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LETTERS

Palladium-Catalyzed Synthesis of Fused Indoles

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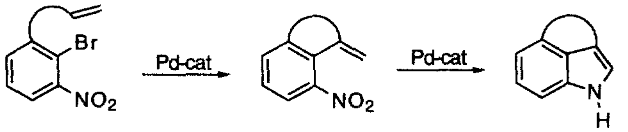
Abstract

A novel route to fused indoles *via* two consecutive palladium catalyzed reactions, an intramolecular Heck reaction followed by a reductive *N*-heteroannulation, has been developed. For example, reaction of 2-bromo-3-nitro-1-(3-butenyloxy)benzene with palladium diacetate, and tri(o-tolyl)phosphine in the presence of triethylamine gave a readily separable mixture (18:4:1) of dihydro-4-methylene-5-nitro-2*H*-1-benzopyran, 4-methyl-5-nitro-2*H*-1-benzopyran, and 4-methyl-5-nitro-4*H*-1-benzopyran. Reaction of pure dihydro-4-methylene-5-nitro-2*H*-1-benzopyran with palladium diacetate, 1,3-bis(diphenylphosphino)propane, and carbon monoxide in DMF (120 °C, 70 h, 60 psi CO) gave 3,5-dihydro-2*H*-pyrano[4,3,2-*cd*]indole in 63% yield.

Keywords: Palladium; Catalysis; Indoles; Annulation

The intramolecular Heck reaction has become a versatile tool in natural product synthesis [1-4]. Recent examples include: synthesis of 20(*S*)-camptothecin [5], (+)-γ-lycorane [6], *Amaryllicidae* alkaloids [7], diazonamide A [8], chanoclavine-I [9], aphidicoline [10], cephalotaxine [11], tazettine and 6a-epipretazettine [12], herbertenediol [13], halenaquinone and halenaquinol [14-15], and tabersonine [16] to name only a few.

We envisioned a novel route to fused indoles *via* two consecutive palladium catalyzed reactions, an intramolecular Heck reaction followed by a recently developed, mild, and very efficient palladium catalyzed reductive *N*-heteroannulation (Scheme 1) [17-19]. Using this route, it should, in principle, be possible to assemble indoles having a variety of ring sizes anchored to the 3- and 5-position of the indole nucleus. Furthermore, considering the two reactions' high tolerance of a number of functional groups, both carbon and heteroatom substituents should be possible in (or attached to) the additional ring.



(1)

In order to examine the proposed synthetic relay, compound **2** was prepared by *O*-alkylation of 2-bromo-3-hydroxy-1-nitrobenzene (**1**) with 1-bromo-3-butene in the presence of sodium iodide and potassium hydroxide. Heck reaction of **2**, under standard conditions, produced a readily separable mixture of three isomeric 5-nitro-1-benzopyrans (**3** - **5**) in an 18:4:1 ratio (Scheme 2) [20]. The cyclization reaction was rapid, and the starting material was completely consumed within 30 min at 125 °C. The relatively high rate of reaction is

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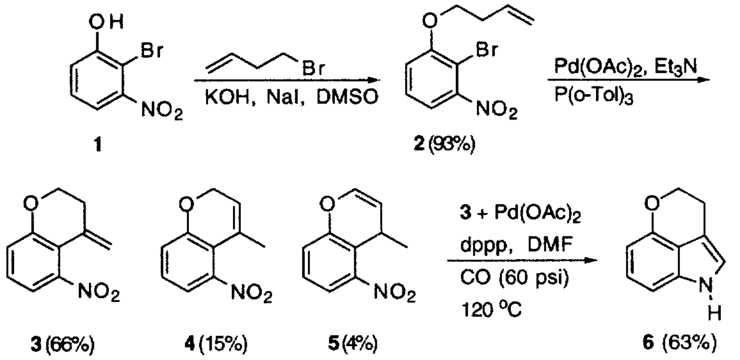
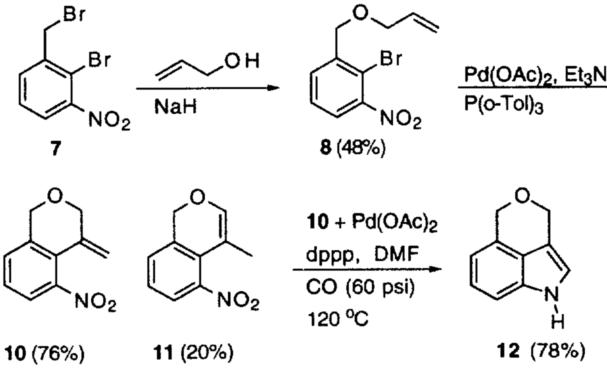
most likely due to the presence of the nitro group. For example, reaction of the corresponding compound lacking the nitro group required 48 h to go to completion [21]. Furthermore, a substantially lower isomer ratio (1.7:1, endo:exo) was observed. The high exo-endo ratio in our case is unusual, perhaps a result of the rapid reaction not allowing time for isomerization to occur.

Attempted reductive *N*-heteroannulation of **3** using conditions previously employed for substituted 2-nitrostyrenes, 6 mol-% $Pd(OAc)_2$ and 24 mol-% PPh_3 in acetonitrile at 70 °C under 50 psi of carbon monoxide for 19.5 h, gave the expected indole **6** in low isolated yield (11%). In addition to the product, a substantial amount of starting material was recovered (51%). The yield of indole **6** was improved to 37% upon prolonged reaction (70 h) at a higher temperature (100 °C). However, a considerable amount of starting material was still recovered (32%). Finally, using 1,3-bis(diphenylphosphino)propane in place of PPh_3, dimethylformamide in place of acetonitrile, and 120 °C as the reaction temperature, an acceptable 63% yield of **6** was realized after 70 h. A somewhat higher catalyst load (10 mol-%) was also used. Although the starting material was completely consumed in the reaction, no other organic products were observed by ^1H NMR of the crude reaction mixture.



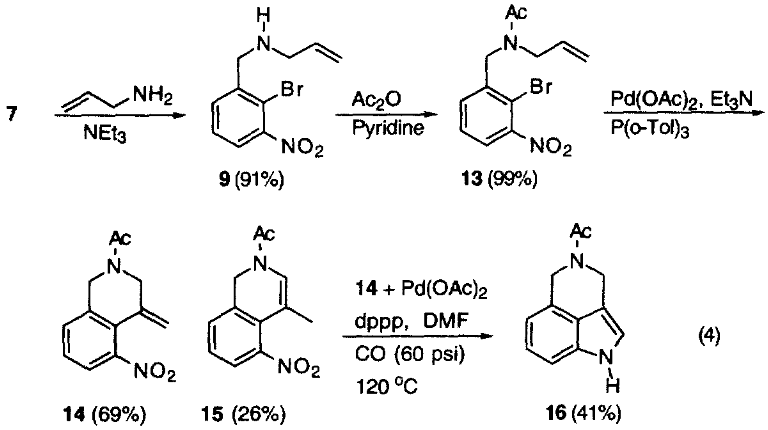
(2)

Relays to three additional fused indoles were pursued using the reaction conditions described above. In the second example, the isomeric substrate **8**, having the oxygen atom moved one step in the tether was prepared by alkylation of allyl alcohol with the benzylic bromide **7**. Again, a very facile Heck reaction was observed, and the exocyclic 2-benzopyran **10** (76%) together with the endocyclic isomer **11** (20%) was obtained starting from **8** (Scheme 3). The isomers were separated by chromatography, and cyclization of pure **10** gave the expected indole **12** in good isolated yield.



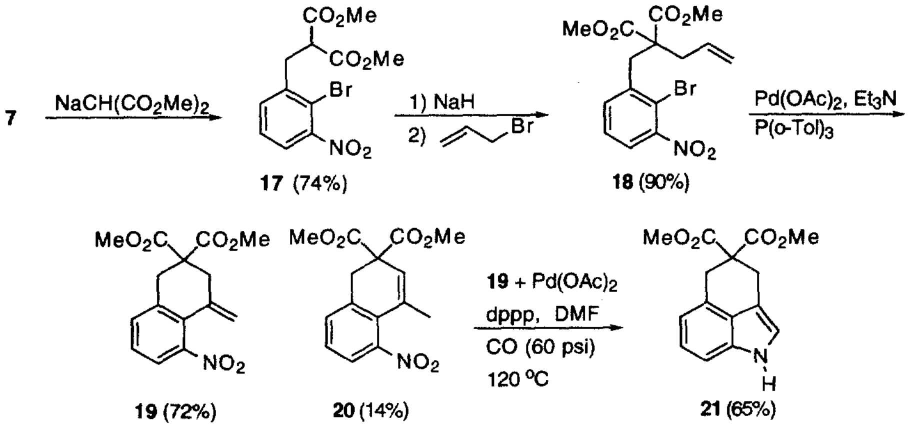
(3)

In a similar reaction, the amine **9** was prepared by amination of **7**. However, attempted Heck reaction of **9** did not produce the anticipated cyclization products but gave, in addition to recovered starting material, a complex mixture of unidentified products. It is not unlikely that the initial σ-complex, formed by oxidative insertion of palladium(0) into the aryl-bromine bond in **9**, is coordinated to the pendant amine, forming a relatively stable complex. This effectively removes palladium from the catalytic cycle, and the reaction is quenched. To modify the coordinative ability of the substrate, the amine **9** was transformed almost quantitatively to the amide **13** by reaction with acetic anhydride in pyridine. Heck reaction of **13** was exceedingly fast, and the reaction was complete within five minutes at 100 °C (Scheme 4). Again a readily separated mixture of exo and endo isomers was obtained in 95% combined yield. *N*-heteroannulation of the exocyclic isomer **14** gave the expected indole **16** in moderate yield.

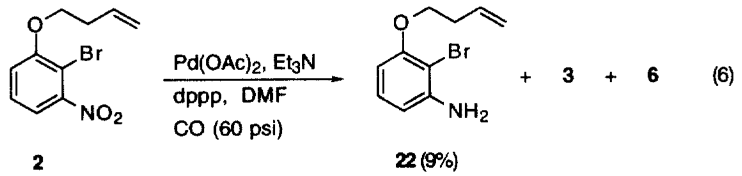


(4)

As the fourth and final example, a carbocyclic variation of the above sequence was pursued. The carbon tether was assembled by reaction of benzylbromide **7** with, in sequence, sodium dimethylmalonate and allyl bromide producing **18**. The two subsequent annulation reactions proceeded uneventful, and the anticipated fused indole **21** was isolated as the sole product.



Very little is known about the mechanism of the reductive annulation reaction. For example, to our knowledge it is not known if the reaction is catalyzed by palladium(II) or palladium(0). We have previously shown that both oxidation states can be used with almost equal success to form indoles from 2-nitrostyrenes. Considering the very similar reaction conditions for the two annulation reactions, if palladium(0) is the actual catalyst for the latter, a tandem, one pot Heck reaction-*N*-heteroannulation may be feasible. Thus, compound **2** was reacted under the conditions used to cyclize benzopyran **3** (Scheme 3) but in the presence of triethylamine. However, only minor amounts of the expected indole **6** (3%), together with the benzopyran **3** (5%), were obtained (Scheme 6). The major product isolated was the amine **22**, derived from reduction of the nitro group [22].



In conclusion, a novel route to fused indoles has been developed based on two palladium catalyzed reactions. Further studies of this novel synthesis of fused indoles and its application in total synthesis are currently underway in our laboratories.

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