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A new synthetic route to 1-chlorophenazines. The electrochemical monodechlorination of 3,3,6,6-tetrachloro-1,2-cyclohexanedione as a key step

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Abstract

A convenient new method for the synthesis of 1-chlorophenazines has been established. The first step involves an almost quantitative electrochemical reduction of 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1** to 3,6,6-trichloro-2-hydroxy-2-cyclohexen-1-one **2**. The reaction of **2** with aromatic 1,2-diamines followed by aromatisation through treatment with 2,6-lutidine leads to the title compounds in high yields.

Keywords: phenazines; electrosynthesis; dehydrohalogenation; aromatisation.

We have recently reported a new entry to 1,4-dichlorophenazines.[1] As a further result of our research project in improved synthesis of chlorophenazines a new, highly efficient and versatile method for the synthesis of 1-chlorophenazines is reported here. It should be remarked that both very low yields and lack of versatility are common features of all precedent methods for the synthesis of this class of compounds. This determines the few members pertaining to the 1-chlorophenazine family previously prepared. The synthesis of the parent compound **4a** has been achieved by different methods involving thermal cyclation of 2′-chloro-2-nitrodiphenylamine in the presence of ferrous oxalate[2] (4.4%), a Wohl–Aue reaction[3] (18%), treatment of phenazine-*N*-oxide with thionyl chloride[4] (23%), chlorination of catechol followed by oxidation with silver oxide and treatment with 1,2-phenylenediamine[5] (16% overall yield) or direct chlorination of phenazine[6] (negligible yield). Some low yield preparations of polychlorinated phenazines bearing a chlorine substituent at C-1 have also been reported.[7,8] All the above procedures seem to be incompatible with the synthesis of functionalized 1-chlorophenazines.

Phenazine has a general reluctance to be attacked by electrophiles.[9] This peculiar reactivity notably enhances the interest of chlorophenazines since incapable functualization processes via

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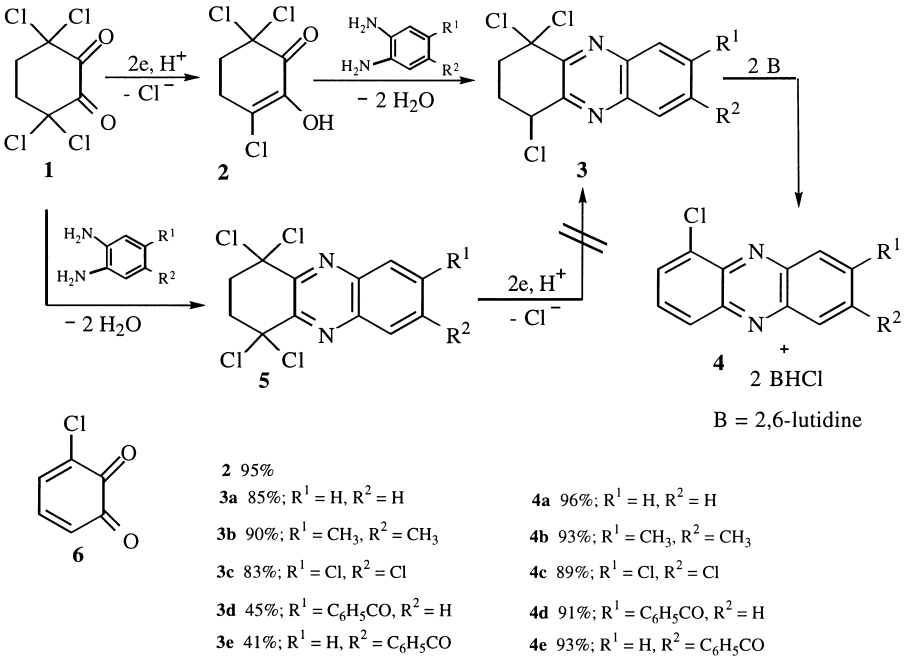
direct electrophilic substitution can be replaced by nucleophilic displacement reactions. In fact, chlorophenazines provide good entries to many functionalized phenazine derivatives via nucleophilic substitution.[9] However, 1-chlorophenazines still remain almost inaccessible.

Given the interest of the expansion of the number of 1-chlorophenazines available, a new and general entry to this class of compounds was attempted, as shown in Scheme 1. 3-Chloro-1,2-benzoquinone **6** is a rare and difficultly accessible compound.[5,10–12] However, 3,6,6-trichloro-2-hydroxy-2-cyclohexen-1-one **2** was found to be an excellent synthetic equivalent of **6**. Intermediate **2** could be quantitatively prepared[13] by electrochemical reduction of 3,3,6,6-tetrachloro-1,2-cyclohexanedione **1**, which is a cheap, readily available starting material that can be quantitatively generated by simple chlorination of commercial *trans*-cyclohexanediol.[9] Reaction of **2** with 1,2-phenylenediamines gave the corresponding intermediates **3** in high yields. In the case of the reaction with 3,4-diaminobenzophenone the two possible isomers **3d** and **3e** were formed in a similar ratio. Intermediates **3** were isolated and efficiently converted into the corresponding 1-chlorophenazines **4** by simple treatment with 2,6-lutidine. In contrast to previously reported methods a wide range of functionalized 1-chlorophenazines are presumably accessible by this approach. It should be noted that compounds **5** could not be directly converted into the intermediates **3** since their electrochemical reductions were non-selective towards monodechlorination.



2 95%

3a 85%; $R^1 = H$, $R^2 = H$

3b 90%; $R^1 = CH_3$, $R^2 = CH_3$

3c 83%; $R^1 = Cl$, $R^2 = Cl$

3d 45%; $R^1 = C_6H_5CO$, $R^2 = H$

3e 41%; $R^1 = H$, $R^2 = C_6H_5CO$

4a 96%; $R^1 = H$, $R^2 = H$

4b 93%; $R^1 = CH_3$, $R^2 = CH_3$

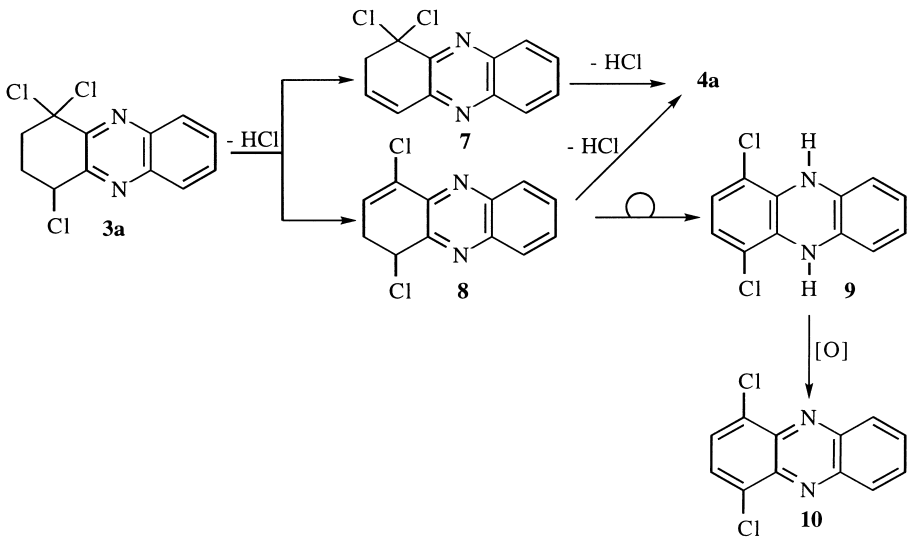
4c 89%; $R^1 = Cl$, $R^2 = Cl$

4d 91%; $R^1 = C_6H_5CO$, $R^2 = H$

4e 93%; $R^1 = H$, $R^2 = C_6H_5CO$

Scheme 1.

On working in the conversion of intermediates **3** into the final products **4** a surprising competitive aromatization mode involving only one dehydrochlorination process was observed. For example, **3a** (Scheme 2) reacted with pyridine yielding the expected 1-chlorophenazine **4a** (62%) but accompanied by 1,4-dichlorophenazine[1] **10** (26%). A similar result gave the reaction with sodium methoxide.



Scheme 2.

The crucial influence of the site where a first deprotonation takes place is the most plausible explanation that may be offered for these facts. Thus, deprotonation at C-3 would promote the formation of intermediate **7**, which would lead exclusively to the targeted product **4a**. However, deprotonation at C-2 would generate intermediate **8** which could reasonably undergo dehydrochlorination to **4a** but also rearrangement to 1,4-dichloro-5,10-dihydrophenazine **9**, whose oxidation explains the formation of product **10**. This reactivity scheme is well supported by the facts: (1) the great proclivity of 5,10-dihydrophenazines towards undergoing oxidation yielding phenazines is well known;[14] (2) when a sample of 1,4-dichloro-5,10-dihydrophenazine[15] **9** was exposed to similar experimental conditions to those operating in the conversion of **3** to **4**, an almost instantaneous and quantitative formation of **10** was observed even when working under nitrogen; and (3) the generation of product **10** was fully prevented by using 2,6-lutidine instead of pyridine. In this case the exclusive formation of 1-chlorophanazine (96%) occurred. This result is in excellent agreement with the expected effect of a bulky base determining regioselectivity towards the less hindered reactive site. It seems reasonable, therefore, in this case to assume a process with the exclusive generation of **7** without participation of **9**.

To conclude, a convenient new method for the synthesis of 1-chlorophenazines is reported. Versatility, good yields, easy availability of starting materials, mildness and simple experimental procedure are noteworthy advantages of this approach, which has high potentiality in the access to previously unattainable phenazines.

1. Experimental

*Electrochemical reduction of **1***: A reductive electrolysis was carried out under a constant cathodic potential in a concentric cylindrical cell with two compartments separated by a circular glass frit (medium) diaphragm. A mercury pool (diameter 5 cm) was used as the cathode and a platinum plate as the anode. The catholyte was magnetically stirred. The temperature was kept at approximately 18°C by external cooling. The reduction was performed in MeCN (40 mL)–AcOH

(10 mL)–$LiClO_4$ (3 g); 35 mL and 15 mL were placed in the cathodic and the anodic compartments, respectively. Sodium acetate (0.2 g) was placed in the anode compartment. A solution of **1** (5 mmol) was electrolyzed under a cathode potential of –0.05 V versus SCE. The electricity consumption was 2 F/mol. Isolation of product **2** was carried out by removing the solvent in vacuo, adding water (150 mL) and extracting the mixture with chloroform (3×40 mL). The combined organic layers were washed with cold water and dried on anhydrous sodium sulphate. After evaporation of chloroform under reduced pressure the solid residue was crystallized from petroleum ether, mp 119–120°C. *Preparation of products* ***3***: A benzene solution (75 mL) of **2** (5.56 mmol) and the appropriate diamine (5.48 mmol) was refluxed with a Dean–Stark water separator for 24 h. Then the solvent was evaporated under reduced pressure and the residue was shaken with ether (75 mL). The small amount of a white solid remained in suspension was removed by filtration. After evaporation of ether, highly pure products **3** were isolated and crystallized from appropriate solvent. Products **3d** and **3e** were isolated by column chromatography (silica gel dichloromethane:ethyl acetate:hexane, 8:1:1). Compound **3a** (pet. ether) mp 135–137°C; **3b** (pet. ether) mp 197–198°C; **3c** (pet. ether) mp 152–153°C; **3d** (chloroform–pet. ether) mp 161–162°C, **3e** (ether–hexane) mp 138–140°C. *Preparation of products* ***4***: A dimethylformamide solution (30 mL) of the corresponding intermediate **3** (3.5 mmol) and 2,6-lutidine (2 ml) was refluxed for 2 h. After cooling the reaction products were isolated by dropping the solution onto cold brine (400 mL) and filtration. The directly collected solid crude products were washed with cold water, dried and crystallized from the appropriate solvent. Compound **4a** (hexane) mp 123–124°C (lit.[2] mp 121–122°C); **4b** (pet. ether–chloroform) mp 224–225°C; **4c** (pet. ether) mp 237–238°C; **4d** (chloroform) mp 184–186°C; **4e** (chloroform) mp 277–279°C.

All novel compounds gave satisfactory IR, ^1H NMR, ^{13}C NMR, mass spectra, and elemental analyses. Structures of isomers **3d–e** and **4d–e** were established on the basis of X-ray crystallography[16] of **3d**.

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15. Compound **9** was prepared by electrochemical reduction of **8**.
16. Details of the structure determination will be reported in a future full paper.