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Synthesis of Tenidap: An Improved Process for the Preparation of 5-Chloro-2-oxindole-1-carboxamide†

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Abstract:

An industrially viable, robust, and economic process is developed for Tenidap sodium and its important intermediate 5-chloro-2-oxindole-1-carboxamide. Use of inorganic cyanates, in place of organic isocyanates, makes the process simple and commercially viable. The advantage of using acetic anhydride and sodium acetate over reported reagents such as trifluoroacetic acid and its anhydride on industrial scale is described. Drastic reduction of DMAP in the final step and overall improvement of yields makes the process economical.

Introduction

Oxindole-1-carboxamide derivatives, particularly 5-chloro-3-(2-thenoyl)-2-oxindole-1-carboxamide sodium salt, tenidap sodium (1) (Figure 1), are for the treatment of rheumatoid arthritis[1] and osteoarthritis[2]. Tenidap is an inhibitor of prostaglandin[3] and interleukin-1[4] production in the body. It inhibits both the enzymes cycloxygenase and 5-lypoxygenase,[5] which convert arachidonic acid into prostaglandin and leukotrienes[3], and exhibits superior activity compared to other nonsteroidal antiinflammatory drugs (NSAIDs) such as naproxen,[6] piroxicam,[7] diclofenac sodium,[8] indomethacin,[9] and so forth, currently available in the market. Tenidap sodium has not been launched in the market because of toxic effects found in clinical trials.

Introduction

5-Chloro-2-oxindole-1-carboxamide[10] (**4**) is an important intermediate in the preparation of tenidap sodium (**1**), which is commonly prepared by one of the following methods.

(a)*N*-acylation of 5-chloro-2-oxindole (**2**) with chlorosulfonyl isocyanate produced intermediate (**3**) which on hydrolysis with aqueous acetic acid gave 5-chloro-2-oxindole-1-carboxamide (**4**) as shown in Scheme 1.

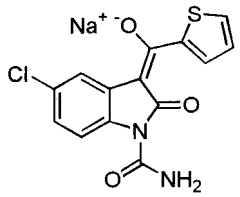

Figure 1.

(b)Reaction of 5-chloro-2-oxidnole (**2**) with isobutyryl isocyanate and cyclohexyl carbonyl isocyanate in toluene gave the intermediate (**5**). Hydrolysis of (**5**) in potassium hydroxide yielded 2-(5-chloro-2-ureidophenyl)acetic acid[10] (**6**), which was cyclised with a mixture of trifluoroacetic acid and trifluoroacetic anhydride to give the desired 5-chloro-2-oxidnole-1-carboxamide (**4**) (Scheme 2).

(c)Reaction of 5-chloro-2-oxindole (**2**) with trichloroacetyl isocyanate[11] in toluene followed by warming the reaction mixture to 80 °C to give 5-chloro-2-oxindole-1-carboxamide (**4**) in one step (Scheme 3).

It is evident from the literature that the preparation of the key intermediate (**4**) of tenidap sodium (**1**) is uneconomical and employs hazardous organic isocyanates. Further, the reported process for condensation of thiophene-2-carbonyl chloride with 5-chloro-2-oxindole-1-carboxamide (**4**) to prepare tenidap (**7**) (Scheme 4) employs an excess of the expensive base *N*,*N*-dimethylaminopyridine (DMAP), thereby making the process cost-ineffective.

Therefore, it was felt necessary to develop an improved process for the preparation of tenidap sodium (**1**) by employing nonhazardous, inexpensive, and easy-to-handle chemicals on large scale.

Results and Discussion

The synthetic route discussed in this paper is presented in Scheme 5. The salient features are discussed below.

(a) Expensive and highly reactive organic isocyanates are substituted by inorganic cyanates which are not only inexpensive but also easy to handle even at large scale operations for the preparation of 2-(5-chloro-2-ureidophenyl)-acetic acid (**6**).

(b) The cyclisation of 2-(5-chloro-2-ureidophenyl)acetic acid (**6**) to 5-chloro-2-oxindole-1-carboxamide (**4**) is carried out with acetic anhydride and sodium acetate, thereby avoiding the expensive trifluoroacetic acid and trifluoroacetic anhydride mixture. The above cyclisation can also be carried

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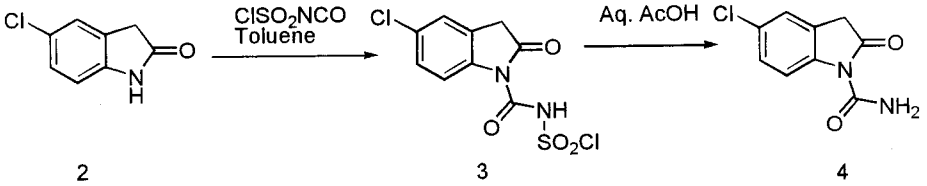
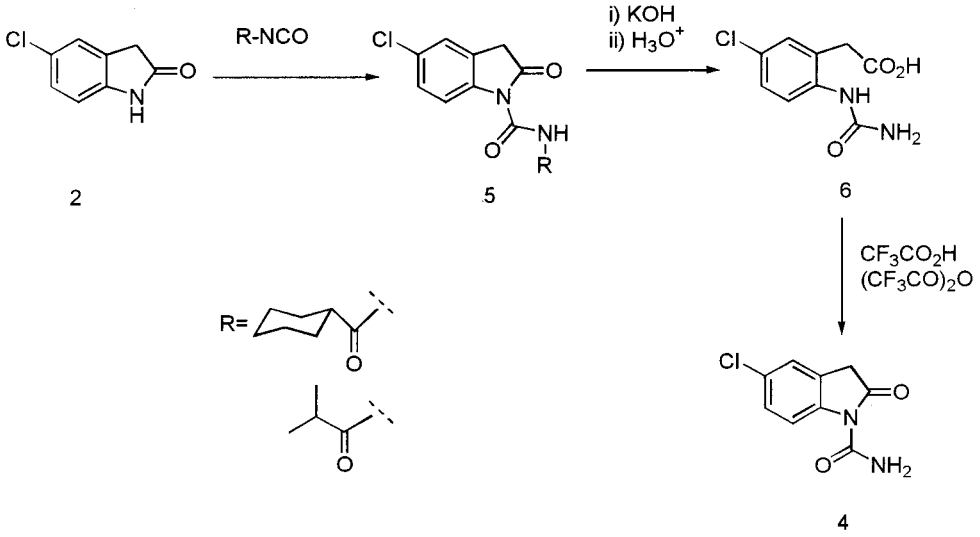
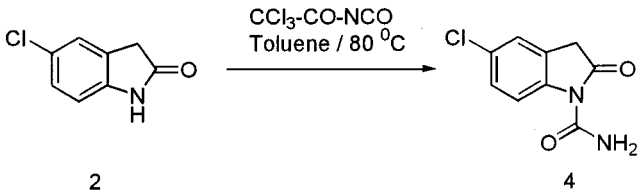
Scheme 1



Scheme 2



Scheme 3



out with thionyl chloride or *p*-toluene sulfonic acid in moderate yields.

(c) The condensation of 5-chloro-2-oxindole-1-carboxamide (**4**) with thiophene-2-carbonyl chloride is accomplished by using inexpensive trialkylamines and a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP). The reduction of expensive DMAP from 2 M equiv[10] to a catalytic amount (0.2 M equiv) greatly reduces the cost of the final compound.

(d) The cost benefits are also due to the improved yields in the synthesis of the two intermediates **4** and **7**.

Many procedures are reported in the literature[12] for the preparation of 5-chloro-2-oxindole (**2**). Keeping in view scale-up and process convenience, compound **2** is prepared from 5-chloroisatin[10] under Wolff−Kishner reduction conditions. 5-Chloro-2-oxindole (**2**) (Scheme 5) on hydrolysis with aqueous sodium hydroxide followed by acidification gave an unstable 2-amino-5-chlorophenylacetic acid which without isolation on reaction with in situ generated isocyanic acid (from the reaction of potassium cyanate with acetic acid) gave 2-(5-chloro-2-ureidophenyl)acetic acid (**6**) in good yield.

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The cyclisation of compound **6** was accomplished by using acetic anhydride and sodium acetate to give 5-chloro-2-oxindole-1-carboxamide (**4**) in good yield. The above cyclisation can also be carried out with thionyl chloride and/or *p*-toluene sulfonic acid. The ^{1}H NMR spectrum of compound (**4**) in $CDCl_3$ has two broad peaks resonating at δ 5.4 and 8.5 which are due to exchangeable amidic protons. It is interesting to note that they resonate at different frequencies. This could be rationalised in terms of restricted C−N− bond rotation due to the strong intramolecular hydrogen bonding with one of the amidic proton with C^2-carbonyl as showed in Figure 2. Tenidap (**7**) is obtained by condensation of above carboxamide (**4**) with thiophene-2-carbonyl chloride by using a mixture of triethylamine and a catalytic amount of DMAP.

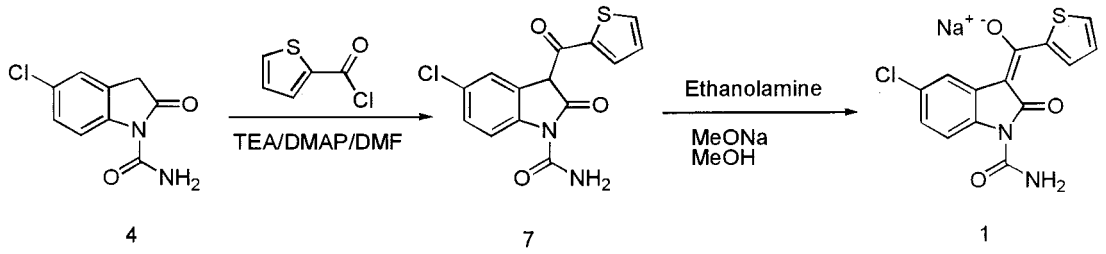
The pharma grade tenidap sodium (**1**) is obtained by known methods[10] by first converting tenidap (**7**) into its sodium salt using ethanolamine and sodium methoxide in methanol and finally recrystallising the product from glacial acetic acid. The ^{1}H NMR spectrum of the compound **7** and compound **1** showed the same pattern of amidic protons as in compound **4**.

Scale-Up Trials. The process mentioned in Scheme 5 is fully optimized and the scale-up trials were performed on 1 to 2 kg scale. This route performed routinely and reliably, affording the expected yields and purities in all stages of the synthesis, thus demonstrating the robustness and viability of the process.

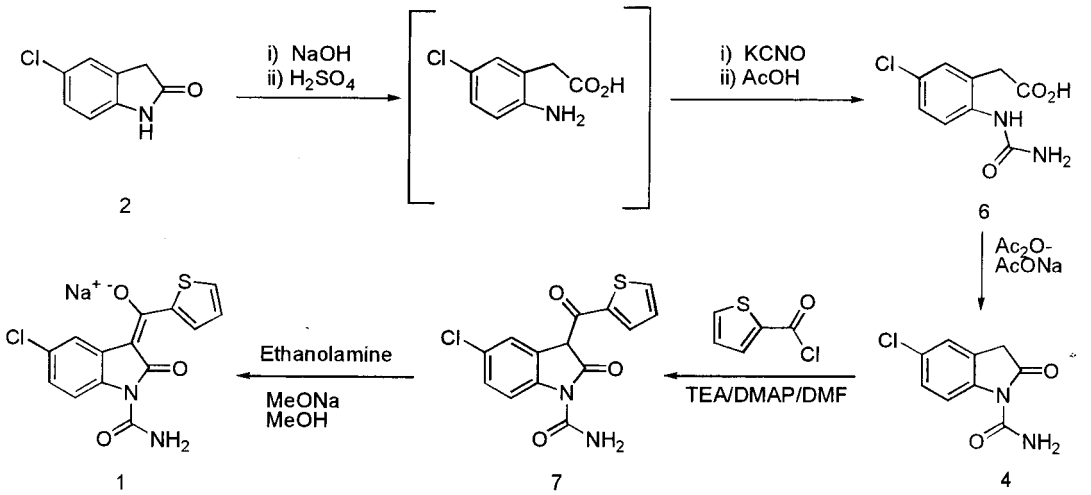
Experimental Section

Solvents and reagents are obtained from commercial sources and are not purified unless specified. Proton NMR

Scheme 4



Scheme 5



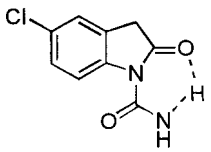


Figure 2.

data was obtained on a Varian Gemini 200 MHz FT NMR spectrometer. Infrared spectra (IR) were recorded on a Perkin-Elmer 1650 FT-IR spectrophotometer. Mass spectra were recorded on an HP-5989A quadrapole mass spectrometer. All of the melting points are uncorrected.

Preparation of 2-(5-chloro-2-uridophenyl)acetic acid (6). 5-Chloro-2-oxindole (**2**) (20 g, 0.12M) and sodium hydroxide (200 mL, 10% solution) were refluxed for 7 h. The reaction mixture was cooled to 0° C, neutralized with concentrated sulfuric acid while maintaining the temperature between 0 and 5° C, and filtered. To the filtrate, acetic acid (36 mL) was added slowly while stirring to obtain a white precipitate. A freshly prepared solution of potassium cyanate (19.5 g in 50 mL water) was added dropwise to the above reaction mixture at room temperature. Stirring was continued for 1 h. The precipitate was filtered and dissolved in 5% sodium bicarbonate solution (250 mL). After removal of undissolved matter by filtration, the solution was extracted with ethyl acetate (2 × 100 mL) to remove soluble impurities; the organic layer was discarded. The bicarbonate solution was acidified with sulfuric acid, and the precipitated material was filtered and dried under vacuum: mp 180−182° C (lit. mp = 187.5 °C),[10] purity 98.5%, yield 18.6 g (68%). ^{1}H NMR (CD_3OD) δ 3.5 (s, 2H), 7.2−7.5 (m, 3H). IR (KBr) 1234, 1350, 1540, 1575, 1657, 1702, 3272, 3340, 3486 cm^{-1}. Mass *m*/*z* 265, 228, 211, 185, 168, 140, 112.

Preparation of 5-chloro-2-oxindole-1-carboxamide (4). (a) A solution of 2-(5-chloro-2-uridophenyl)acetic acid (**6**) (10 g, 0.47 M) dissolved in dichloroethane (150 mL) was cooled to 10 °C. Thionyl chloride (4.5 mL) was added slowly to the reaction mixture with stirring over a period of 20 min. The temperature was raised to 30 °C, and the mixture was stirred for 4 h more. The reaction mixture was evaporated to dryness under vacuum. The residue was washed first with sodium bicarbonate solution and then with water. The crude product was purified by column chromatography packed with silica gel to give 5-chloro-2-oxindole-1-carboxamide: yield 3.8 g (41%).

(b) 2-(5-Chloro-2-uridophenyl)acetic acid (**6**) (10 g) was dissolved in 300 mL of toluene and *p*-toluenesulfonic acid (2.5 g) in a flask arranged for azeotropic reflux. The reaction mixture was refluxed for 8 h and then washed with water. The toluene layer was dried over sodium sulfate and evaporated. The crude product thus obtained was chromatographed over silica gel to give 5-chloro-2-oxindole-1-carboxamide (**4**): yield 9.03 g (35%).

(c) To cooled (0 °C) acetic anhydride (60 mL, freshly distilled over sodium acetate), anhydrous sodium acetate (2 g) was added. To the above solution, 2-(5-chloro-2-uridophenyl)acetic acid (**6**) (10 g) was added slowly, while maintaining the temperature between 0 and 5 °C; stirring was continued for 1 h more at the same temperature. The white precipitate which formed was filtered, washed with 10% sodium bicarbonate solution followed by water, and dried under vacuum. The first crop yield was 5 g. The filtrate was

poured onto crushed ice and set aside for 2 h; the separated material was filtered, washed with 10% sodium bicarbonate solution and water, and dried under vacuum to yield 2.7 g of additional 5-chloro-2-oxindole-1-carboxamide (**4**). The yield from the two crops was 7.7 g (83%). This compound can be used in the next step without further purification. The crude product (1 g) was recrystallised from acetonitrile to give 300 mg of pure product: mp 210−211 °C (lit. mp 211 °C), HPLC purity 98%. ^{1}H NMR ($CDCl_3$) δ 3.8 (s, 2H), 5.3 (1H, D_2O exchangeable), 7.3 (d, 2H), 8.1 (d, 1H), 8.4 (s, D_2O exchangeable). IR (KBr) 1093, 1166, 1290, 1370, 1471, 5585, 1710, 1749, 3212, 3367 cm^{-1}. Mass *m*/*z* (70 ev) 210, 167, 138, 112, 102.

Preparation of 5-chloro-3-(2-thenoyl)-2-oxindole-1-carboxamide (Tenidap) (7). To a solution of 5-chloro-2-oxindole-1-carboxamide (**4**) (10 g) dissolved in dimethylformamide (90 mL), *N*,*N*-dimethylaminopyridine (1.45 g, 0.01 M) and triethylamine (1.96 mL, 0.14 M) were added and cooled to 8 °C. Thiophene-2-carbonyl chloride (5.6 mL, 0.052 M) in dimethylformamide (18 mL) was added to the above mixture slowly while maintaining the temperature between 8 and 15 °C. Dilute hydrochloric acid (8 mL, concentrated HCl in 200 mL of water) was added to the above reaction mass and kept for 2 h at room temperature. The precipitate was washed with water followed by methanol. The above crude material was refluxed in methanol (200 mL) for 1 h. Ethanolamine (3 mL) and active carbon (2 g) were added to the above methanolic solution and refluxed for 30 min and filtered. The filtrate was cooled to room temperature and acidified with hydrochloric acid. The yellow solid was filtered and dried to obtain tenidap (**7**): yield 13.4 g, (88.1%), mp 226−229 °C (lit. mp 229−231 °C)[10] (dec).

Preparation of Sodium Salt of 5-Chloro-3-(2-thenoyl)-2-oxindole-1-carboxamide. (Tenidap Sodium) (1). 5-Chloro-3-(2-thenoyl)-2-oxindole-1-carboxamide (10 g, 0.031M) was dissolved in a mixture of methanol (200 mL) and ethanolamine (3 mL) and filtered to remove any insoluble matter. To the above solution, sodium methoxide (3.7 g) in methanol (10 mL) was added and refluxed for 1 h. The reaction mixture was maintained at room temperature for 10 h while stirring. The crystallised yellow material was filtered and washed with methanol (3 mL) and dried under vacuum to yield 8.7 g of tenidap sodium (**1**). The filtrate was concentrated to half its volume to obtain a second crop of tenidap sodium (1.2 g): the total yield (two crops) was 96%, mp 232−233 °C (lit. mp 236−238 °C),[10] purity 99%. ^{1}H NMR ($CDCl_3$) δ 6.5 (s, 1H, exchangeable), 6.8 (dd, 1H), 7.1 (d, 1H), 7.5 (d, 1H), 8.1 (t, 1H), 8.4 (d, 1H), 9.6 (s, 1H, exchangeable). IR (KBr) 722, 787, 1039, 1075, 1177, 1374, 1421, 1642, 1673, 1698, 3043, 3668 cm^{-1}. Mass *m*/*z* (20 ev) 277, 193, 167, 137, 127, 111.

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