2,3-Dihydroxy-1,4-dioxane: A Stable Synthetic Equivalent of Anhydrous Glyoxal

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Glyoxal is a key reagent for the preparation of a number of carbocyclic and heterocyclic ring systems. However, the major drawback associated with pure, anhydrous glyoxal is its tendency to polymerize, necessitating the use of monomer, freshly prepared by a difficult procedure[1a], at temperatures below 0°C. Alternatively, aqueous glyoxal or glyoxal hydrogen sulfite (liberated *in situ* with base) have been used in the place of the anhydrous monomer[1b]. All these sources of glyoxal possess distinct experimental disadvantages, requiring either rapid reaction at low temperature or reaction in aqueous media.

In encountering these problems, we have found that 2,3-dihydroxy-1,4-dioxane (1) functions as a stable synthetic equivalent of anhydrous glyoxal in almost all applications, allowing reactions to be carried out in organic solvents at ambient temperature in most cases, and with ethylene glycol as the sole byproduct. Although 1 is a known compound[2] and has been prepared in numerous ways, mainly in the patent literature for use as a photographic fixative[3], its synthetic utility has been virtually ignored. In this communication, we present a convenient laboratory scale preparation of 1 (see below) and some representative examples of its application to the synthesis of a number of ring systems (Scheme A).

The most common use of glyoxal in synthesis is the preparation of condensed pyrazines from *ortho*-diamino compounds.

The aqueous reaction requires both hydrogen sulfite and heat to avoid a low yield due to polymerization[4]. However, even with this modified procedure, yields as low as 17% have been reported[5,6,7]. In direct contrast, condensed pyrazines 2, 3, and 4 were prepared from the corresponding diamino compound and 1 in ethanol at room temperature in 30 minutes. Evaporation and purification provided the condensed pyrazines in excellent yields, avoiding the tedious extractions associated with the hydrogen sulfite procedure.
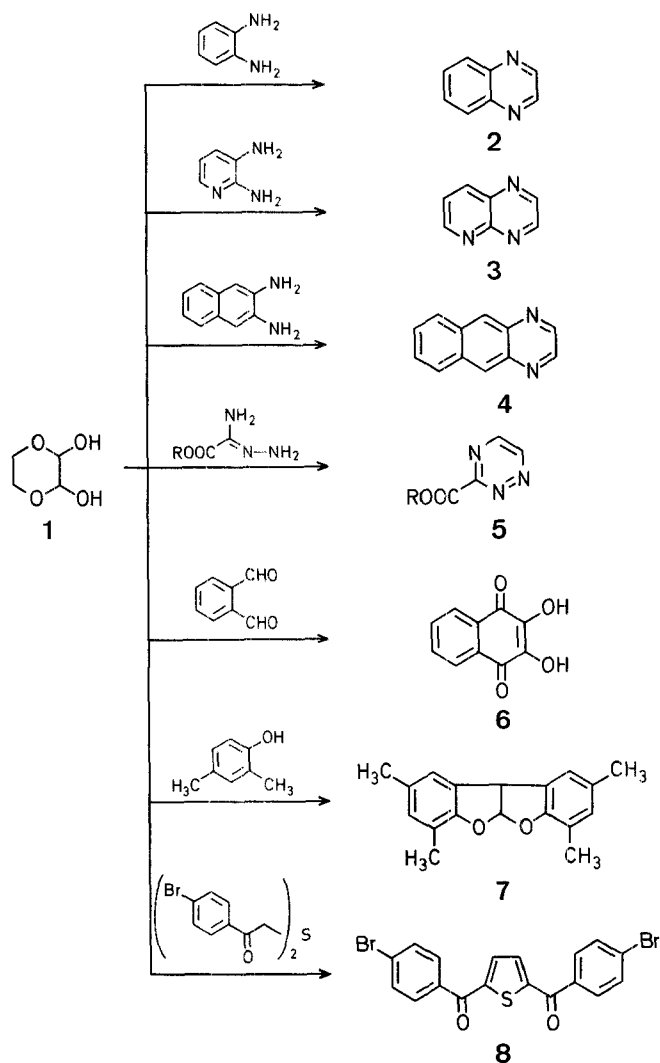
Scheme A

The 1,2,4-triazine system has been prepared by various routes, most of which rely on the condensation of an amidrazone with glyoxal at some stage in the sequence. For example, with 40% aqueous glyoxal, the yields of 1,2,4-triazines 5 (R = CH₃, C₂H₅, t-C₄H₉), precursors of the parent heterocycle, were uniformly less than 10%. Using monomeric glyoxal, the yield of 5 (R = C₂H₅) was increased to 55%[8]. The yields reported directly reflect the problems described above, namely either poor reaction in aqueous media or the preparation of monomeric glyoxal. With 1 as glyoxal source, the 1,2,4-triazine ring system of 5 (R = t-C₄H₉) was prepared in 39% yield, a reasonable balance between the two reported extremes.

Isonaphthazarin (6) has been prepared most straightforwardly by the condensation of o-phthalaldehyde with glyoxal

as described by Weygand[9]. Under the conditions of the reaction, the monoalkali salt of 6 is the primary reaction intermediate. However, this salt, soluble in the aqueous reaction medium, is prone to further base-catalyzed decomposition prior to acidification, especially on a preparative scale. With 1 as the glyoxal source, the reaction may be carried out in ethanol with a minimum amount of water, which causes the precipitation of the intermediate salt, protecting it from further reaction until acidification is completed. By this procedure, and on a preparative scale, the condensation to give 6 has been accomplished in 60–70% yields.

Some novel reactions requiring glyoxal for heterocycle synthesis demonstrated further uses of 1 under both acid and base catalysis. The acid-catalyzed condensation of 2,4-disubstituted phenols with glyoxal affords either benzofuro[2,3-b]benzofurans with sulfuric acid[10] or 2(3H)-benzofuranones with aqueous hydrochloric acid[11], depending on the catalyst used. The base-catalyzed reaction of glyoxal and 1,4-keto-3-sulfides gives 2,5-diacylthiophenes[12]. Under both acid- and base-catalyzed anhydrous reaction conditions, glyoxal equivalent 1 functioned as expected, giving the condensation products 7 and 8, respectively, in yields comparable to those previously obtained. The ease of preparation and successful use of 1 in the examples detailed above recommend its wide use as a stable source of anhydrous glyoxal.

2,3-Dihydroxy-1,4-dioxane (1):

A solution of 40% aqueous glyoxal (528 g, 3.62 mol) and ethylene glycol (230 g, 3.70 mol) in benzene (2 l) is heated under reflux with efficient stirring and with azeotropic removal of water via a Dean-Stark trap. After 10 h, removal of water is complete, and the reaction mixture is allowed to cool, separating into two layers. The supernatant benzene layer is decanted away, the residual amber syrup is thoroughly triturated with cold acetone (500 ml), and then refrigerated. The solid material is collected by filtration, washed with cold acetone (500 ml) and dried in vacuo over phosphorus pentoxide for 72 h to give a lumpy solid which is powdered by spinning on a rotary evaporator to give a fine, white powder; yield: 197 g (45%); m.p. 100–104°C (Lit.², m.p. 100–103°C).

¹H-N.M.R. (DMSO-d_6): δ = 6.45 (d, J = 5 Hz, 2 H); 4.32 (d, J = 5 Hz, 2 H); 3.20–4.05 ppm (m, 4 H).

I.R. (KBr): ν = 3350 cm⁻¹.

Quinoxaline (2):

To a solution of 1 (15.6 g, 130 mmol) in ethanol (250 ml) is added o-phenylenediamine (10.8 g, 100 mmol). The brown solution is stirred for 30 min at room temperature, at which time T.L.C. analysis (silica gel GF plates, 3 : 1 dichloromethane/ethyl acetate as solvent, ammonium molybdate char development) shows complete conversion to product. The reaction mixture is evaporated, and the residue is distilled to give 2; yield: 12.4 g (95%); b.p. 80–85°C/3 torr (Lit.⁵, b.p. 220–223°C/760 torr); the product solidifies on cooling; m.p. 29–31°C (Lit.⁵, m.p. 27°C).

¹H-N.M.R. (CDCl₃): δ = 8.95 (s, 2 H); 8.10–8.35 (m, 2 H); 7.70–8.05 ppm (m, 2 H).

Pyrido[2,3-b]pyrazine (3):

The reaction is carried out as described for 2 on a 10 mmol scale. After evaporation, filtration of the residue through silica gel (3 : 1 dichloromethane/ethyl acetate) affords 3 which is recrystallized from petroleum ether; yield: 1.15 g (87%); m.p. 146–147°C (Lit.⁶, m.p. 147–148°C).

¹H-N.M.R. (CDCl₃): δ = 9.30 (d of d, 1 H); 9.25 (d, 1 H); 9.05 (d, 1 H); 8.62 (d of d, 1 H); 7.38 ppm (d of d, 1 H).

Benzo[g]quinoxaline (4):

The reaction is carried out as described for 3, with brief heating to effect dissolution of the 2,3-diaminonaphthalene. Filtration through silica gel (3 : 1 dichloromethane/ethyl acetate) affords 4 which is recrys-

tallized from petroleum ether; yield: 1.38 g (77%); m.p. 125-126°C (Lit.[7], m.p. 125-126°C).

^{1}H-N.M.R. (CDCl₃): $\delta = 9.00$ (s, 2 H); 8.80 (s, 2 H); 8.05-8.35 (m, 2 H); 7.55-7.85 ppm (m, 2 H).

3-*t*-Butyloxycarbonyl-1,2,4-triazine (5, R =*t*-C₄H₉):

To a solution of 1 (9.0 g, 75 mmol) in dry tetrahydrofuran (112.5 ml) cooled to 0°C under a blanket of dry nitrogen is added a chilled solution of *t*-butyl oxalamidrazonate[8] (11.93 g, 75 mmol) and acetic acid (11.15 ml) in ethanol (225 ml). The resulting yellow solution is stirred for 30 min at 0°C. Triethylamine (15.7 ml, 113 mmol) is added, and the mixture is allowed to warm to room temperature, where it is maintained overnight. The reaction mixture is filtered to remove the precipitated material, and the pad is washed with additional tetrahydrofuran. The combined filtrates are evaporated to a volume of 100 ml, brought to pH 10 with 10% aqueous potassium carbonate, and extracted with dichloromethane (6 × 150 ml). The organic extract is dried with anhydrous potassium carbonate, filtered, and evaporated to give a dark oil. Kugelrohr distillation (100°C/0.5 torr) affords 5 as a yellow solid which is recrystallized from ether/petroleum ether; yield: 5.22 g (39%); m.p. 52-53°C (Lit.[8], m.p. 52.5-53.5°C).

^{1}H-N.M.R. (CDCl₃): $\delta = 9.50$ (d, $J = 3$ Hz, 1 H); 8.90 (d, $J = 3$ Hz, 1 H); 1.70 ppm (s, 9 H).

I.R. (CHCl₃): $\nu = 1735$ cm⁻¹.

Isonaphthazarin (6):

To a mechanically stirred solution of 1 (15.6 g, 130 mmol) and *o*-phthalaldehyde (13.40 g, 100 mmol) in ethanol (100 ml) in a 1-l flask is added a solution of potassium cyanide (6.50 g, 100 mmol) and potassium carbonate (6.0 g, 50 mmol) in water (10 ml) in one portion. The reaction immediately becomes a thick purple paste. Before the solution darkens to blue-black (1 min), the reaction mixture is acidified with 6 molar hydrochloric acid (50 ml) to give a yellow color. Further addition of water (250 ml) gives a red-orange precipitate of product, which is collected by filtration and air dried; yield: 11.78 g (62%); m.p. 285-286°C (Lit.[9], m.p. 285°C).

2,4,7,9-Tetramethyl-5a,10b-dihydrobenzofuro[2,3-*b*]benzofuran (7):

A solution of 2,4-dimethylphenol (12.2 g, 100 mmol) and 1 (13.2 g, 110 mmol) in acetic acid (100 ml) and sulfuric acid (0.5 ml) is heated at 100°C for 6 h, at which time T.L.C. analysis (system as for 2) shows complete consumption of phenol. After cooling, diethyl ether (100 ml) is added to complete the precipitation of the product 7 which is collected by filtration and air dried; yield: 7.50 g (56%); m.p. 250-251°C.

C₁₈H₁₈O₂	calc.	C 81.17	H 6.81
(266.3)	found	81.21	6.83

^{1}H-N.M.R. (CDCl₃): $\delta = 6.99$ (s, 2 H); 6.85 (d, $J = 7$ Hz, 1 H); 6.77 (s, 2 H); 4.91 (d, $J = 7$ Hz, 1 H); 2.25 (s, 6 H); 2.20 ppm (s, 6 H).

2,5-Bis[4-bromobenzoyl]thiophene (8):

To a solution of bis[4-bromophenacyl] sulfide[12] (4.28 g, 10 mmol) and 1 (1.44 g, 12 mmol) in methanol (50 ml) and dioxane (20 ml) warmed to 40°C is added solid sodium methoxide (27 mg, 0.5 mmol)[13]. Within minutes, a fine precipitate of product has formed. After 30 min of stirring at room temperature, the product is collected by filtration and air dried; yield: 4.20 g (93%); m.p. 260-261°C (Lit.[12], m.p. 254-255°C).

^{1}H-N.M.R. (DMSO-d_6/CF₃COOH): $\delta = 7.83$ (d, $J = 8$ Hz, 4 H); 7.79 (d, $J = 8$ Hz, 4 H); 7.78 ppm (s, 2 H).

I.R. (KBr): $\nu = 1630$ cm⁻¹.

Received: August 4, 1981

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¹³ The stoichiometry requires only catalytic methoxide, instead of a full equivalent as was used previously (Ref.¹²), since ethylene glycolate is generated from 1.

* Contribution No. 607 from the Syntex Research Institute of Organic Chemistry.

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