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Mini-Review

Discovery and disposition of the 1,4-diradical intermediate during reactions of isocyanates with alkenes

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ABSTRACT

Isocyanates react by a concerted mechanism for [2+2] cycloaddition reactions when the alkene is electron-deficient. Alkenes that are sufficiently electron-rich release a pi electron to the isocyanate which leads to a 1,4-diradical intermediate *via* the single electron transfer (SET) pathway. The triplet 1,4-diradical intermediate is in equilibrium with the singlet form. At temperatures around 15 °C and above the 1,4-diradical is in the triplet state; but it rearranges to the singlet form below 15 °C. The 1,4-diradical intermediate can close to give *beta*-lactam products, or it can be intercepted with a second isocyanate to give uracil products.

KEYWORDS: triplet 1,4-diradical, singlet 1,4-diradical, NMR line broadening, isocyanates, [2+2] cycloaddition with alkenes, trapping the 1,4-diradical.

INTRODUCTION

Chlorosulfonyl isocyanate (CSI) is the most reactive isocyanate [1]. CSI reaction with alkenes provide [2+2] sulfonyl adducts that are readily reduced to β-lactams (Eq. 1) [2, 3]. Graf proposed a 1,4-dipolar intermediate for this reaction, and for many years a dipolar specie supported the performance of CSI with alkenes (Figure 1) [4]. Subsequent authors presented calculations for an orthogonal [5], and later an in-plane parallel [6] transition state for the concerted pathway. The dipolar intermediate for reaction of CSI with electron-rich alkenes was accepted in the literature until the use of a radical trap reagent to inhibit the reaction progress [7].

The 1,4-diradical intermediate

Kinetic studies with CSI and alkenes show a linear correlation for a plot of ln k *vs.* calculated vertical ionization potential (IP) of the alkenes that have IP values > 8.8 eV [7]. Alkenes with IP values less than 8.8 eV gave kinetic data off the line indicating a change from the concerted pathway. Reaction of CSI with alkenes having IP values < 8.8 eV were inhibited in the presence of TEMPO, a radical inhibitor [7]. The single electron transfer (SET) pathway for reaction with electron-rich alkenes to give 1,4-diradical intermediates is described in Scheme 1. The pre-equilibrium complex is indicated in Scheme 1 since reactions are more efficient at lower temperatures where the reagents formed a complex and react *via* a unimolecular second order rather than a bimolecular second order process [8]. For example, CSI reacts with styrene in methylene chloride at room temperature in 25 minutes, but at 10-15 °C the reaction gets completed in 10 minutes with a higher yield [8] (See Supporting Information in reference 8 for more examples).

To further confirm a di-radical intermediate we attempted an electron paramagnetic resonance (EPR) study at another institution which was unsuccessful. This was discouraging in light of the successful radical trapping experiments [7].

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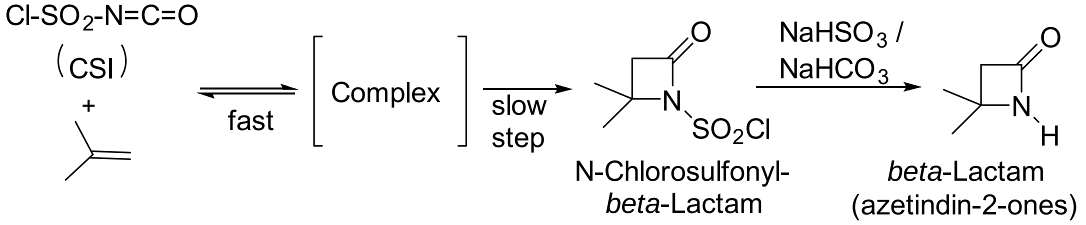


(1)

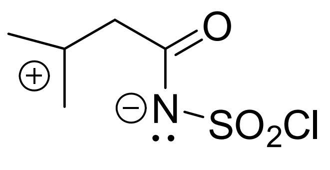
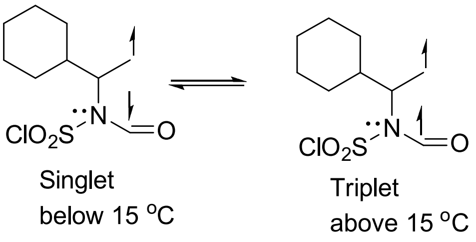


Figure 1. Proposed 1,4-dipolar intermediate.

NMR studies, described below, show the EPR experiment was unsuccessful because it was carried out at -78 °C.

During an NMR study of CSI with electron-rich alkenes we noticed line-broadening that disappeared after the reaction was complete. We expanded the singlet internal standard of TMS or fluorotrichloromethane from - 0.08 to + 0.08 ppm, and then recorded the peak width at half-height of the reference singlet. For example, the internal standard for a solution of 4-methylstyrene before addition of CSI has a peak width at half-height of 2.7 Hz. Three minutes after addition of CSI the standard singlet has a peak width at half-height of 4.9 Hz which returns to 2.7 Hz after the reaction is complete [9]. A careful line-broadening study of fifteen electron-rich alkenes confirmed the presence of 1,4-diradical intermediates for reaction of CSI with electron-rich alkenes [9].

Two radicals in a single molecule that do not interact with each other are referred to as bi-radicals [10]. When two radicals are in the same molecule and do interact, they are referred to as di-radicals. Hund's rule may not apply if the interaction between the electrons in a di-radical is small, and thus the singlet state can exist [10]. We found that line-broadening disappeared when the temperature was lowered, but the lowering was not enough to stop the reaction progress. For example, methylenecyclohexane reacts with CSI to give line-broadening at + 15 °C, but not at 0 °C [9]. The 1,4 di-radical from methylenecyclohexane at + 15 °C or higher temperature has both electrons unpaired and it is in the triplet state. At 0 °C the equilibrium for the 1,4-diradical favors the paired singlet state and line-broadening disappears (Eq. 2) [9]. The diradical intermediate can be shifted from the triplet to singlet and back to the triplet multiple times during the reaction.



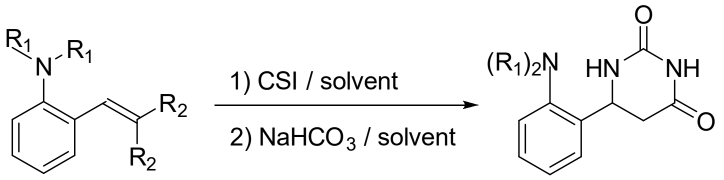
(2)

1,4-di-radical equilibrium

Trapping the 1,4-diradical with a second CSI

The life-time for 1,4-diradical intermediates should be longer than that of a 1,4-dipolar species. Thus, trapping a 1,4-diradical should be easier than trapping a dipolar intermediate. In solution, very reactive alkenes like *o*-dialkylaminostyrenes [2] and 7-methylenenorbornadiene [11] give 2:1 uracil adducts (Eqs. 3 & 4). Neat inverse addition, that is adding neat alkene to neat excess CSI, gives uracil products from a second molecule of

CSI trapping the 1,4-diradical intermediate [12]. For example, 2-fluorodec-1-ene is an electron-deficient alkene and it reacts slowly with CSI in nitromethane at 50 °C. It does not show line-broadening in solution at this elevated temperature indicating a concerted process [9]. However, inverse addition of neat 2-fluorodec-1-ene to neat CSI at room temperature gives predominately a 2:1 product suggesting a di-radical component for this unreactive alkene under these conditions (Eq. 5) [12]. We have not maximized the reaction conditions to obtain the 2:1 product exclusively with this or other electron-deficient alkenes.



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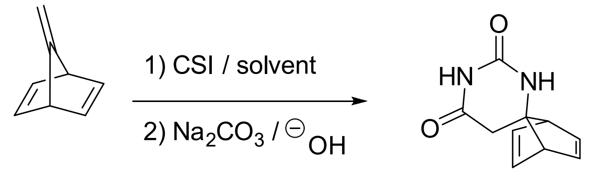

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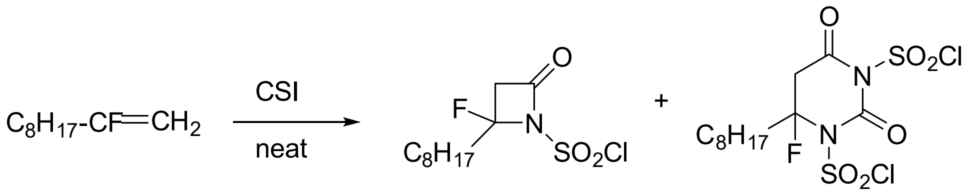
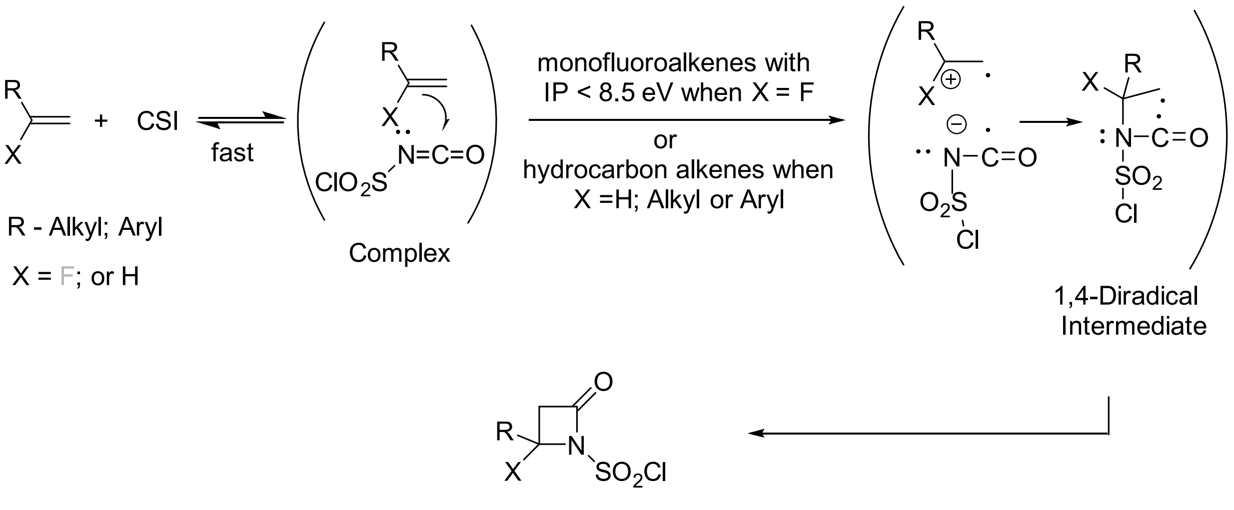
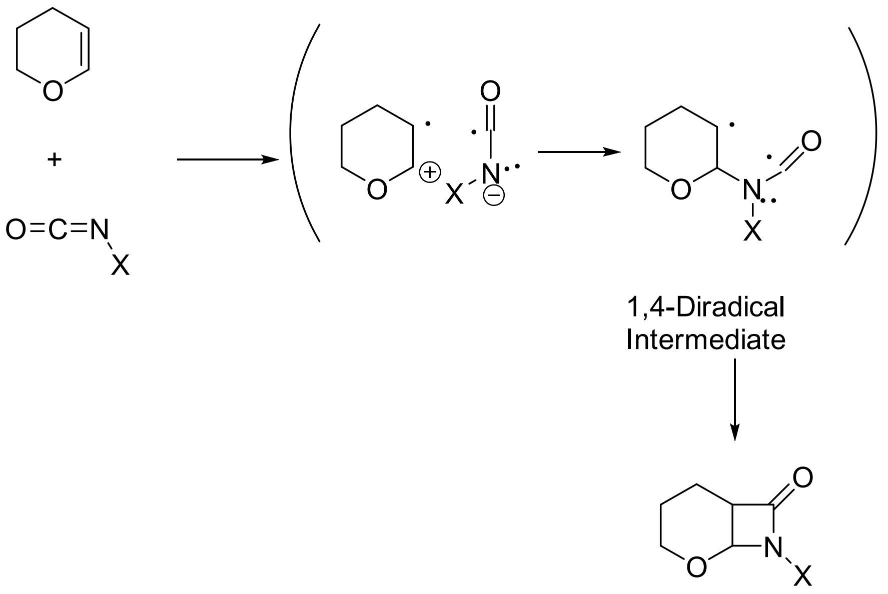


(5)

Trapping the intermediates



Scheme 1. Single electron pathway to give 1,4-diradical intermediates.



Scheme 2. *p*-toluenesulfonyl isocyanate and 3,4-dihydro-2H-pyran showing the SET pathway.

Other isocyanates

p-toluenesulfonyl isocyanate reacts with electron-rich alkenes like methylenecyclohexane, 2-methyl-2-butene, and various reactive styrene's to give tosyl-β-lactams [13]. Product yields are moderate in solution but the reaction time is decreased and the product yields improved with inverse addition and without solvent. Line-broadening for reaction of *p*-toluenesulfonyl isocyanate with 3,4-dihydro-2H-pyran in $CDCl_3$ was observed and shows that other isocyanates can also react *via* the SET pathway if the alkene is sufficiently electron-rich to release its electron to the isocyanate (Scheme 2) [13]. Less reactive alkenes are forced to react with *p*-toluenesulfonyl isocyanate by a concerted path, but the higher temperatures required can decompose the delicate β-lactam products.

CONCLUSION

Isocyanates react with alkenes by way of a single electron transfer process if the alkene is electron-rich enough to allow transfer of a single electron to a particular isocyanate. CSI is the most reactive isocyanate, and it will transfer the electron from most alkenes to the isocyanate. Less reactive isocyanates, like *p*-toluenesulfonyl isocyanate, require the alkene to be more electron-rich to deliver the alkene electron to the isocyanate. When the 1,4-diradical intermediate is formed, it can be trapped by a second isocyanate. A concerted pathway, at a higher temperature, is required for less reactive alkenes when the isocyanate is unable to transfer an electron from the alkene.

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest concerning this material.

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