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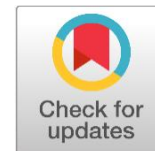
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Review Article:

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 SOCl₂ 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, SOCl₂ 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 (SOCl₂) 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). SOCl₂ 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 SOCl₂ 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, SOCl₂ is widely used in Li/SOCl₂ 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 SOCl₂ molecule has an electrophilic core, a sulfur atom, and two leaving groups, chlorine atoms in the sulfoxide, as illustrated in **Figure 1**.

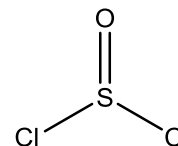


Figure 1. Chemical structure of SOCl₂

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These structural characteristics are in charge of the chemical 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 SOCl_2 (22–24).

Table 1. The general properties of SOCl_2

IUPAC name	Thionyl chloride
Chemical formula	SOCl_2
Molecular weight	118,97 g/mole
Density	1.631 g.cm^{-3}
Boiling point	76°C
Miscibility	miscible in chloroform, benzene and carbon tetrachloride
Physical description	Colorless to pale yellow liquid with pungent sharp smell

1.2. Role of SOCl_2 in synthesis of some chemical compounds

1.2.1 Acid chloride and alkyl chloride

In these reactions, 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 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

SOCl_2 and dimethylformamide (DMF) can be used to create esters from primary and secondary alcohols in the presence of LiI or KI (28). Also esters can be prepared by one-pot two-steps method by converting carboxylic acid to ester, amide and dipeptide using SOCl_2 and oxyma, as displayed in **Scheme 1** (29–31).

Also 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 α,β -unsaturated ketone functional group which can be synthesized by aldol condensation using SOCl_2 as a catalyst, as displayed in **Equation 4** (4,38).

1.2.4 Hydrochloric acid

A combination of SOCl_2 and a mixture of water and deuterium oxide can be used to produce HCl/DCl gas and SO_2 gas as shown in **Equation 5** (39,40).

1.2.5 Maltol-derived complex

SOCl_2 combined with kojic acid and CH_2Cl_2 are used to produce Maltol-derived ruthenium cymene complex (**NS2**) which has a tumor inhibiting activity, as displayed in **Equation 6** (41).

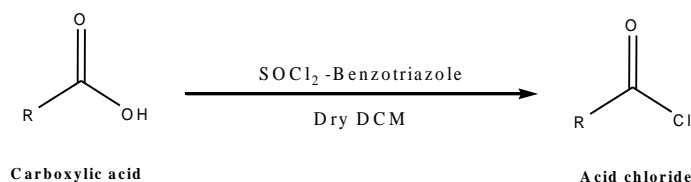
1.3 Reactions with specific functional groups

1.3.1 Reactions with an amino group

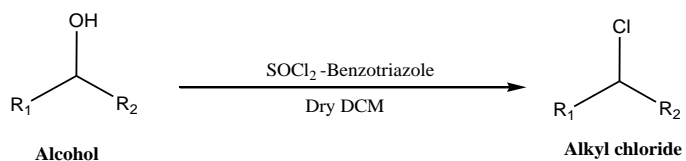
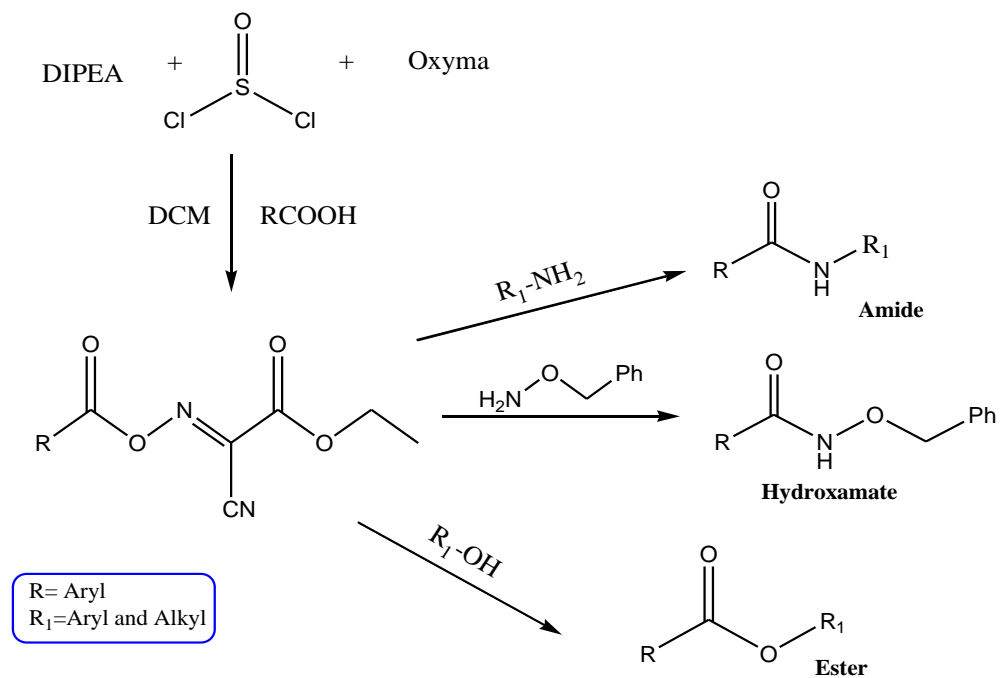
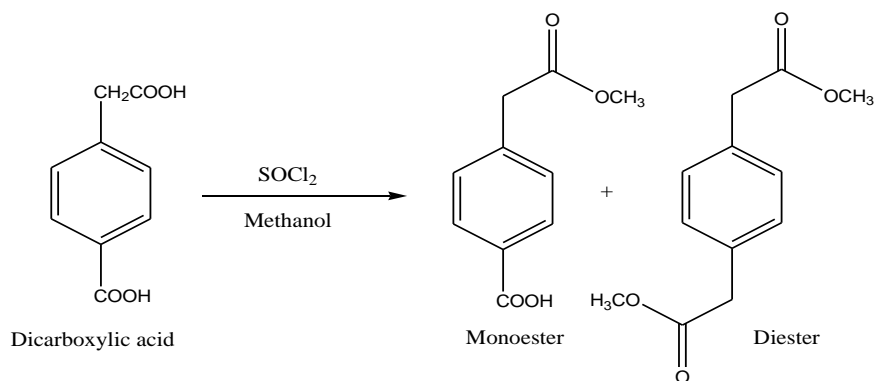
The reaction of primary amines with SOCl_2 is still the most commonly employed approach to synthesize sulfinylamines. In the past, this was frequently carried out under refluxing conditions, and for weakly nucleophilic sulfonamides, long reaction periods and high temperatures are required to achieve complete conversion. For more sensitive or reactive amine derivatives, the reaction can be conducted at room temperature or at 0°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).

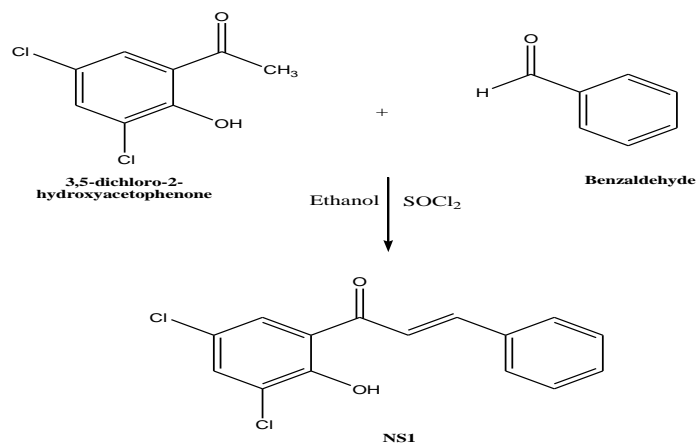
In the presence of pyridine, N-Substituted amidrazones interacts with SOCl_2 to produce the main products 1,2,3,5-thiaziazole derivatives. Different tautomeric versions of these compounds are possible, such as 2,5-dihydro- (**NS8**), 2,3-dihydro-1,2,3,5-thiaziazole-1-oxide (**NS9**), or 2H-1,2,3,5-thiaziazol-1-ium hydroxide (**NS10**), as displayed in **Equation 7** (45,46).

New monomers that possess sulfinylimine functionality have been synthesized in the presence of 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)

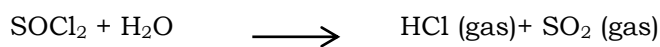


Equation 1. Synthesis of acid chloride

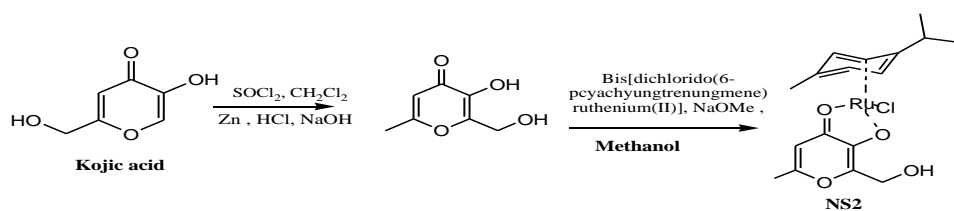
**Equation 2.** Synthesis of alkyl chloride**Scheme 1.** The one-pot two-steps method for preparing carboxylic acid derivatives**Equation 3.** The esterification of the unconjugated carboxyl group



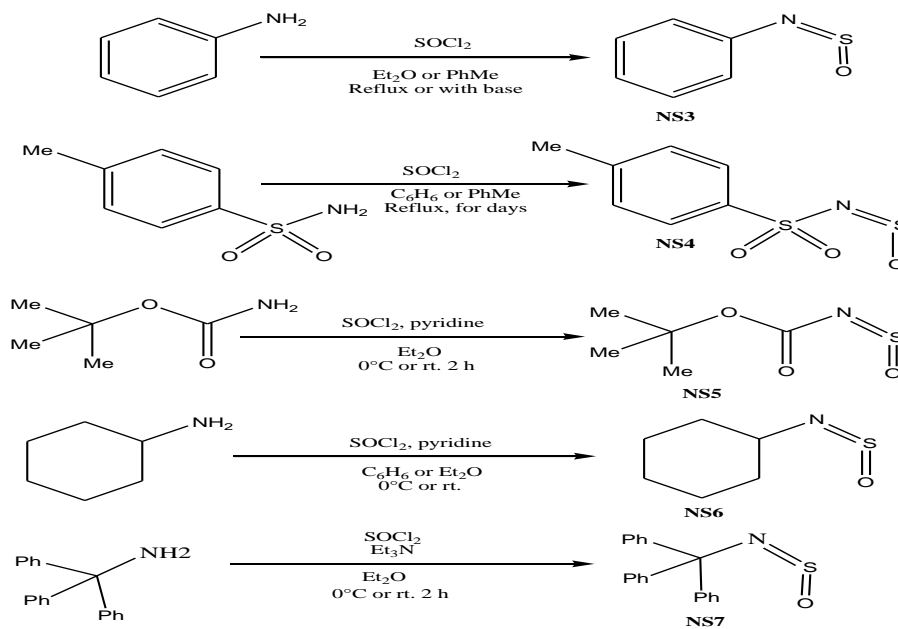
Equation 4. Synthesis of chalcones



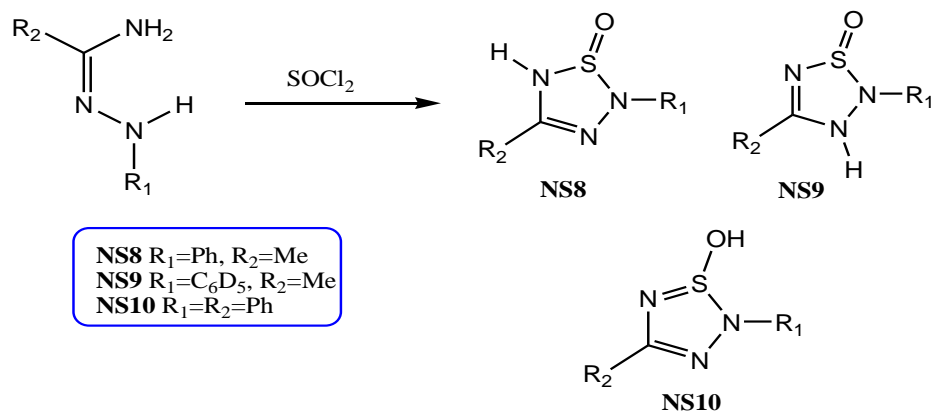
Equation 5. Synthesis of HCl



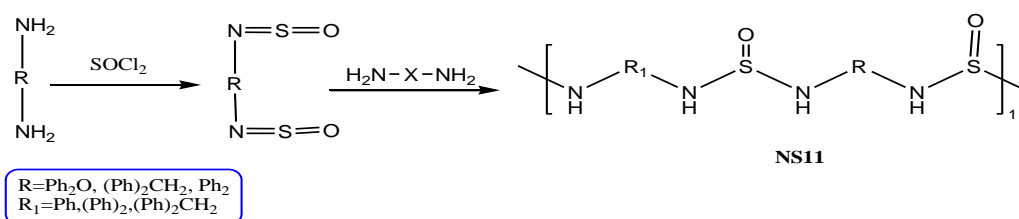
Equation 6. Synthesis of Maltol-derived ruthenium cymene complex (NS2)



Scheme 2. Preparation of different classes of sulfinylamines



Equation 7. N-Substituted amidrazones reaction with SOCl_2



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_2 . 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

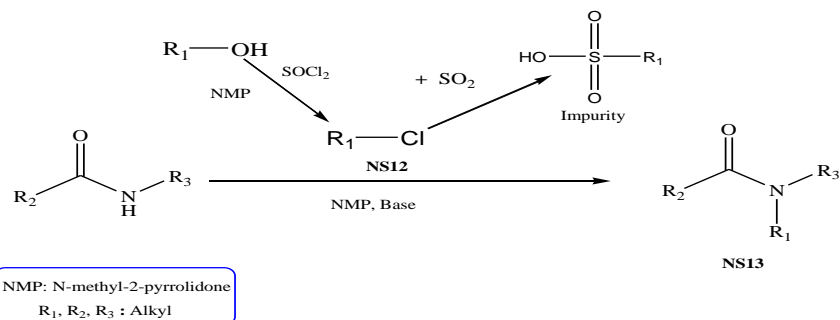
The reaction of 2,2'-(1,2-phenylenebis(oxy)) diethanol with SOCl_2 yields a mixture of [1,3,6,9,2] tetraoxathiacycloundecine 5-oxide (**NS14**) and

[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).

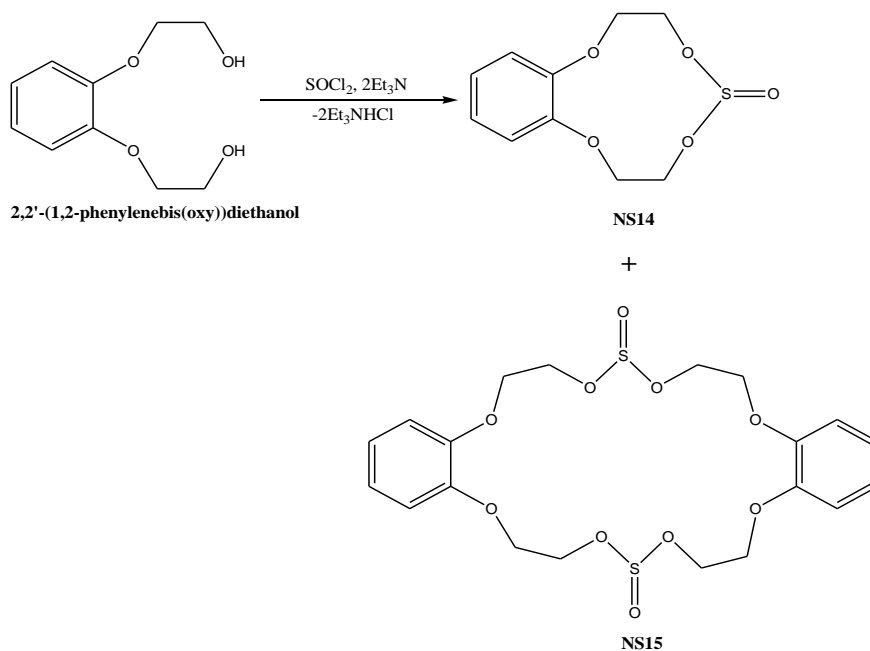
In addition, ortho-diols and SOCl_2 interact to produce sulfites, which are a mixture of the two diastereomers, giving excellent yields. In this reaction, SOCl_2 will serve as the stereogenic center. **Equation 9** has shown the formation of (3aR,6aS)-3a,6a-dibutyltetrahydrothieno[3,4-d][1,3,2]dioxathiole 2-oxide (**NS16**) (53,54).

With hydroxyamine

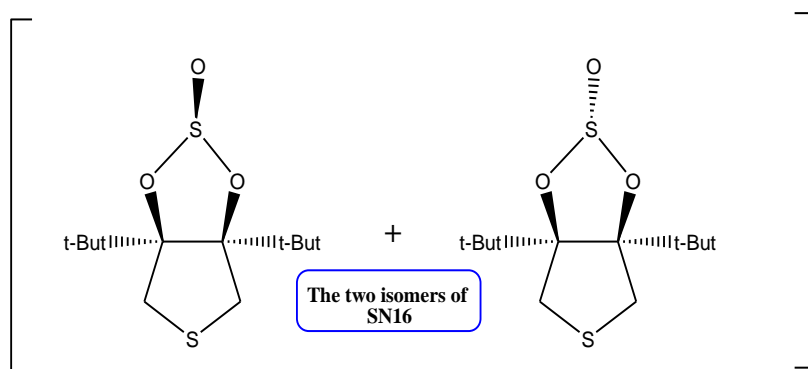
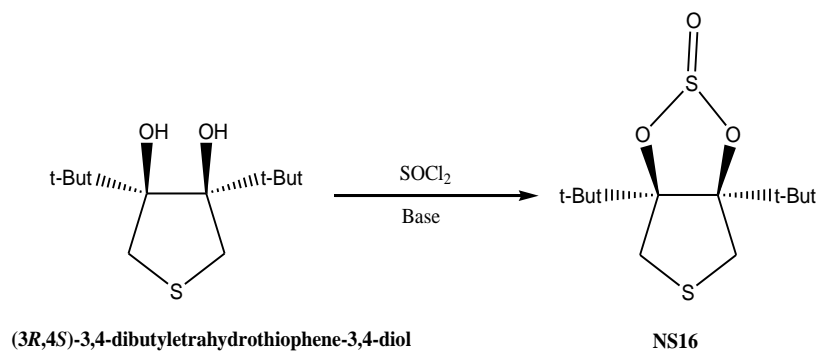
SOCl_2 can also react with hydroxyamine to produce benzimidoyl derivatives. The major product of the reaction of SOCl_2 with N-benzoyl-N-butyl hydroxyamine was (Z)-N-((chlorosulfonyl)oxy)benzimidoyl chloride (**NS17**), as shown in **Equation 10** (55).



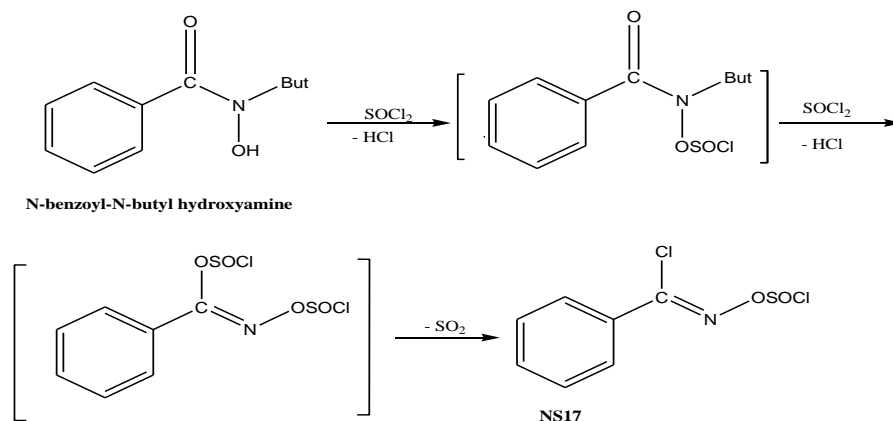
Scheme 4. The reaction of alcohol with thionyl chloride



Equation 8. The reaction of SOCl_2 with diethanol to produce **NS14** and **NS15**



Equation 9. The reaction of SOCl_2 and ortho-diols to produce sulfites

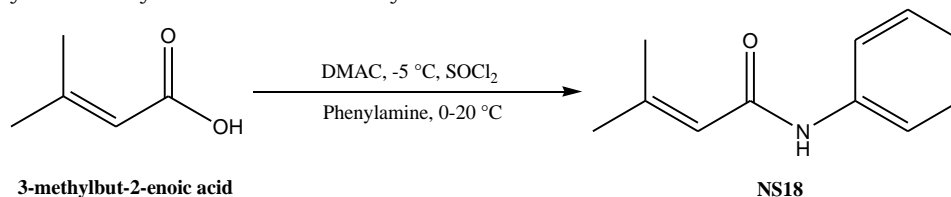


Equation 10. The reaction of SOCl_2 with hydroxylamine

1.3.3 Reactions with a carboxyl group

As mentioned previously, SOCl_2 can be used to synthesize acid chloride (25,56), however, there are situations where 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 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 SOCl_2 as a catalyst (57,58).



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

1.4 SOCl_2 as a special reagent

1.4.1 Condensing agent

SOCl_2 serves as a condensing reagent in some reactions to form more reactive compounds. Acetanilides and dialkylformamides react in the presence of 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 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).

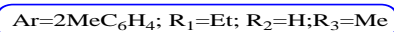
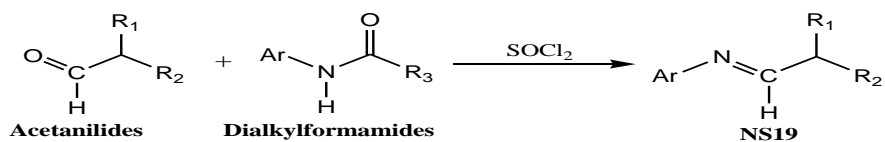
Also, derivatives of N-oxysulfonyl formamidine (**NS21**) have been successfully produced under friendly circumstances. Through the direct condensation of several sulfamates and formamides in the presence of chloroform and thionyl chloride, as displayed in **Equation 14** (63,64).

1.4.2 Oxidizing agents

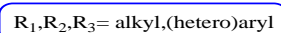
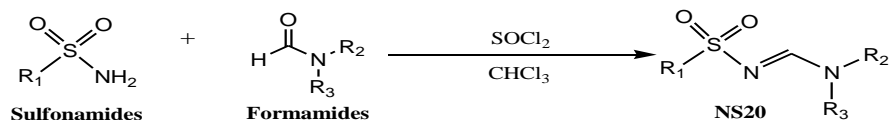
SOCl_2 can unexpectedly acts as an oxidant agent for different organic compounds. Amino acids attached to cobalt are quickly oxidized by this reagent to give imines. As a result, the cobalt-alanine complex was oxidized by SOCl_2 in DMF to produce imino acid complexes (**NS22**), as displayed in **Equation 15** (65,66)

Also, 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**). SOCl_2 served as a convenient alternative oxidant for lead tetraacetate in this system, as displayed in **Equation 16** (67,68).

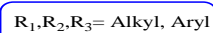
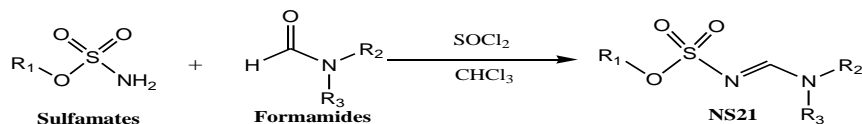
An unusual oxidation reaction noticed when the furoacridone was reacted with SOCl_2 . This unexpected oxidation process was found to be useful in 1,3-dihydro-2-[2-(dimethylamino) ethyl]-1,3-dioxopyrrolo [3,4-c] acridine (**NS25**) synthesis, which is a potent DNA topoisomerase II inhibitor, as displayed in **Equation 17** (69,70).



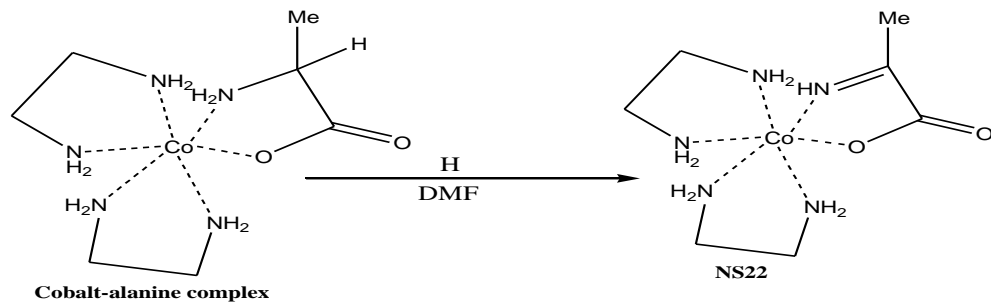
Equation 12. Formamidines synthesis in the presence of SOCl₂ as a condensing agent



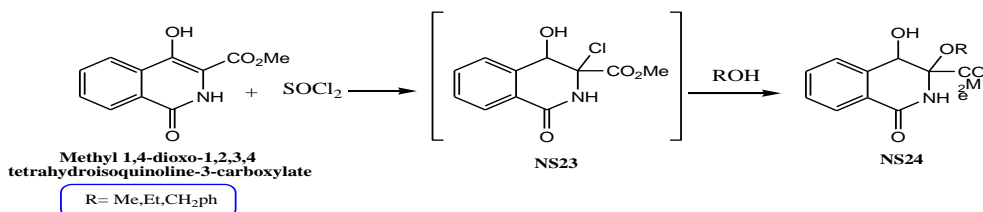
Equation 13. Production of N-sulfonylformamide derivatives in the presence of SOCl₂ as a condensing agent



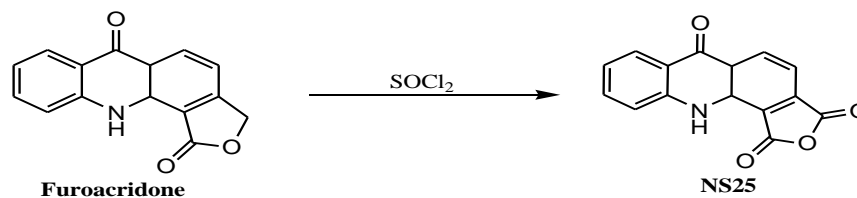
Equation 14. Production of N-Oxysulfonyl formamide derivatives in the presence of SOCl₂ as a condensing agent.



Equation 15. The cobalt-alanine complex oxidation by SOCl₂



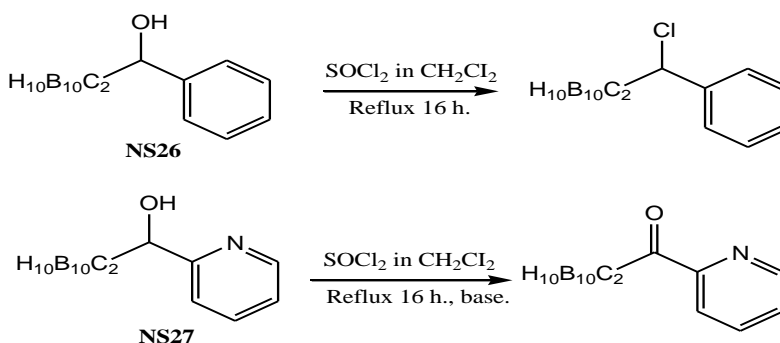
Equation 16. Role of SOCl₂ as an oxidant agent



Equation 17. An unusual oxidation reaction of furoacridone in the presence of SOCl_2

Moreover, 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).

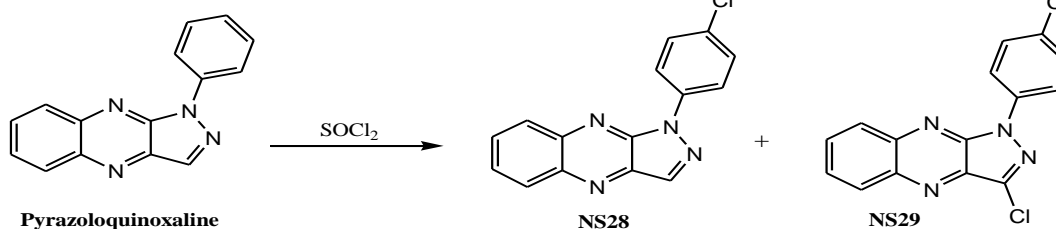


Scheme 5. Halogenation and unexpected oxidation reaction of SOCl_2

1.4.3 Chlorinating agent

The mechanism by which 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

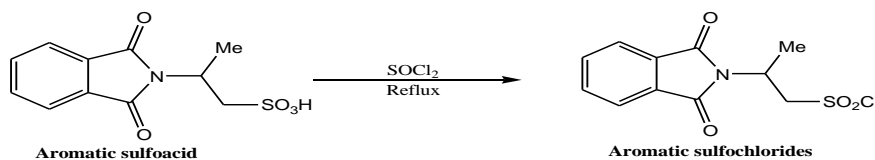
ambient oxygen to sulfuryl chloride, that is a well-known chlorinating agent for organic compounds. Chlorination of the pyrazoloquinoxaline with SOCl_2 reagent produces different chloro-substituted derivatives (**NS28** and **NS29**), as displayed in **Equation 18** (73).



Equation 18. Chlorination of the pyrazoloquinoxaline with SOCl_2

The reagent 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

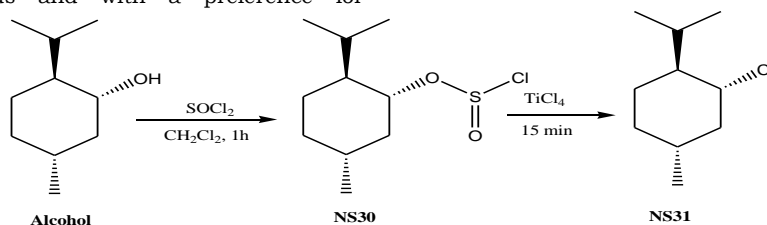
acids derivatives, respectively, as displayed in **Equation 19** (13,74).



Equation 19. Chlorinating action of SOCl_2 reagent

A chlorination reaction of alcohols was achieved using the traditional 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).

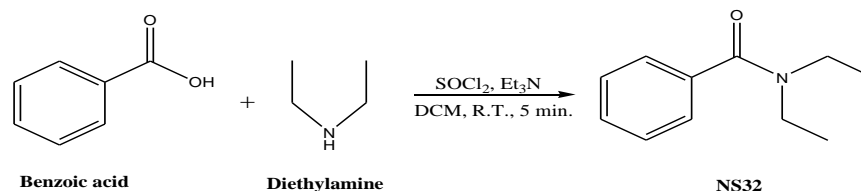


Equation 20. Role of SOCl_2 as an oxidant agent

1.4.4 Coupling agent

The 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 SOCl_2 to produce *N,N*-Diethyl-benzamide (**NS32**) (72,77).

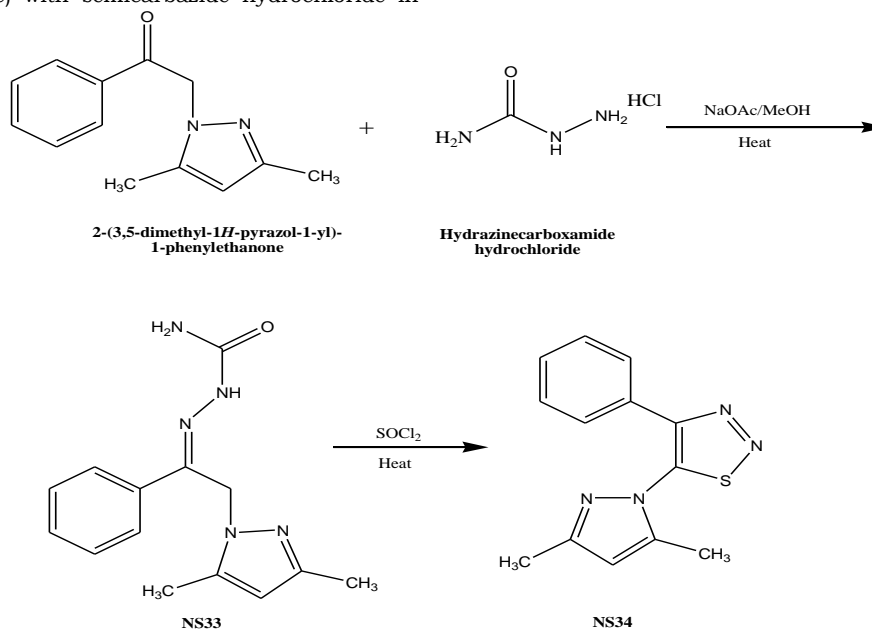


Equation 21. The coupling action of SOCl_2 in reaction of benzoic acid with diethyl amine

1.4.5 Cyclizing agent

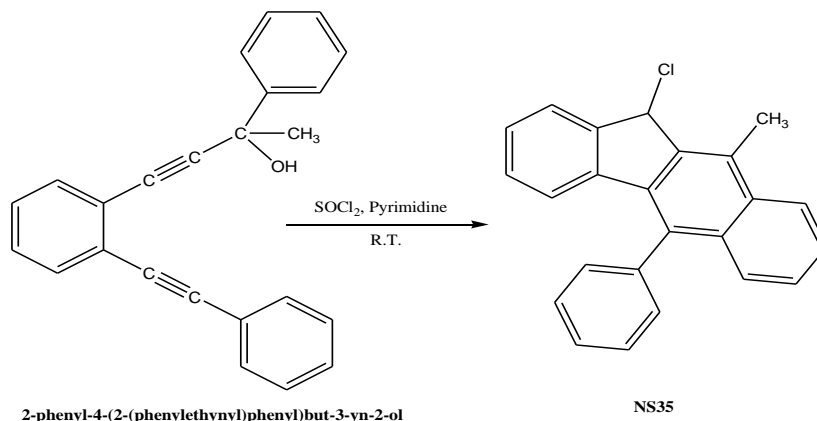
SOCl_2 has been successfully employed in the synthesis of pyrazolyl-1,2,3-thiadiazoles via the Hurd and Mori cyclization reaction. Pyrazolyl-1,2,3-thiadiazoles have been reported to have many important biological and pharmacological activities (56,78). The reaction of various pyrazolyl-phenylethanones (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 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 SOCl_2 via Hurd–Mori cyclization reaction

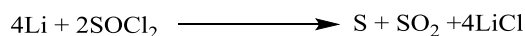
Also, mild treatment of tertiary aryl-diacetylene alcohols with SOCl_2 resulted in intramolecular classical (4+2) cycloaddition reactions (cyclo-aromatization) and afforded



Equation 22 . The SOCl_2 as a cyclizing agent to synthesize chlorinated 2,3-benzo[b]fluorenes

1.5 The role of SOCl_2 in batteries industry

The reagent SOCl_2 is an essential element of lithium- 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- SOCl_2 batteries

2. Conclusion

The reagent 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, 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, 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 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 SOCl_2 تسريع وتقليل مدة التفاعلات التقليدية الطويلة ، وبالتالي زيادة أهميتها.

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