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Direct, One-Step Synthesis of Condensed Heterocycles: A Palladium-Catalyzed Coupling Approach

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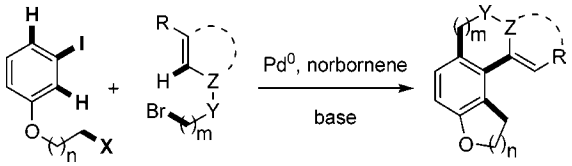
ABSTRACT



A palladium-catalyzed one-step synthesis of fused aromatic heterocycles from bifunctional bromoenoates or bromoalkyl indoles and iodoarenes is reported. This method provides an efficient route to a wide variety of substituted polycyclic aromatic and heteroaromatic compounds from readily accessible starting materials.

Oxygen- and nitrogen-containing polycyclic compounds have attracted considerable attention as a result of their biological activity and their presence in a variety of natural and unnatural products.[1] For example, naphthofuran analogues, which have been isolated from various natural sources such as *Fusarium oxysporum*[2] and *Gossypium barbadense*,[3] are known to exhibit antitumor, antifertility, mutagenic, growth inhibitory, and oestrogenic activities.[4] Thus, several approaches have been developed for their synthesis.[5] One might therefore expect that general and versatile synthetic methods for the construction of these frameworks would find significant utility in organic synthesis. In this area, we have recently reported a practical and efficient route to annulated heterocycles based on a tandem palladium-catalyzed alkylation/arylation or alkenylation sequence.[6]

In the current study, we examine a different aspect of the reaction with the goal of observing up to three C−H functionalizations and two ring formations so as to quickly assemble tri- and pentacyclic heteroatom-containing compounds. Such a coupling is considerably more ambitious than the examples previously described because both ortho positions of the iodoarene are to be functionalized in the two ring-closing steps and the timing of those processes is important.

Our initial attempts to test the feasibility of this reaction employed iodoarene **1** and bromoenoate **2**. Under the optimized reaction conditions, **1a** (0.20 mmol, 1 equiv), $Pd(OAc)_2$ (10 mol %), triphenylphosphine (20 mol %), Cs_2CO_3 (6 equiv), norbornene (5 equiv), and **2** (5 equiv) in DME

(1) (a) Zhang, Q.; Tu, G.; Zhao, Y.; Cheng, T. *Tetrahedron* **2002**, *58*, 6795−6798 and references therein. (b) Szawkalo, J.; Zawadzka, A.; Wojtasiewicz, K.; Leniewski, A.; Drabowicz, J.; Czarnocki, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 3619−3621.

(2) Stipanovic, R. D.; Bell, A. A.; Howell, C. R. *Phytochemistry* **1975**, *14*, 1809−1811.

(3) Tatum, J. H.; Baker, R. A.; Berry, R. E. *Phytochemistry* **1987**, *26*, 2499−2500.

(4) (a) Hagiwara, H.; Sato, K.; Suzuki, T.; Ando, M. *Heterocycles* **1999**, *51*, 497−500. (b) Weill-Thevenet, N.; Buisson, J.-P.; Royer, R.; Hofnung, M. *Mutat. Res.* **1982**, *104*, 1−8. (c) Ribeiro-Rodrigues, R.; Dossantos, W. G.; Oliveira, A. B.; Snieckus, V.; Romanha, A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1509−1512. (d) Mehrotra, P. K.; Karkun, J. N.; Kar, A. B. *Contraception* **1973**, *7*, 115−124.

(5) For a review, see: (a) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955−2020. (b) Ghera, E.; Maurya, R. *Tetrahedron Lett.* **1987**, *28*, 709−712. (c) Naruta, Y.; Uno, H.; Maruyama, K. *Tetrahedron Lett.* **1981**, *22*, 5221−5224. (d) Sestelo, J. P.; Real, M. D.; Mourino, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1999**, *40*, 985−988. (e) Park, K. K.; Jeong, J. *Tetrahedron* **2005**, *61*, 545−553.

(6) (a) Lautens, M.; Piguel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045−1046. (b) Lautens, M.; Paquin, J.-F.; Piguel, S.; Dahlmann, M. *J. Org. Chem.* **2001**, *66*, 8127−8134. (c) Lautens, M.; Paquin, J.-F.; Piguel, S. *J. Org. Chem.* **2002**, *67*, 3972−3974. (d) Pache, S.; Lautens, M. *Org. Lett.* **2003**, *5*, 4827−4830. (e) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148−13149.

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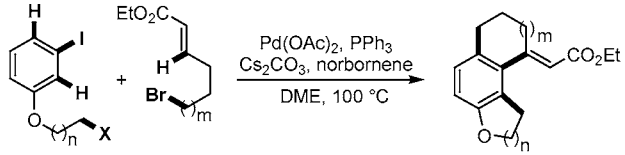
(0.1 M) at 100 °C in a sealed tube for 48 h afforded the fused tricyclic heterocycle **3** in 80% yield (Table 1, entry 1). The use of **1b** with the iodoalkyl tether furnished the same product in only 48% yield.

We next investigated the scope of the reaction using aryliodides by varying the length and the substituents on the halo alkyl ether chain (entries 2 and 3). Six- and seven-membered annulated products, **5** and **7**, were constructed in 51 and 44% yield, respectively, for a two-ring, three-bond formation process. In both cases, use of an alkyl bromide tether resulted in higher yield. Varying the bromoenoate chain length was also explored, and modest yields were obtained for the formation of 7,6,5-, 7,6,6-, and 7,6,7-membered ring annulated compounds (entries 4−6). In the case of bigger rings (entry 6), an increasing amount of the ligand is needed for a better yield. Changing from an ester (entry 1) to an amide (Scheme 1) diminished the yield to 50%.

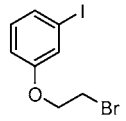
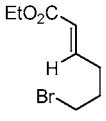
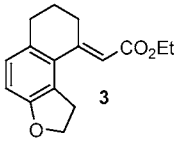
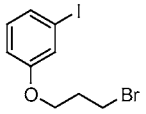
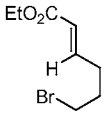
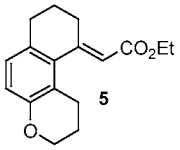
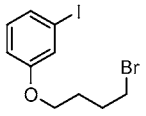
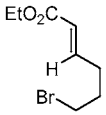
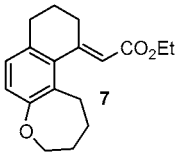
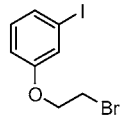
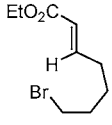
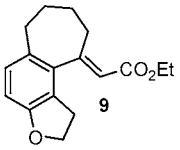
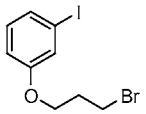
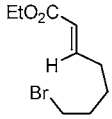
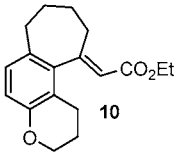
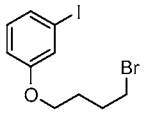
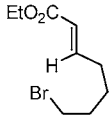
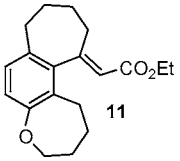
Table 1. Synthesis of Tricyclic Oxygen-Containing Heterocycles[a]



1 (n = 1)
4 (n = 2)
6 (n = 3)

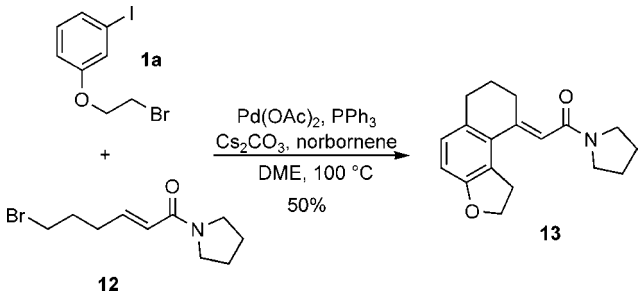
2 (m = 1)
8 (m = 2)

a) X = Br
b) X = I

entry	iodoarene	bromoenoate	product	yield (%)[b]
1	 **1a**	 **2**	 **3**	80
2	 **4a**	 **2**	 **5**	51
3	 **6a**	 **2**	 **7**	44
4	 **1a**	 **8**	 **9**	58
5	 **4a**	 **8**	 **10**	45
6	 **6a**	 **8**	 **11**	35[c]

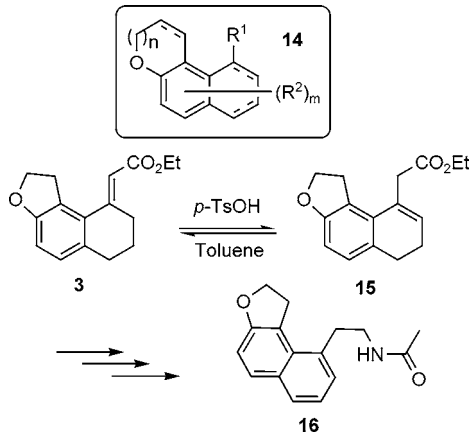
[a] All reactions were run under the following conditions: iodoarene (0.20 mmol), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Cs_2CO_3 (6 equiv), norbornene (5 equiv), and bromoenoate (5 equiv) in DME (2 mL) were heated in a sealed tube at 100 °C for 48 h. [b] Isolated yield. [c] PPh_3 (30 mol %) was used.

Scheme 1



Tricyclic naphthalene derivatives are important constituents in pharmaceutical drug candidates.[7] For instance, compounds of type **14** have a high affinity and selectivity for binding to melatonin receptors, resulting in either melatonin receptor agonist or antagonist activity (Scheme 2).[7] Furthermore, these compounds have been used in the treatment of chronobiological disorders, glaucoma, cancer, psychiatric disorders, and neurodegenerative diseases.[7] Accordingly, tetrahydronaphtho[2,1-*b*]furan derivative **15** is a key intermediate in the formation of one of these compounds,

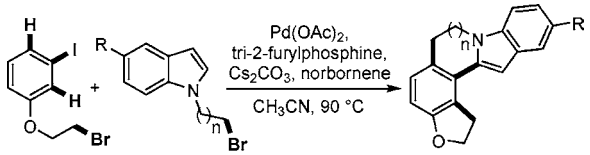
Scheme 2



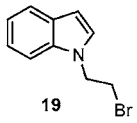
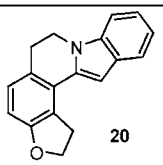
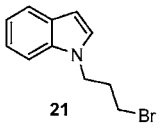
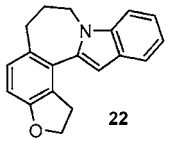
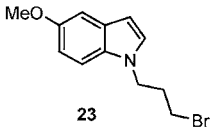
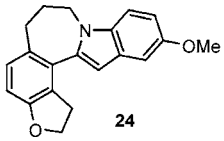
(7) North, P. C.; Ladlow, M. Patent WO 9529173, 1995; *Chem. Abstr. 124*, 175833.

16, which can be readily prepared from compound **3** by acid-mediated isomerization of the double bond in 50% yield

Table 2. Synthesis of Annulated Indoles[a]



1a **19** (n = 1), R = H
21 (n = 2), R = H
23 (n = 2), R = OMe

entry	bromoalkylindole	product	yield (%)[b]
1	 **19**	 **20**	33
2	 **21**	 **22**	62
3	 **23**	 **24**	52

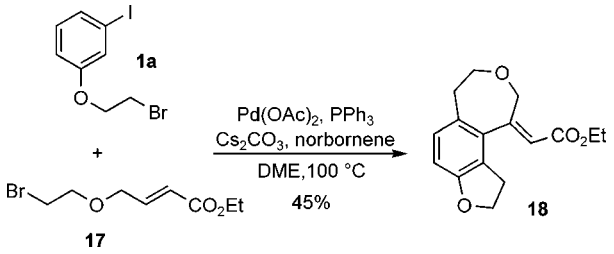
[a] All reactions were run under the following conditions: iodoarene (0.20 mmol, 1 equiv), $Pd(OAc)_2$ (10 mol %), tri-2-furylphosphine (22 mol %), Cs_2CO_3 (2 equiv), norbornene (2 equiv), and bromoalkyl indole (2 equiv) in acetonitrile (2 mL) were heated in a sealed tube at 90 °C for 24 h. [b] Isolated yields.

accompanied by 50% of **3**. Compound **15** has been converted into **16** in three steps.[7] Our method is also readily adapted to making analogues of **14**.

We next turned our attention to the synthesis of an unsymmetrically substituted tricyclic heterocycle, containing a benzoxepine moiety because these structural motifs have received increasing interest because of their occurrence in natural products,[8] their biological activity, and their use as natural herbicides.[9] To this end, iodoarene **1** was reacted with the ether-containing bifunctional acceptor **17** to provide the desired tricyclic compound **18** in modest yield (Scheme 3).

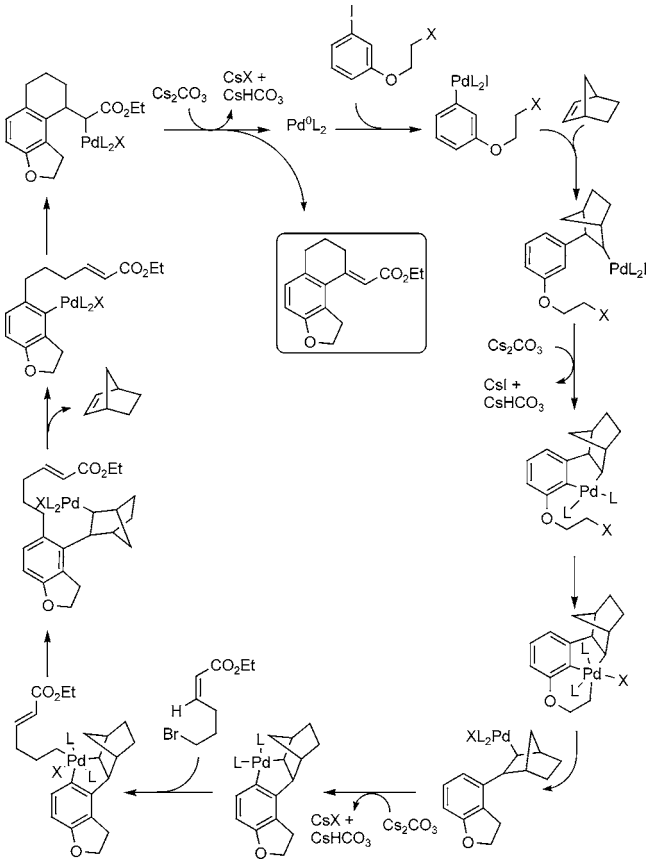
We next sought to expand the scope of the palladium-catalyzed annulation reaction to the construction of interesting pentacyclic oxygen- and nitrogen-containing heterocycles. However, our attempts to obtain **20** from the reaction

Scheme 3



of iodoarene **1** and bromoalkylated indole **19** under the usual conditions ($Pd(OAc)_2$ as a catalyst, Cs_2CO_3 as a base, and

Scheme 4



triphenylphosphine in DME at 100 °C) were unsuccessful. We thus investigated the use of tri-2-furylphosphine (TFP) as a ligand for $Pd(OAc)_2$ in acetonitrile as a solvent. Good results were obtained under these conditions (Table 2, entry 1). The low yield of the desired product was due to the elimination of HBr from bromoalkyl indole **19** in the presence of Cs_2CO_3. A bromoalkylated indole of longer chain length was also studied. Iodoarene **1** was reacted with the bromoalkylated indoles **21** and **23** using TFP to afford the desired products **22** and **24** in 62% and 52% yield, respectively (entries 2 and 3, Table 2).

A possible mechanism for the formation of fused aromatic carbocycle **3** is shown in Scheme 4 and follows a pathway

(8) For recent examples, see: (a) Macias, F. A.; Varela, R. M.; Torres, A.; Molinillon, J. M. G. *Tetrahedron Lett.* **1999**, *40*, 4725−4728 and references therein. (b) Wijnberg, J. B. P. A.; van Veldhuizen, A.; Swarts, H. J.; Frankland, J. C.; Field, J. A. *Tetrahedron Lett.* **1999**, *40*, 5767−5770 and references therein. (c) Mericüli, F.; Mericüli, A. H.; Becker, H.; Ulubelen, A. *Phytochemistry* **1996**, *42*, 1257−1258.

(9) (a) Zimmermann, K.; Waldmeier, P. C.; Tatton, W. G. *Pure Appl. Chem.* **1999**, *71*, 2039−2046. (b) Kaupmann, W.; Ohlendorf, H. W.; Wolf, K. U. *Eur. J. Med. Chem.* **1985**, *20*, 207−212. (c) Vyvyan, J. R.; Looper, R. E. *Tetrahedron Lett.* **2000**, *41*, 1151−1154.

similar to that proposed by Catellani.[10] Pd(0) inserts into the Ar−I bond of **1** and then incorporates a norbornene and inserts into the ortho C−H aryl bond, forming a palladacycle. Elimination of HI by the base (here Cs_2CO_3) regenerates a tetracoordinated Pd(II). Oxidative addition of the internal alkyl halide leads to a cyclic Pd(IV) species. A reductive elimination forms the five-membered oxacycle. An insertion into the second ortho C−H aryl bond occurs, followed by elimination of HX. Intermolecular oxidative addition of bromoenoate takes place, followed by a reductive elimination that puts the external alkyl group on the arene. Extrusion of norbornene gives an aryl−Pd(II) species. This intermediate undergoes a Heck reaction, leading to product **3**.

It is possible to envisage an alternative mechanism leading to **3**, where the first ortho alkylation would occur with the external alkyl halide and the second one would occur with the internal alkyl halide. It seems difficult to distinguish between the mechanisms, and both pathways may be occurring simultaneously.

(10) (a) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem.* **1997**, *109*, 142−145 and references therein; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119−122 and references therein. (b) Catellani, M.; Fagnola, M. C. *Angew. Chem.* **1994**, *106*, 2559−2560; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2421−2422. (c) Catellani, M.; Cugini, F. *Tetrahedron* **1999**, *55*, 6595−6602.

In summary, we have developed an efficient and straightforward one-step approach to fused heterocyclic compounds based on a tandem palladium-catalyzed dialkylation/alkenylation or arylation process which forms at least three new C−C bonds, using readily accessible starting materials. The application of this reaction toward the synthesis of natural compounds is currently under investigation.

Acknowledgment. We thank Dr. Sandrine Pache (AstraZeneca, Canada) for preliminary experiments and Dr. Dino Alberico (University of Toronto) for helpful discussions and practical help. We gratefully acknowledge the financial support of the Natural Sciences and Engineering Research Council (NSERC) of Canada, the Merck Frosst Centre for Therapeutic Research for an Industrial Research Chair, and the University of Toronto. F.J. thanks the Iranian Ministry of Science and Technology for a research abroad fellowship and Professor Hooshang Pirelahi (University of Tehran).

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.

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