ORGANIC LETTERS

2001
Vol. 3, No. 9
1371−1374

Synthesis of *N*-Heteroaryl-7-azabicyclo[2.2.1]heptane Derivatives via Palladium–Bisimidazol-2-ylidene Complex Catalyzed Amination Reactions

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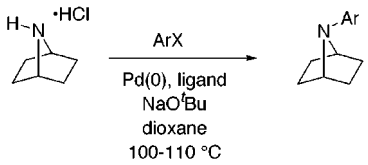
Received February 21, 2001

ABSTRACT



A one-step approach to novel *N*-heteroaryl-substituted-7-azabicyclo[2.2.1]heptanes from readily available heteroaryl halides and 7-azabicyclo-[2.2.1]heptane has been achieved. The cross-coupling amination reaction employs palladium–bisimidazol-2-ylidene complexes as catalysts to give good to moderate yields over a wide variety of substrates.

Recently developed palladium- or nickel-catalyzed amination of aryl halides and triflates has opened great opportunities in many areas of organic synthesis.[1] General, reliable, and practical *N*-arylations of a wide variety of amines and anilines with both electron-rich and electron-deficient aryl halides have been achieved.[2−6] These pioneering studies have shown that a well-tailored metal−ligand catalyst system is crucial for successful aryl C−N bond formation.[7]

The nucleophilic *N*-heterocyclic carbenes have attracted considerable attention as ligands for a variety of palladium-catalyzed coupling reactions.[4,8] We recently reported on the utility of the $Pd_2(dba)_3$−Imes·HCl and $Pd(OAc)_2$−DiImes·HCl catalyst systems for Suzuki-type C−C bond formation reactions of aryl chlorides and arylboronic acids.[9,10] As part of a drug discovery program aimed at the synthesis of *N*-heteroaryl-substituted 7-azabicyclo[2.2.1]heptanes, we sought to investigate the Pd−DiImes·HCl catalyst system in cross-coupling amination reactions of heteroaryl halides with 7-azabicyclo[2.2.1]heptane.

Prior to development of the amination methodology, it was necessary to develop an efficient and practical route for the preparation of 7-azabicyclo[2.2.1]heptane hydrochloride (**1**).[11] To date, the most practical synthesis of **1** was reported by

(1) For a recent review of metal-catalyzed amination reactions, see: (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067.

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(6) Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2000**, *41*, 2875−2879.

(7) For recent examples of catalytic aryl amination, see: (a) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403−1406. (b) Harris, M. C.; Buchwald, S. L. *J.Org. Chem.* **2000**, *65*, 5327−5333. (c) Bei, X.; Uno, T.; Norris, J.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *Organometallics* **1999**, *18*, 1840−1853. (d) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370.

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(11) For a recent review on 7-azabicyclo[2.2.1]heptanes, see: Chen. Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179−1193.

10.1021/ol015746w CCC: $20.00
Published on Web 04/07/2001

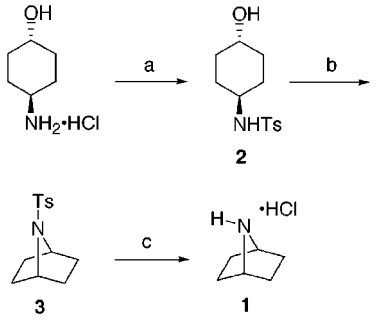
Fraser and Swingle.[12] Their five-step sequence furnished **1** with an overall yield of 18−36%. Alternatively, Nelsen et al. demonstrated that *trans*-4-aminocyclohexanol could be directly converted into **1** (26%) when diethoxytriphenylphosphorane was employed as a cyclodehydrating reagent.[13] However, the utility of this approach was limited due to the formation of 7-ethyl-7-azabicyclo[2.2.1]heptane (18% yield) as a side product which required additional steps to separate it from **1**.

As illustrated in Scheme 1, a three-step synthesis of **1** from commercially available *trans*-4-aminocyclohexanol hydrochloride was achieved by treatment of *trans*-4-aminocyclohexanol hydrochloride with tosyl chloride in the presence of potassium hydroxide with a catalytic amount of triethylamine in acetonitrile. This afforded the desired tosylamide **2** in nearly quantiative yield.[14] The tosylamide **2** was then subjected to Mitsunobu reaction conditions employing PPh_3 (2.5 equiv) and DEAD (2.5 equiv) in THF at room temperature.[15] This effected the ring closure and generated the 7-azabicyclo[2.2.1]heptane **3** in 80% yield. It was determined that excess PPh_3 and DEAD were necessary to achieve high yields of **3**. For example, 1.2 equiv of PPh_3 and DEAD gave only a 66% yield of **3**. In addition, other *N*-acyl groups (e.g., BOC, CBZ) proved to be less effective for ring closure under these reaction conditions. This direct cyclization was a significant improvement over existing methods which required additional protection and deprotection steps prior to ring closure.[12] In addition, the intramolecular cyclization reaction does not appear to be limited by the reaction scale. High yields have been obtained on either a milligram or multigram scale.

The *N*-tosyl group of **3** was removed with freshly prepared sodium naphthalide in THF to furnish the desired 7-azabicyclo-[2.2.1]heptane (**1**).[16] Removal of the tosyl group was also attempted with HBr/HOAc. However, this method was less effective. As previously reported, due to the volatile nature of **1**, the 7-azabicyclo[2.2.1]heptane was routinely isolated as the hydrochloride salt.[12] This short and practical synthetic sequence afforded 7-azabicyclo[2.2.1]heptane (**1**) in 53% overall yield.

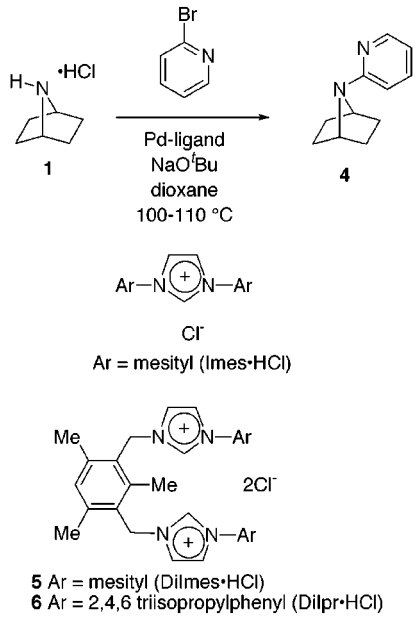
The catalytic cross-coupling reaction of 7-azabicyclo-[2.2.1]heptane (**1**) and 2-bromopyridine in dioxane at 100−110 °C which furnished 7-(2-pyridinyl)-7-azabiyclo[2.2.1]-heptane (**4**) was selected as a model reaction for investigation of the efficiencies of different Pd−ligand catalyst systems (Table 1). As summarized in Table 1, the PPh_3, DPPB, DPPP, and P(*o*-tol)$_3$ ligands exhibited low conversion and were found to be less efficient than the two bisimidazolium salt catalyst precursors, mesityl bisimidazolium salt **5** (DiImes·HCl, entry 6) and the 2,4,6-triisopropylphenyl bisimidazolium salt **6** (DiIpr·HCl, entry 7).[17,18] Comparing the two

Scheme 1[a]



[a] Reagents and conditions: (a) TsCl, KOH, Et_3N (catalytic), CH_3CN; (b) PPh_3, DEAD, THF, 25 °C; (c) NaNp, DME, −35 to 25 °C.

Table 1. Influence of the Pd/Ligand Catalyst System on the Cross-Coupling Amination of **1** with 2-Bromopyridine



entry[a]	Pd−ligand	time (h)	yield (%)[b]
1	$Pd(OAc)_2$−PPh_3	42	37[c]
2	$Pd(OAc)_2$−DPPP	40	25[c]
3	$Pd(OAc)_2$−DPPB	40	11[c]
4	$Pd_2(dba)_3$−P(o−Tol)$_3$	36	51
5	$Pd_2(dba)_3$−DPPF[d]	36	66
6	$Pd_2(dba)_3$−DiImes•HCl (5)	36[e]	61
7	$Pd_2(dba)_3$−DiIpr•HCl (6)	36[e]	67

[a] Typical reaction conditions: 4 mol % of Pd, 4 mol % of ligand, 2.8 mmol of NaOtBu, 1 mmol of 2-bromopyridine, 1.2 mmol of **1**, 5 mL of dioxane, 100−110 °C. [b] Isolated yields. [c] 2-Bromopyridine was not completely consumed and Pd black was observed. [d] Pd/ligand ratio was 1:1.5. [e] Reaction time after a 30 min catalyst activation period.

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(14) Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. *Tetrahedron* **1999**, *55*, 2183−22192.
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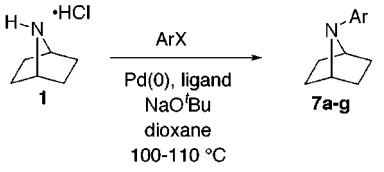
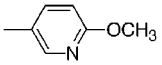
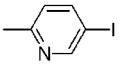
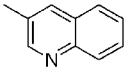
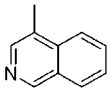
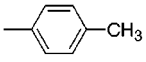
bisimidazolium salts, the catalyst precursor **6** gave a slightly higher yield (entry 7) than **5** (entry 6). The higher performance of the bisimidazolium salt **6** is thought to be due to its better electron-donating ability and more steric hindrance. Only the DPPF ligand gave a yield similar (entry 5) to that of the bisimidazolium salt **6**. However, this required a higher Pd−ligand ratio (1:1.5) to furnish the optimized yield (66%). In addition, when the amination reactions were attempted with the Pd−bisimidazolium salt system, only *tert*-butyl aryl ethers were isolated and no amination products were observed.

The successful amination of **1** then prompted a further investigation of the scope and limitations of the $Pd_2(dba)_3$−bisimidazolium salt **6** catalyst system for general cross-coupling amination reactions. As summarized in Table 2, a number of structurally and electronically diverse aryl halides were employed. Under the reaction conditions, 2- and 3-bromopyridines gave the corresponding *N*-pyridinyl-7-azabicyclo[2.2.1]heptane derivatives (**4** and **7a**) in 67% and 71% yields, respectively. 4-Bromopyridine hydrochloride also underwent the amination reaction and furnished **7b** in 58% yield (4.2 equiv of NaO^{t}Bu employed). Conversely, introduction of a methoxy group as electron donor on the pyridine ring resulted in an incomplete reaction even after long reaction times (41 h), and the yield of **7c** was low (36%). The quinoline and isoquinoline heterocyclic systems gave results similar to those of the pyridine analogues and afforded **7e** and **7f** in good yields. However, longer reaction times were needed to complete the cross-coupling reaction of quinoline and isoquinoline heterocyclics relative to the formation of **4**. As a comparison, the tolyl bromide provided **7h** in 66% yield.

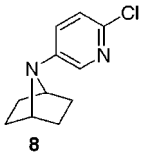
As expected, the 2-chloro-5-iodopyridine gave a predominant coupling product at the 2-position (**7d**). However, a small amount of 7-(2-chloro-5-pyridinyl)-7-azabicyclo-[2.2.1]heptane (**8**) was isolated (5% yield) that resulted from amination at the 5-iodo substituent. The regioselectivity of this reaction is noteworthy since it has been shown that the reaction of the polyfunctionalized heteroaromatic core in the cross-coupling reaction gave a regioisomeric mixture.[19]

Table 2. Pd−Bisimidazol-2-ylidene (**6**) Complex Catalyzed Cross-Coupling Reactions of Aryl Halides and **1**



cmpd [a]	X	Ar	time (h) [b]	yield (%) [c]
4	Br		36	67
7a	Br		24	71 [d]
7b	Br[e]		25	58
7c	Br		41	36 [f]
7d	Cl		30	56 [g]
7e	Br		36	67
7f	Br		36	71
7g	Cl		30	66

[a] All products were characterized by NMR, IR, MS, and C, H, N analysis. [b] Reaction time after a 30 min catalyst activation period. [c] Isolated yields. [d] $Pd(OAc)_2$ was used as the Pd source. [e] 4-Bromopyridine•HCl was employed with 4.2 equiv of NaO^{t}Bu. [f] Yield based on recovered starting material. [g] 7-(2-Chloro-5-pyridinyl)-7-azabicyclo[2.2.1]heptane (**8**) was also isolated in 5% yield.



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In summary, application of the Pd−bisimidazolium salt catalyzed cross-coupling amination methodology provides a general and convenient route for the construction a wide range of *N*-aryl-substituted-7-azabicyclo[2.2.1]heptane derivatives. The synthetic utility of this catalyst system appears to be broad and useful for the construction of *N*-arylamine systems. The biological results and structure−activity relationships of the *N*-aryl-substituted-7-azabicyclo[2.2.1]heptane

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(18) The bisimidazolium salt **6** was made in a fashion similar to that of the bisimidzolium salt **5** (ref 9). A mixture of 1,3-di(α-chloromethyl)-2,4,6-trimethylbenzene (1.0 mmol) and *N*-(2,4,6-triisopropylphenyl)imidazole (2.0 mmol) was heated in xylene at 120 °C for 48 h and furnished **6** in 76% yield.

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derivatives are under further investigation and will be reported in due course.

Acknowledgment. We are grateful to the National Institute on Drug Abuse for the financial support of this research.

Supporting Information Available: Experimental procedures and spectroscopic data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015746W