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# 3,3,6,6-Tetrachloro-2,2-dihydroxycyclohexanone as a synthetic equivalent of unavailable 3-chloro-6-hydroxy-1,2-benzoquinone: first synthesis of 4-chloro-1-hydroxyphenazines

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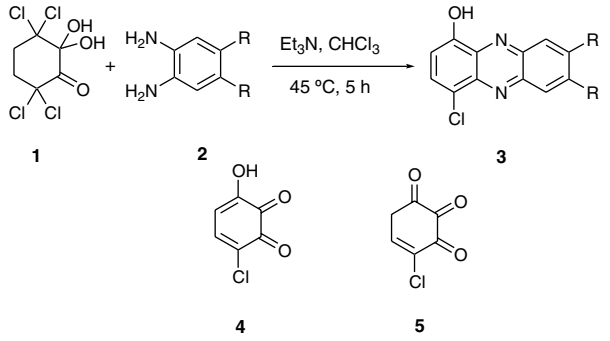
**Abstract**—3,3,6,6-Tetrachloro-2,2-dihydroxycyclohexanone has been found to be an excellent synthetic equivalent of unavailable 3-chloro-6-hydroxycyclohexa-1,2-benzoquinone. Reactions with 1,2-phenylenediamines provide hitherto unattainable 4-chloro-1-hydroxyphenazines in fair to high yields.


The chemistry of phenazines has been excellently reviewed, showing that these are substances with an extensive range of important applications.[1–7] Numerous members of this family of compounds, which have a significant biological activity, are continuously being found.[6,7] Consequently, the progress in the synthesis of phenazines is a subject of renewed interest. Indeed, the development of biosynthetic studies on naturally occurring phenazines as well as the synthesis of analogues with similar or enhanced properties, and a wealth of other research work are still limited by serious obstacles inherent in the existing preparative methodology. Harsh experimental conditions, low yields and incompatibility with the presence of functional groups are common problems found in studies on phenazine preparation.[1–7] Moreover, these substances are strongly deactivated towards electrophilic substitution reactions,[6–8] which represents a further important difficulty when accessing phenazine derivatives.

Given the precariousness of the existing methodology to prepare 1,4-dichlorophenazines as well as 1-chlorophenazines, we recognized the opportunity to develop exclusive approaches to these compounds[9,10] on the basis of highly efficient reactions of 1,2-phenylenediamines with inexpensive and easily available 3,3,6,6-tetrachloro-1,2-cyclohexanedione or 3,6,6-trichloro-2-hydroxy-2-cyclohexen-1-one.

Owing to the vicinal accumulation of chlorine atoms present in 3,3,6,6-tetrachloro-1,2-cyclohexanedione, this compound is able to form an isolable crystalline hydrate, 3,3,6,6-tetrachloro-2,2-dihydroxycyclohexanone **1**, in near quantitative yield.[11,12]

We report a very useful synthetic application of **1** since it provides an efficient, direct approach to 4-chloro-1-hydroxyphenazines **3**, which pertain to a hitherto unknown family of compounds. In this new approach, **1** proves to be an excellent synthetic equivalent of the hypothetical quinone **4** or its tautomer **5**, which are




**Scheme 1.**

*Keywords*: Phenazines; 1,2-Phenylenediamines; Dehydrochlorination; Dehydration; Aromatization.
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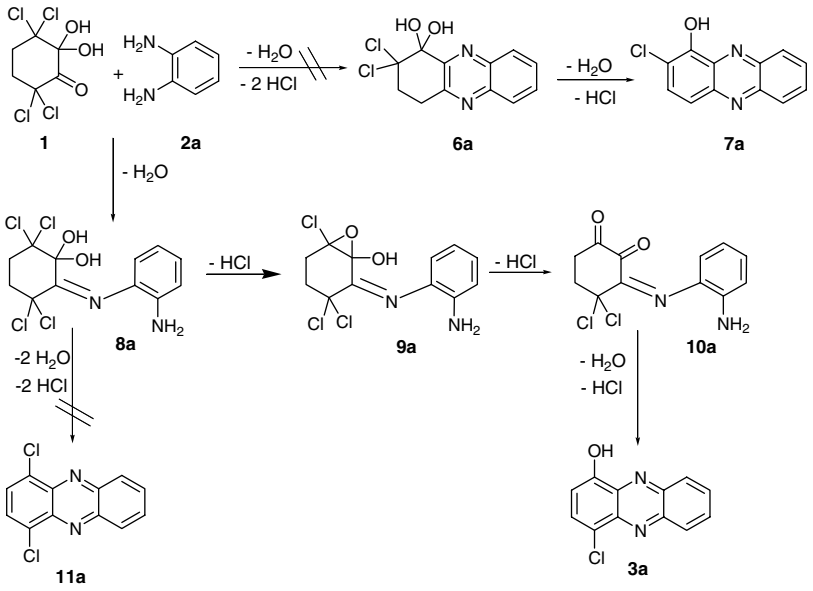



**Scheme 2.**

unavailable compounds (Scheme 1). Regarding the biological significance of 1-hydroxyphenazine and some of its derivatives,[13] such as pyocyanine and phenazinomycin, this new preparative methodology is of particular interest to provide related compounds.

Compound **1** reacted with *o*-phenylenediamine **2a** in the presence of triethylamine under mild experimental conditions[14] (Scheme 2) leading to a phenazine compound but no 1,4-dichlorophenazine **11a**, which would correspond to the expected product from reaction with the dehydrated starting material. However, the compound formed revealed the existence of a hydroxyl group and a chlorine atom as the only two substituents supported by the ring system. Reactions with further 1,2-phenylenediamines **2** gave similar results.

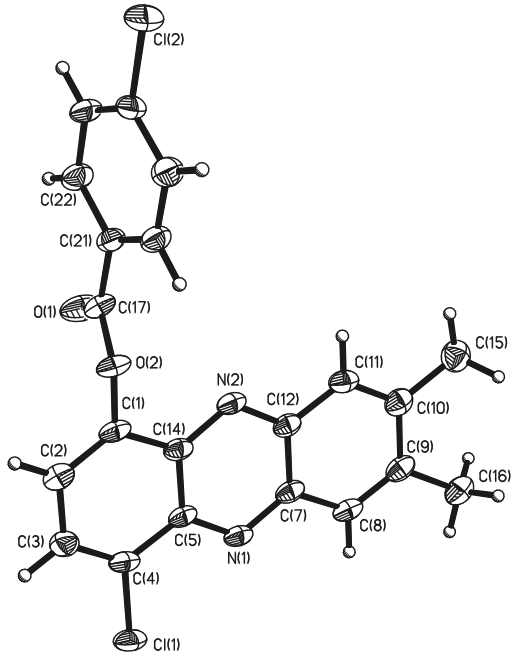
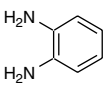
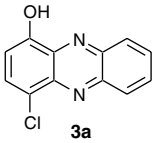
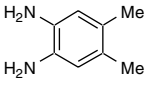
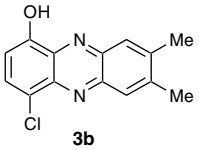
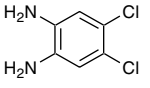
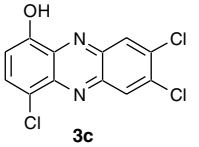
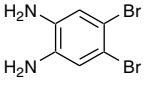
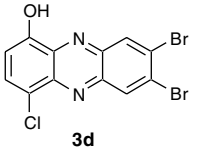



**Figure 1.** ORTEP of **12**, with thermal ellipsoids shown at 50% probability.

Compounds **3** were unambiguously identified, thanks to the preparation of a benzoylated derivative[15] of **3b**: 4-chloro-1-(4-chlorobenzoyloxy)-7,8-dimethylphenazine **12**, which was able to provide single crystals suitable for X-ray crystallographic analysis[16] (Fig. 1). The structural arrangement found evidenced a complex effect on the reactivity of **1** by the geminal diol group. It is clear that a mere blockade of the carbonyl function protecting the formation of **11a**, which would provoke the alternative generation of 2-chloro-1-hydroxyphenazine **7a**, does not occur. In contrast, **3a** would be necessarily originated by participation of a rearrangement process, which can be explained in view of the low capacity of oxiranes to support a halogen atom linked to any of the oxygenated carbon atoms. For example, 1-chloroepoxycyclohexane undergoes a rapid conversion to 2-chloro- and 2-hydroxycyclohexanone on exposure to moist air;[17] 2-chloro-2,3-epoxynorbornane is stable at dry-ice temperature, but on being left at room temperature undergoes a violent exothermic reaction with evolution of hydrogen chloride.[18] The relatively low stability of these compounds is the consequence of a remarkable proclivity to rearrange to α-chlorocarbonyl derivatives. It has been shown that this transformation proceeds through the formation and subsequent collapse of an ion pair composed of a chlorine anion and an α-ketocarbocation.[18,19]

In our case it seems reasonable, therefore, to assume an initial condensation step[20] (Scheme 2) to give **8a**, followed by epoxidation leading to the key intermediate **9a**, which would be converted into **10a** and plausibly through an α-ketocarbocation. Then, the final product **3a** would be formed following a sequence consisting of condensation, hydrogen chloride elimination, and tautomeric aromatization. Four reaction examples gave the results displayed in Table 1.

**Table 1.** Synthesis of 4-chloro-1-hydroxyphenazines **3** from the reaction of 3,3,6,6-tetrachloro-2,2-dihydroxycyclohexanone **1** with *o*-phenylenediamines **2**

| Entry | Diamine | Product | Yield (%) |
|---|---|---|---|
| 1 |  **2a** |  **3a** | 90 |
| 2 |  **2b** |  **3b** | 78 |
| 3 |  **2c** |  **3c** | 58 |
| 4 |  **2d** |  **3d** | 59 |

In conclusion, an effective new method on phenazine synthesis is provided. Good yields, easy availability of starting materials and the mild reaction conditions are valuable advantages of the reported procedure, which give access to the previously unattainable 4-chloro-1-hydroxyphenazines.

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## Supplementary data

Detailed experimental procedures and spectroscopic and analytical data for compounds **1**, **3a**–**d**, and **12**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.120.

## References and notes

1. Swan, G. A.; Felton, D. G. I. In *Phenazines, The Chemistry of Heterocyclic Compounds*; Weissberger, A., Ed.; Interscience: New York, 1957; Vol. 11.
2. Porter, A. E. A. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A., Rees, C., Potts, K., Eds.; Pergamon Press: Oxford, 1984; Vol. 3, pp 157–197.
3. McCullough, K. J. In *Rodd's Chemistry of Carbon Compounds*; Ansell, M. F., Ed.; Elsevier: Amsterdam, 1989; Vol. 4, Part I J, pp 354–416.
4. Urleb, U., 4th ed. In *Methods of Organic Chemistry (Houben-Weyl)*; Schaumann, E., Ed.; Thieme: Stuttgart, 1998; Vol. E9b/Part 2, pp 266–303.
5. Bolton, R. In *Rodd's Chemistry of Carbon Compounds*; Sainsbury, M., Ed.; Elsevier: Amsterdam, 2000; Vol. 4, Part I J, pp 162–171.
6. Laursen, J. B.; Nielsen, J. *Chem. Rev.* **2004**, *104*, 1663.
7. Beifuss, U.; Tietze, M. *Top. Curr. Chem.* **2005**, *244*, 77.
8. Olah, G. A. *Friedel–Craft and Related Reactions*; Interscience: New York, 1964.
9. Guirado, A.; Cerezo, A.; Ramírez de Arellano, C. *Tetrahedron* **1997**, *53*, 6183.
10. (a) Guirado, A.; Cerezo, A.; Andreu, R. *Tetrahedron Lett.* **2000**, *41*, 6579; (b) Guirado, A.; Cerezo, A.; Andreu, R.; López-Sánchez, J. I.; Bautista, D. *Tetrahedron* **2004**, *60*, 6747.
11. Sucrow, W.; Wanzlick, H. W. *Chem. Ber.* **1959**, *92*, 2516.
12. De Buyck, L.; Vanslembrouck, J.; De Kimpe, N.; Verhé, R.; Schamp, N. *Bull. Soc. Chim. Belg.* **1984**, *93*, 913.
13. For example: (a) Usher, L. R.; Lawson, R. A.; Geary, I.; Taylor, C. J.; Bingle, C. D.; Taylor, G. W.; Whyte, M. K. B. *J. Immunol.* **2002**, *168*, 1861; (b) Kerr, J. R.; Taylor, G. W.; Rutman, A.; Hoiby, N.; Cole, P. J.; Wilson, R. *J. Clin. Pathol.* **1999**, *52*, 385; (c) Lauredo, I. T.; Sabater, J. R.; Ahmed, A.; Botvinnikova, Y.; Abraham, W. *J. Appl. Physiol.* **1998**, *85*, 2298; (d) Kitahara, T.; Kinoshita, Y. *Tetrahedron Lett.* **1997**, *38*, 4993; (e) Kinoshita, Y.; Watanabe, H.; Kitahara, T.; Mori, K. *Synlett* **1995**, *186*; (f) Muller, M. *Biochim. Biophys. Acta* **1995**, *185*; (g) Kitahara, T.; Kinoshita, Y.; Aono, S.; Miyake, M.; Hasegawa, T.; Watanabe, H.; Mori, K. *Pure Appl. Chem.* **1994**, *66*, 2083; (h) Watson, D.; MacDermot, J.; Wilson, R.; Cole, P. J.; Taylor, G. W. *Eur. J. Biochem.* **1986**, *159*, 309.
14. *Typical procedure*: a mixture of 3,3,6,6-tetrachloro-2,2-dihydroxycyclohexanone **1** (3.8 mmol), the corresponding *o*-phenylenediamine **2** (3.8 mmol), triethylamine (14 mmol), and chloroform (50 mL) was stirred for 5 h at 45 °C. After evaporation to dryness under reduced pressure, water (150 mL) was added and the mixture was extracted with chloroform ($3 \times 60$ mL). The combined extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure giving a solid residue that provided highly pure phenazines **3** by either direct crystallization in the appropriate solvent (**3a**,**b**) or by column chromatography (**3c**,**d**; silica gel/ethyl acetate–hexane, ratio 3:1).
15. The procedure followed by us to prepare this compound is reported as Supplementary data.
16. Tables of fractional atomic coordinates, thermal parameters, bond lengths and angles have been deposited at the Cambridge Crystallographic Center (CCDC 607589).
17. Mousseron, M.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1950**, *17*, 698.
18. McDonald, R. N.; Tabor, T. E. *J. Org. Chem.* **1968**, *33*, 2934.
19. (a) McDonald, R. N.; Schwab, P. A. *J. Am. Chem. Soc.* **1963**, *85*, 820; (b) McDonald, R. N.; Schwab, P. A. *J. Org. Chem.* **1964**, *29*, 2459; (c) Dufraise, Ch. C. R. *Acad. Sci.* **1921**, *172*, 162; (d) McDonald, R. N.; Tabor, T. E. *J. Am. Chem. Soc.* **1967**, *89*, 6573; (e) McDonald, R. N.; Steppel, R. N. *J. Org. Chem.* **1970**, *35*, 1250.
20. The starting material **1** was recovered unaltered from experiments under the same preparative experimental conditions but in the absence of *o*-phenylenediamine.