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RECENT ADVANCES IN THE SYNTHETIC USES OF CHLOROCARBONYL ISOCYANATE

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Abstract - Chlorocarbonyl isocyanate is a versatile reagent and finds extensive applications in the organic synthesis, in particular for the syntheses of heterocyclic compounds. This review updates its recent uses in the synthetic organic chemistry and describes its potentiality in the preparation of biologically important heterocycles.

Contents:

1. Introduction

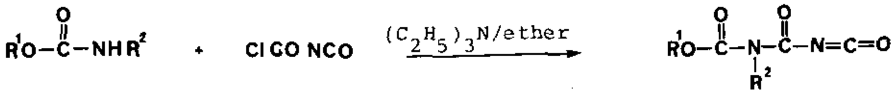
Chlorocarbonyl isocyanate (CCI) was first synthesized by Hagemann[1] in 1968. Although the preparation and reactions of this reagent were reviewed earlier,[2] a considerable amount of publications followed in recent years. Therefore, it seems of significance to update these findings in the present review.

CCI has been prepared by treatment of cyanogen chloride with phosgene over an active charcoal catalyst under pressure, followed by partial hydrolysis of the intermediate adduct, *N*-chlorocarbonyl isocyanide dichloride, by methanesulfonic acid.[1]

CCI exhibits a great diversity of the chemical reactions primarily due to the combination of two highly reactive functional groups and partly, due to the inherent symmetry of this molecule, which is manifested in its adduct with hydrogen chloride, *N*-(chlorocarbonyl)carbamoyl chloride. On account of this symmetry, it is difficult to conclude whether CCI reacts with weak nucleophiles such as water or alcohol primarily at the acid chloride or at the isocyanate grouping. However, many new derivatives of the parent iminodicarboxylic acid have been prepared, and furthermore CCI has been found to be a very versatile reagent for heterocyclic synthesis.

2. Reactions of CCI with

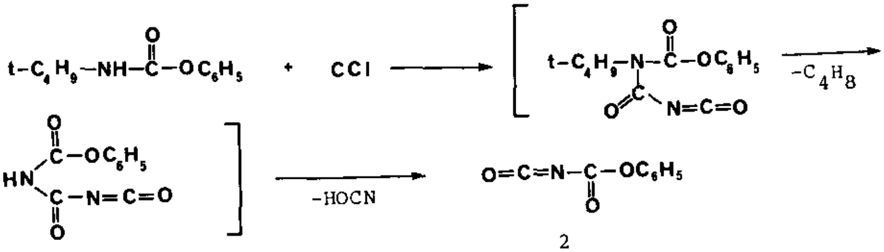
2.1 Carbamates: CCI reacts with *N*-alkylcarbamates in anhydrous ether at 20°C in the presence of triethylamine to give the alkyl N-alkyl-N-isocyanotocarbonylcarbamates 1.[3]



R^1=R^2= alkyl

1

Reactions of N-substituted aryl carbamates with CCI also yield the corresponding isocyanates, but the isocyanate form phenyl t-butylcarbamate interestingly undergoes the elimination of isobutene to give phenoxycarbonyl isocyanate 2.[4]



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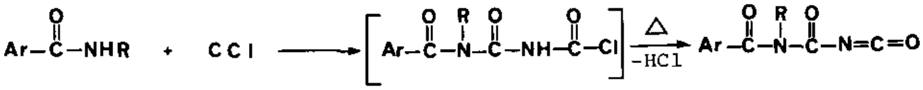
2.2 Alkylamides of aromatic carboxylic acids: Like secondary amines, the alkylamides of aromatic carboxylic acids react with CCI under mild conditions via the unstable adducts 3 which evolve hydrogen chloride at the boiling point of the reaction mixture to give N-alkyl-N-aroylaminocarbonyl isocyanates 4 in good yields.[5] Unlike the reaction products of secondary amines the isocyanate 4 are not shown to undergo reversible [4+2] cycloaddition.[6]

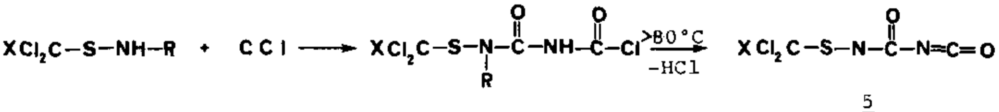


R = alkyl

3

4

2.3 Trihalomethanesulfenamide: Reaction of CCI with N-alkyltrihalomethanesulfenamide gives N-alkyl-N-(trihalomethylthio)aminocarbonyl isocyanate 5.[7]



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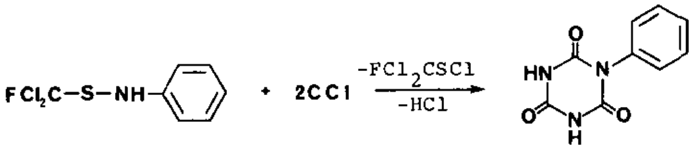
X = F,Cl; R = alkyl

When R is phenyl the reaction with CCI affords 2,4,6-trioxo-1-phenylhexahydro-1,3,5-triazin 6.



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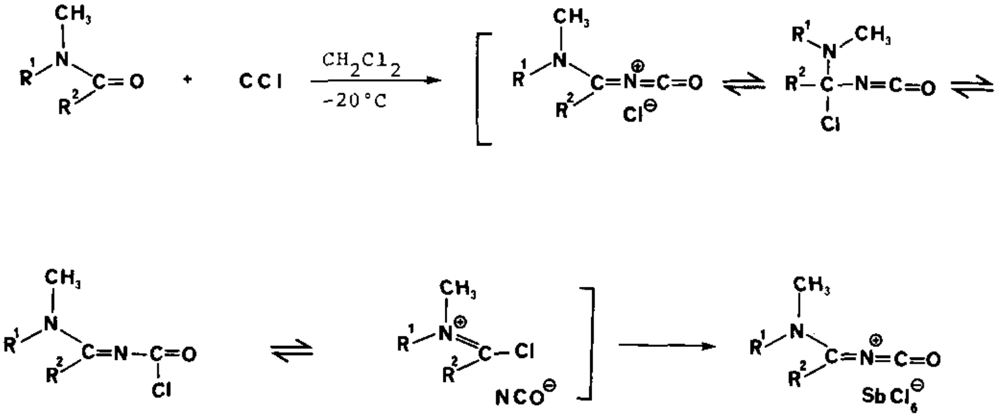
2.4 Tertiary amides: The reaction of CCI with tertiary amides such as N,N-dimethylformamide or N,N-dimethylpivalamide in the presence of antimony pentachloride affords the amino substituted 1-oxo-3-azabutatrienium hexachloroantimonates 7.[8] Its structure was confirmed by X-ray diffraction analysis. This transformation parallels the Vilsmeier-Arnold reaction of tertiary carboxamides with phosgene.

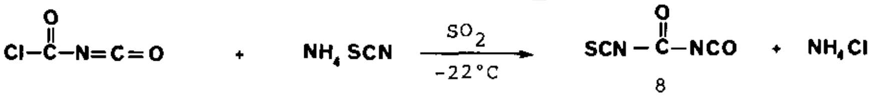


7

$R^1 = R^2 =$ alkyl

There are also examples, wherein the reaction of aldehydes and ketones with CCI in the presence of $SbCl_5$ affords convenient route for azallenium salts.[9]

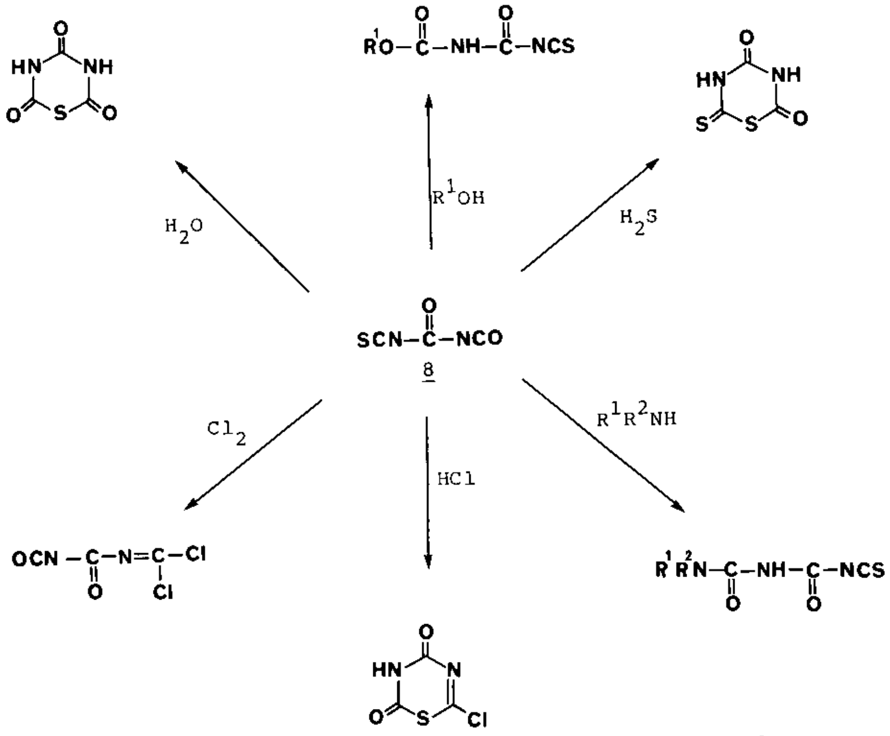
2.5 Ammonium rhodanide: The reaction of CCI with ammonium rhodanide leads to the formation of carbonyl isocyanate isothiocyanate 8.[10]



$$Cl-\overset{\overset{\large O}{\|}}{C}-N=C=O + NH_4SCN \xrightarrow[-22^\circ C]{SO_2} SCN-\overset{\overset{\large O}{\|}}{C}-NCO + NH_4Cl$$

8

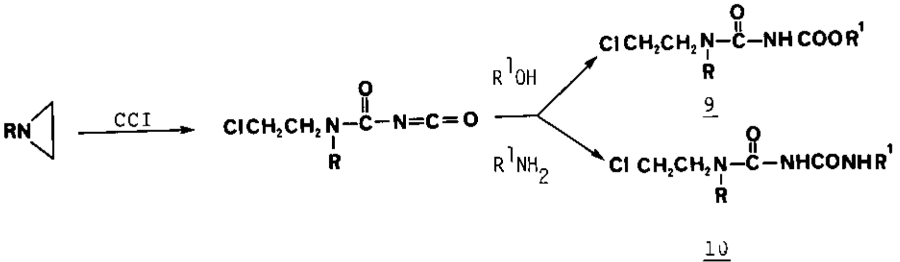
Compound 8 is a useful reagent in the synthesis of a variety of organic intermediates and as well for the sulfur containing heterocyclic compounds. The following Scheme 1 depicts its salient applications.



$R^1 = R^2 = $ alkyl

Scheme 1

2.6 Aziridines: The reaction of CCI with aziridines gives the isocyanate adducts which on treatment with alcohols and amines yield carbamoyl carbamates 9 and ureas 10 respectively.[11]

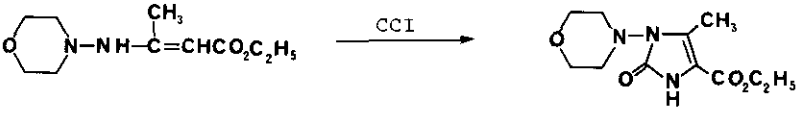


$R = CH_2CH_2CN, P(O)(OC_2H_5)_2$; R^1 = alkyl

3. Synthesis of heterocycles

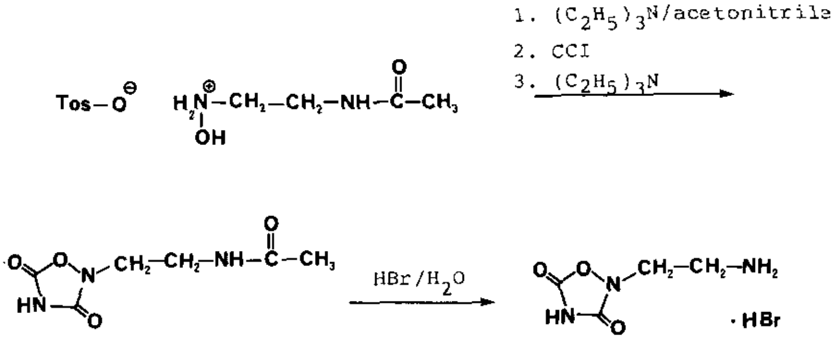
CCI is of value in the synthesis of heterocyclic compounds. Despite the high degree of reactivity of both functional groups in CCI, reaction may occur at one or other of these groups, depending on the nature of the other reactant, thus making this reagent suitable for the construction of a wide variety of heterocyclic compounds and in particular for fused heterocycles. Some of its recent applications are described below.

3.1 Imidazoles: Cyclocondensation of ene hydrazines with CCI affords the imidazole system 11.[12]



11

3.2 1,2,4-Oxadiazolidine-3,5-dione: A new synthetic route was developed by employing CCI in forming the oxadiazolidine ring system in the total synthesis of quisqualamine. A novel GABA-related depressant amino acid, quisqualamine is isolated from the Chinese plant *Quisqualis indica*. The reaction of *N*-hydroxy-2-acetylaminoethanaminium tosylate with CCI gives *N*-acetylquisqualamine which on treatment with hydrobromic acid yields quisqualamine hydrobromide 12.[13]



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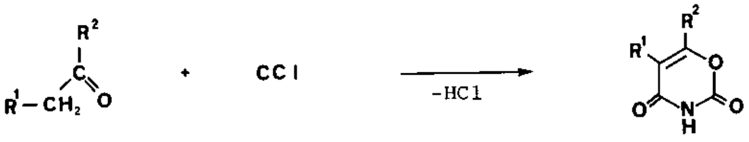
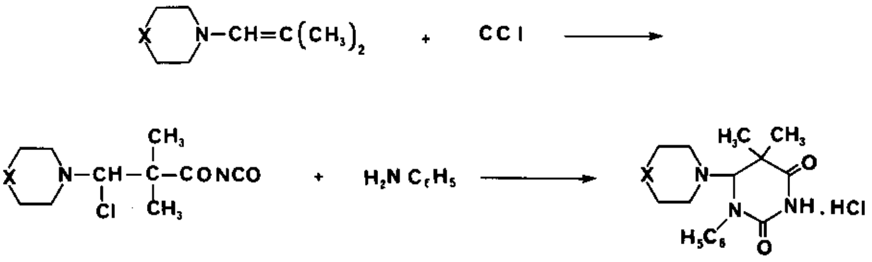
3.3 1,3-Oxazine-2,4-diones: Ketones on reaction with CCI yield 1,3-oxazine-2,4-diones 13.[14]



13

$R^1 = R^2$ = alkyl

3.4 1,3-Diazine-2,4-diones: The reaction of enamines with CCI followed by the condensation with aniline gives diazino system 14.[15]



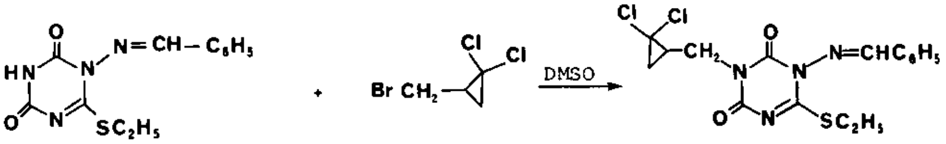
14

3.5 1,3,5-Triazine-2,4-diones: CCI finds use in the synthesis of potent herbicide as depicted below.[16]

$$C_6H_5OH \quad + \quad ClCONCO \xrightarrow[60°C]{Toluene} (C_6H_5O_2C)_2NH$$

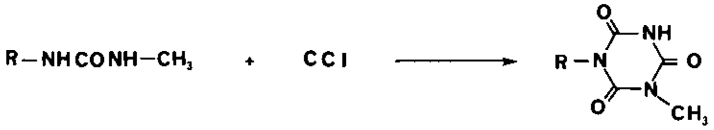
15

$$\underline{15} \quad + \quad C_6H_5CH{=}NNHC(:NH)SC_2H_5 \xrightarrow[105°C]{Toluene}$$



16

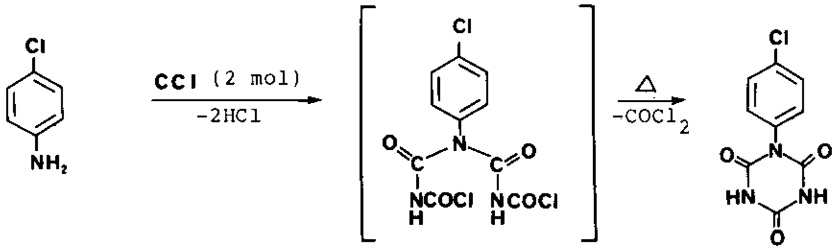
3.6 <u>1,3,5-Triazine-2,4,6(1H,3H,5H)-triones</u>: Treatment of substituted ureas with CCI in toluene afforded the 1,3,5-triazinetriones <u>17a</u> which exhibited a variety of biological properties, such as for the control of coccidiosis,[17] plant growth and herbicidal activity.[18]



R = aroxyaryl

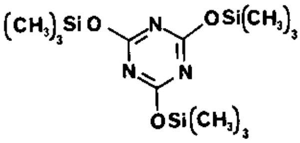
<u>17a</u>

Triazinetrione <u>17b</u> is also obtained by the reaction of 2 moles of CCI with primary aromatic amines.[2]



<u>17b</u>

3.7 <u>1,3,5-Triazine derivatives</u>: CCI has been found very much useful in the synthesis of 1,3,5-triazine derivatives e.g. <u>18</u>[19] and <u>19</u>.[20]



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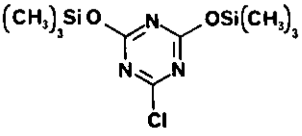
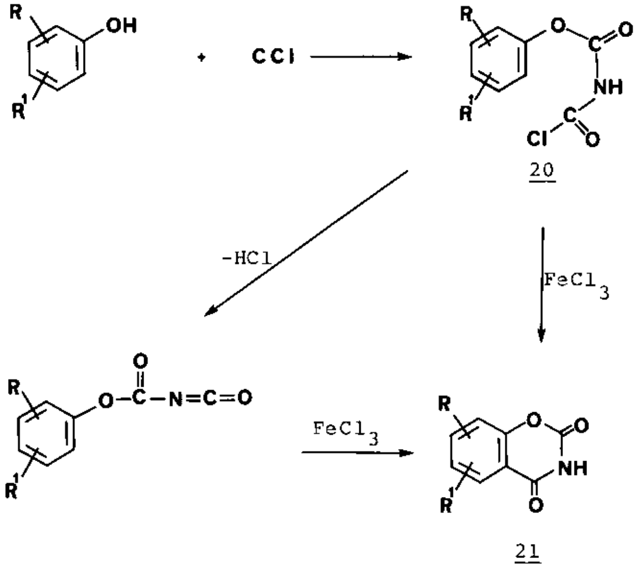


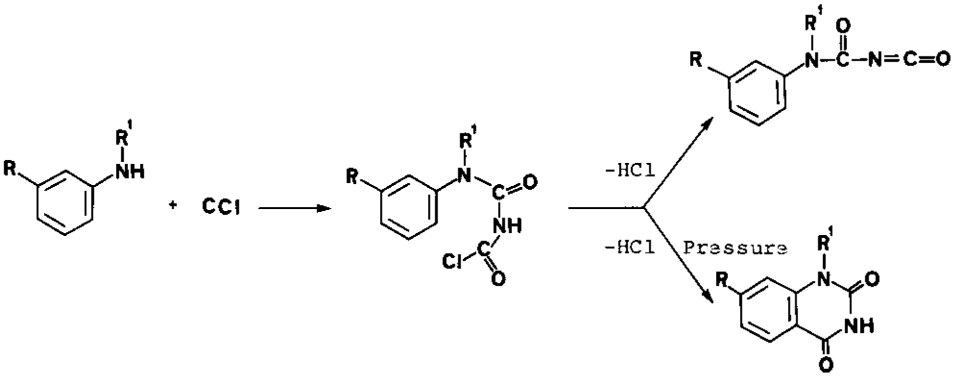
<u>19</u>

3.8 1,3-Benzoxazine-2,4-diones: CCI reacts with phenols to give stable adducts, namely phenyl ester chlorides of iminodicarboxylic acid 20. These intermediates, however, at higher temperatures in the presence of catalytic amounts of iron (III) chloride in an intramolecular Friedel-Crafts reaction yield benzoxazinediones 21.[21] The isocyanate obtained without $FeCl_3$ from 20, is thermally stable but is smoothly cyclized by iron (III) chloride.



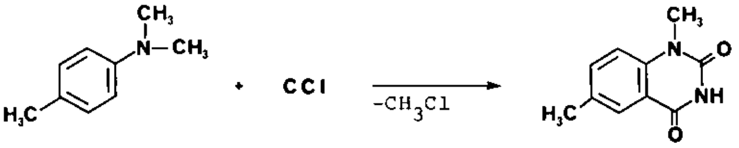
R = R^1 = H,Cl,alkyl

3.9 Quinazoline-2,4-diones: In a similar manner, N-substituted anilines react with CCI to give allophenoyl chlorides, which can be converted into either the carbamoyl isocyanates or the quinazolinediones 22 (under pressure) as desired.[21]

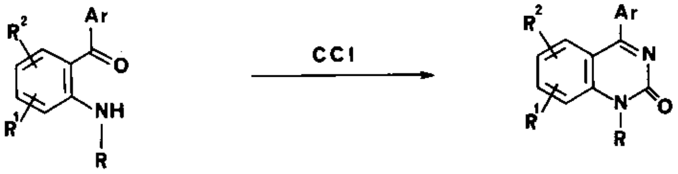


R = H,Cl; R^1 = alkyl,aryl

Interestingly, the same type of heterocycle is obtained from the reaction of CCI with *N*,*N*-4-trimethylaniline. In this case, methyl chloride is eliminated instead of hydrogen chloride in this tertiary amine which is somewhat analogous to von Braun degradation.[2]



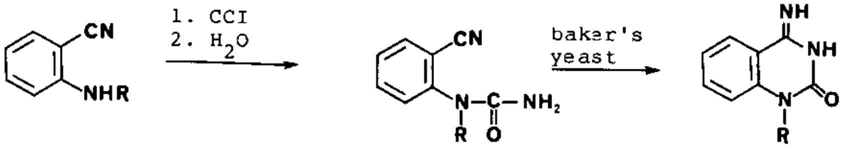
3.10 4-Aryl-2(1H)-quinazolinones: CCI is useful in the preparation of biologically important 4-aryl-2(1*H*)-quinazolinones 23[22] by its reaction with 2-aminobenzophenones.



23

R = H,alkyl; R^1 = R^2 = H,Cl,alkyl

3.11 4-Imino-2-quinazolinones: The reaction of CCI with 2-aminobenzonitriles affords ureas, which upon thermal cyclization[23] or by employing ultrasonically baker's yeast[24] yields the 3,4-dihydro-4-imino-2(1*H*)-quinazolinones 24.



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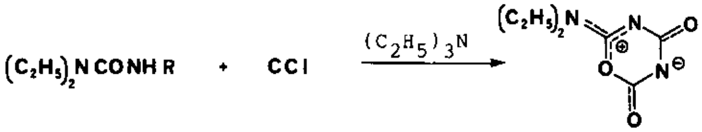
3.12 Mesoionic heterocycles:

3.12.1 Oxadiaziniumolates: Reactions of CCI with ureas containing a nitrogen-hydrogen bond give oxadiaziniumolates 25.[25]



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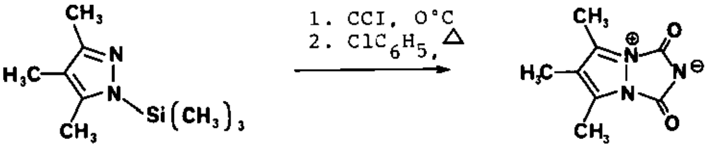
R = $i-C_3H_7$, $n-C_4H_9$

3.12.2 1,2,4-Triazolo[1,2-a]pyrazol-4-ium-3-olate: The reaction of CCI with an activated pyrazole gives an adduct which upon heating in chlorobenzene affords a new mesoionic 4nπ-heterocycle, namely 4,5,6-trimethyl-1-oxo-1H-1,2,4-triazolo-[1,2-a]pyrazol-4-ium-3-olate 26.[26]



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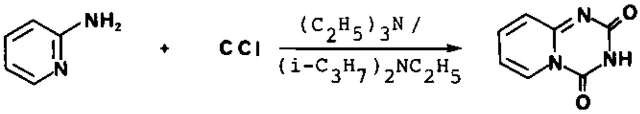
3.13 Fused heterocycles:

3.13.1 Ring-fused 1,3,5-triazine-2,4-diones: The addition of CCI to 2-aminopyridine followed by treatment with triethylamine/diisopropylethylamine leads to 2H-pyrido[1,2-a]-1,3,5-triazine-2,4(3H)-dione 27.[27]



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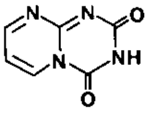
Similarly, other α-amino-N-heteroarenes on reaction with CCI yielded pyrimido-[1,2-*a*]-1,3,5-triazine-2,4-dione 28 and triazino[1,2-*a*]quinazoline-1,3-diones 29.



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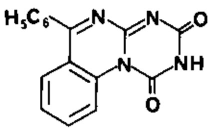

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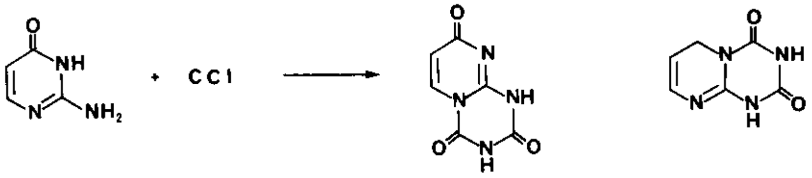
Whereas, reaction of CCI with isocytosine gives pyrimido[1,2-*a*][1,3,5]triazine derivative[28] which might be either of the two possible isomeric structures 30 and 31. The structure was found to be 30 and not 31 by derivatization, X-ray analysis and chemical evidences.



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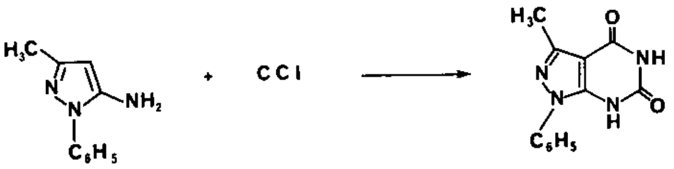
31

3.13.2 Pyrazolo[3,4-d]pyrimidines: Cyclocondensation of aminopyrazoles with CCI affords 1H-pyrazolo[3,4-*d*]pyrimidines 32.[29]



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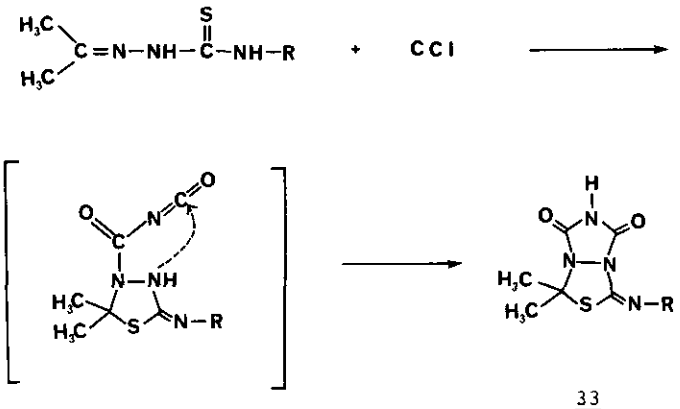
3.13.3 1,2,4-Triazolo[1,2-c][1,3,4]thiadiazole-5,7-diones: The reaction of *N*-substituted 2-isopropylidenehydrazinecarbothioamides with CCI at room temperature yields 1-(substituted imino)-3,3-dimethyl-1*H*,3*H*,5*H*-[1,2,4]triazolo[1,2-*c*]-[1,3,4]thiadiazole-5,7(6*H*)-diones 33.[30]

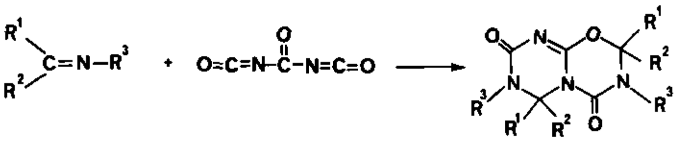


33

R = CH_3,C_6H_5,allyl

This reaction of thiosemicarbazone with CCI demonstrates the useful nature of this reagent for the synthesis of new type of heterocyclic compounds in one-pot.

3.13.4 Oxadiazinotriazinones: CCI is also useful in the preparation of another versatile reagent, carbonyl diisocyanate.[31] This reagent undergoes Diels-Alder type cycloadditions with many compounds containing multiple bonds affording fused heterocycles. Thus, reaction of azomethines with carbonyl diisocyanate gives 1,3,5-oxadiazino-1,3,5-triazinones 34.[32]



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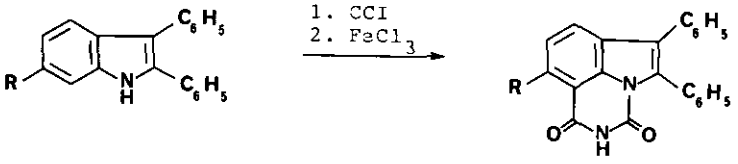
R^1 = H,CH_3; R^2 = CH_3,C_6H_5; R^3 = alkyl

3.13.5 Pyrrolo[3,2,1-ij]quinazoline-1,3-diones: Reaction of CCI with 2,3-diphenylindoles and followed by cyclization under Freidel-Crafts conditions with ferric chloride yields 1*H*-pyrrolo[3,2,1-*ij*]quinazoline-1,3(2*H*)-diones 35.[33]



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R' = CH_3,OCH_3

4. Conclusion:

It is seen from the foregoing applications of CCI that this reagent with its diverse chemistry is useful in the synthesis of a wide range of organic compounds particularly the heterocyclic compounds. However, it is hoped that the scope of this reagent will be further broadened in due course of time.

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