New Process for the Synthesis of Imidazo[4,5-*b*]pyridine Derivatives as Potent Orally Active Thromboxane A_2 Receptor Antagonists

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A new synthetic route to prepare the 4-[3-(4-chlorophenyl)methyl-6-chloroimidazo[4,5-*b*]pyridin-2-yl]-3,3-dimethylbutanoic acid (UP 116-77) is described. UP 116-77 is a potent orally active TXA_2/PGH_2 receptor antagonist currently under pharmacological investigation. Its development needed a suitable synthesis for industrial processing. The cyclization of 3-amino-5-chloro-2-(4-chlorophenyl)methylaminopyridine **4** with 3,3-dimethylglutaric anhydride in refluxing acetic acid affords a new efficient and simple way to UP 116-77 and subsequently to various 2-substituted imidazo[4,5-*b*]pyridine derivatives.

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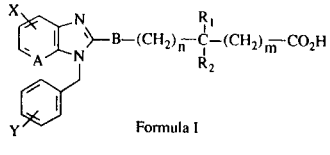
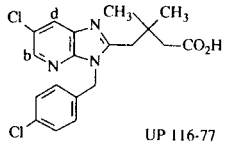
Introduction.

In a recent paper [1] we have described the synthesis and the structure-activity relationships of a series of benzimidazole and imidazo[4,5-*b*]pyridine derivatives of formula **I** (Chart I) as potent TXA_2/PGH_2 receptors antagonists. These compounds were potentially useful in the treatment of conditions in which TXA_2 is believed to be implicated and especially in a variety of cardiovascular, renal and respiratory diseases [2]. In this series, the 4-[3-(4-chlorophenyl)methyl-6-chloroimidazo[4,5-*b*]pyridin-2-yl]-3,3-dimethylbutanoïc acid (UP 116-77, Chart I) was selected as the lead compound and is currently under extensive pharmacological development.

Chart I : Structures of UP 116-77 and Formula I derivatives.



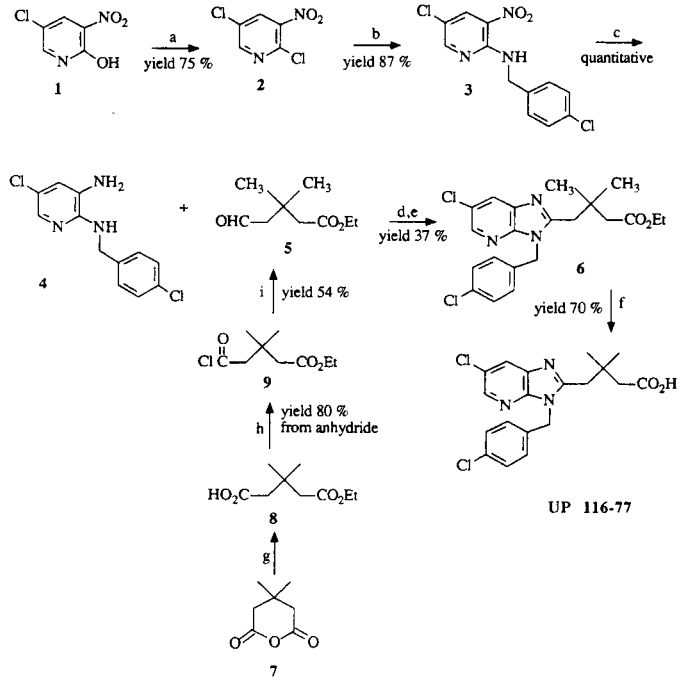
Formula I



UP 116-77

A = CH, N
X, Y = Halogen, H, methoxy, methylthio
B = S, a bond
R_1, R_2 = H, alkyl or R_1 + R_2 = cycloalkyl
n, m = 0,1,2

Scheme I [1] : Synthesis of UP 116-77 (laboratory scale)



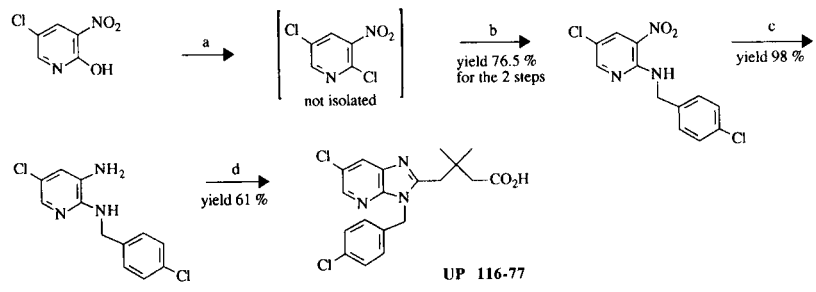
[a] Ph $POCl_2$, 180°C, 2 hours 30 minutes.[b] 4-chlorobenzylamine, 5-ethyl-2-methyl pyridine, xylene, reflux 30 hours. [c] Raney Nickel, H_2, THF. [d] AcOH, EtOH, room temperature, 4 hours. [e] I_2, 1,2-dimethoxy ethane, 50°C, 16 hours. [f] Concentrated HCl, AcOH, H_2O, reflux, 4 hours. [g] EtOH, reflux, 12 hours. [h] $SOCl_2$, toluene, 80°C, 2 hours. [i] H_2, 5 % Pd/C, 2,6-lutidine, THF.

The original synthesis of UP 116-77 which was carried out on a laboratory scale [1,3a-c] involved 9 steps as depicted in Scheme I; the overall yield was 17%. The scale up of the process needed improved yield, more available starting materials and elimination of chromatographic purification. We would like to describe here a new process which makes the synthesis of UP 116-77 available on an industrial scale and offers an efficient method for the synthesis of imidazo[4,5-*b*]pyridine derivatives.

Chemistry.

The new synthesis of UP 116-77 was achieved in a 4-step procedure and is outlined in Scheme II. The first 3 steps were the same as those of the original synthesis, depicted in Scheme I but used new experimental conditions. The 2,5-dichloro-3-nitropyridine **2** was prepared by chlorination of 5-chloro-2-hydroxy-3-nitropyridine [4] with thionyl chloride and *N,N*-dimethylformamide at reflux for 2 hours. The condensation of 4-chlorobenzylamine with **2** was achieved by heating in toluene to 80° for 2.5 hours in the presence of sodium carbonate to afford the 2-(4-chlorobenzyl)amino derivative **3**. The latter was hydrogenated with Raney Nickel in methanol under 20 atmospheres of hydrogen to lead to diamino derivative **4**. The cyclization

Scheme II : Industrial process for the synthesis of UP 116-77



[a] $SOCl_2$ / DMF catalytic ; reflux 2 hours 15 minutes. [b] 4-chlorobenzylamine, Na_2CO_3, toluene, 80-85°C, 2 hours 30 minutes. [c] H_2 (20 atm), Raney Nickel, MeOH. [d] 3,3-dimethylglytaric anhydride, AcOH, reflux 8 hours 30 minutes.

step was carried out by reaction of the diamine **4** with 3,3-dimethylglutaric anhydride in refluxing acetic acid for 8 hours and afforded directly UP 116-77 without isolation of the 2-methyl derivative which could be expected as a side product by the reaction of the diamine **4** and acetic acid. The overall yield of this 4-step synthesis proceeding from 5-chloro-2-hydroxy-3-nitropyridine was 46%.

Discussion.

In the original synthesis [1] of UP 116-77 the cyclization of diamine **4** was performed by condensation with aldehyde **5** and subsequent oxidation with iodine (because attempts to make it by direct condensation with acid chloride **9** in ethanol and gaseous hydrochloric acid has failed) and led to ester **6** which had to be purified by chromatography and hydrolyzed to afford UP 116-77. These 2 steps were very critical for the overall yield since the yield was 26% and furthermore the synthesis of aldehyde **5** needed 3 additional steps proceeding from 3,3-dimethylglutaric anhydride (yield 43%). Therefore it was important to improve the yield of this cyclization step in order to make the synthesis suitable for an industrial process. In the method used herein (Scheme II) the cyclization was achieved by heating directly diamine **4** with 3,3-dimethylglutaric anhydride in acetic acid to reflux to afford UP 116-77 in one step with a 61% yield. Improvements have also been made in the first 2 steps. The use of thionyl chloride/DMF as the chlorinating agent and subsequent reaction of the 2,5-dichloro-3-nitropyridine (not isolated) with 4-chlorobenzylamine in toluene in the presence of sodium carbonate at 80-85° led to an increase in the yield of 11% for these 2 steps.

Conclusion.

The overall yield of the former synthesis of UP 116-77 was 17% in 9 steps. The process described herein needs 4 steps from 5-chloro-2-hydroxy-3-nitropyridine, the overall yield is 46% (first crop), the chromatographic purification of the ester **6** is avoided and the 3-step synthesis of the aldehyde **5** is no longer necessary. The cyclization step of the diamino derivatives such as **4** with various carboxylic acid anhydrides in acetic acid could be applied more widely to lead to 2-substituted imidazo[4,5-*b*]pyridine derivatives in good yields and by a simple process.

EXPERIMENTAL

The ^1H nmr spectra were measured at 200 MHz on a Bruker 200 spectrometer and recorded in deuteriochloroform or DMSO-d_6. Chemical shifts were reported in δ (ppm) units relative to the internal reference, tetramethylsilane. Melting points were recorded on an Electrothermal digital capillary melting point apparatus and are uncorrected. Elemental analyses were obtained by using a Carlo Erba Model 106 elemental analyser. The hplc experiments were performed on a Varian liquid chromatograph with an uv detector (λ = 260 nm) and a suitable integration system (C8 lichrosorb column).

Starting materials were commercially available or their preparation could be found in references [1,3a-c].

2-[(4-Chlorophenyl)methyl]amino-3-nitro-5-chloropyridine (**3**).

To a suspension of 20 g (0.114 mole) of 5-chloro-2-hydroxy-3-nitropyridine **1** [4] in 40 ml of thionyl chloride (0.547 mole, 4.8 equivalents) heated to reflux with stirring was added rapidly 1.6 ml (0.02 mole) of *N,N*-dimethylformamide. After 2 hours 15 minutes at reflux, the thionyl chloride was evaporated off under vacuum and 260 ml of toluene was added. The distillation of 80 ml of toluene allowed the elimination of the remaining thionyl chloride and the resulting solution was cooled to room temperature. To this solution was added 30.2 g (0.285 mole) of sodium carbonate, the mixture was stirred for 30 minutes under a nitrogen stream and a solution of 18.7 ml (0.154 mole) of 4-chlorobenzylamine in 20 ml of toluene was added. The mixture was heated to 80-85° for 2 hours 30 minutes and after cooling the

solid material was filtered off. The organic layer was washed with water, dried over magnesium sulfate and passed over 3S charcoal. The solvent was evaporated off under vacuum and the solid residue (40 g) was taken up with 120 ml of isopropyl alcohol. The mixture was refluxed for 1 hour and cooled, the crystals were collected by filtration, washed with isopropyl alcohol and dried to give 26 g (77%) of **3** as yellow crystals, mp 113°; ^{1}H nmr (deuteriochloroform): 4.78 (d, J = 5.7 Hz, 2H, NCH_2Ph), 7.3 (br s, 4H, PhCl), 8.37 (d, J = 2.3 Hz, 1H, H_b), 8.44 (d, J = 2.3 Hz, 1H, H_d), 8.6 (br t, J = 5.7 Hz, 1H, $NHCH_2$); hplc purity: 99.55%.

Anal. Calcd. for $C_{12}H_9Cl_2N_3O_2$: C, 48.35; H, 3.04; N, 14.09. Found: C, 48.50; H, 3.04; N, 14.13.

3-Amino-5-chloro-2-[(4-chlorophenyl)methyl]aminopyridine (**4**).

A suspension of 60 g (0.201 mole) of **3** in 400 ml of methanol was placed in a bomb and 6 g of Raney Nickel (washed with water, dilute hydrochloric acid and methanol) were added. The mixture was hydrogenated under 20 atmospheres of hydrogen for 6 hours 30 minutes. The catalyst was filtered off and the methanolic solution was dried over sodium sulfate and passed over 3S charcoal. The methanol was evaporated off under vacuum to give 52.9 g (98%) of **4** as grey crystals, mp 118°; ^{1}H nmr (deuteriochloroform): 3.1-3.5 (br s, 2H, NH_2), 4.35-4.5 (br s, 1H, NH), 4.54 (s, 2H, NCH_2Ph), 6.86 (d, J = 2.1 Hz, 1H, H_d), 7.28 (br s, 4H, PhCl), 7.68 (d, J = 2.1 Hz, 1H, H_b); hplc purity: 99.61%.

Anal. Calcd. for $C_{12}H_{11}Cl_2N_3$: C, 53.75; H, 4.14; N, 15.67. Found: C, 53.60; H, 4.07; N, 15.43.

4-[3-[(4-Chlorophenyl)methyl]-6-chloroimidazo[4,5-*b*]pyridin-2-yl]-3,3-dimethylbutanoic Acid (**UP 116-77**).

A mixture of 25 g (0.0932 mole) of diamine **4** and 14.6 g (0.102 mole) of 3,3-dimethylglutaric anhydride in 125 ml of acetic acid was refluxed for 8 hours 30 minutes with stirring under nitrogen atmosphere. The acetic acid was evaporated off under vacuum and 100 ml of toluene were added and distilled in order to eliminate the remaining acetic acid by azeotropic distillation (azeotrop E_{760} = 104°). The oily residue was taken up with 100 ml of toluene and stirred at room temperature for 4 hours. The solid material was collected, washed with 60 ml of tolulene and dried to give 30 g of a beige amorphous solid which upon recrystallization in 90 ml of 95% ethanol led to 22.3 g (61%) of UP 116-77 as white crystals, mp 138°; ^{1}H nmr (DMSO-d_6): 1.05 (s, 6H, $C(CH_3)_2$), 2.46 (s, 2H, CH_2CO_2H), 2.98 (s, 2H, CH_2), 5.56 (s, 2H, CH_2PhCl), 7.17 (d, J = 8.4 Hz, 2H, PhCl), 7.38 (d, J = 8.4 Hz, 2H PhCl), 8.24 (d, J = 2.1 Hz, 1H, H_d), 8.35 (d, J = 2.1 Hz, 1H, H_b), 10.8 (br s, 1H, CO_2H); hplc purity: 99.81%.

Anal. Calcd. for $C_{19}H_{19}Cl_2N_3O_2$: C, 58.17; H, 4.88; N, 10.71. Found: C, 58.30; H, 4.93; N, 10.65.

Concentration of ethanolic mother liquor to half its volume afforded an additional crop of 5 g (14%) of UP 116-77 analytically pure, mp 138°.

UP 116-77 was polymorphic and could be obtained as 3 different crystalline forms with mp of 106°, 124° and 138°, respectively. The use of ethanol as the recrystallization solvent allows us to obtain exclusively the most stable form, mp 138°.

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REFERENCES AND NOTES

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