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An Advantageous Route to Oxcarbazepine (Trileptal) Based on Palladium-Catalyzed Arylations Free of Transmetallating Agents

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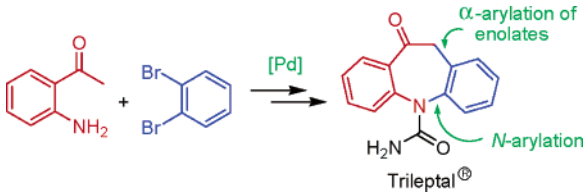
ABSTRACT



A new route to oxcarbazepine (Trileptal), the most widely prescribed antiepileptic drug, starting from commercially available 2′-aminoacetophenone and 1,2-dibromobenzene, is reported. The sequentially accomplished key steps are palladium-catalyzed intermolecular α-arylation of ketone enolates and intramolecular N-arylation reactions. After several experiments to establish the best conditions for both arylation processes, the target oxcarbazepine is obtained in a satisfactory overall yield, minimizing the number of steps and employing scalable catalytic procedures developed in partially aqueous media.

Oxcarbazepine **1** (Trileptal) has become the most widely prescribed drug for the treatment of epilepsy, both in adults and children, improving the tolerability profile of previously established antiepileptic agents such as carbamazepine **2** (Tegretol), but without loss in its therapeutic potency (Figure 1).[1] Moreover, its analgesic properties and its efficacy in the treatment of mood disorders and mania make Trileptal an appealing target.[2]

A number of routes to oxcarbazepine **1** have been described in the literature.[3] Most of them are based on transformations in the iminostilbene or iminodibenzyl framework obtained from *o*-nitrotoluene or *o*-nitrobenzyl chloride through a sequence of oxidation and reduction reactions. Unfortunately the relatively harsh conditions required prevented the preparation of analogues.[3] More recently Novartis Pharma has designed two different protocols for the access to Trileptal based on remote metalation and Friedel−Crafts acylation as the key steps, respectively. Although the scale-up process in the Friedel−Crafts protocol has been successfully achieved, in the remote metalation approach it failed as the result of a required excess of LDA-TMEDA.[4]

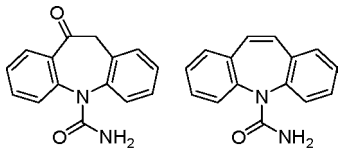


Figure 1.

(1) Clemens, B.; Menes, A.; Nagy, Z. *Acta Neurol. Scand.* **2004**, *109*, 324.

(2) (a) Lande, R. G. *Int. J. Psychiatry Clin. Pract.* **2004**, *8*, 37. (b) Hopwood, M.; Manning, D. WO Patent Application 2004035041, 2004; *Chem. Abstr*. 2004, *140*, 363050.

(3) Milanese, A. PCT Int. Appl. WO 9621649, 1996; *Chem. Abstr*. **1996**, *125*, 195448.

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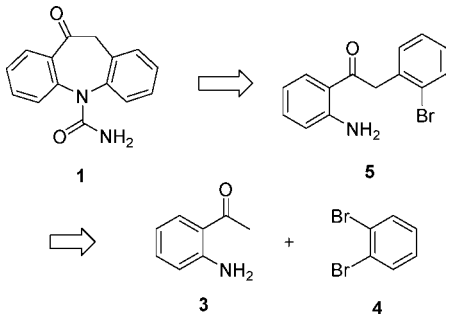
Continuing with our research on palladium-catalyzed arylation reactions of different nucleophiles,[5] we envisaged a straightforward approach to the Trileptal skeleton through a sequence of palladium-mediated C- and N-arylation reactions in intermolecular and intramolecular fashions, respectively. Such an ambitious strategy, based on an entirely catalytic reaction in the key steps of the sequence and avoiding the use of any transmetallating agent, starts from commercially available 2′-aminoacetophenone **3** and 1,2-dibromobenzene **4**. According to this plan, the synthesis of intermediate deoxybenzoin **5** through an intermolecular palladium-catalyzed α-arylation of ketone enolates and its subsequent cyclization employing palladium-mediated N-arylation protocols would provide the tricyclic framework of oxcarbazepine **1** (Scheme 1).

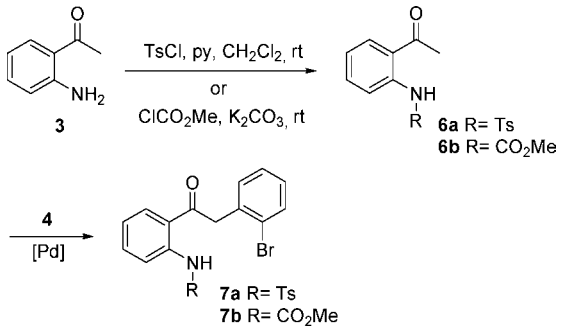
Scheme 1



To promote the initial selective C-arylation reaction, the nucleophility of substrate **3**[6] was diminished by transforming it into sulfonamide **6a** and carbamate **6b**. A full range of reaction conditions evaluated to promote such C-arylation reaction revealed first that, in comparison with carbamate **6b**, *N*-tosyl derivative **6a** displayed a higher chemoselectivity.[7]

To our surprise, several of the previously reported procedures for the α-arylation of acetophenone enolates and related substrates[8] clearly failed in our case, rendering unreacted **6a** (Table 1, entries 1−5). Paradoxically, a ligand commonly employed in N-arylation reactions but barely used in α-arylation of enolates, Xantphos,[9] turned out to be the key for the best conditions leading to C-arylated product **7a** (Table 1, entries 6, 7, and 9−12). The use of K_3PO_4 as the base provided the best conversion (Table 1, entry 10), and despite the bidentate nature of Xantphos, the optimized L/Pd ratio was set at 2 (Table 1, entries 9−12). The addition of relatively small quantities of water resulted in an enhancement of the selectivity so that the reaction proceeded more cleanly, but the rate of the process was noticeably slower (Table 1, entry 11). The use of water to mediate several palladium-catalyzed reactions has already been described in the literature, but it usually requires specifically designed water-soluble ligands, in almost entirely aqueous media as the one described in entry 12.[10]

Table 1. Selected α-Arylation Assays Performed on Substrates **6a,b**



entry	reaction conditions	7[a]
1	**6a**, 1.7% Pd_2dba_3, 4.5% BINAP, 2.6 equiv NaO^tBu, THF, 80 °C, 22 h[b]	**7a** 0 (0)
2	**6a**, 2% $Pd(dba)_2$, 4% $P(^tBu)_3$, 5 equiv K_3PO_4, PhMe, 80 °C, 24 h[b]	**7a** 0 (100)
3	**6a**, 4.7% $Pd(OAc)_2$, 10% PPh_3, 2.4 equiv Cs_2CO_3, DMF, 80 °C, 22 h[b]	**7a** 0 (0)
4	**6a**, 7.3% $Pd(dba)_2$, 9% DPPF, 2.3 equiv NaO^tBu, THF, 80 °C, 8 h[b]	**7a** 0 (0)
5	**6a**, 4.5% $Pd(OAc)_2$, 6% IPr·HCl, 1.5 equiv NaO^tBu, 1,4-dioxane, 80 °C, 8 h[b]	**7a** 0 (0)
6	**6a**, 3.7% $Pd(OAc)_2$, 5.4% Xantphos, 1.4 equiv Cs_2CO_3, PhMe, 130 °C, 5 h[b]	**7a** 61 (76)
7	**6b**, 4.7% $Pd(OAc)_2$, 4.9% Xantphos, 2.8 equiv Cs_2CO_3, PhMe, 130 °C, 20 h[c]	**7b** 17 (20)
8	**6b**, 1.4% Pd_2dba_3, 3.7% BINAP, 1.5 equiv NaO^tBu, THF, 80 °C, 24.5 h[d]	**7b** 0 (10)
9	**6a**, 3.6% $Pd(OAc)_2$, 7.7% Xantphos, 1.4 equiv Cs_2CO_3, PhMe, 130 °C, 5 h[b]	**7a** 76 (73)
10	**6a**, 3.6% $Pd(OAc)_2$, 7.8% Xantphos, 1.5 equiv K_3PO_4, PhMe, 130 °C, 29 h.[e]	**7a** 72 (96)
11	**6a**, 4.4% $Pd(OAc)_2$, 8.5% Xantphos, 1.4 equiv Cs_2CO_3, PhMe/H_2O, 120 °C, 48 h.[f,g]	**7a** 86 (85)
12	**6a**, 4% $Pd(OAc)_2$, 8% Xantphos, 1.4 equiv Cs_2CO_3, PhMe/H_2O, 120 °C, 48 h.[f,h]	**7a** 79 (66)

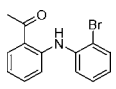
[a] Isolated yields calculated on the basis of the conversion rate. The value in parentheses indicates conversión rates of substrates **7**. [b] [**6a**]:[**4**] = 1:1.1. [c] [**6b**]:[**4**] = 1.2:1. [d] [**6b**]:[**4**] = 1:1.2. [e] 3.15 equiv of **4**. [f] 2.4 equiv of **4**. [g] PhMe/H_2O (v/v = 5.2). [h] PhMe/H_2O (v/v = 0.2).

(4) (a) Lohse, O.; Beutler, U.; Fünfschilling, P.; Furet, P.; France, J.; Kauffmann, D.; Penn, G.; Zaugg, W. *Tetrahedron Lett.* **2001**, *42*, 385. (b) Kauffmann, D.; Fünfschilling, P.; Beutler, U.; Hoehn, P.; Lohse, O.; Zaugg, W. *Tetrahedron Lett.* **2004**, *45*, 5275.

(5) (a) Hernández, S.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2002**, *4*, 1591. (b) Churruca, F.; SanMartin, R.; Carril, M.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2004**, *60*, 2393.

(6) Initial attempts to perform α-arylation directly from aminoketone **3** gave negligible results.

(7) All α-arylation assays performed on substrate **6b** provided, apart from null or very low yields of target intermediate **7b**, variable amounts of *N*-arylated/deprotected product **9**.



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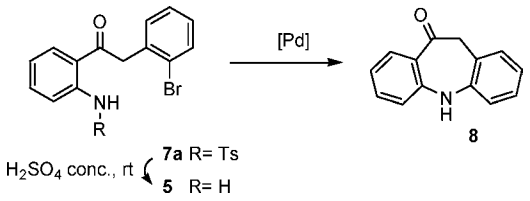
(8) (a) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.

(9) For one of the few examples in which Xantphos is used for the α-arylation of carbonyl compounds, see: Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.

Acidic hydrolysis of sulfonamide **7a** was effectively (95%) performed in order to attain the cyclization step by an intramolecular N-arylation process,[11] which was evaluated over a full range of experimental conditions on the presumed amine derivative **5**. As shown in Table 2, the optimized conditions provided target azepinone **8** in excellent yield (91%), thus minimizing the amount (<4%) of dehalogenated byproducts. Once again, the addition of water produced a clearly beneficial effect on the process by surprisingly accelerating the reaction (Table 2, compare entries 4 and 8). Although in this case water might merely act as a better cosolvent for the employed base (K_3PO_4) thus promoting the target amination, the accelerating properties of water when used as a convenient additive or cosolvent in other palladium-catalyzed reactions have been reported and therefore other roles cannot be discounted.[10] Several reaction conditions not included in Table 2, such as Ullmann-type copper-mediated procedures and the use of heterogeneous palladium catalysts, failed to afford the target tricycle **8**.

Table 2. Selected *N*-Arylation Assays Performed on Intermediate **5**

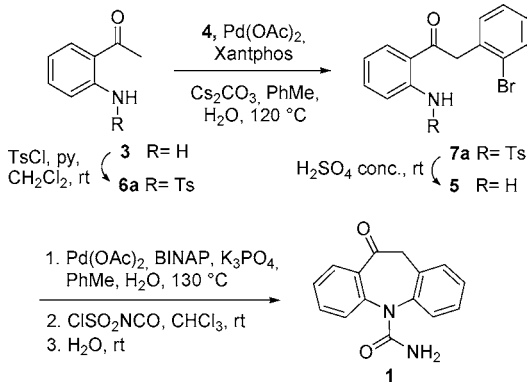


entry	reaction conditions	8[a]
1	10% $Pd(PPh_3)_4$, 1.5 equiv K_2CO_3, 1.6 equiv NaO^tBu, PhMe, 100 °C, 4 h	0
2	6.7% $Pd(OAc)_2$, 5.5% Xantphos, 1.5 equiv Cs_2CO_3, PhMe, 130 °C, 21.5 h	0
3	5.3% $Pd(OAc)_2$, 4.4% BINAP, 1.5 equiv Cs_2CO_3, PhMe, 100 °C, 22 h	32[b]
4	3.6% $Pd(OAc)_2$, 7.7% BINAP, 1.6 equiv K_3PO_4, PhMe, 130 °C, 22 h	85
5	3.4% $Pd(OAc)_2$, 7.5% BINAP, 1.5 equiv Cs_2CO_3, THF, 100 °C, 22 h[c]	0
6	4% $Pd(OAc)_2$, 7.2% BINAP, 1.9 equiv K_3PO_4, PhMe/H_2O, 130 °C, 5 h[d]	84
7[d]	3.3% $Pd(OAc)_2$, 7.6% BINAP, 1.9 equiv K_3PO_4, PhMe/H_2O, 130 °C, 4.5 h[d]	87
8[d]	4.9% $Pd(OAc)_2$, 7.9% BINAP, 1.97 equiv K_3PO_4, PhMe/H_2O, 130 °C, 5 h[d]	91

[a] Isolated yields. Conversion rates were >98% except when indicated. [b] The conversion rate of substrate **5** was 54%. [c] The reaction was performed in a sealed tube. [d] PhMe/H_2O (v/v = 2.3).

Finally, carbamoylation of the latter dibenzoazepinone **8** was carried out by using chlorosulfonyl isocyanate (Scheme 2). In our hands, such established procedure was slightly modified, providing a clear improvement (50% yield) compared with previously patented results.[3,12]

Scheme 2



In summary, we have developed a straightforward (only five steps) and high-yielding route to oxcarbazepine **1** (Scheme 2) employing the use of water as cosolvent, catalytic reactions as the key steps of the synthetic sequence, and milder conditions involving carbonate and phosphate salts as bases. Moreover, the availability of the starting materials and the low catalyst loading of the employed simple palladium sources and ligands are also appealing features that make the proposed synthetic path to Trileptal economically advantageous. It should be pointed out that the whole synthetic sequence can be performed in gram scale without significant decrease in the overall yield.

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Supporting Information Available: Experimental procedures and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051291P

(10) (a) Ueda, M.; Nishimura, M.; Miyaura, N. *Synlett* **2000**, 856. See also: (b) Catalytic Organic Reactions in Water (special issue); *Adv. Synth. Catal*. **2002**, *3*−*4*. (c) Fan, Q.-H.; Li, Y.-M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385−3466. (d) Genet, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305−317.

(11) Some assays performed to effect α-arylation of N-tosylated derivative **6a** provided traces of the so-cyclized azepinone. Although strictly preliminary, we consider such results as promising.

(12) Novartis Pharma claims a 70−80% yield for the same carbamoylation reaction, but reference the procedure reported in ref 3, in which only a 35% is obtained. See also ref 4.