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A Facile One-Pot Synthesis of 4-Hydroxy-3-methoxycarbonyl-2-methyl-2h-1,2-benzothiazine 1,1-Dioxide, a Key Intermediate in the Synthesis of Oxicam Anti-Inflammatory Agents

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A FACILE ONE-POT SYNTHESIS OF 4-HYDROXY-3-METHOXYCARBONYL-2-METHYL-2H-1,2-BENZOTHIAZINE 1,1-DIOXIDE, A KEY INTERMEDIATE IN THE SYNTHESIS OF OXICAM ANTI-INFLAMMATORY AGENTS.

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4-Hydroxy-3-methoxycarbonyl-2-methyl-2H-1,2-benzothiazine 1,1-dioxide (**8**) was synthesized by a one-pot procedure, starting from the readily available saccharine. The synthesis involves 4 transformations with an overall yield equivalent to that from the stepwise process.

In the last years several 1,2-benzothiazine derivatives have shown to be highly effective non-steroid anti-inflammatory agents, piroxicam **1**[1], isoxicam **2**[2], and sudoxicam **3**[3] being representative examples. Most of the syntheses of this type of compounds are closely related to the original work of Abe,[4] whose key transformation consisted in a base-catalyzed isomerization of saccharine derivatives to the 1,2-benzothiazine nucleus.[5] Due to our interest in the preparation of derivatives of this nucleus, with potential biological activity, we tried to reproduce the reported ring expansion of the 5-member heterocycle with sodium methoxide in DMSO[6], but we obtained **7**, in variable yields, instead of the expected cyclic compound **5**, which we planned to transform in **8** (see scheme). Therefore we decided to investigate the synthesis of **8**, a key intermediate for the preparation of, not only piroxicam **1** and isoxicam **2**, but other structurally related compounds .[7,8] Herein, we report an efficient and facile one-pot preparation of **8**.

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Although the previous preparation of the title compound are based on the pathway reported by Abe [4] and later improved by Lombardino,[6] there are other approaches to this nucleus[9], including the patent filed by Unverferth, et al. describing the transformation of the N-methyl derivative **6** to the corresponding 1,2-benzothiazine **8** (see scheme).[10, 11] On the other hand, Pátek reported a detailed study of the Dieckmann condensation of **6** to produce **8**, investigating the effect of temperature and solvent on the reaction rate, using different bases.[12]

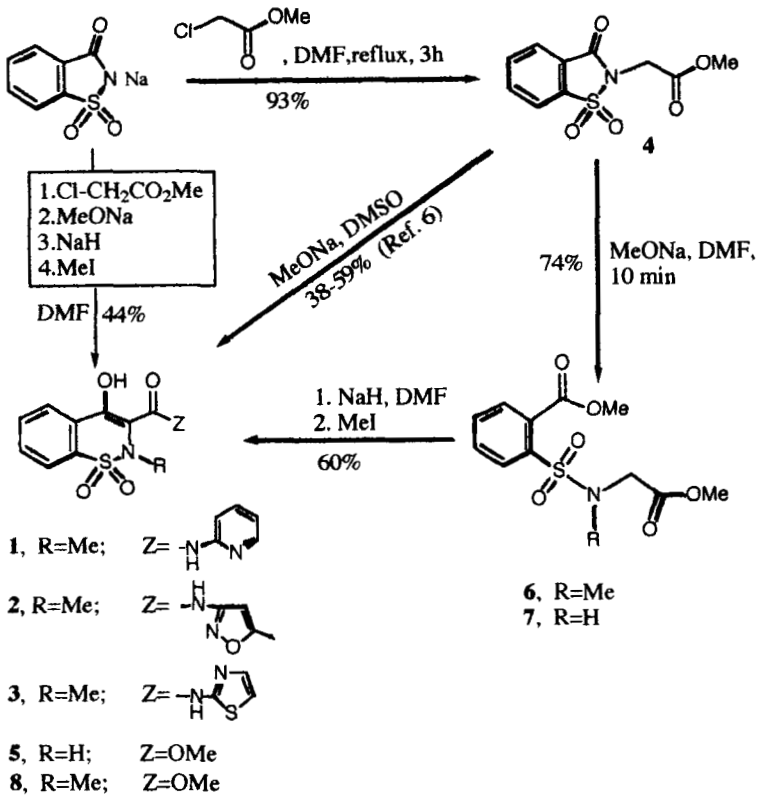
In spite of all these reports, it seemed to us very interesting to develop a preparation procedure for **8**, which could be used for the preparation of other related compounds with potencial biological activity[13] and other uses.[14] Besides, a process involving a minimum of unitary operations could led to decrease in purifications, amount of reagents and solvents, time and cost.

First, we carried out the preparation of **8** in a four steps process (N-alkylation, ring cleavage, N-methylation, and ring closure) (see Scheme), where each step was studied separately with the idea of designing a one-pot procedure. Although there are reports of aqueous methods for the N-alkylation of sodium saccharine in up to 70% yield,[15] we decided, in accordance with our goal to develop a one-pot procedure, to try this first step under non-aqueous conditions. So, the N-alkylation of sodium saccharine was carried out in DMF and gave **4**, in 93% yield. Then, the cleavage of the heterocycle in **4** was achieved by treatment with sodium methoxide in methanol, giving **7** in 92% yield. Next, we explored the possibility to carry out the cyclization of **7**, followed by in-situ N-methylation to give **8**, using the same base i.e., NaH in DMF for both transformations. Indeed, **8** was prepared in this manner in 60% overall yield.

This last step encouraged us to proceed with our original idea to design a one-pot procedure. For the second step, ring cleavage to give **7**, switching the solvent to DMF was unsuccessful. Later we found that the addition of a few drops of methanol allowed the reaction to produce **7** in 74% yield.

Because all the separated reactions were done in DMF, we decided to carry out the process in one-pot, as described on the Scheme, resulting in the direct preparation of **8** in 44%

SCHEME



overall yield, with no isolation of any of the intermediates, as compared with 41% from the stepwise process.[16]

In conclusion we are presenting an efficient and easy one-pot procedure for the synthesis of **8**, in good yield and purity, requiring a minimum of operations.

Experimental:

^{13}C and ^{1}H NMR spectra were recorded at 50 and 200 MHz respectively on a Varian Geminis 200 spectrometer, in $CDCl_3$ as solvent. The chemical shifts are reported respect

to TMS, used as internal reference. IR spectra were determined on a Perkin-Elmer 1600FT spectrometer. MS spectra were recorded on a JEOL JMS-SX102A spectrometer.

Synthesis of methyl 1,2-benzothiazoline-3(2H)-one-2-acetate 1,1-dioxide (**4**).

Methyl chloroacetate (11.9 g, 109.6 mmol) was added to a solution of sodium saccharine (15.0 g, 73.1 mmol) in DMF (30 ml), the mixture was heated at 100° C during 3 h. The reaction mixture was cooled to room temperature and poured over cold water (60 ml), resulting in an immediate formation of a white solid, which was filtered and washed with water. The solid was dried (70° C overnight) to produce 17.3 g (67.8 mmol, 93%) of **4** as crystalline solid; mp 115-116°C (lit. 118° C [17]).

Synthesis of methyl 2-[N-(methoxycarbonyl)sulfamoyl] benzoate (**7**).

Ester **4** (3.0 g, 11.8 mmol) was added to a solution of sodium methoxide (0.79 g, 14.2 mmol) in methanol (9 ml). The reaction mixture was stirred for 5 min. and poured over ice-water (20 ml); the mixture was acidified to pH=3, with 15% HCl. The resulted solid was filtered, washed with cold water and dried (70° C overnight) to produce 3.1 g (10.8 mmol, 92%) of **7**; mp 94-95° C.

Synthesis of 4-hydroxy-3-carbomethoxy-2-methyl-2H-1,2-benzothiazine 1,1-dioxide (**8**).

Sodium hydride (50% in oil; 0.25 g, 5.2 mmol) was suspended in DMF (3 ml), under nitrogen. The suspension was cooled to 0-5° C and a solution of **7** (0.5 g, 1.8 mmol) in DMF (3 ml) was added dropwise, keeping the temperature under 5° C. The cooling bath was removed and the reaction mixture was stirred at room temperature for additional 15 min. (note: the reaction mixture turned red); followed by the addition of methyl iodide (0.6 g, 4.2 mmol) (note: the reaction mixture turned green). The reaction mixture was stirred for 30 min. and poured over ice-water (20 ml); the mixture was then acidified to pH=3, with 15% HCl. The solid was filtered and dried (70° C overnight) to produce 0.28 g (1.0 mmol, 60%) of **8**; mp 163-165° C (lit. 162-165° C [6]).

IR (KBr): υ= 3437, 2920, 1667 cm^{-1}

^1H NMR ($CDCl_3$): δ 2.94 (s, 3H), 3.95 (s, 3H), 7.6-8.2 (m, 4H), 12.04 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 38.50, 52.81, 109.95, 123.77, 126.52, 127.81, 132.18, 132.84, 135.58, 158.78, 169.78.

HRMS (FAB+); Estimated m/z=270.0436; Observed m/z=270.0420.

One-pot preparation of 4-hydroxy-3-carbomethoxy-2-methyl-2H-1,2-benzothiazine 1,1-dioxide (**8**).

In a three neck round-bottomed flask dry sodium saccharine (1.0 g, 4.9 mmol) was dissolved in DMF (3 ml), under nitrogen. Then methyl chloroacetate (0.79 g, 7.3 mmol) was added over a 2 min. period, at room temperature. The reaction mixture was heated at 98-100° C for 3 h. After cooling the reaction mixture to room temperature, sodium methoxide (0.3 g, 5.4 mmol), DMF (3 ml), and methanol (0.3 ml) were added keeping the temperature between 17-22° C and stirred for 10 min. Then all volatile compounds were removed at 10 Torr during 5 min. The nitrogen atmosphere was restored and the temperature of the reaction was set at 0° C, followed by the addition of sodium hydride (0.47 g, 9.8 mmol). The cooling bath was removed and the reaction mixture was stirred for 15 min. at room temperature, followed by dropwise addition of methyl iodide (1.2 g, 8.4 mmol), during 15 min., the temperature reached 33° C and the stirring was continued for 30 min. at room temperature. The reaction mixture was poured over ice-water (20 g) and acidified to pH=3, with 15% HCl. The precipitate was filtrate and dried (70° C overnight) giving 0.58 g (2.2 mmol) of **8**, 44% overall yield, mp 157-161° C. Recrystallization from 96% ethanol gave pure **8**, mp 163-165° C (lit.162-165° C [6])

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