First Multigram Preparation of SCP-123, A Novel Water-Soluble Analgesic

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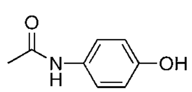
Abstract:

A short multigram process for the preparation of the analgesic compound SCP-123 (4) and its sodium salt has been developed.

Introduction

The analgesic acetaminophen (**1**) is widely used for the acute and chronic control of pain.[1] While the therapeutic window of **1** is quite broad, the low water solubility is problematic for some delivery applications.[2−4] A water-soluble analogue of **1** is the prodrug propacetamol hydrochloride (**2**).[5,6] This form of acetaminophen is rapidly and completely hydrolyzed by plasma esterases to release **1**.[7] The pharmacological effects in clinical trials have shown that **2** possesses efficacy similar to that of **1**; however, due to its greater water solubility it can be parenterally administered and thus be employed when oral administration is not possible.[5,6]



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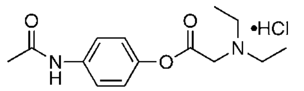

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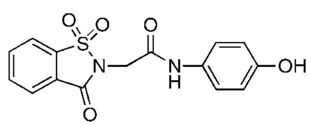
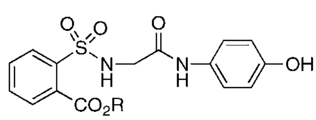


3 (SCP-1)



4 R = H (SCP-123)
5 R = Na (SCP-123ss)

The recent discovery that the analgesic properties of the saccharin derivative of acetaminophen, SCP-1 (**3**), possess a potency equal to that of the properties of acetaminophen, with significantly diminished hepatotoxicity, has prompted an extensive investigation into this class of compounds as a new generation of analgesic drugs.[8−12] The lead compound **3** was found to possess an analgesic and antipyretic profile similar to that of **1**.[10−12] However, recent studies with **3** have shown that it is extensively and rapidly hydrolyzed *in vivo*.[10] The metabolite SCP-123 (**4**) and corresponding sodium salt SCP-123ss (**5**) are equipotent on a molar basis with **3** in analgesic models. Presumably, the efficacy of **3** is derived from the hydrolysis product **4**. Therefore, it was of interest to develop large-scale syntheses of **4** and **5** for further drug development studies.

Results and Discussion

For the developmental studies, multigram quantities of **4** and **5** were required. Previous work with these compounds had revealed that the most efficient way to prepare the gram quantities of these metabolites was via the hydrolysis of the saccharin ring of **3**.[10] Therefore, the design of a multigram synthesis focused on the initial preparation of **3**, followed by the subsequent hydrolysis to afford either **4** or **5**. Two synthetic routes have been established for the preparation of gram quantities of **3**.[8−10] As illustrated in Scheme 1, the two routes differ primarily in the sequence in which the saccharin moiety is added to the acetyl unit. In Route A,[9,10] the saccharin moiety is added in the last step to the 2-chloroacetamide intermediate **8** that has been previously generated from 4-aminophenol (**6**) and 2-chloroacetyl chloride (**7**). This yields **3** via a two-step process. Alternatively in Route B,[8] the intermediate acetic acid **11** is formed initially from sodium saccharin (**9**) and bromoacetic acid (**10**). The acid **11** is then coupled to **6** to furnish **3** also via a two-step process. Route A was deemed to be of greater merit due the low cost of the commercially available starting materials and also because both the intermediate **8** and **3** could be obtained in a state of high purity (>95%) by precipitation or recrystallization. Alternatively, Route B is potentially limited by the hygroscopic intermediate acid **11**, which is difficult to handle, as well the multiple recrystallizations of **3** that are

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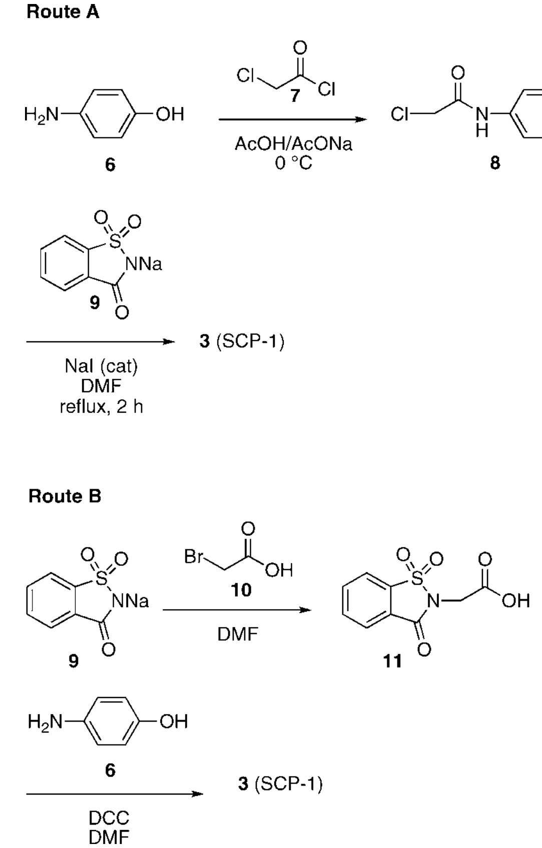
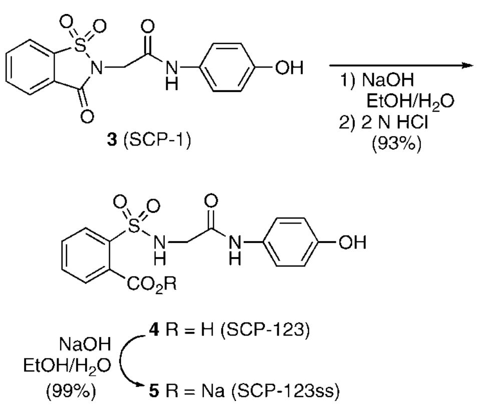
10.1021/op900113b CCC: $40.75
Published on Web 06/25/2009

Scheme 1. **Synthetic routes to SCP-1 (3)**



Scheme 2. **Synthesis of SCP-123 (4) and SCP-123ss (5)**

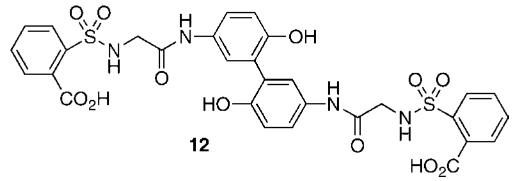


necessary to remove dicyclohexylurea present as a byproduct from the coupling reaction.

Based upon our evaluation, Route A was scaled 15-fold and run on a mole scale. The 2-chloroacetyl chloride (**7**) was added at a controlled rate to a suspension of **6** in an acetate buffer at ≤5 °C. As the addition of the acid chloride progressed, the reaction mixture became clear, and the intermediate 2-chloro-acetamide (**8**) began to crystallize. The 2-chloroacetamide intermediate **8** was obtained in 70% yield, and no further purification was required for advancement to the next step. Preparation of **3** was routinely performed on a mole scale. **8** and saccharin sodium salt (**9**) were heated to reflux in DMF with a catalytic amount of NaI. The saccharin derivative was then easily obtained by precipitation in ice water. A single recrystallization from ethanol/water furnished **3** in 72% yield.

The hydrolysis of **3** was readily achieved with NaOH solution followed by treatment with 2 N HCl (Scheme 2).[10,13] This afforded the corresponding acid **4** (SCP-123) in 93% yield.

The hydrolysis step was found to be sensitive to the concentration of the saccharin derivative **3** in the basic solution. If the reaction mixture was not sufficiently dilute, the formation of side product **12**, that resulted from oxidative phenolic coupling, was obtained.[14,15]



This impurity **12** was present from 10−25%, depending upon the concentration of the reaction mixture relative to **3**. The coupling product **12** was initially identified by LC/MS [*m*/*z* 698] but was difficult to detect by NMR. However, **12** could be clearly differentiated from **4** by HPLC. An optimized concentration of **3** in 0.5 N NaOH was determined to be 0.25 M. At this concentration, the hydrolysis of **3** proceeded cleanly, and the oxidative-coupling product **12** was not observed. These conditions were preferred to using tedious degassing procedures and performing the reaction under anaerobic conditions. Due to the large reaction volumes at this concentration we were limited by our equipment and thus typically performed the hydrolysis on a 50-g scale. The resultant hydrolysis product could be manipulated easily by precipitation with acid to give **4** in >99% purity. Despite the smaller scale of the hydrolysis reaction, this step was typically executed in multiple simultaneous batches that could be combined to rapidly generate subkilogram quantities of **4**. However, we have no evidence to suggest that this reaction is limited to this scale and could be performed on a larger scale if needed.

The preparation of the sodium salt **5** was achieved by titration of the acid **4** with one equivalent of NaOH (Scheme 2). The advantage of this procedure over the direct conversion of **3** into **5** was that the direct method gave an unquantifiable mixture of mono- and disodium salts due to the acidic phenol moiety. Alternatively, the titration of **4** with one equivalent of NaOH afforded the sodium carboxylate **5**, which could be precipitated cleanly out of solution as the monosodium salt. Filtration and vacuum drying gave **5** as the monohydrate (**5·H_2O**) in quantitative yield and high purity (>99%) as determined by HPLC and combustion analysis. The monohydrate **5·H_2O**, albeit somewhat hygroscopic, was stable to extensive drying and gave consistent combustion analysis when stored in a dry environment.

Conclusion

We have developed a multigram process for the preparation of **4** (SCP-123) and its sodium salt, **5·H_2O**. The overall yields

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for both **4** and **5·H$_2$O** were 47% and 46%, respectively. Both processes required no chromatography, and the desired compounds **4** and **5·H$_2$O** were isolated in high purity (>99%).

Experimental Section

General Methods. NMR spectra were recorded on a Varian-400 MHz nuclear magnetic resonance spectrometer at ambient temperature in DMSO-d_6. HPLC was used to monitor the purity of all intermediates using standard HPLC equipment with UV detection (254 nm) and data system. Separations were performed with a Waters Nova-Pak C18 (3.9 mm × 150 mm) steel analytical column. The mobile phases for isocratic and gradient separations were prepared using 0.01% TFA in water and 0.01% TFA in CH_3CN.

***N*-(4-Hydroxyphenyl)-2-chloroacetamide (8).** 4-Aminophenol (**6**, 150 g, 1.37 mol) was added to a saturated solution of sodium acetate (500 mL) followed by acetic acid (500 mL). The suspension was cooled to 0 °C, and the 2-chloroacetyl chloride (**7**, 155 g, 109 mL, 1.37 mol) was added portionwise to the suspension at ≤5 °C. As the addition of **7** progressed, the suspension dissipated, and the mixture clarified. Prior to completion of the addition of **7**, a white precipitate began to form. Upon completion of the addition, the heterogeneous mixture was brought to 25 °C and stirred at room temperature for 2 h. The white precipitate was filtered, washed with distilled water solution (2 × 100 mL) and dried under vacuum to afford 177 g of **8** as a white solid (70% yield). Mp 142−144 °C. ^{1}H NMR: δ 4.17 (s, 2H), 6.70 (d, J = 8.8, 2H), 7.35 (d, J = 8.8, 2H), 9.26 (s, 1H), 10.02 (s, 1H). ^{13}C NMR: δ 44.2, 115.9, 121.9, 130.7, 154.5, 164.6. Anal. Calcd for $C_8H_8ClNO_2$: C, 51.77; H, 4.34; N, 7.55. Found: C, 51.87; H, 4.31; N, 7.49.

SCP-1 (3). 2-Chloroacetamide (**8**, 326 g, 1.75 mol) and saccharin sodium salt hydrate **9** (433 g, 2.10 mol) were mixed together in the presence of NaI (1.0 g, 0.0067 mol, 0.4 mol %) in DMF (1 L). The mixture was heated to reflux for 2 h, cooled to 25 °C, and poured into ice water (500 mL). A white precipitate formed, and more ice (∼100 g) was added until no additional precipitate formed. The sticky white precipitate was collected by vacuum filtration and allowed to dry in air for 30 min. The filter cake was dissolved in 50% ethanol−water (2 L) and recrystallized to furnish 419 g of **3** as white crystals (72% yield). Mp 204−207 °C. ^{1}H NMR: δ 4.54 (s, 2H), 6.73 (d, J = 8.8, 2H), 7.36 (d, J = 8.8, 2H), 8.00 (dt, J = 6.8, 14.3, 2H), 8.11 (d, J = 7.5, 1H), 8.30 (d, J = 7.6, 1H), 9.26 (s, 1H), 10.07 (s, 1H). ^{13}C NMR: δ 41.2, 115.9, 121.8, 122.3, 125.8, 127.2, 130.8, 135.9, 136.5, 137.6, 154.4, 159.4, 163.3. Anal. Calcd for $C_{15}H_{12}N_2O_5S$: C, 54.21; H, 3.64; N, 8.43. Found: C, 54.15; H, 3.58; N, 8.41.

SCP-123 (4). A suspension of **3** (50 g, 0.15 mol) and aqueous 0.5 N NaOH (600 mL, 0.30 mol) was stirred at 25 °C for 1 h. Ethanol (400 mL) was added until the solution became clear. Stirring was continued for an additional 1 h. The solution was acidified with a 2 N HCl (500 mL) solution to a pH of 1 (pH meter). The white precipitate that formed was filtered and washed with distilled water (100 mL). The filter cake was dried under vacuum to afford 49 g of **4** as a white solid (93%, yield). Mp 184−186 °C. ^{1}H NMR: δ 3.72 (d, J = 5.1, 2H), 6.65 (d, J = 8.8, 2H), 7.20 (d, J = 8.8, 2H), 7.39 (s, 1H), 7.65−7.77 (m, 3H), 7.93 (m, 1H), 9.21 (s, 1H), 9.71 (s, 1H), 13.81 (b, 1H). ^{13}C NMR: δ 46.5, 115.8, 121.7, 129.3, 130.4, 130.7, 131.7, 133.2, 133.4, 138.2, 154.2, 166.0, 169.5. Anal. Calcd for $C_{15}H_{14}N_2O_6S$: C, 51.42; H, 4.03; N, 8.00. Found: C, 51.42; H, 4.15; N, 7.86.

SCP-123ss·H$_2$O (5·H$_2$O). The acid **4** (71.5 g, 0.24 mol) was suspended in ethanol (400 mL) and cooled to 0 °C. A precooled (0 °C) solution of NaOH (8.2 g, 0.24 mol) in distilled water (40 mL) was added dropwise to the ethanolic suspension over 10 min. After the addition of the basic solution was complete, more ethanol was added to the mixture, if needed, to dissolve all the solids. The clear reaction mixture was stirred for an additional 2 h. The reaction volume was reduced by 10% (∼50 mL) on a rotoevaporator without a water bath. Once a precipitate started to form, the mixture was removed from the rotoevaporator and cooled at 0 °C for 1 h. The white precipitate was filtered and washed with distilled water (100 mL). The filter cake was dried under vacuum at 60 °C to afford 93 g of **5·H$_2$O** as white solid (99% yield). Mp 188−190 °C. ^{1}H NMR: δ 3.57 (s, 2H), 6.65 (d, J = 8.8, 2H), 7.24 (d, J = 8.8, 2H), 7.39 (t, J = 7.0, 1H), 7.51 (t, J = 7.5, 1H), 7.63 (d, J = 6.6, 1H), 7.74 (d, J = 7.7, 1H), 9.00 (s, 1H), 9.58 (s, 1H), 10.03 (s, 1H). ^{13}C NMR: δ 47.1, 115.7, 121.7, 128.0, 128.1, 130.7, 130.8, 132.9, 136.3, 142.5, 154.3, 166.4, 171.3. Anal. Calcd for $C_{15}H_{13}N_2NaO_6S \cdot H_2O$: C, 46.15; H, 3.87; N, 7.18. Found: C, 46.01; H, 3.89; N, 7.14.

Acknowledgment

We are grateful to the National Institute on Neurological Disorders and Stroke for the support of this research. The project described was supported by Grant Number U44NS046891 from the National Institute of Neurological Disorders And Stroke. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders And Stroke or the National Institutes of Health.

Supporting Information Available

Proton NMR of compounds **4**, **5**, and **12**, HPLC conditions and retention times for compounds **3**, **4**, and **12**, and LC-ESI MS spectrum of **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review May 4, 2009.

OP900113B