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Direct Synthesis of Dihydrobenzo[*a*]carbazoles *via* Palladium-Catalyzed Domino Annulation of Indoles

Farnaz Jafarpour[a,*] and Hamideh Hazrati[a]

[a] School of Chemistry, University College of Science, University of Tehran, 14155-6455 Tehran, Iran
Fax: (+98)-21-66495291; e-mail: jafarpur@khayam.ut.ac.ir

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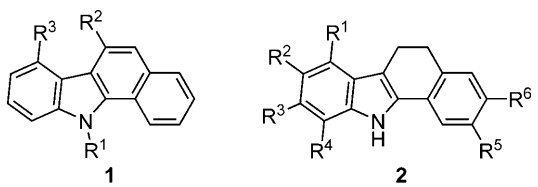
Abstract: A straightforward one-step synthesis of annulated indoles *via* palladium-catalyzed, norbornene-mediated sequential intermolecular aryl *ortho*-alkylation/intramolecular indole C–H activation has been devised. This method provides an efficient route to a wide variety of substituted 6,11-dihydro-5*H*-benzo[*a*]carbazoles from readily accessible 3-bromoalkylindoles and iodoarenes.

Keywords: benzo[*a*]carbazoles; bromoalkylindoles; domino reactions; one-step synthesis; palladium catalyst

Annellated indoles have attracted considerable attention as they constitute an important class of natural compounds with interesting biological activities.[1] While the benzo[*a*]carbazoles, and benzannulated carbazoles in general, are rarely found as natural products, these structural motifs have elicited considerable biological attention. For instance, compounds of type **1** show antitumor (leukemia, renal, colon)[2] and anti-inflammatory[3] activities. Simple benzo[*a*]carbazoles (Scheme 1) have been shown to bind to estrogen receptors and inhibit the growth of mammary tumors in rats.[4] Furthermore, dihydrobenzo[*a*]carbazole derivatives of type **2** have been identified as a novel agonist of the human thrombopoietin (Tpo) receptor.[5] Benzo[*a*]carbazole derivatives have also found extensive applications as photographic materials.[6] Thus, several approaches have been developed for their syntheses which often consist of multi-step reaction processes.[1a,7] Some general methods include C-2 arylation of indole-3-carbaldehydes followed by light- and base-assisted cyclization reactions,[8] a merged directed *ortho* and remote metalation-Suzuki–Miyaura cross-coupling strategy[9] and Fischer indolization of α-tetralones in the presence of suitable protic or Lewis acids.[10] However, these reactions often suffer from the need for the synthesis of complex starting materials, prior functionalization of the heteroarene, harsh reaction conditions and low yields. One might therefore expect that a one-step, straightforward and generally applicable reaction protocol for the construction of this framework would find significant utility in organic synthesis.



Scheme 1. Benzo[*a*]carbazole derivatives with biological activities.

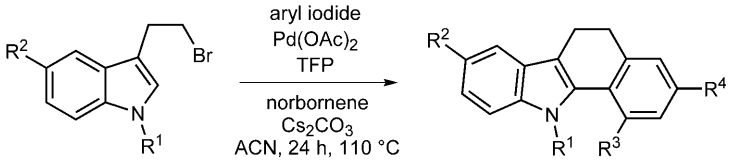
We have recently reported an efficient and straightforward route to annulated imidazole derivatives[11] based on a previously reported palladium-catalyzed/norbornene-mediated sequential aromatic alkylation/aryl-heteroaryl coupling reaction.[12] Herein, we set out to explore the possibility of this methodology to construct dihydro-5*H*-benzo[*a*]carbazole derivatives *via* direct C-2 arylation of 3-bromoalkylindoles.

The approach involved the use of readily accessible 3-(2-bromoethyl)-indoles and iodoarenes, so that an intramolecular direct C-2 arylation of the indole can follow *ortho* alkylation of an aryl iodide, forming two carbon-carbon bonds from two carbon-hydrogen bonds in a one-step process. This protocol takes advantage of readily available indole and aryl building blocks, regioselectivity for indole C-2 functionalization and one-step construction of benzo[*a*]carbazole building blocks.

To test the feasibility of this reaction, we initially examined the reaction of bromoalkylindole **3** with 5-nitro-2-iodotoluene **4** under various reaction conditions. To this end different palladium sources and li-

gands were examined. While with $PdCl_2$ and $Pd(dba)_2$ low yields of the desired product were obtained, use of $Pd(OAc)_2$ resulted in higher yields. A ligand screen revealed that trialkylphosphines such as tricyclohexylphosphine and its HBF_4 salt gave inferior reactivity in this annulation reaction. Better results were obtained with dppe, PPh_3 and TFP. Screening the ratios of starting materials revealed that lowering the amount of bromoalkylindole **3** to 2 equivalents resulted in a lower yield of the expected annulated heterocycle. The large excess amount of this partner was necessary due to the elimination of hydrogen bromide from the bromoalkyl tether in the presence of Cs_2CO_3. We were pleased to find that, under the optimized reaction conditions of bromoalkylindole **3** (0.6 mmol, 3 equiv.), iodoarene **4** (0.2 mmol, 1 equiv.), $Pd(OAc)_2$ (10 mol%), TFP (22 mol%), Cs_2CO_3 (0.4 mmol, 2 equiv.) and norbornene (0.4 mmol, 2 equiv.) in CH_3CN (0.1 M) at 110 °C in a sealed tube for 24 h, the construction of the fused tricyclic heterocycle **5** was feasible in 63% yield (Table 1, entry 1). We next used these optimal reaction conditions to investigate the

Table 1. Annulation of indoles *via* Pd-catalyzed, norbornene-mediated domino reaction.[a]



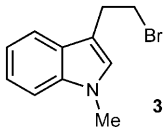
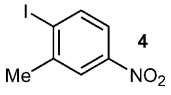
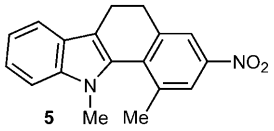
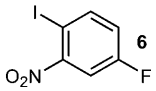
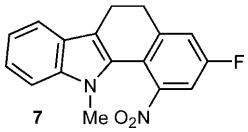
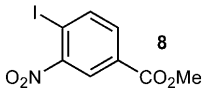
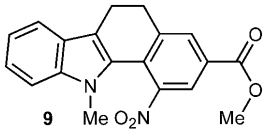
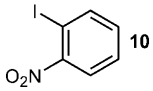
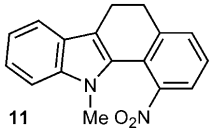
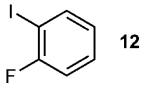
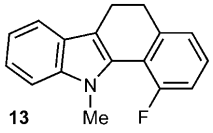
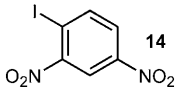
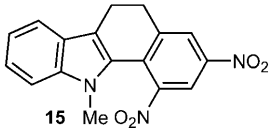
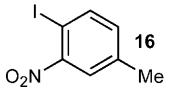
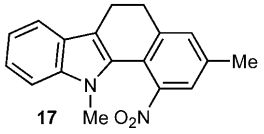
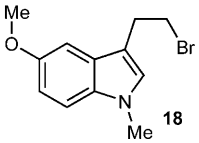
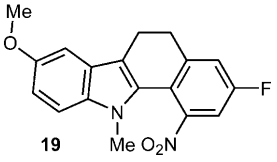
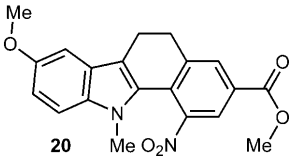
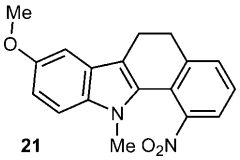
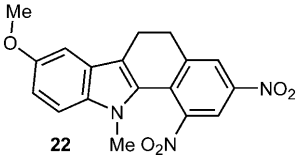
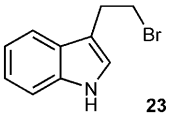
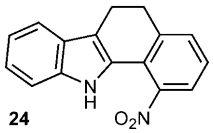
Entry	Substrate	Aryl Iodide	Product	Yield [%][b]
1				63
2	**3**			76
3	**3**			50
4	**3**			60
5	**3**			35
6	**3**			46
7	**3**			61[c]
8		**6**		59

Table 1. (Continued)

Entry	Substrate	Aryl Iodide	Product	Yield [%][b]
9	**18**	**8**	 **20**	62
10	**18**	**10**	 **21**	58
11	**18**	**14**	 **22**	45[c]
12	 **23**	**10**	 **24**	35

[a] All reactions were run under the following conditions: $Pd(OAc)_2$ (10 mol%), TFP (22 mol%), Cs_2CO_3 (2 equiv.), norbornene (2 equiv.) and bromoalkylindole (3 equiv.) in CH_3CN (0.1 M) were heated in a sealed tube at 110 °C for 24 h.
[b] Isolated yields.
[c] As the product was contaminated by an uncharacterized impurity, an approximate yield is given and full characterization was not obtained for this product.

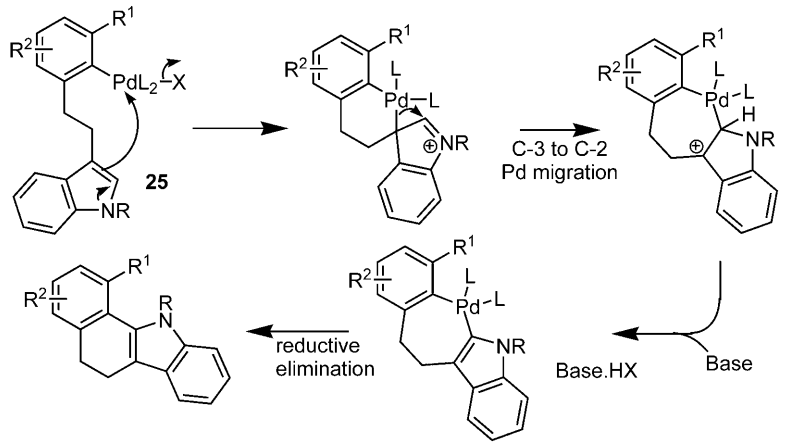
scope of the reaction with a range of aryl iodides. The results showed that a variety of substituents were tolerated under the reaction conditions. The *para*-fluoro-substituted iodoarene **6** resulted the annulated indole **7**, a good partner for further functionalizations, in high yield, while the *ortho*-substituted one **12** afforded product **13** in only 35% yield (the acyclic *ortho*-alkylated product was the major one) (Table 1, entries 2 and 5). We next expanded the scope of aryl iodides to include carbonyl groups. The *para*-carbonyl-substituted iodoarene **8**, gave a satisfactory result (50%, Table 1, entry 3), however, the *ortho*-substituted one, was not tolerated under the reaction conditions. This was in accord with the results previously reported.[13a] With *ortho*- and *para*-substituted nitro coupling partners, good to moderate yields of the desired products, **11** and **15**, were obtained (60% and 46%, respectively, Table 1, entries 4 and 6). Nitro- and methyl-substituted iodoarene partners **4** and **16** gave comparable results (63% and 61%, respectively, Table 1, entries 1 and 7). We next investigated the scope of the reaction with more sterically encumbered aryl iodides. With an *ortho*-blocking CF_3 group, only a low yield of the desired product was obtained, presumably due to steric hindrance between the C–F bonds of the CF_3 group and C–H bonds of N-Me unit (data not reported in Table 1).

It was also desirable to test whether substituted indole derivatives could be applied in the reaction. In this regard, 3-(2-bromoethyl)-5-methoxy-1-methylindole **18** was employed. While with the *ortho*- and *para*-nitro-substituted coupling partners **10** and **14**, comparable results were obtained, the *para*-carbonyl substituted one **8**, resulted in higher yield of the annulated product **20** (Table 1, entries 9–11).

Finally, we examined the scope of the reaction with the free NH bromoalkylindole **23**. The reaction of the substrate **23** with iodoarene **10**, resulted in lower yields compared to the N-protected one, which is attributed to catalyst poisoning (Table 1, entry 12).

The possible mechanism for the first step, the *ortho*-alkylation of iodoarene, is based upon the findings of Catellani.[13] The intermolecular *ortho*-alkylation step likely proceeds through a Pd(II)-Pd(IV) catalytic cycle and generates heteroaryl-tethered arylpalladium(II) intermediate **25** (Scheme 2). In accord with these findings, when the reaction was carried out in the absence of norbornene, no *ortho*-alkylated aryl iodide was isolated. The reaction products consisted of C-2 arylated indole and traces of the biaryl by-product.

Excluding the reaction of iodoarene **12** with bromoalkylindole **3**, no acyclic *ortho*-inserted products were isolated in these reactions which is in accord



Scheme 2. Electrophilic aromatic substitution mechanism for the intramolecular direct arylation of π-excessive heteroarenes.

with a subsequent direct C-2 arylation of indoles under the optimized reaction conditions. There are three reaction mechanisms that may rationalize the palladium-catalyzed direct C-2 arylation of indoles: (1) carbometalation,[14] (2) non-electrophilic metalation of the 2-position,[15] and (3) electrophilic metalation-migration.[16]

Sames recently provided a rational explanation for the high C-2 selectivity in the palladium-catalyzed arylation of indoles through kinetic studies and a Hammett plot.[16] The results showed that the most likely pathway is an electrophilic substitution at the C-3 position, followed by a C-3 to C-2 palladium migration. Exploring aryl iodides of different electronic character, good results obtained with electron-deficient aryl iodides (Table 1). It was suggested that electron-rich aromatic systems stabilize Pd(II) species **25**, thus reducing it's electrophilicity and subsequent reactivity in the direct heteroarylation step.[12e] Therefore, we have considered the electrophilic aromatic substitution mechanism to be the most probable one for the intramolecular direct arylation reaction forming the aryl–N-heteroaryl bond at the 2-position of the N-heteroaryl compound. (Scheme 2).

In summary, we have developed a straightforward and general one-step approach to highly functionalized benzo[*a*]carbazoles using readily accessible 3-bromoalkylindoles and iodoarenes. We have explored the scope of domino palladium-catalyzed, norbornene-mediated sequential aromatic alkylation/arylheteroaryl coupling reaction for construction of these structural motifs that are not easily accessible by conventional methods. Expansion of the derived methodology for the construction of similar heteroaromatics such as pyrroles and imidazoles and further functionalization of the annulated products are under investigation.

Experimental Section

Typical Experimental Procedure for the Annulation of Indoles

A vial equipped with a stir bar was charged with iodoarene (0.200 mmol, 1.0 equiv.), 3-(2-bromoethyl)indole (0.600 mmol, 3.0 equiv.), tri-2-furylphosphine (0.044 mmol, 22 mol%), $Pd(OAc)_2$ (0.020 mmol, 10 mol%), norbornene (0.400 mmol, 2.0 equiv.) and Cs_2CO_3 (0.400 mmol, 2.0 equiv.). Dry degassed CH_3CN (0.1 M) was then added and the vial was capped and further degassed. The resulting mixture was heated in an oil bath at 110 °C for 24 h, cooled then filtered through a short plug of silica. Removal of the solvent gave a crude mixture which was purified by flash column chromatography (hexane/EtOAc gradient).

1,11-Dimethyl-3-nitro-6,11-dihydro-5*H*-benzo[*a*]carbazole (5): Following the general procedure for the annulation of indoles, 5-nitro-2-iodotoluene **4** (53.0 mg, 0.200 mmol) and 3-(2-bromoethyl)-1-methylindole **3** (143.0 mg, 0.600 mmol) were reacted at 110 °C for 24 h. The crude mixture was purified by flash column chromatography on silica gel (EtOAc/hexane, 10%) to afford **5** as an oil; yield: 37 mg (63%); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.65$ (s, 3H, CH_3), 2.87 (m, 2H), 2.93 (m, 2H), 3.69 (s, 3H, NCH_3), 7.21 (ddd, $J = 8.4$, 6.4, 1.0 Hz, 1H), 7.32 (ddd, $J = 8.0$, 6.4, 1.6 Hz, 1H), 7.41 (dd, $J = 8.4$, 1.6 Hz, 1H), 7.64 (dd, $J = 8.0$, 1.0 Hz, 1H), 8.04 (d, $J = 2.2$ Hz, 1H), 8.08 (d, $J = 2.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.1$, 22.6, 31.6, 110.7, 115.0, 118.1, 119.5, 120.5, 123.4, 125.3, 132.7, 136.4, 141.3, 145.4; IR (KBr): $\nu = 1334$, 1518, 2957, 3050 cm^{-1}; MS: m/z (%) = 292 (M^+, 44%), 221 (34), 188 (100), 142 (83), 115 (29), 73 (51); anal. calcd. for $C_{18}H_{16}N_2O_2$: C 73.95, H 5.52, N 9.58; found: C 74.09, H 5.61, N 9.47.

Supporting Information

Experimental procedures and characterization data for new compounds are available as Supporting Information.

Acknowledgements

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References

[1] a) H.-J. Knolker, K. R. Reddy, *Chem. Rev.* **2002**, *102*, 4303–4428; for selected examples of annulated indoles, see: b) A. P. Kozikowski, D. Ma, J. Brewer, S. Sun, E. Costa, E. Romeo, A. Guidotti, *J. Med. Chem.* **1993**, *36*, 2908–2920; c) R. Gastpar, M. Goldbrunner, D. Marko, E. von Angerer, *J. Med. Chem.* **1998**, *41*, 4965–4972; d) R. Faust, P. J. Garratt, R. Jones, L.-K. Yeh, *J. Med. Chem.* **2000**, *43*, 1050–1061.

[2] U. Pindur, T. Lemster, *Recent Res. Devel. Org. Biorg. Chem.* **1997**, 33–54.

[3] D. W. Beight, M. D. Kinnick, H. Lin, J. M. Morin, M. E. Richett, D. J. Sall, J. S. Sayer, US Patent WO 2002050034, **2002**; *Chem. Abstr.* **2002**, *137*, 47114.

[4] E. Lescot, G. Muzard, J. Markovits, J. Belleney, B. P. Roques, J. Le Pecq, *J. Med. Chem.* **1986**, *29*, 1731–1737.

[5] a) P. B. Alper, T. H. Marsilje, D. Mutnick, W. Lu, A. Chatterjee, M. J. Roberts, Y. He, D. S. Karanewsky, D. Chow, J. Lao, A. Gerken, T. Tuntland, B. Liu, J. Chang, P. Gordon, H. M. Seidel, S.-S. Tian, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5255–5258; b) T. H. Marsilje, P. B. Alper, W. Lu, D. Mutnick, P.-Y. Michellys, Y. He, D. S. Karanewsky, D. Chow, A. Gerken, J. Lao, M.-J. Kim, H. M. Seidel, S.-S. Tian, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5259–5262.

[6] S. Tomoyuki, S. Masaomi, T. Chiaki, Japanese Patent JP 09048757, **1997**; *Chem. Abstr.* **1997**, *126*, 244806d.

[7] a) D. B. Grotjahn, K. L. Dötz, *Synlett* **1991**, 381–390; b) H.-J. Knölker, H. Goesmann, C. Hofmann, *Synlett* **1996**, 737–740; c) W. Harris, C. H. Hill, E. Keech, P. Malsher, *Tetrahedron Lett.* **1993**, *34*, 8361–8364.

[8] C. B. de Koning, J. P. Michael, A. L. Rousseau, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1705–1713.

[9] X. Cai, V. Snieckus, *Org. Lett.* **2004**, *6*, 2293–2295.

[10] a) L. Martarello, D. Joseph, G. Kirsch, *Heterocycles* **1996**, 43, 367–379; b) T. Okubo, R. Yoshikawa, S. Chaki, S. Okuyamac, A. Nakazato, *Bioorg. Med. Chem.* **2004**, *12*, 3569–3580.

[11] F. Jafarpour, P. T. Ashtiani, *J. Org. Chem.* **2009**, *74*, 1364–1366.

[12] a) B. Laleu, M. Lautens, *J. Org. Chem.* **2008**, *73*, 9164–9167; b) C. Blaszykowski, E. Aktoudianakis, D. Alberico, C. Bressy, D. G. Hulcoop, F. Jafarpour, A. Joushaghani, B. Laleu, M. Lautens, *J. Org. Chem.* **2008**, *73*, 1888–1897; c) A. Martins, ; M. Lautens, *J. Org. Chem.* **2008**, *73*, 8705–8710; d) C. Blaszykowski, E. Aktoudianakis, C. Bressy, D. Alberico, M. Lautens, *Org. Lett.* **2006**, *8*, 2043–2045; e) A. Martins, D. Alberico, M. Lautens, *Org. Lett.* **2006**, *8*, 4827–4829; f) C. Bressy, D. Alberico, M. Lautens, *J. Am. Chem. Soc.* **2005**, *127*, 13148–13149.

[13] a) M. Catellani, F. Frignani, A. Rangoni, *Angew. Chem.* **1997**, *109*, 142–145; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 119–122; b) M. Catellani, *Top. Organomet. Chem.* **2005**, *14*, 21; c) J. Tsuji, in: *Palladium Reagents and Catalysis – New Perspectives for the 21st Century*, 1st edn., John Wiley & Sons, New York, **2004**, pp 409–416; d) M. Catellani, *Synlett* **2003**, 298–313; e) M. Catellani, in: *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Eds.: E.-I. Negishi, A. de Meijere), John Wiley & Sons, New York, **2002**, pp 1479–1489; f) M. Catellani, C. Mealli, E. Motti, P. Paoli, E. Perez-Carreno, P. S. Pregosin, *J. Am. Chem. Soc.* **2002**, *124*, 4336–4346.

[14] a) A. P. Kozikowski, D. Ma, *Tetrahedron Lett.* **1991**, *32*, 3317–3320; b) R. Grigg, V. Sridharan, P. Stevenson, S. Sukirthalingam, T. Worakun, *Tetrahedron* **1990**, *46*, 4003–4018.

[15] a) S. Tollari, F. Demartin, S. Cenini, G. Palmisano, P. Raimondi, *J. Organomet. Chem.* **1997**, *527*, 93–102; b) T. Motoyama, Y. Shimazaki, T. Yajima, Y. Nakabayashi, Y. Naruta, O. Yamauchi, *J. Am. Chem. Soc.* **2004**, *126*, 7378–7385; c) E. Capito, J. M. Brown, A. Ricci, *Chem. Commun.* **2005**, 1854–1856.

[16] B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057.

