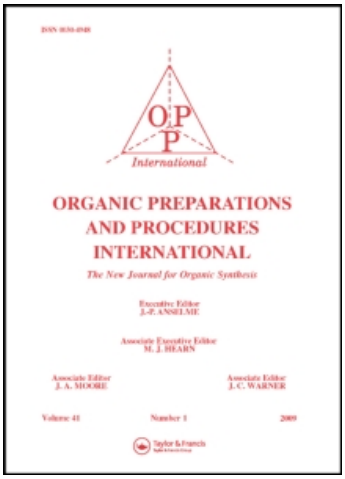

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AN EXPEDITIOUS, PRACTICAL LARGE SCALE SYNTHESIS OF 4-AMINO-2-CHLORO-6,7-DIMETHOXYQUINAZOLINE

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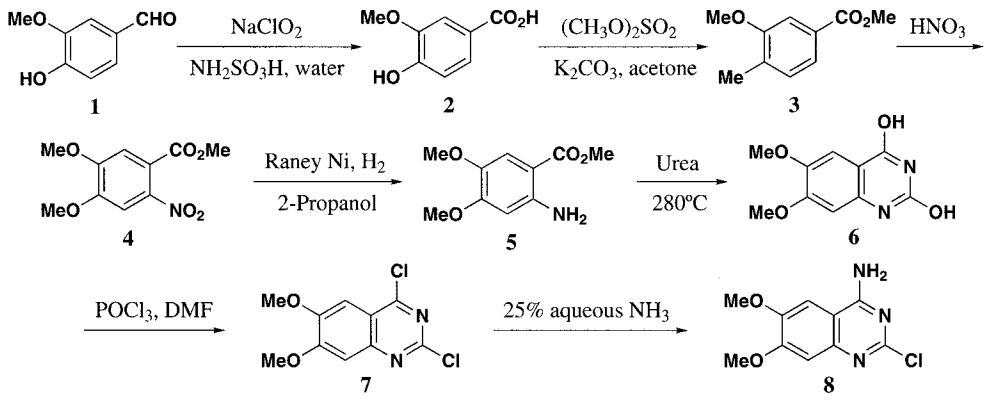
Quinazolines bearing various substituents are receiving significant attention because of their various biological properties.[1] Important drugs of the quinazoline family in current use for the treatment of hypertension are prozocin, doxazocin, tetrazocin, bunazocin, neldazocin, metazocin, and alfuzocin. 4-Amino-2-chloro-6,7-dimethoxyquinazoline (**8**) is a common precursor for these generic antihypertensive drugs. Publications[2] and subsequent patent[3] information for the preparation of 4-amino-2-chloro-6,7-dimethoxyquinazoline (**8**) involve the reaction of substituted anthranilic acid or its amide with a suspension of sodium cyanate followed by the treatment either with alkali or acid gives substituted 2,4-dihydroxyquinazoline **6**. Reaction of **6** with phosphorus pentachloride and phosphorus oxychloride at reflux led to 2,4-dichloro-6,7-dimethoxyquinazoline (**7**), which is converted to **8** by treatment with anhydrous ammonia at ambient temperature in dilute THF.

In connection with our process development of (±)-doxazocin mesylate,[4] we had an opportunity to evaluate the synthesis of **8**. Three major challenges were encountered in course of reproducing the above synthetic route: (i) oxidation of vanillin (**1**) to vanillic acid (**2**) using traditional methods such as KOH melt[5] or silver oxide[6] gave a product contaminated with unreacted starting material or over-oxidized impurities, (ii) the conversion of methyl 2-aminoveratrate (**5**) to 2,4-dihydroxy-6,7-dimethoxyquinazoline (**6**) using sodium cyanate under acid conditions resulted in the required product along with 20-40% of 3,4-dimethoxyisatoic anhydride. Furthermore, the reproducibility of results became problematic, (iii) the conversion of 2,4-dichloro-6,7-dimethoxyquinazoline **7** to **8** require the use of large volume of anhydrous tetrahydrofuran with a constant flow of anhydrous ammonia for a period of 42 h[3a]. Even then, the resulting product was contaminated with 10-15% unreacted starting material. Extensive efforts for further purification by crystallization gave final product in poor yield (50%).

In view of these findings, we now report an alternative, reliable route for the synthesis of 4-amino-2-chloro-6,7-dimethoxyquinazoline (**8**) as shown below.



Among several reagents investigated for the oxidation of vanillin (**1**),[7] we found that sodium chlorite-sulfamic acid in water afforded vanillic acid (**2**) in 83% yield with only a 2-3% of starting material impurity (by NMR).[8] Treatment of the crude product with dimethyl sulfate in the presence of anhydrous potassium carbonate in refluxing acetone gave a solid material, which upon nitration and the usual work-up led to pure methyl 2-nitroveratrate (**4**) in 90% yield (two steps). The nitro group was reduced over Raney Ni in 2-propanol at 70 psi H_2 pressure to yield **5** (80%).[9] Reactive distillation of **5** and urea in a 1:3 mole ratio by slow increase of the temperature of a sand bath from 0 to 280°C over 2 h. The solid material obtained was treated with 10% NaOH aqueous solution and allowed to stand 4-5 h, then acidified to pH 4, gave the crude product **6** (> 100%). After considerable experimentation, **6** was converted to **7** in 75% yield by reflux in a mixture of DMF and phosphorus oxychloride. Though in most instances, reactions involving phosphorus oxychloride are performed in combination with PCl_5 or *N,N*-dimethyl-anilline, in our case DMF gave good yield of product **7**. Amination of **7** was achieved using aqueous ammonia (25%) and THF as a co-solvent,[10] at ambient temperature, to lead to compound **8** in 90% yield with purity of 98.5%.

The results presented above have the following advantage and worthwhile to mention the salient features of this process. a) The oxidation of aldehyde (**1**) to acid **2** is complete in 90 min. and the reaction may be performed in an open vessel in aqueous medium. Furthermore, in a modification to the original procedure,[8] we have not only reduced amount of water but also used the same water for a subsequent batch without the need of additional sulfamic acid; there was no effect on the yields and/or purity of the product. The condensation of methyl 2-aminoveratrate with urea is a facile and high yield reaction which proceeds without any solvent acid-base control. The amination was carried out in aqueous ammonia using aqueous medium, thus avoiding costly anhydrous solvents and special cooling apparatus to maintain sub-zero temperatures. With the exception of methyl 2-aminoveratrate which was crystallized before use in the

subsequent step, crude products were used in all the steps. Thus, an expeditious, practical and economically viable route without rigorous purification of intermediate products, has been developed from compound **1** to compound **8** in 45% overall yield.[11]

EXPERIMENTAL SECTION

Mps were determined on an electrothermal-9100 Melting Point Apparatus and are uncorrected. Commercial reagent grade solvents were used. ^{1}H NMR were recorded on a Gemini 200 MHz Varian or Bruker 300 MHz. Mass spectra were obtained on a VG-AUTOSPEM.M (FAB) and VG-70704 (EI) instrument. HPLC analysis was performed using SHIMADZU-LC 10AVP APP instrument. YMC ODS 25cms, 5m column was used. A 50:50 mixture of acetonitrile and methanol (modified with 0.05% v/v triethylamine in water) at a flow rate of 1 mL min^{-1} was used as the mobile phase. The detection wavelength was 254 nm.

Synthesis of Vanillic Acid (2).- A 10 L cylindrical, vertical, jacketed glass reactor fitted with a stirrer was charged with vanillin (200 g, 1.31 mol), sulfamic acid (177 g, 1.82 mol) and 5 L of water. The reaction mixture was stirred at room temp. Sodium chlorite (148 g, 1.64 mol) dissolved in 1 L of water was added dropwise to the stirred mixture over a period of 1 h. After half of the addition, the reaction mixture became homogeneous and precipitation immediately started. Stirring was continued for an additional 30 min. The solid product was collected, washed with ice-cold water (2 x 1 L) and dried to afford 183 g (83%) of colorless solid, mp. 205-208°C, *lit.*[8] 205-207 °C.

^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.95 (s, 6H), 6.82 (m, 1H), 7.54 (m, 2H), 9.79 (broad s, 1H); Mass: m/z: 168 (M^+) , 153, 125, 97, 81, 44.

Synthesis of Methyl Veratrate (3).- A 3 L round-bottom flask fitted with a stirrer, condenser and a thermowell was charged with vanillic acid (170 g, 1.01 mol), potassium carbonate (291 g, 2.1 mol) and 1.4 L of acetone. Dimethyl sulfate (256 g, 2.0 mol) was added dropwise over a period of 1 h, to the stirred mixture. After addition was complete, the reaction mixture was heated at reflux for 2 h, cooled, and the solid was collected. The filter cake was washed with additional acetone (2 x 100 mL). The combined filtrate was evaporated *in vacuo* to give a white solid (195 g, mp. 57-58°C which was subjected to next step without purification.

^{1}H NMR ($CDCl_3$): δ 3.85 (s, 6H), 3.95 (s, 3H), 6.80 (d, J = 5.6Hz, 1H), 7.50 (s, 1H), 7.60 (d, J = 5.8 Hz, 1H); Mass: m/z: 196 (M^+) , 165, 153, 125, 79, 51.

Synthesis of Methyl 2-Nitroveratrate (4).- A 3 L round-bottom flask, fitted with a stirrer and thermowell, was charged with nitric acid (1050 mL), and cooled to 0 to –5°C. Methyl veratrate (190 g, 0.97 mol) was added portionwise over a period of 40 min. The temperature was maintained –5 to 0°C. The reaction mixture allowed to stir an additional 30 min. and the entire contents were poured onto crushed ice with vigorous stirring. The precipitated solid was collected and dried to give 213 g (91%, purity 98% by HPLC) of a yellow solid, mp.140-141°C, *lit.*[2a] 143°C.

^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H), 3.92 (s, 6H), 7.02 (s, 1H), 7.40 (s, 1H); Mass: m/z 241 (M^+), 210, 195, 181, 136, 77.

Synthesis of Methyl 2-Aminoveratrate (5).- Methyl 2-nitroveratrate (190 g, 0.788 mol), Raney Ni (38 g) and 2-propanol (500 mL) were added to a 2 L autoclave, and hydrogenated at 6 kg/cm^2 at 70°C. After hydrogen absorption had ceased, the reaction mixture was cooled to room temperature and the catalyst was filtered off, and washed with hot 2-propanol (2 x 100 mL). The combined filtrates were cooled in an ice-bath and the precipitated solid was collected (1st crop product). Further, the filtrate was evaporated to one-fourth of its volume, cooled and the precipitated solid was collected (2nd crop product). The combined yield of the product was 125 g (80%, purity 97.5% by HPLC) of purple color solid, mp. 127-129°C, *lit.*[2a] 128-130°C.

^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H), 3.95 (s, 6H), 5.58 (broad s, 1H), 6.07 (s, 1H), 7.21 (s, 1H); Mass: m/z 211 (M^+), 210, 196, 180, 164, 136, 94.

Synthesis of 2,4-Dihydroxy-6,7-dimethoxyquinazoline (6).- Methyl 2-aminoveratrate 110 g (0.52 mol) and urea 94.5 g (1.57 mol) were added to a 1 L round-bottom flask fitted with a stirrer and a condenser. The reaction mixture was heated to 120°C and the solid mixture started to melt. The sand bath temperature was gradually increased to 280°C with stirring over a period of 40 min. During this time methanol was distilled off, and stirring was discontinued after solidification began. After cooling to room temperature, 20% aqueous NaOH solution (200 mL) was added and allowed to stand 4 h. The suspension was then transferred into a beaker. The stirred mixture was acidified to pH 5-6 using acetic acid. The resulting precipitate was collected and washed with water and ethanol, followed by air-dried overnight to give 116 g of light brown solid, mp. 320-324°C, *lit.*[2a] 323-325°C.This was subjected to the next step without purification.

^{1}H NMR (DMSO-d_6): δ 3.00 (broad s, 2H), 3.95 (s, 6H), 6.30 (s, 1H), 7.80 (s, 1H); Mass: m/z 222 (M^+), 207, 179, 164, 136, 108, 93, 77.

Synthesis of 2,4-Dichloro-6,7-dimethoxyquinazoline (7).- Into a 1 L round-bottom flask fitted with a stirrer, condenser and thermowell were added 2,4-dihydroxy-6,7-dimethoxyquinazoline (100 g, 0.45 mol), $POCl_3$ (300 mL) followed by DMF (10 mL). The combined reaction mixture was heated to reflux for 8 h. Excess $POCl_3$ (200 mL) was distilled off and the liquid residue was poured onto stirred crushed ice. The resulting precipitate was collected, washed with water, and dried. The crude product was crystallized from toluene to give 87 g (75%, purity 98% by HPLC) of cream-colored solid, mp.157-159°C, *lit.*[2a] 158°C.

^{1}H NMR ($CDCl_3$): δ 4.02 (s, 6H), 7.21 (s, 1H), 7.28 (s, 1H); Mass: m/z 258 (M^+), 215, 168, 153, 95.

Synthesis of 4-Amino-2-chloro-6,7-dimethoxyquinazoline (8).- 2,4-Dichloro-6,7-dimethoxyquinazoline (85 g, 0.329 mol), and THF (500 mL) were added to a 5 L round-bottom flask provided with a stirrer. The reaction mixture was stirred 1 h at ambient temperature and then ammonium hydroxide (1765 mL, 25%) was added and the mixture was stirred for 24 h. The precipitated product was collected and washed with water (2 x 400 mL). The dried colorless

solid, weighed 71 g (90%, purity 97.8% by HPLC), mp. 300°C (dec.), *lit.*[3a] 302°C.

^{1}H NMR (DMSO-d_6): δ 2.95 (s, 6H), 4.50 (s, 2H), 7.02 (s, 1H), 7.50 (s, 1H); Mass: m/z 239 (M^+), 224, 204, 196, 160, 135, 104, 92.

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9. Reduction on 5% Pd-C gave 10% higher yield of **5**. To the best of our knowledge there is no report in literature using Raney Ni for the reduction of methyl 2-nitro-3,4-dimethoxy benzoate **4**.

10. MeOH and dioxane were also evaluated as co-solvent and found to be inferior to THF.

11. Although compound **8** (96% pure), mp. 260°C, is commercially available from Aldrich at $245/25 g, we estimate the total cost of producing it by the present route to be $2,000/kg.

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