Large-Scale Synthesis of (*E*)-4-Amino-2-Methylbut-2-en-1-ol: Key Building Block for the Synthesis of *trans*-Zeatin

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In this paper a large-scale synthesis of (*E*)-4-amino-2-methylbut-2-en-1-ol was disclosed and *trans*-zeatin could be accessed on industrial scale.

Keywords: (*E*)-4-Amino-2-methylbut-2-en-1-ol, *trans*-Zeatin, Large-scale synthesis.

INTRODUCTION

(*E*)-4-Amino-2-methylbut-2-en-1-ol is the structural unit of natural products such as Cytokinins *trans*-zeatin[1,2] and 9-(2-deoxy-β-D-ribofuran-osyl)-*trans*-zeatin[3]. Isolated from immature sweet corn (Zea mayes) kernels, *trans*-zeatin shows as the most active cytokinin. To our best of knowledge, *trans*-zeatin is currently an expensive commercial cytokinin in the market, which is attributed to the difficulty of affording key building block (*E*)-4-amino-2-methylbut-2-en-1-ol on industrial scale. Although numerous procedures for the synthesis of (*E*)-4-amino-2-methylbut-2-en-1-ol have been reported[4-13], those experimental procedures are not suitable for scale-up. Additionally, toxic or expensive reagents were involved in those protocols. Jordis *et al.*[14] reported an optimized synthesis of some γ,γ-disubstituted allylamine, however raw material is expensive and not suitable for commercial purpose. We herein report a practical large-scale synthesis of (*E*)-4-amino-2-methylbut-2-en-1-ol and with this key intermediate, *trans*-zeatin could be accessed on industrial scale.

EXPERIMENTAL

Solvents and reagents were obtained from commercial sources without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400-MHz spectrometer using CDCl$_3$ or DMSO-D$_6$ as solvent. Melting points were determined on WRS-2 melting-point apparatus (Shanghai, China) and uncorrected.

Synthesis of 1-[(*E*)-4-bromo-3-methyl-2-butenyl]-1-azonia-3,5,7-triaza-tricyclo [3.3.1.1]decane bromide (2): To a solution of (*E*)-1,4-dibromo-2-methylbut-2-ene (**1**) (4 kg, 17.5 mol) in dichloromethane (32 L) was added hexamethylene-tetramine (2.46 kg, 17.5 mol) at 0 °C, and the mixture was allowed to warm to room temperature. It was stirred overnight and filtered. The obtained white solid was dried to give **2** (5.22 kg, 92 % yield). It was directly applied to next step.

Synthesis of (*E*)-*tert*-butyl 4-hydroxy-3-methylbut-2-enylcarbamate (4): To a solution of **2** (4 kg, 12.4 mol) in methanol (10 L) was added concentrated hydrochloric acid (6 L, 29 mol) carefully, and the mixture was heated to reflux for 2 h. The resulting solution was cooled down to 0 °C, and then filtered. The filtrate was concentrated to half of its volume, cooled down to 0 °C again and filtered. The filtrate was concentrated to dryness to give 3 kg of **3** as a colourless oil.

To a solution of sodium carbonate (4.82 kg, 37.2 mol) and Boc anhydride (2.7 kg, 12.4 mol) in ethyl acetate (16 L) and water (24 L) was added dropwise the above obtained **3** (3 kg) in ethyl acetate (4 L) at 0 °C, and then the mixture was allowed to warm to room temperature. It was stirred overnight and the water phase was extracted with ethyl acetate. Combined organic phase was washed with brine and dried over Na$_2$SO$_4$. It was evaporated to give 2.7 kg of *N*-Boc protected derivative of **3** as a colorless oil.

To a solution of the above obtained colorless oil in 95 % ethanol (15 L) was added sodium acetate (1.52 kg, 18.6 mol), and the reaction mixture was refluxed for 4 h. The resulting solution was cooled down to room temperature and 20 % aqueous solution of sodium hydroxide (34 L, 19.6 mol) was added into the reaction mixture, which was refluxed for 2 h, and then evaporated. The resulting residue was layered with ethyl acetate (10 L) and water (10 L), and water phase was extracted with ethyl acetate (3 × 10 L). The combined organic

phase was washed with saturated solution of sodium bicarbonate and brine, dried over Na_2SO_4. The filtrate was concentrated to give 2.5 kg of **4**. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.41 (s, 9H), 1.66 (s, 3H), 3.70-3.76 (m, 2H), 3.97 (s, 2H), 5.43 (t, *J* = 8Hz, 1H). ^{1}H NMR spectral data were consistent with described[9].

Synthesis of (*E*)-4-amino-2-methylbut-2-en-1-ol (5): To a solution of 2.5 kg of **4** in dichloromethane (3.5 L) was added trifluoroacetic acid (1.4 kg, 12.4 mol). The mixture was stirred for 2 h and then neutralized with sodium hydroxide, concentrated. The residue was distilled over high vaccum (0.01 mmHg) at 60 °C to give 751 g of **5** as a colourless oil in 60 % yield. ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.63 (s, 3H), 3.30 (t, *J* = 8 Hz, 2H), 3.95 (s, 2H), 5.49 (t, *J* = 8 Hz, 1H). ^{1}H NMR spectral data were consistent with described[7].

Synthesis of *trans*-zeatin: To a solution of 6-chloropurine (656 g, 4.25 mol) and triethylamine (516 g, 5.1 mol) in butyl alcohol (1.8 L) was added **5** (430 g, 4.25 mol). The reaction mixture was heated to reflux for 4 h, and cooled down to room temperature slowly. The solvent was evaporated and the residue was twice recrystallized with water and ethanol to give 661 g of *trans*-zeatine as a white solid in 71 % yield with 99 % HPLC purity. m.p. 208-209 °C. ^{1}H NMR (400 MHz, DMSO-*d$_6$*) δ: 1.64 (s, 3H), 3.33 (s, 2H), 4.09 (br, 1H), 4.73 (br, 1H), 5.51 (t, *J* = 8 Hz, 1H), 7.70 (br, 1H), 8.06 (s, 1H), 8.16 (s, 1H), 12.84 (br, 1H). ^{1}H NMR spectral data were consistent with described[7].

RESULTS AND DISCUSSION

Recently Madhusudhan *et al.*[15] discovered that hexamethylenetetramine, a bulky amine, could be applied to large-scale synthesis of (*Z*)-4-chlorobut-2-en-1-amine hydrochloride starting from (*Z*)-1,4-dichlorobut-2-ene. The substitution of (*Z*)-1,4-dichlorobut-2-ene with hexamethylenetetramine in dichloromethane under refluxing gave mono-amination salt in nearly quantitative yield, and the formed salt has very low solubility in reaction solvent, which prevented the further substitution. Different from (*Z*)-1,4-dichlorobut-2-ene, (*E*)-1,4-dibromo-2-methylbut-2-ene has more reactive bromide group and methyl group marks *E*-1,4-dibromo-2-methylbut-2-ene as an un-symmetric unit, which results in regio-selective amination involved. Initially, we refluxed (*E*)-1,4-dibromo-2-methylbut-2-ene and hexamethylenetetramine in dichloromethane (**Scheme-I**). Unfortunately, we obtained a complex mixture. Further, the reaction mixture was stirred at ambient temperature. A white solid **2** was obtained in 92 % yield. Further

solvent optimization such as chloroform (85 % yield), toluene (60 % yield) and dichloroethane (80 % yield) was explored. Thus far, dichloromethane gave best yield. Interestingly, we only obtained one isomer **2**, and another isomer **2'** was not detected.
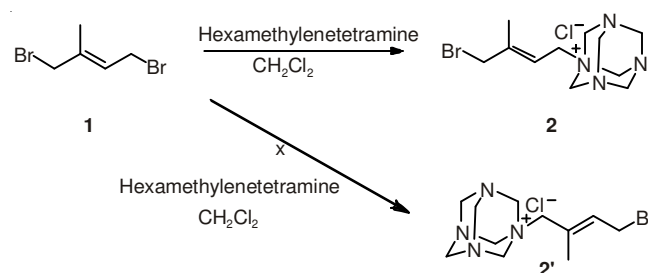
Scheme-I: Regioselective amination *via* **1** and hexamethylenetetramine

Using delepine reaction condition compound **2** was converted to compound **3**, which was subjected to *N*-Boc-protection, subsequent acetoxylation and hydroxylation to give compound **4**. De-protection of compound **4** with trifluoroacetic acid and distillation under vacuum gave (*E*)-4-amino-2-methylbut-2-en-1-ol (**5**) in 60 % overall yield (**Scheme-II**).
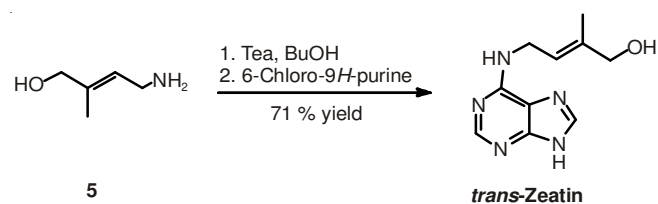

Scheme-III: scale-up synthesis of *trans*-zeatin

Furthermore, (*E*)-4-amino-2-methylbut-2-en-1-ol (**5**) was coupled with 6-chloropurine to give > 99 % purity of *trans*-zeatin in 71 % yield after twice recrystallization (**Scheme-III**).

Eventually, *trans*-zeatin was prepared in 39 % overall yield starting from *trans*-1,4-dibromo-2-methylbut-2-ene and hexamethylenetetramine.

In conclusion, we developed an efficient large-scale preparative method for (*E*)-4-hydroxy-3-methylbut-2-enyl. *trans*-Zeatin could be accessed on industrial scale, based on readily available starting material, operational simplicity and good yield.
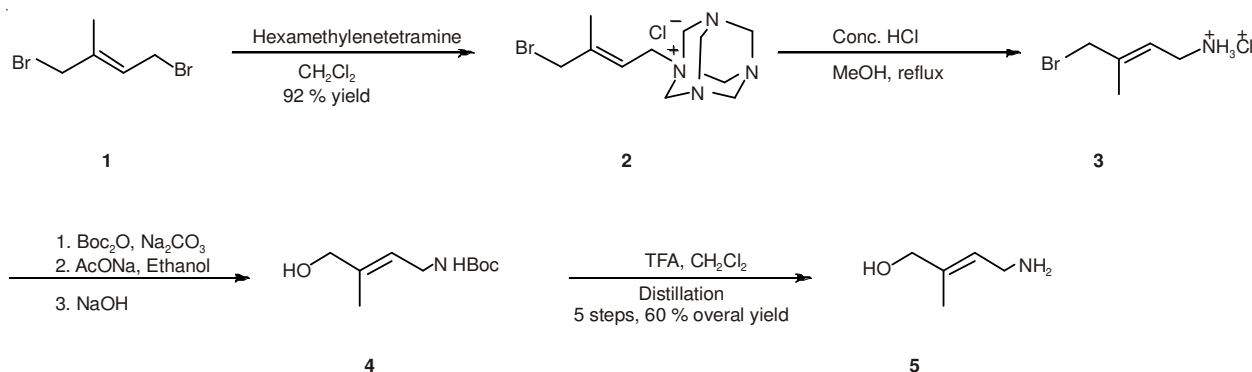
Scheme-II: Large-scale synthetic route of (*E*)-4-amino-2-methylbut-2-en-1-ol

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