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The Dithianyl Group as a Synthon in Porphyrin Chemistry: Condensation Reactions and Preparation of Formylporphyrins under Basic Conditions

Mathias O. Senge,*,† Sabine S. Hatscher,† Arno Wiehe,‡ Katja Dahms,† and Andrea Kelling†

Institut für Chemie, Universität Potsdam, Karl-Liebknecht-Str. 24-25, D-14476 Golm, Germany, and Institut für Chemie, Organische Chemie, Freie Universität Berlin, Takustr. 3, D-14495 Berlin, Germany

Received August 7, 2004; E-mail: mosenge@chem.uni-potsdam.de

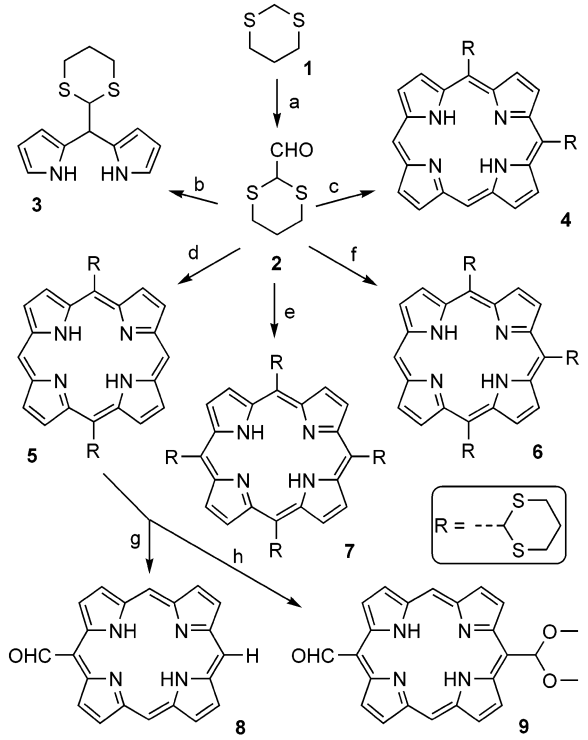
Despite an increasing number of technical, biomedicinal, and chemical applications of porphyrins, only few methods exist to introduce functional groups at the meso positions of the macrocycle.[1a] Newer developments are transition metal-catalyzed coupling reactions requiring use of halogenoporphyrins[1b] and S_NAr reactions using strong nucleophiles.[1c] Historically, S_EAr reactions have been used widely, notably Vilsmeier formylation and related reactions.[2] Formylporphyrins are excellent precursors for subsequent transformations; however, their utility is rather limited, as formylation requires use of acidic conditions and works well only with Ni^{II} or Cu^{II} complexes and introduction of a CHO group deactivates the system toward further formylations. Thus, no practical methods exists for *meso*-polyformylporphyrins.[3] To overcome these limitations we have developed a new synthetic concept for functionalized porphyrins using the 1,3-dithianyl residue as a synthon in porphyrin chemistry.

Current progress[1a] toward unsymmetrically substituted tetrapyrroles, both with condensation or substitution methods, offers the possibility to introduce functional groups in a strategic and regiochemical manner provided that appropriate synthons are available.[4] A classic synthon is the 1,3-dithiane-2-yl residue developed by Seebach and Corey.[5] Derivatives thereof are useful acyl anion equivalents and were used both as a functional and protected formyl group.[6] Thus, the lithio derivative of **1** offers the possibility to introduce latent formyl groups under nucleophilic instead of electrophilic conditions.

The dithianyl synthon can be used in two different strategies for the preparation of novel porphyrins.[7] First, reaction of **1** with DMF yields the aldehyde **2**,[8] which we have used as a key building block for porphyrins via condensation reactions (Scheme 1).[9] Aldehyde **2** can be converted in quantitative yield into the dipyrromethane **3**,[10a] which in turn is a useful building block for various condensations. Depending on the other reactants or the reaction conditions, **2** was used to prepare porphyrins with two to four dithianyl residues. For example, a 3 + 1 condensation gave the 5,10-disubstituted derivative **4** in low yield,[10b] while the 5,15-derivative **5** was obtained by reaction with dipyrromethane and TFA catalysis in 16%.

More complicated were reactions aimed at the preparation of the seemingly simple 5,10,15,20-tetrasubstituted porphyrin **7**. Standard condensations, for example, reaction of **3** with **2** or reaction of **2** with pyrrole under $BF_3{\cdot}OEt_2$ catalysis, afforded the 5,10,15-trisubstituted porphyrin **6** in 56% yield, each. Presumably, the target compound **7** is rather unstable. Related fragmentation reactions for nonporphyrinic systems have thus far been observed only in mass spectrometric studies.[11] However, **7** is accessible from **2** and pyrrole by using traces of BF_3 followed by neutralization with NEt_3 to afford the 5,10,15,20-tetrakis(1,3-dithianyl)-porphyrinogen in 53% yield. Subsequent oxidation with DDQ followed by rapid workup gave **7** in 15% yield with respect to **2**. Isolated **7** rapidly decomposed in solution in the presence of traces of acid and air under intermediary formation of **6**.[12]

Scheme 1. Synthesis of 1,3-Dithianylporphyrins via Condensation Reactions[a]



[a] Conditions: (a) *n*-BuLi, THF, −78 °C, 1 h; then −10 °C, DMF, 2 h; then 0 °C, 16 h; then ice, 85%. (b) Pyrrole, $BF_3{\cdot}OEt_2$, rt, 40 min, then NaOH, 96%. (c) CH_2Cl_2, tripyrrane, pyrrole, 45 min, rt; then TFA, rt, 16 h; then DDQ; then NEt_3, 3%. (d) CH_2Cl_2, dipyrromethane, TFA, 14 h, rt; then DDQ, 10 min, reflux, 16%. (e) CH_2Cl_2, pyrrole, $BF_3{\cdot}OEt_2$, 1 h, rt; then NEt_3, DDQ, 4 min, 15%. (f) CH_2Cl_2, pyrrole, $BF_3{\cdot}OEt_2$, 1 h, rt; then excess DDQ, 1 h, 46%. (g) $CHCl_3$, 8 equiv of bis(trifluoroacetoxy)iodobenzene (BTIB), 45 °C, 30 min, 62%. (h) $CHCl_3$, 4 equiv of BTIB, rt, 30 min, 30%.

Porphyrins with both meso alkyl/aryl and dithianyl groups are much more stable. For example, standard 2 + 2 condensation reactions gave porphyrin **12** with two dithianyl residues accompanied by **10** (due to scrambling) in low yields (Scheme 2). These compounds and those having not more than two dithianyl groups are reasonably stable toward chemical transformations. For example, **10** could be metalated with zinc acetate at room temperature in 60% yield and demetalated with BBr_3 in 50% yield.[14]

Our initial results on the dethioacetylation[15] reactions mimic these stabilities. While **10** and **12** could be quickly and quantitatively converted into the formylporphyrins **11** and **13** using DDQ,[16a] all attempts with **6** or **7** gave only partial deprotection and complex

† Universität Potsdam.
‡ Freie Universität Berlin.

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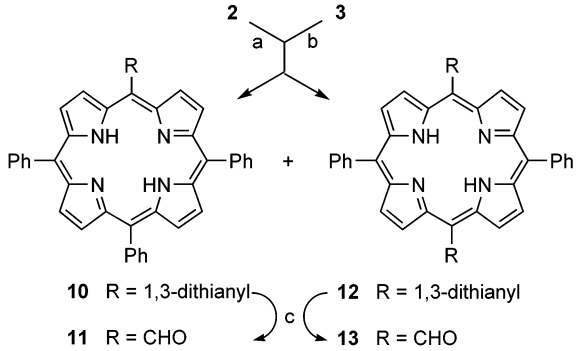
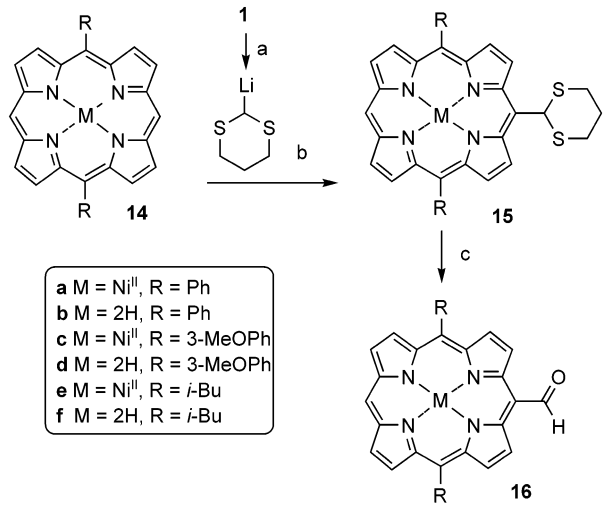
Scheme 2. 2 + 2 Condensation Reactions[a]



[a] Conditions: (a) CH_2Cl_2, 5-phenyldipyrromethane, catalytic TFA, 16 h, rt; then DDQ, 45 min, **10** 3%, **12** 2%. (b) CH_2Cl_2, benzaldehyde, catalytic TFA, 16 h, rt; then DDQ, 45 min, **10** 2%, **12** 4%. (c) CH_2Cl_2, DDQ, $BF_3{\cdot}OEt_2$, rt, 10 min, 97%.

Scheme 3. Synthesis of Formylporphyrins via S_NAr Reactions[a]



[a] Conditions: (a) *n*-BuLi, THF, −40 °C, 2 h, 100%. (b) THF, −78 °C, TMED, 15 min; then rt, H_2O, 15 min; then DDQ, rt, 15 min, **15a** 54%, **15b** 47%, **15c** 53%, **15d** 4%, **15e** 50%, **15f** 10%. (c) CH_2Cl_2, DDQ, then $BF_3{\cdot}OEt_2$, rt, 45 min, 96−100%.

mixtures. A variety of different oxidants were tested with **5**, and reproducible results were obtained so far only with bis(trifluoroacetoxy)-iodobenzene.[16b17] Use of 4 equiv at 50 °C or 8 equiv at room temperature resulted in formation of the monoformylporphyrin **8**[18] in 60% yield, while 4 equiv gave the dimethoxy derivative **9**.

Second, a potentially more useful strategy involves direct use of the lithio derivative of **1** as a nucleophile for the substitution of porphyrins. We have shown that various alkyl and aryllithium reagents can be used for the direct meso substitution of unactivated porphyrins in high yield.[1c] These reactions are regioselective and may be used for the substitution of all four meso positions, allowing the synthesis of ABCD porphyrins. Indeed, conversion of **1** into the lithio nucleophile and reaction with either Ni^{II} or free base porphyrins gave promising results.

As shown in Scheme 3, both meso aryl or alkyl Ni^{II} porphyrins and 5,15-diphenylporphyrin **14b** could be substituted in about 50% yield (unoptimized). Substitution of other free bases (e.g., **14d**[19] and **14f**) is possible but requires further optimization. All respective formylporphyrins **16**, including the free bases, were easily obtained with DDQ/$BF_3{\cdot}OEt_2$ in quantitative yield.

In conclusion, we have shown the dithianyl residue to be a convenient synthon in porphyrin chemistry, both for condensation and substitution reactions. This opens a new access to formylporphyrins under either mildly acidic or basic reaction conditions and offers the potential to prepare all possible homologues and regioisomers of poly-*meso*-formylporphyrins. Currently, we are optimizing the reactions described herein and trying to develop methods for the deprotection of **6** and **7**. Additionally, the possibility to use derivatives of **1** as photocleavable linkers in supramolecular multiporphyrin systems exists, as the photolytic cleavage of dithianyl derivatives has been described.[20]

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Supporting Information Available: Selected experimental procedures and compound characterization data (PDF) and full crystallographic data for **12** (CIF-file). This material is available free of charge via the Internet at http://pubs.acs.org.

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