

[A0009]

Sulfidation of Heterocyclic 1,3-Dicarbonyl Systems

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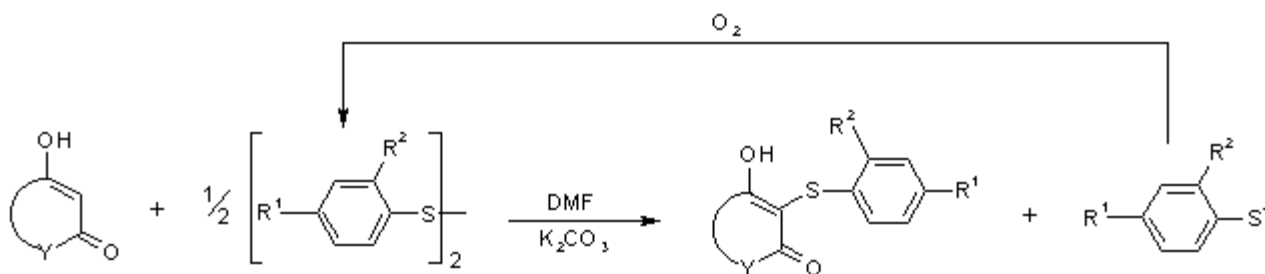
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Abstract

Anions of heterocyclic five- or six-membered 1,3-dicarbonyl systems react with aromatic disulfides and other -S-S- systems, such as dithiuramdisulfides in DMF in the presence of potassium carbonate to yield sulfides. The heterocyclic systems studied include pyrazol-1,3-diones, barbituric acid [1], 6-hydroxy-3(2H)-pyridazinones [2], 4-hydroxy-2-pyrones, 4-hydroxy-2-pyridones, and their benzo derivatives (e.g. coumarins and 2-quinolones [3]).

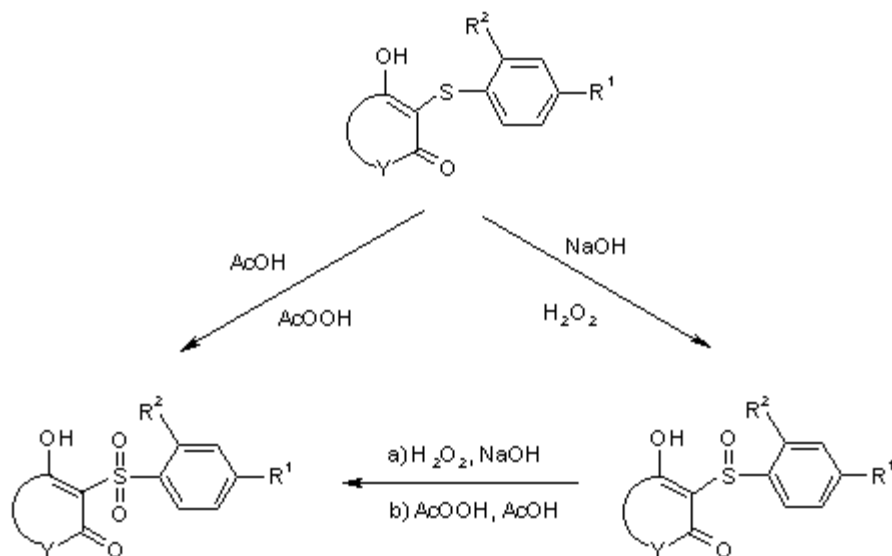
Oxidation of the aromatic sulfides with peracids yields sulfones, while careful oxidation with hydrogen peroxide in alkaline medium affords the sulfoxides. The latter class of compounds are heteroanalogs of the well known cyclic tricarbonyl methane derivatives (SO instead of CO) which show a broad range of biological activity, especially in agricultural chemistry.

General Scheme for the Preparation of Aromatic Sulfides from Heterocyclic 1,3-Dicarbonyl Systems (in DMF/ potassium carbonate)



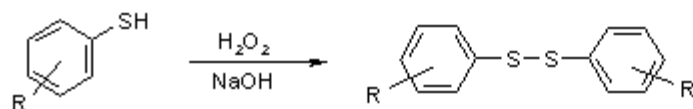
Note that the thiolate anion is easily oxidized by oxygen (air) to yield the aromatic disulfide back. Thus only 0.5 equivalents of the aromatic disulfide is needed.

General Scheme for the Oxidation of Aromatic Sulfides

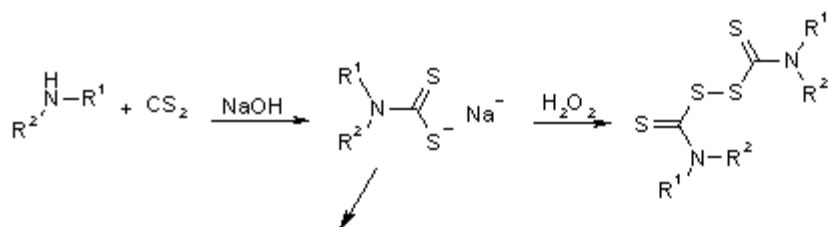


The oxidation with hydrogenperoxide in dilute sodium hydroxide solution yields usually the sulfoxides while oxidation under more drastic conditions, e.g. with peracids in acetic acid leads to the sulfones.

Synthesis of the Starting Disulfides



2-Cl; 4-Cl comm. available
 2-NO₂; 4-NO₂ comm. available
 2-CO₂H comm. available

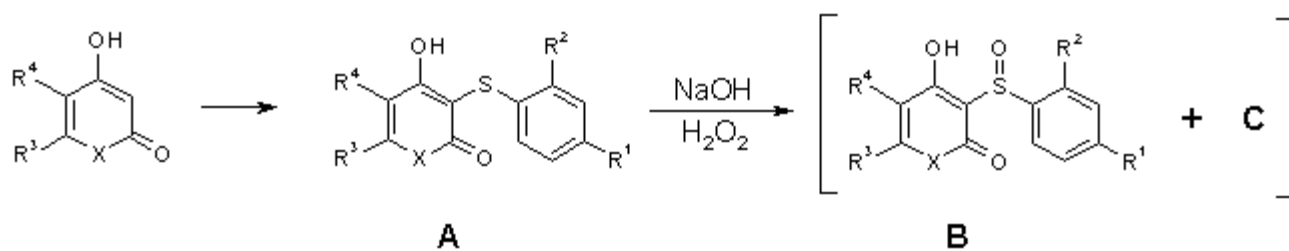


a powerful nucleophile!

R¹ = R² : Me, Et comm. available
 R¹ = Me; R² = Ph
 R¹-R²: -(CH₂)₆-; -CH₂-CH₂-O-CH₂-CH₂-

Most of the aromatic disulfides used in our study are commercially available. If not, they can quantitatively be obtained by oxidizing the alkaline solution of the thiophenolates with hydrogenperoxide. The thiuram disulfides can be obtained by oxidizing the solution prepared from secondary amine, sodium hydroxide and carbondisulfide with hydrogenperoxide.

Sulfidation of 4-Hydroxy-2-pyrones and 4-Hydroxy-2-pyridones and Oxidation of the Thioethers



X = O, NH, NCH₃, NPH

R¹ = H, Cl, NO₂

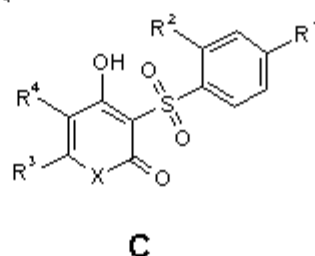
R² = H, NO₂

R³ = CH₃, Ph, C₃H₇-l

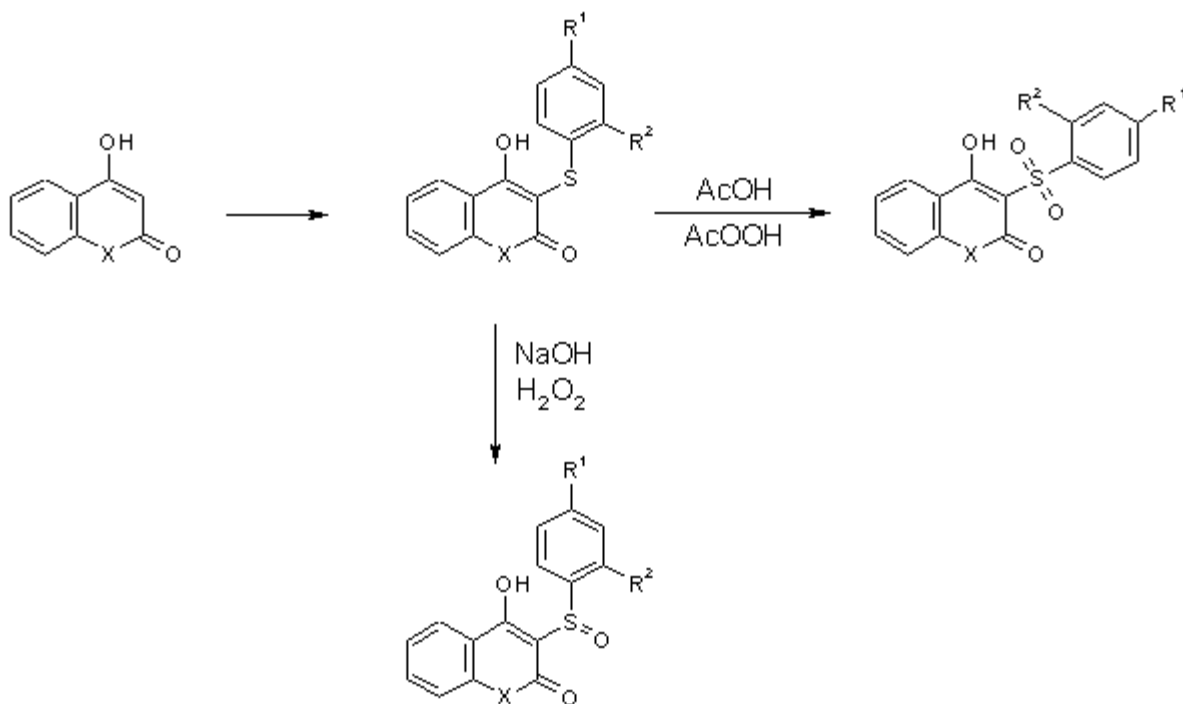
C₄H₉-t

R⁴ = H, CH₃, C₂H₅

obtained



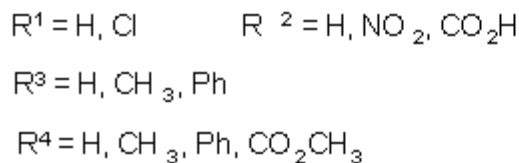
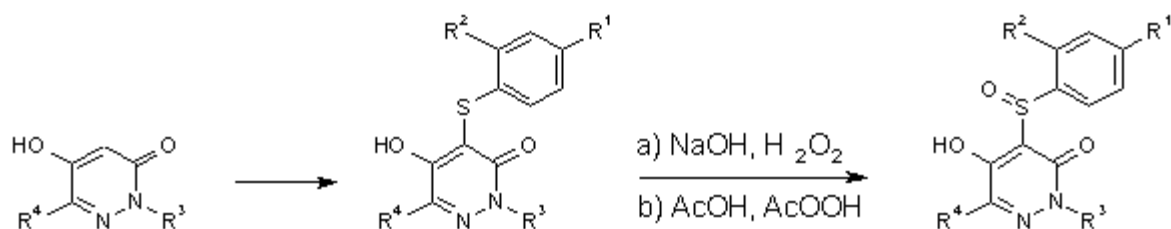
Sulfidation and Subsequent Oxidation of 4-Hydroxy-coumarins and 4-Hydroxy-2-quinolones [3]



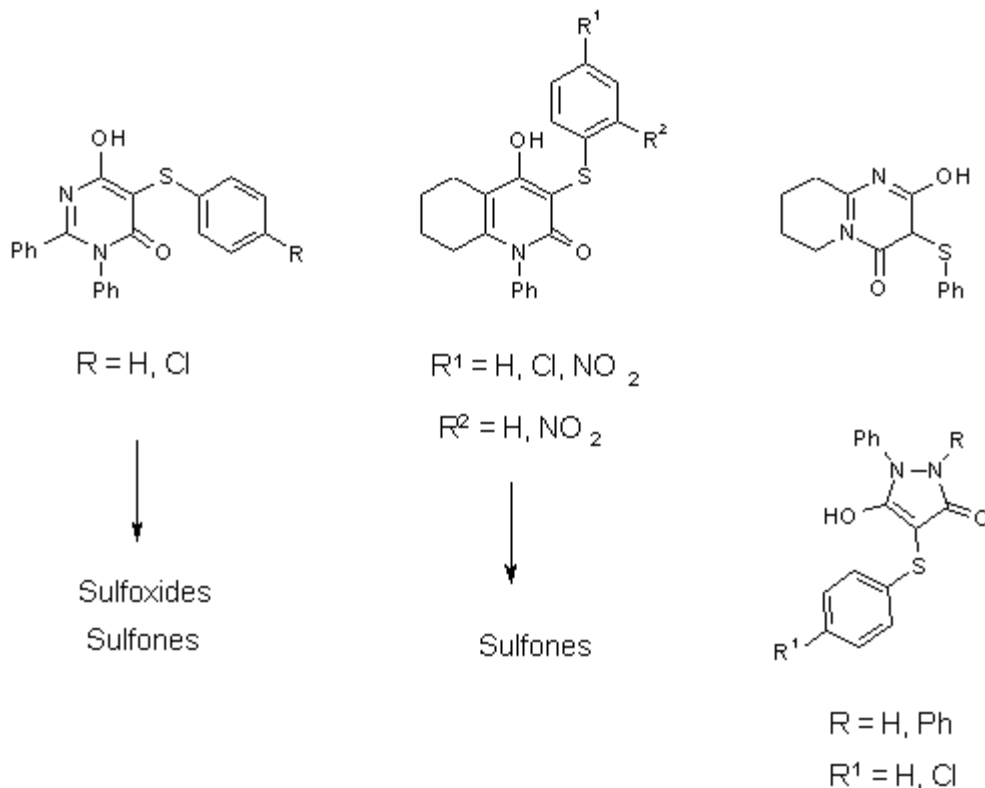
X = O, NH, NCH₃, NPh, NCH₂Ph

R¹ = H, Cl, NO₂ R² = H, NO₂, CO₂H

Sulfidation and Oxidation of 5-Hydroxy-3(2H)-pyridazinones [2]



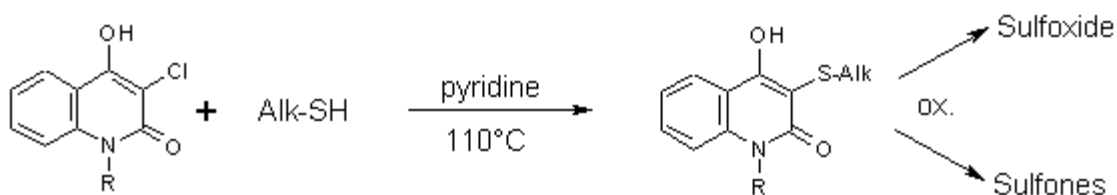
Reaction Products obtained from 6-Hydroxy-4-pyrimidones, 4-Hydroxy-5,6,7,8-tetrahydro-2-quinolones, 2-Hydroxy-pyridopyrimidin-4-ones and 5-Hydroxy-3-pyrazolones („Pyrazoldiones“, as Examples



of 5-Membered Ring Systems)

Synthesis of Aliphatic Sulfides and Their Oxidation Products

Aliphatic thioesters cannot be obtained by this method. The aliphatic disulfides are not electrophilic enough. They are available by the reaction of 3-chloro-4-hydroxy-2-quinolones with the corresponding alkylthiol.



R = H, Me

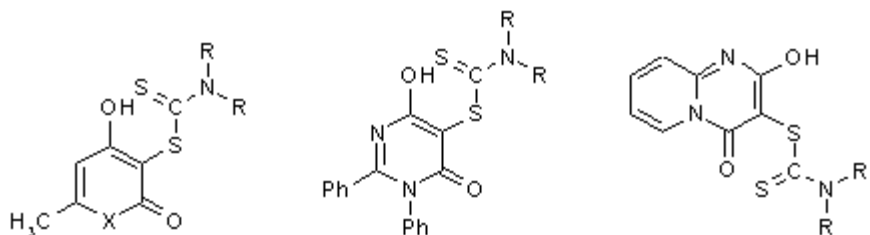
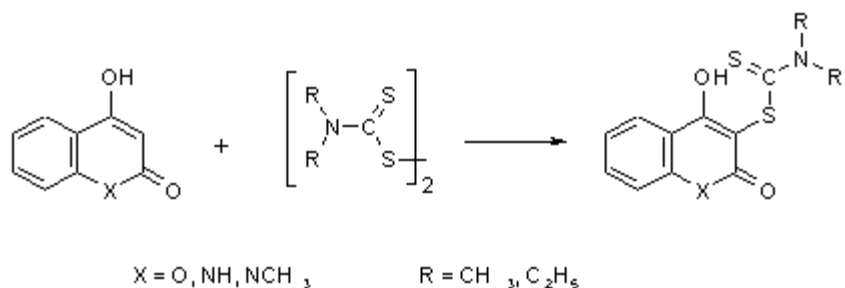
80 - 90%

Alk: Ph-CH₂-
 HO-CH₂-CH₂-
 HO₂C-CH₂-
 C-hexyl
 1-butyl
 t-butyl

(pyridine, Et₃N) 80% (4d)

The Reaction of Heterocyclic 1,3-Dicarbonyl Systems with Dithiuram-disulfides

In these reaction one equivalent of the disulfide is needed. No reoxidation of the produced anion with air is possible (hydrogenperoxide would be necessary, see synthesis of disulfides)



[1] O.Y. Neilands, I. Sudmale, B. Schnell, K. Georgieva and Th. Kappe, *J. Heterocyclic Chem.*, **35**, 157 (1998).

[2] Th. Kappe: "Pyridazines Functionalized in Position 3 and 5 with Heteroatoms" (Review). *J. Heterocyclic Chem.* **35**, 1111-1122 (1998).

[3] B. Schnell and Th. Kappe, *Monath.* 1999 in press.

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