

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

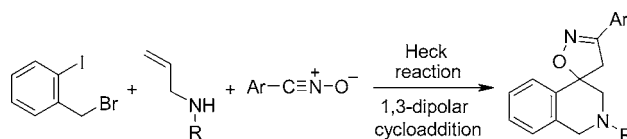
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Received July 10, 2006

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-iodobenzilation/intramolecular Heck reaction/1,3-dipolar cycloaddition. A variety of Heck cyclization conditions were surveyed. When using Pd(PPh₃)₄ as catalyst, stable σ -alkylpalladium iodide complexes were isolated and characterized.

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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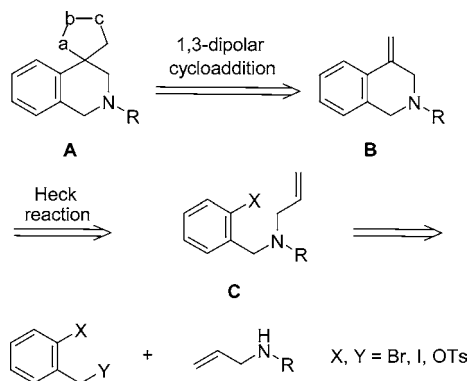
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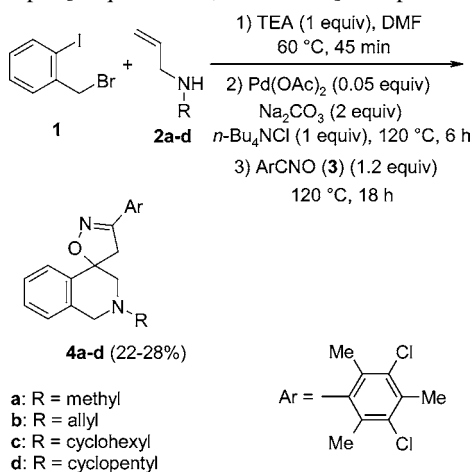
Scheme 1. Retrosynthetic Analysis of 4-Spiroannulated Tetrahydroisoquinolines



though intramolecular Heck couplings⁴ 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 oxide⁸ (**3**) (Scheme 2). The latter 1,3-dipolar substrate was chosen due

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



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 allyl-

amines **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), Na₂CO₃ (2 equiv), and *n*-Bu₄NCl (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.

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 ¹³C 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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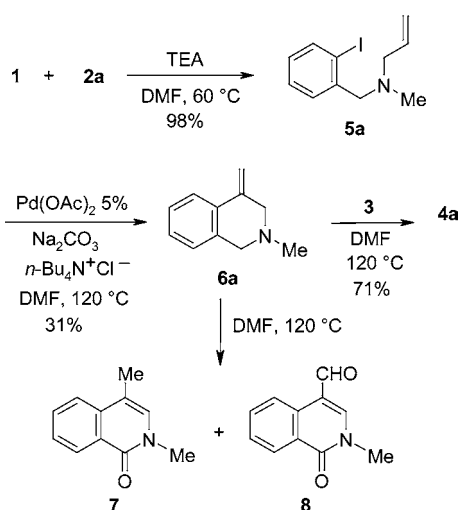
(12) Crystal data: triclinic, space group *P*-1 (No. 2), *a* = 9.458(2) Å; *b* = 11.332(2) Å; *c* = 13.604(2) Å, α = 76.51(1)°; β = 86.68(2)°; γ = 82.32(2)°; *V* = 1404.6(4) Å³, *Z* = 2, CCDC 613934.

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

entry	catalyst ^a	additive/ligand ^b	base ^c	solvent	T (°C)	time (h)	yields of 6a (%)
1	Pd(OAc) ₂	Bu ₄ NCl	Na ₂ CO ₃	DMF	120	6	34
2	Pd(OAc) ₂	Bu ₄ NCl	Na ₂ CO ₃	NMP	120	8	26
3	Pd(OAc) ₂	PPh ₃	Cs ₂ CO ₃	DMF	120	6	55
4	Pd ₂ (dba) ₃ ·CHCl ₃	PPh ₃	Et ₃ N	DMF	120	5	61
5	Pd(PPh ₃) ₄		Et ₃ N	CH ₃ CN	reflux	24	12

^a Pd(OAc)₂, 5 mol %; Pd₂(dba)₃·CHCl₃, 2.5 mol %; Pd(PPh₃)₄, 10 mol %. ^b *n*-Bu₄NCl, 1 equiv; PPh₃, 0.2 equiv. ^c Na₂CO₃, 2 equiv; Cs₂CO₃, 2 equiv; Et₃N, 3 equiv.

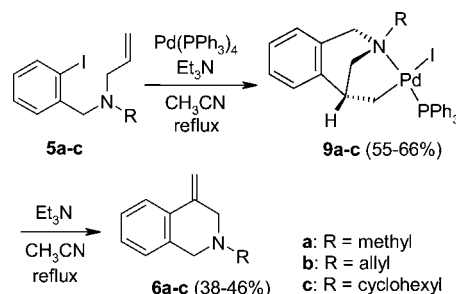
2,4-dimethylisoquinolin-1(2*H*)-one (**7**) and 4-formyl-2-methylisoquinolin-1(2*H*)-one (**8**) (Scheme 3). The formation of

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

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

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 Cs₂CO₃ as a base and PPh₃ as a ligand (entry 3). The best result was observed under Pd₂(dba)₃·CHCl₃ catalysis in DMF at 120 °C in the presence of Et₃N and PPh₃ (entry 4). Conversely, the extent of the Heck reaction dramatically fell when Pd(PPh₃)₄ was used as catalyst in refluxing CH₃CN in the presence of only Et₃N (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(PPh₃)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 ¹³C NMR analysis suggested the structure of a Pd complex containing a unity of PPh₃. The same type of product was obtained when the reaction was repeated on the allylamines **5b–c** (Scheme 4). Two-

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

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 σ -alkyl-Pd-PPh₃-iodine complex. X-ray diffractometric analysis¹² 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(PPh₃)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*-Pr₂NEt and pyridine in CHCl₃). The capture of σ -alkylpalladium Heck

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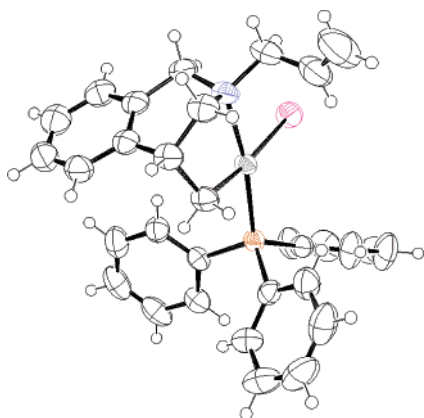


Figure 1. ORTEP drawing of compound **9b**. Thermal ellipsoids are drawn at the 50% probability level. Hydrogen atoms are given with arbitrary radii.

intermediates with inhibition of β -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 σ -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 β -hydride elimin-

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ation. 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 σ -alkylpalladium complex intermediate in an intramolecular Heck reaction promoted by $\text{Pd}(\text{PPh}_3)_4$.

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.

Acknowledgment. Thanks are due to the Ministero dell'Istruzione, dell'Università e della Ricerca for financial support. We are also grateful to the Centro Interuniversitario sulle Reazioni Pericicliche and to Fondazione CARIPO.

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>.

OL061693C