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A New Industrial Process for Oxcarbazepine

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Abstract:

A novel industrial process for the antiepileptic drug oxcarbazepine 1 has been developed. Unlike the old process, the new process is free from halogenated solvents and can be performed in standard production equipment. It starts from commercially available 1,3-dihydro-1-phenyl-2H-indol-2-one 10. In the key step, an electrophilic ring closure reaction of 2-[(methoxycarbonyl)phenylamino] benzeneacetic acid 5 to 10,11-dihydro-10-oxo-5H-dibenz[*b,f*]azepine-5-carboxylic acid methyl ester 6 in poly phosphoric acid was applied. For the manufacture of 5, a highly efficient process using a dianion strategy was developed.

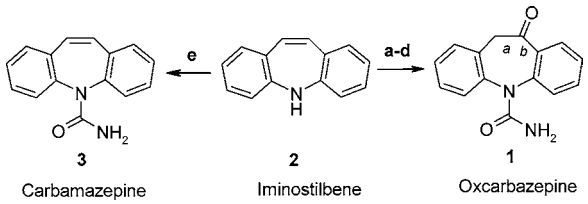
1. Introduction

The antiepileptic drug oxcarbazepine **1** (Trileptal) was until recently manufactured via the tricyclic intermediate iminostilbene **2**. For the industrial manufacture of **2**, starting from *o*-nitrotoluene a four-step process comprising oxidation and reduction reactions[1] requiring special production equipment is applied. Historically, intermediate **2** had been developed as the key intermediate for the production of the older drug, carbamazepine **3** (Tegretol), a compound with a similar mode of action. Because of the structural similarity of **1** and **3**, iminostilbene **2** was considered to be also the logical starting material for the production of **1**. As a consequence, the four-step process **2** → **1** was developed and introduced into production some years ago (Scheme 1).

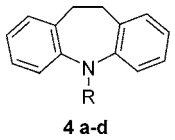
However, whereas the transformation **2** → **3** can easily be performed in a single chemical step, the conversion **2** → **1** is not only rather lengthy but also uses the environmentally unfriendly solvent 1,2-dichloroethane in the cyanation step, and oxidation and reduction reactions are required (steps b and c in Scheme 1). Thus, starting from *o*-nitrotoluene, for the manufacture of oxcarbazepine a total of two reductions and three oxidation steps using drastic reaction conditions are applied. In view of the increasing demand for oxcarbazepine, a synthetic program was set up aiming at a more efficient and more economical process for **1** that uses existing standard production equipment and avoids halogenated solvents.

In a first approach, the direct benzylic oxidation of the iminodibenzyl derivatives **4b**−**d** (Figure 1) to their corresponding keto-analogues was investigated. If successful, such an approach would have easily outperformed the multistep sequence **2** → **1** of the old process.

Scheme 1. **Old production process for oxcarbazepine and current process for carbamazepine[a]**



[a] Reagents and conditions: (a) ClCN, 1,2-dichloroethane, *N*,*N*-dimethyl acetamide; (b) N_2O_4, 90% acetic acid, 55 °C; (c) Fe, 37% HCl, ethanol; (d) H_3BO_3, acetic acid; (e) NaOCN/HCl, ethyl acetate.



4a: R = H
4b: R = $COOCH_3$
4c: R = $CONH_2$
4d: R = CN

Figure 1. **Iminodibenzyl (R = H) and iminodibenzyl derivatives.**

However, attempts to identify reaction conditions allowing a selective direct benzylic oxidation of the iminodibenzyl derivatives **4b**−**d** proved to be unsuccessful.[2] An oxidative approach starting from **2** or an N-protected derivative thereof seemed not to be promising either. Indeed, it has been reported that the transformation of *N*-acetyl-iminostilbene via epoxidation followed by rearrangement to the corresponding keto derivative and further transformation to 10-methoxy-iminostilbene proceeds only in moderate yield.[3] Also considered were processes based on the chlorination or bromination of N-protected **2** or **4** followed by a consequent transformation to **1**.[4] However, we eventually arrived at the conclusion that such an approach would probably offer only minor economic advantages but would be leading to ecological problems.

We therefore decided to develop a new synthetic approach to the tricyclic ring system completely avoiding oxidation or reduction steps and to abstain also from using halogenated reagents and solvents. Thus, our development activities were focused on a new synthetic strategy using as the key step

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(1) Step 1: oxidative coupling (O_2/KOtBu) of *o*-nitrotoluene to 2,2′-dinitrodibenzyl. Step 2: catalytic reduction (Pd−C/H_2) to 2,2′-diaminodibenzyl. Step 3: ring-closure reaction with PPA at 330 °C to iminodibenzyl **4a**. Step 4: catalytic dehydrogenation (FeOx/550 °C) to **2**.

(2) Iminodibenzyl derivatives **4b**−**d** were treated with various oxidizing agents such as Co^{3+}/O_2: Ishii, Y.; Iwahama, T.; Sakaguchi, S.; Nakayama, K.; Nishiyama, Y. *J. Org. Chem.* **1996**, *61*, 4520. CrO_3/t-BuOOH: Muzart, J. *Tetrahedron Lett.* **1987**, *28*, 2131. $CuCl_2$/t-BuOOH: Feldberg, L.; Sasson, Y. *Tetrahedron Lett.* **1996**, *37*, 2063. None of these reactions proved to be as clean as it is required for the development of an industrial process. This work was carried out by B. Pugin at Solvias.

(3) Haász, F.; Galamb, V. *Synth. Commun.* **1994**, *24*, 683.

(4) Milanese, A. WO 9621649, 1996.

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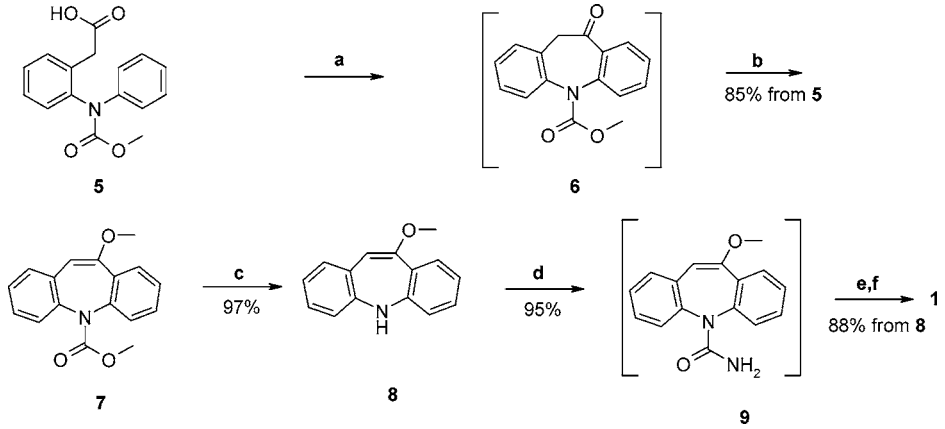
Scheme 2. **New Process for oxcarbazepine starting from 5**[a]



[a] Reagents and conditions: (a) PPA, 95 °C, 3 h; (b) water, MeOH; (c) poly(ethylene glycol) 200, NaOH, water, 110 °C, 2 h; (d) NaOCN, acetic acid, 20 °C; (e) aqueous HCl; (f) HCOOH/water.

either the formation of bond ***a*** or bond ***b*** in **1** (Scheme 1). We were able to show that the concept using the formation of bond ***a***, based on remote metalation of protected *N*-*o*-tolyl-anthranilamides, is suitable for the preparation of **1** on a large scale; in addition, this strategy offers also an elegant access to new oxcarbazepine analogues.[5] The concept of aiming at the formation of bond ***b*** in the key step is cationic in its nature and requires Friedel−Crafts type chemistry; this approach was investigated in parallel to the remote metalation strategy.[6]

In the course of our investigation it was found that for large-scale production the synthetic methodology based on "cationic" Friedel−Crafts type chemistry has economic advantages compared to the "anionic" remote metalation concept, and the cationic approach was eventually chosen for the development of the final production process for oxcarbazepine. In this contribution, we report the design and technical aspects of the new process, which will enable the production of **1** on a multi-hundred-ton scale.[7] In this connection, particular emphasis is also given to the description of the manufacture of the pre-cyclization compound **5**.

2. Results and Discussion

2.1. Outline of New Process. The newly developed process is outlined in Scheme 2. To realize this sequence on production scale, two main hurdles had to be overcome. First, an efficient access to the pre-cyclization compound **5** was required, and second, a straightforward strategy for the conversion of the cyclized compound **6** to oxcarbazepine **1** had to be found. Furthermore, the choice of the "right" protection group in **5** proved to be an important element for the success of the new process. Among the protecting groups investigated, the best results were obtained with the methoxycarbonyl group; details of the protection group considerations have been described elsewhere.[6]

2.2. Manufacture of 2-[(methoxycarbonyl)phenylamino]-benzeneacetic Acid (5). As starting material for the manufacture of the pre-cyclization compound **5**, the commercially available 1,3-dihydro-1-phenyl-2H-indol-2-one (**10**)[8] was used (Scheme 3). In our first route to **5**, lactam **10** was hydrolyzed with sodium hydroxide in an ethanol/water mixture, leading to sodium salt **11**. Methyl ester **13a**, obtained by treating **11** with methyl iodide, was converted with phosgene in pyridine to **13b**, which furnished after methanolysis and subsequent ester saponification the desired compound **5**.

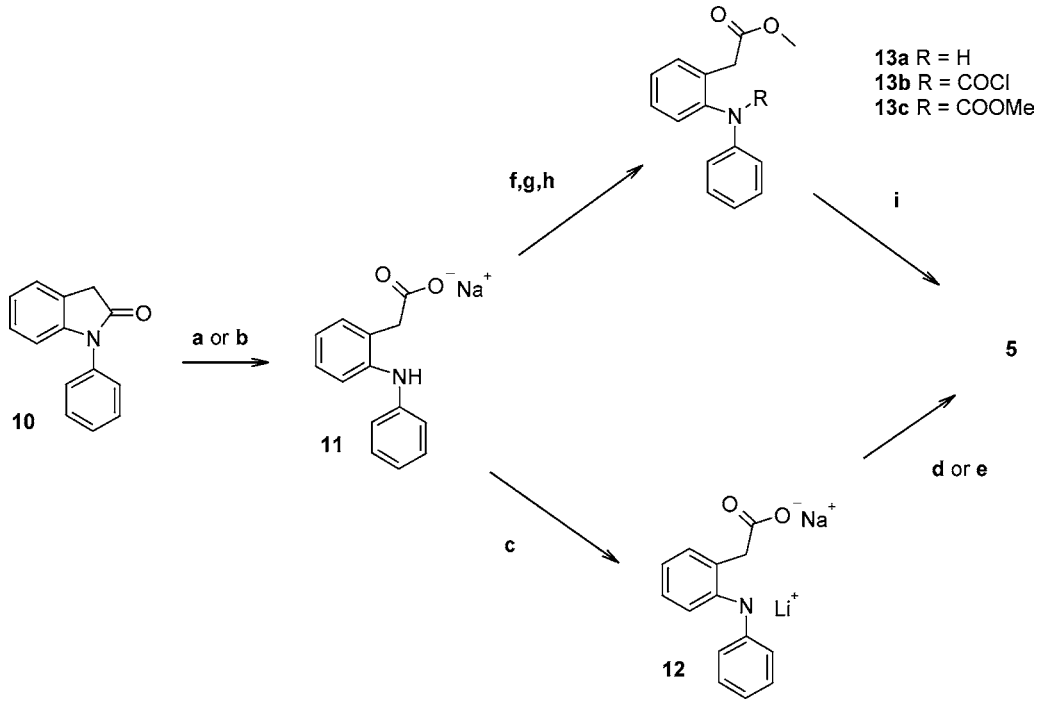
Although the overall yield for the multistep synthesis sequence for **5** (steps f−i in Scheme 3) proved to be relatively high (61%, not optimized), this route was considered to be too long; in addition, it also has some environmental and toxicological drawbacks (methyl iodide, phosgene). We felt therefore that a shorter access to **5** was required to succeed industrially with our cationic cyclization strategy.

A more direct route to **5** was found when we discovered that dianion **12**, easily prepared by treating monoanion **11** with butyllithium in tetrahydrofuran, can be smoothly converted to **5** by reacting with either dimethyl carbonate or methyl chloroformate. To succeed with this route on a production scale, nonaqueous reaction conditions for the ring opening of **10** needed to be found that enabled the production of **12** without isolating and drying of **11**. Thus, we were glad to find that the ring opening of **10** can be accomplished under nearly water-free conditions by using sodium hydroxide pellets in tetrahydrofuran. This finding allowed us to perform the whole sequence **10** → **11** →**12** → **5** (Scheme 3) as a one-pot reaction with tetrahydrofuran as the only solvent.

2.2.1. Ring Opening of Lactam 10 under Nearly Water-Free Conditions. After the addition of sodium hydroxide pellets to a solution of **10** in tetrahydrofuran, two liquid phases are formed. The small lower phase contains mainly highly concentrated aqueous sodium hydroxide, whereas lactam **10** and its enolate **14** are dissolved in the much larger upper phase.[9] To achieve complete conversion of **10** to the sodium salt **11**, efficient stirring is mandatory. In the course

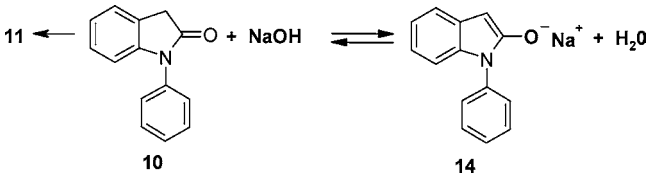
(5) Lohse, O.; Beutler, U.; Fünfschilling, P.; Furet, P.; France, J.; Kaufmann, D.; Penn, G.; Zaugg, W. *Tetrahedron Lett*. **2001**, *42*, 385.
(6) Kaufmann, D.; Fünfschilling, P.; Beutler, U.; Hoehn, P.; Lohse, O.; Zaugg, W. *Tetrahedron Lett.* **2004**, *45*, 5275.
(7) Since its introduction into production, several hundred tons of oxcarbazepine have been manufactured with this new process.
(8) Crestini, C.; Saladino, R. *Synth. Commun.* **1994**, *24*, 2835. Tamura, Y.; Uenishi, J.; Maeda, H.; Choi, H.-D.; Ishibashi, H. *Synthesis* **1981**, 534. For our investigation compound **10** was purchased from Amoli Organic Ltd., 407 Dalamal House, J. B. Road, Nariman Point, Mumbai-21, India.
(9) Mass ratio upper phase/lower phase = 60:1.

Scheme 3. **Routes to the oxcarbazepine precursor 5**[a]



[a] Reagents and conditions: (a) NaOH/EtOH/water, 50 °C, 1 h; (b) NaOH/THF, 67 °C, 5 h; (c) BuLi, −10 °C; (d) $(MeO)_2CO$, −10 °C, 2 h; HCl/water; (e) ClCOOMe, −40 °C, 2 h; HCl/water; (f) MeI/DMF, 20 °C, 4 h; (g) $COCl_2$/pyridine/toluene, 50 °C, 24 h; (h) MeOH/pyridine, 100 °C, 22 h; (i) NaOH/water/MeOH, 20 °C, 24 h.

Scheme 4. **Ring-opening of lactam 10**



of the reaction, the lower phase disappears, and eventually a dark solution of **11** is formed.

For the ring opening of lactam **10** we assume a reaction mechanism as depicted in Scheme 4. Since the enolate **14** is protected from attack by sodium hydroxide, the desired reaction from **10** to **11** can only be brought to completion if the equilibrium between **10** and **14** is shifted during the course of the reaction in the direction of **10**. This is achieved by keeping the reaction water within the reaction vessel.[10]

2.2.2. Acylation of Dianion 12 To Prepare 5. The solution of the sodium salt **11** in tetrahydrofuran is treated with one equivalent of butyllithium in cyclohexane at −10 °C, furnishing a clear solution of dianion **12**, which is stable over several hours when kept below −20 °C. Above −10 °C, **12** begins to decompose, which is indicated by precipitation of solid material.[11] Therefore, if working at −10 °C, a good cooling capacity allowing a relatively rapid addition of butyllithium is mandatory for achieving a good yield.[12]

For the acylation of **12**, either dimethyl carbonate or methyl chloroformate was used. The reaction with dimethyl carbonate is less exothermic, and thus, it is the reagent of choice when working at −10 °C.[13] At this temperature, it can be added relatively fast to the solution of **12**, causing very little to no decomposition.[14] A 1.5-fold excess of dimethyl carbonate is necessary to obtain a complete conversion. After acidic workup, compound **5** is isolated by crystallization from toluene in high purity and 75% yield. Thus far, this variant has been used to produce **5** on industrial scale.

However, potential exists to increase the yield by using the more reactive acylation reagent methyl chloroformate. In this case, the acylation is performed at −40 °C, i.e., at a temperature where the dianion **12** is perfectly stable.[15] With methyl chloroformate, no excess of this reagent must be used so that side reactions are avoided. Under optimal conditions, **5** can be isolated in up to 90% yield.

2.2.3. Continuous Mode for the Manufacture of 5. It is a demanding task to scale-up the formation of **12** and of **5** to production scale when using methyl chloroformate as the acylating agent. Since both the formation of **12** and the acylation reaction are strongly exothermic, the poor heat removal rate at −40 °C forces extension of the addition time

(10) If the water formed during the reaction is removed by evaporation under reduced pressure, the conversion to **11** comes to a complete standstill. The equilibrium between **10** and **14** is also supported from literature data indicating the relatively easy deprotonation of benzolactams: Kresge, A. J.; Meng, Q. *Can. J. Chem.* **1999**, *77*, 1528. Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218; for example: pK_a of *N*-methylindolin-2-one: 18.5 and pK_a of the open-chain analogue *N*-phenyl-*N*-methyl phenylacetamide: 24.6.

(11) The nature of this precipitate has not been investigated.

(12) Reaction enthalpy of the lithiation step: −226 kJ/mol. To get an optimal yield, the addition of butyllithium should be performed in 2 h or less.

(13) Reaction enthalpy of the acylation with dimethyl carbonate is −21 kJ/mol and with methyl chloroformate is −185 kJ/mol. To get an optimal yield, the addition of dimethyl carbonate and methyl chloroformate should not exceed 2 h.

(14) A 1:1 mixture of the dianion **12** and the alkali salt of **5** slowly decomposes at −10 °C; however, the mixture is stable at −40 °C over several hours.

(15) Since the deprotonation of monoanion **11** is very fast, lithiation to **12** can also be performed at −40 °C. Acylation with dimethyl carbonate at −40 °C is too slow for a production process.

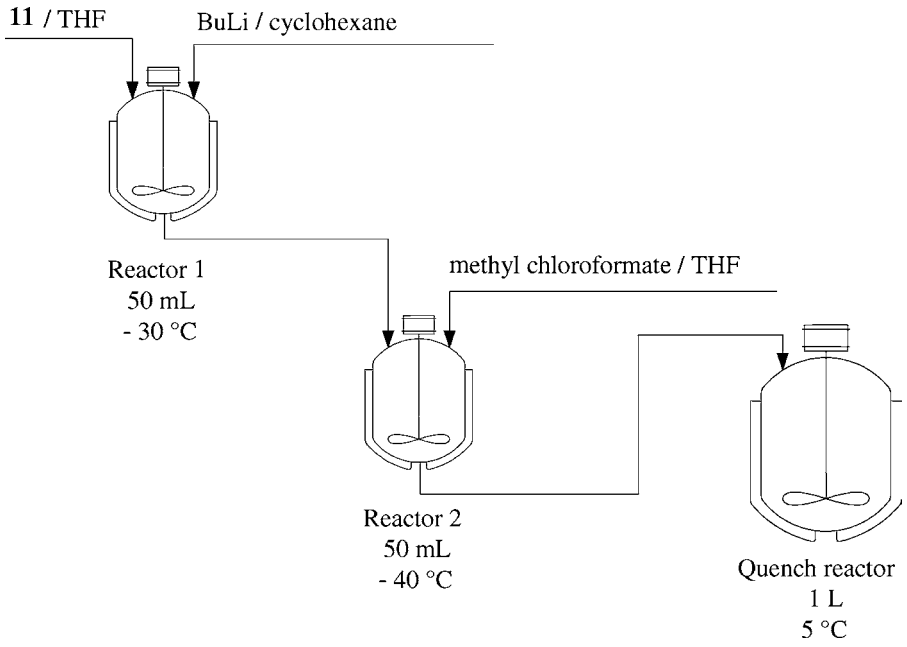


Figure 2. **Experimental setup for the continuous preparation of 5.**

of the reagents, which slows down the production rate significantly.

To overcome such a throughput limitation, both reactions can be conducted in a continuous mode of operation. Therefore, in our investigation for both the lithiation and the acylation, we used a cascade of two continuously stirred tank reactors.[16] Solutions of **11** in THF and of butyllithium in cyclohexane were continuously fed to the first reactor in a stoichiometric ratio. This reaction mixture and a solution of 1−1.1 mol equiv of methyl chloroformate in THF (chilled to −40 °C) were fed to the second reactor. The feed flows were adjusted to match precisely the stoichiometric ratios,[17] so that mean residence times of 4−20 min were achieved for both reactors. The reaction mixture was quenched continuously by adding it to excess 0.1 M hydrochloric acid at 5 °C. The experimental setup is shown in Figure 2.

The highest yields (86−90%) were obtained for combinations of low temperatures (−30 °C for lithiation, −40 °C for acylation) with short mean residence times (4 min), i.e. conditions which are difficult to maintain with conventional semi-batch operation. Under optimal reaction conditions, the space−time yield for the formation of **5** in two consecutive stirred tank reactors is 2.5 mol L^{-1} h^{-1}. Good agitation of the reaction mixtures is necessary to obtain high yields. Therefore, relatively small continuous reactors with static mixing and large specific heat transfer areas would be most suitable to carry out the reaction sequence on a production scale.[18]

2.3. Conversion of 5 to Oxcarbazepine 1. For the key step of the synthesis, the ring closure of **5** to the tricyclic compound **6**, polyphosphoric acid (PPA) proved to be the reagent of choice. The reaction proceeds well in the absence of a solvent and was performed by heating 1 equiv in 4 equiv of PPA at 95 °C for 3 h.[19] The intermediate keto-compound **6** is not isolated but directly converted to the enol ether **7**. This is achieved by treating the reaction mixture first with water to hydrolyze the excess of PPA followed by methanol,[20] which allows the isolation of **7** by filtration in >80% yield (Scheme 2). Intermediate **7** is not dried but directly used as a wet filter cake in the next step.[21]

It is particularly noteworthy that there is no advantage to use trimethyl orthoformate to complete the transformation **6** to **7**.[22] The use of methanol both as the reagent for the formation of the enol ether and as the solvent for the crystallization of **7** proved to be an elegant and economical way to proceed. The enol ether function in **7** acts both as a protecting and as a reaction-enhancing group. The protecting properties of the enol ether are required for the removal of the methoxycarbonyl group under strong alkaline conditions,[23] whereas the activating effect plays an important role in the carbamoylation reaction **8** to **9**, which proceeds under rather mild conditions (vide infra).

(16) Volumes are 50 mL each. Alternatively, a cooled reactor tube was used but proved to be unsuitable due to insufficient mixing.

(17) Water traces in the solution of **11** were compensated by an equivalent increase of the butyllithium feed.

(18) A scale-up to 0.2 or 0.5 m^3 continuous reactors was found to be technically feasible but has not been implemented because existing batch reactor equipment was available.

(19) Dilution with toluene affords no advantages. The use of P_2O_5/methane sulfonic acid [Eaton, P. E.; Carlsen, G. R.; Lee, J. T. *J. Org. Chem*, **1973**, *38*, 4071] led not to **6** but gave 10-methansulfonyloxy-*N*-methoxycarbonyliminostilbene in moderate yield. On the other hand, Friedel−Crafts acylation via the acid chloride of **5** with aluminium chloride in a chlorinated solvent proved to be a feasible alternative to PPA for the conversion of **5** to **6**.

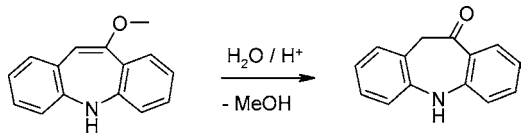
(20) Heat of reaction for the addition of water: $\Delta H_R = -54$ kJ/mol. Heat of reaction for the addition of methanol: $\Delta H_R = -180$ kJ/mol.

(21) Drying of the wet filter cake would not only decrease productivity but would also have a negative impact on the stability of **7**. Traces of acid catalyze the hydrolysis of **7** to the keto-compound **6**. It was found that the dry compound **7** is very sensitive to moisture, whereas the methanol damp product is stable. No such problems are encountered in the drying process of **8** due to the alkaline reaction and working-up conditions applied.

(22) Initially, trimethyl orthoformate was used to complete the enol ether formation according to literature methods. Later it was found that a complete reaction is also obtained with methanol alone; apparently the precipitation of **7** is sufficient for shifting the reaction equilibrium completely to the product side.

(23) The alkaline hydrolysis of **6** to **15** is feasible, but somewhat less clean than the hydrolysis of **7**.

Scheme 5. **Hydrolysis of 8 to 15**



8 **15**

The clean removal of the methoxycarbonyl protecting group to 10-methoxy-iminostilbene **8** is performed in poly(ethylene glycol) 200/50% aqueous sodium hydroxide (4 h/100 °C). The product is isolated in 98% yield and high purity by adding water (to dissolve all of the formed sodium carbonate), cooling to 20 °C, filtration, washing, and drying.

The last two steps of the synthesis are combined in a one-pot process. If compared to the synthesis of carbamazepine **3**, the carbamoylation of **8** to **9** is remarkably enhanced by the activating effect of the 10-methoxy protecting group.[24] Whereas the carbamoylation of iminostilbene **2** needs relatively drastic acidic conditions and elevated temperature (isocyanic acid and dry HCl in ethyl acetate, 65 °C), the carbamoylation of **8** can be performed at ambient temperature under mild acidic conditions (sodium cyanate in acetic acid). Crucial for a clean reaction is the complete absence of water to avoid hydrolysis of the enol ether function.[25] Once hydrolyzed to **15** (Scheme 5), no carbamoylation of **15** to **1** takes place under the applied reaction conditions.[26]

In the last chemical step, enol ether **9** is hydrolyzed with aqueous HCl, leading to oxcarbazepine crude, which is isolated by addition of water and filtration. After thoroughly washing[27] with water and acetone, the wet filter cake is recrystallized from formic acid and water, and pure oxcarbazepine **1** is isolated by filtration, washing, and drying.

3. Summary

Starting from 1,3-dihydro-1-phenyl-2H-indol-2-one **10**, the entire new production process for oxcarbazepine has an overall yield of around 60% and comprises only three isolated and dried steps, namely the intermediates **5**, **8**, and the final product, oxcarbazepine **1**. Unlike the old production process, no halogenated solvents are required. The efficiency of the process is mainly based on avoiding any oxidation and reduction steps and on using the dianion strategy for the straightforward introduction of the methoxycarbonyl protecting group in **5**.

4. Experimental Section

2-[(Methoxycarbonyl)phenylamino]benzeneacetic Acid (5) with Dimethyl Carbonate. A mixture of **10** (80 g, 0.382 mol), sodium hydroxide (16.06 g, 0.402 mol), and tetrahydrofuran (113 mL) is heated to reflux (67 °C) for 5 h. The solution is diluted with another portion of tetrahydrofuran (169 mL) and cooled to −10 °C. A 20% solution of butyllithium in cyclohexane (122.3 g, 0.382 mol) is added at this temperature followed by dimethyl carbonate (51.7 g, 0.573 mol). Afterwards, the solution is stirred at −10 °C for 2 h. Concentrated hydrochloric acid (38 mL) and water (125 mL) are added, and the organic solvents are distilled off at reduced pressure. After addition of toluene (345 mL) to the suspension, the pH of the water phase is adjusted to 1.5 using hydrochloric acid (34 mL). After phase separation at 75 °C, the organic phase is washed with another portion of water (120 mL), concentrated at reduced pressure, and allowed to crystallize at 0 °C to yield 81.2 g of pure **5** (75%): mp 141−142 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.3−3.6 (m, 2H, CH_2), 3.6 (s, 3H, OCH_3), 7.1−7.5 (m, 9H, arom H), 12.3 (s, 1H, COOH); MS (ES^-) *m*/*z* 284 (M − H); IR (KBr) 3487, 3062, 2957, 1718, 1494, 1340, 1325, 1315, 1282, 1067 cm^{-1}. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91; O, 22.43. Found: C, 67.42; H, 5.26; N, 4.85; O, 22.55.

2-[(Methoxycarbonyl)phenylamino]benzeneacetic Acid (5) with Methyl Chloroformate. A mixture of **10** (80 g, 0.382 mol), sodium hydroxide (16.82 g, 0.421 mol), and tetrahydrofuran (113 mL) is heated to reflux (67 °C) for 5 h. The solution is diluted with another portion of tetrahydrofuran (169 mL) and cooled to −40 °C. A 20% solution of butyllithium in cyclohexane (122.3 g, 0.382 mol) is added at this temperature, followed by methyl chloroformate (36.1 g, 0.382 mol). Afterwards, the solution is stirred at −40 °C for 2 h. Concentrated hydrochloric acid (8 mL) and water (125 mL) are added, and the organic solvents are distilled off at reduced pressure. After addition of toluene (400 mL) to the suspension, the pH of the water phase is adjusted to 1.7 using hydrochloric acid (30 mL). After phase separation at 75 °C, the organic phase is washed with another portion of water (120 mL), concentrated at reduced pressure, and allowed to crystallize at 0 °C to yield 94.0 g of pure **5** (86%).

10,11-Dihydro-10-oxo-5H-dibenz[*b*,*f*]azepine-5-carboxylic Acid Methyl Ester (6). Acid **5** (285.3 g, 1.0 mol) is added to warm (90 °C) polyphosphoric acid (83% P_2O_5, 684 g, 4.0 mol) 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. The reaction mixture is extracted with toluene (3 × 1000 mL), and the combined organic phases are 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 at 0 °C for 3 h to afford white crystals which are filtered and dried to give pure **6** (194 g, 70%): mp 139−141 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H, $COOCH_3$), 3.82−4.40 (AB, 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.

10-Methoxy-5H-dibenz[*b*,*f*]azepine-5-carboxylic Acid Methyl Ester (7). Acid **5** (285.3 g, 1.0 mol) is added to

(24) Under comparable reaction conditions, the carbamoylation of **8** is ca. 500 times faster than that of **2**.

(25) Addition of small amounts of 2-methoxypropene, which eagerly consumes water under the applied reaction condition, helps to suppress the hydrolysis to **15**.

(26) Carbamoylation of **15** to **1** could be achieved only by using chlorosulfonyl isocyanate. No reaction occurs with isocyanic acid at 50 °C, and no 10,11-dihydro-10-chloro-5H-dibenz[*b*,*f*]azepine-5-carbonyl chloride is formed if phosgene is added to **15**.

(27) Washing with water is performed to eliminate sodium chloride and acetamide; the latter is formed in a parallel reaction of acetic acid with isocyanic acid, T. Takahashi et al. Japan Patent, JP 48020522, 1973. Washing with acetone is performed to eliminate a drying step. The major part of water has to be reduced from the wet filter cake to keep the amount of formic acid small for dissolving the material in the final purification step.

warm (90 °C) polyphosphoric acid (83% P_2O_5, 684 g, 4.0 mol) and stirred at 95 °C for 3 h. The reaction mixture is cooled to 80 °C, and water (52.2 g) is carefully added while cooling is applied to hold the temperature below 98 °C. After addition of methanol (1000 mL), the mixture is seeded with **7** at 75−80 °C and gradually cooled to 0 °C over 2−3 h. The suspension is stirred for at least 8 h at 0 °C, filtered, re-slurried/suspended, and washed with cold methanol (1600 mL) in four portions. This product is suspended in methanol (310 mL) and directly used in the next reaction to **8**. Alternatively, the filter cake, which should have a pH > 4.5, is dried at 60 °C/10 mbar, to obtain 241.2 g (85%) of **7** as a white powder: mp 146−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H, $COOCH_3$), 3.91 (s, 3H, OCH_3), 6.14 (s, 1H, CH), 7.2−7.75 (m, 8H, arom H); MS (ES^+) *m*/*z* 282 (MH^+); IR (KBr) 2954, 2836, 1705, 1623, 1493, 1441, 1343, 1233, 1203, 1060, 765 cm^{-1}. Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98; O, 17.06. Found: C, 72.40; H, 5.34; N, 4.94; O, 17.12.

10-Methoxy-5H-dibenz[*b*,*f*]azepine (8). A suspension of **7** (200 g, 0.71 mol) in methanol (300 mL) is added to preheated (50 °C) poly(ethylene glycol) 200 (160 mL). An aqueous solution of sodium hydroxide 50% (110 mL, 2.1 mol) is carefully added, and methanol is distilled off (340 mL) up to an internal temperature of 110 °C. After 2 h of stirring at 105−110 °C, water is added (340 mL), and the mixture stirred for another half an hour at reflux temperature to dissolve the salts. The reaction mixture is then cooled to 30 °C within 2 h, stirred at this temperature for half an hour, filtered, and washed/reslurried with five portions of water (5 × 300 mL) until a pH < 8 is reached. After drying at 60 °C and 50 mbar to constant weight, 154 g of **8** (97% yield, 100 area %, and 0.3% sulfate ash) was obtained as a bright-yellow solid: mp 125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H, OCH_3), 5.14 (bra s, 1H, NH), 5.86 (s, 1H, CH), 6.6−7.5 (m, 8H, arom. H); MS (ES^+) *m*/*z* 224 (MH^+); IR (KBr) 3355, 1635, 1470 1200, 1099, 761 cm^{-1}. Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27; O, 7.17. Found: C, 80.52; H, 5.86; N, 6.15; O, 7.02.

10,11-Dihydro-10-oxo-5H-dibenz[*b*,*f*]azepine-5-carboxamide (1). To a stirred mixture of **8** (50 g, 0.22 mol) and anhydrous acetic acid (154 g, water content < 0.08% w), 97% sodium cyanate (22.75 g, 0.34 mol) is added in five portions over 50 min, keeping the temperature between 20 and 30 °C under argon. After complete addition, the yellow, thick mixture is heated to 45 °C for 2 h. Acetone (30 g) followed by 36% aqueous HCl (49.9 g, 0.49 mol) is added at 40 °C, and the mixture is stirred for another 2 h. Finally, a 30% aqueous sodium hydroxide solution (170.2 g, 1.28 mol) is added at 40−50 °C. The mixture is cooled to 20 °C, filtered, and washed with water. The wet filter cake is then washed with acetone (50 mL), transferred to a 500-mL round-bottomed flask, and dissolved in formic acid (190 g) at 25−30 °C. Water (200 mL) is added slowly over 9 h. The resulting slurry is filtered, transferred to a 500-mL round-bottomed flask, mixed with water (200 g), and stirred at room temperature for 4 h. After filtration, the filter cake is washed several times with water and dried 15 h at 75 °C in a vacuum to give 50.1 g (88.5% yield) of **1** as an off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (d, 1H, J = 14 Hz), 4.38 (d, 1H, J = 14 Hz), 4.83 (br s, 2H, NH_2), 7.25−7.6 (m, 7H, H arom.), 8.04 (dd, 1H, J = 8 Hz, J = 1.6 Hz); MS (ES^+) *m*/*z*: 270 (MNH_4^+), 253 (MH^+); IR (KBr) 3469, 3340, 1686, 1653, 1595, 1564, 1489, 1474, 1448, 1286, 1269, 1235, 1154, 1104, 1026, 772 cm^{-1}.

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