Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 8535–8537
Tetrahedron Letters

A novel synthesis of *N*-(piperidin-4-yl)-1,3-dihydroindol-2-one via an intramolecular Pd-catalyzed amination

Adri van den Hoogenband,* Jack A. J. den Hartog, Jos H. M. Lange and Jan Willem Terpstra

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

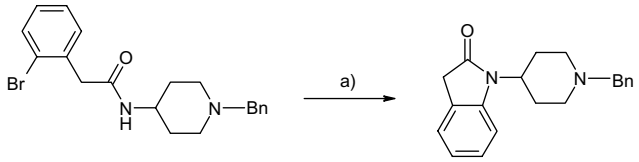
Received 20 July 2004; revised 7 September 2004; accepted 16 September 2004
Available online 1 October 2004

Dedicated to Professor Victor Snieckus for his stimulating work in the area of organometallic chemistry

Abstract—A novel efficient synthetic route to the pharmaceutical key intermediate *N*-(piperidin-4-yl)-1,3-dihydroindol-2-one is described. The key step involves a high-yielding intramolecular palladium-catalyzed amination reaction using Buchwald's X-Phos ligand under mild reaction conditions.

1,3-Dihydroindol-2-one (oxindole) derivatives are of great pharmaceutical interest as growth hormone secretagogues,[1] P-glycoprotein-mediated multiple drug resistance inhibitors,[2] anti-inflammatory agents,[3] and serotonergics.[4] In addition, the oxindole moiety constitutes a key structural element in several natural products.[5] The 1,3-dihydroindol-2-one derivative **6** (Scheme 3) is of current pharmaceutical interest as a key intermediate[6] in the synthesis of ORL-1 receptor ligands. As a consequence, the development of novel synthetic strategies leading to substituted oxindole derivatives is of great importance. Hitherto, two different synthetic approaches to the 3-unsubstituted 1-(piperidinyl-4-yl)oxindole **6** have been described. Unfortunately, these routes either consist of a lengthy five-step synthesis[7] or a three-step synthesis from *N*-benzylpiperidin-4-one, which suffers from harsh reaction conditions[6] ($AlCl_3$, 160 °C) in the last intramolecular Friedel–Crafts acylation step. It is clear that such harsh conditions do not comply with the presence of vulnerable substituents on the oxindole aromatic ring.

Our interest[8] in *N*-arylations prompted us to devise an efficient route for the synthesis of the pharmaceutical key intermediate **6**. The resulting approach is based on the Pd-catalyzed intramolecular amination of the aryl bromide **1**, thereby leading to the *N*-protected oxindole derivative **2** as schematically depicted in Scheme 1. Such reactions proceed under relatively mild basic conditions. In particular, the effect of different phosphine ligands on the efficiency and yield of this conversion is highlighted herein.



1 2

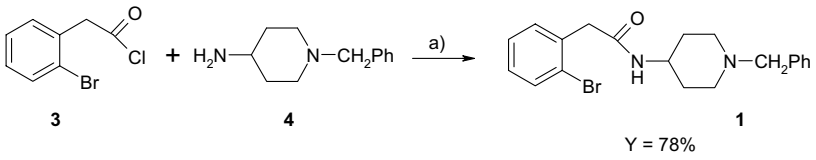
Scheme 1. (a) Conditions described in Table 1.

The starting material **1** is known[9] but we slightly improved its preparation, resulting in a considerably higher yield (Scheme 2). Thus the acid chloride **3** was amidated with amine **4** (both commercially available) to afford compound **1** in high yield. Its ^1H NMR data were in full accordance with the literature data.

The resulting amide **1** was subjected to several reaction conditions, based on the earlier work of Buchwald[10] in order to find the optimal combination of parameters leading to the oxindole **2** (Scheme 1 and Table 1).

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

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.09.121

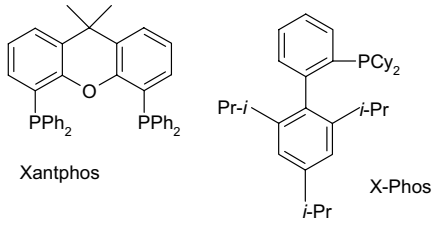


Scheme 2. Reagents and conditions: (a) 1 equiv **3**; 1.2 equiv K_2CO_3; 1.1 equiv **4**, CH_3CN, room temperature.

Table 1. Reaction conditions in the intramolecular Pd-catalyzed formation of compound **1**

Entry	Conditions	Time (h)	Yield (%)
1	1 equiv compound **1**, 1.4 equiv K_2CO_3, 1.5 mol% Pd_2dba_3, 4.5 mol% Xantphos[a], toluene, 100 °C	40	Trace
2	1 equiv compound **1**, 5 equiv K_2CO_3, 1.5 mol% Pd_2dba_3, 4.5 mol% Xantphos, toluene, 100 °C	40	15
3	1 equiv compound **1**, 5 equiv K_2CO_3, 7.5 mol% Pd_2dba_3, 30 mol% P(*o*-tolyl)$_3$, toluene, 100 °C	64	58
4	1 equiv compound **1**, 2.5 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	90

[a]



Van Leeuwen's Xantphos ligand[11] has been reported to assist in the arylation of amides and a number of aza-containing heterocycles.[12] The application of this ligand in the conversion of **1** to **2** initially gave only a trace of desired product. Although slightly better yields could be obtained by increasing the amount of base (K_2CO_3) in this Xantphos-mediated conversion, the yields still remained unsatisfactory.

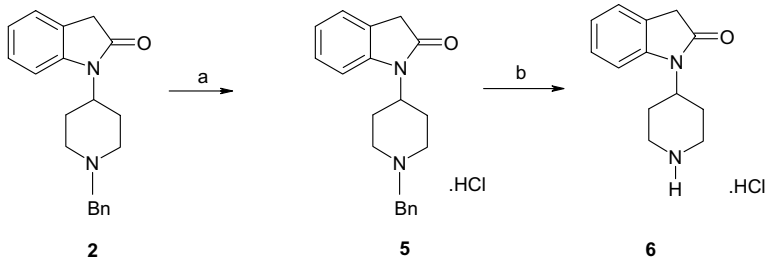
It was envisioned that the use of the monodentate tris-tolylphosphine in the intramolecular Pd-catalyzed amination of **1** into **2** would lead to better results.[10] As can be seen in Table 1 (entry 3) use of the P(*o*-tolyl)$_3$ ligand led to an isolated yield of the desired oxindole **2** of 58%. However, the reaction required relatively large amounts of $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$ ligand and proceeded very slowly. Furthermore, a problematic chromatographic purification was required in the work-up.

The discovery by Buchwald and co-workers of the X-Phos ligand[13] prompted the use of this exciting catalyst in the conversion of **1** into **2** (Table 1, entry 4). We found that the X-Phos ligand effected an amazingly efficient formation of **2** in a high yielding and clean reaction.[14]

The resulting *N*-benzyl protected oxindole **2** was subsequently debenzylated to the target oxindole **6** by a catalytic hydrogenation reaction via the isolated corresponding hydrochloric acid salt **5** in quantitative yield[15] (Scheme 3).

Conclusion

A novel synthetic approach has been devised for the pharmaceutically important *N*-piperidin-4-yloxindole **6**.



Scheme 3. Reagents and conditions: (a) 2 equiv acetyl chloride/EtOH; (b) $Pd(OH)_2$/C, H_2, MeOH, 50 psi (quant.).

The key step comprises an intramolecular Pd-catalyzed amination reaction. The X-Phos ligand was found to be superior in this conversion, leading to both a high reaction rate and an excellent yield. The prospects of the X-Phos ligand for the synthesis of structurally related oxindole derivatives, having vulnerable aromatic substituents, are promising as the applied reaction conditions are very mild. Furthermore, due to the specific Pd-mediated cyclisation at the bromo-substituted *ortho* position of **1**, this approach will produce exclusively one regioisomer in the case of the presence of additional substitutent(s) on the aryl ring.

Acknowledgements

We wish to thank Mrs. Alice Borst and Mr. Pieter Spaans for analytical support, and Mr. Peter Koelman for screening the literature.

References and notes

1. Nagata, R.; Tokunaga, T.; Hume, W.; Umezone, T.; Okazaki, U.; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi, H. *J. Med. Chem.* **2001**, *44*, 4641–4649.
2. Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharmacol.* **1995**, *47*, 241–247.
3. Asmawi, M. Z.; Moilanen, E.; Alanko, J.; Vapaatalo, H. *Eicosanoids* **1988**, *1*, 35–39.
4. Mokrosz, M. J.; Duszynska, B.; Misztal, S.; Klodinska, A.; Tatarzynska, E. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 325–330.
5. Thiericke, R.; Tang, Y. Q.; Sattler, I.; Grabley, S.; Feng, X. Z. *Eur. J. Org. Chem.* **2001**, 261–267.
6. Zaveri, N. T.; Jiang, F.; Olsen, C. M.; Deschamps, J. R.; Parrish, D.; Polgar, W.; Toll, L. *J. Med. Chem.* **2004**, *47*, 2973–2976.
7. Forbes, I. T. *Tetrahedron Lett.* **2001**, *42*, 6943–6945.
8. Lange, J. H. M.; Hofmeyer, L. J. F.; Hout, F. A. S.; Osnabrug, S. J. M.; Verveer, P. C.; Kruse, C. G.; Feenstra, R. W. *Tetrahedron Lett.* **2002**, *43*, 1101–1104.
9. Mach, R.; Huang, Y.; Hammond, P. S.; Whirrett, B. R.; Kuhner, R. J.; Wu, L.; Childers, S. R. *J. Med. Chem.* **1998**, *41*, 2361–2370.
10. Buchwald, S. L.; Yang, B. H. *Org. Lett.* **1999**, *1*, 35–37.
11. Kamer, P.; van Leeuwen, P.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895–904.
12. (a) Lovely, C. J.; Browning, R. G.; Badarinarayana, V.; Mahmud, H. *Tetrahedron* **2004**, *60*, 359–365; (b) Wallace, D. J.; Kluber, D. J.; Chen, C.; Volante, P. *Org. Lett.* **2003**, *5*, 4749–4752; (c) Buchwald, S. L.; Yin, J. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048; (d) Buchwald, S. J.; Yin, J. *Org. Lett.* **2000**, *2*, 1101–1104.
13. (a) Buchwald, S. L.; Gelman, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993–5996; (b) Buchwald, S. L.; Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655; (c) Blackmond, D. G.; Buchwald, S. L.; Strieter, E. R. *J. Am. Chem. Soc.* **2003**, *125*, 13978–13980; (d) Buchwald, S. L.; Nguyen, H. N.; Huang, X. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819.
14. Procedure for the intramolecular Pd-catalyzed amination of compound **1**: A dried 100 mL three-necked reaction vessel was charged with 35 mL dry and degassed *t*-BuOH. At a temperature of 35 °C, compound **1** (0.97 g, 2.5 mmol) was added. The temperature was raised to 80 °C, until a clear solution was obtained. After cooling down to 35 °C, $Pd(OAc)_2$ (16.8 mg, 0.075 mmol), $PhB(OH)_2$ (22.8 mg, 0.1875 mmol), X-Phos (89.4 mg, 0.1875 mmol) and K_2CO_3 (0.86 g, 6.25 mmol) were successively added. Under stirring and nitrogen atmosphere, the reaction mixture was heated at 85 °C. After 3 h, the starting compound **1** had disappeared (TLC: CH_2Cl_2/MeOH/NH_4OH 96:3.75:0.25). After cooling down to room temperature, the reaction mixture was diluted with dichloromethane and filtered. The filtrate was evaporated under reduced pressure and purified by chromatography with the above-mentioned eluent. Compound **2** was isolated in a yield of 90%. Analytical data for **2**: mp 100.4–101.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): identical with the ^{1}H NMR data given in the literature.[6] HRMS ES+: calculated for $C_{20}H_{23}N_2O$ (M+H) 307.1810, found: 307.1809.
15. Procedure for the debenzylation of compound **2** to compound **6**: Compound **2** (0.55 g, 1.8 mmol) was dissolved in 15 mL EtOH. To the magnetically stirred solution was added 3.6 mmol HCl in EtOH (from 3.6 mmol AcCl in 10 mL EtOH). The solution obtained was evaporated under reduced pressure and the crude residue was treated with diethyl ether. The obtained solid substance was isolated and dissolved in 25 mL MeOH. After addition of a catalytic amount of $Pd(OH)_2$/C, the reaction mixture was hydrogenated at 50 psi for 24 h. After filtration of the Pd/C, and evaporation of the filtrate under reduced pressure, compound **6** was isolated in quantitative yield. Analytical data for compound **6** (as free base): ^{1}H NMR δ ppm ($CDCl_3$, 400 MHz): 1.68–1.82 (m, 3H), 2.28–2.40 (m, 2H), 2.72–2.82 (m, 2H), 3.22–3.28 (m, 2H), 3.52 (s, 2H), 4.32–4.42 (m, 1H), 7.02 (t, J = 8 Hz, 1H), 7.15 (d, J = 8 Hz, 1H), 7.22–7.28 (m, 2H). HRMS ES+: calculated for $C_{13}H_{17}N_2O$ (M+H) 217.1341, found: 217.1307.