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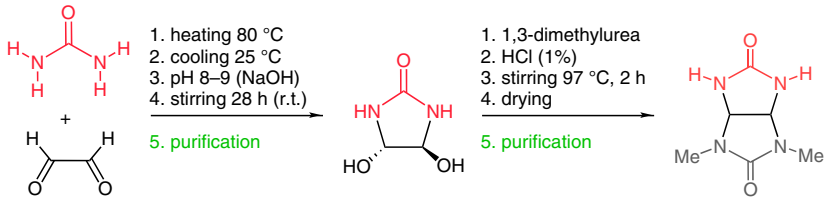
Easy Synthesis of *trans*-4,5-Dihydroxy-2-imidazolidinone and 2,4-Dimethylglycoluril

Henrique D. Correia
Renato S. Cicolani
Raphael F. Moral
Grégoire J. F. Demets*

Departamento de Química, Faculdade de Filosofia Ciências e Letras de Ribeirão Preto, Universidade de São Paulo, Av. Bandeirantes 3900, CEP 14040-901, Ribeirão Preto S. P., Brazil
greg@usp.br



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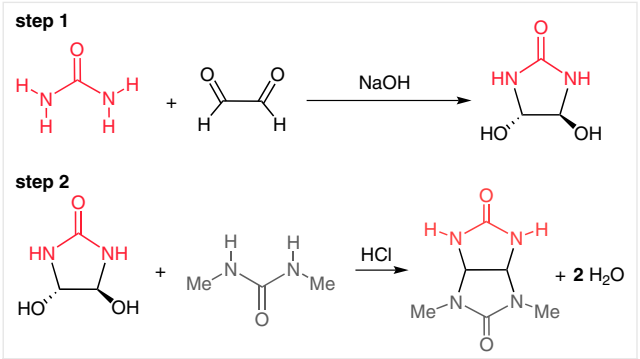
Abstract A simple and efficient synthesis of 2,4-dimethylglycoluril involving the formation of *trans*-4,5-dihydroxy-2-imidazolidinone is presented as well as a reproducible protocol to reduce contamination with its decomposition products, identified as urea and 1,3-dimethylimidazolidine-2,4-dione.

Key words glyoxal, urea, 1,3-dimethylurea, *trans*-4,5-dihydroxy-2-imidazolidinone, 2,4-dimethylglycoluril

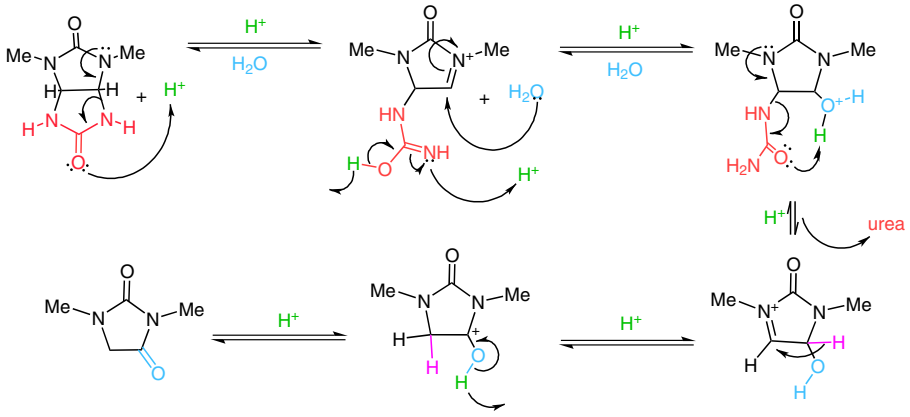
2,4-Dimethylglycoluril is the starting material to prepare a series of important compounds such as bambus[6]uril.[1–3] Some procedures have been described in the literature to prepare 2,4-dimethylglycoluril, from glyoxal, urea, and 1,3-dimethylurea. Most of these procedures show a series of limitations as low purity, low yields, special reactants, or catalysts, or long reaction times.[3–7] Several attempts to reproduce the easier procedure have failed, due to the lack of experimental details, and many of them simply do not work according to our experience. The synthesis is now realized in two steps to produce *trans*-4,5-dihydroxy-2-imidazolidinone, which condenses with 1,3-dimethylurea in a second step (Scheme 1).

The first step involves the reaction of urea and glyoxal in basic medium and the second one is carried out in HCl. The drawbacks arise essentially from the high reactivity of aqueous glyoxal in basic medium, which forms a series of oligomers[8] and disproportionates to glyoxal products;[9–11] also from the instability of 2,4-dimethylglycoluril that decomposes slowly to urea and 1,3-dimethylimidazolidine-2,4-dione, pushing down the synthesis yields (Scheme 2).



Scheme 1 Successive steps for the preparation of 2,4-dimethylglycoluril

We have addressed these issues, identified these impurities, and developed a simple and reproducible procedure, by introducing a few but crucial modifications in the procedures described by Grillon[5] and Sindelar.[3] The first modification refers to the addition of the base in the first step of the reaction. They have to be done stepwise and after the solution has cooled down, since glyoxal disproportionates in basic medium at 80 °C.[9–11] We have determined minimum and maximum reaction and precipitation times, and the ideal conditions to get a considerable amount of *trans*-4,5-dihydroxy-2-imidazolidinone by precipitation at low temperature and readjusting the pH. The precipitate was washed with aqueous NaOH to obtain a purer product. The second step of this synthesis was carried out in a beaker, with a strict volume and temperature control, and a complete 2,4-dimethylglycoluril purification procedure was developed. This protocol is very simple and leads to highly pure products with very satisfactory yields, by reducing the formation of side products. These procedures were successfully repeated more than 20 times.



Scheme 2 A possible mechanism of 2,4-dimethylglycoluril decomposition in acidic medium

Urea, 1,3-dimethylurea and aqueous glyoxal solution 40% were purchased from Sigma-Aldrich. Concd HCl (37%), EtOH, and NaOH were procured from Synth (Diadema, S.P. Brazil). NMR spectra were recorded on a DRX400-Ultra Shield® (^{1}H: 400.13 MHz, ^{13}C: 100.61 MHz) Bruker spectrometer. FTIR spectra were recorded on an ABB Bomem, MB 100 spectrophotometer, of samples prepared as KBr pellets. Theoretical IR spectra were calculated using Wavefun Spartan® 14 software using Density Function Theory and the B3LYP method [6-31G** basis set, an equivalent to 6-31G(d,p)]. Purity calculations were carried out using ^{1}H NMR, following the procedure described in literature,[12] using hydroquinone as the standard (Tables S1–S4 and S5–S8 and Figures S1–S3 and S9–S11 in the Supporting Information).

trans-4,5-Dihydroxy-2-imidazolidinone

Aqueous glyoxal (40%, 41 mL, 0.16 mol) was mixed with urea (42.2 g, 0.7 mol) using a magnetic stirrer in a 100 mL beaker. The reaction mixture was stirred and heated until exactly 80 °C. The mixture was immediately cooled in an ice bath to 25 °C precisely. Once at 25 °C, aq 9 N NaOH (400 µL) was added to the beaker, always under stirring. At this point, the solution became yellow. Three more additions of the same aq NaOH (100 µL) were made at 45 min intervals, and the color of the solution turned to orange. These additions were sufficient to keep the pH around 8 to 9. After the last addition of NaOH, the beaker was sealed with parafilm and the mixture was kept under stirring at r.t. for 28 hours. In such conditions, a colorless solid started precipitating in no more than 7 h and stopped after approximately 21 h. After this, the mixture was cooled in a refrigerator for 1 h at 5 °C to achieve the complete precipitation of the solid. The mixture was filtered immediately after cooling to acquire a first portion of *trans*-4,5-dihydroxy-2-imidazolidinone and the filtrate was kept to obtain a second one. Both portions were purified the same way (described below). Second portion: The filtrate was placed in a beaker and the pH was adjusted to 8–9 by the addition of aq 9 N NaOH (200 µL). Then, the beaker was sealed again with parafilm and cooled in a refrigerator at 5 °C for 15 days affording more *trans*-4,5-dihydroxy-2-imidazolidinone. Purification: After filtration, each portion of the solid was washed with EtOH (30 mL) and then with cold aq NaOH (15 mL, pH 12). Finally, the product was washed with EtOH (2 × 30 mL) and dried under vacuum for 48 h. The synthesis of *trans*-4,5-dihydroxy-2-imidazolidinone was realized in triplicate. Typical yields and purities: synthesis 1: first portion: 12.136 g, second portion: 2.096 g, (total yield: 34%), purity 97.6%; synthesis 2: first portion: 12.554 g, second portion: 1.354 g (total yield: 33%), purity 96.9%; synthesis 3: first portion: 11.214 g, second portion: 2.71 g (total yield: 33%), purity 98.9%. White solid; mp 140 °C.

IR (KBr): 1676 (ν C=O), 1483 (δ CNH in-plane), 1246 (ν C–N), 1058 (ν C–O), 644–580–544 cm^{-1} (ω N–H out-of-plane CNC).

^{1}H NMR (400 MHz DMSO-d_6, 23 °C): δ = 7.1 (s, 2 H, NH), 5.85 (d, J = 8 Hz, 2 H, OH), 4.60 (d, J = 8 Hz, 2 H, CH).

^{13}C NMR (400 MHz, DMSO-d_6, 23 °C): δ = 160.4 (s, C=O), 83.9 (s, CH).

2,4-Dimethylglycoluril

Prior to the synthesis, a level line at 11 mL was marked with a pen on a clean 100 mL beaker using this volume of H_2O. The H_2O was poured out and the beaker was dried. In this beaker, *trans*-4,5-dihydroxy-2-imidazolidinone (11 g, 0.09 mol), 1,3-dimethylurea (8.22 g, 0.09 mmol), distilled H_2O (46 mL), and concd HCl (37%, 1.39 mL) were mixed under stirring with a watch glass covered over the top of the beaker. The reaction mixture was stirred and boiled at 97 °C for 2 h. After this period, the watch glass was removed and the solvent was evaporated, until the level reached the marked level line or until solid precipitated. At this point, heating was interrupted and the beaker was cooled to r.t. While cooling, crude 2,4-dimethylglycoluril precipitated as a light yellow solid. The solid was dried still in the beaker, under reduced pressure for 2 h approximately. Purification: To the solid in the beaker was added EtOH (25 mL) and the solid 2,4-dimethylglycoluril was crushed with a pestle to smaller pieces. Once it was finely divided, the beaker was placed in an ultrasonic bath for 5 min. During this procedure, depending on the yield of the synthesis, the mixture formed a paste or a suspension. The resulting paste, or suspension was cooled to 5 °C for 20 h in the beaker covered with parafilm. When treating pastes, they were resuspended in cold EtOH (25 mL) and the suspension was filtered. All suspensions were filtered without addition of EtOH. The filtered solids were washed with 95% (v/v) aq EtOH (20 mL) and absolute EtOH (20 mL). They were dried under reduced pressure for 48 h. The synthesis was realized in triplicate. Typical yields and purities: synthesis 1: 6.59 g (42%), purity 96.3%; synthesis 2: 5.128 g (32%), purity 99.8%; synthesis 3: 6.75 g (43%), purity 93.5%. White solid; mp 260 °C.

IR (KBr): 1741 (ν C=O urea fragment), 1705 (ν C=O 1,3-dimethylurea fragment), 1515 (ν OC–N 1,3-dimethylurea, coupling with $\delta_{s\text{-}cis}$ H of CH_3 out-of-plane OCN) 1463 (ν OC–N, coupling with δ CNH in-plane and $\delta_{s\text{-}cis}$ H of CH_3), 1418 (ν N–CH_3, coupling with δ C–H of CH_3 and ν OC–N urea), 1318–1286–1234 (ν C–N), 570 ($\delta_{s\text{-}cis}$ N–CH_3), 432 cm^{-1} (ω N–H out-of-plane CNC).

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C): δ = 7.53 (s, 2 H, NH), 5.11 (s, 2 H, CH), 2.64 (s, 6 H, CH_3).

^{13}C NMR (400 MHz, DMSO-d_6, 23 °C): δ = 161.14 (s, C=O urea fragment), 157.8 (s, C=O 1,3-dimethylurea fragment), 67.24 (s, CH), 27.81 (s, CH_3).

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560831.

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