ORGANIC LETTERS

2012
Vol. 14, No. 1
398–401

Synthesis of Tricyclic Nitrogen Heterocycles by a Sequence of Palladium-Catalyzed N–H and C(sp^3)–H Arylations

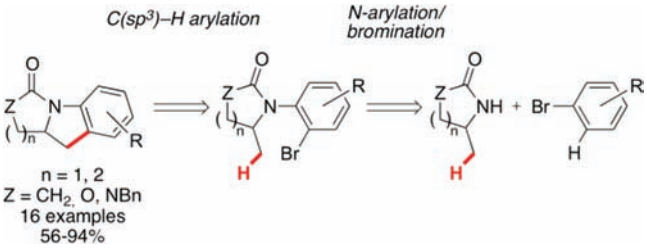
Mathieu Guyonnet and Olivier Baudoin*

CNRS UMR 5246 - Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, Université Claude Bernard Lyon 1, CPE Lyon, 43 Boulevard du 11 Novembre 1918, 69622 Villeurbanne, France

olivier.baudoin@univ-lyon1.fr

Received November 28, 2011

ABSTRACT



A range of tricyclic nitrogen heterocycles were synthesized in a straightforward and efficient manner via a sequence involving palladium-catalyzed *N*-arylation and C(sp^3)–H arylation as the key steps. Whereas the C(sp^3)–H arylation furnished fused 6,5,6-membered ring systems efficiently, the formation of the more strained 6,5,5-membered systems proved to be more challenging and required a subtle adjustment of the reaction conditions.

In recent years, transition-metal-catalyzed C–H bond functionalization has emerged as a powerful tool to transform otherwise unreactive C–H bonds into carbon–carbon or carbon–heteroatom bonds.[1,2] In particular, this approach has been utilized to construct[3] and functionalize[4] heterocyclic systems, which have broad interest for the synthesis of bioactive molecules and organic materials. Most existing C–H functionalization methods employed to assemble heterocycles involve the cleavage of C(sp^2)–H bonds, and in comparison much less effort has been devoted to methods involving the somewhat more challenging activation of nonacidic C(sp^3)–H bonds.[5–7] Inspired by former work on the synthesis of indolines by palladium(0)-catalyzed C(sp^3)–H arylation,[6f,k] we envisioned that a similar strategy could be utilized to access fused tricyclic

(1) *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005.

(2) *Topics in Current Chemistry*; Yu, J.-Q., Shi, Z., Eds.; Springer: Heidelberg, 2010; Vol. 292.

(3) (a) Thansandote, P.; Lautens, M. *Chem.–Eur. J.* **2009**, *15*, 5874. (b) Stokes, B. J.; Driver, T. G. *Eur. J. Org. Chem.* **2011**, 4071.

(4) (a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (b) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (c) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (d) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (e) Hirano, K.; Miura, M. *Synlett* **2011**, 294.

(5) (a) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.–Eur. J.* **2010**, *16*, 2654. (b) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902.

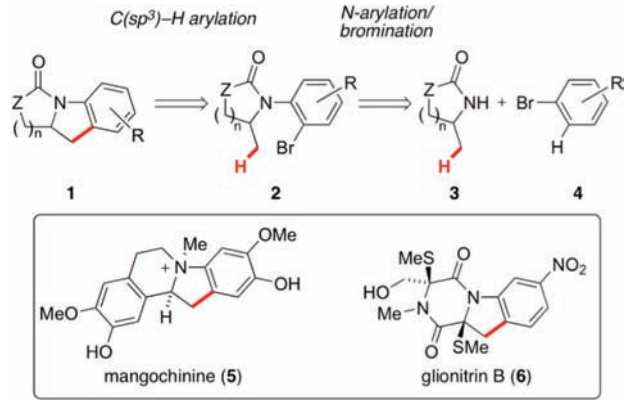
(6) For the synthesis of heterocycles via palladium(0)-catalyzed C(sp^3)–H activation: (a) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023. (b) Ren, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3462. (c) Ren, H.; Li, Z.; Knochel, P. *Chem.–Asian J.* **2007**, *2*, 416. (d) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570. (e) Liron, F.; Knochel, P. *Tetrahedron Lett.* **2007**, *48*, 4943. (f) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759. (g) Salcedo, A.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2008**, *73*, 3600. (h) Kim, H. S.; Gowrisankar, S.; Kim, S. H.; Kim, J. N. *Tetrahedon Lett.* **2008**, *49*, 3858. (i) Huang, Q.; Larock, R. C. *Tetrahedon Lett.* **2009**, *50*, 7235. (j) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 10692. (k) Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706. (l) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438.

(7) For the synthesis of heterocycles via palladium(II)-catalyzed C(sp^3)–H activation: (a) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274. (b) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496. (c) Liégault, B.; Fagnou, K. *Organometallics* **2008**, *27*, 4841. (d) Neumann, J. J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892. (e) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680. (f) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378. (g) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 6541. (h) Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2011**, *133*, 12584.

10.1021/ol2031763
Published on Web 12/16/2011

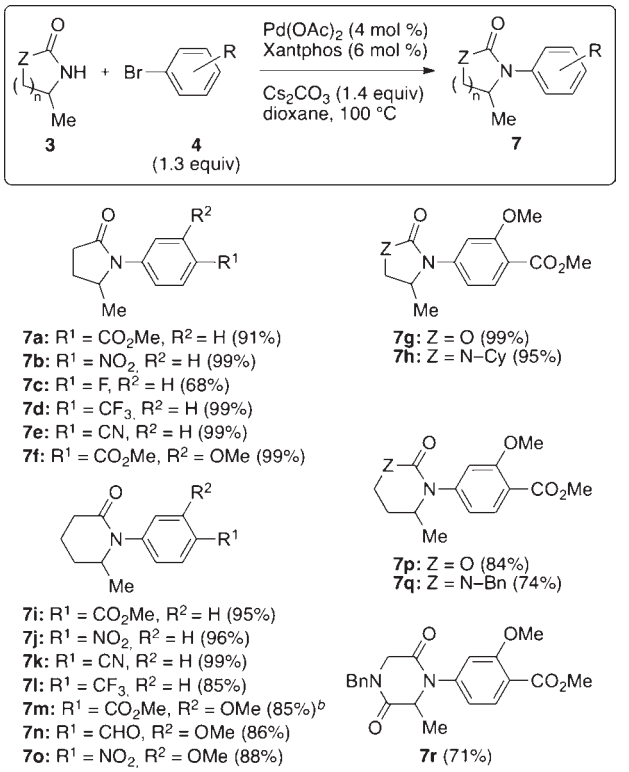
γ- and δ-lactams **1** (Z = CH_2) and analogues from aryl bromides **2** (Scheme 1). An efficient synthesis of these rather unique heterocycles[8] should streamline access to bioactive alkaloids such as mangochinine (**5**)[9] and glionitrin B (**6**).[10] In turn, aryl bromides **2** would be obtained by a Buchwald–Hartwig *N*-arylation/electrophilic bromination sequence, thereby securing a straightforward and modular synthesis of target lactams **1**.

Scheme 1. Retrosynthetic Analysis



We began our study with the exploration of the first key *N*-arylation step (Scheme 2). The Pd-catalyzed *N*-arylation of γ-lactams has been reported to occur with high yields.[11] In line with these data, *N*-arylated γ-lactams **7a**–**f** bearing electron-withdrawing substituents on the benzene ring were obtained in good-to-excellent yield (68–99%) by using $Pd(OAc)_2$/Xantphos as the catalyst.[12] Similarly to γ-lactams, analogous oxazolidinone (Z = O) and imidazolidinone (Z = NCy) also underwent *N*-arylation efficiently (**7g**,**h**), in line with literature precedents.[13] In contrast, δ-lactams have been shown to be less reactive than γ-lactams, and as a consequence the Pd-catalyzed *N*-arylation of the former has been much less developed.[11a] Nevertheless, the above reaction conditions were found to be also applicable to δ-lactams (**7i**–**o**) as well as analogous 6-membered cyclic carbamate (**7p**), urea (**7q**), and diketopiperazine (**7r**). Indeed, high yields of the corresponding *N*-arylated products were obtained, provided that electron-deficient aryl bromides were used as coupling partners.[14] However, the *N*-arylation of the corresponding ε-lactam (**3** with *n* = 3) failed under the same conditions.

Scheme 2. Synthesis of *N*-Arylated Lactams and Analogues[a]



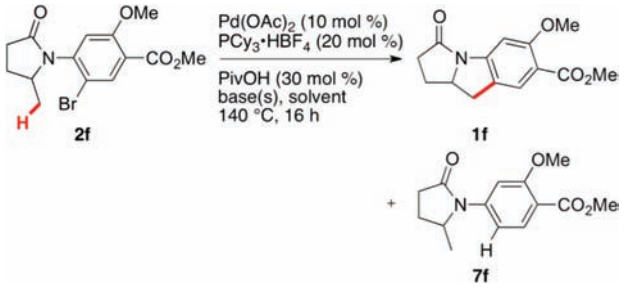
[a] Yield of the isolated products in parentheses.
[b] Obtained under microwave heating (160 °C).

Following *N*-arylation, the regioselective bromination of compounds **7a**–**r** was performed, giving rise to the corresponding aryl bromides **2a**–**r** in 73–97% yield by using either $Br_2/AgNO_3$ or *N*-bromosuccinimide (see the Supporting Information for details). Next, the second key $C(sp^3)$–H arylation step was investigated. We first applied conditions initially reported by Fagnou et al.[6d] and then successfully transposed to other heterocyclic systems[6f,j–l] to aryl bromide **2f** (Table 1, entry 1). Thus, with $Pd(OAc)_2$/PCy_3 as the catalyst and cesium carbonate/pivalic acid as the base/additive in mesitylene at 140 °C, protodebromination product **7f** was formed with complete conversion. This failure can be ascribed to the excessive strain of the target tricyclic ring system, as compared to previously successful bi- and tricyclic systems.[6f] Changing the base to potassium carbonate (entry 2) or the solvent to DMF (entry 3) failed to provide any observable trace of desired product **1f**. Interestingly, compound **1f** was formed in small amounts with toluene as the solvent (entry 4). A reexamination of different carbonates with this solvent

(8) For an alternative approach giving moderate yields, see: Lu, H.; Li, C. *Tetrahedron Lett*. **2005**, *46*, 5983.
(9) Qiu, S.; Liu, C.; Zhao, S.; Xia, Z.; Farnsworth, N. R.; Fong, H. H. S. *Tetrahedron Lett*. **1998**, *39*, 4167.
(10) Park, H. B.; Kim, Y.-J.; Park, J.-S.; Yang, H. O.; Lee, K. R.; Kwon, H. C. *J. Nat. Prod*. **2011**, *74*, 2309.
(11) (a) Shakespeare, W. C. *Tetrahedron Lett*. **1999**, *40*, 2035. (b) Yin, J.; Buchwald *Org. Lett*. **2000**, *2*, 1101. (c) Browning, R. G.; Mahmud, H.; Badarinarayana, V.; Lovely, C. J. *Tetrahedron Lett*. **2001**, *42*, 7155. (d) Browning, R. G.; Badarinarayana, V.; Mahmud, H.; Lovely, C. J. *Tetrahedron* **2004**, *60*, 359. (e) Shirai, A.; Miyata, O.; Tohnai, N.; Miyata, M.; Procter, D. J.; Sucunza, D.; Naito, T. *J. Org. Chem*. **2008**, *73*, 4464.
(12) Aryl substituents R^1, R^2 were chosen for their ability to direct bromination in *ortho* position to the lactam during the next step.
(13) (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett*. **2001**, *3*, 2539. (b) Madar, D. J.; Kopecka, H.; Pireh, D.; Pease, J.; Pliushchev, M.; Sciotti, R. J.; Wiedeman, P. E.; Djuric, S. W. *Tetrahedron Lett*. **2001**, *42*, 3681. (c) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 6043.
(14) For instance, *N*-arylation failed with Z = CH_2 and R^1 = R^2 = OMe.

(entries 5–8) led to an optimal result with potassium carbonate (entry 6). Moreover, by combining K_2CO_3 with various amounts of Na_2CO_3 (entries 9–12), we found that the selectivity of **1f** vs **7f** could be reversed, with **1f** becoming the major product.

Table 1. Optimization of the Intramolecular C(sp^3)–H Arylation[a]

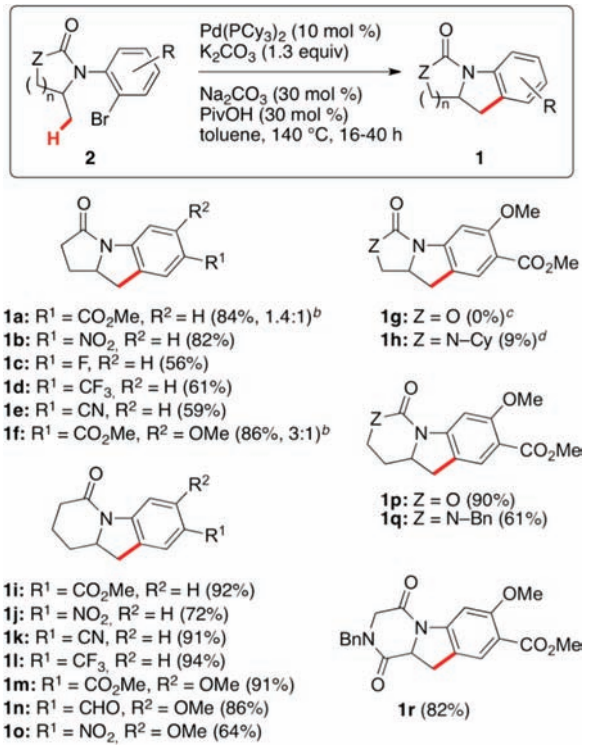


entry	base(s) (equiv)	solvent	conversion[a] (%)	**1f**:**7f**[a]
1	Cs_2CO_3 (2.0)	mesitylene	>99	<1:99
2	K_2CO_3 (2.0)	mesitylene	>99	<1:99
3	Cs_2CO_3 (2.0)	DMF	>99	<1:99
4	Cs_2CO_3 (2.0)	toluene	>99	1:49
5	Rb_2CO_3 (2.0)	toluene	>99	1:11
6	K_2CO_3 (2.0)	toluene	>99	1:1.6
7	Na_2CO_3 (2.0)	toluene	4	1:1
8	Li_2CO_3 (2.0)	toluene	14	<1:99
9	K_2CO_3 (1.3)	toluene	>99	1:2
10	K_2CO_3 (1.3) Na_2CO_3 (1.3)	toluene	>99	3:1
11	K_2CO_3 (1.3) Na_2CO_3 (0.9)	toluene	>99	2.8:1
12	K_2CO_3 (1.3) Na_2CO_3 (0.3)	toluene	>99	2.7:1
13	**K_2CO_3 (1.3) Na_2CO_3 (0.3)**	**toluene**	**>99**	**3:1 (86%)[b]**

[a] Conversion of **2f** and ratio of **1f**:**7f** determined by ^{1}H NMR and GCMS analysis of the crude mixture. [b] $Pd(PCy_3)_2$ was used instead of the $Pd(OAc)_2/PCy_3 \cdot HBF_4$ mixture. Yield of the isolated mixture in parentheses.

In related reactions, the C(sp^3)–H activation step was shown to occur through the base-induced, concerted metalation–deprotonation (CMD) mechanism.[6d,j,k,15] The beneficial effect of the combination of K_2CO_3 and Na_2CO_3 highlights the impact of the base countercation, lying in the second coordination sphere of Pd, in such mechanism. Finally, more reproducible results were obtained when the well-defined $Pd(PCy_3)_2$ complex was employed instead of the in situ mixture of $Pd(OAc)_2$ and phosphine ligand (entry 13). Under these conditions, an inseparable mixture of **1f**:**7f** (3:1) was isolated in 86% combined yield. The above results show that, for difficult cases of C(sp^3)–H arylation, subtle adjustments of the solvent and base must be performed to form the desired product at the expense of the competitive protodebromination product.

Scheme 3. Synthesis of Fused Tricyclic Lactams and Analogues[a]



[a] Yield of the isolated products in parentheses.

[b] Yield and ratio of the mixture of desired:protodebromination products.

[c] Protodebromination and degradation were observed by GCMS analysis.

[d] 85% of the starting material was recovered after 48 h.

The optimized conditions were then applied to various aryl bromides obtained by the *N*-arylation/electrophilic bromination sequence (Scheme 3). In line with the above results, fused γ-lactams **1a**–**f** were obtained in moderate-to-good yields together with the corresponding protodebromination products, that could be separated in most instances (**1b**–**e**). Unfortunately, the more rigid oxazolidinone **2g** and imidazolidinone **2h** failed to undergo intramolecular C(sp^3)–H arylation under the same conditions. In contrast, the reaction of the less rigid δ-lactams **2i**–**o**, oxazinanone **2p** and tetrahydropyrimidone **2q** provided the corresponding tricyclic products **1i**–**q** in good-to-excellent yields. In addition, original fused diketopiperazine **1r** was also obtained efficiently by this method.[10,16]

The X-ray crystal structures of representative target molecules **1m** and **1r** were elucidated (Figure 1), showing that these compounds exhibit a relatively similar rigid tricyclic scaffold.

(15) (a) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157. (b) Kefalidis, C. E.; Baudoin, O.; Clot, E. *Dalton Trans* **2010**, *39*, 10528.

(16) 2,5-Diketopiperazines are important structural motifs in natural product and medicinal chemistry: (a) Martins, M. B.; Carvalho, I. *Tetrahedron* **2007**, *63*, 9923. (b) Huang, R.; Zhou, X.; Xu, T.; Yang, X.; Liu, Y. *Chem. Biodivers.* **2010**, *7*, 2809.

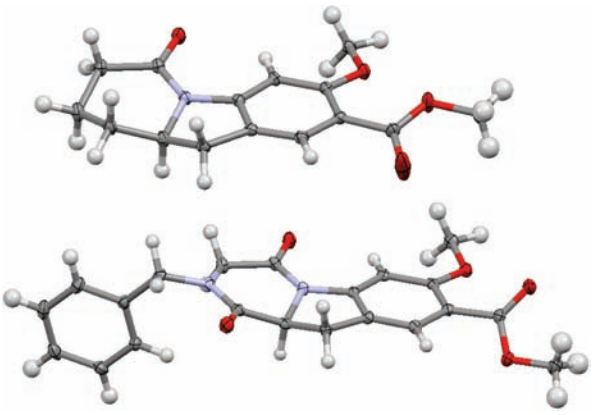


Figure 1. X-ray crystal structure of compounds **1m** (top) and **1r** (bottom) (30% probability ellipsoids plot).

In conclusion, we have described a straightforward strategy to synthesize original fused tricyclic nitrogen heterocycles by using Pd-catalyzed *N*-arylation and C (sp^3)−H arylation as the key steps. This work further illustrates the impact of emerging C−H functionalization methods on the synthesis of new interesting molecular scaffolds.

Acknowledgment. We thank the Ministère de l'Enseignement Supérieur et de la Recherche (fellowship to M.G.), Agence Nationale de la Recherche (programme blanc "AlCaCHA"), Institut Universitaire de France, and Johnson Matthey PLC (loan of palladium acetate). We are also grateful to R. Jazzar and E. Jeanneau (Université Claude Bernard Lyon 1) for the synthesis of Pd complexes and X-ray diffraction analyses, respectively.

Supporting Information Available. Full characterization of all new compounds, detailed experimental procedures, copies of NMR spectra for target molecules, and X-ray crystal structure data (CIF) for compounds **1m** and **1r**. This material is available free of charge via the Internet at http://pubs.acs.org.