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A new synthesis of oxcarbazepine using a Friedel–Crafts cyclization strategy

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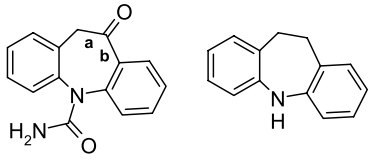
Abstract—A novel, simple, and straightforward process for the large-scale synthesis of oxcarbazepine, the active ingredient of Trileptal®, a medicine for the treatment of epilepsy, has been developed. Starting from readily available 1,3-dihydro-1-phenyl-2*H*-indol-2-one, a Friedel–Crafts cyclization strategy provides a direct route to the tricyclic framework of the target molecule. Crucial to the success of the strategy was the choice of the proper nitrogen-protecting group.

1. Introduction

Oxcarbazepine **1**, the active ingredient of Trileptal®, is effective as monotherapy and as adjunctive therapy for epilepsy, both in adults and children.[1] A few syntheses for **1** have been described in the literature.[2] Most of them start from *o*-nitrotoluene or *o*-nitrobenzyl chloride to build first 10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine **2**, which is then further functionalized by a cascade of oxidation and reduction reactions.[3]

Since we wanted to avoid oxidation and reduction reactions, which generally require special equipment, we focused our efforts toward the investigation of two ring closure strategies aiming at the formation of bond **a** or **b** (Fig. 1). With such an approach, the proper functionality of **1** can be built into the precursor of the cyclization reaction, avoiding the need to perform manipulations of the oxidation state in the ring closed tricyclic system. Since **1** is readily oxidized to the diketo compound 10,11-dihydro-10,11-dioxo-5*H*-dibenz-[*b*,*f*]-azepine-5-carboxamide by exposure to air, a controlled introduction of the mono-keto-functionality by a direct oxidation process into **2** or a derivative thereof is difficult to perform in a selective way.



1 2

Figure 1. Oxcarbazepine **1** and its commonly used precursor **2**.

For the formation of bond **a**, we have recently shown that the core of **1** can be efficiently built by applying a remote metalation approach in the key step.[4] However, since **1** will be produced on a multi-hundred-ton scale, the remote metalation approach has its technical limits.[5] We therefore felt that the formation of bond **b** in the key step via a Friedel–Crafts cyclization strategy might be the method of choice for the production of **1** on an industrial scale. Our synthetic plan was to prepare the parent and the nitrogen-protected 2-(phenylamino)benzeneacetic acid derivatives **3a**–**e**, and to study their tendency to form the tricyclic compounds **4a**–**e** under Friedel–Crafts reaction conditions (Scheme 1).

From the beginning, we were well aware that the choice of a suitable nitrogen-protecting group would be crucial for the success of this approach. Any cleavage of the protecting group under the harsh cyclization conditions

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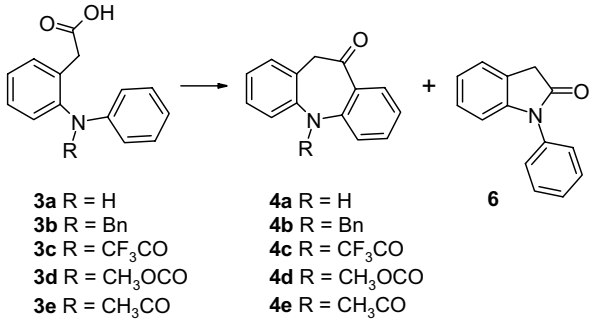
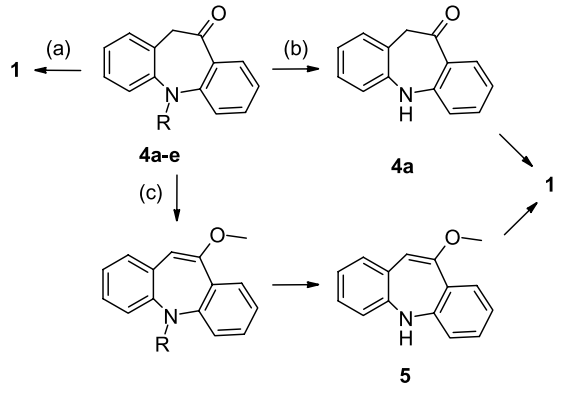


Scheme 1. Ring closure reaction with compounds **3a**–**e**. Formation of **6** reflects the cleavage of the protecting group in the course of the reaction.



Scheme 2. Possible transformations of **4a**–**e** to **1**.

would not lead to the desired seven-membered ring system, but rather to the γ-lactam **6**.[6] Compared to its seven membered ring isomer **4a** (Scheme 2), **6** is not only kinetically favored but also thermodynamically the more stable compound.[7,8] With the tricyclic products **4a**–**e** in hand, three straightforward pathways to **1** are conceivable depending on the nature of the nitrogen-protecting group: (a) direct conversion of the protecting group into the desired urea derivative by treatment with ammonia, (b) cleavage of the protecting group to give **4a** followed by urea formation or (c) enol ether formation and cleavage of the nitrogen protecting group leading to 10-methoxy-5*H*-dibenz[*b*,*f*]azepine **5**, a compound, which has already been transformed efficiently to **1**.[9] In this communication, we would like to present the results of our ring closure experiments, as well as the completion of the synthesis of oxcarbazepine **1** via the intermediate **5** or **4a**.

2. Preparation of the pre-cyclization compounds 3a–e

As starting material for the preparation of the pre-cyclization compounds **3a**–**e**, the easily accessible γ-lactam **6** was used.[10] The unprotected acid **3a** was obtained via ring opening with sodium hydroxide to give **7** followed by careful acidification to pH 2. While **7** is a stable, characterizable compound, **3a** readily cyclizes to **6**.[11] Methylester **8a**, obtained by treating **7** with either methyl iodide or dimethyl sulfate, was used for the preparation of the carbamate **3d**, while the trifluoroacetyl-protected compound **3c** was prepared via the benzylester **8b**. The use of esters **8a** and **8b** as intermediates was necessary, since the direct acylation of **7** with either trifluoroacetic anhydride or methyl chloroformate did not lead to **3c** and **3d**, respectively, but quantitatively to **6**, apparently via the formation of mixed anhydrides.[12] Deprotonation of **7** with sodium hydride or butyllithium and subsequent treatment of the resulting dianion with benzyl bromide or acetic anhydride furnished the benzyl protected compound **3b** and the acetyl protected compound **3e**, respectively (Scheme 3).

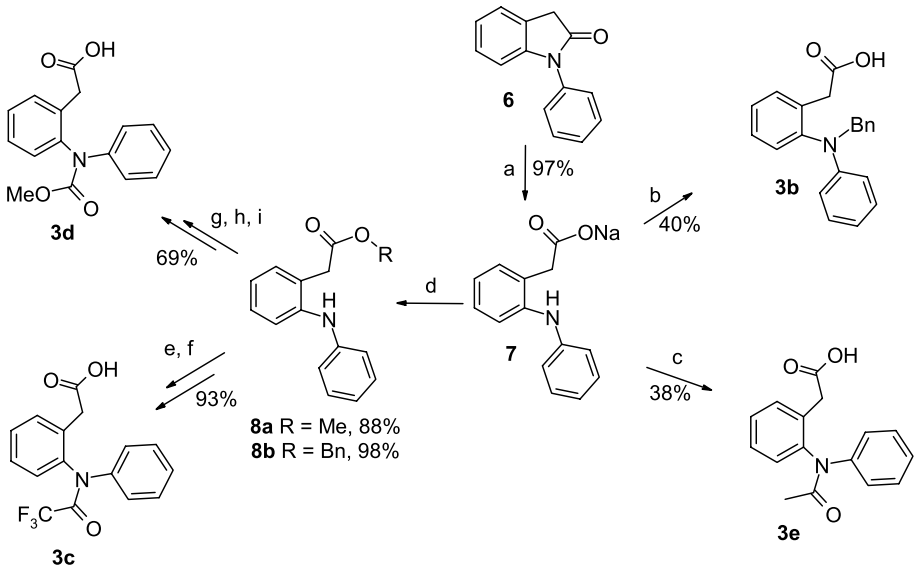
3. Results of ring closure experiments

In order to achieve maximal throughput and easy handling, polyphosphoric acid (PPA), requiring no additional solvent, was considered to be the reaction media of choice for the cyclization of compounds **3a**–**e** (Table 1).[13]

With both **3a** and **3b** the desired Friedel–Crafts ring closure reaction was not observed, but instead quantitative formation of **6**. Whereas this finding was expected in the case of the unprotected compound **3a**,[16] the outcome with the benzyl-protected compound **3b** was somehow surprising; apparently the cleavage of the benzyl group is much faster than the desired ring closure reaction. In the case of **3e** not only the formation of **6** was observed, but also 5-acetyl-1,3-dihydro-1-phenyl-2*H*-indol-2-one was formed. The mechanism of this migration of the nitrogen protecting group was not investigated. The best results were obtained with the trifluoroacetyl derivative **3c** and with the methyl carbamate **3d**. Since **1** is to be produced in a multi-hundred-ton scale, the use of ecologically questionable reagents or solvents should, whenever possible, be avoided.[17] Thus, based on ecological and economical considerations, **3d** was selected as the starting material for the development of the final synthesis of **1**. Starting from **3d**, the cyclized product can be isolated either as **4d** or as the corresponding enol ether **9d** (Scheme 4). The latter was obtained by reaction of **4d** with trimethyl orthoformate under acid catalysis or by simply quenching the reaction mixture of **4d** with water and methanol.[18]

4. Completion of the synthesis of 1

At first glance, both **4d** and **9d** look like immediate precursors of **1** requiring only a simple treatment with ammonia (in the case of **4d**) or ammonia followed by hydrolysis of the enol ether function in the case of **9d**.[19] However, all attempts to convert the carbamate function of **4d** or **9d** into a urea function by treatment with ammonia failed. Under all applied reaction conditions the nitrogen carbon bond, not the nitrogen–carbon bond, was cleaved leading to **4a** and **5**, respectively.[20]



Scheme 3. Preparation of the precursors **3a–e** for cyclization studies under Friedel–Crafts conditions. Reagents and conditions: (a) 3 M aq NaOH, 100 °C, 6 h; (b) NaH, DMF, BnBr, 24 °C, 15 h; (c) BuLi, THF, Ac_2O, −10 °C, 2 h; (d) 1.4 equiv MeI, DMF, 24 °C, 4 h or 1.6 equiv BnBr, DMF, 24 °C, 4 h; (e) With **8b**, 2 equiv TFAA, 1.5 equiv Et_3N, 5 mol% DMAP, CH_2Cl_2, 20–40 °C, 3.5 h (98%); (f) H_2, 2 mol% Pd/C, MeOH, 30 °C, 3 h (95%); (g) With **8a**, 1.1 equiv $COCl_2$, 1.2 equiv pyridine, toluene, 50 °C, 24 h (85%); (h) 1 equiv pyridine, MeOH, 100 °C, 22 h (90%); (i) 1.1 equiv 30% aq NaOH, MeOH, 25 °C, 24 h (90%).

Table 1. Results from Friedel–Crafts ring closure experiments with compounds **3a–e**

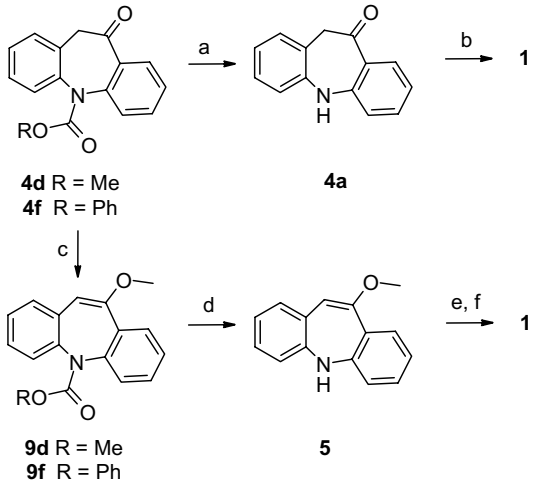
Pre-cyclization compound	Conditions[a]	Yield of **4a–e** (%)	Product ratio **4a–e**:**6**
3a	a	0	<1:>99 (**4a**:**6**)
3b	b	0	<1:>99 (**4b**:**6**)
3c	a	40 (70)[b]	95:5 (**4c**:**6**)
3d	b or c	70[c]	95:5 (**4d**:**6**)
3e	c	0	<1:65[d] (**4e**:**6**)

[a] Reaction conditions: (a) toluene, PPA, 110 °C, 11 h; (b) chlorobenzene, 28 equiv PPA, 90 °C, 2 h; (c) **3d** or **3e** was added to PPA at 95 °C and stirred for 3 h.[14]

[b] The protecting group of **4c** was partly removed during work-up. Complete hydrolysis yields **4a** in 70% overall yield starting from **3c**.[15]

[c] Yield after isolation by crystallization. If **4d** is not isolated but further converted to **9d** and then crystallized the optimized isolated yield over two steps is 85%.

[d] Besides of **6**, formation of 5-acetyl-1,3-dihydro-1-phenyl-2*H*-indol-2-one (ca. 35% a, HPLC) was also observed.



Scheme 4. Cleavage of the carbamate function and further conversion to **1**. Reagents and conditions: (a) With **4d**; KOH, H_2O, ethylene glycol, 30 min, 108 °C (72%); (b) $ClSO_2NCO$, CH_2Cl_2, 25 °C, 17 h, then H_2O (70%); (c) $CH(OMe)_3$, cat. *p*-TsOH, MeOH, 60 °C, 5 h (99%); (d) 50% aq NaOH, PEG 200, 100 °C, 4 h (96%); (e) 1.5 equiv NaOCN, AcOH, 25 °C, 7 h; (f) aq H_2SO_4 or aq HCl, 25 °C, 17 h (step e and f 84%).

Apparently in the initially formed tetrahedral intermediate a more efficient release of steric constraints is obtained when the tricyclic ring system and not methoxy acts as the leaving group.[21] The transformation to oxcarbazepine **1** was therefore completed either by cleavage of the carbamate function of **9d** to give **5**[22] followed by treatment with isocyanic acid and hydrolysis of the enol ether function,[23] or by reaction of **4a** with chlorosulfonyl isocyanate and hydrolysis.[24]

In conclusion, starting from the commercially available γ-lactam **6**, a new process for oxcarbazepine **1** has been developed using, in the key-step, a Friedel–Crafts cyclization strategy for the formation of the tricyclic ring system 5,11-dihydro-10*H*-dibenz[*b*,*f*]azepin-10-one. A suitable nitrogen-protecting group was essential to obtain the desired ring closure reaction. Two protecting groups, methoxycarbonyl and trifluoroacetyl, have been identified as suitable. For the development of a large scale process the methoxycarbonyl group was preferred.

Acknowledgements

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2. (a) Milanese, A. WO Patent Application 9621649, 1996; *Chem. Abstr.* **1996**, *125*, 195448; (b) Aufderhaar, E. Eur. Patent. 28028, 1981; *Chem. Abstr*. **1981**, *95*, 115325; (c) Schindler, W. DE Patent 2011087, 1970; *Chem. Abstr*. **1970**, *73*, 109711.
3. For a review of dibenz[*b*,*f*]azepines, see: Kricka, L. J.; Ledwith, A. *Chem. Rev.* **1974**, *74*, 101.
4. Lohse, O.; Beutler, U.; Fünfschilling, P.; Furet, P.; France, J.; Kaufmann, D.; Penn, G.; Zaugg, W. *Tetrahedron Lett.* **2001**, *42*, 385.
5. The limitation is in particular due to the use of 2.5 equiv LDA-TMEDA in the cyclization step.
6. The importance of choosing the right protecting group in our system is also illustrated by the example reported by Schulenberg and Archer. The use of the benzoyl protecting group led solely to the formation of **6** Schulenberg, J. W.; Archer, S. *J. Am. Chem. Soc.* **1960**, *82*, 2035.
7. Based on combustion data γ-lactam **6** has a 10 kJ/mol lower heat of formation than **4a**. Furthermore, under the applied cyclization conditions **6** is stable whereas **4a** is partly converted to **6**.
8. Cyclization of **3a** to **6** starts in solution at 50 °C.
9. Schindler, W. DE Patent 2011087, 1970; *Chem. Abstr*. **1970**, *73*, 109711.
10. Compound **6** was prepared similarly to 1-(2,6-dichlorophenyl)-1,3-dihydro-indol-2-one as described by Moser, P.; Sallmann, A.; Wiesenberg, I. *J. Med. Chem.* **1990**, *33*, 2358.
11. Cyclization **3a** to **6** is observed at pH < 2.
12. Later in this investigation we found that the additional steps via the methylester **8a** could be omitted for the preparation of **3d** when the deprotonated form of **7** is used, as described for the preparation of **3e**. For details of this approach see: Fünfschilling, C. P.; Zaugg, W.; Beutler, U.; Kaufmann, D.; Lohse, O.; Mutz, J.-P.; Onken, U.; Reber, J.-L.; Shenton, D. *Org. Process Res. Dev*. in preparation.
13. Friedel–Crafts cyclization of the corresponding acid chloride of **3d** with 1.2 equiv $AlCl_3$ in CH_2ClCH_2Cl at 25 °C gave **4d** in 88% yield. However, from a technical point of view the process in neat PPA was felt to be more attractive.
14. Typical reaction conditions: **3d** (285.3 g, 1 mol) is added to PPA (83% P_2O_5, 684 g) at 90 °C and stirred at 95 °C for 3 h. The reaction is cooled to 80 °C, water (2500 mL) is carefully added while the temperature is kept below 98 °C. Then the reaction mixture is extracted with toluene (3 × 1000 mL), the combined organic phases washed with sodium hydrogen carbonate solution (5%, 1000 mL) and concentrated to a weight of 975 g. The solution is cooled to 0 °C and stirred for 3 h to afford white crystals, which are filtered and dried to give pure **4d** (194 g, 70%): mp 139–141 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H, $COOCH_3$), 3.82–4.40 (2H, $J_{AB} = 14.3$ Hz), 7.2–8.1 (m, 8H, arom H); MS (ES^-) m/z 266 (M−H); IR (KBr) 1714, 1674 1439, 1340, 771 cm^{-1}. Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24; O, 17.96. Found: C, 71.72; H, 4.88; N, 5.21; O, 17.98.
15. Complete removal of the protecting group of **4c** to give **4a** was achieved by stirring crude product **4c** with 1 M aq Na_2CO_3, MeOH, 23 °C, 30 min.
16. The tendency of **3a** to cyclize to **6** is so pronounced (Refs. 6 and 11) that only the complete blocking of the nitrogen atom by protonation would have forced the reaction to proceed in the direction of the desired Friedel–Crafts reaction.
17. In one process step for the industrial production of **1** the environmentally unfriendly reagents 1,2-dichloroethane and chlorocyanide are used. The elimination of this process step was also an important impetus for this work.
18. Compound **4d** (22.3 g, 0.083 mol) is dissolved in methanol (112 mL) at 50 °C. *p*-Toluenesulfonic acid (0.45 mg) is added, followed by trimethyl orthoformate (11.5 mL). The mixture is stirred for 5 h then methanol and formic acid methyl ester is distilled off. Fresh methanol is added continuously to replace the distillate. After distilling off ca. 100 mL of methanol, the mixture is cooled to 3 °C and filtered. The filter cake is washed with cold methanol and dried under vacuum for 15 h (50 °C, 50 mbar). Pure **9d** is obtained as a light yellow powder (18.0 g, 81% yield). For experimental details using no trimethyl orthoformate see Ref. 12.
19. Examples of ammonolysis: (a) Betts, R. L.; Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 1568; (b) Porcs-Makkay, M.; Simig, G. *Org. Process Res. Dev.* **2000**, *4*, 10; (c) Zielinski, W.; Zaki, M. E. A. *Pol. J. Chem.* **1994**, *68*, 1569.
20. Cleavage of the carbamate function resulted when **4d** or **4f** was heated with 24% aq NH_3, 25 °C, 24 h or NH_3, MeOH, 100 °C. For **9d** or **9f**: NH_3, MeOH, 220 °C, 15 h.
21. Even when using the phenyl carbamates **4f** or **9f** (with phenoxy being a better leaving group than methoxy), **4a** and **5**, respectively, were again obtained.
22. A mixture of **9d** (19 g, 67.5 mmol), polyethylene glycol 200 (20 mL) and sodium hydroxide solution 50% (13 mL, 246 mmol) is heated to 100 °C for 4 h. Water (30 mL) is added and the suspension is cooled to 20 °C and filtered. The filter cake is washed with water and dried at 60 °C/30 mbar to yield 14.7 g of **5** (98%).
23. Acetic acid (150 mL) is added dropwise to a stirred mixture of **5** (25.0 g, 112 mmol) and NaOCN (9.25 g, 142 mmol) under a nitrogen atmosphere at 24 °C. After stirring for 7 h, water (12.5 mL, 694 mmol) and 98% H_2SO_4 (ca. 7.5 mL, 140 mmol) are added to the yellow suspension until a pH of $\leqslant 1$ is achieved. After stirring for another 17 h, water (275 mL) is added. The precipitated **1** is filtered and dried under vacuum (overall yield 78% starting from **5**).
24. Milanese, A. WO Patent Application 9621649, 1996; *Chem. Abstr.* **1996**, *125*, 195448. With **4a** and isocyanic acid no reaction was observed. For further details see Ref. 12.