ORGANIC
LETTERS

2000
Vol. 2, No. 15
2225−2228

Palladium-Catalyzed Intramolecular Coupling of Vinyl Halides and Ketone Enolates. Synthesis of Bridged Azabicyclic Compounds

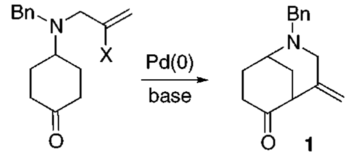
Daniel Solé,* Emma Peidró, and Josep Bonjoch*

*Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona,
08028-Barcelona, Spain*

bonjoch@farmacia.far.ub.es

Received April 20, 2000

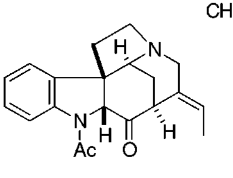
ABSTRACT



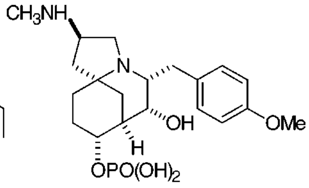
1

The palladium-mediated intramolecular coupling of amino-tethered vinyl halides and ketone enolates is a useful methodology for the synthesis of nitrogen heterocycles and constitutes a new synthetic entry to the 2-azabicyclo[3.3.1]nonane framework. A study about the reaction conditions and the scope of the process is reported.

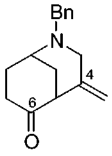
As part of our ongoing program in the synthesis of natural products embodying the 2-azabicyclo[3.3.1]nonane framework,[1] we became interested in the synthesis of compounds with this bridged system bearing a carbonyl at C-6 and substituted at the 4-position by an alkylidene appendage (e.g., **1**). This framework is an attractive target not only because it is found in some alkaloids (e.g., strychnopivotine[2]) but also because it could be elaborated into more functionalized systems, such as those of the immunosuppressant FR901483[3,4] or the cytotoxic agent madangamine-A.[5]



Strychnopivotine



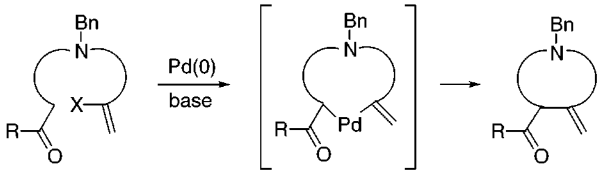
FR901483



1

We considered that the Pd-catalyzed intramolecular coupling of vinyl halides and ketone enolates (Scheme 1) could be a suitable methodology for the synthesis of the target system, despite the fact that these types of cyclizations have been completely ignored for a long time.[6] To our knowledge,

Scheme 1. Pd-Catalyzed Intramolecular Coupling of Vinyl Halides and Ketone Enolates



---

[1] (a) Bonjoch, J.; Solé, D.; García-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230−7240. (b) Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem.* **1998**, *63*, 968−976. (c) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem. Eur. J.* **2000**, *6*, 655−665.

[2] (a) Isolation: Tits, M.; Tavernier, D.; Angenot, L. *Phytochemistry* **1980**, *19*, 1531−1534. (b) Synthetic studies: Teuber, H.-J.; Tsaklakidis, C.; Bats, J. W. *Liebigs Ann. Chem.* **1992**, 461−466.

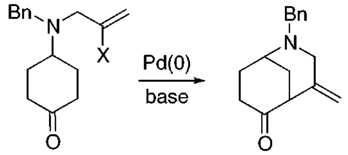
[3] (a) Isolation: Sakamoto, K.; Tsujii, E.; Abe, F.; Nakanihi, T.; Yamashita, M.; Shigematsu, N.; Izumi, S.; Okuhara, M. *J. Antibiot.* **1996**, *49*, 37−44. (b) Total synthesis: Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778−7786.

10.1021/ol005973i CCC: $19.00

there are only two examples of this reaction, which was developed by Piers in the carbocyclic series and successfully applied to the synthesis of the diterpenoid crinipellin B.[7] The reaction exploits the electrophilic character of the palladium atom and it is presumed to proceed by sequential oxidative addition and deprotonation, followed by conversion to a palladacycle, which undergoes a simple reductive elimination.

In this paper we report the implementation of the above methodology to the synthesis of nitrogen heterocycles.[8] Our efforts were initially focused on the cyclization of vinyl halides **2a** and **2b** (Table 1), which were readily available by alkylation of 4-(benzylamino)cyclohexanone.[9] In the presence of 0.2 equiv of $Pd(PPh_3)_4$ and 1.5 equiv of KO*t*-Bu in refluxing THF (entry 1), vinyl bromide **2a** underwent the desired cyclization reaction to give 2-azabicyclo[3.3.1]-nonan-6-one **1** in 40−50% yield,[10] together with minor amounts of dimer **3**. The formation of **3** can be explained by the Pd-catalyzed coupling of **2a** with the alkyne **4** formed by elimination of HBr from the starting vinyl bromide.[11] The

Table 1. Pd-Catalyzed Cyclization of **2a** and **2b**

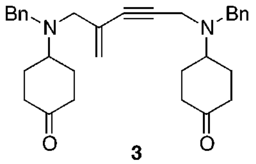


2a X = Br
2b X = I

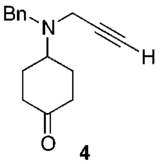
1

entry	X	catalyst (equiv)	base (equiv)	solvent (temp)	products (%)[a]
1	Br	$Pd(PPh_3)_4$ (0.2)	KO*t*-Bu (1.5)	THF (rfx)[c]	**1** (40−50) **3** (5)
2	Br	$Pd(PPh_3)_4$ (0.1)	KO*t*-Bu (1.5)	THF (rfx)[c]	**1** (43) **3** (10)
3	Br	$Pd[P(o\text{-tol})_3]_2Cl_2$ (0.2)	KO*t*-Bu (1.5)	THF (rfx)[c]	**1** (50)
4	Br	$Pd(OAc)_2$ (0.2) PPh_3 (0.4)	KO*t*-Bu (1.5)	THF (rfx)[d]	**1** (40) **3** (5)
5	Br	$Pd(PPh_3)_4$ (0.2)	NaH (1.5)	THF (rfx)[e]	**1** (22)
6	Br	$Pd(PPh_3)_4$ (0.2)	TBAF (2)[b]	THF (rfx)[e]	**1** (15) **3** (8)
7	Br	$Pd(PPh_3)_4$ (0.2)	KO*t*-Bu (1.5)	CH_3CN (rfx)[d]	**1** (7) **3** (7) **4** (10)
8	Br	$Pd(PPh_3)_4$ (0.2)	KO*t*-Bu (1.5)	DMF (70 °C)[d]	**3** (5) **4** (22)
9	I	$Pd(PPh_3)_4$ (0.2)	KO*t*-Bu (1.5)	THF (rfx)[c]	**1** (55−60)
10	I	$Pd(PPh_3)_4$ (0.2)	KO*t*-Bu (1.3)	THF (rt)[f]	**1** (42)

[a] Yields refer to pure isolated products. [b] HMPA (6 equiv). [c] 30 min. [d] 1 h. [e] 3.5 h. [f] 24 h.



3



4

amount of the catalyst could be reduced to 0.1 equiv without any significant effect on the yield of the cyclization (entry 2), although smaller amounts of $Pd(PPh_3)_4$ resulted in worse yields. The use of $Pd[P(o\text{-tolyl})_3]_2Cl_2$ (entry 3) and $Pd(OAc)_2/PPh_3$ (entry 4) as the catalyst afforded similar yields of cyclized product. Bases other than KO*t*-Bu were examined,[12] and among them only NaH (entry 5) and TBAF (entry 6) afforded the desired azabicyclic compound **1**, although in low yields.

Other bases studied (HMDS, NaOH, TMG, KF, and CsF) did not give any reaction, even after long reaction times at reflux. The solvent was also important; thus, although the cyclized product **1** was also observed in CH_3CN (entry 7), DMF (entry 8) failed to promote the cyclization, with considerable amounts of alkyne **4** being isolated. The use of Cs_2CO_3 as the base in toluene at reflux[6a] mainly resulted in dealkylation of the starting material to give 4-(benzylamino)-cyclohexanone. It is noteworthy that dealkylation of the 2-haloallylamine seems to be a common competing reaction since the secondary amine was detected, although not quantified, in nearly all the cyclization mixtures. Finally, addition of $n\text{-}Bu_4NCl$ to the otherwise standard cyclization of **2a** increased the amount of dimer **3**, while the addition of $AgNO_3$ resulted in recovery of the starting vinyl bromide. On the other hand, as expected, vinyl iodide **2b** was more efficient in the intramolecular coupling than **2a**. Thus, treatment of **2b** with 0.2 equiv of $Pd(PPh_3)_4$ and 1.5 equiv

---

[4] For our studies in this field, see: Bonjoch, J.; Diaba, F.; Puigbó, G.; Solé, D.; Segarra, V.; Santamaría, L.; Beleta, J.; Ryder, H.; Palacios, J.-M. *Bioorg. Med. Chem.* **1999**, *7*, 2891−2897.

[5] (a) Isolation: Kong, F.; Andersen, R. J.; Allen, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 6007−6008. (b) Synthetic studies: Matzanke, N.; Gregg, R. J.; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 1920−1921.

[6] For the Pd-catalyzed intramolecular coupling of aryl halides and enolates, see: (a) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581−7582. (b) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546−6553. (c) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355−2358. For the Pd-catalyzed intermolecular coupling of aryl halides and enolates, see: (d) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370 and references therein.

[7] (a) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454−3455. (b) Piers, E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11−13.

[8] For the elaboration of 3-alkylidene piperidine rings by Heck reactions in the synthesis of alkaloids, see: (a) Rawal, V. H.; Michoud, C.; Monestel, R. F.*J. Am. Chem. Soc.* **1993**, *115*, 3030−3031. Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685−2686. (b) Birman, V. B.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 7219−7222. Birman, V. B.; Rawal, V. H. *J. Org. Chem.* **1998**, *63*, 9146−9147. (c) See ref 1c.

[9] Quirante, J.; Escolano, C.; Massot, M.; Bonjoch, J. *Tetrahedron* **1997**, *53*, 1391−1402.

[10] For other recent synthetic methods to build up this azabicyclic system, see: (a) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 7418−7429. (b) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280−8281. (c) Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1157−1162.

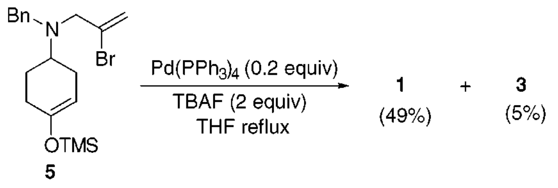
[11] The detection of alkynes was also reported by Piers, who minimized the formation of such byproducts by slowly adding the base at room temperature.[7a]

[12] Following the suggestion of a reviewer, sodium *tert*-butoxide[6b,d] has also been tried as a base for this process. Using the reaction conditions of entry 1 (Table 1) and the aforementioned base, there was no significant change in the yield of compound **1**.

of KO*t*-Bu in refluxing THF (entry 9) gave **1** in 55−60% yield. Moreover, starting from vinyl iodide **2b** the cyclization was achieved at room temperature (entry 10) to afford **1** in acceptable yield and without the formation of appreciable amounts of byproducts. In contrast, under the same reaction conditions vinyl bromide **2a** was recovered unchanged.

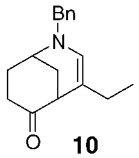
The Pd-catalyzed intramolecular coupling could also be accomplished by generating the enolate starting from the corresponding silyl enol ether.[13] Thus, treatment of **5** with 0.2 equiv of Pd(PPh_3)$_4$ and 2 equiv of TBAF in refluxing THF afforded azabicyclic ketone **1** in 49% yield together with a small amount of dimer **3** (Scheme 2). An alternative explanation for the formation of **1** involving a Heck reaction upon the silyl enol ether double bond, followed by F$^-$-mediated desilylation of the cyclized product, was rejected, because in the absence of TBAF and under the same reaction conditions the starting silyl enol ether **5** was recovered.

Scheme 2



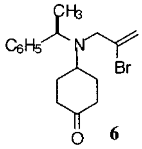
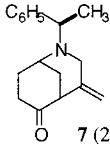
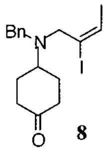
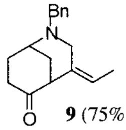
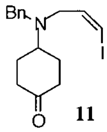
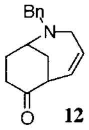
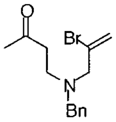
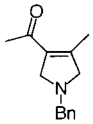
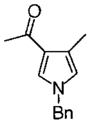
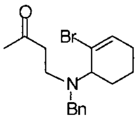
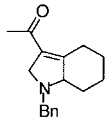
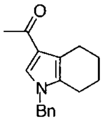
The Pd-catalyzed intramolecular coupling of vinyl halides and ketone enolates was extended to other substrates (Table 2). Under the standard cyclization conditions, vinyl bromide **6** afforded bicycle **7** in 24% yield (entry 1). The lower yield of the cyclization could be interpreted on conformational grounds. Thus, the introduction of a bulkier substituent at the nitrogen atom hampers the conformational change previous to the cyclization step.

Starting from vinyl iodide **8** the bridged compound **9** was obtained in good yield (entry 2). It is interesting to note that on standing this compound, which is the only one detected in the reaction mixture, isomerized to the enamine **10**.



10

Table 2. Synthesis of Nitrogen Heterocycles by Pd-Catalyzed Cyclization of Vinyl Halides and Ketone Enolates

entry	substrate	method[a]	products (yield)
1	 **6**	A[b]	 **7** (24%)[c,d]
2	 **8**	A	 **9** (75%)
3	 **11**	A	 **12** (23%)[e]
4	 **13**	A	 **14**  **15** (32%, 1:1)
5	**1 3**	B	**15** (45%)
6	 **16**	B	 **17**  **18** (34%, 2:3)
7	**1 6**	A	**18** (12%)[f]

[a] Method A: KO*t*-Bu (1.5 equiv), Pd(PPh_3)$_4$ (0.2 equiv), THF reflux, 30 min. Method B: Cs_2CO_3 (3 equiv), Et_3N (3 equiv), $PdCl_2(PPh_3)_2$ (0.2 equiv), toluene 110 °C, sealed tube, 24 h. [b] 1.5 h. [c] 4-[*N*-(α-Methylbenzyl)amino]cyclohexanone was also detected in the reaction mixture. [d] 1.5:1 mixture of diastereomers. [e] Alkyne **4** was also detected in the reaction mixture along with several unidentified products. [f] *N*-Benzyl-2-cyclohexenylamine (29%) was also isolated.

On the other hand, the 2-azabicyclo[4.3.1]decane system[14] (e.g., **12**) can be obtained, although in low yield, starting from vinyl iodide **11** (entry 3). Finally, we examined the Pd-catalyzed annulation of β-aminoketones **13** and **16**, which led to the formation of five-membered nitrogen heterocycles. Treatment of **13** under the standard cyclization conditions (entry 4) afforded a reaction mixture in which the only product detected was pyrroline **14**, which arises when the initially formed annulation product undergoes an isomerization to the more stable conjugated ketone under strongly basic reaction conditions.[15] Nevertheless, after column chromatography a 1:1 mixture of **14** and pyrrole **15** was obtained.[16] Interestingly, the Pd-catalyzed cyclization of **13** can also be accomplished by using Cs_2CO_3 as the base (entry 5). Under these conditions and after column chromatography, pyrrole

---

(13) (a) For Pd-catalyzed intermolecular arylation of tin enolates, prepared in situ from silyl enol ethers and Bu_3SnF, see: Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831−6833. (b) For Pd-catalyzed intermolecular alkenylation of tin enolates, prepared in situ from enol acetates and Bu_3SnOMe, see: Kosugi, M.; Hagiwara, I.; Sumiya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 242−246.

(14) Quirante, J.; Escolano, C.; Bonjoch, J. *Synlett* **1997**, 179−180.

(15) The isomerization of the initially formed annulation products to the conjugated enones under the reaction conditions was also observed by Piers.[7a]

(16) For the easy air oxidation of 3-acylpyrrolines to 3-acylpyrroles, see: Chou, S.-S. P.; Yuan, T.-M. *Synthesis* **1991**, 171−172.

15 was obtained in acceptable yield. Similar results were obtained starting from **16**, which underwent cyclization to afford mixtures of hydroindoles **17** and **18**, after column chromatography, although in lower yields (entries 6 and 7).

In summary, the utility of the Pd-catalyzed intramolecular coupling of vinyl halides and ketone enolates to the synthesis of nitrogen heterocycles has been reported. Further studies directed toward the application of this methodology to the synthesis of natural products embodying the 2-azabicyclo[3.3.1]-nonane framework are in progress and will be reported on in due course.

Acknowledgment. This work was supported by the DGICYT, Spain (Project PB97-0877). Financial support for DGEU, Catalonia (1999SGR00067) is also acknowledged.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **1**, **3**, **4**, **7**, **9**, **10**, **12**, **14**, **15**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL005973I