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A New Industrial Process for 10-Methoxyiminostilbene: Key Intermediate for the Synthesis of Oxcarbazepine

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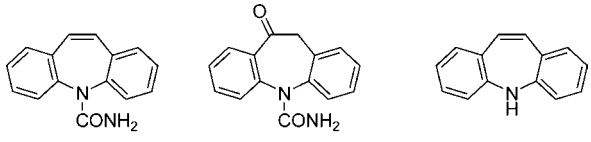
Abstract:

A new industrial process, involving only two isolation and drying steps, for 10-methoxyiminostilbene (MISB), an advance intermediate of widely prescribed antiepileptic drug, oxcarbazepine, has been developed. A salient feature of this process is the novel use of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) to afford bromohydrin methyl ether from *N*-acetyliminostilbene. The byproducts of this process namely acetic acid, 5,5-dimethylhydantoin and $Et_3N \cdot HBr$ are recyclable as well as nontoxic. This process is amenable for the large-scale production of MISB.

Introduction

Carbamazepine (CBZ, **1**) is a well-known anticonvulsant and mood-stabilizing drug which is also used for the treatment of trigeminal neuralgia and acute mania and for prophylactic treatment in bipolar disorder.[1] CBZ possesses some structural similarity to the tricyclic antidepressant drug imipramine, and in fact, CBZ was first synthesized as a potential antidepressant. Oxcarbazepine (OCBZ, **2**) is a relatively novel second-generation antiepileptic drug primarily used for the treatment of psychometric disturbance,[2] epilepsy, and trigeminal neuralgia,[3] and for Parkinson's disease.[4] In fact **2** was initially isolated as an active metabolite of **1**,[5] and it is structurally a derivative of carbamazepine, adding an extra oxygen atom on the dibenzazepine ring. This small difference helps reduce the impact on the liver of metabolizing the drug. OCBZ **2** has assumed the status of the most widely prescribed drug for the treatment of epilepsy due to its improved tolerability profile as compared to that of CBZ **1**, but without loss in its therapeutic potency.[6]



1 Carbamazepine **2** Oxcarbazepine **3** Iminostilbene

Historically, CBZ **1** is synthesized primarily following synthetic schemes utilizing the tricyclic iminostilbene **3** as the key starting material, and it involves only a single chemical step employing the reaction of **3** with phosgene,[7a] or urea[7b] or sodium cyanate in acetic acid.[7c] There are several efficient synthetic routes[8−10] available for the synthesis of **3** which enabled the supremacy of **3** as the most logical, economically viable starting material for **1**. Due to the structural similarity of **1** and **2**, iminostilbene **3** is considered to be also the logical starting material for the production of oxcarbazepine **2**. A strong demand for OCBZ **2** led to the development of several synthetic schemes for its synthesis[11,12] including those involving the transformation, **3** → **2**,[12] albeit involving multistep procedures using reagents such as phosgene, cyanogen halides, halogens, etc. which are known to be potentially hazardous at the commercial scales of production besides being environmentally degrading. Search for a practically simpler method led Novartis Pharma to design two protocols without involving iminostilbene **3** as the key starting material, employing either remote metalation[13] or Friedel−Crafts acylations[14] as key steps in the construction of the tricyclic skeleton. The scale-up process for

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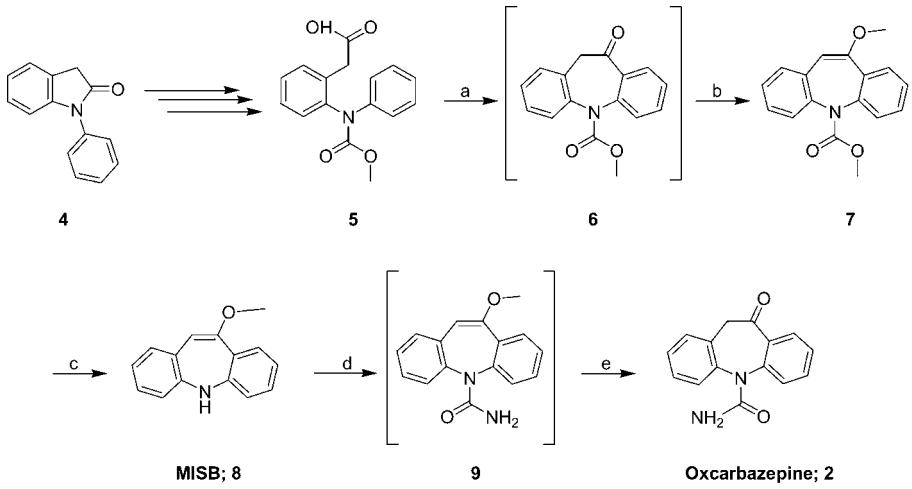
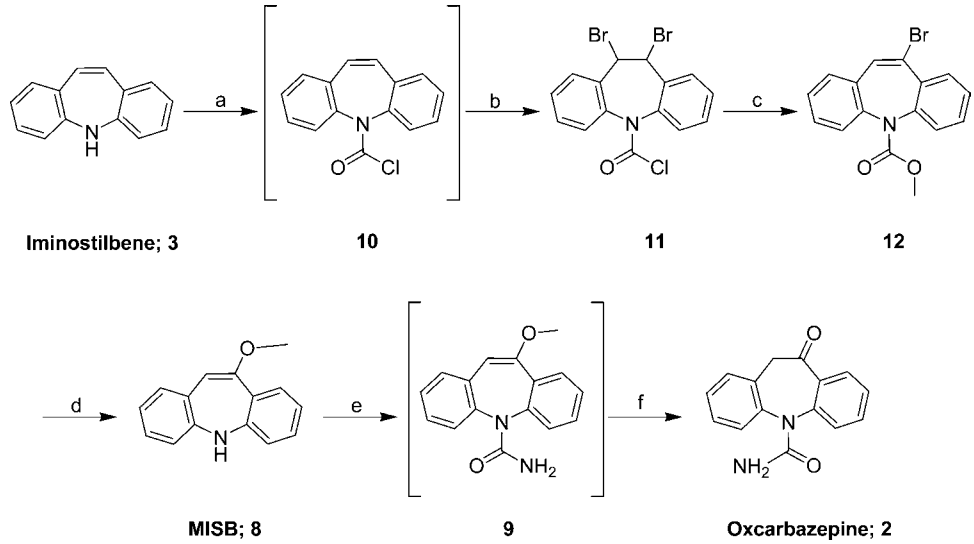
Scheme 1. **Novartis Pharma's synthetic process[11a] for the preparation of oxcarbazepine[a]**



[a] Reagents and conditions: (a) PPA; (b) H_2O, CH_3OH; (c) PEG-200, NaOH; (d) NaOCN, CH_3COOH; (e) HCl, HCOOH, H_2O.

Scheme 2. **Sun Pharma's synthetic process[12a] for the preparation of oxcarbazepine[a]**



[a] Reagents and conditions: (a) $COCl_2$/toluene; (b) CH_3COOH/Br_2; (c) CH_3ONa/CH_3OH; (d) CH_3ONa/DMF; (e) $NaOCN/CH_3COOH$; (f) H_2SO_4.

the latter protocol has been successfully achieved[11a,15] employing 1,3-dihydro-1-phenyl-2*H*-indol-2-one (**4**) as a starting material which was converted into 2-[(methoxycarbonyl)phenylamino]-benzeneacetic acid (**5**) in multistep procedures involving the use of reagents such as phosgene or butyllithium (Scheme 1). **5** was made to participate in a Friedel−Crafts cyclization strategy providing OCBZ **2** in five further steps. Although this protocol provides ready access to **2** via intermediate 10-methoxyiminostilbene (MISB, **8**), it is too long in addition to having some environmental and toxicological drawbacks.

Another synthetic procedure of industrial importance[12a] was developed by Sun Pharma utilizing a multistep strategy involving halogenation−dehalogenation on iminostilbene **3** to generate intermediate **12** (Scheme 2). The enol ether 10-methoxyiminostilbene (MISB, **8**) is prepared by nucleophilic substitution of the vinylic bromide **12**. MISB **8** could readily be converted into OCBZ **2** by treatment with sodium cyanate in acetic acid. However, the major disadvantages of this route are the use of potentially lethal reagents in addition to generation of large amounts of effluents.

A perusal of these synthetic processes revealed that 10-methoxyiminostilbene (MISB, **8**) is a key intermediate in both these industrial processes[11a,12a] as well as several other synthetic strategies,[12g,16] and the transformation **8** → **2** is rather simple, often employing a reaction with urea or sodium cyanate which introduces the *N*-carboxamide

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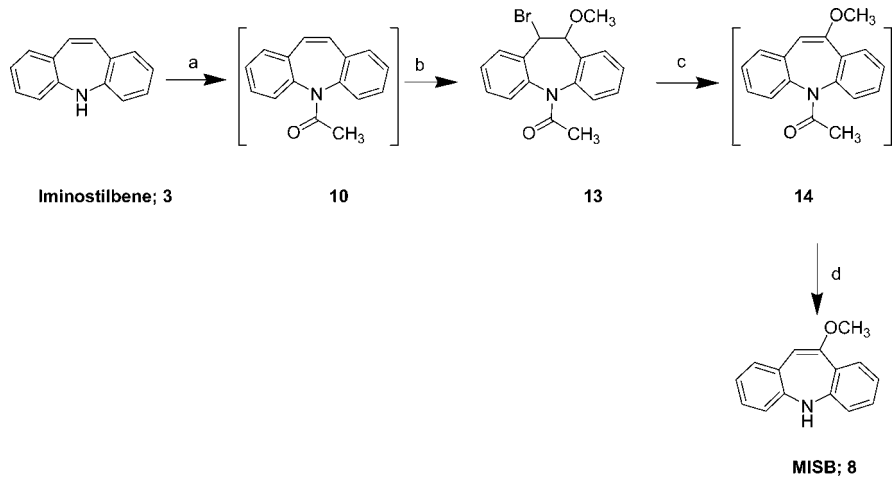
Scheme 3. **New process for the preparation of MISB (8) starting from iminostilbene (3)[a]**



[a] Reagents and condition: (a) Ac_2O, 120 °C, 3−4 h; (b) DBDMH, CH_3OH, 6−8 h 5−15 °C, 86−92%; (c) Et_3N, toluene, reflux, 24 h; (d) KOH/toluene, PEG-200, reflux, 4−6 h, 85−91%.

group followed by acid-mediated ether cleavage. We envisioned that an efficient route to intermediate **8** without involving halogenated solvents or hazardous reagents should make economic sense besides giving a new practical industrial method within the acceptable environmental and toxicological concerns. We further reasoned that the new method would be more appealing if it can employ commercially available conventional starting material for CBZ and OCBZ; iminostilbene **3**. In this contribution, we report the design and technical aspects of our new process,[17] which enables the commercial production of **8** from **3**.

Results and Discussion

The first task of our project was to remove or minimize the use of halogenated solvents and reagents. However, it was apparent that, in order to achieve an efficient synthesis, the best option would be to find a suitable method that can functionalize the carbon−carbon double bond of the central ring of iminostilbene in such a way so as to install an ether functionality (such as a OCH_3 group) as well as a suitable leaving group in a single step on the adjacent carbons at positions 10 and 11. Being a symmetrical molecule, no regioselectivity issues are involved here. The leaving group then can be made to participate in a β-elimination process leading to the 10-methoxyiminostilbene (**8**). As described in Scheme 3, our synthesis of **8** begins with the protection of the imino nitrogen by heating iminostilbene with slight excess (4.35 mol equiv) of acetic anhydride for 3 h at 120−125 °C. The solubility of iminostilbene is poor in acetic anhydride, thus warranting the use of over 4 equiv of acetic anhydride which is used as a reagent as well as a solvent. It was found that, at this concentration, a clear solution results as the reaction temperature approaches 70 °C. TLC examination of this clear solution indicates a clean reaction with partial formation of **10**. A temperature study of this reaction was carried out that shows that the reaction is very slow below 100 °C, whereas at a temperature range of 120−125 °C the reaction is complete in about 3−4 h.

After the completion of the acetylation, the volatiles are removed under vacuum, the resulting viscous material is dissolved in methanol at 40−45 °C and water is added to the clear solution resulting in separation of solid *N*-acetyliminostilbene (**10**) in 85−90% yield. Considering our strategy of simultaneous functionalization of the carbon−carbon double bond of the central ring of iminostilbene with a leaving group and an ether functionality, we attempted a reaction of **10** with liquid bromine in methanol expecting to get a bromohydrin methyl ether **13**. However, a mixture of **13** and 10,11-dibromo-*N*-acetyliminostilbene was obtained. Reaction of **10** with NBS in methanol was the next to be tried. and it resulted in isolation of the expected **13** in 80−85% yield. Although the yield of **13** in this case was satisfactory, however, the reproducibility of yield was not up to the mark. We shifted our attention to a cheap commercially available brominating agent, 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) which is well-known to effect brominations of aromatic rings.[18,19] Thus, **10** is taken up in methanol (3−4 volumes) and treated with DBDMH at a temperature of 0−10 °C. After stirring for 1 h the product bromohydrin methyl ether **13** starts crystallizing out; however, the reaction takes 6−8 h for completion. The resulting slurry is filtered to give **13** in about 88−92% yield.[20] After a few trials, we were able to perform these two steps—acetylation and the formation of bromohydrin methyl ether—in tandem

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without isolating the intermediate **10**. Thus, volatiles are removed under vacuum from the reaction mixture after the completion of the acetylation reaction, and the residue is taken up in methanol. The methanolic solution is treated with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) for 6−8 h at 5−10 °C to afford, after filtration, **13** in 88−92% overall yield from iminostilbene. Combining these two steps offers significant advantages, as both steps necessitate the use of a single reactor at the plant level, thus lowering the reaction time and utility cost besides saving the costs involved in isolation of **10**. Moreover, the overall yield from **3** to **13** is about 10−13% higher by a one-pot procedure. Dehydrobromination of **13** to **14** was achieved by treating it with triethylamine[21] in toluene and heating the resulting mixture under reflux for 24 h. As the reaction proceeds, the byproduct $Et_3N\cdot HBr$ keeps on precipitating and is filtered at the end of the reaction at room temperature. The remaining organic phase is washed with water, excess toluene is evaporated, and the resulting thick mass is dissolved in methanol at 50−55 °C. **14** is obtained in 83−85% yield as it is precipitated out from the methanolic solution after addition of water at room temperature. Out of many other reaction conditions attempted for dehydrobromination, the use of DBU is worth mentioning, as the reaction takes only 30−40 min to complete at room temperature. However, economic considerations led us to adopt the route involving triethylamine in spite of long reaction times. No further attempts were made to optimize the dehydrobromination by other processes involving inorganic bases, as they were liable to generate more effluent. Deacetylation of **14** is achieved by refluxing in *n*-butanol and KOH for 6−8 h. After completion of the reaction, *n*-butanol is distilled off and the residue is stirred with water for 1−2 h and filtered to afford MISB **8** in 85−90% yield. We were apprehensive about the feasibility of this step at the plant level as the nature of the aqueous slurry at this stage is very thick and thus difficult to handle, resulting in unloading problems. We could achieve a clean deacetylation reaction without any concomitant unloading problems by replacing *n*-butanol with toluene in the presence of a catalytic amount of PEG-200. This gave us the idea of combining the two steps—dehydrobromination and deacetylation. Thus, the reaction mixture obtained after Et_3N/toluene reflux in the dehydrobromination step is filtered to remove $Et_3N\cdot HBr$. KOH and a catalytic amount of PEG-200 are added to the filtrate, and the reaction mixture is refluxed for another 4−6 h. The reaction mixture is washed with water at room temperature, and the toluene is distilled off completely to afford a yellow solid mass which is dissolved in methanol at reflux. Water is added to the cooled reaction mixture under stirring to precipitate the pure **8**, resulting in 88−90% overall yield from **13**. By combining the last two steps, the synthesis is again economically rewarding in terms of increased yield, reduced timings as well as workup hassles. The newly developed protocol for **8** has been found to be a robust process as it has achieved reproducible results on commercial scale.

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Conclusion

Starting from the conventional tricyclic starting material, iminostilbene **3**, the newly developed production process for MISB **8** has an overall yield of around 80% and involves only two isolation and drying steps, namely the intermediate **13** and the target product **8**. The new process offers distinctive advantages over earlier reported procedures in terms of less effluent generation, avoiding the use of liquid bromine as well as significant cost reduction on commercial scale. To the best of our knowledge, we have used the industrially important 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) for halohydrin ether formation for the first time. The byproducts of this process, namely acetic acid, 5,5-dimethylhydantoin, and $Et_3N\cdot HBr$, are recyclable as well as nontoxic. This process is amenable for the large-scale production of **8**.

Experimental Section

Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without further purification. Water used at any stage was deionized. All melting points were uncorrected and determined on Buchi B-545 melting point apparatus. NMR spectra (400 MHz for ^1H and 100 MHz for ^{13}C) were recorded on a Bruker Avance-400 instrument. Mass spectra were recorded on LQC-Avatage Max-Ion Trap (Source: APCI, ESI) instrument. Water content of all reagents, solvents, and intermediates was done on Metrohm-Modetro-787 KF-Titrino instrument. TLC was done on Merck TLC silica gel 60 F_{254} plates using mobile phase hexane/EtOAc (8:2).

Preparation of *N*-Acetyl-10-bromo-11-methoxy-10,11-dihydro-5*H*-dibenzo[*b,f*]azepine (13). A mixture of acetic anhydride (110 mL, 1.16 mol) and iminostilbene **3** (100 g, 0.518 mol) was heated to 120−125 °C for a period of 3−4 h. After completion of reaction (TLC), volatiles were removed under vacuum. Methanol (250 mL) was added to the residue and cooled to 5−10 °C. Solid 1,3-dibromo-5,5-dimethylhydantoin (DBDMH; 81.5 g, 0.284 mol) was added at 5−10 °C, and the reaction mixture stirred for 6−8 h at 5−10 °C. The resulting slurry was filtered, washed with chilled methanol, and dried under vacuum to give the intermediate **13** (162 g, 90.6%): R_f = 0.46; mp 135−138 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H, $-COC\underline{H}_3$), 3.60 (s, 3H, $OC\underline{H}_3$), 5.08 (d, 1H, C<u>H</u>OMe), 5.21 (d, 1H, -C<u>H</u>Br), 7.26−7.59 (m, 8H, arom-<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 54.8, 59.3, 83.8, 125.7, 126.0, 127.1, 127.4, 128.3, 128.6, 128.7, 128.9, 133.7, 133.8, 169.6; IR (KBr, cm^{-1}) 3066, 2948, 2932, 1671, 1598, 1438, 1372, 1125, 772, 602, 588 cm^{-1}; MS (ES^+) *m/z*: 346 (MH^+) and 348 ($MH^+ + 2$). Anal. Calcd for $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.05; Found: C, 58.62; H, 4.76; N, 3.81.

Preparation of 10-Oxo-10,11-dihydro-5*H*-dibenzo[*b,f*]-azepine-5-carboxamide (10-Methoxyiminostilbene; MISB; 8). A mixture of compound **13** (160 g; 0.463 mol), toluene (800 mL), and Et_3N (95 g, 0.938 mol) was heated to reflux under stirring for 24 h. After completion of reaction (TLC), the reaction mixture was cooled to room temperature, and the precipitated $Et_3N\cdot HBr$ was filtered. A mixture of toluene layer,

KOH (70 g, 1.24 mol), and PEG-200 (4.8 g, 3% w/w) was refluxed for 4−6 h. After completion of reaction (TLC), the reaction mixture was cooled to room temperature and washed with water (2 × 100 mL). The organic layer was concentrated to dryness. Methanol (300 mL) was added to the residue and heated under reflux for 1 h. The resulting mixture was cooled to room temperature, and water (100 mL) was added slowly and stirred for 2 h. The resulting slurry was filtered, and the solid was washed with chilled methanol (100 mL). The resulting yellow solid was dried under vacuum to give **8** (91.1 g, 88%): R_f = 0.35; mp 120−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H, -OC<u>H</u>$_3$), 5.16 (s, 1H, N<u>H</u>), 5.89 (s, 1H, C<u>H</u>), 6.67−7.6 (m, 8H, arom-<u>H</u>); IR (KBr, cm^{-1}) 3360, 1640, 1480, 1220, 1105, 779, 740; MS (ES$^+$) *m*/*z*: 224 (MH$^+$).

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