Development and a Practical Synthesis of Nepafenac Intermediate *via* Modified Gassman Reaction

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Abstract: Modification of nepafenac intermediate synthesis (**5A**) *via* Gassman specific *ortho*-substitution is reported. According to the process, 2-aminobenzophenone (**1A**) and 2-(methylthio)acetamide (**2**) were reacted in the convenient temperature conditions, in the presence of N-chlorophthalimide (**3**) or 1,3-dichloro-5,5-dimethylhydantoin (**4**), to activate the formation of azasulfonium salt and rearrangement thereof to pure 2-amino-3-benzoyl-α-(methylthio)phenylacetamide (**5A**). The procedure appears to be suitable for a reaction carried out in a large scale.

Keywords: Gasmann reaction, Nepafenac, N-chlorophthalimide.

INTRODUCTION

Nepafenac (0.1% ophthalmic suspension) non-steroidal anti-inflammatory drug (NSAID) has been introduced for commercial use in the US and EU [1]. Originally, nepafenac was synthesized using Gassman's procedure for the preparation of indole ring [2-5]. Gassman's indole synthesis involves a one-pot process in which a hypohalite and a β-carbonyl sulfide are added sequentially to substituted aniline to form an azasulfonium salt. Then the salt is treated with base to cause Sommelet-Hauser-type rearrangement, to provide 3-thioalkoxyindoles [6]. The selection of reagent addition sequence seems to be connected with the effect of substituent on the aniline ring. In the presence of electron-donating group, which destabilizes the *N*-chloroaniline intermediate, the enhanced synthetic strategy is a formation of chlorosulfonium salt followed by reaction with appropriate aniline (Scheme **1**). Wright *et al.* have developed a modification of the Gassman synthesis that affords the improved yields in many cases [7]. The key feature of the modification was the formation of the chlorosulfonium salt from sulfoxide and oxalyl chloride. The reaction was successful for a number of substrates that are particularly sensitive to halogenations, and for which the use of the ethyl (methylthio)acetate/ chlorine or *tert*-butyl hypochlorite condition was unsuitable, although it required low temperature and dry, inert atmosphere. Firstly described nepafenac intermediate (**5A**) synthesis was carried out in a one-pot sequence in the presence of *tert*-butyl hypochlorite [8]. 2-aminobenzophenone (**1A**) was reacted with a 2-(methylthio)acetamide to give an azasulfonium salt (Scheme **1**), followed by triethylamine addition to cause rearrangement to 2-amino-3-benzoyl-α-(methylthio) phenylacetamide (**5A**) intermediate. Recently, the improved process for preparing **5A** with halogenosuccinic acid imide has been disclosed [9]. The two above mentioned procedures for the preparation of 2-amino-3-benzoyl-α-(methylthio) phenylacetamide (**5A**) require low temperature and dry, inert atmosphere. In the final step of nepafenac synthesis, the nickel sponge desulfurization of **5** gave the final compound.

RESULTS AND DISCUSSION

In the present paper we report a modification of the Gassman reaction that makes it convenient to scale-up the process. At the beginning, the preparation described by Walsh [8] was examined using HPLC for determining the purity of final 2-amino-3-benzoyl-phenyl)-α-(methylthio) phenylacetamide (**5A**). The best results, achieved by the addition of rearrangement agent at -70ºC, yielded about 54% with only 58% HPLC purity after crystallization. The main impurities, extremely difficult to remove from the final **5A** by common purification techniques, were two chlorination by-products i.e. 2-amino-5-chlorobenzophenone [10] (major; **1B**) and 2-amino-3-benzoyl-5-chloro-α-(methylthio)-phenyl acetamide (**5B**). Both compounds were synthesized for our HPLC studies. It's worth noticing that the direct *para*-substitution of 2-aminobenzophenone (**1A**) with *tert*-butyl hypochlorite, leading to **1B**, has never been reported before. Moreover, there is no analytical data for **5B** in literature. As a result of our examination, two chlorination agents - N-chlorophthalimide (**3**) or 1,3-dichloro-5,5-dimethylhydantoin (**4**) were selected for the studies of a new modified Gassman procedure. The most important criteria for our choice were common availability of proposed compounds and the simplicity of by-product (i.e. phthalimide) detection.

In our work we evaluated the influence of the amount of the chlorinating agent and temperature on the purity of **5A**, in the condensation produced by N-chlorophthalimide (Table **1**). In addition, the suitability of 1,3-dichloro-5,5-

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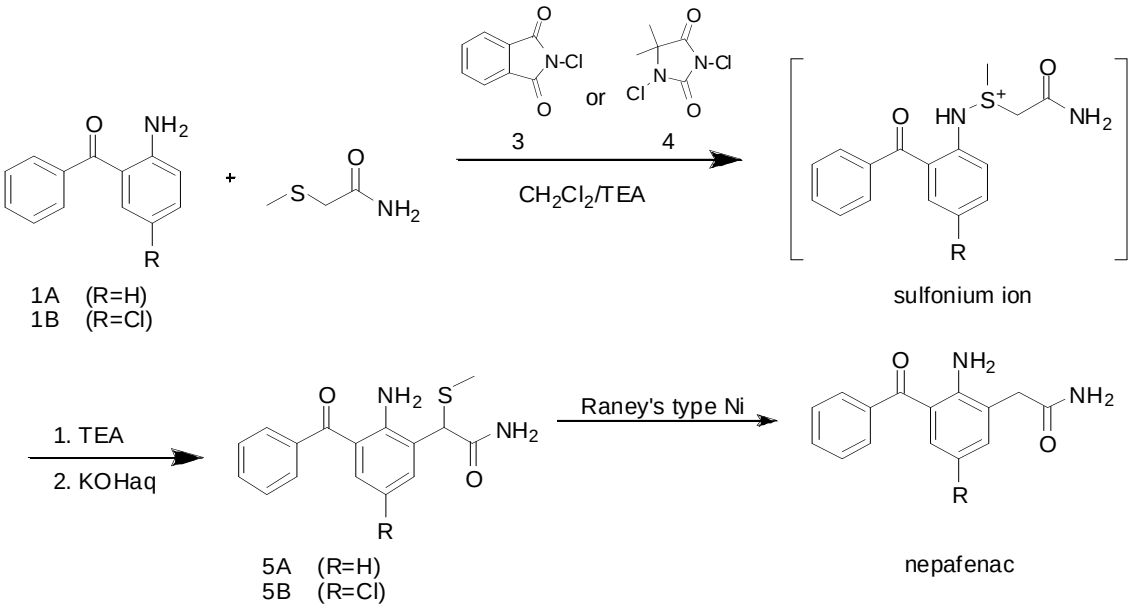

Scheme 1. Synthesis of **5**.

Table 1. The Obtaining of 5A with N-chlorophthalimide (3) Activation, in Various Reaction Conditions

	Starting Temperature [ºC]	3 [eq.]	Yield g [%]	HPLC Purity of Crude Product 5A	Content of Substrate 1A in Crude Product
	-50:-45	1	89.8%	78.59 %	17,64%
	-50:-45	1,2	96.0%	79.07 %	10,37%
	-50:-45	1,4	96.0%	66.72%	9,73%
	-30:-25	1	90.8%	78.86%	19,73%
	-20:-15	1	90.0%	82.47%	15,80%
	-5:0	1	92.0%	77.11%	21,89%
	+10:+15	1	89.6%	61.80%	35,75%

dimethylhydantoin in Gassman rearrangement was checked. The use of N-chlorophthalimide was quite effective in a wide range of temperatures i.e. from -50ºC to 15ºC. All re actions were carried out under normal atmospheric conditions. It seems that inert and dry atmosphere was not essential. The purity varied from about 62% to 82% of **5A** in crude product. The best results were observed in temperatures -20ºC to -15ºC. The quantity increase of **3** (from 1 to 1,4 molar eq.) did not significantly affect the amount of the expected product; however, it led to a negative change in purity profile of **5A**. Instead of an easy removable substrate **1A**, new undefined impurities were formed. In the case of N-chlorophthalimide (with molar ratio 1:1) to promote the reaction, there was no need to isolate a formed azasulfonium salt before the rearrangement to methylthiophenylacetamides **5A** and **5B**. The crude products were easily purified by standard crystallization from 2-propanol. The reactions with 1,3-dichloro-5,5-dimethylhydantoin were not optimized. The enhanced purity of **5A** was achieved in the work-up with the isolation of azasulfonium salt before organic base addition. Compound **5B** was obtained by the crystallization of crude product, which had been isolated after quenching the reaction mixture with triethylamine.

EXPERIMENTAL

Materials and Instruments

Reagent and solvents were purchased from common commercial suppliers and were used without further purification. NMR spectra were recorded on a Varian VNMRS 600 spectrometer (at 298 K) in DMSO-d_6. Melting points were determined from DSC experiments using Mettler- Toledo 822e with an intercooler. Chromatographic studies were performed on a ***Waters Alliance***® (***2695*** Separations Module) HPLC system. Reverse-phase C18 column (2.6 µ particles size, 250 mmx4.5mm) and mobile phase (A: 10mM ammonium formate, adjusted to pH 4 with formic acid; B: acetonitrile) with gradient elution were used for separation.

2-amino-5-chloro-benzophenone (1B)

Tert-butyl hypochlorite [11] (5,4 mL; 0,045 mol) was added dropwise to a stirred solution of 2-amino-benzophenone (8,88 g; 0,045 mol) in methylene chloride (135 mL). The temperature rose from 20ºC to 35ºC and the mixture was stirred for 10 min. The organic solution was washed twice with water (2x50 mL), dried over anhydrous

magnesium sulfate, and evaporated *in vacuo* to give a brown solid. The crude product was purified by column chromatography on silica-gel (eluent: hexanes and ethyl acetate/hexanes 9:1) and crystallization (ethyl acetate/hexanes). Yield 5,09 g (48,8%). HPLC purity 99,74%. M. p. 98 °C (95-99 °C [5]). ^{1}H NMR, ^{13}C NMR data and melting point corresponded with those reported in literature [5].

2-amino-3-benzoyl-α-(methylthio)phenylacetamide (5A)

Preparation with N-chlorophthalimide (3)

A stirred suspension of 2-amino-benzophenone (**1A**) (7,02 g; 35,6 mmol) and 2-(methylthio)acetamide [12] (3,74 g; 35,6 mmol) in methylene chloride (160 mL) was cooled down to -20 -15ºC. A solution of 95% (T) N-chlorophthalimide (**3**) (6,63 g; 36,5 mmol) in methylene chloride (215 mL) was added dropwise during 30 min., while the temperature was maintained in the range -20 - 15ºC. The obtained mixture was stirred in -20 -15ºC for 30 min, then allowed to warm up to - 5 ºC within 150 min. Triethylamine (5,4 mL; 38,8 mmol) was added. Then the organic solution was washed with 1M potassium hydroxide (3x85 mL) and water (3x85 mL), dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The crude product was purified by crystallization from 2-propanol. The formed yellow crystals were filtered and air dried. Yield 6,75 g (63,1%). HPLC purity 99,22%. M.p. 159 °C (153°-155 °C [8]).

^{1}H NMR (600 MHz; DMSO) 2.03 (s, 3H), 4.76 (s, 1H), 6.57 (dd, J_1=J_2=7.8 Hz), 7.22–7.30 (m, 1H), 7.26 (br, 2H), 7.39 (br, 1H), 7.46–7.51 (m, 1H), 7.48–7.53 (m, 2H), 7.53–7.58 (m, 2H), 7.56–7.60 (m, 1H), 7.67 (br, 1H); ^{13}C NMR (600 MHz; DMSO) 14.5, 50.7, 113.9, 117.4, 122.1, 128.2, 128.6, 131.1, 133.9, 134.9, 140.0, 149.3, 171.0, 198.4.

Preparation with 1,3-dichloro-5,5-dimethylhydantoin (4)

A stirred suspension of 2-amino-benzophenone (**1A**) (1,64 g; 8,3 mmol) and 2-(methylthio)acetamide [12] (0,87 g; 8,3 mmol) in methylene chloride (37 mL) was cooled down to -20 - -15ºC. A solution of min. 68% (T) 1,3-dichloro-5,5-dimethylhydantoin (**4**) (1,45 g) in methylene chloride (20 mL) was added dropwise during 15 min., while the temperature was maintained in the range -20 - -15ºC. The obtained mixture was stirred in -20 - -15ºC for 30 min, then allowed to warm up to - 5 ºC within 120 min and the formed salt was collected by filtration. The precipitate was suspended in methylene chloride (20 mL) and triethylamine (1,25 mL; 9,0 mmol) was added. After work-up and crystallization as described above, yellow crystals were filtered and air dried. Yield 0,90 g (36,1%). M.p. 159 °C (153°-155 °C [8]). HPLC purity 99,73%. NMR confirmed.

2-amino-3-benzoyl-5-chloro-α-(methylthio)phenylacetamide (5B)

Preparation with N-chlorophthalimide

A stirred suspension of 2-amino-5-chloro-benzophenone (**1B**) (8,25 g; 35,6 mmol) and 2-(methylthio)acetamide [12] (3,74 g; 35,6 mmol) in methylene chloride (160 mL) was cooled down to -20 - -15ºC. A solution of 95% (T) N-chlorophthalimide (**3**) (6,63 g; 36,5 mmol) in methylene chloride (215 mL) was added dropwise during 30 min., while the temperature was maintained in the range -20 - -15ºC. The obtained mixture was stirred in -20 - -15ºC for 30 min, then allowed to warm up to - 5 ºC within 150 min. Triethylamine (5,4 mL; 38,8 mmol) was added. Then the organic solution was washed with 1M potassium hydroxide (3x85 mL) and water (3x85 mL), dried over anhydrous magnesium sulfate, and evaporated *in vacuo*. The crude product was purified by crystallization from methylene chloride/hexanes. The formed yellow crystals were filtered and air dried. Yield 4,35 g (36,5%). HPLC purity 99,22%. M.p. 191°C.^{1}H NMR (600 MHz; DMSO) 2.04 (s, 3H), 4.79 (s, 1H), 7.18 (d, J_1=2.4 Hz,1H), 7.22 (br, 2H), 7.46 (br, 1H), 7.53–7.56 (m, 2H), 7.58–7.62 (m, 2H), 7.61–7.64 (m, 1H), 7.71 (br, 1H); ^{13}C NMR (600 MHz; DMSO) 14.4, 49.9, 117.0, 118.4, 124.1, 128.4, 128.7, 131.6, 132.01, 134.1, 139.1, 147.8, 170.5, 197.2.

Preparation with 1,3-dichloro-5,5-dimethylhydantoin

A stirred suspension of 2-amino-5-chloro-benzophenone (**1B**) (1,92 g; 8,3 mmol) and 2-(methylthio)acetamide [12] (0,87 g; 8,3 mmol) in methylene chloride (37 mL) was cooled to -20 -15ºC. A solution of min. 68% (T) 1,3-dichloro-5,5-dimethylhydantoin (**4**) (1,45 g) in methylene chloride (20 mL) was added dropwise during 15 min., while the temperature was maintained between -20 - -15ºC. The obtained mixture was stirred in -20 - -15ºC for 30 min, then allowed to warm to - 5 ºC within 120 min. Triethylamine (1,25 mL; 9,0 mmol) was added. After work-up a crystallization as described above, yellow crystals were filtered and air dried. Yield 0,90 g (32,4%). M.p. 191°C. HPLC purity 99,82%. NMR confirmed.

CONCLUSIONS

The present procedures offer an alternative to the work with *tert*-butyl hypochlorite which is unstable and not easy to handle in bulk. The most important advantage of the new chlorinating agents was good purity and the yield of nepafenac intermediate, in comparison to the original method. The activation by N-chlorophthalimide (**3**) and 1,3-dichloro-5,5-dimethylhydantoin (**4**) in Gassman-type *ortho*-substitution results in mild reaction conditions, the ease of manipulation and selectivity. The use of N-chlorophthalimide (**3**) is quite effective in a wide range of temperatures (up to 15ºC), under normal atmospheric conditions. Our procedure not only gives nepafenac intermediate with no chlorination by-products but also enables an easy detection of residual phthalimide as opposed to the synthetic method which generates succinimide impurity. Additionally, the use of N-chlorophthalimide (**3**) significantly improves the workup and purification process of the post-reaction mixture, using the extraction with an aqueous inorganic base to remove the impurity as a phthalate.

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CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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