>Cl<sub>2</sub> (3 ml  $\times$  3), MeOH (3 ml  $\times$  3) and the resin was dried under reduced pressure. A mixture of resin **9a** (0.23 g, 0.23 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (16 mg, 0.017 mmol), P(*o*-Tol)<sub>3</sub> (21 mg, 0.069 mmol), Et<sub>3</sub>N (0.48 ml, 3.45 mmol) and DMF (2 ml) was heated at 110 °C for 12 h under argon atmosphere. The resin was washed with DMF (3 ml  $\times$  3), DMF:H<sub>2</sub>O = 1:1 (3 ml  $\times$  3), DMF (3 ml  $\times$  3), THF (3 ml  $\times$  3), MeOH (3 ml  $\times$  3) and the resin was dried under reduced pressure at 40 °C. The above resin and NaOMe (75 mg, 1.38 mmol) in THF (2 ml) and MeOH (1 ml) was agitated at rt for 6 h to give 28 mg (48%) of methyl 3-phenyl-2-indolecarboxylate **10a**.