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Chapter One

Introduction

1.1. Amides

1.1.1. biological action of amides

Various derivatives of amides were synthesized and evaluated for in vitro and invivo antimycobacterial activities against some kind of mycobacterium tuberculosis.[1] In recently years, amide compounds which were derived from ferulic acid using various amines have been reported and their stimulatory effects investigated on insulin secretion using pancreatic RIN-5F cells. The amide compounds of ferulic acid were synthesized by condensation reaction of O-acetyl feruloyl chloride with various amines, followed by deacetylation to yield corresponding amide.[2] Capsicum with a common structure comprising a group of acid amides of vanillylamine and fatty acids have been used for their medicinal effect. Primarily for stomach disorder and as a topical counter irritants for relief of pain and in?ammation.[3,4] The preparation method has been noticed.[5] Chloramphenicol is an antimicrobial agent. It has been used since the 1950s to combat a wide range of microbial infections, including typhoid fever, meningitis, and certain infections of the central nervous system.[6]

Nicotinamide (niacinamide) is a water-soluble vitamin and is part of the vitamin B group.[7] Nicotinamide has demonstrated anti-inflammatory actions that may be of benefit in patients with inflammatory skin conditions.[8] Niaprazine (Nopron) is a sedative-hypnotic drug of the phenylpiperazine class.[9] It has been used in the treatment of sleep disturbances since the early 1970s in several european countries.[10,11] Originally believed to act as an antihistamine and anticholinergic[12] (Fig. 1.1).

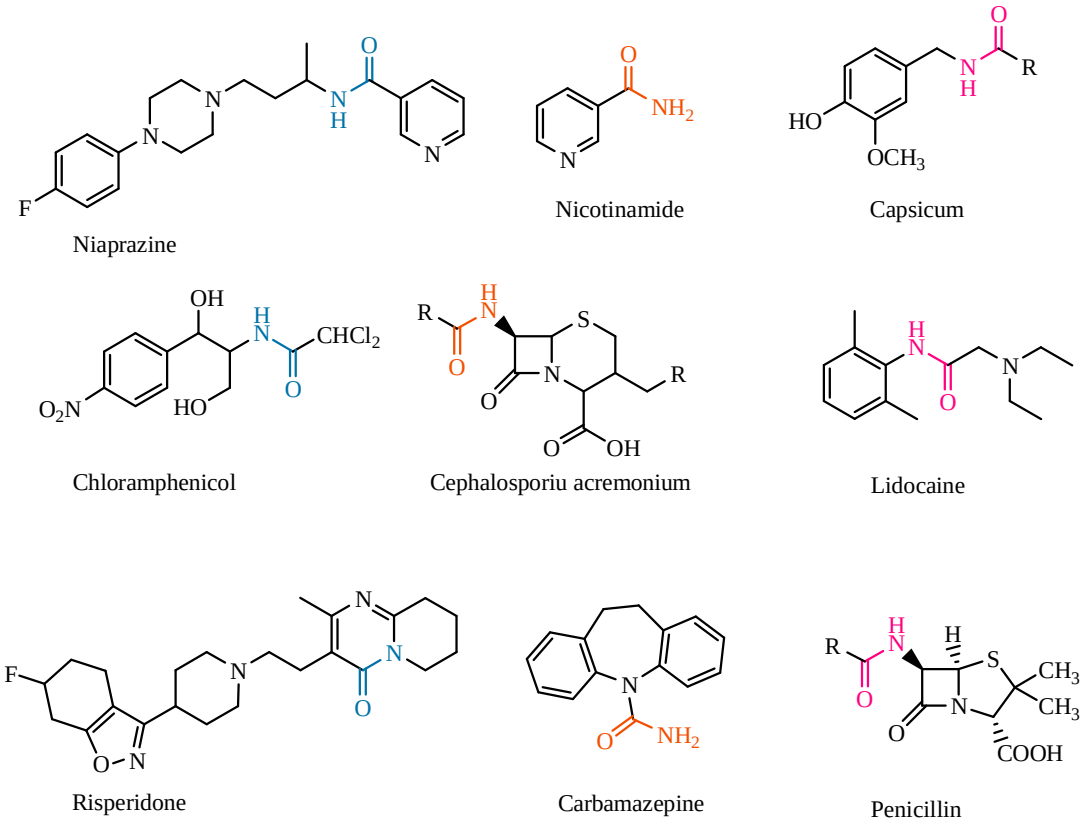


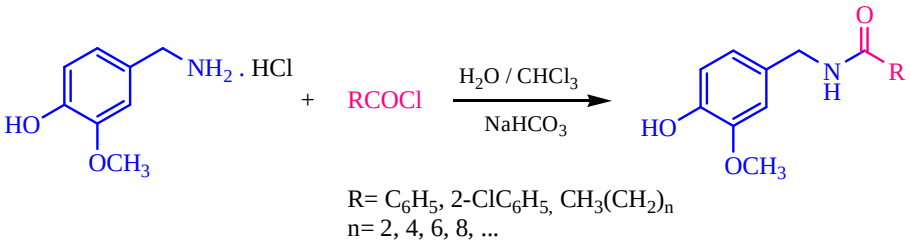
Figure 1.1

Also amides are valuable chemical intermediates in some organic reactions, they can be dehydrated to nitriles, hydrolyzed to carboxylic acids, and degraded to amines in Hofmann rearrangement.[13]

1.1.2. Synthesis of amides

1.1.2.1. Synthesis of capsaicin analogues by condensation reaction

The most convenient method for preparation of capsaicinoids is by selective acylation of vanillylamine with acyl chloride. However vanillylamine is poorly soluble in anhydrous systems, and acyl chloride is easily hydrolysed when water is present, so it is very difficult to obtain a satisfactory yield. Recently *J. Tang et al.*[5] reported a highly efficient method for synthesis of capsaicin analogues by interfacial reaction of vanillylamine-H_2O with acyl chloride-$CHCl_3$ (Scheme 1.1).



Scheme 1.1

During this condensation, esterification of the phenolic hydroxyl and hydrolysis of the acyl chloride can occur, as well as the expected acylation of the amino group. To inhibit this side reactions, a biphase $H_2O/CHCl_3$ system was used (Fig. 1.1).

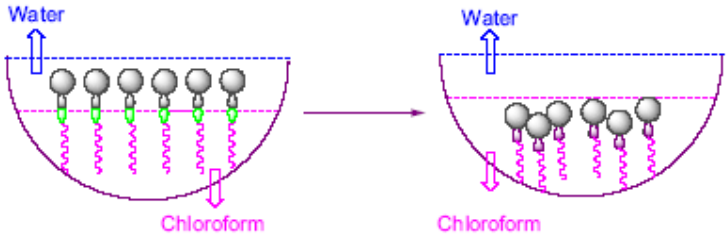
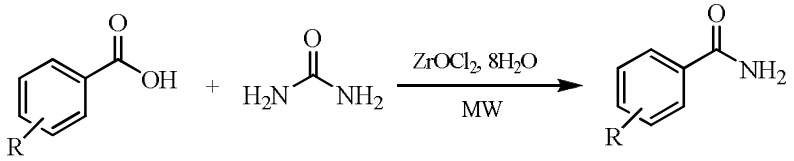


Figure 1.2. Schematic drawing of the condensation reaction

1.1.2.2. $ZrOCl_2$

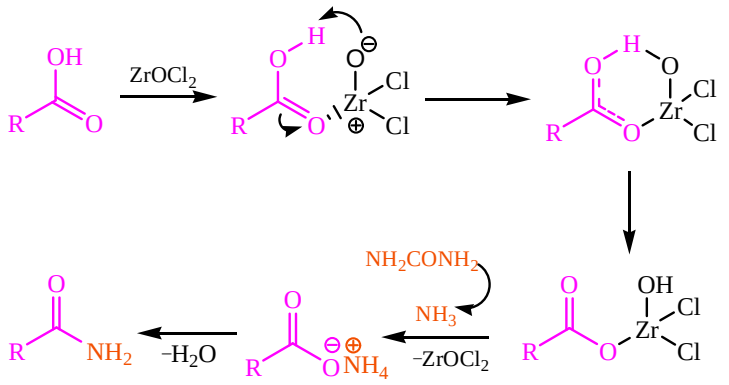
C. S. Reddy. et al.[14] reported a solid phase synthesis of amide derivatives from carboxylic acids and urea catalyzed by zirconyl chloride under microwave irradiation condition (Scheme 1.2).



Scheme 1.2

A tentative mechanism to rationalize the product formation is shown in Scheme 1.3. Formation of zirconium carboxylate salt is expected in the first instance. This salt may increase absorption of the microwave energy and the energy absorption increment may

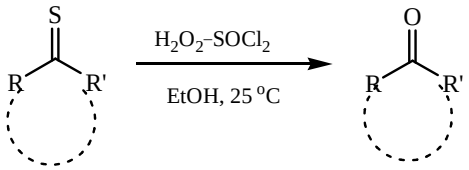
cause the pyrolysis of urea and hence liberation of ammonia. In the second step, the zirconium may get exchanged with ammonia to form the ammonium carboxylate salt which on elimination of water results in the formation of the corresponding carboxamide.



Scheme 1.3

1.1.2.3. H_2O_2–$SOCl_2$

Recently, *K. Bahrami et al.*[15] reported a reasonably method to desulfurize thiocarbonyls to their oxo analogues using H_2O_2 in the presence of $SOCl_2$ for deprotection of thiocarbonyls to carbonyl compounds (Scheme 1.4).

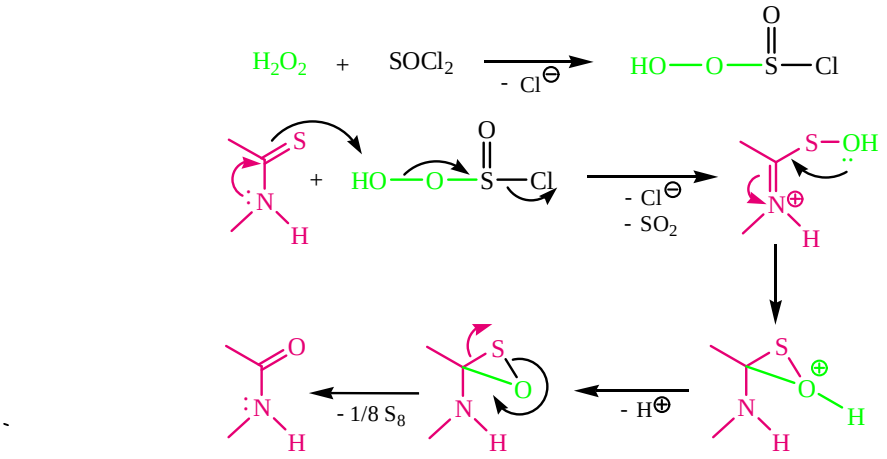


R = Alkyl, aryl

R' = Alkyl, aryl, NHPh, 4-MeC_6H_4NH

Scheme 1.4

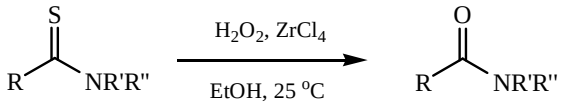
The possible mechanism for this reaction is outlined in Scheme 1.5. It is acceptable to assume that the nucleophilic attack of H_2O_2 on $SOCl_2$ makes oxygen atom more electrophilic. Therefore, the mechanism proceeds probably through a cyclic intermediate that undergoes sulfur extrusion.



Scheme 1.5

1.1.2.4. H_2O_2–$ZrCl_4$

K. Bahrami et al.[16] reported a Friendly method that enables desulfurization of thioamides to their oxo analogues with the hydrogen peroxide/zirconium(IV) chloride reagent system in excellent yields (Scheme 1.6).

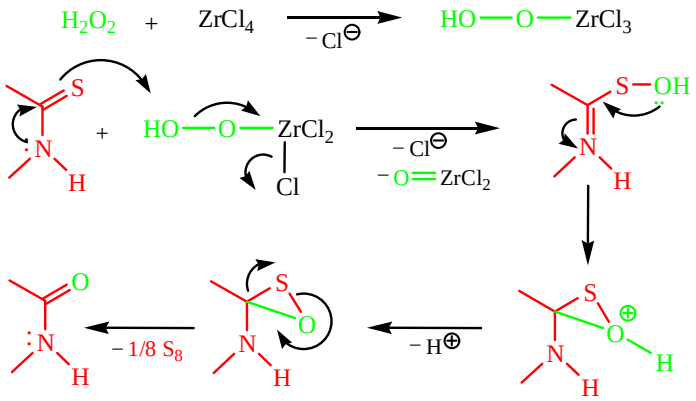


R = Ph, 4-MeC_6H_4, 4-$O_2NC_6H_4$, 4-ClC_6H_4 , Me

NR'R'' = NHPh, 4-MeC_6H_4NH, 4-BrC_6H_4, 1-naphthylamino, piperidino, NHBu

Scheme 1.6

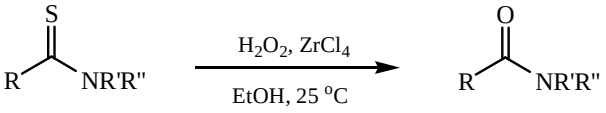
The proposed mechanism for the desulfurization of thioamides is shown in Scheme 1.7.



Scheme 1.7

1.1.2.5. n-$Bu_4N IO_4$

A mild and efficient conversion of thioamides and thioureas into the corresponding oxo compounds by using tetrabutylammonium periodate (n-$Bu_4N^+ IO_4^-$) was reported by *A. R. Pourali.*[17] As shown in Scheme 1.8 various thioamides and thioureas were reacted with the reagent at room temperature to afford the corresponding amides or ureas in good to excellent yields.



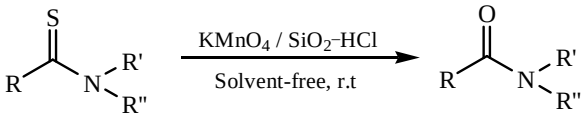
R = Ph, 4-MeC_6H_4, 4-$O_2NC_6H_4$, 4-ClC_6H_4 , Me

NR'R" = NHPh, 4-MeC_6H_4NH, 4-BrC_6H_4, 1-naphthylamino, piperidino, NHBu

Scheme 1.8

1.1.2.6. $KMnO_4$–SiO_2

M. N. Esfahani. et al.[18] reported a new method for conversion of thioamides to their corresponding amides by acidified wet silica supported permanganate under solid phase conditions. (Scheme 1.9).

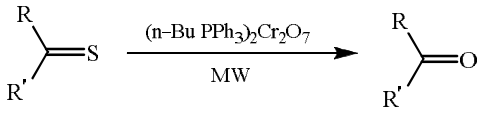


Scheme 1.9

In the absence of acid, the conversion of thioamides decreased to 5-10%, and in the absence of SiO_2 the thioamides remained intact. It was found that in these reactions sulfur is converted to sulfate and replaced by oxygen, which is indicated by addition of a solution of $BaCl_2$.

1.1.2.7. (n-$BuPPh_3)_2Cr_2O_7$

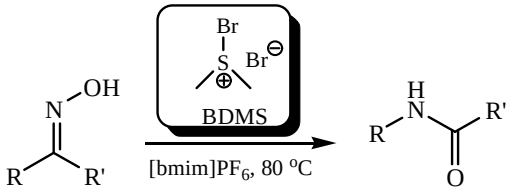
I. Mohammadpoor-Baltork et al.[19] investigated transformation of thiocarbonyls to their carbonyl compound under microwave irradiation. The results show that under microwave irradiation, the reaction times are short and the yields are high (Scheme 1.10).



Scheme 1.10

1.1.2.8. Bromodimethylsulfonium bromide (BDMS) in ionic liquid

S. Yadav et al.[20] reported a new Beckmann rearrangement by BDMS in the imidazolium-based ionic liquid [bmim]PF_6 under mild condition for conversion ketoxime to their amide (Scheme 1.11).



R, R' = Alkyl, aryl

Scheme 1.11

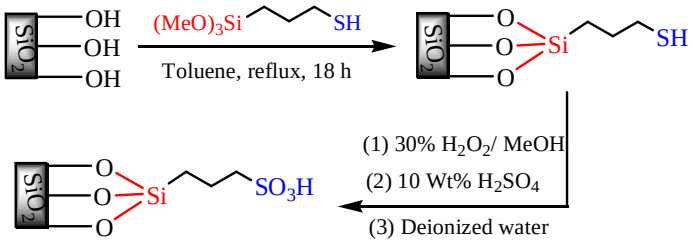
1.2. Dithioacetals

The protection of carbonyl groups as acetals or thioacetals is an integral part of organic manipulations such as the preparation of monomer building blocks, ? ne chemicals precursors for pharmaceuticals, and natural products. The importance of thioacetals is due in part to their inherent stability under both acidic or basic condition and also because of their behavior as masked acyl anions or methylene functions in C-C bond forming reactions.[21]

Commonly, these compounds are prepared by condensation of carbonyl compounds with thiols or dithiols catalyzed by protic acids or Lewis acids.[22,23]

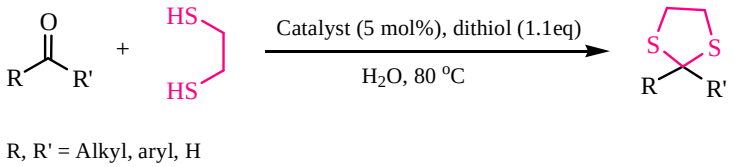
1.2.1. Silica functionalized sulfonic acid

A new method for chemoselective thioacetalization of a variety of carbonyl compounds described by *B. Karimi et al.*[24] using a dithiol in the presence of a catalytic amount of solid silica-based sulfonic acid in water (Scheme 1.12).



Scheme 1.12

This catalyst was examined as a heterogeneous catalyst in thioacetalization of a variety of carbonyl compounds in water (Scheme 1.13).

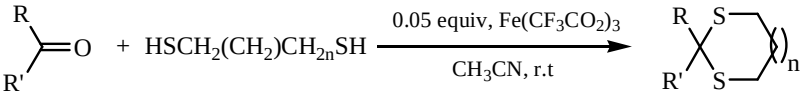


R, R' = Alkyl, aryl, H

Scheme 1.13

1.2.2. $Fe(CF_3CO_2)_3$

Iron(III) trifluoroacetate was used by *H. Adibi et al.*[25] as a recyclable Lewis acid catalyst for protection of a variety of carbonyl compounds as thioacetals under nearly neutral conditions. With the use of this catalyst, 1,3-dithiolanes and 1,3-dithianes were obtained from various aldehydes. Under the same conditions ketones were similarly but more slowly thioketalized (Scheme 1.15).



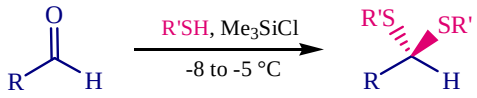
R, R'= Alkyl, aryl, H

n = 0, 1

Scheme 1.14

1.2.3. Me_3SiCl

L. K. Papernaya. et al.[26] continued studies on reactions of aldehydes of the thiophene series in the system thiol-Me_3SiCl. This reaction carried out at -8 to -5 ℃ to avoid oxidation of thiols and polymerization of aldehydes (Scheme 1.15).



R= 2-thienyl, 5-methyl-2-thieny, 5-chloro-2-thienyl

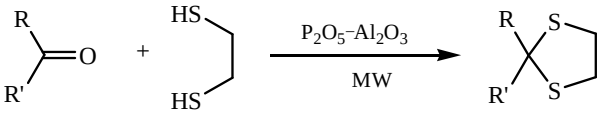
R'= Et, Pr

Scheme 1.15

1.2.4. P_2O_5–Al_2O_3

A. Zarei et al.[27] reported a new procedure for the chemoselective thioacetalization of carbonyl compounds to their corresponding 1,3-dithiolanes in the presence of 1,2-ethanedithiol and catalytic amount of P_2O_5-Al_2O_3 (Scheme 1.16).

P_2O_5 is difficult to handle due to its moisture sensitivity at room temperature, but P_2O_5 on alumina P_2O_5-Al_2O_3 is easy to prepare and to handle;[28,29] whereas both cyclic and acyclic aliphatic ketones gave good yields of the desired 1,3-dithiolanes. However, aromatic ketones were slowly converted to their corresponding 1,3-dithiolanes in good yield.

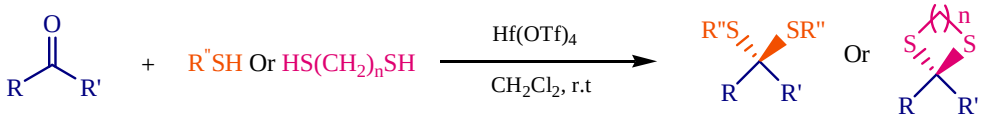


R, R' = Alkyl, aryl, H

Scheme 1.16

1.2.5. $Hf(OTf)_4$

J. Zhu et al.[30] reported the use of hafnium trifluoromethanesulfonate for conversion a range of aliphatic and aromatic aldehydes and ketones to the corresponding thioacetals in high yields. The high oxophilicity[31] and low thiophilicity[32] of $Hf(OTf)_4$ led them to hypothesize that it could potentially act as a catalyst for the conversion of carbonyl compounds to their corresponding thioacetals/thioketals (Scheme 1.17).



R, R'= Alkyl, aryl

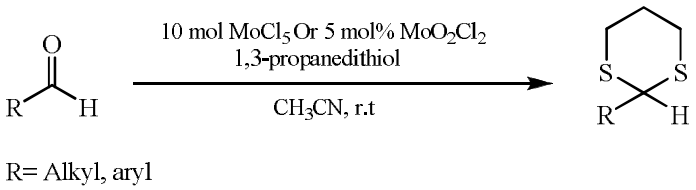
R"= Et

n= 0, 1

Scheme 1.17

1.2.6. $MoCl_5$ and MoO_2Cl_2

S. Goswam et al.[33] have developed a method for the thioacetalization of heterocyclic, aromatic and aliphatic aldehydes to the corresponding dithianes with 1,3-propanedithiol and MoO_2Cl_2 or $MoCl_5$ as catalysts under a nitrogen atmosphere in moderate to excellent yield. Although, by using MoO_2Cl_2 reaction time was less than $MoCl_5$ (Scheme 1.18).

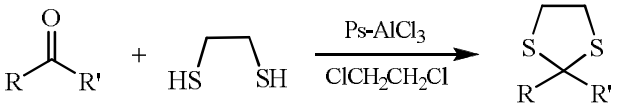


R= Alkyl, aryl

Scheme 1.18

1.2.7. Ps–$AlCl_3$

B. Tamami et al.[34] have shown mild and chemoselective heterogeneous catalyst for thioacetalization of carbonyl compounds. 1,3-dithiolanes are obtained in excellent yields in the presence of Ps-$AlCl_3$ from various aldehydes and ketones containing electron donating and withdrawing groups (Scheme 1.19).



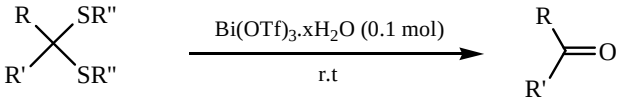
R, R'= Alkyl, aryl, H

Scheme 1.19

1.3. Deprotection of thioacetals

1.3.1. $Bi(OTf)_3$

A. Kamal et al.[35] reported deprotection of thioacetals to their corresponding carbonyl compound with a catalytic amount of bismuth triflate in a biphasic system involves stirring the substrate in a solution of CH_2Cl_2/H_2O (8:2 v/v) in the presence of bismuth(III) triflate as catalyst. Furtheremore they observed that longer reaction times were required for the deprotection of thioacetals derived from propane and ethane dithiols (Scheme 1.20).



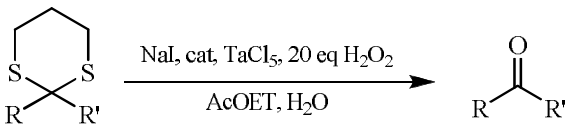
R, R' = Alkyl, aryl

R" = Et

Scheme 1.20

1.3.2. $TaCl_5/NaI/H_2O_2$

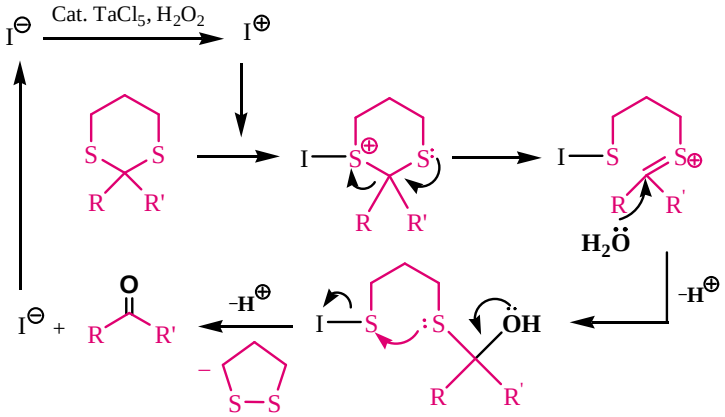
M. Kirihara et al.[36] developed dethioacetalization to afford carbonyl groups by employing the tantalum pentachloride ($TaCl_5$) catalyzed oxidation of halogen anions (I^-) into the halogen cation (I^+) by H_2O_2 and this system is expected to be used as an environmentally benign dedithioacetalization agent (Scheme 1.21).



R, R'= Alkyl, aryl, H

Scheme 1.21

The plausible reaction mechanism is presented in Scheme 1.22.

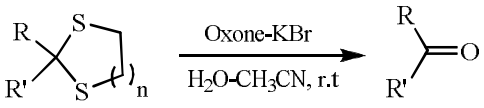


Scheme 1.22

1.3.3. Oxone-KBr

U. V. Desai et al.[37] developed a new method for chemoselective dethioacetalization of dithioacetals to aldehydes and ketones using Oxone-KBr[38] in aqueous acetonitrile. The Br^+ ion generated by the combination of Oxone-KBr would be attacked by the dithiane,

making it a good leaving group with a subsequent attack by a water molecule leading to the carbonyl (Scheme 1.23).

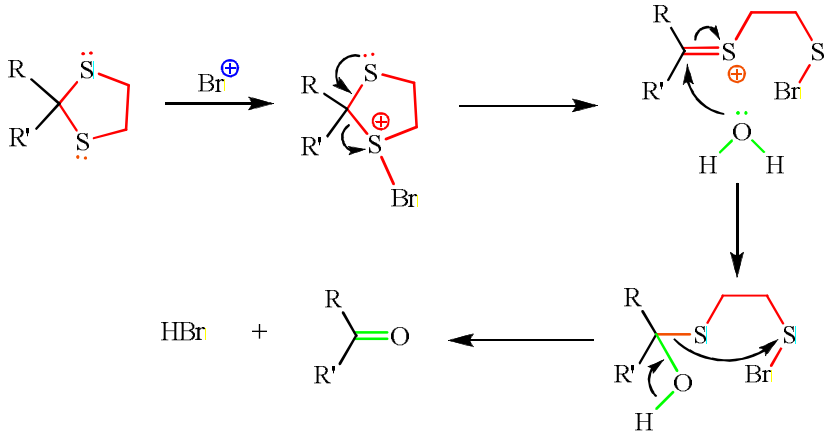


R, R'= Alkyl, aryl, H

Oxone = $KHSO_5$:$KHSO_4$:K_2SO_4 (2:1:1)

Scheme 1.23

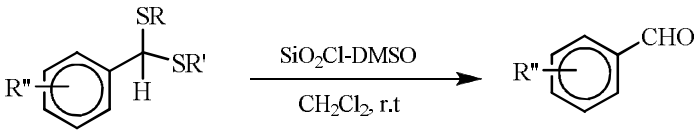
A possible reaction mechanism is presented in Scheme 1.24.



Scheme 1.24

1.3.4. SiO_2Cl-DMSO

H. Firouzabadi et al.[39] applied SiO_2Cl-DMSO as a new heterogeneous system for deprotection of open-chain and cyclic thioacetals (1,3-dithiolanes or 1,3-dithianes) of aromatic aldehydes into their corresponding aldehydes (Scheme 1.25).



R, R'= $-CH_2CH_2-$, $-CH_2CH_2CH_2$, n-Butyl

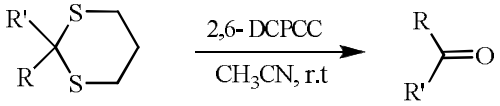
R"= H, 4-Me, 4-Cl, 3-MeO, 4-MeO

Scheme 1.25

In these reactions silica acts as an oxophilic and activating reagent for DMSO to generate dimethylsulfonium chloride. They believe that dimethylsulfonium chloride is the responsible intermediate for these reactions to occur. Therefore, they have generated this active species by independent known method.[40, 41]

1.3.5. 2,6-Dicarboxypyridinium chlorochromate (2,6-DCPCC)

2,6-DCPCC was found to be a proper reagent for the conversion of acetals, thioacetals, and 1,1-diacetates to their corresponding carbonyl compounds under neutral and anhydrous conditions. This method investigated by *R. Hosseinzade et al.*[42] (Scheme 1.26).

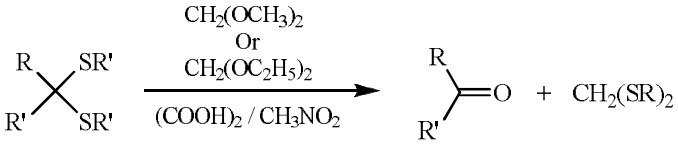


R,R' = alkyl, aryl, H

Scheme 1.26

1.3.6. Oxalic acid

H. Miyake et al.[43] found that oxalic acid catalyzes the hydrolysis of dithioacetals of not only aldehydes, but also ketones in the presence of dimethoxymethane (DMM) or diethoxymethane (DEM) (Scheme 1.27).



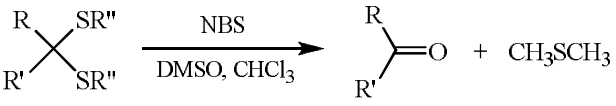
R, R' = Alkyl, aryl, H

Scheme 1.27

The dithioacetals, which have no polar functional group are insoluble to nitromethane. Low solubility often causes a prolonged reaction time. Other solvents such as DMF, THF, $CHCl_3$, CH_2Cl_2, and acetonitrile, were not as effective as nitromethane.

1.3.7. N-Bromosuccinimide (NBS)

N. Iranpoor. et al.[44] used NBS as a source of electrophilic bromines for deprotection of s,s-acetals and ketals in the presence of DMSO in $CHCl_3$. Here, DMSO acts as a source of oxygen (Scheme 1.28).



R, R' = Alkyl, aryl, H

R" = Ph, Alkyl, –(CH_2)n– [n= 2,3]

Scheme 1.28

1.4. Surfactant

Surfactant molecule has a hydrophilic (water-loving) head that is attracted to water molecules and a hydrophobic (water-hating) tail that repels water. In english the term **surfactant** (short for ***surface-active-agent***) designates a substance which exhibits some superficial or interfacial activity (Fig 1.3). It is worth remarking that all amphiphiles do not display such activity. In effect only the amphiphiles with more or less equilibrated hydrophilic and lipophilic tendencies are likely to migrate to the surface or interface. It does not happen if the amphiphilic molecule is too hydrophilic or too hydrophobic, in which case it stays in one of the phase.[45]

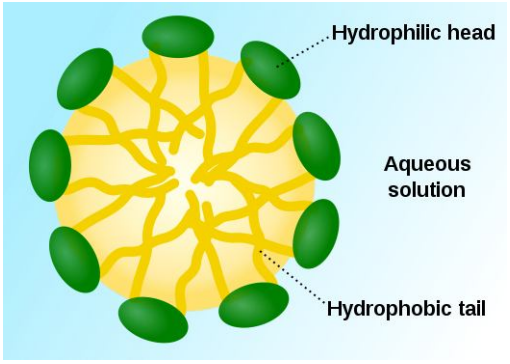


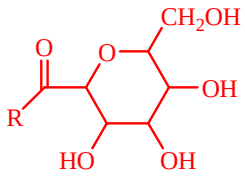
Figure 1.3

1.4.1. Classification according to the composition of their head

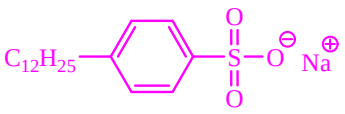
A surfactant can be classified by the presence of formally charged groups in its head. A non-ionic surfactant has no charge groups in its head. Nonionic Surfactants do not ionize in aqueous solution, because their hydrophilic group is of a non-dissociable type, such as alcohol, phenol, ether, ester, or amide **(1)**.

The head of an ionic surfactant carries a net charge. If the charge is negative, the surfactant is more specifically called anionic (sulfates, phosphates, sulfonates (detergents), fatty acids, soaps, or carboxylates) **(2)**; if the charge is positive, it is called cationic (secondary or tertiary amines for example CTAB). They are only used in two cases (1) as bactericide (2) as positively charged substance which is able to adsorb on negatively charged substrates to produce antistatic and hydrophobant effect **(3)**.

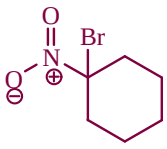
If a surfactant contains a head with two oppositely charged groups, it is termed amphoteric or zwitterionic **(4).** Figure 1.4 show a few typical examples of each class.[46]



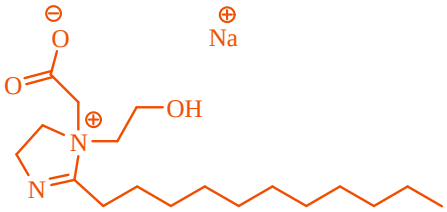
Sorbitan Monoester **(1)**



Sodium Dodecyl BenzeneSulfonate **(2)**



5-Bromo-5-Nitro-1,3-Dioxane **(3)**



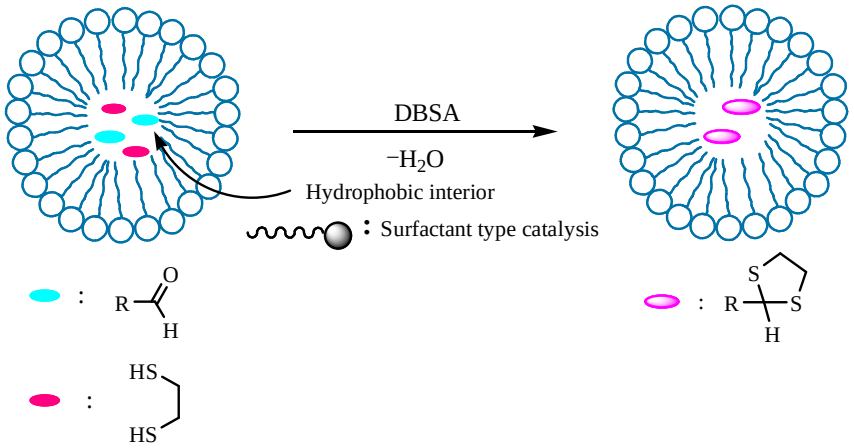
Sodium lauroamphoacetate **(4)**

Figure 1.4

1.4.2. Surfactant-type acid catalyst

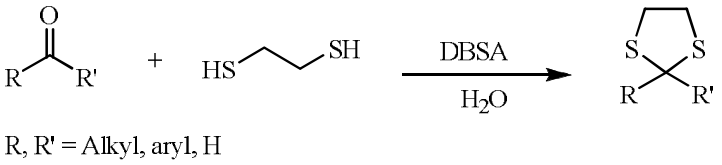
1.4.2.1. Dodecylbenzenesulfonic acid (DBSA)

S. Kobayashi et al.[47] realized dithioacetal formation in water by using DBSA as surfactant-type catalyst (Scheme1.29).



Scheme 1.29

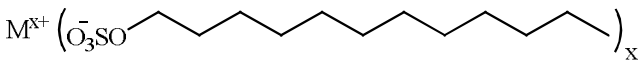
Emulsion droplets are formed in water in the presence of a surfactant-type catalyst and organic substrates. The emulsion droplets have a hydrophobic interior which would concentrate acid catalysts onto the surface of droplets and enhance the reaction rate toward the side of the dehydrated product. On the other hand, water molecules generated during the reaction are removed from droplets due to the hydrophobic nature of their interior, which shift the equilibrium toward the desired side. [48-50]



Scheme 1.30

1.4.2.2. $Zr(DS)_4$

M. A Zolfigol et al.[51] prepared some new metal dodecyl sulfates by adding a solution of sodium dodecyl sulfate to an aqueous solution of metal nitrates. (Scheme 1.31). All of the prepared salts catalyzed the condensation of indoles with aldehydes and ketones.



Scheme 1.31

Fe^{+3}, Al^{+3}, Cr^{+3}, Ca^{+2}, Sr^{+2}, Pb^{+2}, and Zr^{+4} dodecyl sulfates were prepared at room temperature in good yields, but among of them, zirconium tetrakis (dodecyl sulfate), $Zr(DS)_4$, was superior to others (Scheme 1.32).