CHLOROSULFONYL ISOCYANATE: A NOVEL REAGENT FOR THE SYNTHESIS OF HETEROCYCLES

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Abstract - Chlorosulfonyl isocyanate, a novel reagent employed towards the synthesis of heterocycles and related compounds, finds extensive use. An effort has been made in this review to catalogue and update its applications for the synthesis of nitrogen, oxygen and sulphur containing ring systems.

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1. Introduction

Chlorosulfonyl isocyanate (CSI), the most reactive isocyanate discovered by Graf 30 years ago, finds
extensive use in the synthesis of various heterocyclic ring systems. Its chemistry and synthetic reactions
have been the subject of many reviews. In view of its versatile nature and high degree of reactivity
it was considered of interest to broaden the scope of its usefulness in the synthesis of heterocycles
and also to update its applications in this review.

Reactions of CSI cited in literature have been broadly classified based mainly on the site of initial
attack, i.e., type I generally involving the initial attack at the carbon of the isocyanate moiety, while
type II deals with cycloadditions (2+2) across the isocyanate C-N bond and whereas type III involves
nucleophilic additions at the sulfonyl group.

Though CSI has enabled numerous types of synthetic transformations which is evident from the rich
chemistry of this reagent covering the literature through 1968, its usefulness in the synthesis
of a variety of heterocyclic compounds and often novel systems is of immense importance. Thus, the present review describes the applications of CSI for simple, small heterocycles to large, fused and unusual heterocycles.

2. β-Lactams

2.1 2-Azetidinones: 2-Azetidinones 3 are produced by the (2+2) cycloaddition of chlorosulfonyl isocyanate to a variety of unsaturated linkages 3-7. Cycloaddition reactions of CSI with different types of olefins have been studied thoroughly 8-11. Although for the formation of β-lactam, a two-step mechanism, has been proposed, a concerted cycloaddition can also take place. There are citations 5,9 of evidence for both the mechanisms.

R
\[ R' \]
\[ C=O \]
\[ C=O \]
\[ \text{CSI} \]
\[ \text{HCl} \]

Examples illustrating the degree of usefulness of chlorosulfonyl isocyanate for the synthesis of a variety of 2-azetidinones 4-16 12-22 are as follows.

\text{SCHEME I}
SCHEME I (Contd.)

1. $\text{Ar} \quad \text{CSI/}^{30^\circ\text{C}} \quad \text{H}_2\text{O} \quad \text{Ar}$

2. $\text{CH}_3\text{CH} = \text{CH}_2 \quad \text{CSI/}^{60^\circ\text{C}} \quad \text{H}_2\text{O} \quad \text{CH}_3\text{NH}$

3. $\text{CH}_3 \quad \text{CH}_3 \quad \text{CSI/} \quad \text{Na}_2\text{SO}_3 \quad \text{CH}_3\text{NH}$

4. $\text{CH}_3 \quad \text{CH}_3 \quad \text{CSI/} \quad \text{Na}_2\text{SO}_3 \quad \text{CH}_3\text{NH}$

5. $\text{CSI/} \quad \text{H}_2\text{O} \quad \text{NH}$

6. $\text{H}_2\text{O} \quad \text{NH}$

7. $\text{H}_2\text{O} \quad \text{NH}$

8. $\text{H}_2\text{O} \quad \text{NH}$

9. $\text{H}_2\text{O} \quad \text{NH}$

10. $\text{H}_2\text{O} - \text{Na}_2\text{SO}_3 \quad \text{NH}$
SCHEME I (Contd.)

[Chemical structures and reactions depicted with arrows indicating reagents and conditions.]

- CSI/H₂O
- CSI/-60°C, NaOH
- CSI/-60°C, H₂O
- CSI, Na₂SO₃
- CSI/-78°C, Na₂SO₃
- CSI, NaHCO₃

Chemical structures and corresponding numbers indicated.
Reaction of CSI with conjugated or non-conjugated dienes also leads to N-chlorosulfonyl-\(\beta\)-lactams which on hydrolysis give 2-azetidinones\textsuperscript{10,23}.

\[
\text{CSI / -10° C} \xrightarrow{\text{PhSH / Py / H}_2\text{O}} \text{17}
\]

\[
\text{CSI} \xrightarrow{\text{H}_2\text{O}} \text{18}
\]

2.2 4-Acloyxy-2-azetidinones: The reaction of CSI with heterosubstituted olefins such as vinyl acetates leads to 4-acloyxy-2-azetidinones\textsuperscript{24} upon hydrolysis.

\[
\text{CSI} \xrightarrow{\text{H}_2\text{O}} \text{19}
\]

\(R^1 = \text{H}, \text{CH}_3; \quad R^2 = \text{CH}_3, \text{Ar}\)

The 2-azetidinones obtained by the reaction of CSI with a variety of olefins like vinyl esters present ideal building blocks for the total synthesis of penicillin, cephalosporin and oxacephem class of antibiotics\textsuperscript{25-30}. The general reaction scheme II is given below where the cyclization of the 2-azetidinones usually involves a Wittig-type of reaction via the intermediate 20.

\[
\text{R} \xrightarrow{\text{CS}_{2}} \text{R'} \xrightarrow{\text{OH}} \text{20}
\]

\[
\text{X} = \text{CH}_2, \text{S}, \text{O}
\]

\text{SCHEME II}
3. Oxetes
The reaction of CSI with acetylenes such as 1-diethylamino-1-propyne at low temperatures leads to oxete-type system $^{22}$.

\[
\text{H}_3\text{CC}≡\text{CN(C}_2\text{H}_3)_2 + \text{CSI} \rightarrow \begin{array}{c}
\text{H}_3\text{C} \quad \text{N(C}_2\text{H}_3)_2 \\
\text{ClO}_2\text{SN} \\
22
\end{array}
\]

4. Diazetidinone-imine
Reaction of CSI with dicyclohexylcarbodiimide gives diazetidinone-imine $^{23}$. In this reaction the mode of addition plays an important role, i.e., only the addition of CSI to dicyclohexylcarbodiimide will lead to diazetidinone.

\[
\text{H}_{11}\text{C}_6\text{N}≡\text{C}≡\text{NC}_6\text{H}_{11} + \text{CSI} \rightarrow \begin{array}{c}
\text{H}_{11}\text{C}_6\text{N} \quad \text{NC}_6\text{H}_{11} \\
\text{O} \\
23
\end{array}
\]

5. Lactone
The reaction of CSI with diphenylmethylene-cyclopropane afforded ring-opened iminolactone $^{25}$. The proposed mechanism involves the initial formation of $\beta$-lactam, which could then open to dipolar intermediate $^{25}$, followed by ring opening of the cyclopropylcarbinyl cation and closure through oxygen.
6. Oxazolones

The facile reaction of CSI with the hydroxy group of 2-hydroxy ketones leads to O-carbamoyl ketones 26. These carbamates on heating to 175-250°C undergo ring closure which results in the formation of oxazolones 27.

\[
\begin{align*}
\text{R} \quad \text{CSI} \quad \text{H}_2\text{O} \\
\text{R}^1 \quad \text{R}^2 \\
\text{O} \quad \text{O} \\
\text{R}^1 \quad \text{R}^2 \\
\text{N} \\
\text{O} \\
\text{N} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} = \text{t-Bu} , \text{Ar} : \text{R}^1 = \text{R}^2 = \text{CH}_3 , \text{Ar}
\end{align*}
\]

7. 3-Oxo-2-isothiazolidine-1,1-dioxides

CSI reacts with olefins under free radical conditions to yield 2-chloroalkanesulfonyl isocyanates. Interestingly, an excess of olefin changes the course of reaction and 3-oxo-2-(2-chloroalkyl)-isothiazolidine-1,1-dioxides 28 are obtained in good yields.

\[
\text{CH}_2 = \text{CH}_2 \cdot \text{CSI} \quad \xrightarrow{\text{Radical initiator}} \quad \text{CH}_2-\text{CH}_2\text{Cl}
\]

8. 5-Oxo-Δ²-triazoline

Reaction of CSI with diazoacetic esters leads to an ester of 1-chlorosulfonyl-5-oxo-Δ²-triazoline-4-carboxylic acid 29.

\[
\begin{align*}
\text{ROOC-CH-\text{N}}\equiv\text{N} \quad \xrightarrow{\text{CSI}} \quad \text{ROOCHC-\text{N}}\equiv\text{N- SO}_2\text{Cl}
\end{align*}
\]
9. 2,3-Dihydro-3,4-oxadiazoles

The reaction of CSI with 1,3-diaryltrilimine gives exclusively 2-chlorosulfonylimino-3,5-diphenyl-2,3-dihydro-1,3,4-oxadiazole via addition of the 1,3-dipole nitrilimine to the C=O function of CSI.

\[
\begin{align*}
\text{Cl} & \quad \text{Ar} - \text{C} = \text{N} - \text{NH} - \text{Ar} \\
\text{Et}_2\text{N} & \quad \rightarrow \\
\text{Ar} & \quad \text{C} = \text{N} - \text{N} - \text{Ar} \\
\text{Ar} & \quad \text{N} - \text{NH} - \text{Ar} \\
\text{CSI} & \quad \rightarrow \\
\text{Ar} & \quad \text{C} = \text{N} - \text{N} - \text{Ar} \\
\end{align*}
\]

10. Benzimidazole-2-one

Reaction of CSI with 2-nitroaniline followed by hydrolysis leads to a urea derivative which on reductive cyclization yields benzimidazol-2-one.

\[
\begin{align*}
\text{NHCONH}_2 & \quad \rightarrow \\
\text{H}_2\text{O} & \quad \rightarrow \\
\text{NH} & \quad \text{CONH} \\
\end{align*}
\]

11. Benzoisothiazole-1,1-dioxide

CSI reacts with non-enolizable ketones such as benzophenone to give a cyclized product, i.e., benzoisothiazole-1,1-dioxide via a N-chlorosulfonylazomethine intermediate.

\[
\begin{align*}
\text{Ar} & \quad \text{C} = \text{N} - \text{SO}_2\text{Cl} \\
\text{CSI} & \quad \rightarrow \\
\text{Ar} & \quad \text{C} = \text{N} - \text{SO}_2\text{Cl} \\
\end{align*}
\]
12. Tetrazolones
Reaction of CSI with alkylazides at ambient temperature gives alkylchlorosulfonyl tetrazolones which on hydrolysis afford stable alkyltetrazolones $33^{39}$.

$$ R - N_3 \xrightarrow{\text{CSI, H}_2\text{O}} R - \text{NCSO}_2\text{H} $$

$R = \text{n-Bu, C}_6\text{H}_{11}$

13. 2-Pyridone
Addition of CSI with dimethylphenylethylynamine has been reported to yield 2-pyridone $34^{40}$.

$$ \text{C}_6\text{H}_5\text{C}≡\text{CN(CH}_3)_2 \xrightarrow{\text{CSI}} \text{C}_6\text{H}_5\text{C}_6\text{H}_5\text{N}-(\text{CH}_3)_2 $$

14. 1,4-Cyclo-adducts
Though CSI reacts with conjugated 1,3-dienes to form N-chlorosulfonyl-β-lactams, these can be thermally rearranged to form 1,4-cyclo-adducts $35^{41}$.

$$ \text{CH}_3\text{CH}_3 \xrightarrow{\text{CSI}} \text{NCSO}_2\text{Cl} \xrightarrow{\text{H}_2\text{O}} $
The reaction of CSI with cyclohexa-1,3-diene yields N-chlorosulfonyl-β-lactam which opens to a dipolar intermediate and provides access to 1,4-addition products, 36 and 37.

15. 1,3-Oxazin-2-ones
CSI reacts with α,β-unsaturated ketones to yield 3,4-dihydro-1,3-oxazin-2-ones. Hydrolysis produces the unsubstituted compounds 38.

16. 1,3-Oxazine-2,4-diones
Reaction of CSI with enolizable ketones by an electrophilic attack on the 2-methylene carbon atom provides unstable N-chlorosulfonyl-β-ketocarboxamides. These, on reaction with excess of CSI followed by hydrolysis, yield 3,4-dihydro-2H-1,3-oxazine-2,4-diones 39. Further, 1,3-oxazine-2,4-diones can be easily converted to 5,6-disubstituted uracils 40.

\[ R^1 = R^2 = R^3 = \text{H, Alkyl, Ar} \]
17. Uracils

Recently it has been reported that the reaction of CSI with various 2-dialkylaminostyrenes gives 6-substituted dihydrouracils \(^{41,46}\), i.e., by involving two equivalents of CSI.

The formation of uracils has been explained on the basis of a distinct 1,4-dipolar intermediate with opposing charges being stabilized by the dialkylamino group at the positive end of the sulfonyl chloride and by the carbonyl moiety at the negative end.
18. 2(1H)-Quinazolinones

The reaction of CSI with 2-aminoacetophenones/benzophenones leads to 2(1H)-quinazolinones in good yields. This is a convenient alternate route of synthesis for 2(1H)-quinazolinones.

\[
\begin{align*}
&\begin{array}{c}
\text{CSI} \\
\end{array} \\
&\begin{array}{c}
\text{H}_2\text{O} \\
\end{array} \\
&\begin{array}{c}
\text{R} = \text{Me}, \text{Ar} ; \text{R}' = \text{Me}, \text{Ar}
\end{array}
\end{align*}
\]

CSI reacts with methyl anthranilates to give urethanes upon hydrolysis which are cyclized in presence of a base to afford 2,4-quinazolinediones.

\[
\begin{align*}
&\begin{array}{c}
\text{CSI} \\
\end{array} \\
&\begin{array}{c}
\text{H}_2\text{O} \\
\end{array} \\
&\begin{array}{c}
\text{base} \\
\end{array} \\
&\begin{array}{c}
\text{R} = \text{H}, \text{CH}_3
\end{array}
\end{align*}
\]

19. 1,3-Benzoxazin-2-ones

Reaction of CSI with 2-hydroxybenzaldehydes and 2-hydroxyacetophenones gives 1,3-benzoxazin-2-ones whereas CSI reacts with 2-hydroxybenzophenones to yield O-carbamoyl compounds, and these are also cyclized in presence of a base to.

\[
\begin{align*}
&\begin{array}{c}
\text{CSI} \\
\end{array} \\
&\begin{array}{c}
\text{H}_2\text{O} \\
\end{array} \\
&\begin{array}{c}
\text{R} = \text{H}, \text{CH}_3
\end{array}
\end{align*}
\]
Reaction of CSI with 2-hydroxybenzoates gives O-carbamoyloxybenzoates \(45^{50}\) which are cyclized in presence of a base to 1,3-benzoxazine-2,4-diones \(46^{48}\).

\[
\begin{array}{c}
\text{R} = \text{CH}_3, \text{C}_6\text{H}_5
\end{array}
\]

In a recent report CSI has been further employed for the synthesis of 1,3-benzoxazine-2,4-diones by another route \(51\). Salicylic acid chloride is reacted with CSI, cyclized by the addition of base and hydrolyzed to afford 1,3-benzoxazine-2,4-dione as shown below.

20. \textbf{1,3,5-Triazine-diones}

The reaction of CSI (2 moles) with compounds having carbon-nitrogen double bonds give triazine-dione systems. Thus, CSI reacts with azomethines to produce 1,3,5-triazine-diones \(47^{39}\) in the following way.

CSI also reacts with amidines to give amino-substituted triazine-diones \(48^{52}\).
While addition of dialkylcarbodiimide to two moles of CSI affords triazinedioneimine $^{49}$, in this case the mode of addition, i.e., the addition of carbodiimide to two moles of CSI, only leads to the formation of triazinedione system.

It is evident from the above reactions that CSI provides a convenient route to hexahydrotriazine-2,4-diones.

21. 1,2,4-Benzothiadiazinones

The reaction of CSI with aniline derivatives under Friedel-Crafts conditions leads to 2H-1,2,4-benzothiadiazin-3-one-1,1-dioxides $^{50}$.

Antihypertensive drug, diazoxide $^{51}$, can be prepared starting from 4-chloroaniline employing CSI under the Friedel-Crafts conditions as illustrated above and later heating with acetic acid. Thus CSI offers an alternative method of synthesis for this pharmaceutically important heterocyclic compound.
22. 1,2,3-Oxathiazine-2,2-dioxides

The reaction of CSI with many acetylenic compounds gives 1,2,3-oxathiazine-2,2-dioxides. The ratio between the two isomers 52 and 53 depends on the nature of R¹ and R² substituents.

\[
R^1-C≡C-R^2 + CSI \rightarrow \begin{array}{c}
\text{52} \\
\text{53}
\end{array}
\]

CSI reacts with enolizable ketones via α-methylene carbon atom to produce N-chlorosulfonyl-β-ketocarboxamides. Excess of CSI in ether solvent acts as a Lewis acid in promoting the cyclization of 54 to 1,2,3-oxathiazin-4(3H)-one-2,2-dioxide compounds 56, probably through an N-sulfonylamine intermediate 55.

Ar-C-CH₂-R + CSI \rightarrow \begin{array}{c}
\text{54} \\
\text{55}
\end{array}

CSI also adds to the methylene group of t-butyl acetoacetate to give N-chlorosulfonyl adduct which upon thermolysis yields N-chlorosulfonylacetoacetamide 57 along with carbon dioxide and isobutylene. Then successive cyclodehalogenation gives an access to oxathiazinonedioxide 58.
Though CSI at room temperature reacts with phenolic compounds at carbon atom of its isocyanate function, at elevated temperature CSI reacts at the sulfur atom of the chlorosulfonyl group. Thus, the reactions of CSI with 2-hydroxybenzaldehyde, 2-hydroxyacetophenones or 2-hydroxybenzophenones at higher temperatures (100-105°C) undergo cycloaddition to yield 1,2,3-benzoxathiazine-2,2-dioxides 58, 59, 60.

Similarly, reaction of CSI with 2-hydroxybenzoates at higher temperatures (100-108°C) gives 2-sulfamoyloxybenzoates 60 which are cyclized in presence of a base to 1,2,3-benzoxathiazine-2,2-dioxideones 61, 62.
24. 1,2,4,6-Thia triazine-1,1-dioxide-3-ones

Isothioureas react with CSI to afford substituted 1,2,4,6-thiatriazine-1,1-dioxide-3-ones.\(^5^7\)

\[
\begin{align*}
\text{SCH}_3 & \quad \text{1. CSI} \\
\text{H}_3\text{C}_6 - \text{N} = \text{NH}_2 & \quad \text{2. (i-C}_6\text{H}_4)_2\text{C}_2\text{H}_4\text{N} \\
\text{NC} & \quad \text{62}
\end{align*}
\]

The reaction of CSI with 5-aminotetrazole and subsequent treatment with ethylisopropylamine gives the thia triazine azide.\(^5^8\) Treatment of this with water converted it to the urea derivative in which the tetrazole system was reconstituted. Thus, CSI provides an alternative synthesis for 5-tetrazoly lureas too.

\[
\begin{align*}
\text{N-H} & \quad \text{1. CSI} \\
\text{N-N} & \quad \text{2. (i-C}_6\text{H}_4)_2\text{C}_2\text{H}_4\text{N} \\
\text{N-H} & \quad \text{62}
\end{align*}
\]

25. 2-Azepinone

Addition of CSI to trans-2-phenylisopropenylcyclopropane yields N-chlorosulfonyl-2-azepinone.\(^6^3\)\(^5^9\), the formation of which has been rationalized on the basis of the different stabilizations available to the dipolar intermediates.

\[
\begin{align*}
\text{C}_6\text{H}_5 & \quad \text{CSI} \\
\text{C}_6\text{H}_5 & \quad \text{63}
\end{align*}
\]
26. **1,2,4,7-Thiaatriazepin-3(2H)-one-1,1-dioxides and 2,1,3,5-benzothiaatriazepin-4(5H)-one-2,2-dioxides**

The reaction of 1,2-diamine with CSI gives 4,5,6,7-tetrahydro-1,2,4,7-thiaatriazepin-3(2H)-one-1,1-dioxide \[64\] while CSI reacts with o-phenylenediamine to afford 1,3-dihydro-2,1,3,5-benzothiaatriazepin-4(5H)-one-2,2-dioxide \[65\].

\[
\begin{align*}
\text{NH} & \quad \text{R} \\
\text{NH} & \quad \text{R} \\
& \quad 1. \text{CSI} \\
\text{R} & \quad \text{C}_2\text{H}_5_3\text{N} \\
\text{NH} & \quad \text{R} \\
\text{NH} & \quad \text{R} \\
& \quad 1. \text{CSI} \\
\text{R} & \quad \text{C}_2\text{H}_5_3\text{N} \\
\end{align*}
\]

\[ R = \text{Alkyl, Ar} \]

27. **1,2,3,5(3H)-Benzoxathiadiazepine-2,2-dioxide-4(5H)-ones**

Addition of CSI to 2-aminophenols at higher temperature affords (3H)-1,2,3,5-benzoxathiadiazepine-2,2-dioxide-4(5H)-ones \[66\], a new class of seven-membered heterocycles.

\[
\begin{align*}
\text{R} & \quad \text{NH}_2 \\
\text{OH} & \quad \text{CSI} \\
\text{R} & \quad >100^\circ\text{C} \\
\text{H} & \quad \text{Cl} \\
\end{align*}
\]

28. **1,3,2,3(3H)-Benzodioxathiazepine-2,2-dioxide-4-ones**

The reactions of CSI with catechols produce a novel family of seven-membered heterocycles 1,3,2,3(3H)-benzodioxathiazepine-2,2-dioxide-4-ones \[67\].

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{CSI} & \quad 0^\circ\text{C} \\
\text{OH} & \quad \text{SO}_2\text{Cl} \\
\text{OCONH} & \quad 100^\circ\text{C} \\
\text{OH} & \quad \text{SO}_2\text{Cl} \\
\end{align*}
\]
29. **Azocene**

Treatment of 1,4-cyclohexadiene with CSI results in the formation of \( \beta \)-lactam which on O-methylation followed by monobromination and finally dehydrohalogenation yields 2-methoxy-1-azocine \(^{62}\). Thus this route employing CSI offers a direct and novel synthesis of azocene system.

![Chemical diagram]

30. **Miscellaneous fused heterocycles**

30.1 **Triazolotriazolone**: Azines may be considered as bis-anils which are versatile partners in cycloaddition reactions. The two azomethine groups may react with dipolarophiles in 'criss-cross' additions. At ambient temperature with CSI 'criss-cross' adducts are obtained in high yields. The reaction of CSI, for instance, with benzaldehyde azine gives diphenyltriazolotriazolone \(^{62}\).

![Chemical diagram]
30.2 **Thiazolopyrimidines**: CSI reacts with penams such as methyl 6-β-phthalimido penicillinate to give a thiazolo[3,2-c]pyrimidine derivative by ring expansion.

![Chemical structure](image1)

30.3 **Fused 1,2,4,6-Thiatriazine-1,1-dioxides**: Reaction of 2-aminopyridine with CSI produces the N-chlorosulfonyl intermediate which cyclizes on the addition of a base to afford a fused 1,2,4,6-thiatriazine-1,1-dioxide system. Such systems have also been obtained by the reaction of CSI with 2-aminopyrazine and 2-aminothiazoline.

![Chemical structure](image2)

In case of 2-aminothiazoline it has been established that CSI attacked the ring nitrogen preferentially to give product.
30.4 **Thiatriazinobenzimidazole**: Addition of CSI to 2-aminobenzimidazole leads to 2H[1,2,4,6]-thiatriazino[2,3-a]benzimidazol-3(4H)-one-1,1-dioxide \(^{73}\). 

![Thiatriazinobenzimidazole](image)

30.5 **Thiatriazoquinazoline**: Reaction of CSI with 2-amino-4-arylquinazoline yields 6-aryl[1,2,4,6]-thiatriazino[2,3-a]quinazoline-3(2H)-one-1,1-dioxide \(^{74}\). 

![Thiatriazoquinazoline](image)

30.6 **Azabullvalene**: It has been demonstrated by Paquette that the reaction of CSI with bullvalene emerges as a practical route of synthesis for methoxyazabullvalene \(^{75}\). 

![Azabullvalene](image)
31. Novel (unusual) heterocycles

Some bicyclic hydrocarbons undergo formal cycloaddition reactions with CSI at the strained, carbon-carbon single bonds on account of their high degree of $\pi$ character. The products formed are often novel heterocycles and may be difficult to prepare by any other method. Some examples are illustrated below.

![Chemical Structures]

76

77

78

32. Conclusion

It is seen from the foregoing pages that CSI has truly been a reactive, broad based reagent for the synthesis of a variety of novel heterocycles. In addition, it affords an alternate and convenient method of synthesis for a number of known heterocyclic systems. It is hoped that CSI will further open up new vistas in heterocyclic synthesis.
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