Pergamon

Tetrahedron Letters 43 (2002) 1621–1624

TETRAHEDRON
LETTERS

Novel palladium-catalyzed synthesis of 1,2-dihydro-4(3*H*)-carbazolones

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Received 30 November 2001; revised 3 January 2002; accepted 4 January 2002

Abstract—Two sequential palladium-catalyzed reactions are the key steps in a novel synthetic route to carbazolones, an intermolecular Stille coupling followed by a recently developed palladium-catalyzed reductive *N*-heteroannulation. A number of functionalized 1,2-dihydro-4(3*H*)-carbazolones were prepared using this sequence. © 2002 Elsevier Science Ltd. All rights reserved.

Carbazolones have been used as intermediates in total synthesis of a variety of naturally occurring carbazole alkaloids for example, pyrayaquinones A and B, murrayaquinone A, koeniginequinone A,[1] and murrayafoline A.[2] In addition, the synthetic drug ondansetron (Fig. 1) is a potent 5HT$_3$ receptor agonist used for the prevention of nausea caused by chemotherapy and radiation treatment of cancer patients.

A variety of methods have been utilized to obtain carbazolones. One of the most common methods used is the Fischer indole synthesis. For example, the parent system, 1,2-dihydrocarbazol-4(3*H*)-one, was prepared in 51% yield by reaction of phenylhydrazine with 1,3-cyclohexanedione followed by treatment of the hydrazone with sulfuric acid.[3] Drawbacks of this methodology are the highly acidic reaction conditions and the formation of regioisomeric products using unsymmetrical substrates.

We have recently developed a relatively mild and very efficient palladium-catalyzed route to substituted indoles via a reductive *N*-heteroannulation of functionalized 2-nitrostyrenes.[4] Based on these results, we envisioned a short and novel route to the carbazole ring system via two consecutive palladium-catalyzed reactions, a Stille coupling followed by the reductive *N*-heteroannulation. Thus, in our initial synthetic sequence, 2-iodo-2-cyclohexenone (**2**)[5] was reacted with 2-(tri-*n*-butylstannyl)-1-nitrobenzene (**1**)[6] in the presence of bis(benzonitrile)palladium dichloride (PdCl$_2$(PhCN)$_2$, 5 mol%), triphenylarsine (AsPh$_3$, 10 mol%), and copper iodide (10 mol%) in *N*-methylpyrrolidinone (NMP) to give the expected coupling product **3** in good isolated yield. Attempted *N*-heteroannulation of **3** using palladium diacetate (6 mol%), triphenylphosphine (24 mol%), and carbon monoxide (4 atm) in acetonitrile at 70°C, reaction conditions previously employed for the preparation of a large variety of indoles, surprisingly gave only recovered starting material. Palladium–phenanthroline complexes have been shown to be particularly active catalysts for the reductive carbonylation of nitrobenzenes to give isocyanates.[7] Thus, using somewhat modified conditions, palladium bis(dibenzylideneacetone) (Pd(dba)$_2$, 6 mol%), 1,3-bis(diphenylphosphino)propane (dppp, 12 mol%), 1,10-phenanthroline (12 mol%), and CO (6 atm) in dimethylformamide (DMF) at 80°C, the expected 1,2-dihydro-4(3*H*)-carbazolone **4** was obtained in good isolated yield (Scheme 1). In later reactions, 1,10-phenanthroline dihydrate was used with no apparent detrimental effect. In the absence of the diphosphine, a somewhat lower yield of product was observed. Thus, all reactions discuss herein were performed with both ligands present.

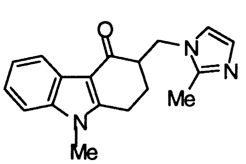

Figure 1.

The polarity of the coupling reagents can readily be switched, i.e. using an arylhalide and a 2-trialkyltin substituted enone. The required tin compound was prepared by reaction of the vinylbromoketal **5**[8] with 2 equiv. of *t*-butyllithium followed by addition of tri-*n*-

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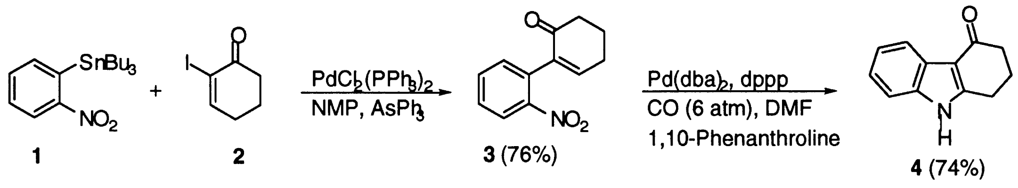
PII: S0040-4039(02)00072-2



Scheme 1.

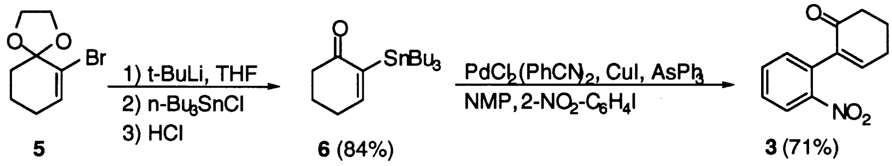
butyltin chloride. The crude reaction mixture was stirred with HCl (10%, aq.) affording the deprotected ketone **6**[9] in high overall yield (Scheme 2). Palladium-catalyzed cross coupling of **6** with 2-nitroiodobenzene gave the expected cross coupling product **3** in 71% yield.

A number of additional examples of the cross coupling–annulation sequence to 1,2-dihydro-4(3*H*)-carbazolones were examined, and the results thereof are summarized in Table 1.[10] A variety of substituted 2-(2-nitrophenyl)-2-cycloalkenones (**7**–**12**) were prepared as depicted in Schemes 1 and 2 via a palladium-catalyzed Stille-type coupling of **1** or **6** with 2-iodo-2-enones[11] or aryl halides, respectively (Table 1). The Stille couplings proceeded uneventfully; however, lower yields of product were observed for the more sterically hindered aryl bromides seen in entries 3 and 5. Some modifications of the reaction conditions were required for the synthesis of compounds **9** and **11**. Although still moderate, the best yield of **9** was obtained by replacing $AsPh_3$ with 1,1′-bis-(diphenylphosphino)ferrocene (dppf) as the ligand. Compound **11** was prepared using $PdCl_2(PPh_3)_2$ as the catalyst in DMF (110°C) without added ligand. It should be noted that, minor amounts (<10%) of homocoupled dimers of **1** and **6** were seen in most cases.

Palladium-catalyzed *N*-heteroannulation of **7**–**12** gave the expected 2,3-fused indoles **13**–**18** in 61–89% isolated yield (Table 1). The reactions were monitored by TLC until all starting material had been consumed (22–96 h). Five- and seven-membered rings were readily fused to the indole skeleton (entries 1 and 2). The annulation reaction is relatively unaffected by electron-withdrawing and electron-donating substituents on the aromatic ring. As can be seen in entries 3 and 4, both ester and alkoxy groups work well. Substituents adjacent to the alkene or the nitro group of the aromatic ring also do not appear to affect the yield of the reaction (entries 5 and 6). Similar results were obtained in our previous studies of the formation of indoles by reductive *N*-heteroannulation.[4]

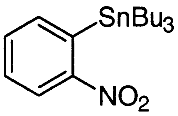
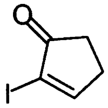
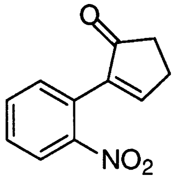
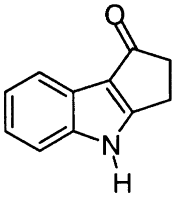
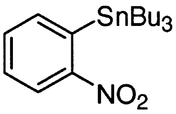
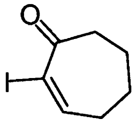
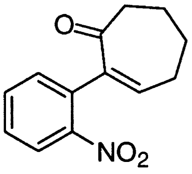
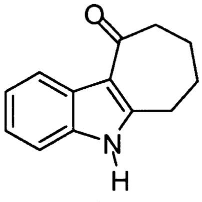
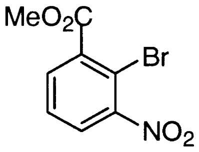
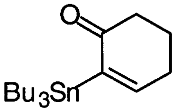
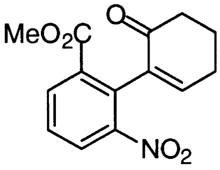
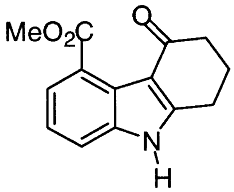
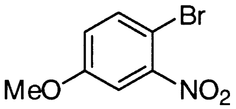
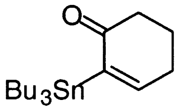
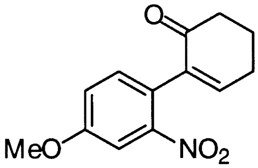
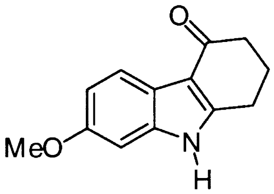
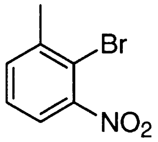
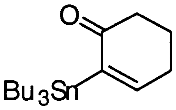
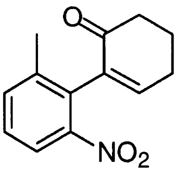
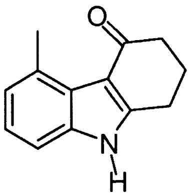
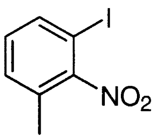
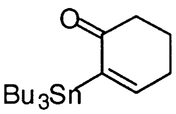
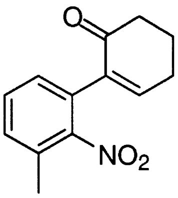
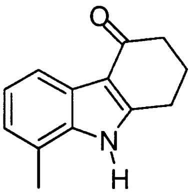
The mechanism of metal-catalyzed reductive *N*-heteroannulations of aromatic nitro compounds, in the presence of CO, has been examined in some detail. Watanabe, Cenini, and others have suggested the formation of a metal bound nitrene intermediate formed via sequential deoxygenations of the nitro group and elimination of 2 equiv. of carbon dioxide.[12,13] One possible mechanism is presented in Scheme 3 for the simpler 2-nitrostyrene substrate. Reaction of the nitrogroup with palladium(0) and carbon monoxide would give **19**. Elimination of carbon dioxide to give a metal bound nitrosamine **20** followed by insertion of carbon monoxide would afford metallacyclobutanone **21**. A second elimination of carbon dioxide produces the metal bound nitrene **22**. Cyclization of the metal bound nitrene to a six-membered metallacycle **23**, and reductive elimination followed by a [1,5]-hydrogen shift would give the observed product and regenerate the active palladium catalyst. A number of partially deoxygenated, closely related, or isomeric metallacyclo-pentanes, -butanes, and -propanes have been isolated in support of the depicted mechanism.[14] A ruthenium bound biphenylnitrene complex, related to **22**, has been characterized by X-ray diffraction. Thermolysis of this complex gave carbazole, the expected nitrene insertion product.[15] Reduction of the nitro group to an amino group followed by aminopalladation and reductive-elimination, was recently disproved as a major pathway.[16]

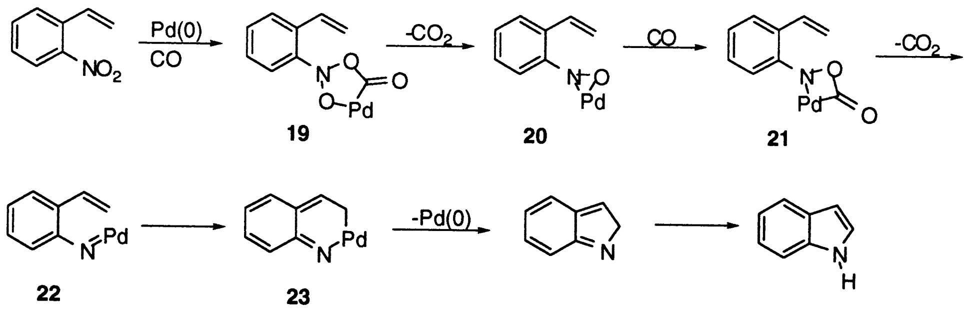
In summary, a novel route to tricyclic substituted 2,3-fused indoles in general and carbazolones in particular has been developed. The scope and limitation of this route together with applications thereof in total synthesis are presently being examined in our laboratories.



Scheme 2.

Table 1. Stille cross coupling followed by *N*-heteroannulation

Entry	Nitrobenzene	Alkenone	Coupling product	Indole
1			 **7** (65%)	 **13** (85%)
2			 **8** (68%)	 **14** (66%)
3			 **9** (44%)	 **15** (75%)
4			 **10** (69%)	 **16** (89%)
5			 **11** (31%)	 **17** (79%)
6			 **12** (62%)	 **18** (75%)



Scheme 3.

Acknowledgements

This work was supported by a research grant from the National Institutes of Health (R01 GM57416). Copy editing by Diana G. Duran is gratefully acknowledged.

References

1. For a review, see: Bouaziz, Z.; Nebois, P.; Poumaroux, A.; Fillion, H. *Heterocycles* **2000**, *52*, 977.
2. Chakraborty, D. P.; Chowdhury, B. K. *J. Org. Chem.* **1968**, *33*, 1265.
3. Rodriguez, J.-G.; Temprano, F.; Esteban-Calderon, C.; Martinez-Ripoll, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2117.
4. Söderberg, B. C.; Chisnell, A. C.; O'Neil, S. N.; Shriver, J. A. *J. Org. Chem.* **1999**, *64*, 9731.
5. (a) Boße, F.; Tunoori, A. R.; Niestroj, A. J.; Gronwald, O.; Maier, M. E. *Tetrahedron* **1996**, *52*, 9485; (b) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917.
6. Kosugi, M.; Ohya, T.; Migita, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3855.
7. Gallo, E.; Ragaini, S.; Cenini, S.; Demartin, F. *J. Organomet. Chem.* **1999**, *586*, 190 and references cited therein.
8. Anderson, J. C.; Pearson, D. J. *J. Chem. Soc., Chem. Commun.* **1998**, 2023.
9. For a previous synthesis, see: Adam, W.; Klug, P. *Synthesis* **1994**, 557.
10. *2-(6-Methyl-2-nitrophenyl)-2-cyclohexen-1-one (**11**)*: mp 79–80°C; IR 1671, 1520, 1356 cm^{-1}; ^{1}H NMR δ 2.09–2.20 (m, 2H), 2.22 (s, 3H), 2.51 (q, $J=5.7$, 2H), 2.57–2.74 (m, 2H), 6.72 (t, $J=4.2$ Hz, 1H), 7.33 (t, $J=7.8$ Hz, 1H), 7.46 (d, $J=7.5$ Hz, 1H), 7.78 (d, $J=8.1$ Hz, 1H); ^{13}C NMR δ 20.0, 22.5, 26.0, 38.2, 121.6, 127.9, 131.4, 134.4, 137.2, 138.3, 146.8, 149.4, 196.8; HRMS calcd for $C_{13}H_{13}NO_3$: 231.0895; found: 231.0902.
11. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919.
12. Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 3375.
13. Cenini, C.; Ragaini, F. *Catalytic Reductive Carbonylation of Organic Nitro Compounds*; Kluwer Academic: Dordrecht, Netherlands, 1997.
14. (a) Pizzotti, M.; Porta, F.; Cenini, S. *J. Organomet. Chem.* **1987**, *330*, 265; (b) Gargulak, J. D.; Berry, A. J.; Noirot, M. D.; Gladfelter, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 8933.
15. Crotti, C.; Cenini, S.; Bassoli, A.; Rindone, B.; Demartin, F. *J. Mol. Catal.* **1991**, *70*, 175.
16. Ragaini, F.; Sportiello, P.; Cenini, S. *J. Organomet. Chem.* **1999**, *577*, 283.