New synthesis of oxcarbazepine via remote metalation of protected \(N-o\)-tolyl-anthranilamide derivatives

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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. 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.

Several routes to oxcarbazepine 2 have been described in the literature. They are nearly all based on the transformation of the iminostilbene or iminodibenzyl ring using strong oxidative reagents. Furthermore, the iminostilbene ring is not prone to functionalization and oxcarbazepine analogs cannot be easily prepared. 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). Recently, Snieckus also reported the remote metalation and cyclization of diethyl \(N\)-methyl-\(o\)-tolylanthranilamide to \(N\)-methyl dipenzazepinone. 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. Furthermore, given the recent development of a diarylamine synthesis by Buchwald–Hartwig coupling, we recognized that a number of new oxcarbazepine analogs would become readily accessible. We
Table 1. Synthesis of protected dibenzazepinones 10-13

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pre-cyclization Product</th>
<th>N-Protection Yield</th>
<th>LDA-TMEDA Cyclization</th>
<th>React. time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Product</td>
<td>Yield</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>From 6a</td>
</tr>
<tr>
<td>1</td>
<td><img src="54x737" alt="Image" /></td>
<td>6a (R=Me): 72%</td>
<td>94% &amp; 86%</td>
<td>1 hr</td>
</tr>
<tr>
<td></td>
<td><img src="54x737" alt="Image" /></td>
<td>6b (R=Et): 97%</td>
<td>6% &amp; 86%</td>
<td>1 hr</td>
</tr>
<tr>
<td></td>
<td><img src="54x737" alt="Image" /></td>
<td>6c (R=iPr): 70%</td>
<td>15% &amp; 8%</td>
<td>1 hr</td>
</tr>
<tr>
<td></td>
<td><img src="54x737" alt="Image" /></td>
<td>6d (R=-(CH₂)₂O): 79%</td>
<td>12% &amp; 8%</td>
<td>1 hr</td>
</tr>
<tr>
<td>2</td>
<td><img src="54x737" alt="Image" /></td>
<td>7a (R=Me): 89%</td>
<td>95% &amp; 86%</td>
<td>1 hr</td>
</tr>
<tr>
<td></td>
<td><img src="54x737" alt="Image" /></td>
<td>7b (R=Et): 99%</td>
<td>95% &amp; 86%</td>
<td>1 hr</td>
</tr>
<tr>
<td>3</td>
<td><img src="54x737" alt="Image" /></td>
<td>8a (R=Me): 99%</td>
<td>90% &amp; 80%</td>
<td>3 hr</td>
</tr>
<tr>
<td>4</td>
<td><img src="54x737" alt="Image" /></td>
<td>9a (R=Me): 82%</td>
<td>91% &amp; 70%</td>
<td>1 hr</td>
</tr>
<tr>
<td></td>
<td><img src="54x737" alt="Image" /></td>
<td>9b (R=Et): 85%</td>
<td>92% &amp; 72%</td>
<td>2 hr</td>
</tr>
</tbody>
</table>

(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.](54x737)

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 were coupled with o-toluidine 4 using 0.8% Pd(OAc)₂ and 1.7% rac-BINAP as a catalytic system. Crude yields were almost quantitative and the N-o-tolyl anthranilamides 5a-d were isolated as pure compounds in 85–91% yield. 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. The benzylation of 5a-d was best performed by deprotonation of the diaryl amines with NaH in DMF followed by quenching of the salt with the benzyl chlorides. Good yields of the protected anthranilamides 6-9 were obtained (Table 1).

We then turned our attention to the remote metalation and cyclization reaction. The conditions were optimized using the benzyldiarylamine 6b (Scheme 3). Metalation with LDA at -10°C as reported by Snieckus 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 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 metalation-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
chlorosulfonyl isocyanate and delivered oxcarbazepine in 80% yield (Scheme 4).

An alternative strategy was to first protect the carbonyl function in 13 as its methyl enol ether 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).

Thus we have demonstrated that the remote metatlation 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. Scale-up development and application of this strategy to various analogs are on-going and will be reported in due course.

Acknowledgements

We are greatly indebted to S. MacNeil and V. Snieckus for useful discussion and for sharing with us unpublished information (Regioselective Dibenzo[b,f]azepinone Formation by Directed Remote Lateral Metatlation, personal communication and work in progress). We also thank K. Killius and M. Weibel for their technical assistance.

References

7. The remote metatlation and cyclization of diethyl N-methyl-o-tolylantranilamide 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., personal communication.
10. We prepared different amides (R = Me, Et, iPr, morpholine) in order to test their reactivity and to find crystalline intermediates.
11. P(o-Tol), gave only 10% conversion, DPEPhos proved less efficient than BINAP and P(t-Bu), 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).
17. Such an amide effect (NMe₂>NEt₂>NPr₂) 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 DMSO (15 ml) containing diiso

Scheme 5.
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%).
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