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

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**Rh(II)-catalyzed N–H insertion reaction of immobilized α-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.**

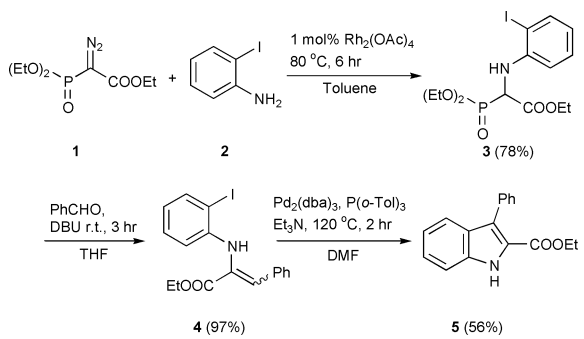
The insertion reactions of carbene and carbenoid species have been widely used as one of the important methods in recent organic chemistry.[1] Moody and coworkers reported the N–H insertion reaction of rhodium carbenoids, which allow functionalization of amides, carbamates and anilines effectively.[2]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

First, we started with a solution phase investigation for our indole synthesis. Triethyl α-diazophosphonoacetate **1**[6] was reacted with iodoaniline in the presence of $Rh_2(OAc)_4$ and the rhodium-catalyzed N–H insertion reaction proceeded smoothly to give the desired α-anilinophosphonoacetate **3** in 78% yield (Scheme 1). Subsequent Horner–Emmons reaction[7] of **3** with benzaldehyde gave α-(2-iodophenyl)amino substituted α,β-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[8] 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.

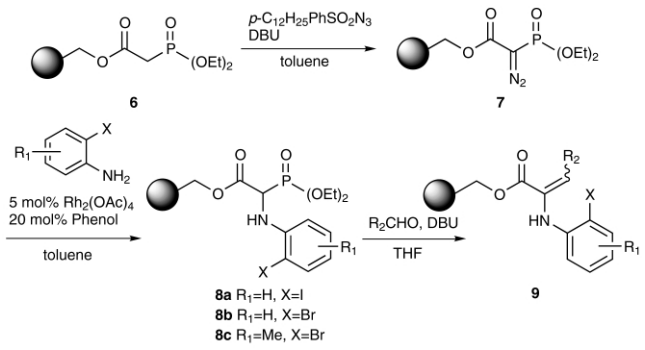
Polymer-bound diethylphosphonoacetate **6** was easily synthesized from hydroxymethyl polystyrene resin. The condensation of hydroxymethyl polystyrene resin (1% DVB) with diethylphosphonoacetic acid was carried out using the mixed anhydride method.[9] Diazo transfer to the phosphonoacetate **6** was achieved by the treatment of **6** with dodecylbenzenesulfonyl azide using DBU as a base in toluene (Scheme 2). The resulting polymer-bound α-diazophosphonoacetate showed characteristic absorptions at 2124 and 1702 $cm^{-1}$ 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 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**.[10] 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 $cm^{-1}$ 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.[2c] 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 $cm^{-1}$ disappeared and was replaced by a new absorption for the enaminoester at 1702 $cm^{-1}$. Polymer-bound α-anilinophosphonoacetates were found to be useful precursors for the preparation of immobilized α-anilino-α,β-unsaturated esters; acid catalyzed condensation of α-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% $Pd_2(dba)_3$, P(*o*-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 $SiO_2$ column chromatography based on the loading of **9a**




**Scheme 1**




**Scheme 2**

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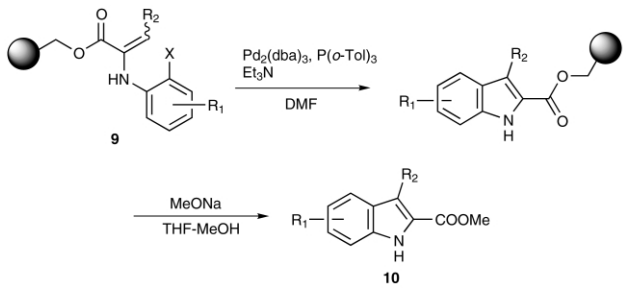


**Scheme 3**

**Table 1** Palladium catalyzed cyclization of haloarylenamino esters **9**

| **9** | X | Loading/mmol $g^{-1}$ | **10** | $R_1$ | $R_2$ | Yield (%) |
|---|---|---|---|---|---|---|
| **a** | I | 1.00 | **a** | H | Ph | 48 |
| **b** | Br | 1.04 | **a** | H | Ph | 52 |
| **c** | I | 0.94 | **b** | H | 4-$MeOC_6H_4$ | 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 α-diazophosphonoacetate 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), $Rh_2(OAc)_4$ (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 × 3), DMF (15 ml × 3), THF (15 ml × 3), $CH_2Cl_2$ (15 ml × 3), MeOH (15 ml × 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 $g^{-1}$. 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 × 3), DMF (3 ml × 3), THF (3 ml × 3), $CH_2Cl_2$ (3 ml × 3), MeOH (3 ml × 3) and the resin was dried under reduced pressure. A mixture of resin **9a** (0.23 g, 0.23 mmol), $Pd_2(dba)_3$ (16 mg, 0.017 mmol), P(*o*-Tol)$_3$ (21 mg, 0.069 mmol), $Et_3N$ (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 × 3), DMF:$H_2O$ = 1:1 (3 ml × 3), DMF (3 ml × 3), THF (3 ml × 3), MeOH (3 ml × 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**.