Tetrahedron Letters 50 (2009) 2437–2439

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave-assisted direct biaryl coupling: first application to the synthesis of aporphines

Sandeep Chaudhary, Stevan Pecic, Onica LeGendre, Wayne W. Harding *

Department of Chemistry, Hunter College, and the Graduate Center of the City, University of New York, 695 Park Avenue, New York, NY 10065, USA

ARTICLE INFO

Article history:
Received 19 November 2008
Revised 2 March 2009
Accepted 5 March 2009
Available online 11 March 2009

ABSTRACT

We have investigated the use of microwaves in a direct biaryl coupling reaction for the synthesis of analogs of the aporphine alkaloid nantenine. Our study shows that the aporphine core may be rapidly accessed from benzyl-tetrahydroisoquinoline substrates with this method. This is the first report of a microwave-assisted direct biaryl coupling reaction in the synthesis of aporphine molecules.

Microwave irradiation is being increasingly utilized in organic synthesis due often to superior reaction rates, selectivity, and product yields as compared to standard thermal conditions.[1–3] Microwave-assisted versions of biaryl coupling methodologies such as the Suzuki, Heck, and Negishi reactions have been reported extensively in the literature.[4–9] However, there have been relatively few reports on the use of microwave irradiation in direct biaryl coupling procedures.

Direct biaryl coupling is similar to the Heck reaction in terms of substrates used. However, whereas the Heck reaction couples an activated arene (such as an aryl halide or aryl triflate) and an alkene, direct biaryl coupling uses an activated arene and an aromatic ring as substrates.[10] There is evidence that the Heck and direct biaryl coupling reactions are mechanistically dissimilar, with direct biaryl coupling likely proceeding via a concerted metalation–deprotonation pathway.[11–13]

The direct biaryl coupling procedure is very useful for construction of biaryl bonds, in both inter- and intra-molecular reactions, and has been used in the synthesis of a number of bioactive molecules including aporphines.[14,15] Recently, this methodology has also been applied to synthesis of heterocyclic biaryl motifs.[16–18]

Aporphines are a diverse group of alkaloids found in several plant species and have been found to show a range of interesting biological activities such as antiserotonergic, dopaminergic, antiplasmoidal, antihelminthic, and anticancer activities.[19–23] This has led to several syntheses of this class of compounds.[24,14,25] One of our current interests is in the synthesis of aporphine alkaloids related to the serotonergic 5-HT_{2A} and α_1 adrenergic receptor antagonist nantenine (**1**, Fig. 1).[26,21,27,28] We were particularly interested in preparing *N*6 and C1 nantenine analogs (general structures **2** and **3**, respectively) for our structure–activity relationship (SAR) studies and envisaged that the direct biaryl coupling route would be a facile strategy for accessing the required analogs.

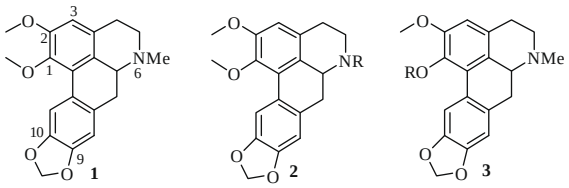


Figure 1. Structure of nantenine and target analogs.

For the synthesis of *N*6 analogs we required compound **2b** (Fig. 2). We anticipated that **2b** could be readily obtained from benzyl-tetrahydroisoquinoline **4** via **2a**. Synthesis of **2a** via direct biaryl coupling under thermal conditions has been reported to occur in high yield ($Pd(OAc)_2$, ligand A, K_2CO_3, DMA, 130 °C, 99%).[14,15] However, in our hands only a 48% yield of cyclized product was ob-

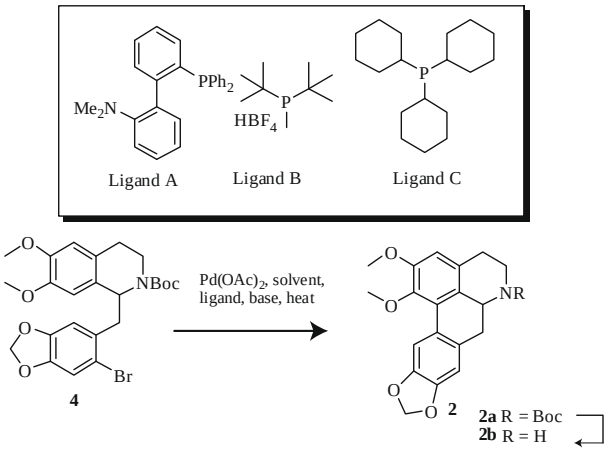


Figure 2. Approach to synthesis of *N*6 nantenine analogs.

* Corresponding author. Tel.: +1 212 772 5359; fax: +1 212 772 5332.
E-mail address: whardi@hunter.cuny.edu (W.W. Harding).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.03.029

Table 1
Thermal cyclization[a] of **4** and **5**

Entry	Substrate	Product	Solvent	Ligand	Yield (%)
1	**4**	**2b**	DMA	A	48
2[b]	**4**	**2b**	DMA	A	47
3	**5**	**7**	DMA	A	47

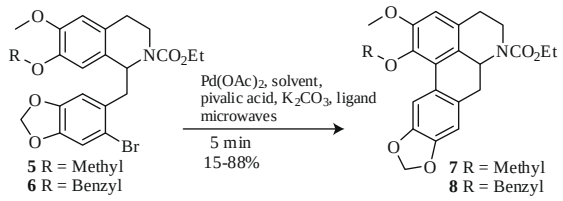
[a] Conditions: $Pd(OAc)_2$, K_2CO_3, DMA, ligand A, 130 °C, 24 h.
[b] Pivalic acid added to the reaction.

tained using the previously reported thermal conditions (Table 1, entry 1). Addition of pivalic acid which has been reported to enhance some biaryl coupling reactions and overall yields, did not result in any improvement in the yield of **2a** (Table 1, entry 2).[29] Furthermore, attempts to remove the boc group of **2a** under typical acidic conditions (TFA/DCM) gave only a moderate yield (52%) of **2b**. Given the apparent sensitivity of the aporphine nucleus to acidic conditions, we decided to prepare the ethyl carbamate derivative **7** (Scheme 1) since we envisaged that cleavage of the ethyl carbamate group to give **2b** could be readily effected under basic conditions.

Following this approach, we prepared compound **5** (Scheme 1). However, when the direct biaryl coupling procedure was attempted under standard thermal conditions (Table 1, entry 3) we only obtained a 47% yield of the aporphine **7**. We observed that a significant amount of starting material remained after reacting for 24 h. Even after reacting for 48 h, the reaction did not proceed to completion. At this juncture, we decided to attempt to improve the yield of this biaryl cyclization and increase the overall efficiency of our synthesis through the use of microwaves.

In our first attempt at microwave-assisted direct biaryl cyclization of **5**, we employed ligand A with DMA as solvent (Table 2, entry 1). Disappointingly, we found that the yield was significantly reduced as compared to the analogous thermal conditions, there being formed a significant amount of an unidentified by-product. Nevertheless, to examine the effect of different ligands, we conducted the microwave-assisted reaction with ligand B using DMA as solvent (Table 2, entry 2) and were elated to find that there was considerable improvement in the yield. With ligand B, other polar, high boiling solvents (DMF and DMSO) also gave excellent yields (Table 2, entries 3 and 4). We next decided to apply our microwave conditions to the synthesis of **8** (Scheme 1). Compound **8** is a versatile intermediate for the synthesis of *N*6 as well as C1 nantenine analogs. With substrate **6** we obtained a high yield of cyclized product **8** with the ligand B/DMA combination (Table 2, entry 5). Ligands A and C were also effective in achieving biaryl cyclization with DMA as solvent (Table 2, entries 6 and 7) in very good yields. From compound **8** we were able to synthesize several C1 and *N*6 nantenine analogs using standard synthetic transformations.

To further explore the substrate scope of the newly developed microwave-assisted conditions, we decided to investigate cyclization of the less reactive arene substrate **9a** which is devoid of electron-releasing groups in the haloarene component. Previous attempts at cyclization of this compound with a ligand A/DMA



Scheme 1. Microwave-assisted direct biaryl coupling.

Table 2
Microwave-assisted biaryl coupling[a] of **5** and **6**[30]

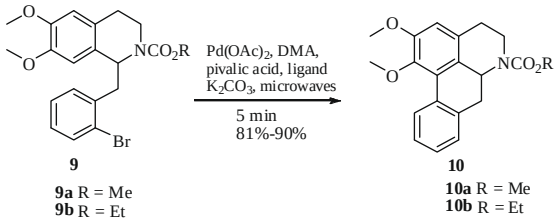
Entry	Substrate	Product	Solvent	Ligand	Yield (%)
1	**5**	**7**	DMA	A	15
2	**5**	**7**	DMA	B	72
3	**5**	**7**	DMF	B	82
4	**5**	**7**	DMSO	B	88
5	**6**	**8**	DMA	B	87
6	**6**	**8**	DMA	A	82
7	**6**	**8**	DMA	C	78

[a] Conditions: $Pd(OAc)_2$, K_2CO_3, solvent, pivalic acid, ligand, microwaves, 5 min.

Table 3
Thermal and microwave-assisted[a] cyclization of **9**

Entry	Substrate	Product	Solvent	Ligand	Yield (%)
1	**9a**	**10a**	DMA	A	40
2[b]	**9a**	**10a**	DMA	A	58
3[a]	**9a**	**10a**	DMA	A	51
4[a,b]	**9a**	**10a**	DMA	A	81
5[a,b]	**9a**	**10a**	DMA	B	90
6[a,b]	**9b**	**10b**	DMA	B	82

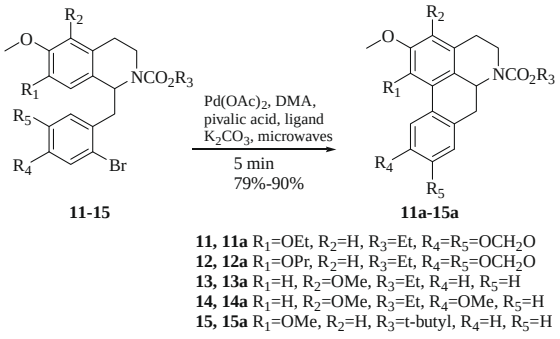
[a] Conditions: $Pd(OAc)_2$, K_2CO_3, solvent, ligand microwaves, 5 min.
[b] Pivalic acid added to the reaction.



Scheme 2. Direct biaryl cyclization of **9**.

combination gave only a moderate yield of **10a** under thermal conditions.[14] We also found this to be the case, although addition of pivalic acid gave a slight improvement in yield (Table 3, entries 1 and 2) (see Scheme 2).

Using ligand A, in the absence of pivalic acid under microwave conditions, gave a moderate yield (Table 3, entry 3); addition of pivalic acid substantially improved the yield of the microwave-assisted reaction to 81% (Table 3, entry 4). Ligand B gave a slightly improved yield as compared to ligand A using otherwise identical conditions (Table 3, entry 5). With the ethyl carbamate congener **9b**, cyclization was effected in 82% yield with ligand B (Table 3, entry 6).



Scheme 3. Microwave-assisted direct biaryl cyclization of **11–15**.

Table 4
Microwave-assisted cyclization of **11**–**15**

Entry	Substrate	Product	Solvent	Ligand	Yield (%)
1	**11**	**11a**	DMA	B	82
2	**12**	**12a**	DMA	B	79
3	**13**	**13a**	DMA	B	90
4	**14**	**14a**	DMA	B	84
5	**15**	**15a**	DMA	B	79

To further explore the substrate diversity of the microwave reaction, we then applied our optimized conditions for the synthesis of aporphines **11a**–**15a** (Scheme 3). These results which demonstrate broader substrate applicability of the reaction conditions are presented in Table 4.

In conclusion, our study demonstrates the utility of microwaves for rapid direct biaryl coupling in the synthesis of aporphines. Additionally, we found that the microwave method is operationally simpler because no special precautions need to be taken to avoid exposure of the reaction to air. This is the first report on microwave-assisted direct biaryl coupling in the synthesis of aporphines. We are continuing to examine substrate tolerance in this microwave-enhanced reaction and will report our findings in due course.

Acknowledgments

O.L. acknowledges the RISE program at Hunter College for financial support. We also thank Dr. Robert Bittman at Queens College, CUNY for providing access to the microwave reactor and other general assistance. This publication was made possible by Grant No. RR03037 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health.

References and notes

1. Mavandadi, F.; Pilotti, A. *Drug Discovery Today* **2006**, *11*, 165–174.
2. Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Disc.* **2006**, *5*, 51–63.
3. Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95–105.
4. Lindh, J.; Enquist, P. A.; Pilotti, A.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2007**, *72*, 7957–7962.
5. Arvela, R. K.; Leadbeater, N. E. *J. Org. Chem.* **2005**, *70*, 1786–1790.
6. Datta, G. K.; Vallin, K. S.; Larhed, M. *Mol. Divers* **2003**, *7*, 107–114.
7. Hogermeier, J.; Reissig, H. U. *Chemistry* **2007**, *13*, 2410–2420.
8. Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973–2976.
9. Walla, P.; Kappe, C. O. *Chem. Commun. (Camb)* **2004**, 564–565.
10. Campeau, L. C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186–9187.
11. Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.
12. Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5*, 31–44.
13. Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H. F.; Fugami, K.; Kosugi, M. *Org. Lett.* **2001**, *3*, 3313–3316.
14. Lafrance, M.; Blaquiere, N.; Fagnou, K. *Chem. Commun. (Camb)* **2004**, 2874–2875.
15. Lafrance, M.; Blaquiere, N.; Fagnou, K. *Eur. J Org. Chem.* **2007**, *5*, 811–825.
16. Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493–2500.
17. Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589–1591.
18. Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013–1025.
19. Stevigny, C.; Bailly, C.; Quetin-Leclercq, J. *Curr. Med. Chem. Anticancer Agents* **2005**, *5*, 173–182.
20. Rasoanaivo, P.; Ratsimamanga-Urverg, S.; Rafatro, H.; Ramanitrahasimbola, D.; Palazzino, G.; Galeffi, C.; Nicoletti, M. *Planta Med.* **1998**, *64*, 58–62.
21. Indra, B.; Matsunaga, K.; Hoshino, O.; Suzuki, M.; Ogasawara, H.; Ishiguro, M.; Ohizumi, Y. *Can. J. Physiol. Pharmacol.* **2002**, *80*, 198–204.
22. Ayers, S.; Zink, D. L.; Mohn, K.; Powell, J. S.; Brown, C. M.; Murphy, T.; Brand, R.; Pretorius, S.; Stevenson, D.; Thompson, D.; Singh, S. B. *Planta Med.* **2007**, *73*, 296–297.
23. Zhang, A.; Zhang, Y.; Branfman, A. R.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **2007**, *50*, 171–181.
24. Kupchan, S. M.; Kameswaran, V.; Findlay, J. W. *J. Org. Chem.* **1973**, *38*, 405–406.
25. Furstner, A.; Mamane, V. *Chem. Commun. (Camb)* **2003**, 2112–2113.
26. Indra, B.; Tadano, T.; Nakagawasai, O.; Arai, Y.; Yasuhara, H.; Ohizumi, Y.; Kisara, K. *Life Sci.* **2002**, *70*, 2647–2656.
27. Indra, B.; Matsunaga, K.; Hoshino, O.; Suzuki, M.; Ogasawara, H.; Ohizumi, Y. *Eur. J. Pharmacol.* **2002**, *437*, 173–178.
28. Orallo, F. *Planta Med.* **2003**, *69*, 135–142.
29. Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015–6020.
30. *Typical microwave-assisted biaryl coupling procedure (using* **6** *as an example)*: To a solution of compound **6** (50.0 mg, 0.09 mmol), in DMA (4 ml) were added $Pd(OAc)_2$ (2.0 mg, 0.1 mmol), ligand A (6.9 mg, 0.2 mmol), K_2CO_3 (37.5 mg, 0.3 mmol), and pivalic acid (2.8 mg, 0.03 mmol). The mixture was irradiated in a Smith Creator microwave reactor in a sealed vial for 5 min with the power level at 150 W. After cooling to room temperature, the reaction mixture was loaded onto a deactivated silica gel column and eluted with 40% ethyl acetate-hexanes. This gave compound **8** (35.0 mg, 0.074 mmol, 82%). Compound **8**, white solid, ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.27 (t, J = 5.6 Hz, 3H), 2.65 (d, J = 13.8 Hz, 1H), 2.72 (d, J = 13.8 Hz, 1H), 2.87 (t, J = 12.6 Hz, 2H), 2.96 (t, J = 12.6 Hz, 1H), 3.89 (s, 3H), 4.21 (q, J = 5.6 Hz, 2H), 4.51 (br s, 1H), 4.66 (d, J = 10.2 Hz, 1H), 4.67 (1H, obscured), 4.81 (d, J = 10.2 Hz, 1H), 5.96 (s, 1H), 5.99 (s, 1H), 6.66 (s, 1H), 6.74 (s, 1H), 7.31 (m, 3H), 7.37 (d, J = 6.6 Hz, 2H), 8.05 (s, 1H).