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Mini-Review

Reaction pathways for [2+2] cycloadditions of chlorosulfonyl isocyanate with alkenes

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ABSTRACT

The reaction mechanism for [2+2] cycloaddition of chlorosulfonyl isocyanate (CSI) with alkenes is presented. Electron-deficient alkenes react by a concerted pathway while most alkenes, and especially electron-rich alkenes, react by a single electron transfer (SET) pathway to give a 1,4-diradical intermediate. NMR line-broadening studies show that the triplet 1,4-diradical intermediate can be converted to the singlet form at lower temperatures. UV data give evidence for a pre-equilibrium charge transfer complex that is confirmed by kinetic studies. That is, the reaction is more efficient at a lower temperature where the pre-equilibrium favors the charge transfer complex compared to a slightly higher temperature where the pre-equilibrium favors the dissociated reagents. These mechanistic findings were incorporated to enhance the synthetic usefulness of CSI [2+2] cycloaddition reactions.

KEYWORDS: [2+2] cycloaddition, 1,4-diradical, single electron transfer, NMR line-broadening.

INTRODUCTION

Clauss reported in 1969, from kinetic measurements, that chlorosulfonyl isocyanate (CSI) is the most reactive isocyanate [1]. CSI is also the most versatile isocyanate and its latest review was in 2005 [2]. Versatility of this [2+2] cycloaddition reaction is from easy reduction of the N-chlorosulfonyl-β-lactam to the β-lactam (2-azetidinone) product (Scheme 1) [3, 4]. Reduction of the N-chlorosulfonyl-β-lactams to β-lactams is with aqueous sodium sulfite [3], sodium hydrogen sulfite [4] or other less versatile methods listed in reference [3]. Reduced β-lactams are important in medicinal chemistry [5, 6]. The reaction sequence in Schemes 1, 2 and 3 provide β-lactams that can give products through ring-opening of N-chlorosulfonyl-β-lactams [7-13], and other products from N-alkylation [14] and O-alkylation [8, 15] of the reduced β-lactams. In this review two reaction pathways for the [2+2] cycloaddition of CSI with alkenes are reported. The mechanistic pathways described in Schemes 2 and 3 gave inspiration to suggest methods that improved product yields and reduced reaction times.

In 1963 Graf proposed a 1,4-dipolar intermediate (Scheme 1) for the cycloaddition reaction of CSI with alkenes that helped describe the electrophilic behavior of this reagent [16]. Subsequent authors presented evidence for a concerted pathway for this reaction [8]. In this review we describe our research that supports a concerted path for CSI reaction with electron-deficient alkenes (Scheme 2); and discovery of the single electron transfer (SET) process leading to 1,4-diradical intermediates during CSI reactions with electron-rich alkenes as described in Scheme 3.

DISCUSSION

Evidence of two separate pathways for reaction of CSI with alkenes came from a kinetic study where

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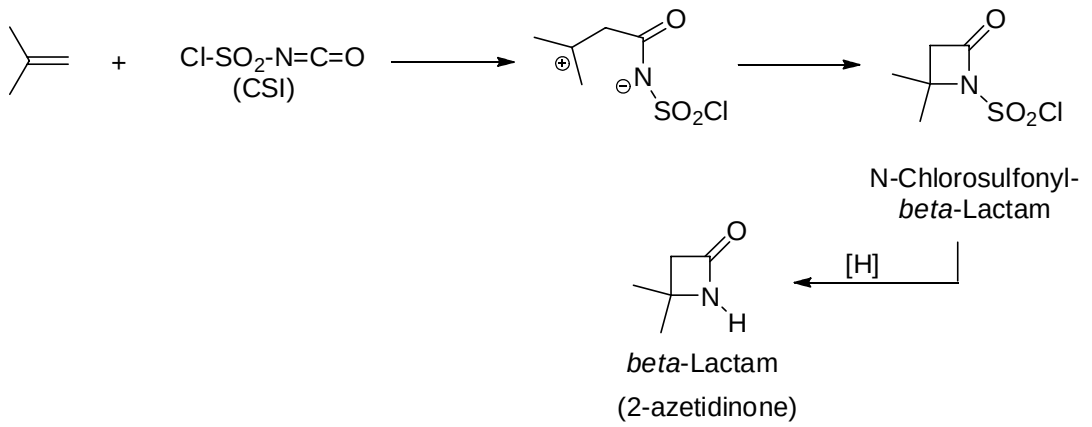
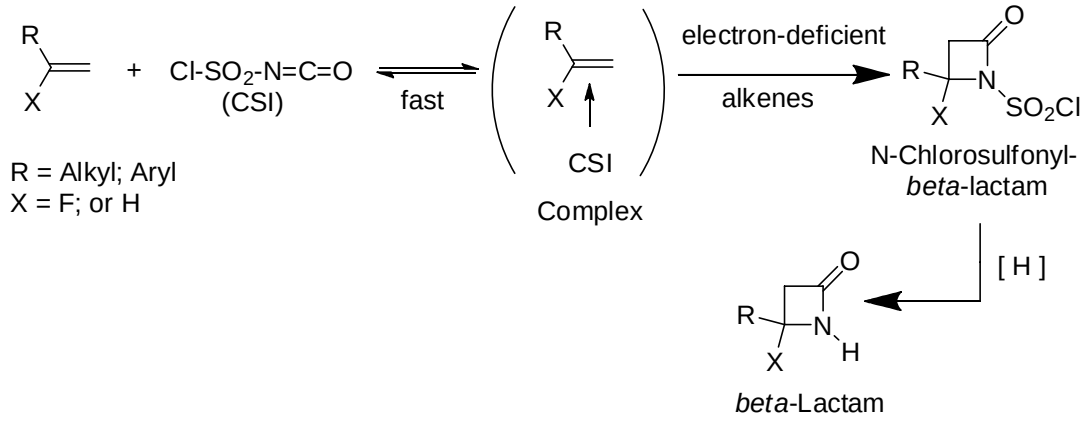
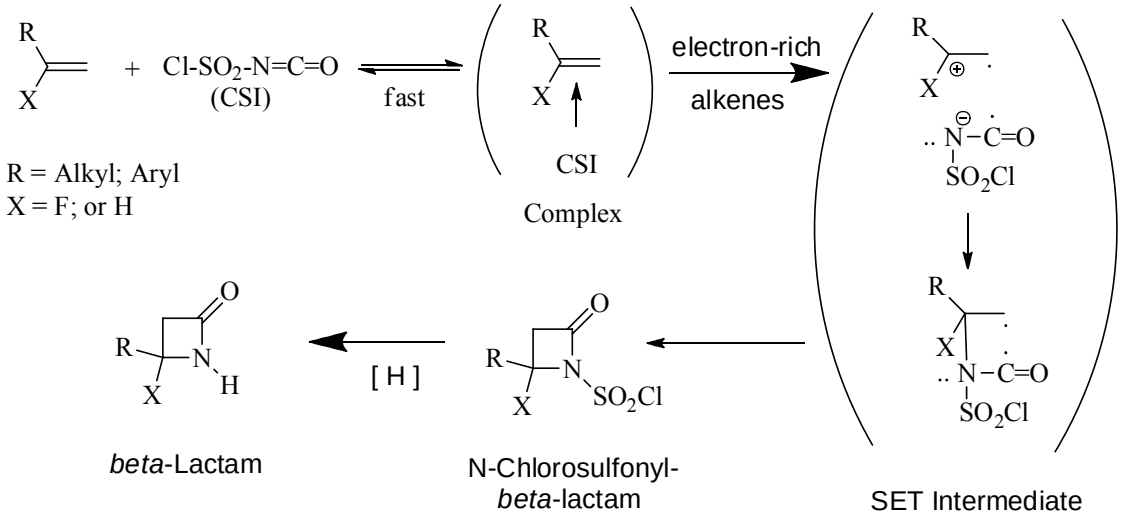


Scheme 1. Early dipolar pathway and reduction of the N-Chlorosulfonyl-β-lactams.



Scheme 2. Concerted pathway.



Scheme 3. Stepwise pathway: single electron transfer (SET).

a graph of ln k *vs*. calculated alkene vertical ionization potentials displayed a break in the line suggesting a change in mechanism [17]. Quantum chemical calculations at the MP2/6-311 G(dp) level of theory with CSI and vinyl fluoride show the stepwise transition state to be 26.6 kcal/mole higher than the concerted transition state for this electron-deficient alkene [18]. The concerted transition state has both reagents in almost the same plane which does not support the expected orthogonal $\pi^2(s) + \pi^2(a)$ geometry for [2+2] cycloadditions. A six electron process involving the lone pair electrons on nitrogen allows for an almost parallel transition state *via* a $\pi^2(s) + \pi^2(s) + n^2(s)$ orbital mix [18]. Lemal [19] and others [20] propose an orthogonal pseudopericyclic six electron transition state where π-electrons from the carbonyl of CSI contribute to the process. Our calculations on this very unreactive vinyl fluoride indicated that the carbonyl π-electrons were not perturbed as expected for the pseudopericyclic process; but significant mixing between the π-bond C=N electrons and the nitrogen lone pair electrons was observed by our calculations [18].

Support for the di-radical intermediates in Scheme 3 come from trapping experiments with TEMPO. TEMPO inhibits the reaction of CSI with electron-rich alkenes like α-fluoro-*p*-methylstyrene, but not with less electron-rich substrates like α-fluorostyrene [17]. A more elegant and accurate method to detect radicals is with NMR from line-broadening [21]. The line-width at half-height was measured on an internal standard (TMS for ^1H, and $CFCl_3$ for ^{19}F) before addition of CSI; then again after addition of CSI to start the reaction. Line-broadening was found for reaction of CSI with most alkenes, but not with electron-deficient alkenes like (E)-3-fluoro-3-hexene or 1-decene [21]. Line-broadening is a more sensitive probe to detect radicals than TEMPO. For example, the di-radical intermediates from alkenes like α-fluorostyrene that were not trapped by TEMPO showed line-broadening when investigated by NMR [21].

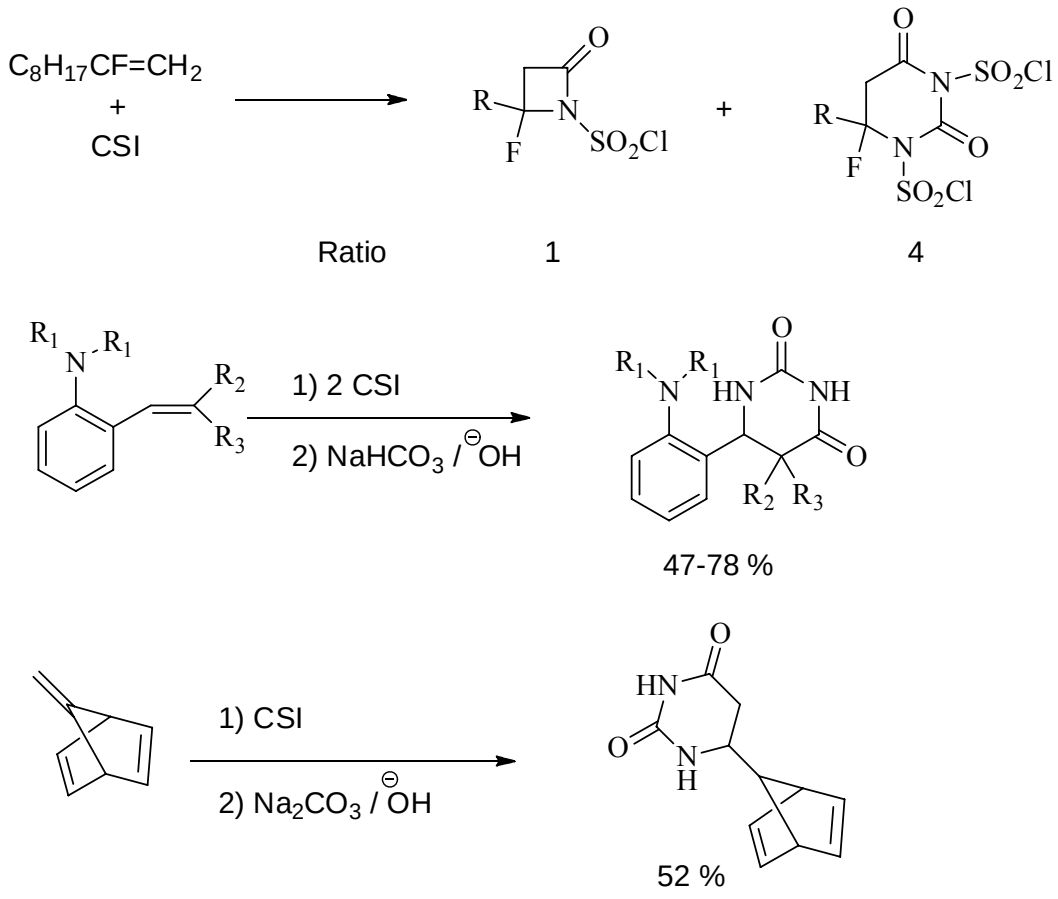
Di-radicals can be in the singlet state when the orbital overlap between the radicals is small due to distance or geometry [22]. Evidence for conversion of the triplet 1,4-diradicals to the 1,4-singlet specie during CSI reactions with electron-rich alkenes are also from line-broadening [21]. Reaction of CSI with methylenecyclohexane shows line-broadening at or above + 15 ^oC, but not at 0 ^oC. At 0 ^oC methylenecyclohexane reacts smoothly with CSI and the reaction is complete in less than three hours [21, 23]. Furthermore, when the reaction is warmed back to + 15 ^oC line-broadening is again apparent [21].

Data to support a pre-equilibrium complex for both the concerted (Scheme 2) and the stepwise SET paths (Scheme 3) are from UV and kinetic studies [17]. For example, addition of CSI to α-fluoro-*p*-methylstyrene in methylene chloride at room temperature gives an intense blue color with a λ_{max} at 642 nm. Dilution at room temperature to an absorbance of 1.0, and then cooling the cuvette to 0 ^oC raises the absorbance to ~2.0. The absorbance goes back to ~1 when warmed to room temperature, and then again to 2 when returned to 0 ^oC. The colored complex is in equilibrium with the two colorless dissociated reagents. Kinetic studies provide additional support for the complex. An Arrhenius plot for reaction of CSI with styrene displays normal behavior between 25.0 to 37.0 ^oC in that the rate increases with increasing temperature [17]. Below 25.0 ^oC the rate increases from 25 ^oC down to 0 ^oC. Below 0 ^oC the rate again decreases with decreasing temperature as expected. Similar behavior was found for CSI reaction with α-fluorostyrene by recording the reaction times between 0 to -20 ^oC [17]. These data show that reactions of CSI with alkenes are more efficient at the temperature where the equilibrium is completely shifted to the complex (Schemes 2 and 3) [17]. Apparently the second order unimolecular reaction from the complex is more efficient than the bimolecular reaction of the dissociated reagents. This improved efficiency was demonstrated by investigating CSI reactions of electron-rich alkenes over temperatures that include the temperature where the pre-equilibrium favors the complex [23]. For example, CSI reacts with styrene at 25 ^oC in methylene chloride in 25 minutes, but at 10-15 ^oC the reaction is complete in 10 minutes with a higher product yield (See Supporting Information [23] for other examples). Less electron-rich alkenes that do not react or react too slowly at their pre-equilibrium complex temperatures do not benefit from this feature [23].

The synthetic utility of these CSI reactions can also be improved by not using solvents [24]. For example, the best product yield for reaction of CSI with *trans*-3-hexene in solvent is with nitromethane at 50 °C for two days to give a 50% product yield. The neat reaction only requires 25 hours at room temperature and gives a 94% yield of the chlorosulfonyl-β-lactam product [24].

Inverse addition, that is adding the neat alkene to neat excess CSI, is an efficient method to trap the 1,4-diradical intermediate and isolate 2:1 uracil products. Even in nitromethane as solvent inverse addition with 2-fluorodec-1-ene gives mainly 2:1 uracil product (Scheme 4) [25]. In solution, very electron-rich alkenes like *o*-Dialkylaminostyrenes [4] and 7-methylenenorbornadiene [26] (Scheme 4) also gave 2:1 uracil adducts reportedly from very stable intermediates that we now recognize as 1,4-diradicals. A 2:1 chlorosulfonyl uracil intermediate was proposed to explain subsequent ring-opened acyclic products for reaction of CSI with alkenes [27].

Neat reaction of the less reactive *p*-toluenesulfonyl isocyanate with alkenes and monofluoro alkenes also gives tosyl-β-lactam products [28]. In solution *p*-toluenesulfonyl isocyanate reacts with very reactive alkenes like the vinyl ether 3,4-dihydro-2H-pyran. In solution, line-broadening was observed for reaction of *p*-toluenesulfonyl isocyanate with 3,4-dihydro-2H-pyran indicating the presence of a 1,4-diradical intermediate during that reaction [28]. This finding suggests that other [2+2] cycloaddition reactions of isocyanates may also proceed *via* the stepwise process if the isocyanate and alkene are sufficiently reactive to participate in the SET pathway.



Scheme 4. Trapping the intermediate.

CONCLUSION

This mini review summarizes previous papers describing two mechanisms for reaction of CSI with alkenes, the concerted and stepwise SET pathway. We have shown that 1,4-diradicals can equilibrate between the singlet and triplet states. Trapping the 1,4-diradical intermediate with a second CSI provides a convenient method to make uracil and fluorouracil products. Understanding the reaction mechanism also led to using the complex in the pre-equilibrium to improve the synthetic utility of some CSI reactions; that is if the alkene is reactive enough to give products at the temperature where the complex predominates. Neat reactions of alkene and CSI generally give improved results eliminating the need for solvent recovery and disposal.

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CONFLICT OF INTEREST STATEMENT

There is no conflict of interest concerning this material.

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