Efficient Synthesis of Dipyrazino[2,3-*f*; 2′,3′-*h*]quinoxaline

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Abstract: The condensation of benzenehexamine (**2**) with the masked forms **3a** or **3b** of glyoxal leads to the title compound (**4**) in good yields; aqueous glyoxal is highly unsatisfactory.

Dipyrazino[2,3-*f*;2′,3′-*h*]quinoxaline (or 1,4,5,8,9,12-hexaazatriphenylene, **4**) is both an interesting tris-chelating ligand giving mono-, di-, and trimetallic complexes with transition metals[1, 2], and the basis skeleton of a series of compounds examined, among other reasons, as nitrogen-containing models of disc-shaped liquid crystals[3]. Judging from numerous requests, this molecule arouses much interest in several laboratories because of its threefold symmetry, high electron affinity, and other properties.

A recent paper by *Rogers*[4] claims that compound **4** can be synthesized by an efficient route based on the condensation of benzenehexamine (**2**) with an excess of aqueous glyoxal. Our both laboratories having been engaged since years in the improvement of this synthesis, we contacted each other, and our findings in this connection prompt us to publish a joint paper.

Compound **4** was first prepared in one of our laboratories by a 10-step scheme[1] with a low overall yield. There was obviously good hope to improve this result since recent work by *Breslow* et al.[5] and the TU Berlin group[3, 6–8] provided easy access to benzenehexamine (**2**).

It was thus attempted to reproduce *Rogers'* results but, whatever the source of educt **2** (reduction with phenylhydrazine[3], hydrogenation[5–8], or Birch reduction[4]), we repeatedly obtained less than a 3% yield of **4** when the condensation was attempted with an excess of aqueous glyoxal, despite systematic experiments by many researchers and wide variations in experimental conditions. This confirms earlier findings[3] and it is thus clear that *Rogers'* results cannot be reproduced.

It occurred to us that the use of aqueous glyoxal was responsible for these failures and we independently looked for *masked forms of glyoxal* which would slowly release the dialdehyde. We now report on the use of 1) *Le Rouzic*'s reagent **3a**[9], a dimorpholinodioxane derivative, which, in preliminary experiments, gave very high yields of quinoxaline and 6-chloroquinoxaline when reacted with the corresponding benzene-1,2-diamines, and 2) the bis-imine of glyoxal with cyclohexylamine **3b**[10] which was reacted with **2** under acid-free conditions similar to the procedure described for condensations of **2** with various α-diketones[3, 11].

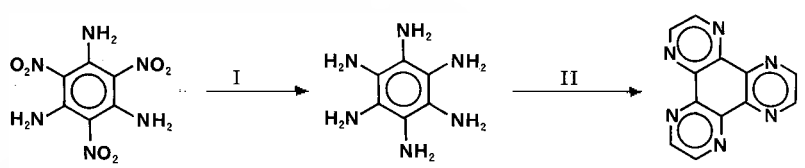
When the crude mixture from the catalytic hydrogenation[5–8] of 2,4,6-trinitrobenzene-1,3,5-triamine (**1**) was quickly filtered and the resulting dark powder added to a suspension of *Le Rouzic*'s reagent **3a**[9] in water, product **4** was reproducibly isolated with a yield of 64% (based on **1**). Similarly, when **1** was reduced with sodium in ammonia/methanol[4] and the resulting **2** reacted with the bis-imine **3b**, finally **4** was obtained with yields approaching 50% (based on **1**)[12].

These improved procedures give *easily* and *reliably* access to the heterocyclic compound **4** in much larger amounts than the previous synthesis and open the way to more applications of this molecule.

Experimental

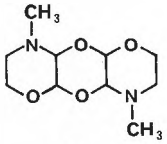
*1. Condensation of benzenehexamine (**2**) with Le Rouzic's masked glyoxal* **3a**: A 0.5 L Parr bottle was charged with 2.5 g **1** (9.7 mmol), 0.6 g of 10% Pd on charcoal, and 60 mL of ethyl acetate. A pressure of 0.4 MPa (4 atm) of H_2 was applied and the mixture was stirred for 48 h. The resulting suspension was filtered, the solid washed with ethyl acetate and dried under reduced pressure. This black powder was then added to a suspension of **3a**[9] (4.5 g, 19 mmol) in 30 mL water and stirred for 24 h; 4.5 g (19 mmol) more of masked glyoxal was then added, and the stirring extended for an additional 24 h. The mixture was then continuously extracted with three successive batches of chloroform for two days. The organic extracts were collected, dried over magnesium sulfate, and evaporated to give a brown solid. Chromatography on neutral alumina with chloroform/ethanol (98:2) gave 1.4 g of **4** (6.2 mmol, 64% based on **1**) as a white powder. TLC: Alox N, chloroform/ethanol (98:2). When sprayed with an aqueous solution of Mohr salt ($Fe^{2\oplus}$), **4** gives a deep blue spot, $R_f = 0.64$.

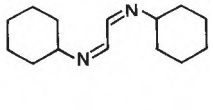
*2. Condensation of benzenehexamine (**2**) with the glyoxal bis-imine* **3b**: 1.01 g (6 mmol) **2**, freshly prepared by reduction of **1** with sodium in ammonia/methanol[4], was added to a solution of 4.36 g (19.8 mmol) **3b** in a mixture of 25 mL ethanol and 20 mL water at room temperature. After 4 h reflux under argon, the mixture was concentrated to dryness and the residue purified by flash chromatography (Alox N, chloroform/ethanol (98:2)) yielding 688 mg (2.9 mmol, 49% based on **1**) of **4** as a slightly brownish powder. On TLC, this material shows the same blue color reaction mentioned before. Sublimation above 370°C, leads to nearly colorless **4** with decomposition (?) around 490°C (Mettler TA 3000/DSC 30). UV (Cary 118, CH_2Cl_2, $c = 1.02$ mg of sublimed **4** in 50 mL): $\lambda_{max} = 256.5$ and 296.0 nm ($\varepsilon = 25370$ and 14960 $L \cdot mol^{-1} \cdot cm^{-1}$, respectively). IR ($CHCl_3$): $\nu = 2995, 1470, 1385, 1100, 863\ cm^{-1}$. MS (MAT 711, 150°C): m/z 234 (M^+, 100%), 207 (M^+–



1 **2** **4**

I: $C_6H_5NHNH_2$[3], or H_2/Pd/C/AcOEt[5–8], or Na/NH_3/MeOH[4]





II: **3a**[9] (UL Bruxelles); **3b**[10] (TU Berlin)

3a **3b**

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HCN, 44), 180 (207 – HCN, 24), 154 (22), 117 (6), 100 (9), and no further fragment ions with more than 10% intensity. The ^{1}H- and ^{13}C-NMR spectra of **4** are in full agreement with published data[1, 13]; the structure of **4** has in the meantime also been proven by a single crystal X-ray analysis[14].

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[12] It is interesting to note that when **2**, prepared according to *Rogers'* procedure[4], is condensed with biacetyl under our conditions[3], a 51% yield of the expected hexamethyl-dipyrazinoquinoxaline was obtained (correct spectral data[3]) as compared with 46% from **2** obtained by the reduction of **1** with phenylhydrazine[3].
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