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$POCl_3$-PCl_5 mixture: A robust chlorinating agent†

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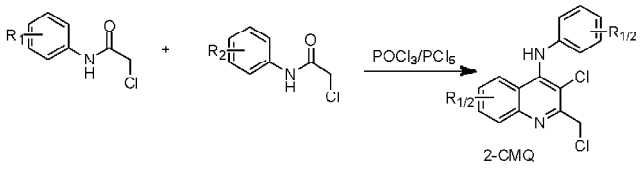
$POCl_3$-PCl_5 mixture has been widely used as a very strong chlorinating agent for a number of decades. This mixture together can chlorinate a wide variety of compounds in a very reasonable time period. Their effectiveness has attracted a large number of scientists as one of the important stairs for multistep reaction. Apart from the chlorinating property $POCl_3$-PCl_5 mixture can lead to other very interesting reactions like ring cyclisation, aromatization etc. There is large number of reports in literature for chlorination using $POCl_3$ or PCl_5 separately but here in this review article we only concentrate in the $POCl_3$/PCl_5 mixture. Sometime $POCl_3$ alone is not that strong chlorinating agent but addition of PCl_5 makes it strong for the same reaction. Some of the reactions using $POCl_3$/PCl_5 mixture have been compiled below.

Keywords: $POCl_3$-PCl_5 mixture, chlorinating agent, coumarin, pyridine, phenanthrene, benzimidazole.

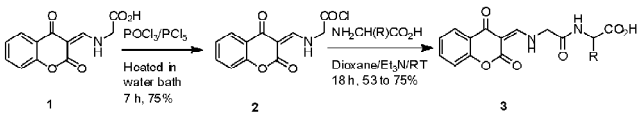
Introduction

Chloromethylquinolines can bind covalently and potentialy with various cellular protein targets, such as heme oxygenase 2 (HMOX2), glutathione *S*-transferase ω-1 (GSTO1), and prostaglandin E synthase 2 (PTGES2). Since chloromethylquinolines bind potently with PTGES2 enzymes, the enzymatic conversion of prostaglandin E is not occurred. Hence the inflammation is not produced and thus chloromethylquinoline acts as an anti-inflammatory agent. Zhang *et al.* reported the synthesis[1] of a novel electrophile, 2-chloromethylquinoline (2-CMQ) by means of a condensation reaction in PCl_5/$POCl_3$ mixture (Scheme 1) and explored its reactivity in the proteome. The 2-CMQ exhibit good anti-inflammatory activity.



Scheme 1

Variety of coumarin based compounds have been reported by Faty *et al*. These compounds have studied exclusively for the antibacterial activity. Coumarin based carboxylic acid (**1**) has been converted[2] to its corresponding acid chloride (**2**), which is reacted with a number of amino acids to produce different dipeptides (**3**) shown in the Scheme 2. The acid chloride (**2**) shows promising antibacterial activity against Gram-positive and Gram-negative bacteria. Also it shows the fluorescence property in both solid as well as in solution phases. In solid phase the fluorescence maximum shifted bathochromically by an amount of 50 nm as compare to in solution phase.

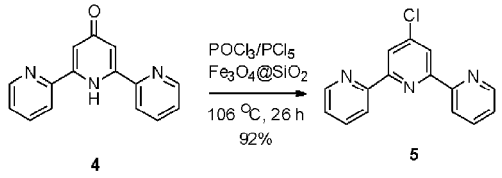


Scheme 2

Unique class of functional compounds such as terpyridines that are widely spotlighted in diverse fields like synthesis of nanomaterials, medicinal chemistry intermediates, supramolecular chemistry, drugs and active pharmaceutical ingredients and so on. The synthon 4′-chloro-2,2′:6′,2″-terpyridine has been extensively used for the synthesis of terpyridine. When 2,6-bis(2-pyridinyl)-4-pyridine (**4**) was ex-

†**Review.**

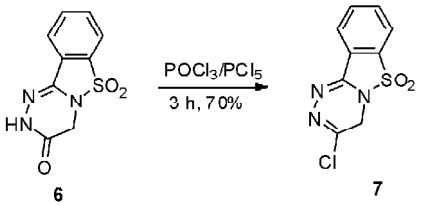
posed in $PCl_5/POCl_3$ and acidic silica gel [Fe_3O_4@SiO_2] aromatization[3] take place and provided the chloro compound (**5**) in about 92% yield (Scheme 3).



4 **5**

Scheme 3

Oxotriazinobenzisothiazole (**6**) has converted to its corresponding chloro[4] derivative (**7**), 6-chloro1,2,4-triazino[4,3-*b*][1,2]benzisothiazole, by refluxing on a steam bath for 3 h using the mixture of reagent, $POCl_3$ and PCl_5 shown in Scheme 4.



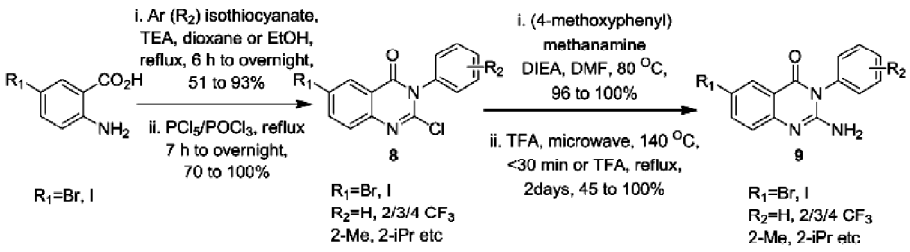
6 **7**

Scheme 4

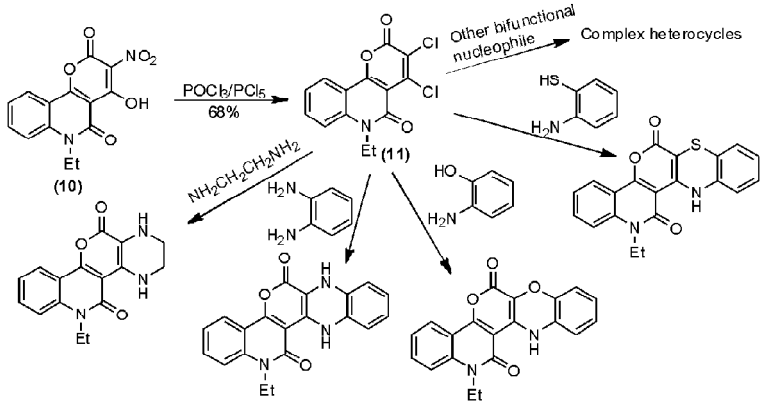
While working on the discovery of selective small molecule type III phosphatidylinositol 4-kinase alpha (PI4IIIα) inhibitors as anti hepatitis C agents Botyanszki and co-worker reported[5] the synthesis of multiple series of inhibitors. To achieve their target first synthesise the quinazolinone derivatives (**8**) through the cyclization of commercially available isothiocyanates with 2-aminobenzoic acids. Installation of chlorine at C2 was done by treatment of (**8**) with neat $POCl_3$ in presence of PCl_5. Subsequent replacement of chlorine atom with amino group was achieved by the expose of the chloro derivatives into (4-methoxyphenyl) methanamine in DMF, followed by cleavage of the *para*-methoxybenzyl (PMB) protecting group by heating in neat trifluoroacetic acid (TFA) to give the intermediates (**9**) shown in Scheme 5. Further chemical transformations (cross-coupling, borylation etc.) were done with other intermediates to obtain the aryl tail of the quinazolinone core.

Ibrahim and co-worker reported an efficient and convenient synthesis[6] of several novel annulated heterocyclic compounds which consist of a bioactive pyrano[3,2-*c*]quinolinedione moiety which is a parent ring structure present in pyranoquinoline alkaloids. Pyranoquinoline alkaloids exhibit good pharmaceutical activities such as antifungal, anti-allergic, anti-coagulant, anti-histaminic, coronary constricting and anti-inflammatory. To achieve their target they first synthesise the novel precursor 3,4-dichloro-6-ethyl-2*H*-pyrano[3,2-*c*]quinoline-2,5(6*H*)-dione (**11**) from 6-ethyl-4-hydroxy-3-nitro-2*H*-pyrano[3,2-*c*]quinoline-2,5(6*H*)-dione (**10**) by chlorination reaction using $POCl_3$ and PCl_5 mixture. To obtain the heteroannulated pyrano[3,2-*c*]quinolinedione derivatives they condensed the precursor (**11**) with different symmetrical 1,4-bifunctional nucleophiles such as ethylenediamine, *o*-phenylenediamine in absolute alcohol as well as unsymmetrical 1,4-bifunctional nucleophiles such as 2-aminophenol and 2-aminothiophenol in absolute alcohol in presence of few drops of triethylamines shown in Scheme 6. Similarly Ibrahim *et al*. achieved the synthesis of some other complex hetero cycles by condensation of (**11**) with different 1,4-bifunctional nucleophiles.

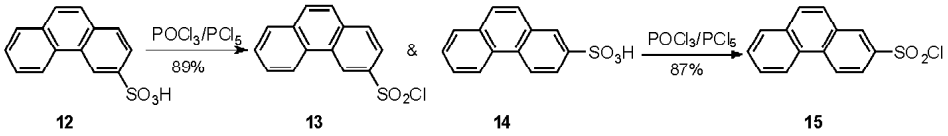
In 2012 Russikh *et al*. optimized the synthesis[7] of phenanthrene-2-sulfonyl chloride (**13**) and phenanthrene-3-sulfonyl chloride (**15**) from their corresponding sulphonic acids (**12**) and (**14**) respectively which shown in the Scheme 7. In that



Scheme 5



Scheme 6



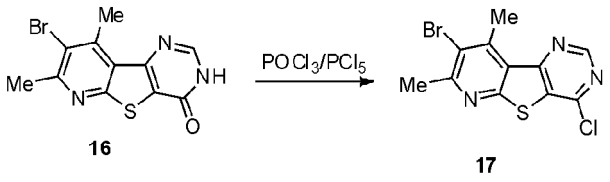
Scheme 7

article they reported the preparation of phenanthrenesulfonyl chloride in an optimum condition using $POCl_3$ and PCl_5 mixture in high yield. They also have suggested that even the mixture of sodium salts of the corresponding sulfonic acids resulted the pure 2- and 3-sulfonyl chlorides in a moderate yield.

Sun *et al.* reported the large scale synthesise i.e. multigram and kilogram synthesis of the important synthetic intermediate chloropyrimidine and its analogues in solvent free or low solvent condition using equimolar or less quantity of chlorinating agents[8]. Synthesis of chloropyrimidine from hydroxyl pyrimidine needs use of excess $POCl_3$ which is not good at all for the environment. Sun and co-worker did the same conversion using reduce amount of chlorinating agent with increasing the temperature up to 180°C in a sealed reactor. One equivalent of $POCl_3$ and pyridine as base provide the maximum yield of 95%. On the other hand 0.5 equivalent of $POCl_3$ and 0.5 equivalent of PCl_5 mixture yielded a bit less in pyridine.

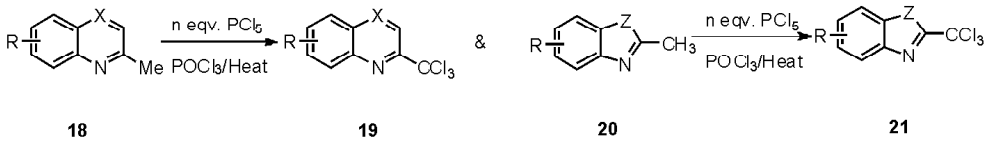
Marzouk reported[9] the use of $POCl_3$-PCl_5 mixture as one of the reagent in the key steps for the preparation of the variety of tetrazolo and triazolo derivatives.

Thienopyrimidinone (**16**) derivative has been successfully converted into its corresponding chloro derivative[10] resulting in chloropyrimidine (**17**) derivative using the $POCl_3$-PCl_5 mixture shown in the Scheme 8.



Scheme 8

α-Trifluoromethylated nitrogen containing heterocyclic compounds e.g. mafloquine has pharmaceutical interest. The well known precursor of the trifluoromethylated nitrogen containing derivative is trichloromethyl compound which could be synthesis in single step by using SbF_5 or SbF_3. On the other hand Vanelle and co-worker reported that in the field of radical reaction the aromatic α-trichloromethylated nitrogen containing derivatives shows very interesting roll. There are methods reported in the literature for chlorination but those methods required long reaction time, provided low to medium yield etc. Vanelle *et al.* reported[11] that the N-α-trichloromethyl derivatives (**19** and **21**) could be synthesized from the corresponding α-methylated nitrogen containing heterocyclic compounds (**18** and **20**) under microwave as-



Scheme 9

sisted condition. This methodology introduced very high yielding (75–98%) reaction in time economic condition (5–20 min) shown in Scheme 9.

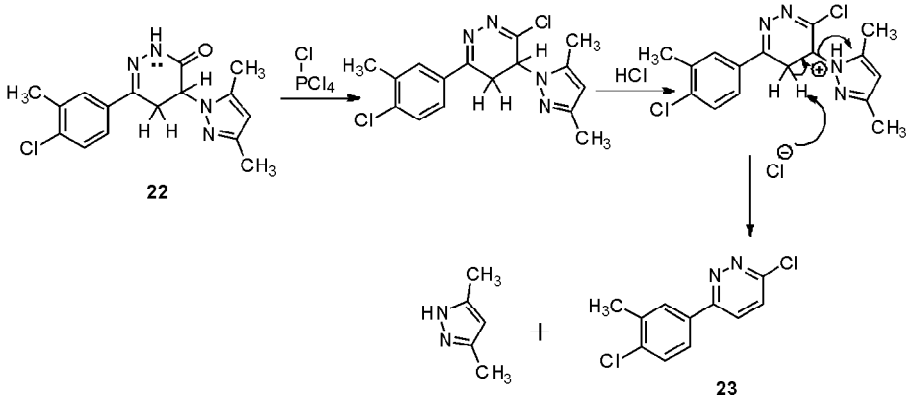
Kassab exclusively studied and reported[12] the different reactions of 4-(4′-chloro-3′-methylphenyl)-1(2*H*)-phthalazinone with a variety of carbon nucleophiles under Grignard reaction condition followed by the chlorination using the $POCl_3$-PCl_5 mixture.

Pyridazin-3-one derivatives normally exhibit allergenic, insecticidal, bactericidal, anti-inflammatory, analgesic and antihypertensive activities. To prepare this type of derivative a group of chemist[13] from Ain Shams University and El-Tahdi University did reaction of (**22**) with a phosphorous pentachloride-phosphorous oxychloride mixture (Scheme 10) followed by HCl yielded 6-aryl-3-chloropyridazine derivative (**23**).

head heterocycles[14] using PCl_5 and $POCl_3$. These chlorinated derivatives have been treated further with suitable reagents described in the article to obtain biologically active novel heterocyclic compounds.

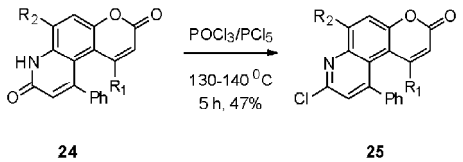
1,8-Naphthyridines, quinolinamines and quinoline derivatives has promising pharmaceutical significant. In this paper Kidwai and co-worker showed the synthesis of dibenzo(*b*,*g*)-5-methyl-1,8-naphthyridines starting from 2-hydroxy-4-methylquinoline. PCl_5-$POCl_3$ has been reported as one of the important chlorinating agent[15] for the preparation of variety of 1,8-naphthyridines. Conversion of 2-hydroxy-4-methylquinoline (**26**) to 2-chloro-4-methylquinoline (**27**) using the mentioned reagent mixture has been carried out in this reported methodology which shown in the Scheme 12.

Chlorination of 4,6-dinitro-1,2-benzisothiazol-3-ones (**28**)

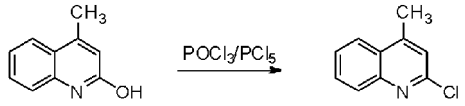


Scheme 10

Coumarin moiety is present in the pyranoquinolines derivative. Coumarin exhibits various biological activities such as antibacterial, antifungal, anticoagulant and insecticidal. Pyranoquinolines (**24**) has been converted into the chloropyranoquinolines (**25**) shown in Scheme 11 which have been used as a building block for the synthesis of bridge-

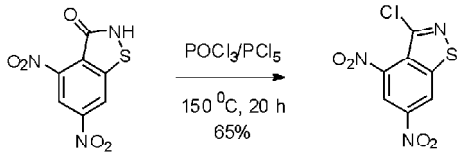


Scheme 11



Scheme 12

using PCl_5-$POCl_3$ to produce the expected 3-chloroisothiazoles (**29**) has been well reported[16] (Scheme 13) while reporting the synthetic utilization of polynitroaromatic compounds.

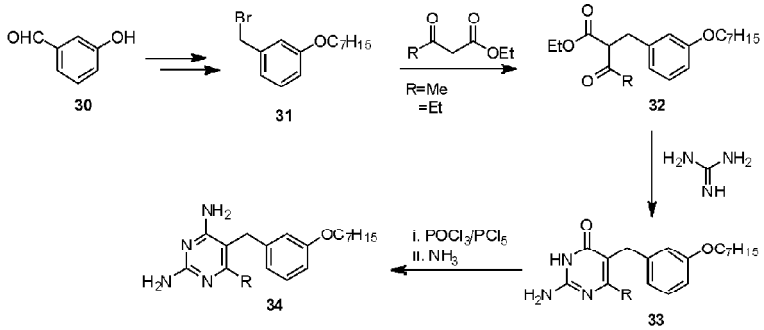


Scheme 13

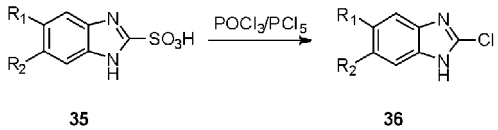
Ian H. Gilbert and co-worker reported[17] the design, synthesis and biological evaluation of 5-substituted as well as 5,6-disubstituted 2,4-diaminopyrimidine derivatives as inhibitors of trypanosomal and leishmanial dihydrofolate reductase. The 5,6-disubstituted 2,4-diaminopyrimidine derivatives shows good activity. Compound (**31**) was synthesised from compound (**30**) in three steps. Alkylation of ethyl acetoacetate or ethyl propionylacetate with appropriately functionalized benzyl derivatives (**31**) produced compound (**32**). Codensation of (**32**) with guanidine gave (**33**) and the compound (**33**) on treatment with $POCl_3$/PCl_5 mixture followed by reaction with NH_3 yielded the 5,6-disubstituted 2,4-diaminopyrimidine derivatives (**34**) shown in Scheme 14.

A novel and improved method has been established to prepare substituted benzimidazole-2-sulfonic acids from the corresponding 2-mercaptobenzimidazoles. 2-Chlorobenzimidazoles derivative[18] (**35**) was obtained in very high yield (Scheme 15) from the corresponding sulfonic acids (**36**) upon reaction with PCl_5 in $POCl_3$. The mentioned mixture of reagents has been used in gram-mole scale.

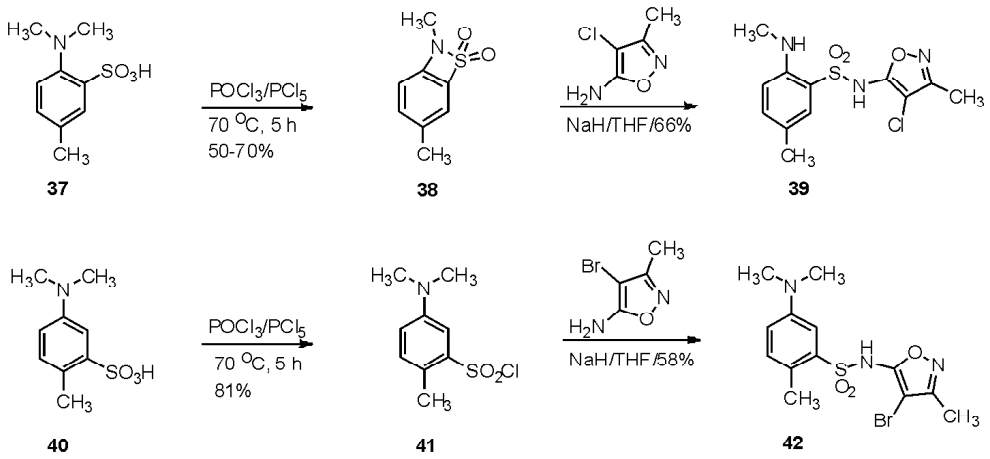
Wu and co-worker while working for the preparation of the endothelin receptor antagonists they need to synthesize 2-(dimethylamino)-5-methylbenzenesulfonamides from 2-(dimethylamino)-4-methylbenzenesulfonyl chloride. To obtain the chloro derivative[19] of the sulfonic acid they heated the acid (**37**) with PCl_5/$POCl_3$ mixture at 60–80°C for 4–6 h and did not get the desired chloro derivative. They found the dimethylamino group was monodemethylated and the four-membered-ring sultam (**38**) formed in good yield (Scheme 16) which is insoluble in water and can be stored at –20°C for at least 1 week. This demethylation reaction was not expected because under the same experimental conditions 5-(dimethylamino)-2-methylbenzenesulfonic acid (**40**) was converted to the corresponding sulfonyl chloride (**41**) rather uneventfully. Compound (**41**) was coupled with the bromoisoxazol to afford sulfonamide (**42**). They also reported in that article that the sultam ring can be opened by coupling with an amine and functions as a sulfonyl chloride substitute.



Scheme 14



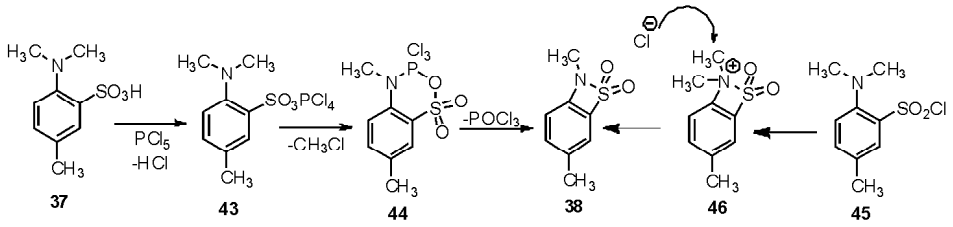
Scheme 15



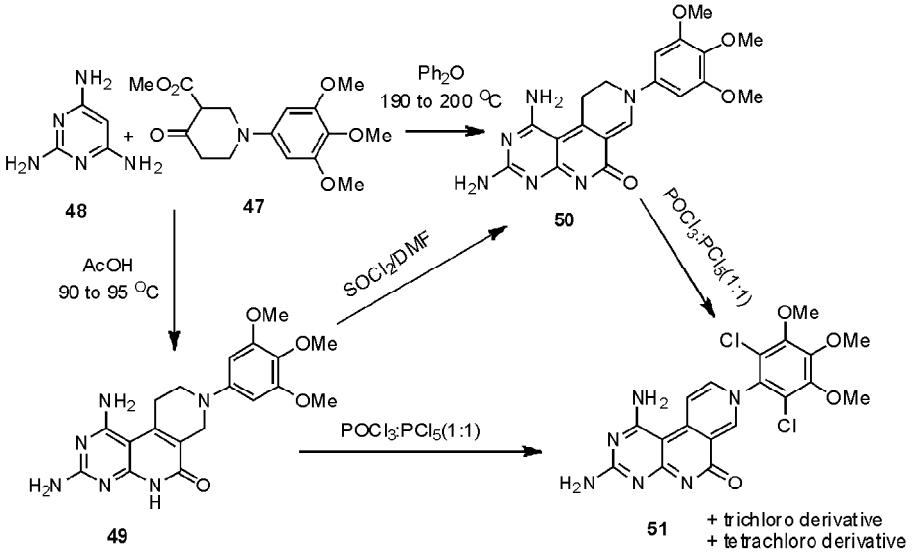
Scheme 16

The mechanism for the formation of the four-membered benzosultam is shown in the Scheme 17.

Aleem Gangjee and co-worker reported the synthesis[20] of pyrimido[4,5-*c*][2,7]naphthyridones a conformationally restricted, novel tricyclic nonclassical antifolates and also investigate the biological activity as inhibitors of dihydrofolate reductases (DHFR). Gangjee *et al.* synthesize several such compounds but here in this review we are only interested on



Scheme 17



Scheme 18

one compound which has been synthesized by using $POCl_3$/PCl_5 mixture. The synthesis was started with a biselectrophile (keto ester) (**47**) with 2,4,6-triaminopyrimidine (**48**) in AcOH at 90–95°C or in Ph_2O at 190–200°C temperature and achieve the lactam (**49**) and (**50**) respectively. Chlorination of (**49**) with thionyl chloride in DMF produced (**50**) and the structure was confirmed by FAB mass. When (**49**) was thrown in the 1:1 mixture of $POCl_3$/PCl_5 it yielded multiple mixture of chlorinated product. When this mixture of chlorinated compounds were treated with 1 *N* NaOH-MeOH (1:1) solution gave the lactam (**51**) and structure of this compound was confirmed by its FAB mass as well as NMR spectroscopy. The lactam (**51**) does not exhibit good activity against rat liver dihydrofolate reductases (rlDHFR). The reason for the decreased potency of this lactam is because of the introduction of the electron withdrawing chlorine atoms in the aromatic ring.

Thus it can be concluded that this review focus on the chlorination of different substrates using $POCl_3$-PCl_5 mixture including some abnormal interesting cyclisation and aromatization reaction. This robust chlorinating mixture is used for the preparation of some important intermediates which could be converted into biologically useful molecules. There are still some scopes to use this unique mixture to synthesize differently substituted bioactive molecules which are not included in this review article. This chlorinating mixture can do wonders in the era of pharmaceuticals, medicinal, organic chemistry.

Acknowledgement

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