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# New 4-Spiroannulated Tetrahydroisoquinolines by a One-Pot Sequential Procedure. Isolation and Characterization of σ-Alkylpalladium Heck Intermediates

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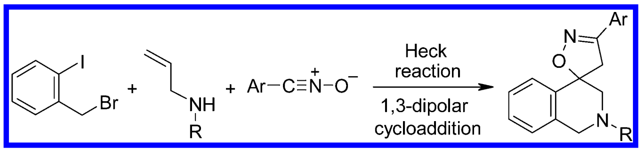
## ABSTRACT



**A simple and efficient entry to new tetrahydroisoquinolines 4-spiroannulated to a five-membered heterocyclic ring has been achieved starting from secondary *N*-allylamines and involving sequential 2-iodobenzylation/intramolecular Heck reaction/1,3-dipolar cycloaddition. A variety of Heck cyclization conditions were surveyed. When using Pd(PPh$_3$)$_4$ as catalyst, stable σ-alkylpalladium iodide complexes were isolated and characterizated.**

Spiroannulated isoquinolines are attractive compounds of growing pharmaceutical interest as documented by many recent patents. Their activity as neuropeptide Y antagonists, SK channel blockers, and Mas receptor ligands make them useful cardioprotective or neuroprotective agents.[1]

Due to our research interest concerning synthesis of nitrogenated heterocycles,[2,3] we envisioned the possibility of assembling spirocompounds of type **A** according to the retrosynthetic sequence described in Scheme 1, namely through a tandem process involving intramolecular Heck reaction and intermolecular 1,3-dipolar cycloaddition. Al-

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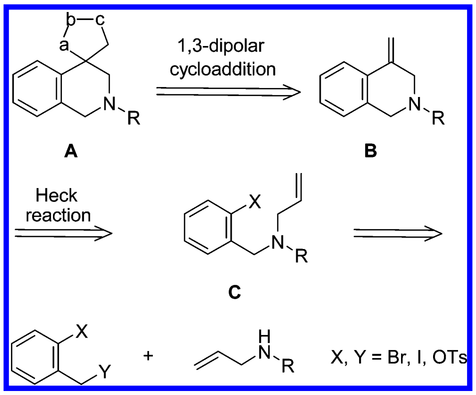
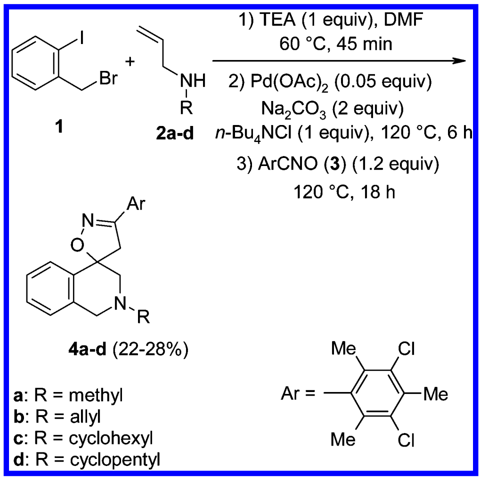
**Scheme 1.** Retrosynthetic Analysis of 4-Spiroannulated Tetrahydroisoquinolines



though intramolecular Heck couplings[4] have found a broad range of applications in tandem processes,[5] to the best of our knowledge such combined methods are the object of only one literature report.[6] The derivatives **B**, built from **C** under Heck conditions, should be easily and variously spiroannulated at the exocyclic C−C double bond by exploiting the well-established versatility of 1,3-dipolar cycloadditions for the construction of five-membered heterocyclic rings.[7] The 1,1-disubstitution of the dipolarophile should induce complete regioselectivity in the cycloadditive process. As an example, nitrile oxides were the 1,3-dipolar species leading to spiro[isoquinoline-4,5′-isoxazole] structures.

Aiming for the above target, we selected as suitable starting materials 2-iodobenzyl bromide (**1**), a number of commercially available allylamines (**2a**−**d**), and the long-known 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide[8] (**3**) (Scheme 2). The latter 1,3-dipolar substrate was chosen due to its stability that seemed essential to realize a sequential one-pot process. As depicted in Scheme 2, the treatment of equimolar amounts of 2-iodobenzyl bromide (**1**) and allylamines **2a**−**d** in the presence of TEA in DMF at 60 °C for 45 min was followed by the addition of $Pd(OAc)_2$ (0.05 equiv), $Na_2CO_3$ (2 equiv), and $n$-$Bu_4NCl$ (1 equiv) to promote the desired Heck reaction. These conditions match those reported for a similar reaction.[9] After heating at 120 °C for 6 h, the nitrile oxide **3** (1.2 equiv) was added as a potential reaction partner toward the intermediate 4-hexomethyleneisoquinolines.

**Scheme 2.** One-Pot Synthesis of Spiro[isoquinoline-4,5′-isoxazole] Compounds



4-Spiroannulated tetrahydroisoquinolines **4a**−**d** were isolated as the final products. In line with the literature data dealing with nitrile oxide cycloadditions to 1,1-disubstituted ethylenes,[10] total regioselectivity (by NMR) was observed. The 4−5′ junction of the isoquinoline−isoxazole system was established by $^1H$ and $^{13}C$ chemical shifts as well as by geminal coupling constants (greater than 18 Hz)[11] of the methylenic group of the isoxazole ring, which are only compatible with the 4-position. It must be noted that, when two dipolarophilic sites were present in the substrate (**2b**), no diaddition product was isolated. The overall yields of the one-pot protocol were in the range of 22−28%.

Despite obtaining the desired products, the observed yields seemed somewhat unsatisfactory. This prompted us to a detailed investigation of the single steps of the sequence and, in particular, to conduct a deeper search for Heck conditions. For this purpose, we isolated the intermediate **5a** in quantitative yield and submitted it to a variety of conditions potentially suitable for the Heck reaction. The results are collected in Table 1, where entry 1 refers to our initial experiment. Under these conditions, the cyclized product **6a** was obtained in 34% yield along with sizable amounts of

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(12) Crystal data: triclinic, space group *P*-1 (No. 2), $a = 9.458(2)$ Å; $b = 11.332(2)$ Å; $c = 13.604(2)$ Å, $\alpha = 76.51(1)°$; $\beta = 86.68(2)°$; $\gamma = 82.32(2)°$; $V = 1404.6(4)$ Å, $Z = 2$, CCDC 613934.

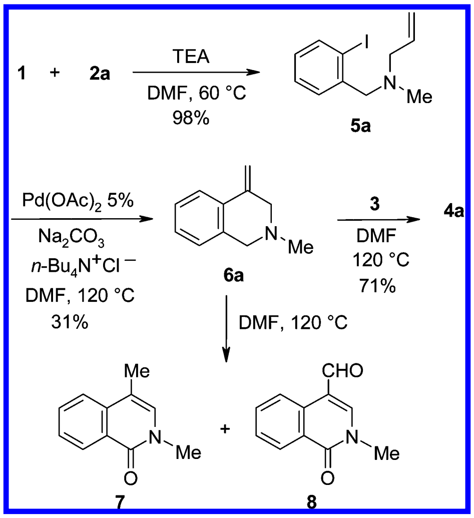
**Table 1.** Reaction Conditions and Yields for Intramolecular Heck Reaction of **5a**

| entry | catalyst[a] | additive/igand[b] | base[c] | solvent | *T* (°C) | time (h) | yields of **6a** (%) |
|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $Bu_4NCl$ | $Na_2CO_3$ | DMF | 120 | 6 | 34 |
| 2 | $Pd(OAc)_2$ | $Bu_4NCl$ | $Na_2CO_3$ | NMP | 120 | 8 | 26 |
| 3 | $Pd(OAc)_2$ | $PPh_3$ | $Cs_2CO_3$ | DMF | 120 | 6 | 55 |
| 4 | $Pd_2(dba)_3{\cdot}CHCl_3$ | $PPh_3$ | $Et_3N$ | DMF | 120 | 5 | 61 |
| 5 | $Pd(PPh_3)_4$ | | $Et_3N$ | $CH_3CN$ | reflux | 24 | 12 |

[a] $Pd(OAc)_2$, 5 mol %; $Pd_2(dba)_3{\cdot}CHCl_3$, 2.5 mol %; $Pd(PPh_3)_4$, 10 mol %. [b] *n*-$Bu_4NCl$, 1 equiv; $PPh_3$, 0.2 equiv. [c] $Na_2CO_3$, 2 equiv; $Cs_2CO_3$, 2 equiv; $Et_3N$, 3 equiv.

2,4-dimethylisoquinolin-1(2*H*)-one (**7**) and 4-formyl-2-methylisoquinolin-1(2*H*)-one (**8**) (Scheme 3). The formation of such byproducts is probably due to the thermally induced isomerization of **6a** to 1,2-dihydro-2,4-dimethylisoquinoline, which in turn could be susceptible to air oxidation. As a support to this result, we demonstrated that the prolonged heating of **6a** in DMF at 120 °C led to a mixture containing **7** and **8**. It is known that, under the same conditions, the 2-unsubstituted term of general formula **6** underwent an oxidative aromatization to 4-methylisoquinoline.[9]

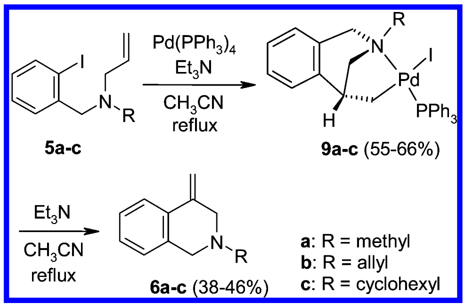
**Scheme 3.** Synthesis of Spiro[isoquinoline-4,5′-isoxazole] **4a** with Isolation of the Intermediates



Replacement of DMF with NMP (entry 2) did not give an improved outcome, while the formation of **6a** was markedly improved when using the same catalyst in DMF at 120 °C in the presence of $Cs_2CO_3$ as a base and $PPh_3$ as a ligand (entry 3). The best result was observed under $Pd_2(dba)_3{\cdot}CHCl_3$ catalysis in DMF at 120 °C in the presence of $Et_3N$ and $PPh_3$ (entry 4). Conversely, the extent of the Heck reaction dramatically fell when $Pd(PPh_3)_4$ was used as catalyst in refluxing $CH_3CN$ in the presence of only $Et_3N$ (entry 5). At this point, we first verified that the reaction of **6a** with **3** took place in good yield (72%) and then we realized for each substrate the one-pot sequential procedure under the different Heck conditions reported in Table 1. The best overall yields, ranging from 30 to 45%, were achieved under the conditions of entry 3.

Further evidence is now presented about the unexpected outcome achieved when attempting the Heck cyclization of **5a** using $Pd(PPh_3)_4$ as catalyst. In addition to the cyclized product **6a** and to a large amount of unreacted allylamine **5a** (47%), a third product was isolated by silica gel column chromatography. The $^1H$ and $^{13}C$ NMR analysis suggested the structure of a Pd complex containing a unity of $PPh_3$. The same type of product was obtained when the reaction was repeated on the allylamines **5b−c** (Scheme 4). Two-dimensional NMR experiments (i.e., HETCOR and COSY), taken on the compound arising from the diallylamine **5b**, were consistent with a single diastereoisomer of a stable $\sigma$-alkyl-Pd−$PPh_3$−iodine complex. X-ray diffractrometric analysis[12] unambiguously confirmed the bridged structure **9b**, containing a five-membered nitrogenated palladacycle with trans disposition of the iodine atom and the methylenic group (see ORTEP representation in Figure 1). Moreover, when the reactions were performed with a stoichiometric amount of $Pd(PPh_3)_4$, the palladacycles **9a−c** were isolated in 55−66% yield. The NMR spectral data indicate the products **9a** and **9c** were formed diastereoselectively. These complexes were found to be highly stable toward air, moisture, heat (ethanol at reflux) and bases (*i*-$Pr_2NEt$ and pyridine in $CHCl_3$). The capture of $\sigma$-alkylpalladium Heck

**Scheme 4.** Synthesis and Conversion of Heck Intermediates **9a−c**



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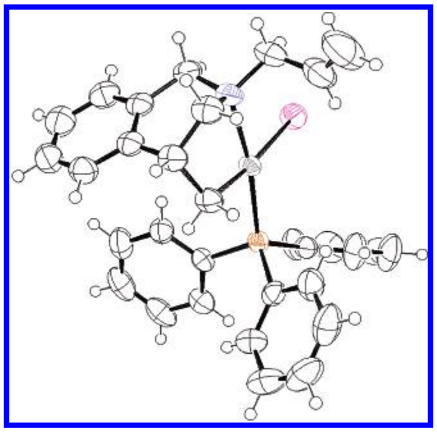

**Figure 1.** ORTEP drawing of compound **9b**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms are given with arbitrary radii.

intermediates with inhibition of $\beta$-hydride elimination is not unprecedented in the literature, but there are only a few examples.[13] As highlighted by Balme's work,[13a] an analogous bridged palladacycle was isolated only when supported on a naphthyl nucleus. The results of our experiments, to the best of our knowledge, constitutes the first example of the systematic isolation of the $\sigma$-alkylpalladium intermediates in intramolecular Heck processes. The marked stability of the complexes **9a**−**c** may be due to the harsh constraint of the palladacycle imposed by the bridged junction, which hinders the cisoid conformation essential to $\beta$-hydride elimination. Moreover, a beneficial stabilization of the intermediate complexes through coordination of the metal with nitrogen atom is reported.[14] Only refluxing **9a**−**c** in $CH_3CN$ and in the presence of $Et_3N$ promotes their conversion to **6a**−**c**.

In conclusion, starting from 2-iodobenzyl bromide and secondary *N*-allylamines, we have successfully developed an effective one-pot, three-component procedure providing new spiro[isoquinoline-4,5′-isoxazole] structures. The procedure is based on a sequential intramolecular Heck reaction and a regioselective intermolecular 1,3-dipolar cycloaddition. On considering that the sequence involves the overall formation of one carbon−nitrogen, two carbon−carbon, and one carbon−oxygen bonds, the yields can be considered satisfactory.

Also, we have brought to light the first example of the systematic isolation and characterization of the $\sigma$-alkylpalladium complex intermediate in an intramolecular Heck reaction promoted by $Pd(PPh_3)_4$.

Further work is ongoing to apply the same strategy to a wider range of 2-halo-substituted aryl systems bearing an allyl moiety and to other 1,3-dipoles.

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**Supporting Information Available:** Experimental procedures, characterization data, and $^1H$ and $^{13}C$ NMR spectra for compounds **4a**−**d**, **6a**−**c**, and **9a**−**c**. Crystal data and experimental procedures for the X-ray structure of **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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