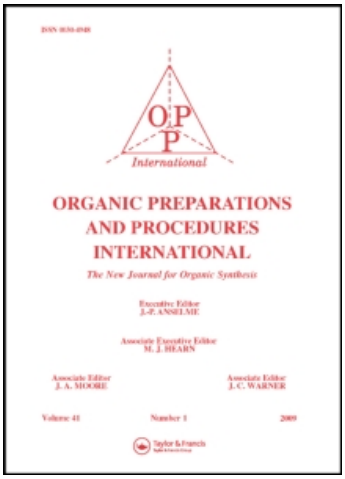

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A New Route for the Synthesis of Ozagrel Hydrochloride

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A New Route for the Synthesis of Ozagrel Hydrochloride

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(*E*)-3-[4-(1*H*-Imidazol-1-ylmethyl)phenyl]-2-propenoic acid hydrochloride (*ozagrel hydrochloride*) is a highly selective inhibitor of thromboxane A2 (TXA2). The beneficial effects of TXA2 inhibition by ozagrel include improved motor coordination after experimental stroke and antihypertensive effects in spontaneously hypertensive rats. Since 1988, ozagrel hydrochloride has been marketed as an antithrombotic drug in Japan.[1] Therefore, the development of an efficient synthetic method is of great interest.

The reported preparations of ozagrel hydrochloride involve the reaction of alkyl 4-bromomethylcinnamate with *N*-acetylimidazole[2] or with imidazole.[3] However, both the methods are costly as the result of either the price of the starting material in the case of *N*-acetylimidazole procedure and the low yield (34%) of the reaction in the imidazole method. We now describe a new cost efficient synthetic route to prepare ozagrel hydrochloride using low-priced reagents, under mild reaction conditions and in high overall yield.

Ozagrel hydrochloride was obtained through a three-step sequence starting from commercially available *p*-tolualdehyde by bromination with elemental bromine to afford 4-(bromomethyl)benzaldehyde **2** in 88% yield. Although bromine was selected as the brominating agent because of its lower price in China, the reaction works equally well (90% yield) by bromination with NBS which had to be used in the bromination of alkyl bromethylcinnamate because the use of bromine lead to reaction at the double bond.[4] The subsequent substitution of **2** with imidazole proceeded smoothly in 92% yield to give 4-(1*H*-imidazol-1-ylmethyl)benzaldehyde (**3**) in the presence of potassium carbonate instead of the much stronger base NaH.[3] The final condensation of **3** with malonic acid[5] in toluene followed by treatment with hydrochloric acid successfully provided ozagrel hydrochloride in 87% yield. The overall yields of ozagrel hydrochloride using bromine and NBS from **1** are 70% and 72%, respectively.

Although intermediates **2** and **3** were purified by chromatography in this article, in a larger scale preparation (30 g), the crude materials are sufficiently pure to be used in the

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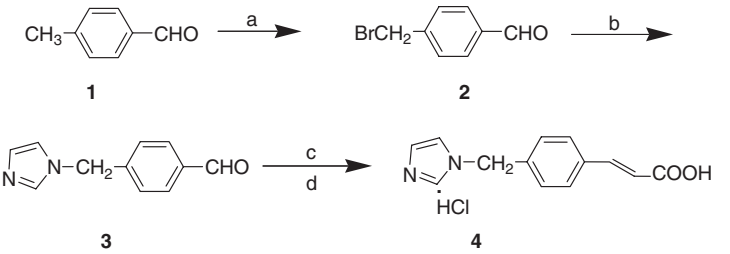

a. Br_2 or NBS/CCl_4/reflux; b. imidazole/K_2CO_3/$CHCl_3$ /rt;
c. $CH_2(COOH)_2/C_6H_5CH_3/C_5H_5N$; d. HCl/$H_2O$.

next steps without chromatography; the excess imidazole in the chloroform solution of **3** was removed by simple washing with water.

Experimental Section

Mps were determined on a Beijing XT-4 melting apparatus and are uncorrected. *p*-Tolualdehyde was purchased from Beijing Ouhe Technology Co. Ltd and the other chemical were obtained from Sinopharm Chemical Reagents Co. Ltd. All NMR experiments were performed on a 400 MHz Bruker Avance spectrometer in CDCl3 using TMS as an internal standard. IR spectra were recorded as potassium bromide pellets on a Bruker VERTEX-70 spectrometer.

4-(Bromomethyl)benzaldehyde using Bromine

To a three-necked flask equipped with a condenser, an addition funnel, compound **1** (2.40 g, 0.02 mol) and carbon tetrachloride (20 ml) were added. After the reaction mixture was heated to reflux, bromine (3.04 g, 0.019 mol) was added dropwise under the light irradiation. The hydrogen bromide generated in the reaction was absorbed in water. After refluxing for 2 h, carbon tetrachloride was removed by distillation (and recycled) and the resulting mixture was purified by chromatography (silica gel. 12/1 petroleum ether/ethyl acetate) to afford **2** (3.50 g, 88%) as a white solid, mp. 95–97°C, *lit.*[6] mp. 95–95.5°. ^{1}H-NMR ($CDCl_3$): δ 4.516 (s, 2H), 7.561 (d, 2H), 7.869 (d, 2H), 10.018 (s, 1H). IR: 3085 cm^{-1}, 1695 cm^{-1}, 1532 cm^{-1}, 675 cm^{-1}.

4-(Bromomethyl)benzaldehyde using NBS

Compound **1** (2.40 g, 0.02 mol), benzoyl peroxide (0.05 g, 0.21 mmol) and carbon tetrachloride (20 ml) were mixed and heated to reflux. NBS (3.56 g, 0.02 mol) was added in 1 h and then refluxed for 2 h. After the reaction was complete, succinimide was collected by filtration, and carbon tetrachloride was removed by distillation (and recycled) and the resulting mixture was purified by chromatography (silica gel. 12/1 petroleum ether/ethyl acetate) to afford **2** (3.58 g, 90%) as a white solid, mp. 96–97°C.

4-(1H-Imidazol-1-ylmethyl)benzaldehyde (3)

To a well-stirred mixture of **2** (2.99 g, 0.015 mol) and potassium carbonate (4.15 g, 0.03 mol) in chloroform (25 ml) was added imidazole (2.18 g, 0.032 mol) and stirred for 2 h at room temperature. The solid was colletedand chloroform was removed by distillation (and recycled). The resulting crude product was purified by chromatography (silica gel, ethyl acetate) to afford **3** (2.57 g, 92%) as a colorless oil, bp. 149–151°C/0.2 mm, *lit.*[7] bp. 150°C/0.2 mm. ^{1}H-NMR ($CDCl_3$): δ 5.247 (s, 2H), 6.956 (s, 1H), 7.098 (d, 1H), 7.296 (d, 2H), 7.60 (s, 1H), 7.850 (d, 2H), 9.980 (s, 1H). IR: 1695 cm^{-1}, 1638 cm^{-1}, 1515 cm^{-1}.

Ozagrel Hydrochloride (4)

To a solution of **3** (1.86 g, 0.01 mol) in toluene (10 ml) was added malonic acid (2.08 g, 0.02 mol) and pyridine (10 ml). The mixture was heated at 95°C for 2 h. The mixture was cooled to room temperature and then 10 ml (5 mol/L) hydrochloric acid was added to give a white precipitate which was collected and recrystallized from ethanol to give pure **4** (2.30 g, 87%) as a white solid, mp. 215–217°C, *lit.*[3] mp. 214–217°C. ^{1}H-NMR (D_2O): δ 5.291 (s, 2H), 6.255 (d, 1H), 7.241 (d, 2H), 7.370 (d, 1H), 7.432 (d, 2H), 7.451 (m, 2H), 8.677 (s, 1H). IR: 3000–2250 cm^{-1}, 1688 cm^{-1}, 1600 cm^{-1}.

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