New synthesis of oxcarbazepine via remote metalation of protected *N-o*-tolyl-anthranilamide derivatives

Olivier Lohse,* Ulrich Beutler, Peter Fünfschilling, Pascal Furet,[†] Julien France,[†] Daniel Kaufmann, Gerhard Penn and Werner Zaugg

Novartis Pharma AG, Chemical and Analytical Development, CH-4002 Basel, Switzerland

Received 18 July 2000; accepted 1 November 2000

Abstract—Benzyl and allyl protected *N-o*-tolyl-anthranilamides were efficiently prepared by Buchwald–Hartwig C–N cross coupling reactions, followed by protection of the amino group. Under directed remote metalation conditions, protected dibenzoazepinones were obtained in good yields. Deprotection of the amine and conversion to an urea furnished a new and efficient synthesis of the antiepileptic drug Trileptal®. © 2001 Elsevier Science Ltd. All rights reserved.

Carbamazepine **1** (Tegretol®) is the most widely prescribed antiepileptic drug for the treatment of partial and generalized tonic-clonic seizures.[1] In an effort to improve the tolerability profile of carbamazepine without affecting its antiepileptic potency, the keto-analog oxcarbazepine **2** (Trileptal®) was developed. Oxcarbazepine has demonstrated its efficacy and its improved safety profile and is now considered as an antiepileptic drug of first choice.[2]


Carbamazepine **1**   Oxcarbazepine **2**
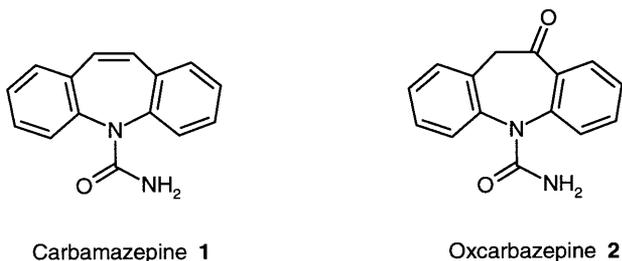
Several routes to oxcarbazepine **2** have been described in the literature.[3] They are nearly all based on the transformation of the iminostilbene or iminodibenzyl ring using strong oxidative reagents.[4] Furthermore, the iminostilbene ring is not prone to functionalization[5] and oxcarbazepine analogs cannot be easily prepared.[5b] We were interested in the work of Fouche and Leger

who described remote metalation and cyclization of *N*-alkyl, *N*-(*o*-tolyl)anthranilic esters (Scheme 1).[6] Recently, Snieckus also reported the remote metalation and cyclization of diethyl *N*-methyl-*o*-tolylanthranilamide to *N*-methyl dipenzazepinone.[7] We found this route very attractive and envisaged that by replacing the *N*-alkyl groups by removable protecting groups, a straightforward access to 10-ketoiminodibenzyl could be achieved.[7,8] Furthermore, given the recent development of a diarylamine synthesis by Buchwald–Hartwig coupling,[9] we recognized that a number of new oxcarbazepine analogs would become readily accessible. We
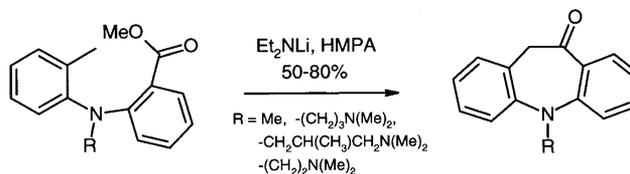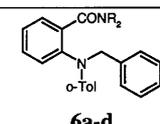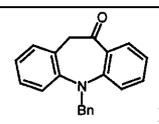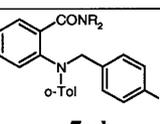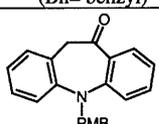

Scheme 1.
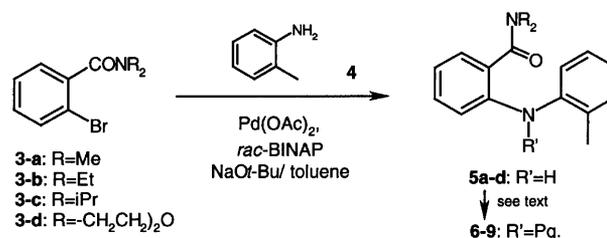
Scheme 2.

* Corresponding author. Fax: +41 61 696 27 11; e-mail: olivier.lohse@pharma.novartis.com
† Novartis Pharma Research.

Table 1. Synthesis of protected dibenzazepinones **10–13**

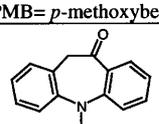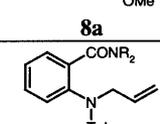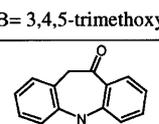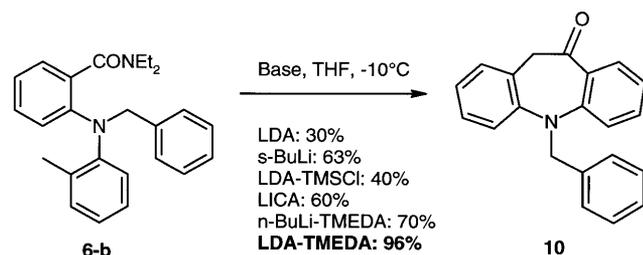| Entry	Pre-cyclization Product	N-Protection Yield[a]	LDA-TMEDA Cylization		
			Product	Yield[b]	React. time
1	**6a-d**	**6a** (R=Me): 72% **6b** (R=Et): 97% **6c** (R=iPr): 70% **6d** (R=-(CH₂CH₂)₂O: 79%	**10** (Bn= benzyl)	*From 6a*: **94%** *From 6b*: **96%** (86%) *From 6c*: **15%**[c] *From 6d*: **12%**[d]	1 hr 4 hr 24 hr 2 hr
2	**7a-b**	**7a** (R=Me): 89% **7b** (R=Et): 99%	**11** (PMB= *p*-methoxybenzyl)	*From 7a*: **95%** *From 7b*: **95%** (86%)	1 hr 4 hr
3	**8a**	**8a** (R=Me): 99%	**12** (TMB= 3,4,5-trimethoxybenzyl)	*From 8a*: **90%** (80%)	3 hr
4	**9a-b**	**9a** (R=Me): 82% **9b** (R=Et): 85%	**13**	*From 9a*: **91%** (70%)[e] *From 9b*: **92%** (72%)[e]	1 hr 2 hr
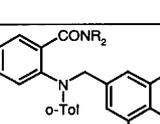
(a) Yields given for pure compounds purified by chromatography or crystallization. (b) Crude yields on preparative scale. Yields in parenthesis are for pure (>99%) compounds after recrystallization. (c) 15% conversion after 24 hr. (d) GC yield, mainly decomposition. (e) purified by chromatography.

Scheme 3.

Base, THF, -10°C

LDA: 30%
s-BuLi: 63%
LDA-TMSCl: 40%
LICA: 60%
n-BuLi-TMEDA: 70%
LDA-TMEDA: 96%

6-b → **10**

Figure 1. Proximal conformation (**6a**).

wish here to report a new synthesis of oxcarbazepine using the strategy described above.

The general route to the azepinone precursors **6–9** is outlined in Scheme 2. The *o*-bromobenzamides **3a–d**[10]

were coupled with *o*-toluidine **4** using 0.8% Pd(OAc)₂ and 1.7% *rac*-BINAP as a catalytic system.[11] Crude yields were almost quantitative and the *N*-*o*-tolyl anthranilamides **5a–d** were isolated as pure compounds in 85–91% yield.[12] In order to protect the nitrogen for the late carbamoyl introduction, we decided to use protecting groups which would be easily removable but not too labile. With scale-up of the process in mind, the protecting reagents had also to be cheap and safe. Therefore we decided to investigate benzyl derivatives.[13]

The benzylation of **5a–d** was best performed by deprotonation of the diarylamines with NaH in DMF followed by quenching of the salt with the benzyl chlorides.[14] Good yields of the protected anthranilamides **6–9** were obtained (Table 1).

We then turned our attention to the remote metalation and cyclization reaction.[15] The conditions were optimized using the benzyldiarylamine **6b** (Scheme 3). Metalation with LDA at −10°C as reported by Snieckus[7] gave only 30% conversion. When using *s*-BuLi as a base, an improved conversion (63%) was obtained albeit accompanied by the formation of by-products. The use of LDA-TMSCl yielded 40% of the corresponding silyl enolether. The more hindered lithium isopropylcyclohexylamide (LICA) improved the conversion to 60%. TMEDA is known to enhance the reactivity of organolithium species[16] and the combination *n*-BuLi-TMEDA yielded 70% of the cyclized product. Finally, we were very satisfied to find that the use of 2.5 equiv. of LDA-TMEDA resulted in complete conversion of **6b** and formation of the *N*-benzyl dibenzazepinone **10** in 96% yield. After recrystallization of
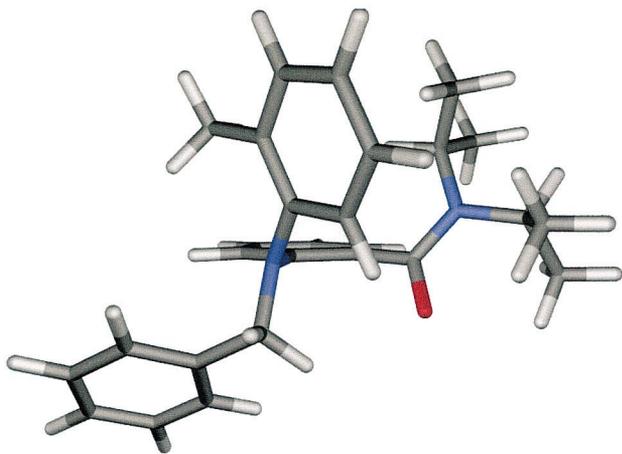
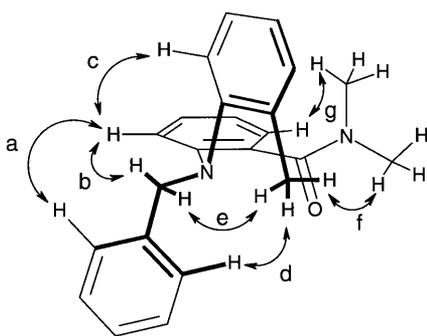**Figure 2.** Distal conformation (**6c**).

Figure 3. NOEs in **6a**.

the crude product, pure **10** (>99.8% by HPLC and GC) was obtained in 86% isolated yield on a 20 g scale.

Application of the LDA-TMEDA conditions to **6a–d**, **7a–b** and **8a** yielded the corresponding azepinones **10**, **11** and **12**, respectively, in good yields (Table 1, entries 1–3). The diisopropylamide **6c** reacted much more slowly than the corresponding diethylamide and only 15% conversion was obtained after 24 h. The morpholine amide **6d** gave mainly degradation products. The methoxy subunit of the *p*-methoxybenzyl protecting group did not slow down the reaction by competitive coordination (entry 2). In contrast, cyclization of the 3,4,5-trimethoxybenzyl protected compound **8a** was noticeably slower than that of the corresponding benzyl compound **6a**, delivering however **12** in 90% yield. Encouraged by these results, we also prepared the *N*-allyl derivatives **9a–b** (entry 4). Their remote metala-

tion-cyclization proceeded smoothly and delivered the *N*-allyl azepinone **13** in good yields.

We observed that in all the series **a–b**, the dimethylamide compounds reacted faster than their diethyl analogues. Noteworthy was also the fact that the diisopropyl derivative **6c** was nearly unreactive under the LDA-TMEDA conditions. Usually, dimethylamides are not good directed metalation groups (DMG) because they tend to react with strong base.[15b] In order to better understand the reactivity of the cyclization precursors, we carried out a conformational analysis of **6a** and **6c**.[17] Fifteen distinct conformations lying within 1 kcal mol^{-1} from the global minimum were identified for **6a**. Similar conformations were found for **6c** in the same energy range. Among those, we noticed the presence of conformations where the carbonyl is proximal to the benzylic CH$_3$ (~ 3.5 Å). Fig. 1 shows the lowest energy conformation of this type for **6a**. In such conformations, the proximity of the two groups allows chelation of the lithium amide and thus fast metalation, followed by ring closure. In contrast, conformations where the two groups are distal (more than 5.5 Å)-and therefore do not allow a directed remote metalation of the tolyl group-were also present in the low energy conformations of both **6a** and **6c**. The lowest energy conformation of this type for **6c** is shown in Fig. 2. Since the computational study was inconclusive in terms of establishing a clear preference for either a proximal type or a distal type conformation in both compounds, we also carried out an NMR analysis.[18] The proximal conformation of **6a** was found to be in good agreement with the observed NOEs (Fig. 3). In contrast, the observed NOEs in **6c** were principally only compatible with a distal conformation. Thus it appears that in the case of **6c** the *N,N*-diisopropyl group is too bulky to allow the same conformation as for **6a** and that the tolyl group is situated too far away from the carbonyl group to allow fast metalation followed by ring closure.

With the protected dibenzazepinones **10–13** in hand, we had to remove the protecting groups and introduce the carbamoyl function. Cleavage of the benzyl group in **10** was best performed with TMSCl/NaI in acetonitrile and delivered 10-ketoiminodibenzyl **14** in 75% yield (Scheme 4). The *p*-methoxybenzyl group from **11** was very cleanly cleaved by TiCl$_4$ at −20°C and gave **14** in 95% yield; however, we could not cleanly remove the trimethoxybenzyl group from **12**. Finally, the allyl protecting group of **13** could be removed by Wilkinson's catalyst in 70% yield. Carbamoylation of 10-ketoiminodibenzyl **14** was efficiently performed with

10: Pg=Bn: TMSCl, NaI (75%)
11: Pg=PMB: TiCl$_4$ (95%)
13: Pg=Allyl: Rh(PPh$_3$)$_3$Cl (70%)
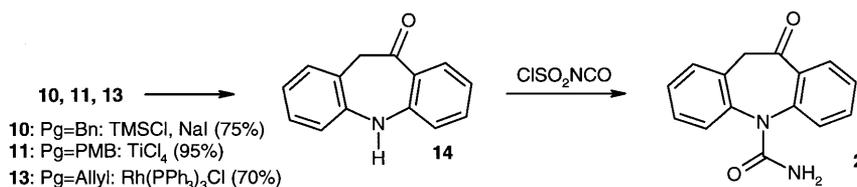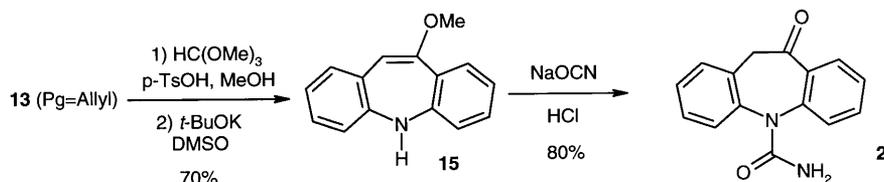
Scheme 4.

Scheme 5.

chlorosulfonyl isocyanate[3] and delivered oxcarbazepine **2** in 80% yield (Scheme 4).

An alternative strategy was to first protect the carbonyl function in **13** as its methyl enol ether[4c] and then to remove the allyl group using *t*-BuOK in DMSO. Advantageously, in the case of the thus obtained enol ether **15**, carbamoylation could be cleanly effected with in-situ generated isocyanic acid (Scheme 5).[3]

Thus we have demonstrated that the remote metalation of *N*-protected *N*-*o*-tolyl-anthranilamides is an efficient strategy for the large-scale synthesis of Trileptal® in only five steps from readily available starting material.[19] Scale-up development and application of this strategy to various analogs are on-going and will be reported in due course.

References

1. *Epilepsy, A Comprehensive Textbook, Volume II*; Engel, Jr., J.; Pedley, T. A., Ed.; Lippincot-Ravens Publishers: Philadelphia, 1998.
2. *Intractable Epilepsy*; Johannessen, S. I.; Gram, L.; Sillanpää, M.; Tomson, T., Ed.; Wrighston Biomedical Publishing: Petersfield, 1995.
3. Milanese, A. WO Patent Application 96/21649, 1996; *Chem. Abstr.* **1996**, *125*, 195448.
4. (a) Ohta, T.; Miyata, N.; Hirobe, M. *Chem. Pharm. Bull. Jpn.* **1981**, *29*, 1221. (b) Belluci, G.; Berti, G.; Chiappe, C.; Lippi, A.; Marioni, F. *J. Med. Chem.* **1987**, *30*, 768. (c) Haász, F.; Galamb, V. *Synth. Commun.* **1994**, *24*, 683. (d) Aufderhaar, E. Eur. Patent. 28028, 1981; *Chem. Abstr.* **1981**, *95*, 115325. (e) Schindler, W.; Blatner, H.; German Patent 1,142,870, 1963; *Chem. Abstr.* **1963**, *59*, P11454e.
5. (a) For a review on dibenz[*b*,*f*]azepines, see: Kricka, L. J.; Ledwith, A. *Chem. Rev.* **1974**, *74*, 101. (b) For a review on dibenz[*b*,*f*]azepinones, see: Renfroe, B.; Harrington, C. In *The Chemistry of Heterocyclic Systems, Azepines*, Part 1, Rosowsky, A., Ed.; John Wiley & Sons: New York, 1984, pp. 384.
6. (a) Fouche, J.; Leger, A., German Patent 2,202,486, 1972; *Chem. Abstr.* **1972**, *77*, 152012. (b) Fouche, J.; Leger, A., German Patent 2,039,396, 1972; *Chem. Abstr.* **1972**, *77*, 5379.
7. The remote metalation and cyclization of diethyl *N*-methyl-*o*-tolylanthranilamide to *N*-methyl dibenzazepinone was first reported by the Snieckus group . See: MacNeil, S. L.; Gray, M.; Briggs, L. E.; Li, J. J.; Snieckus, V. *Synlett* **1998**, 419.
8. Conventional reagents such as activated chloroformates cannot cleave *n*-alkyl groups on the dibenzazepinone system. Martin, P., personnal communication.
9. Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.
10. We prepared different amides (R = Me, Et, *i*Pr, morpholine) in order to test their reactivity and to find crystalline intermediates.
11. P(*o*-Tol)$_3$ gave only 10% conversion, DPEPhos proved less efficient than BINAP and P(*t*-Bu)$_3$ gave no reaction.
12. The reactions were run very concentrated (1.5 M). Yields of pure compound after silica gel filtration and recrystallization: **5a** = 91%, mp 73–74°C (120 g scale); **5b** = 88%, oil; **5c** = 74%, mp 95–97°C; **5d** = 76%, mp 141–143°C.
13. We attempted to introduce silyl-protecting groups however they turned out to be too labile and desilylation was always observed during work-up. Carbamates were not considered as they have been shown to give five-membered ring closure (oxindole).[7]
14. Less satisfactory results were obtained with the method of Vitale and Chiocconi: Vitale, A. A.; Chiocconi, A. A. *J. Chem. Res. (S)* **1996**, 336.
15. (a) For a review on Lateral Directed *Ortho* Metalation, see: Clark, R. D.; Jahangir, A. In *Organic Reactions*, Paquette, L. A., Ed.; Vol. 47, John Wiley & Sons: New York, 1995, p. 1. (b) For a general review on DoM, see: Green, L.; Chauder, B.; Snieckus, V. *J. Heterocyclic Chem.* **1999**, *36*, 1453.
16. Bailey, W. F.; Tao, Y. *Tetrahedron Lett.* **1997**, *38*, 6157.
17. Such an amide effect (NMe$_2$>NEt$_2$>NiPr$_2$) has already been observed in the synthesis of acridones (see Ref. 15b). The conformational analyses were performed with MacroModel v.4.0 using the Monte Carlo/energy minimization procedure (AMBER* force field in conjunction with the GB/SA chloroform solvation model): Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440.
18. ROESY experiment measured in DMSO at 600 MHz.
19. Typical ring-closure experiment: A solution of diisopropylamine (19.0 g, 0.188 mol) and TMEDA (21.82 g,

0.188 mol) in THF (280 ml) was cooled down to −20°C and a 1.6 M solution of *n*-BuLi in hexane (117.4 ml, 0.188 mol) was added. The solution was stirred at −20°C before dropwise addition of a THF (450 ml) solution of **6b** (28.0 g, 0.075 mol). The mixture was stirred for 4 hours and was quenched by addition of saturated aqueous ammonium chloride (100 ml). Phase separation and standard work-up gave 21.15 g of crude azepinone **10** (94% yield). Recrystallization from methanol (100 ml) yielded pure **10** (>99%).