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An efficient one-pot synthesis of novel 4-aryl-1-methyloxindoles

Adri van den Hoogenband,* Jos H. M. Lange, Wouter I. Iwema-Bakker, Jack A. J. den Hartog, Jord van Schaik, Rolf W. Feenstra and Jan Willem Terpstra

Solvay Pharmaceuticals, Research Laboratories, C. J. van Houtenlaan 36, 1381 CP Weesp, The Netherlands

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Dedicated to our colleague Willem Veerman (1959–2005)

Abstract—An unprecedented synthetic approach to novel 4-aryl-1-methyloxindoles is described. The method involves the intramolecular palladium-catalyzed amidation of *N*-methyl-2,6-dibromophenylacetamide followed by an in situ Suzuki cross-coupling reaction with a (hetero)arylboronic acid in a one-pot reaction.
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1,3-Dihydroindol-2-ones (oxindoles) are of great pharmaceutical importance. The oxindole motif is present in the anti-Parkinson's drug ropinirole,[1] in growth hormone secretagogues,[2] P-glycoprotein-mediated multiple drug resistance inhibitors,[3] anti-inflammatory agents,[4] non-opioid nociceptin receptor ligands[5] and serotonergics.[6,7] In addition, the oxindole moiety constitutes a key structural element in several natural products,[8] including the antibiotic speradine[9] and the cytostatic welwistatin.[10] As a consequence, the development of novel synthetic strategies leading to substituted oxindole derivatives is of paramount importance. Recently, we published[11] a new method for the preparation of 1-functionalized oxindoles based on an intramolecular palladium-catalyzed amidation reaction. In that study it was discovered that the excellent Buchwald ligand X-Phos (Scheme 1) plays a key role in the yield and rate of this particular reaction. In addition, we were able to prepare in one of our current projects, a set of differently 1-substituted oxindoles by applying the same methodology.[12] More recently, Turner et al.,[13] utilized microwave irradiation in a closely related reaction and concluded that X-Phos again was the ligand of choice. Kitamura[14] reported the use of alternative phenylnaphthyl phosphines as effective ligands in an analogues intramolecular palladium-catalyzed amidation reaction leading to 1-benzyloxindole.

Due to our interest in the synthesis of novel 4-(hetero)-aryl-1-methyl oxindoles, it was decided to expand the scope of the synthetic methodology outlined above. The 2-bromophenylacetamide derivative **1** was used as the key intermediate in the synthesis that led[11] to the pharmaceutically relevant[5] 1-(piperidin-4-yl)oxindole **2** (Scheme 1). We envisaged that application of the structurally related *N*-methyl-2,6-dibromophenylacetamide **3** would lead to *N*-methyl-4-bromo-1,3-dihydroindol-2-one **4**. The remaining 4-bromo substituent would provide a handle for further transition metal catalyzed cross-coupling reactions. This study focuses on Suzuki-type arylations to produce novel oxindoles of general formula **5**.

The synthesis of the required key intermediate **3**[15] is depicted in Scheme 2. Benzylic bromination of 2,6-dibromotoluene **6** using *N*-bromosuccinimide in CCl_4 gave **7**. The bromide **7** was converted into the corresponding cyanide **8**, which was hydrolyzed to the carboxylic acid **9**. The carboxamide **3** was obtained via conversion of the carboxylic acid to the corresponding acid chloride and an in situ subsequent reaction with methylamine. The yield of this reaction sequence was reasonable (34% overall yield).

Surprisingly, when compound **3** was subjected to the amidation conditions outlined in Scheme 1, no formation of 1-methyl-4-bromooxindole **4** was observed at all. Since all the starting material had disappeared the products formed were isolated and purified. Structure analysis revealed the formation of the dimeric oxindole

* Corresponding author. Tel.: +31 (0)294 479605; fax: +31 (0)294 477138; e-mail: adri.vandenhoogenband@solvay.com

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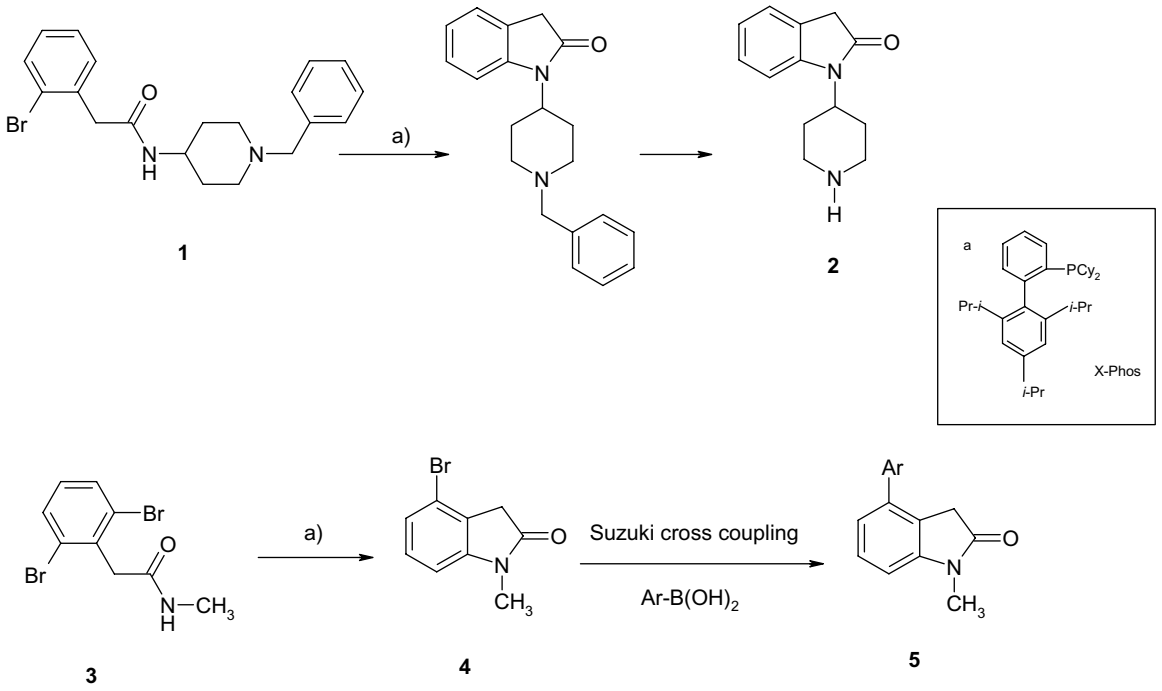
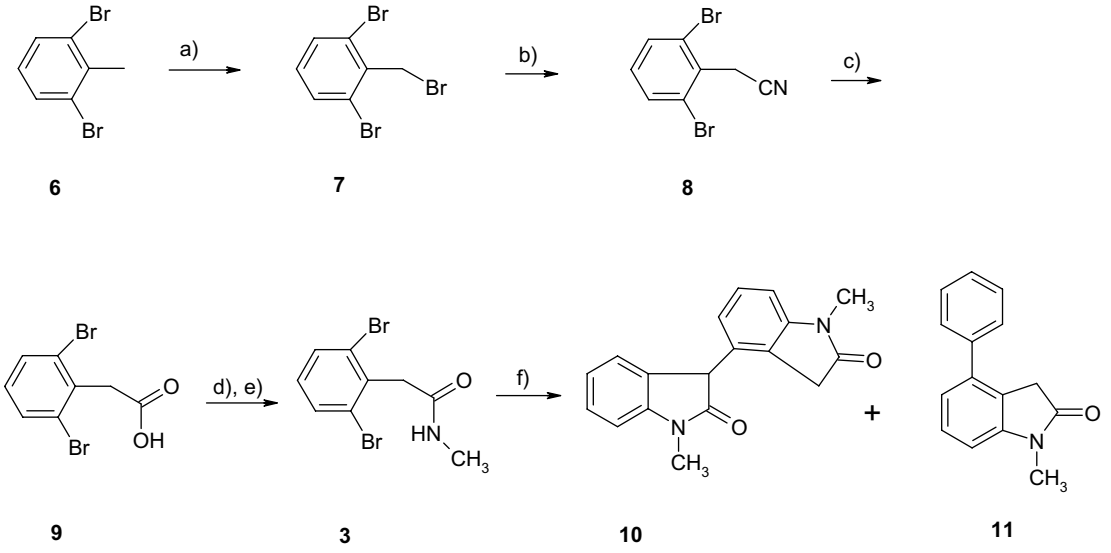


Scheme 1. Reagents and conditions: (a) 1 mol equiv **1**, 2.5 mol equiv K_2CO_3, 3 mol % $Pd(OAc)_2$, 7.5 mol % $PhB(OH)_2$, 7.5 mol % X-Phos,[a] *t*-BuOH, 85 °C, 3 h.



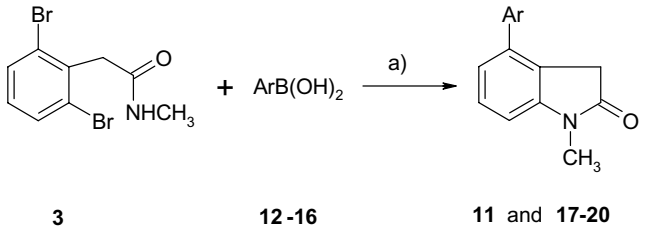
Scheme 2. Reagents and conditions: (a) 1 mol equiv **6**, 1.1 mol equiv NBS, catalytic Bz_2O_2, CCl_4, reflux, 89%; (b) 1 mol equiv **7**, 2.7 mol equiv KCN, EtOH/water 4:1, reflux, 67%; (c) 1 g **8**, 15 ml 70% H_2SO_4, 170 °C, 90%; (d) 1 mol equiv **9**, 20 mol equiv $SOCl_2$, benzene, room temperature; (e) 10 mol equiv $HNCH_3$·HCl, Et_3N 64%; (f) reaction conditions according to Scheme 1.

analogue **10**[16] as the major product together with a trace of the 4-phenyloxindole derivative **11** (Scheme 2). The formation of **10** can be rationalized by invoking the initial formation of compound **4** which undergoes an intermolecular α-arylation,[17] followed by a debromination reaction to give compound **10**. Transition metal-mediated debrominations have been previously reported.[18] Due to the presence of a catalytic amount of phenylboronic acid, needed for a smooth reduction of the cationic palladium complex according to Buchwald's original protocol,[19] a minor fraction of compound **4** would in situ lead to a rapid Suzuki cross-coupling reaction, eventually resulting in the formation of compound **11**.

In order to support this hypothesis, the amidation reaction of **3** was repeated in the presence of a catalytic amount of Pd_2dba_3/X-Phos in the absence of any phenylboronic acid. According to expectation, the dimeric oxindole analogue **10** was produced as the sole product. Moreover, the reaction of **3** under the influence of catalytic $Pd(OAc)_2$/X-Phos in the presence of a stoichio-

metric amount of phenylboronic acid proceeded smoothly, leading to a nearly quantitative yield of compound **11**. A literature survey led to the conclusion that, to the best of our knowledge, 1-methyl-4-aryloxindoles constitute a hitherto unknown compound class. These results prompted an exploration in more depth of this unexpected reaction. The ease with which the 4-bromo substituent in compound **4** is substituted in this reaction sequence led to the concept of combining the intramolecular palladium-catalyzed amidation of *N*-methyl-2,6-dibromophenylacetamide **3** with an in situ Suzuki cross-coupling reaction in a one-pot reaction fashion.

Three arylboronic acid derivatives **12**–**14** and two heteroarylboronic acids **15**–**16** were reacted with **3** under the conditions described in Scheme 3[20,21] (Table 1). It should be noted that all yields refer to isolated pure products and were not optimized. High yields were observed in the reactions with the arylboronic acids **12**–**14** which led to the products **11**, **17** and **18**, respectively. A moderate yield was obtained for the reaction of **3** with furan-2-boronic acid **15** leading to compound **19**. A possible explanation, based on LC/MS results, may be a concurrent side-reaction in which each bromine atom in compound **3** was replaced by a furan ring in a double Suzuki cross-coupling reaction. Disappointingly, the use of thiophene-2-boronic acid **16** as starting boronic acid gave a poor yield of compound **20** even after 16 h heating and reflux. By adding more $Pd(OAc)_2$, X-Phos, K_2CO_3 and **16** to the reaction mixture, we were able to isolate compound **20** in a modest 18% yield after another 48 h reflux period. In this case some of the dimeric compound **10** was formed as well. Apparently, the Suzuki cross-coupling reaction of the in situ formed **4** with the thiophene-2-boronic acid **16** under these reaction conditions is very slow, presumably due to some palladium poisoning or deboronation of **16**, resulting in the concurrent formation of **10**.



Scheme 3. Reagents and conditions: (a) 1.5 mol equiv $ArB(OH)_2$, 3 mol equiv K_2CO_3, 5 mol % $Pd(OAc)_2$, 12.5 mol % X-Phos, *t*-BuOH, 85 °C.

Table 1.

$ArB(OH)_2$	Product	Time (h)	Yield (%)
Phenylboronic acid **12**	**11**	16	90
4-Methoxyphenylboronic acid **13**	**17**	5	75
2-Methylphenylboronic acid **14**	**18**	16	80
Furan-2-boronic acid **15**	**19**	16	55
Thiophene-2-boronic acid **16**	**20**	60	18

We have briefly tried to extend the scope of this reaction by substituting the boronic acid for morpholine with the aim of preparing 1-methyl-4-(morpholin-4-yl)oxindole under the same reaction conditions. However, this initial attempt resulted only in the isolation of compound **10** as the sole reaction product. Optimization of the reaction parameters for this particular reaction is in progress.

A novel two-step reaction procedure has been devised for the preparation of five representative novel 1-methyl-4-(hetero)aryloxindoles **11** and **17**–**20** in moderate to high yields. The key steps comprise an intramolecular palladium-catalyzed amidation reaction followed by an in situ intermolecular Suzuki cross-coupling reaction in a one-pot reaction. We envisage that the scope of this approach can be expanded to the synthesis of a variety of (hetero)aryl-1,3-dihydroindol-2-ones.

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15. Selected analytical data for compound **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.81 (d, $J = 4$ Hz, 3H), 4.04 (s, 2H), 5.25–5.30 (br s, 1H), 7.04 (t, $J = 8$ Hz, 1H), 7.58 (d, $J = 8$ Hz, 2H); HRMS (ES+): calcd for $C_9H_9Br_2NO$ (M+H) 305.9129; found: 305.9128.
16. Selected analytical data for compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (d, $J = 22$ Hz, 1H), 3.11 (s, 3H), 3.16 (d, $J = 22$ Hz, 1H), 3.21 (s, 3H), 4.58 (s, 1H), 6.70 (d, $J = 8$ Hz, 1H), 6.81 (d, $J = 8$ Hz, 1H), 6.84 (d, $J = 8$ Hz, 1H), 6.95–7.02 (m, 2H), 7.20 (t, $J = 8$ Hz, 1H), 7.27 (t, $J = 8$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.01, 26.20, 34.07, 50.52, 107.42, 108.07, 122.71, 123.09, 123.26, 124.47, 127.20, 128.24, 128.53, 132.76, 144.14, 145.55, 174.48, 174.76. HRMS (ES+): calcd for $C_{18}H_{16}N_2O_2$ (M+H) 293.1290; found: 293.1282.
17. Some selected literature references describing Pd-mediated α-arylations: (a) Bignan, G. C.; Battista, K.; Connolly, P. J.; Orsini, J. L.; Middleton, S. A.; Reitz, A. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5022–5026; (b) Barberis, M.; Garcia-Losada, P.; Pleite, S.; Rodriguez, J. R.; Soriano, J. F.; Mendiola, J. *Tetrahedron Lett.* **2005**, *46*, 4847–4850; (c) De Filippis, A.; Pardo, D. G.; Cossy, J. *Synthesis* **2004**, 2930–2933; (d) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308–310; (e) De Filippis, A.; Pardo, D. G.; Cossy, J. *Tetrahedron* **2004**, *60*, 9757–9767; (f) Cossy, J.; De Filippis, A.; Pardo, D. G. *Synlett* **2003**, 2171–2174; For an excellent overview about Pd-catalysed α-arylation reactions: Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245.
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20. General procedure for the preparation of the compounds **11** and **17**–**20** (Table 1): A dried 50 mL, three-necked reaction vessel was charged with anhydrous and degassed *t*-BuOH (25 mL), followed by addition of *N*-methyl-2,6-dibromophenylacetamide **3** (155 mg, 0.5 mmol) at 35 °C. The temperature of the magnetically stirred mixture was then raised to 80 °C, until a clear solution was obtained. After cooling down again to 35 °C, $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), the aryl- or heteroarylboronic acid (0.75 mmol), X-Phos (30 mg, 0.0625 mmol) and K_2CO_3 (410 mg, 3 mmol) were successively added. The resulting reaction mixture was heated at 85 °C under a nitrogen atmosphere until the starting compound **3** had disappeared (LCMS, TLC monitoring: CH_2Cl_2/acetone = 95/5 (v/v)). The reaction mixture was allowed to attain room temperature. Water and ethyl acetate were added. The organic layer was separated and dried over $MgSO_4$, filtered and concentrated in vacuo. The obtained crude product was further purified by flash chromatography (silica gel 60 (0.040–0.063 mm, Merck), CH_2Cl_2/acetone = 95/5 (v/v)).
21. Selected analytical data for compounds **11** and **17**–**20**: Compound **11**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.25 (s, 3H), 3.60 (s, 2H), 6.83 (d, $J = 8$ Hz, 1H), 7.12 (d, $J = 8$ Hz, 1H), 7.36–7.40 (m, 2H), 7.46 (d, $J = 4$ Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.33, 35.81, 107.07, 122.17, 123.01, 127.71, 128.08, 128.40, 128.72, 138.35, 139.61, 145.63, 174.95. HRMS (ES+): calcd for $C_{15}H_{13}NO$ (M+H) 224.1074; found 224.1068. Compound **17**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.24 (s, 3H), 3.59 (s, 2H), 3.86 (s, 3H), 6.79 (d, $J = 8$ Hz, 1H), 6.98 (d, $J = 8$ Hz, 2H), 7.09 (d, $J = 8$ Hz, 1H), 7.32–7.41 (m, 3H). HRMS (ES+): calcd for $C_{16}H_{15}NO_2$ (M+H) 254.1181; found: 254.1169. Compound **18**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.14 (s, 3H), 3.24 (s, 3H), 3.27 (s, 2H), 6.82 (d, $J = 8$ Hz, 1H), 6.92 (d, $J = 8$ Hz, 1H), 7.14 (d, $J = 8$ Hz, 1H), 7.22–7.35 (m, 4H). HRMS (ES+): calcd for $C_{16}H_{15}NO$ (M+H) 238.1232; found: 238.1222. Compound **19**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.24 (s, 3H), 3.74 (s, 2H), 6.53 (dd, $J = 4$ and 2 Hz, 1H), 6.64 (d, $J = 4$ Hz, 1H), 6.75 (d, $J = 8$ Hz, 1H), 7.33 (t, $J = 8$ Hz, 1H), 7.42 (d, $J = 8$ Hz, 1H), 7.53 (d, $J = 2$ Hz, 1H). HRMS (ES+): calcd for $C_{13}H_{11}NO_2$ (M+H) 214.068; found: 214.0862. Compound **20**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.25 (s, 3H), 3.73 (s, 2H), 6.78 (t, $J = 4$ Hz, 1H), 7.14 (t, $J = 4$ Hz, 1H), 7.31–7.34 (m, 3H), 7.38 (d, $J = 4$ Hz, 1H). HRMS ES+: calcd for $C_{13}H_{11}NOS$ (M+H) 230.0640; found: 230.0637.