*In the Name of God*

Razi University

**Faculty of Chemistry**

**Department of Organic Chemistry**

**M. Sc. Thesis**

# Title of the Thesis:

# Application of $H_2O_2$-$TiCl_4$ and $H_2O_2$-$POCl_3$ Systems for Deprotection of Thiocarbonyls and Dithioacetals and the use of TAPC for the Oxidative Coupling of Thiols to Disulfides

**Supervisor:**

**Prof. M. M. Khodaei**

**Dr. K. Bahrami**

**By:**

**Vida Shakibaian**

**September 2011**

**Abstract**

This thesis has been carried out in three parts:

**1. TAPC promotes highly efficient conversion of thiols to disulfides**

We present here the results on the use of TAPC in the conversion of thiols to the corresponding disulfides under solvent-free conditions. This efficient and improved method is general for aromatic, aliphatic, and functionalized thiols affording the disulfides in excellent yields and short reaction times after easy work-up.

**2. $TiCl_4$-promoted desulfurization of thioamides and thioketones in the presence of $H_2O_2$**

$H_2O_2$ in combination with $TiCl_4$ proved to be a highly reactive reagent system for the desulfurization of thioamide and thioketone derivatives in excellent yields and short reaction times with high purity. In most cases these reactions are highly selective and simple affording products in high yields and purity.

**3. A novel approach towards dethioacetalization reactions with $H_2O_2$-$POCl_3$ system**

A simple and efficient protocol for the deprotection of dithioacetal, 1,3-dithianes and 1,3-dithiolanes has been developed using $H_2O_2$-$POCl_3$ system. In addition to the absence of overoxidation products for oxidation-prone substrates, high chemoselectivity, the low cost and availability of the reagents, simplicity of the method, short reaction times, and excellent yields can also be considered as strong points for this method. A plausible mechanism for this reaction is delineated.

***Acknowledgment***

*Endless gratitude and praise be upon most praise worthy almighty God who keeps the light of knowledge in human mind alight and burning, in whose ray human being free from ignorance and reach salvation and sheer bliss.*

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***Dedicated To:***

*My Dear Parents*

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# Chapter One

## Introduction

## 1.1. Disulfides

Disulfides are important in both biological[1] and chemical processes.[2] Disulfides are useful reagents in organic synthesis[2] and essential moieties of biologically active compounds for peptide and protein stabilization. Neuroglobin (Ngb) is a kind of proteins that composed of 151 amino acids and is predominantly expressed in the brain, the retina and other nerve tissues. NGB contains 3 cysteine residues. In the case of human neuroglobin, cysteines form an internal disulfide bond. Formation and cleavage of this disulfide bond influences the functional characteristics of the protein.[3]

When the $O_2$ concentration increases, the free cysteines will be oxidized and will form mainly the intra-molecular disulfide bond with the concomitant increase of the $O_2$ affinity to binding to the iron atom. Concomitant with an $O_2$ release, related to the redox state of the cell, the biosynthesis of NGB is induced in order to be able to bind more $O_2$ during a temporary increase in the $O_2$ partial pressure for release in the forthcoming period of hypoxia (Figure 1.1).

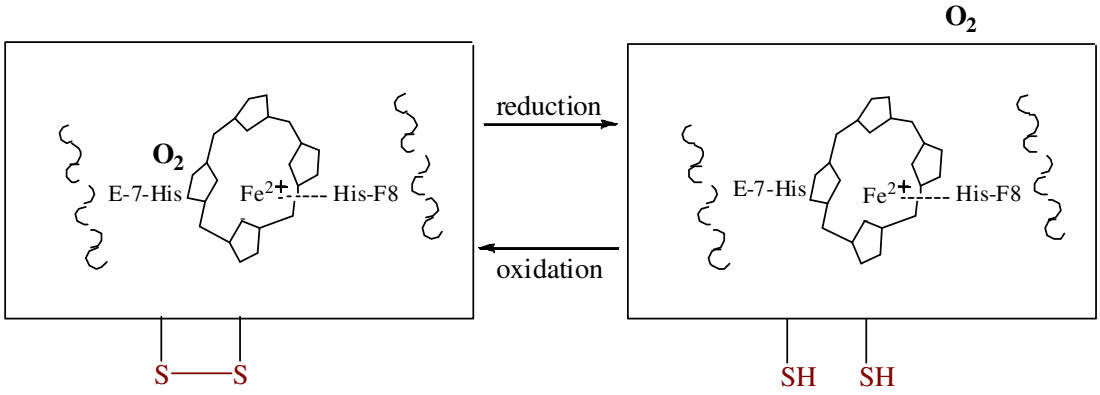



**Figure 1.1**

Arginine vasopressin (AVP), also known as vasopressin or antidiuretic hormone (ADH), is a neurohypophysial hormone found in most mammals, including humans.[4] The vasopressins are peptide consisting of nine amino acids with the cysteine residues forming a disulfide bridge (Figure 1.2).

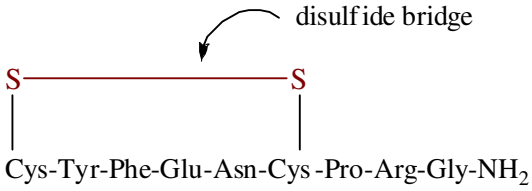



**Figure 1.2**

Gliotoxin is a sulfur-containing mycotoxin produced by several species of fungi (Figure 1.3).[5] In vivo it displays anti-inflammatory activity. It was investigated as an antibiotic and antifungal in the 1940's and recently as an antiviral agent. In this regard, we review some methods for the conversion of thiols to the corresponding disulfides presented below.

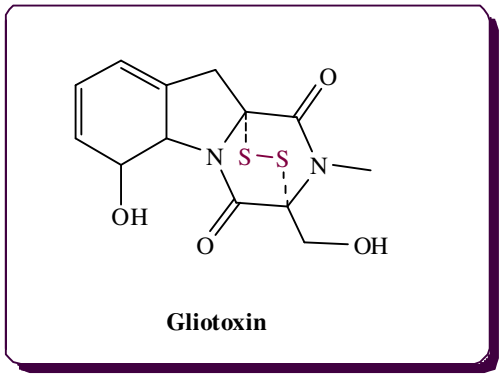



**Figure 1.3**

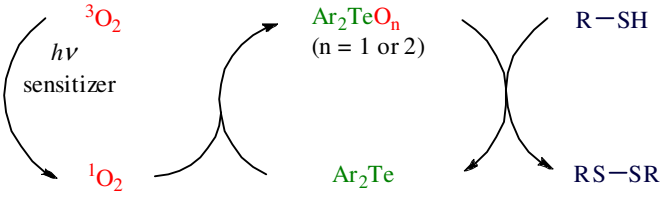
## 1.1.1. Aerial oxidation of thiols

Considering recent trends focusing on the use of nonhazardous, green reagents, molecular oxygen has been regarded as an environmentally benign, sustainable oxidant. The reaction of thiols with oxygen or air is sensitive to the presence of catalyst. However, generally, the air oxidation of thiols is performed in the presence of a base or heavy metal ions. Obviously, neutral and metal-free conditions are preferred.

### 1.1.1.1. Diaryl tellurides under photosensitized conditions

Aerobic oxidation of thiol is efficiently catalyzed by diaryl tellurides under photosensitized conditions to give the corresponding disulfides in good to excellent yields. This method has been reported by *M. Oba et al.*[6]

In this catalytic system, the tellurone oligomer, produced by the reaction of a telluride with singlet oxygen, is assumed to be the active species and is capable of oxidizing 4 equiv of a thiol (Scheme 1.1).



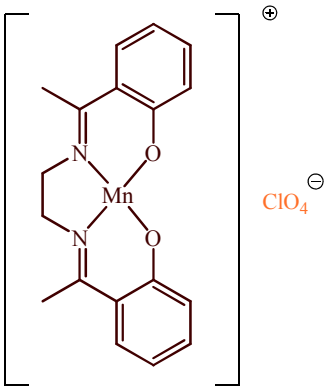

R = Alkyl, aryl

***Reagents and conditions*:** Thiol (1 mmol), $Ar_2Te$ (1 mol %), sensitizer (0.1 mM), $CH_2Cl_2$ (0.1 M), *hv*, air, 0 °C.

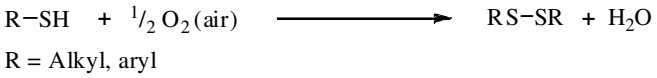
**Scheme 1.1**

### 1.1.1.2. Manganese(III) Schiff-base complex

*H. Golchoubian et al.*[7] reported a method for oxidative coupling of aryl thiols into the corresponding disulfides using molecular oxygen catalyzed by the Mn(III) Schiff-base complex (**I**) in methanol at room temperature (Scheme 1.2).




**I**




R = Alkyl, aryl

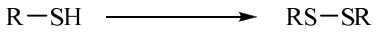
***Reagent and conditions*:** Thiol (1 mmol), Mn(III) Schiff-base (0.05 mmol), MeOH, r.t.

**Scheme 1.2**

## 1.1.2. TCT-DMSO or TMSCl

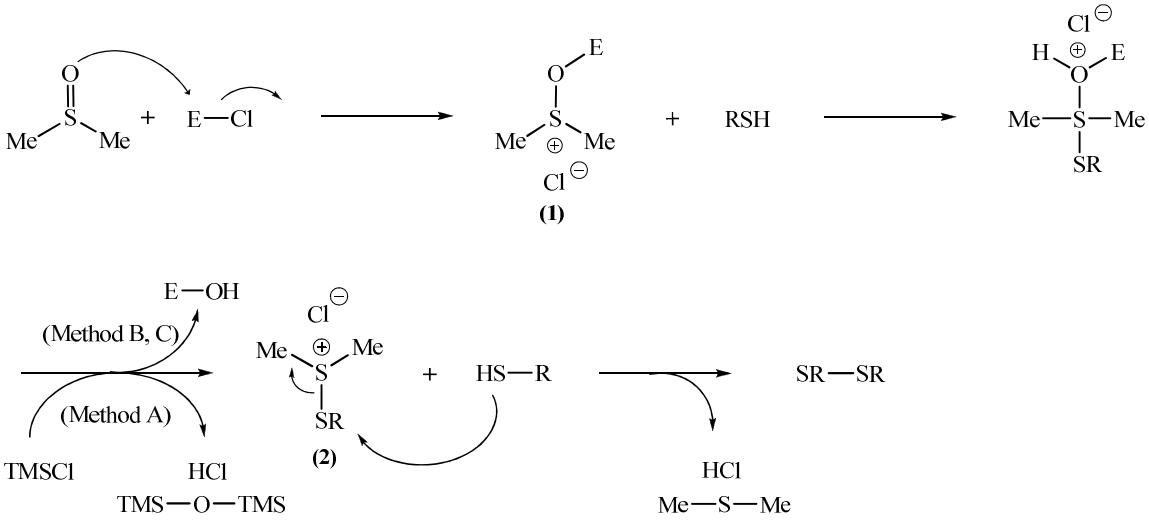
Application of dimethylsulfoxide (DMSO) in organic transformations is of interest because of its stability, ease of handling, none corrosive and safe nature and inexpensiveness. However, the major limitation of the use of DMSO is its low oxidizing power. This problem can be circumvented by prior treatment of DMSO with a variety of oxophilic co-reagents under acidic conditions as shown by the pioneer work of *Swern et al*.[8]

*B. Karimi et al*.[9] have demonstrated new methods for the oxidation of thiols using DMSO in the presence of catalytic amounts of either trimethylchlorosilane (TMSCl) or cyanuric chloride (CC) (Scheme 1.3). Proposed mechanism for this reaction is shown below (Scheme 1.4).




***Reagents and conditions*:** Method A = Thiol:DMSO:TMSCl, 1:3:0.1; Method B = Thiol:DMSO:CC, 1:1.5:0.4; Method C = Thiol:DMSO:CC, 1:3:0.1, $CH_2Cl_2$, r.t.

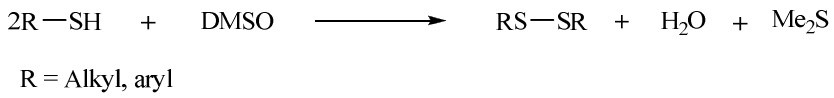

**Scheme 1.3**




**Scheme 1.4**

### 1.1.3. Dichlorodioxomolybdenum(VI)-DMSO

*R. Sanz et al.*[10] presented a mild, efficient and selective oxidation of thiols to disulfides by DMSO catalyzed by a dioxomolybdenum(VI) complex. The overall oxidation process proposed could be written as shown in the Scheme 1.5.



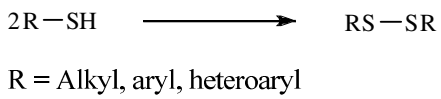

***Reagents and conditions*:** Thiol (2 mmol), $MoO_2Cl_2(DMSO)_2$ (1 mol %), r.t.

**Scheme 1.5**

It is worth noting that thiols having electronwithdrawing substituents were oxidized within 10 minutes whereas, for instance, 4-methoxybenzenethiol needed 30 minutes to afford the corresponding disulfide. This fact suggests that the rate of reaction is dependent on the acidity of the mercaptan.

### 1.1.4. [bmim][$SeO_2(OCH_3)$]

*S. Thurow et al.*[11] presented the results on the use of 1-n-butyl-3-methylimidazolium methylselenite, [bmim][$SeO_2(OCH_3)$], in the synthesis of symmetrical disulfides starting from thiols. This method is general for aromatic, aliphatic, and functionalized thiols affording the disulfides in good to excellent yields. The use of a microwave accelerates the reaction and the [bmim][$SeO_2(OCH_3)$] was reused for further oxidation reactions (Scheme 1.6).




***Reagent and conditions*:** Thiol (1 mmol), [bmim][$SeO_2(OCH_3)$] (1 mL), 60 ºC or MW at 30 ºC, air.

**Scheme 1.6**

### 1.1.5. PVP-$N_2O_4$

*N. Iranpoor et al.*[12] introduced polyvinylpyrrolidone-supported $N_2O_4$ (PVP-$N_2O_4$) as a hetergenous and polymeric reagent for coupling of thiols to disulfides (Scheme 1.7).

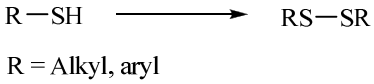

***Reagent and conditions*:** Step (1): Thiol (1mmol), PVP-$N_2O_4$ (0.2 g) at 10 °C, $CHCl_3$ (2 mL). Step (2): r.t.

**Scheme 1.7**

Thiols were converted to *S*-nitrosothiols (thionitrites) using this nitrosating agent in *n*-hexane or $CHCl_3$ at 10 °C. Most of the thionitrites are thermally and photochemically unstable, especially in the presence of $O_2$. It was observed that if the reaction of thiols with PVP-supported $N_2O_4$ was stirred for a longer period of time in the presence of air at room temperature, the thionitrite intermediate could be converted into the corresponding disulfides with high yields without adding any extra reagent.

## 1.1.6. $Br_2$-$SiO_2$

*M. H. Ali et al.*[13] reported the results of the oxidation of thiols to disulfides utilized molecular bromine on hydrated silica gel (Scheme 1.8). The procedure utilizes organic media and does not require a base to neutralize HBr by-products to suppress acid promoted side reactions. The silica gel acts as both a heat sink and as HBr scavenger. No significant amounts of acid-catalyzed side reaction products are found.




***Reagents and conditions*:** Thiol (4.02 mmol), $Br_2$ (4.06 mmol), Hydrated silica gel, $CH_2Cl_2$.

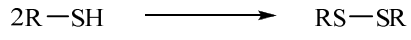
**Scheme 1.8**

## 1.1.7. UHP-Maleic anhydride

Hydrogen peroxide is the most common reagent for oxidation of organic compounds, especially thiols, but it has several problems such as instability of the reagent itself and overoxidation of thiols to sulfonic acids as well as the desired disulfides. The use of hydrogen peroxide adducts is a convenient strategy to control $H_2O_2$ oxidation reactions. In general, hydrogen peroxide adducts are not able to oxidize organic compounds by themselves, therefore introduction of an inorganic catalyst or organic mediator for active

oxygen transfer of these adducts is a necessity in oxidation systems where they are used. Among these adducts urea-hydrogen peroxide is an inexpensive, stable, mild and easy to handle source of pure $H_2O_2$.

*B. Karami et al.*[14] used Urea-hydrogen peroxide (UHP) in the presence of maleic anhydride as mediator in a method for the oxidation in high yield of some thiols to the corresponding disulfides (Scheme 1.9). Peroxymaleic acid formed *in situ* from the reaction of UHP with maleic anhydride has a key role in this oxidation.

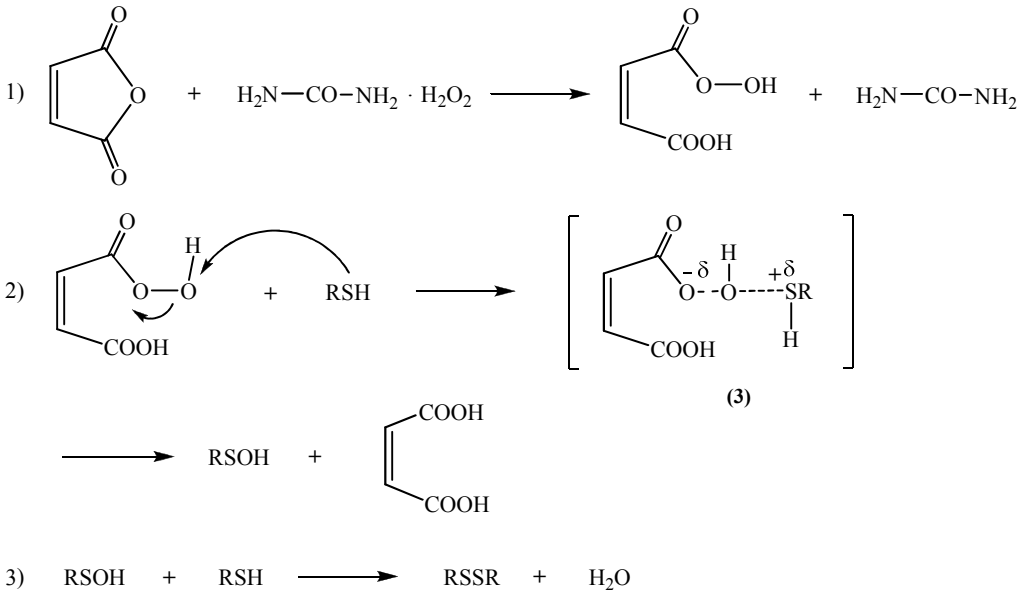


R = Aryl; UHP = $H_2NCONH_2$—$H_2O_2$

***Reagents and conditions*:** Thiol (1 mmol), UHP (1mmol), Maleic anhydride (1 mmol), $CH_3OH$ (10 mL), 0 °C.

**Scheme 1.9**

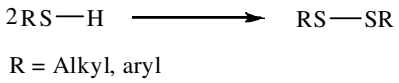
Based on literature precedents, peroxymaleic acid, formed *in situ* from the reaction of hydrogen peroxide with maleic anhydride (eq.1) is the active oxidant. The active oxygen of the peroxymaleic acid oxidizes RSH to RSOH (eq.2) *via* **3**, that reacts with another RSH molecules to produce the disulfide. This is consistent with the fact, that thiols bearing more electron withdrawing substituents, which lead to potentially unstable transition states (**3**) as proposed, are oxidized with more difficulty (Scheme 1.10).



**Scheme 1.10**

### 1.1.8. $(Bu^n PPh_3)_2Cr_2O_7$

*I. Mohammadpoor-Baltork et al.*[15] have introduced *n*-butyltriphenylphosphonium dichromate as a reagent for the oxidation of thiols to disulfides. High yields of the products, easy work-up, and selective oxidation of thiols in the presence of alcohol and sulfide are noteworthy advantages of this method (Scheme 1.11).

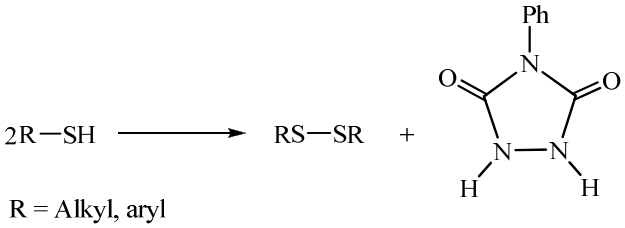



***Reagent and conditions*:** Thiol:BTPPDC, 1:0.5, $CH_3CN$ (10 ml per mmol of thiol).

**Scheme 1.11**

### 1.1.9. N-Phenyltriazolinedione

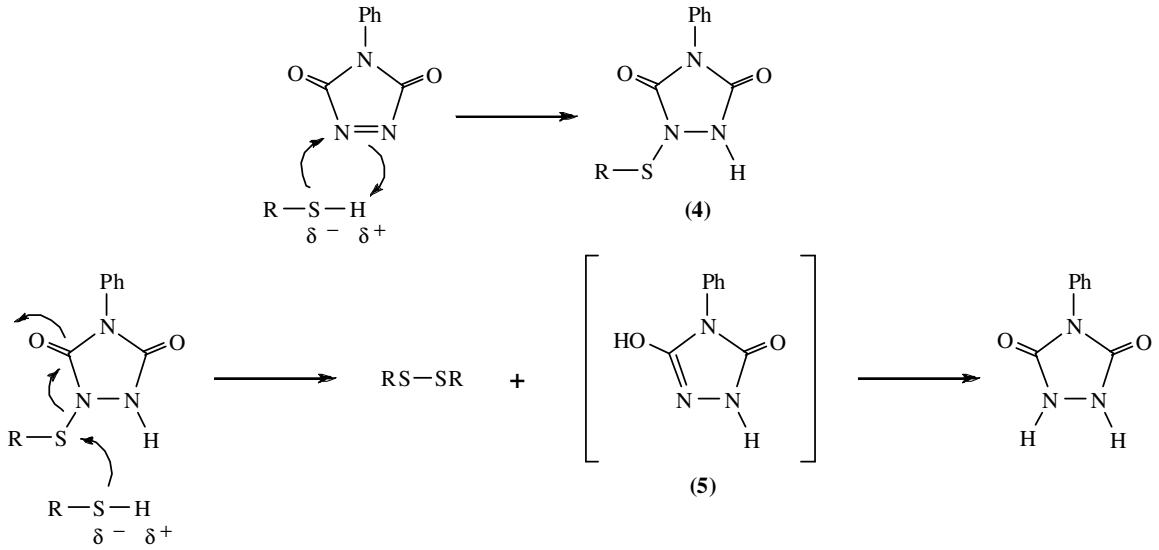
*A. Christoforou et al*.[16] reported a new method for the oxidation of thiols to symmetrical disulfides in good to excellent yields, with the *cis*-locked azocompound N-triazolinedione as the oxidant (Scheme 1.12).




***Reagent and conditions*:** Thiol (1 mmol), N-phenyltriazolinedione (0.5 mmmol), Toluene or no solvent, r.t.

**Scheme 1.12**

They proposed two step sequence for the dimerization–oxidation of thiols with PhTAD. In the first step a thiol molecule is added to the diazene double bond ('displacement' of an electron pair) to yield a sulfenyl urazole derivative **4**. In a subsequent step, a second thiol molecule attacks, as a nucleophile, the sulfur atom of I, to yield a disulfide and the parent N-phenylurazole, after tautomerization through intermediate **5** (Scheme 1.13).




**Scheme 1.13**

## 1.2. Conversion of thiocarbonyl groups into corresponding carbonyl groups

Thiocarbonyl compounds are specific and versatile tools for multi-step synthetic routes leading to various natural products or biologically active molecules.[17] Structures of some carbonyl compounds used as drug candidates is shown in Figure 1.4.

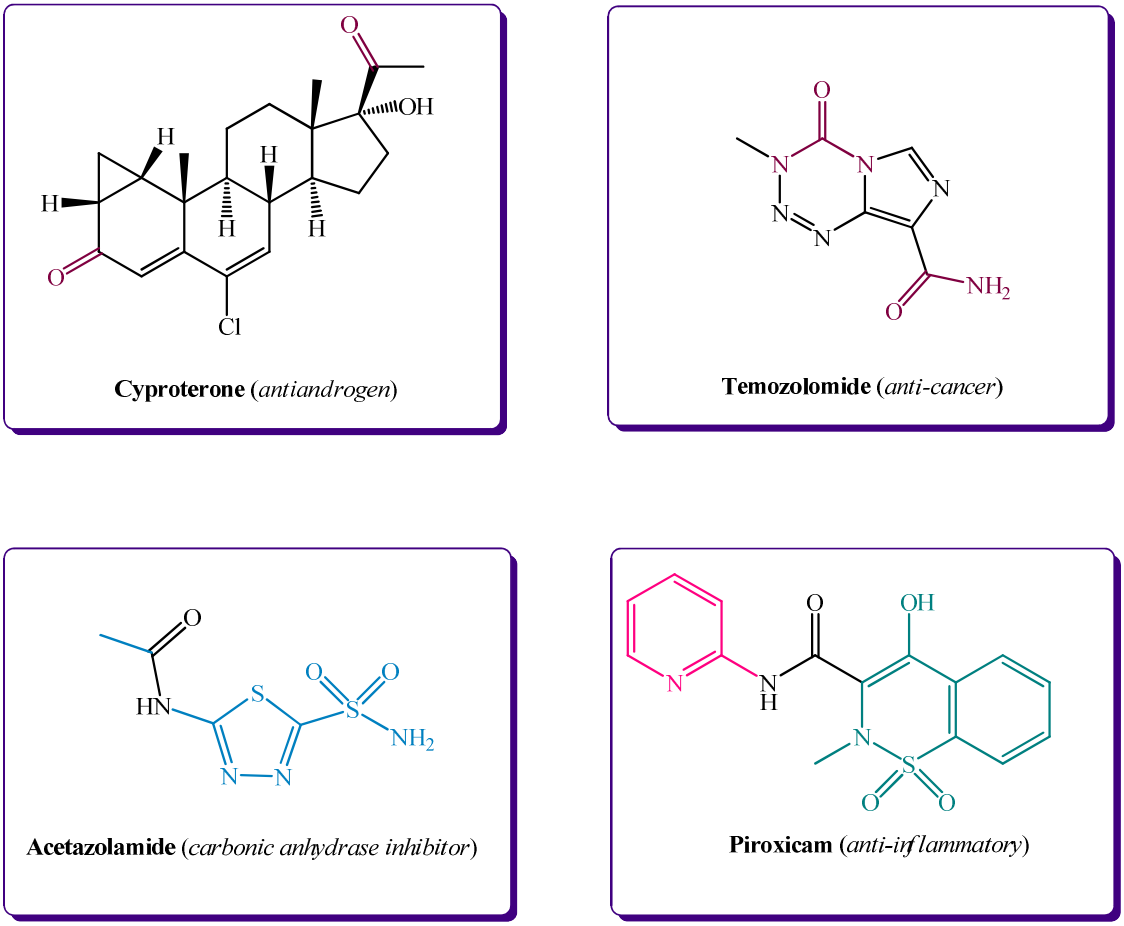



**Figure 1.4**

On the other hand, most physiologically interesting substances contain carbonyl groups. These compounds are found in the nucleic acid of DNA that represented by the letter T-C-G (Figure 1.5). Here, we report several methods for the conversion of thiocarbonyl to carbonyl compounds

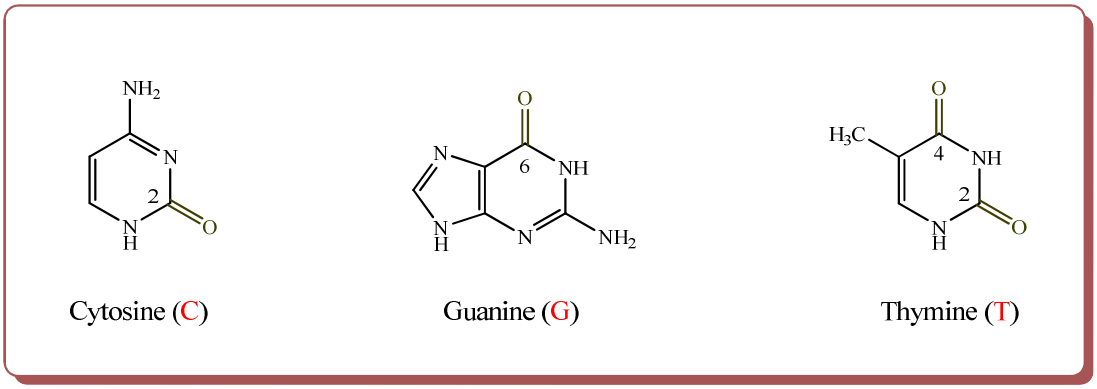
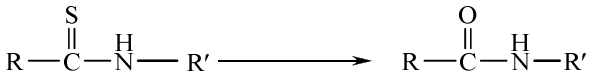



**Figure 1.5**

## 1.2.1. Manganese dioxide

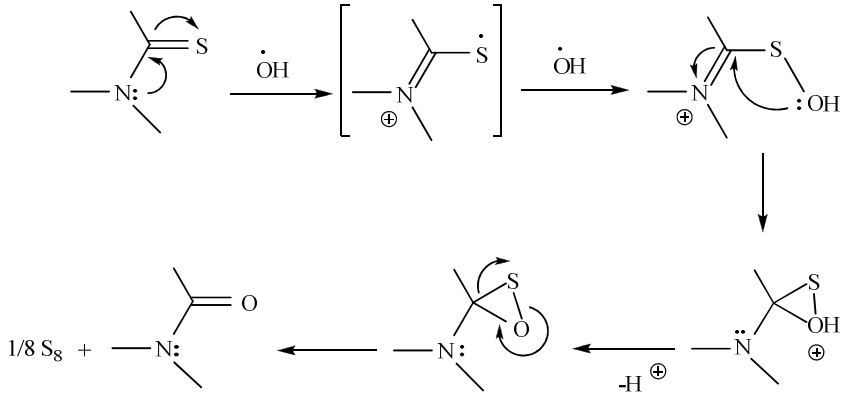
A simple procedure for the conversion of thioamides to amides in good yields using active manganese dioxide was described by *R. Rani et al.*[18] (Scheme 1.14). A possible reaction mechanism is presented in Scheme 1.15.



R = Aryl; R′ = Alkyl, aryl

***Reagent and conditions*:** Thioamide (1 mmol), $MnO_2$, $CHCl_3$.

**Scheme 1.14**



**Scheme 1.15**