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Research Paper

An Alternate Synthesis of 5-Hydroxymethylthiazole: A Key Intermediate of Ritonavir

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Abstract: Zinc mediated synthesis of 5-hydroxymethylthiazole (5-HMT) **1**, one of the key intermediates of Ritonavir **2**, is described.

Introduction

Thiazole derivatives are the integral part of several biologically active molecules.[1] In particular, 5-hydroxymethylthiazole (5-HMT) **1** serves as one of the key intermediates of Ritonavir **2**, a well known protease inhibitor (PI) drug as shown in Figure 1. Ritonavir **2**, along with Lopinavir **3**, has successfully been used for the management of AIDS.[1g]

Industrially compatible hitherto known synthesis of 5-HMT[2] is short but expensive as it involves Pd as a dehalogenating metal.

The synthesis starts with the reaction of 2-chloro-5-chloromethylthiazole **4** and sodium formate followed by hydrolysis gave 2-chloro-5-hydroxymethyl-thiazole **5**, which upon dehalogenation with hydrogen and palladium on carbon afforded the desired molecule **1** as shown in Scheme 1.

Result and discussions

In our endeavor, the synthesis involves the reaction of 2-chloro-5-chloromethylthiazole **4** with water at 80-85 °C to result the 2-chloro-5-hydroxymethyl thiazole **5**. This transformation completely avoids the use of sodium formate (reagent) and heptanes as a solvent as shown in Scheme 1. The intermediate **5**, without isolation, was subjected with zinc instead of $Pd/C/H_2$ (Scheme 1) in presence of HCl to afford 5-

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hydroxymethyl thiazole **1**. There are few reports that disclose the use of Zn but most of them is not very efficient from process stand point.[3] 5-HMT was further allowed to react with p-nitrophenyl chloroformate in dichloromethane solvent and a base to afford5-(*p*-nitrophenyloxy carbonyloxymethyl) thiazole hydrochloride salt **6** as a reactive species amenable to use in the synthesis of Ritonavir **2**.

Water quantity for substitution was optimized and it was found to be 12 volumes. In case of less than 12 volumes of water, we observed certain quantities of dimeric ether that have been formed along with an unidentified polymeric species. Initial screening reveals that 1 to 1.29 equivalent of Zinc is not enough for reductive dehalogenation reaction to afford the title compound **1** in excellent yield therefore we optimized the transformation by employing 1.95 eq. of Zinc that afforded the product in 87% yields (two steps). Quantity of HCl in this transformation was also optimized. The optimal quantity of HCL for the completion of the reaction was found to be 1.04 eq.

In particular, a solution of 2-chloro-5-chloromethylthiazole **4** in water was stirred at 80-85 °C for 2.5 h. After the completion of reaction (TLC), the reaction mass was cooled to 40 °C and Zinc was added in 2 lots followed by drop wise addition of HCl. After the stirring for 4-5 h (TLC shows completion of reaction), reaction mass was cooled to 20-30 °C and pH was adjusted slowly to 8-9 by using Na_2CO_3. Unwanted solid (possibly it could be the mixture of sodium chloride and zinc chloride) was filtered and washed with ethanol. Filtrate was distilled under vacuum at 70-80 °C and residue was diluted with ethanol and stirred for 30 min. Precipitated solid was filtered once again and washed with ethanol. Filtrate was distilled under vacuum at 60-70 °C and the residue was dissolved in ethyl acetate and distilled under vacuum at 60-70 °C. This exercise was performed to remove the residual amount of ethanol. Finally, the residue was dissolved in dichloromethane, dried over sodium sulphate, stirred for 45-60 min, filtered, washed with dichloromethane and concentrated under vacuum at 35-45 °C to afford 5-HMT **1** as brown color liquid in 87% yield and 96% HPLC purity.

Subsequently, 5-HMT **1** was activated with 4-nitrophenyl chloroformate by using dichloromethane as a solvent and triethylamine as a base. In particular, A solution of 4-nitrophenyl chloroformate in dichloromethane was added slowly in 30-40 min at -5 to 0 °C to a solution 5-HMT **1** in dichloromethane. After stirring for 3-4 h at 0-5 °C (Initially by HPLC thereafter, TLC method was adopted) pH was slowly adjusted to 2 with 5 % HCl. After additional stirring for 15-20 min, organic layer was separated and washed with 15% $NaHCO_3$ solution, dried over sodium sulphate, filtered and concentrated under vacuum at 35 °C. Residue was dissolved in ethylacetate:ethanol (3:1) and dry HCl gas was bubbled for 30-40 min. along with stirring at pH < 2. After stirring for 2-3 h, the solid was filtered and washed with ethylacetate, dried at 45-50 °C under vacuum for 4-5 h to obtain **6** as pale yellow color solid in 70% yield and 95% HPLC purity. We screened few conventional solvents e.g. EtOAc, toluene apart from dichloromethane in reaction as well as in extraction. Dichloromethane afforded best yield and purity.

Experimental Section

Solvents and regents were used for all the reactions as received. ^{1}H NMR spectra were recorded on a Varian Mercury spectrometer at 200 or 400 MHz. The proton signal of residual, non-deutrated solvents (δ 7.26 for

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$CDCl_3$, 2.2 ppm for DMSO-*d6*) was used as an internal reference for ^1H NMR. Infrared (IR) spectra were recorded as thin films on a Mattson Galaxy Series FTIR 3000 spectrometer referenced to polystyrene standard.

Synthesis of 5-hydroxymethylthiazole (5-HMT), 1

A solution of 2-chloro-5-chloromethylthiazole **4** (100 g, 0.59 mol) in water (1200 mL) was stirred at 80-85 °C for 2.5 h. After the completion of reaction (TLC), the reaction mass was cooled to 40 °C and Zinc was added in 2 lots (lot; 1: 20 g, 0.30 mol; and lot; 2: 55 g, 0.846 mol) followed by drop wise addition of HCl (75 mL). After the stirring for 4-5 h (TLC shows completion of reaction), reaction mass was cooled to 20-30 °C and pH was adjusted slowly to 8-9 with Na_2CO_3 (225 g). Unwanted solid was filtered and washed with ethanol (300 mL). Filtrate was distilled completely under vacuum at 70-80 °C and residue was diluted with ethanol (700 mL) and stirred for 30 min. Precipitated solid was filtered once again and washed with ethanol (300 mL). Filtrate was distilled completely under vacuum at 60-70 °C and the residue was dissolved in ethyl acetate (200 mL) and distilled completely under vacuum at 60-70 °C. Finally, the residue was dissolved in dichloromethane (500 mL), dried over sodium sulphate (30 g), stirred for 45-60 min, filtered, washed with dichloromethane (200 mL) and concentrated completely under vacuum at 35-45 °C to afford 60 g of 5-HMT **1** as brown color liquid in 87% yield and 96% HPLC purity. Spectroscopic data were found in agreement with the values reported in the literature.[2]

Synthesis of 5-(*p*-nitrophenyloxycarbonyloxymethyl)thiazole hydrochloride salt, 6

To a solution of 5-HMT, 1 (20 g, 0.174 mol) in dichloromethane (200 mL), was added triethylamine (29 mL, 0.208 mol) at 25 °C. A solution of 4-nitrophenyl chloroformate (38.5 g, 0.191 mol) in dichloromethane (300 mL) was added slowly in 30-40 min at -5 to 0 °C. After stirring for 3-4 h at 0-5 °C (TLC shows completion of reaction) pH was slowly adjusted to 2 with 5 % HCl (100 mL). After additional stirring for 15-20 min, organic layer was separated and washed with 15% $NaHCO_3$ solution (150 mL), dried over sodium sulphate, filtered and concentrated under vacuum at 35 °C. Residue was dissolved in ethylacetate:ethanol (120 mL:40 mL) and dry HCl gas was passed for 30-40 min. along with stirring (pH < 2). After stirring for 2-3 h, the solid was filtered and washed with ethylacetate (60 mL), dried at 45-50 °C under vacuum for 4-5 h to obtain 38.5 g of **6** as pale yellow color solid in 70% yield and 95 % HPLC purity. Spectroscopic data were found in agreement with the values reported in the literature.[4]

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Figure 1. Structures of 5-HMT, Ritonavir and Lopinavir

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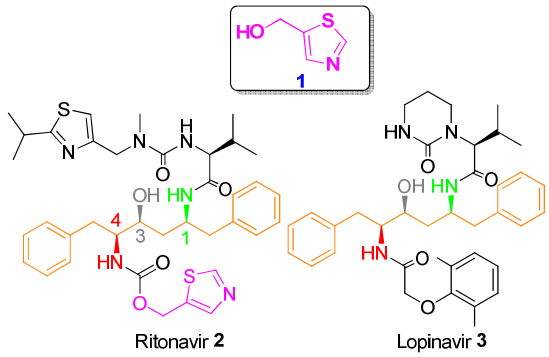
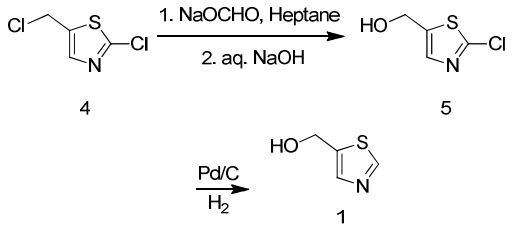
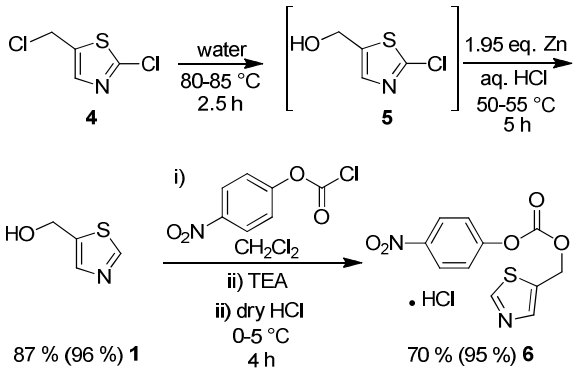


Scheme 1. Precedented approach for the synthesis of **1**



Scheme 2. Novel approach for the synthesis of 5-HMT **1** and its derivative **6**



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