



Review Article:

## Thionyl Chloride: A Catalyst of Synthetic Chemical Interest

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### Abstract

**Background:** Particularly developed ingredients that are easily manufactured and utilized for additional exploitation are used in organic synthetic chemistry. Thionyl chloride serves as a significant illustration of such an ingredient. The usefulness of which has been discussed in a huge number of peer-reviewed papers. **Aim:** The literature that has been released since the previous assessment in 1980, which mainly focused on the responses of active methylene compounds, is where this review places its focus. In the present overview, we also discuss O- and N-nucleophiles. For the most part, patents have been disregarded in this analysis in order to keep it feasible. **Conclusion:** The authors concluded that SOCl<sub>2</sub> has a variety of behaviors, including the ability to function as an initiator or a reactant, which makes it essential for the synthesis of many chemically reactive intermediates and final products. Additionally, SOCl<sub>2</sub> can speed up and reduce the duration of traditionally long reactions, thereby raising its importance.

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## 1. Introduction

### 1.1 Overview

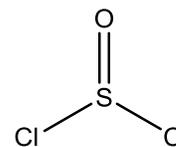
For decades the reagent thionyl chloride (SOCl<sub>2</sub>) considered a milestone in organic chemistry, Its importance came from its diversity of actions, it can act as chlorinating (1–3), oxidizing, condensing (4–6), and cyclizing agent (7–9). Also, it can participate as catalyst or reactant in many well-known reactions (10–12). SOCl<sub>2</sub> offers numerous advantages over other chlorinating chemicals, it is relatively easy to handle, available, easy to isolate the end product, giving high yields, also it is a good solvent for many organic compounds, all these benefits make SOCl<sub>2</sub> preferable over other available catalysts (13–15).

The target reagent exhibits high reactivity with huge number of compounds, that make it preferred in organic industry especially in acid chlorides production which

considered important intermediates for the production of many pharmaceutical and industrial chemicals (16–18). Nowadays, SOCl<sub>2</sub> is widely used in Li/SOCl<sub>2</sub> batteries industry, which has the highest voltage and energy density that make them very popular as primary or reserved battery (19–21).

### 1.1 Chemistry and characteristics

The SOCl<sub>2</sub> molecule has an electrophilic core, a sulfur atom, and two leaving groups, chlorine atoms in the sulfoxide, as illustrated in [Figure 1](#).



**Figure 1.** Chemical structure of SOCl<sub>2</sub>

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These structural characteristics are in charge of the chemical  $\text{SOCl}_2$ 's versatility, which is used in a variety of synthetic processes to produce a variety of intermediates and chemical products in agro-chemistry, fine chemistry, pharmaceuticals, and other fields. The following **Table 1** describes the general properties of  $\text{SOCl}_2$  (22–24).

**Table 1.** The general properties of  $\text{SOCl}_2$

IUPAC name	Thionyl chloride
Chemical formula	$\text{SOCl}_2$
Molecular weight	118,97 g/mole
Density	$1.631 \text{ g.cm}^{-3}$
Boiling point	$76^\circ\text{C}$
Miscibility	miscible in chloroform, benzene and carbon tetrachloride
Physical description	Colorless to pale yellow liquid with pungent sharp smell

## 1.2. Role of $\text{SOCl}_2$ in synthesis of some chemical compounds

### 1.2.1 Acid chloride and alkyl chloride

In these reactions,  $\text{SOCl}_2$  can be used alone or in conjunction with bases like pyridine and triethylamine. However, the reactions are always delayed and frequently need reflux temperature, but by combining  $\text{SOCl}_2$  with 1,2,3-benzotriazole, it is possible to chlorinate carboxylic acids and alcohols in under 10 minutes at room temperature, as displayed in **Equations 1** and **2** (25–27).

### 1.2.2 Ester

$\text{SOCl}_2$  and dimethylformamide (DMF) can be used to create esters from primary and secondary alcohols in the presence of  $\text{LiI}$  or  $\text{KI}$  (28). Also esters can be prepared by one-pot two-steps method by converting carboxylic acid to ester, amide and dipeptide using  $\text{SOCl}_2$  and oxyma, as displayed in **Scheme 1** (29–31).

Also  $\text{SOCl}_2$  can be used for esterification of aromatic and aliphatic dicarboxylic acids (32), its shows that esterification occurs mostly on the unconjugated carboxyl group to give monoester (90%) with very small amount of diester (5%), as displayed in **Equation 3** (33).

### 1.2.3 Chalcones

Chalcones are important biomolecules that can be extracted from plants or synthesized mainly from aldol condensation (4), they possess many biological activities

including anti-inflammatory (34), antituberculosis (35), antidiabetic (36), antibacterial, antiviral and sedative effect (4,37). The biological actions of chalcones, like **NS1**, are caused by their  $\alpha,\beta$ -unsaturated ketone functional group which can be synthesized by aldol condensation using  $\text{SOCl}_2$  as a catalyst, as displayed in **Equation 4** (4,38).

### 1.2.4 Hydrochloric acid

A combination of  $\text{SOCl}_2$  and a mixture of water and deuterium oxide can be used to produce  $\text{HCl}/\text{DCl}$  gas and  $\text{SO}_2$  gas as shown in **Equation 5** (39,40).

### 1.2.5 Maltol-derived complex

$\text{SOCl}_2$  combined with kojic acid and  $\text{CH}_2\text{Cl}_2$  are used to produce Maltol-derived ruthenium cymene complex (**NS2**) which has a tumor inhibiting activity, as displayed in **Equation 6** (41).

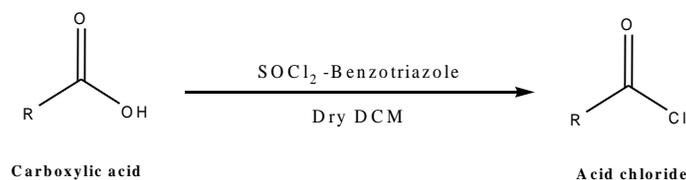
## 1.3 Reactions with specific functional groups

### 1.3.1 Reactions with an amino group

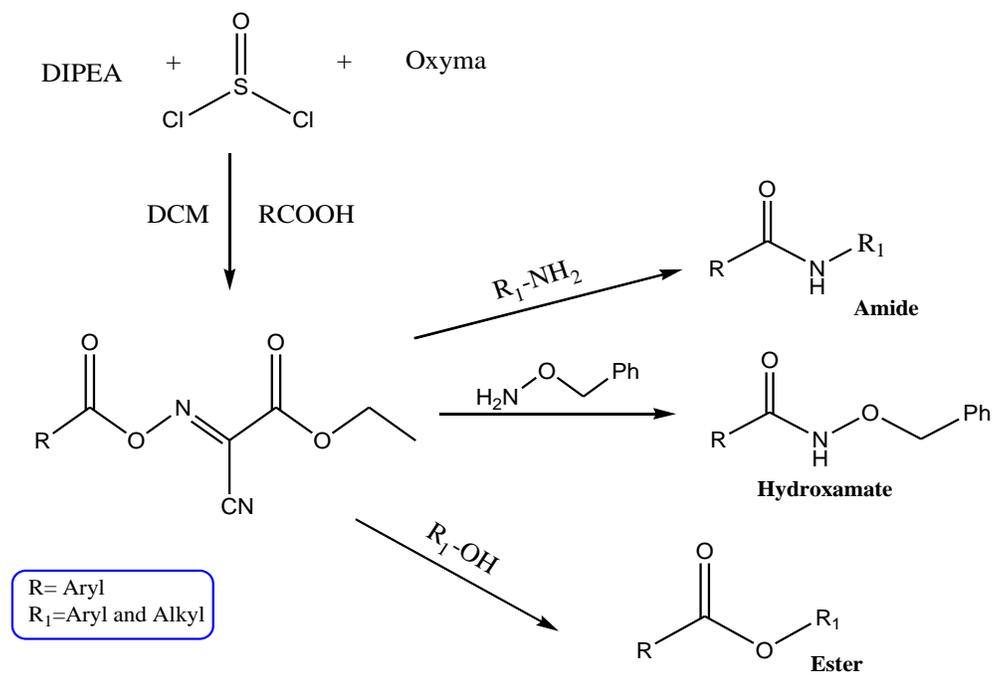
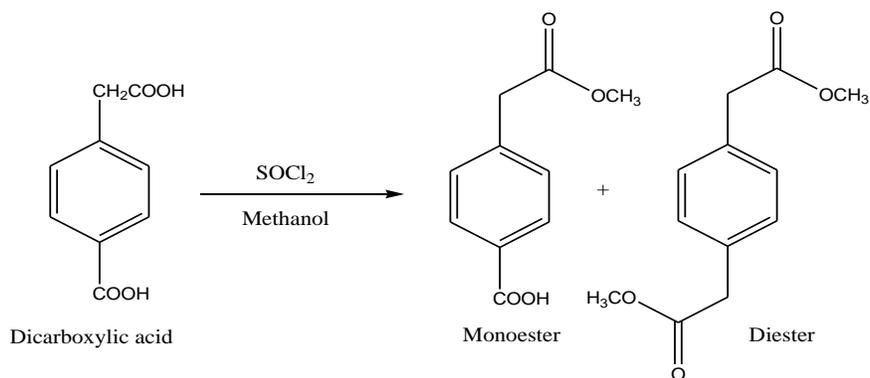
The reaction of primary amines with  $\text{SOCl}_2$  is still the most commonly employed approach to synthesize sulfinylamines. In the past, this was frequently carried out under refluxing conditions, and for weakly nucleophilic sulfonamides, long reaction periods and high temperatures are required to achieve complete conversion. For more sensitive or reactive amine derivatives, the reaction can be conducted at room temperature or at  $0^\circ\text{C}$  conditions with the addition of a base such as pyridine or triethylamine, the conjugate acid of which being filtered out afterward, as displayed in **Scheme 2** (42–44).

In the presence of pyridine, N-Substituted amidrazones interacts with  $\text{SOCl}_2$  to produce the main products 1,2,3,5-thiaziazole derivatives. Different tautomeric versions of these compounds are possible, such as 2,5-dihydro- (**NS8**), 2,3-dihydro-1,2,3,5-thiaziazole-1-oxide (**NS9**), or 2H-1,2,3,5-thiaziazol-1-ium hydroxide (**NS10**), as displayed in **Equation 7** (45,46).

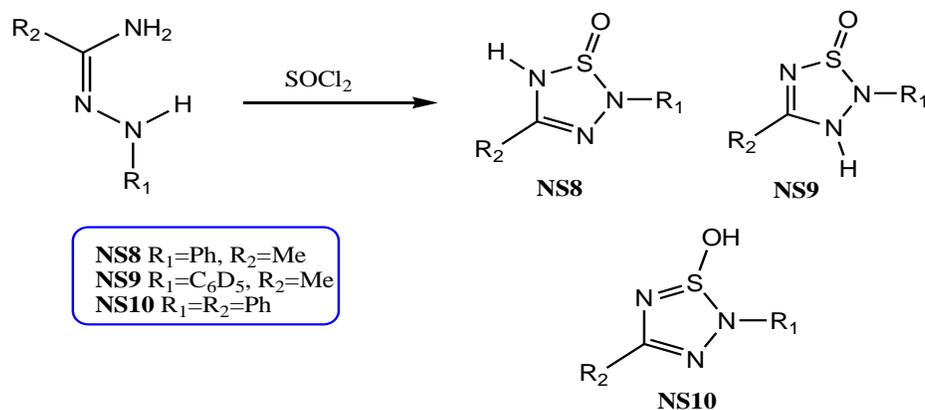
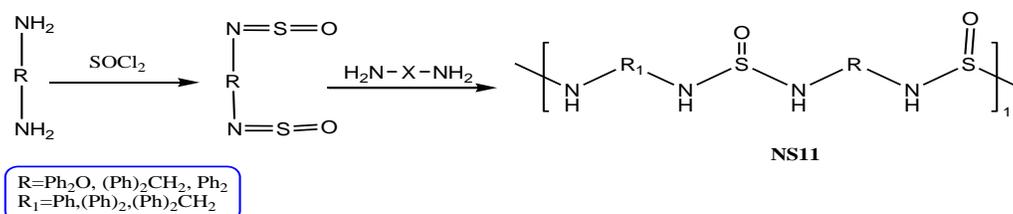
New monomers that possess sulfinylimine functionality have been synthesized in the presence of  $\text{SOCl}_2$ . These monomers then react with aromatic diamines to produce new polymers containing diiminosulfoxide functional group ( $-\text{NH}-\text{SO}-\text{NH}-$ ) in their backbone, as displayed in **Scheme 3** (47–49)



**Equation 1.** Synthesis of acid chloride

**Equation 2.** Synthesis of alkyl chloride**Scheme 1.** The one-pot two-steps method for preparing carboxylic acid derivatives**Equation 3.** The esterification of the unconjugated carboxyl group



**Equation 7.** N-Substituted amidrazones reaction with SOCl<sub>2</sub>**Scheme 3.** Synthetic pathways for the preparation of sulfinylimine monomers and polymers with diiminosulfoxide functional group.

### 1.3.2 Reactions with a hydroxyl group

#### With alcohols

Alcohols are often transformed into more reactive alkyl chlorides using SOCl<sub>2</sub>. Alkyl chloride can be easily converted into a number of compounds that can't be obtained from alcohol directly. Alkyl chloride (**NS12**) undergoes an important reaction, which is nucleophilic substitution, that is frequently carried out under basic conditions, as in displayed in **Scheme 4**, to synthesize an acetamide derivative (**NS13**) (50,51).

#### With diols

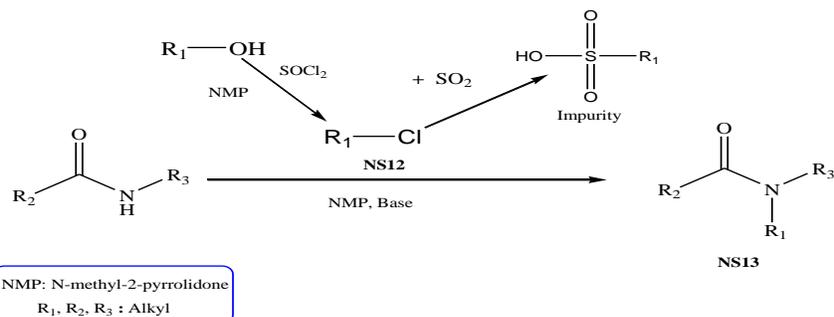
The reaction of 2,2'-(1,2-phenylenebis(oxy)) diethanol with SOCl<sub>2</sub> yields a mixture of [1,3,6,9,2] tetraoxathiacycloundecine 5-oxide (**NS14**) and

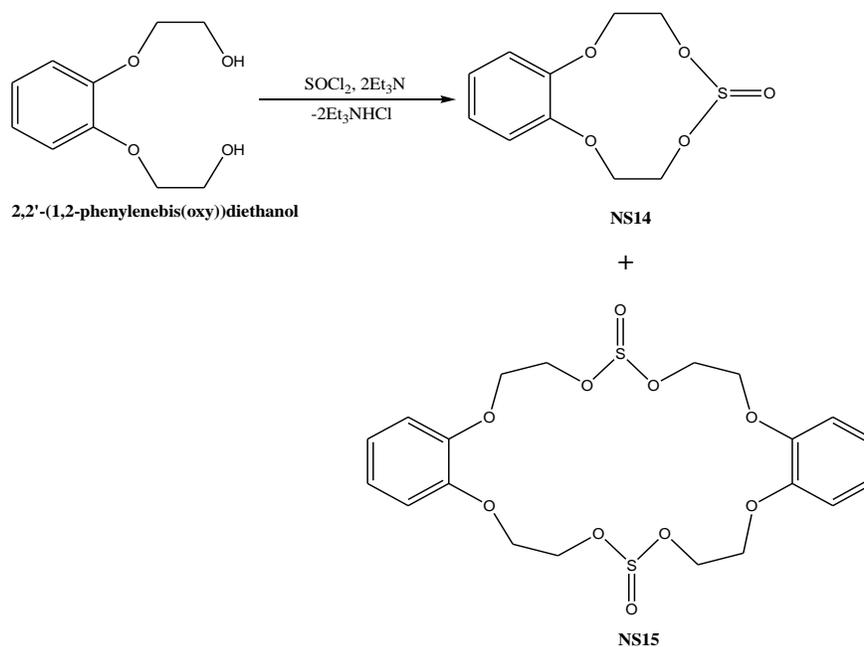
[1,3,6,9,12,14,17,20,2,13] octaoxadithiacyclodocosine 9,22-dioxide (**NS15**) (the 22-crown ether) with one and two sulfinyl groups, respectively as shown in **Equation 8** (52).

In addition, ortho-diols and SOCl<sub>2</sub> interact to produce sulfites, which are a mixture of the two diastereomers, giving excellent yields. In this reaction, SOCl<sub>2</sub> will serve as the stereogenic center. **Equation 9** has shown the formation of (3aR,6aS)-3a,6a-dibutyltetrahydrothieno[3,4-d][1,3,2]dioxathiole 2-oxide (**NS16**) (53,54).

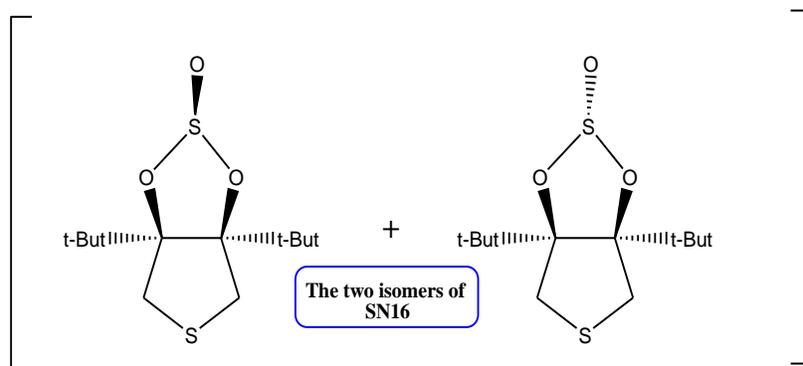
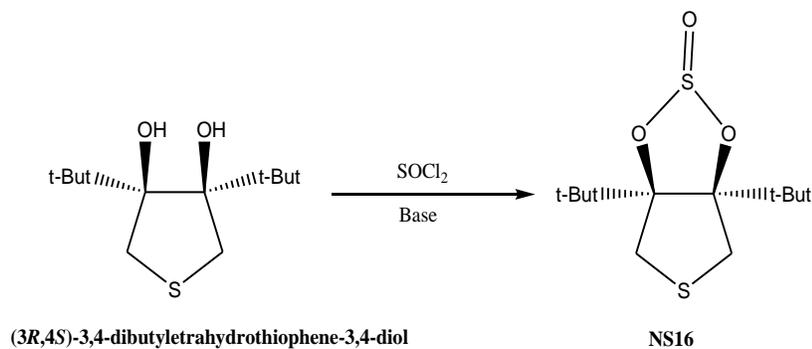
#### With hydroxyamine

SOCl<sub>2</sub> can also react with hydroxyamine to produce benzimidoyl derivatives. The major product of the reaction of SOCl<sub>2</sub> with N-benzoyl-N-butyl hydroxyamine was (Z)-N-((chlorosulfinyl)oxy)benzimidoyl chloride (**NS17**), as shown in **Equation 10** (55).

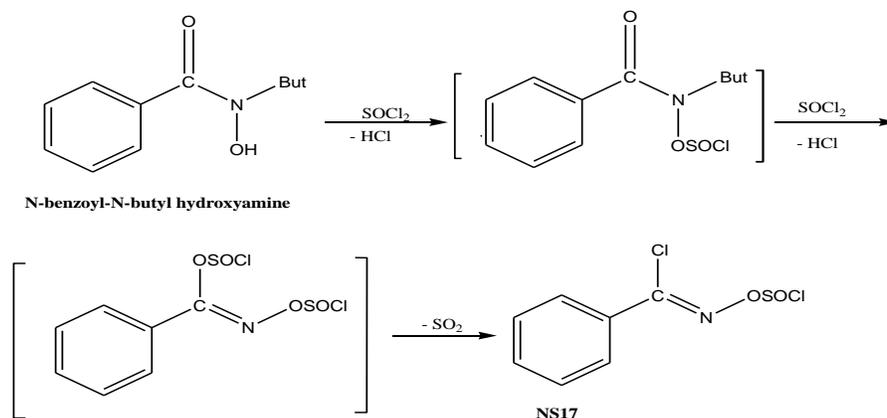
**Scheme 4.** The reaction of alcohol with thionyl chloride



**Equation 8.** The reaction of  $\text{SOCl}_2$  with diethanol to produce **NS14** and **NS15**



**Equation 9.** The reaction of  $\text{SOCl}_2$  and ortho-diols to produce sulfites

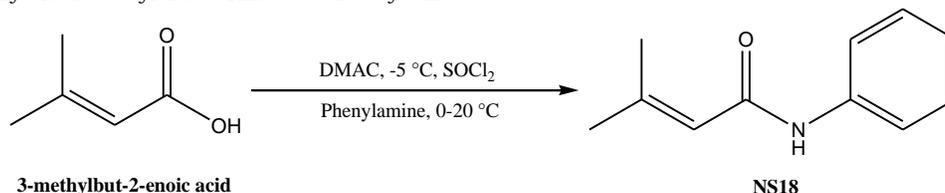


**Equation 10.** The reaction of  $\text{SOCl}_2$  with hydroxylamine

### 1.3.3 Reactions with a carboxyl group

As mentioned previously,  $\text{SOCl}_2$  can be used to synthesize acid chloride (25,56), however, there are situations where  $\text{SOCl}_2$  may react differently. For example, acrylic acid and a number of other carboxylic acids were converted smoothly to anilides in highly isolated yields. This occurs by the

combined action of  $\text{SOCl}_2$  and the phenylamine in dimethylacetamide (DMAC), which offers stability and rate advantages. **Equation 11** has shown the production of 3-methyl-N-phenylbut-2-enamide, which is depicted as **NS18** by the reaction of 3-methylbut-2-enoic acid with phenylamine in the presence of  $\text{SOCl}_2$  as a catalyst (57,58).



**Equation 11.** The synthesis of 3-methyl-N-phenylbut-2-enamide (**NS18**)

## 1.4 $\text{SOCl}_2$ as a special reagent

### 1.4.1 Condensing agent

$\text{SOCl}_2$  serves as a condensing reagent in some reactions to form more reactive compounds. Acetanilides and dialkylformamides react in the presence of  $\text{SOCl}_2$  as a condensing agent to produce formamidines (**NS19**), which are employed as insecticides and/or acaricides, as displayed in **Equation 12** (59,60).

Direct condensation of different sulfonamides and formamides using  $\text{SOCl}_2$  as condensing agent and chloroform as a solvent has been developed as a more efficient method of producing N-sulfonylformamidine derivatives (**NS20**). Comprehensive synthetic studies show that under mild conditions, this process provides the required products in high yields, as showed in **Equation 13** (61,62).

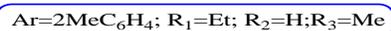
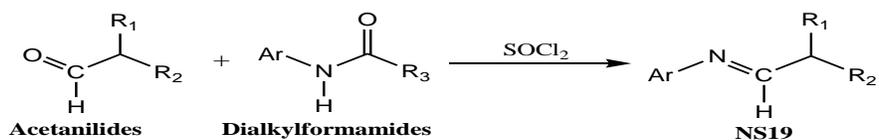
Also, derivatives of N-oxysulfonyl formamidine (**NS21**) have been successfully produced under friendly circumstances. Through the direct condensation of several sulfamates and formamides in the presence of chloroform and thionyl chloride, as displayed in **Equation 14** (63,64).

### 1.4.2 Oxidizing agents

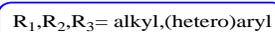
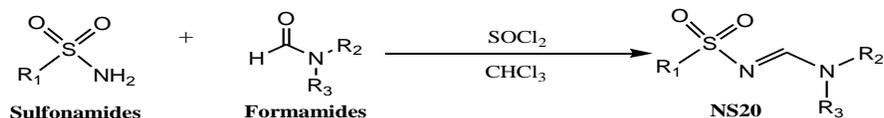
$\text{SOCl}_2$  can unexpectedly acts as an oxidant agent for different organic compounds. Amino acids attached to cobalt are quickly oxidized by this reagent to give imines. As a result, the cobalt-alanine complex was oxidized by  $\text{SOCl}_2$  in DMF to produce imino acid complexes (**NS22**), as displayed in **Equation 15** (65,66)

Also,  $\text{SOCl}_2$  is used to oxidize methyl 1,4-dioxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate to produce an unstable intermediate (**NS23**), which reacts with alcohols to produce 3-alkoxy-1,4-dioxo-1,2,3,4-tetrahydroisoquinolines (**NS24**).  $\text{SOCl}_2$  served as a convenient alternative oxidant for lead tetraacetate in this system, as displayed in **Equation 16** (67,68).

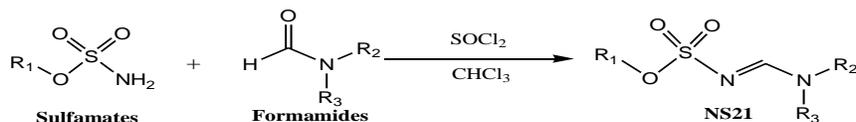
An unusual oxidation reaction noticed when the furoacridone was reacted with  $\text{SOCl}_2$ . This unexpected oxidation process was found to be useful in 1,3-dihydro-2-[2-(dimethylamino) ethyl]-1,3-dioxopyrrolo [3,4-c] acridine (**NS25**) synthesis, which is a potent DNA topoisomerase II inhibitor, as displayed in **Equation 17** (69,70).



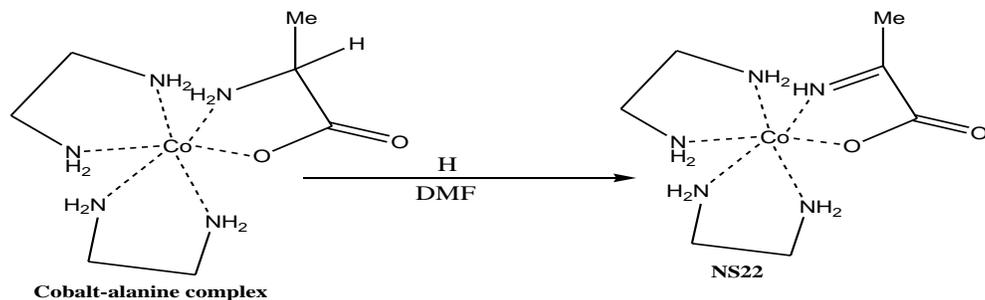
**Equation 12.** Formamidines synthesis in the presence of SOCl<sub>2</sub> as a condensing agent



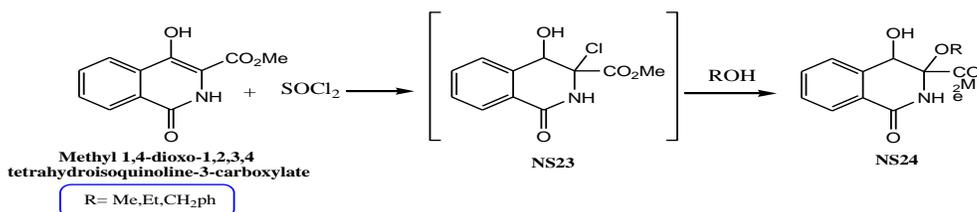
**Equation 13.** Production of N-sulfonylformamide derivatives in the presence of SOCl<sub>2</sub> as a condensing agent



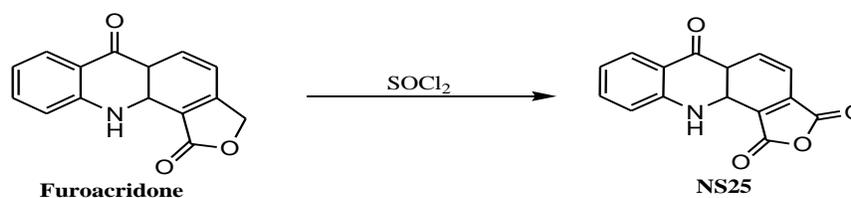
**Equation 14.** Production of N-Oxysulfonyl formamide derivatives in the presence of SOCl<sub>2</sub> as a condensing agent.



**Equation 15.** The cobalt-alanine complex oxidation by SOCl<sub>2</sub>



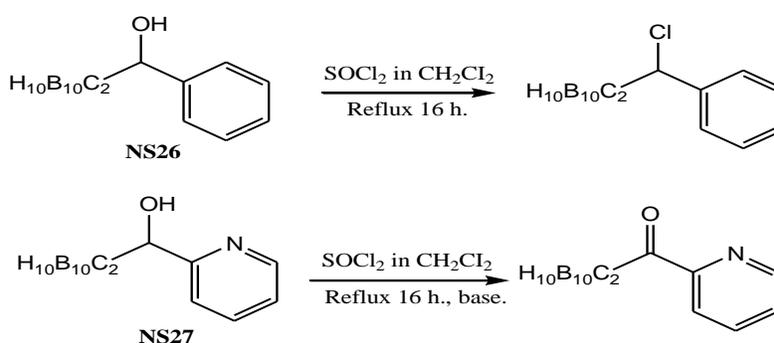
**Equation 16.** Role of SOCl<sub>2</sub> as an oxidant agent



**Equation 17.** An unusual oxidation reaction of furoacridone in the presence of  $\text{SOCl}_2$

Moreover,  $\text{SOCl}_2$  reacts with 1- [phenyl (hydroxy) methyl]-2-R-1,2-dicarbocloso-dodecaborane (**NS26**) as halogenation reagent. But unexpectedly acts as an oxidant agent for 1-[2'-pyridyl (hydroxy) methyl]-2-R-1,2-dicarbocloso-dodecaboranes (**NS27**). The pyridylmethyl alcohols (**NS27**)

did not provide the expected chloro-derivatives under the same reaction circumstances as their phenyl equivalents, but gave ketones as the only reaction products, as displayed in **Scheme 5** (71,72).

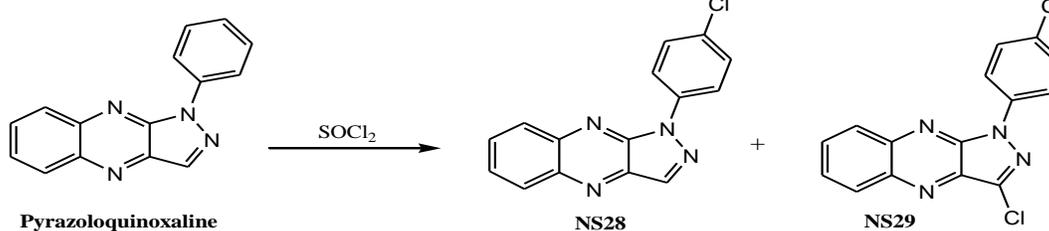


**Scheme 5.** Halogenation and unexpected oxidation reaction of  $\text{SOCl}_2$

#### 1.4.3 Chlorinating agent

The mechanism by which  $\text{SOCl}_2$  behaves as a chlorinating agent is not fully understood. A possible explanation is that thionyl chloride subjected to oxidation in the presence of

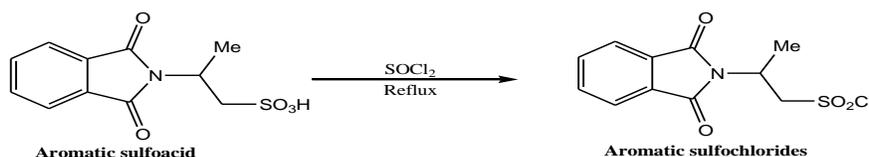
ambient oxygen to sulfuranyl chloride, that is a well-known chlorinating agent for organic compounds. Chlorination of the pyrazoloquinoxaline with  $\text{SOCl}_2$  reagent produces different chloro-substituted derivatives (**NS28** and **NS29**), as displayed in **Equation 18** (73).



**Equation 18.** Chlorination of the pyrazoloquinoxaline with  $\text{SOCl}_2$

The reagent  $\text{SOCl}_2$  is a potent chlorinating agent, where it can be used with aromatic sulfoacid or most carbonyl compounds to give aromatic sulfochlorides or carboxylic

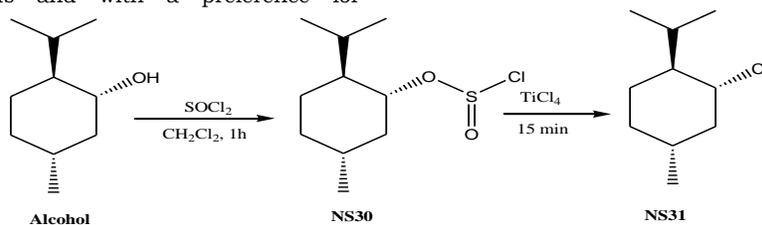
acids derivatives, respectively, as displayed in **Equation 19** (13,74).



**Equation 19.** Chlorinating action of  $\text{SOCl}_2$  reagent

A chlorination reaction of alcohols was achieved using the traditional  $\text{SOCl}_2$  reagent and catalytic titanium IV chloride. The reactions progressed quickly, producing chlorination products in high yields and with a preference for

configuration retention. Chlorosulfites (**NS30**) initially formed and then changed into alkyl chlorides (**NS31**) by titanium tetrachloride, as displayed in **Equation 20** (75,76).

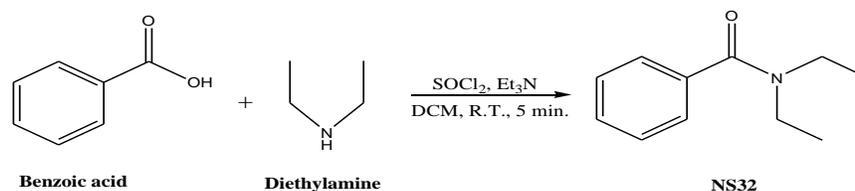


**Equation 20.** Role of  $\text{SOCl}_2$  as an oxidant agent

#### 1.4.4 Coupling agent

The  $\text{SOCl}_2$  functions as a coupling agent in many important reactions. It enables the production of secondary and tertiary amides from carboxylic acids using a one-pot method, in excellent yields, and at room temperature. This

technique achieves nearly complete retention of chiral substrate stereochemical integrity and works successfully in the presence of acid-sensitive groups. **Equation 21** shows the reaction of benzoic acid with diethyl amine in the presence of  $\text{SOCl}_2$  to produce N,N-Diethyl-benzamide (**NS32**) (72,77).

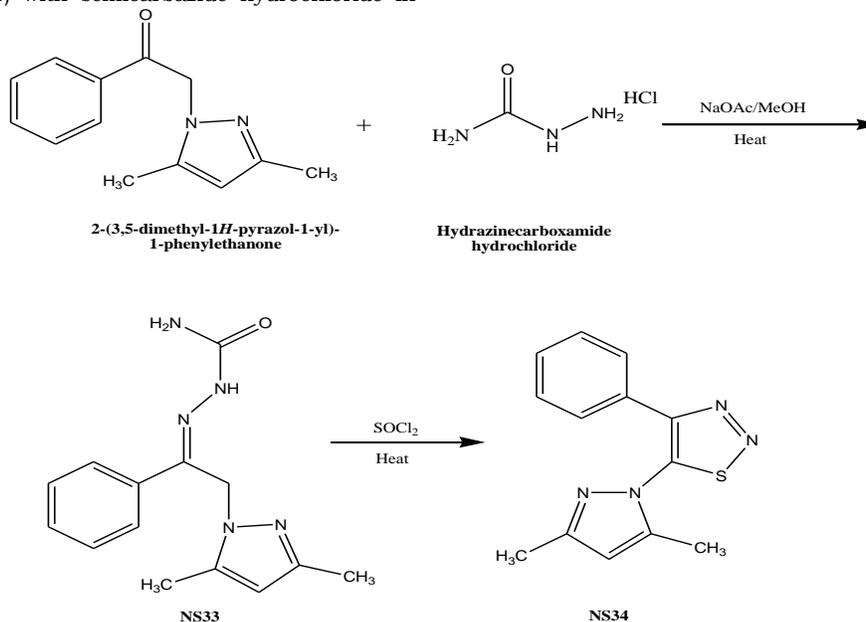


**Equation 21.** The coupling action of  $\text{SOCl}_2$  in reaction of benzoic acid with diethyl amine

#### 1.4.5 Cyclizing agent

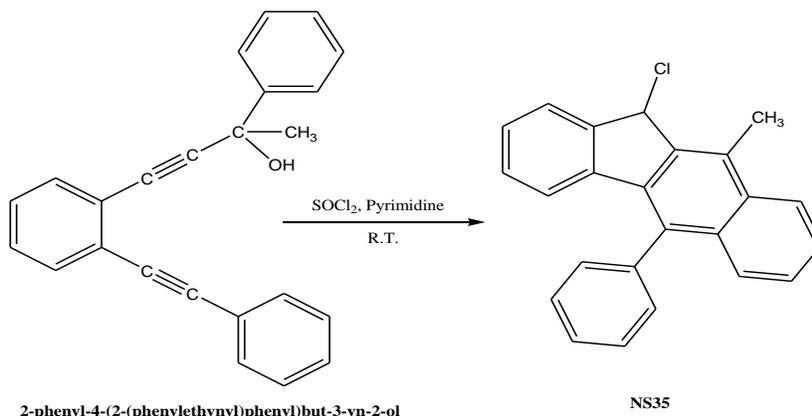
$\text{SOCl}_2$  has been successfully employed in the synthesis of pyrazolyl-1,2,3-thiadiazoles via the Hurd and Mori cyclization reaction. Pyrazolyl-1,2,3-thiadiazoles have been reported to have many important biological and pharmacological activities (56,78). The reaction of various pyrazolyl-phenylethanones (2-(3,5-dimethyl-1H-pyrazol-1-yl)-1-phenylethanone) with semicarbazide hydrochloride in

the presence of methanol and sodium acetate gave the corresponding semicarbazone, (Z)-2-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-1-phenylethylidene) hydrazinecarboxamide (**NS33**). These semicarbazones were further reacted with  $\text{SOCl}_2$  via the Hurd–Mori cyclization conditions to accomplish the final product 5-(3,5-dimethyl-1H-pyrazol-1-yl)-4-phenyl-1,2,3-thiadiazole (**NS34**), as shown in **Scheme 6** (79,80).



**Scheme 6.** Synthesis of Pyrazolyl-1,2,3-thiadiazoles by  $\text{SOCl}_2$  via Hurd–Mori cyclization reaction

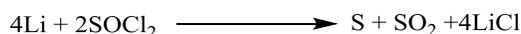
Also, mild treatment of tertiary aryl-diacetylene alcohols with  $\text{SOCl}_2$  resulted in intramolecular classical (4+2) cycloaddition reactions (cyclo-aromatization) and afforded



**Equation 22 .** The  $\text{SOCl}_2$  as a cyclizing agent to synthesize chlorinated 2,3-benzo[b]fluorenes

### 1.5 The role of $\text{SOCl}_2$ in batteries industry

The reagent  $\text{SOCl}_2$  is an essential element of lithium- $\text{SOCl}_2$  batteries, where it serves as the cathode (positive electrode) and lithium serves as the anode (negative electrode). The electrolyte is commonly lithium tetrachloroaluminate and the overall discharge reaction describes as shown in **Equation 23** (83,84).



**Equation 23.** The reaction involves in the lithium- $\text{SOCl}_2$  batteries

## 2. Conclusion

The reagent  $\text{SOCl}_2$  is considered one of the most important reagents in organic chemistry. Because its diversity of actions, it can act as a catalyst or as a reactant that make it crucial in the synthesis of many reactive intermediates as well as end products. Also,  $\text{SOCl}_2$  has the ability to facilitate and shortening the time of previously known long reactions that increases its significance. We believe additional researches must be conducted to explore the unknown abilities of this promising material.

## 3. References

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good yields of chlorinated 2,3-benzo[b]fluorenes (**NS35**). In addition to serving as a cyclizing agent,  $\text{SOCl}_2$  here acted as a chlorinating agent, as shown in **Equation 22** (81,82).

In comparison to other types of lithium batteries, these non-rechargeable batteries possessed a number of advantages, including their high energy density, broad operating temperature range, and prolonged usage and storage lifetime. However, their use has been limited by their expensive price, lack of recharge-ability, and safety issues (85,86).

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## كلوريد الثيونيل: محفز ذو أهمية كيميائية تصنيعية

### الخلاصة

**المقدمة:** يتم استخدام المكونات المطورة بشكل خاص والتي يسهل تصنيعها واستخدامها لاستغلال إضافي في الكيمياء التركيبية العضوية. يعمل كلوريد الثيونيل كدليل مهم لمثل هذا المكون. تمت مناقشة فائدتها في عدد كبير من الأوراق التي راجعها النظراء. **الهدف:** إن الأدبيات التي تم إصدارها منذ التقييم السابق في عام 1980 ، والتي ركزت بشكل أساسي على استجابات مركبات الميثيلين النشطة ، هي المكان الذي تركز فيه هذه المراجعة. في العرض العام الحالي ، ناقش أيضًا محبي النواة O و N في الغالب ، تم تجاهل البراءات في هذا التحليل من أجل إبقائها ممكنة. **الاستنتاج:** خلص المؤلفون إلى أن  $\text{SOCl}_2$  لديه مجموعة متنوعة من السلوكيات ، بما في ذلك القدرة على العمل كبادئ أو متفاعل ، مما يجعله ضروريًا لتخليق العديد من الوسائط التفاعلية كيميائيًا والمنتجات النهائية. بالإضافة إلى ذلك ، يمكن لـ  $\text{SOCl}_2$  تسريع وتقليل مدة التفاعلات التقليدية الطويلة ، وبالتالي زيادة أهميتها.

**الكلمات المفتاحية:** كلوريد الثيونيل ، تفاعل اقتران ، تشالكون ، أمين ، كحول