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Preparation of Annulated Nitrogen-Containing Heterocycles via a One-Pot Palladium-Catalyzed Alkylation/Direct Arylation Sequence

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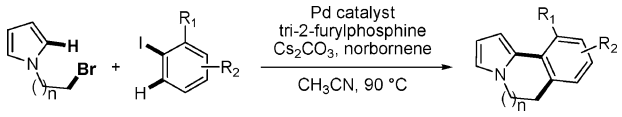
ABSTRACT



A palladium-catalyzed/norbornene-mediated sequential coupling reaction involving an aromatic sp² C–H functionalization as the key step is described, in which an alkyl–aryl bond and an aryl–heteroaryl bond are formed in one pot. A variety of highly substituted six- and seven-membered annulated pyrroles and pyrazoles were synthesized in a one-step process in good yields from readily accessible *N*-bromoalkyl pyrroles or pyrazoles and aryl iodides.

Nitrogen-containing heterocycles are of substantial interest in organic chemistry as they are integral components of natural products, dyes, agrochemicals, and pharmaceuticals. The pyrrole core represents one of the most important heterocycles because it is present in a wide variety of biologically active natural compounds.[1] Recently, increasing attention has been devoted to the 5,6-dihydro-pyrrolo[2,1-*a*]isoquinoline framework **1** since its unique tricyclic structure has been found in several natural and biologically active compounds including Crispine A (**2**),[2] Lettowianthine (**3**)[3] and Lamellarin D (**4**)[4] (Figure 1).[5]

Although annulated pyrroles of type **1** have been prepared via intramolecular cyclization of advanced intermediates using radical,[6] metal-catalyzed,[7] or base-induced processes,[8] few examples of direct synthesis are known.[9] Herein, we report a new and straightforward one-step synthesis of highly functionalized 5,6-dihydro-pyrrolo[2,1-*a*]isoquinoline derivatives **7** using readily accessible starting materials **5** and **6**. Our strategy is based on a palladium-catalyzed/norbornene-mediated sequential aromatic alkylation (**I**)/aryl-heteroaryl coupling (**II**) reaction[10] and involves an aromatic sp² C−H functionalization[10,11] as the key step (Scheme 1).

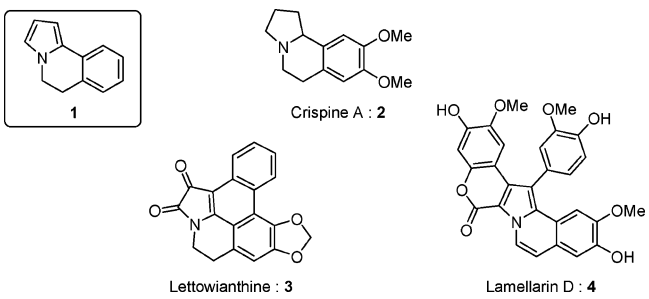


Figure 1. Natural compounds containing tricyclic structure **1**.

(1) For reviews, see for instance: (a) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. S. V., Eds.; Pergamon Press: New York, 1996; Vol. 2, pp 207−257. (b) Le Quesne, P. W.; Dong, Y.; Blythe, T. A. *Alkaloids: Chem. Biol. Perspect.* **1999**, *13*, 237−287. (c) Janosik, T.; Bergman, J. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.; Pergamon: Amsterdam, 2003; Vol. 15, pp 140−166.

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(3) Nkunya, M. H. H.; Jonker, S. A.; Makangara, J. J.; Waibel, R.; Achenbach, H. *Phytochemistry* **2000**, *53*, 1067−1073.

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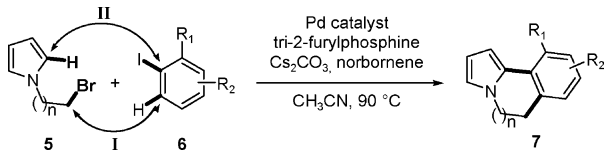
Scheme 1. Synthesis of 5,6-Dihydro-pyrrolo[2,1-*a*]isoquinoline Derivatives



Our initial attempts to effect a tandem alkylation/direct arylation employed bromoalkyl pyrrole **8**. Use of aryl iodide **9** under the optimized reaction conditions [iodoarene (0.20 mmol, 1 equiv), $PdCl_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), norbornene (2 equiv), and bromoalkyl pyrrole (2 equiv) in acetonitrile (0.1 M) at 90 °C in a sealed tube for 23 h] afforded six-membered annulated pyrrole **10** in 77% yield (entry 1, Table 1).

The generality of this reaction sequence was first demonstrated for unsubstituted pyrroles by varying the substituents on the iodoarene (entries 1−7) and the length of the alkyl chain (entries 8 and 9). Both electron-withdrawing and electron-donating groups are tolerated at various positions on the iodoarene and give good to excellent yields when reacted with alkyl pyrrole **8**. However, substrate **19**, bearing an *o*-methoxy substituent, gave a modest yield (entry 6). The chloro-derivative **21** gave the product in 75% yield, and the resulting compound **22** represents a very useful partner for further functionalizations.[12] Seven-membered annulated pyrroles **24** and **25** were also constructed with comparable yields using $Pd(OAc)_2$ as the catalyst (entries 8 and 9). The 1-substituted pyrrole **26** afforded the product **28** in 59% yield (reaction run on a 2 mmol scale), and the resulting product **28** represents an interesting advanced intermediate for the synthesis of biologically active Lamellarin derivatives[4b,7b] (entry 10).

Table 1. Synthesis of Annulated Pyrroles via Palladium-Catalyzed Tandem Alkylation/Direct Arylation Reaction[a]

entry	pyrrole	iodide	product	yield (%)[b]
1	**8**	**9**	**10**	77
2	**8**	**11**	**12**	67
3	**8**	**13**	**14**	91
4	**8**	**15**	**16**	73
5	**8**	**17**	**18**	84
6	**8**	**19**	**20**	59
7	**8**	**21**	**22**	75
8	**23**	**9**	**24**	74[c]
9	**23**	**15**	**25**	69[c]
10	**26**	**27**	**28**	59[d]

[a] Unless otherwise noted, all reactions were run under the following conditions: iodoarene (0.20 mmol, 1 equiv), $PdCl_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), norbornene (2 equiv), and bromoalkyl pyrrole (2 equiv) in acetonitrile (2 mL) were heated in a sealed tube at 90 °C for 23 h (conditions A). [b] Isolated yield. [c] $Pd(OAc)_2$ was used as the catalyst. [d] Reaction run on a 2 mmol scale.

The *ortho* alkylation likely proceeds through the mechanism previously described by Catellani[13] and involves an aromatic sp^2 C−H activation (**A** → **B**) as the key step[10] (Scheme 2). Intermediate **E** arises from the reductive elimination of the proposed $Pd^{(IV)}$ complex **C** followed by expulsion of norbornene (**D** → **E**). Aryl-heteroaryl coupling of **E** via C−H functionalization of the pyrrole C-2 hydrogen finally provides annulated pyrroles.[14] In some cases ($n \geq$

(4) (a) Facompré, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392−7399. (b) Pla, D.; Marchal, A.; Olsen, C. A.; Albericio, F.; Álvarez, M. *J. Org. Chem.* **2005**, *70*, 8231−8234.

(5) For other related natural and/or biologically active compounds, see: (a) Chen, C.-C.; Huang, Y.-L.; Lee, S.-S.; Ou, J.-C. *J. Nat. Prod.* **1997**, *60*, 826−827. (b) Almerico, A. M.; Mingoia, F.; Diana, P.; Barraja, P.; Montalbano, A.; Lauria, A.; Loddo, R.; Sanna, L.; Delpiano, D.; Setzy, M. G.; Musiu, C. *Eur. J. Med. Chem.* **2002**, *37*, 3−10. (c) Yang, Y.-L.; Chang, F.-R.; Wu, Y.-C. *Helv. Chim. Acta* **2004**, *87*, 1392−1399.

(6) (a) Fiumana, A.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 4209−4211. (b) Allin, S. M.; Bowman, W. R.; Elsegood, M. R. J.; McKee, V.; Karim, R.; Rahman, S. S. *Tetrahedron* **2005**, *61*, 2689−2696.

(7) (a) Knölker, H.-J.; Agarwal, S. *Tetrahedron Lett.* **2005**, *46*, 1173−1175. (b) Olsen, C. A.; Parera, N.; Albericio, F.; Álvarez, M. *Tetrahedron Lett.* **2005**, *46*, 2041−2044.

(8) (a) Ishibashi, F.; Miyazaki, Y.; Iwao, M. *Tetrahedron* **1997**, *53*, 5951−5962. (b) Orito, K.; Harada, R.; Uchiito, S.; Tokuda, M. *Org. Lett.* **2000**, *2*, 1799−1801.

(9) See however: Banwell, M.; Flynn, B.; Hockless, D. *Chem. Commun.* **1997**, *23*, 2259−2260.

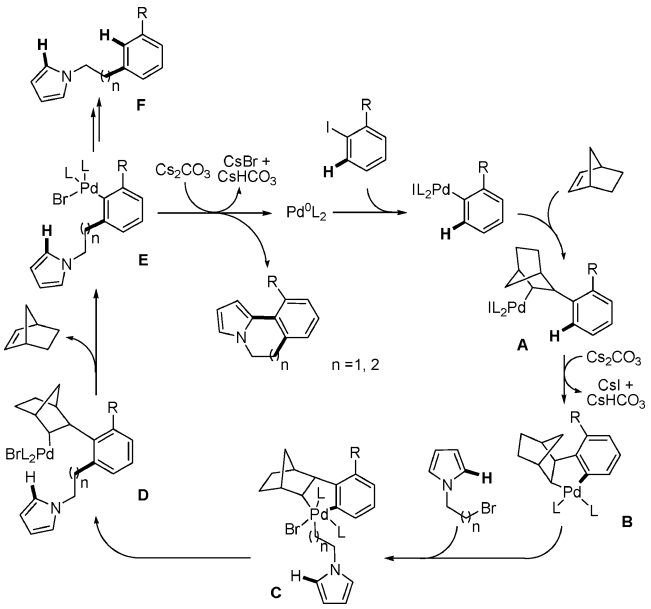
(10) This strategy has previously been applied with success to the preparation of annulated indole derivatives: Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148−13149.

(11) For reviews on aromatic sp^2 C−H functionalizations, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699−1712. (b) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211−241. (c) Campeau, L.-C.; Thansandote, P.; Fagnou, K. *Org. Lett.* **2005**, *7*, 1857−1860.

(12) (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696. For a review on palladium-catalyzed coupling reactions of aryl chlorides, see: (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.

(13) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119−122.

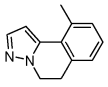
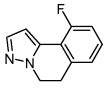
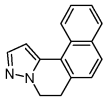
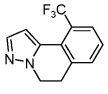
Scheme 2. Proposed Mechanism for the Synthesis of Annulated Pyrroles



3),[15] a slow final cyclization allows the formation of linear *ortho*-alkylated products of type **F**. This observation suggests that *ortho*-alkylation most likely precedes aryl−heteroaryl coupling.

We next turned our attention to reacting pyrazoles (Table 2), since they constitute an important class of compounds that possess widespread pharmacological properties.[16] However, to the best of our knowledge, no C−H functionalization reaction involving pyrazole derivatives has been reported. Our initial attempt employing bromoalkyl pyrazole **29** and iodide **30** resulted in a low yield (<10%) of expected annulated pyrazole **31** using standard conditions A (see Table 1). This low yield may result from catalyst poisoning by the second nitrogen atom.[17] We then ran the reaction using a slow addition (syringe pump for 20 h) of pyrazole **29**. Preliminary results showed annulated pyrazole **31** could be isolated in 54% yield (entry 1, Table 2). Iodides **32**, **34**, and **36** gave comparable yields (entries 2−4).

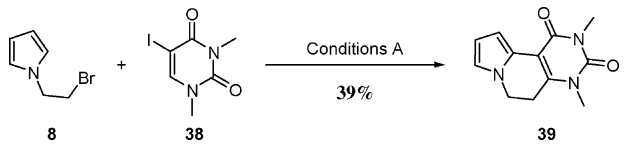
Table 2. Synthesis of Annulated Pyrazoles[a]

entry	pyrazole	iodide	product	yield (%)[b]
1	 **29**	 **30**	 **31**	54
2	 **29**	 **32**	 **33**	49
3	 **29**	 **34**	 **35**	51
4	 **29**	 **36**	 **37**	42

[a] All reactions were run under the following conditions: at 90 °C, to a MeCN (2 mL) solution of iodoarene (0.60 mmol, 1.5 equiv), $Pd(OAc)_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), and norbornene (2 equiv) was added dropwise (20 h addition) bromoalkyl pyrazole (1 equiv) in MeCN (2 mL) using a syringe pump. [b] Isolated yield.

Finally, we wish to report our initial result involving an iodo-heteroaromatic partner. Indeed, iodo-uracil **38** could also undergo the reaction and gave a modest but unoptimized 39% yield (Scheme 3). To the best of our knowledge, this is the first coupling with a heteroaromatic as the iodo-partner.

Scheme 3. Iodo-uracil **38** as the Iodo-Partner



In summary, we have developed a new, straightforward and efficient one-step approach to highly substituted six- and seven-membered annulated pyrroles using readily available starting materials. This method is based on a palladium-catalyzed/norbornene-mediated sequential aromatic alkylation/aryl-heteroaryl coupling reaction and involves a C−H functionalization as the key step. This convenient strategy could also be applied to other nitrogen-containing heterocycles, such as *N*-alkylated pyrazoles, as well as iodo-heteroaromatics, such as iodo-uracil, which constitutes a new class of iodo-partner. Those projects, as well as the use of 1- and 2-substituted pyrroles, are under investigation in the laboratory and will be reported in due course.

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

OL060447Y

(14) The nature of the final cyclization has already been discussed in detail. See ref 10.

(15) Unpublished results.

(16) Stefani, H. A.; Pereira, C. M. P.; Almeida, R. B.; Braga, R. C.; Guzen, K. P.; Cella, R. *Tetrahedron Lett.* **2005**, *46*, 6833−6837 and references therein.

(17) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003−4018.