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REACTIONS OF ARYLHALOCARBENES WITH VINYL ISOCYANATES

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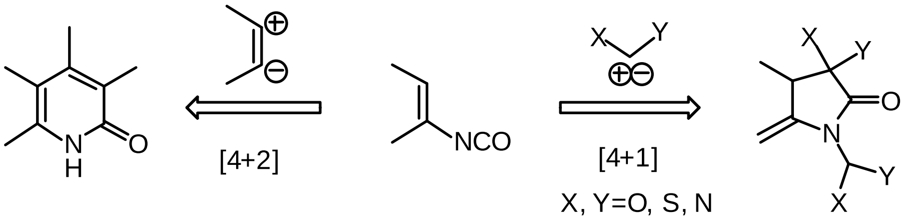
Abstract – A variety of aryhalocarbenes were reacted with 1-cyclohexene-1-isocyanate to provide insight into the factors that control [4+1] versus [2+1] cycloaddition reactivity.

This paper is dedicated to Leo A. Paquette on the occasion of his 70th birthday.

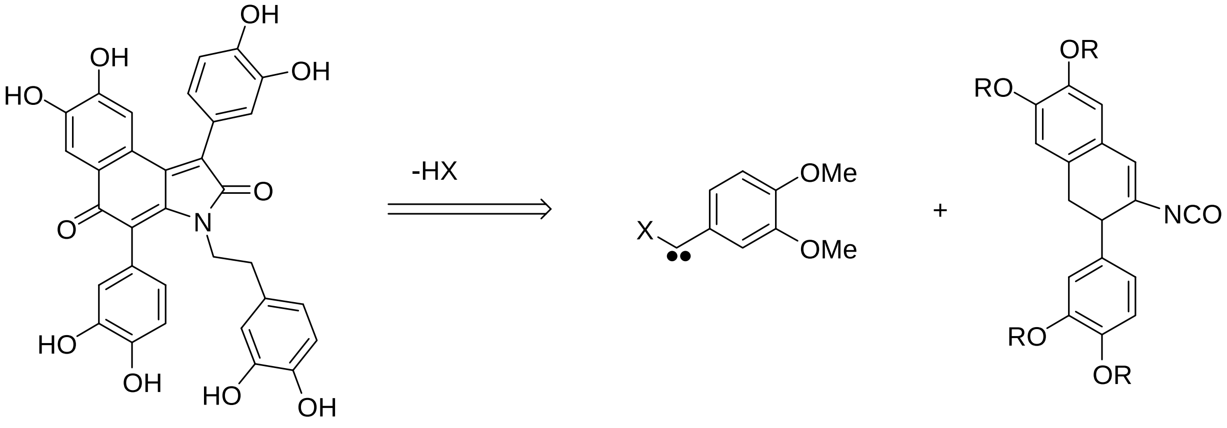
Vinyl isocyanates have emerged as powerful building blocks for the construction of highly functionalized five- and six-membered nitrogen heterocycles.[1] These readily available cummulenes have been shown to react with so-called "1,2-dipoles" such as enamines[2] and benzynes[3] to deliver structurally complex pyridone-based products. More recently, "1,1-dipole" equivalents such as isocyanides and O,S and N-based nucleophilic carbenes have been employed to assemble hydroindolone products[4] (Scheme I).

Scheme I



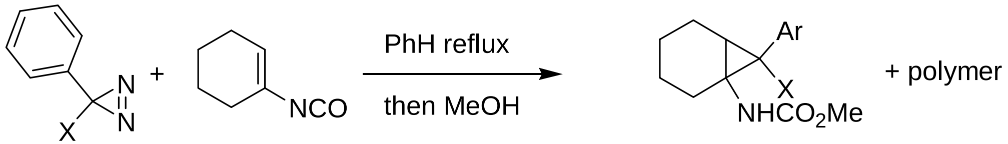
In light of the ability to rapidly construct highly substituted hydroindolones by exploiting the efficient [4+1] cycloaddition of nucleophilic carbenes with vinyl isocyanates,[4] we were attracted to the structurally novel ningalin alkaloids that have been isolated from a western australian ascidian of the genus *Didemnum*.[5] Our strategy called for the addition of an aryl-substituted carbene to a functionally elaborate vinyl isocyanate to assemble much of the core heterocycle in one operation (Scheme II).

Scheme II



Ningalin C (**1**)

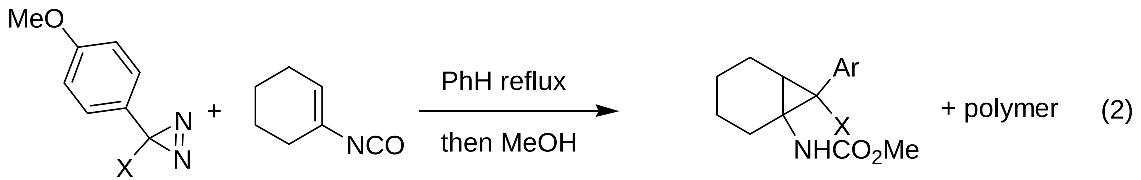
From the outset of this investigation it was unclear how an aryl-substituted carbene would behave in the presence of the highly electrophilic isocyanate function. Being cognizant of the well-known *Moss Carbene Philicity Scale*[6] and its significance to our problem, we elected to perform a systematic study of various arylhalocarbenes to establish reactivity patterns prior to embarking on the synthesis of ningalin C (**1**). The study was initiated by carrying out the reactions depicted in equation (1). The requisite phenylchloro- and phenylbromodiazirine precursors were prepared by Graham oxidation of the commercially available benzaminidine hydrochloride.[7] The phenylfluorodiazirine was prepared by treating the corresponding chloro derivative with anhydrous TBAF at 25°C.[8]



(1)

2, X=Cl, 84%
3, X=Br, 60%
4, X=F, 5%

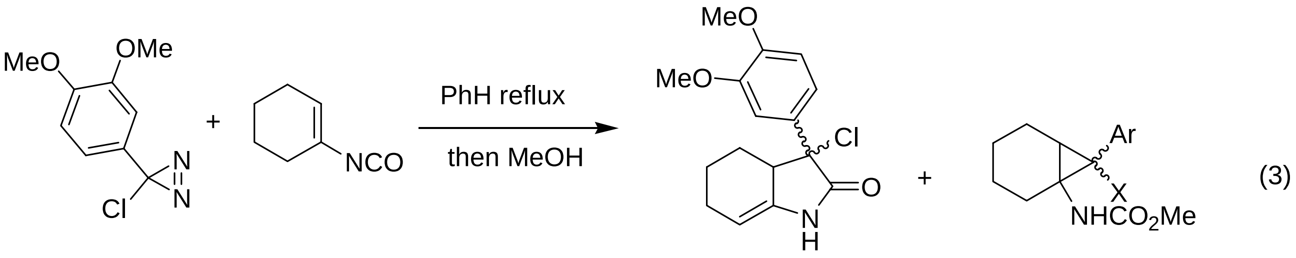
The reactions were performed by heating excess diazirine with cyclohexene-1-isocyanate[1f] followed by trapping with MeOH. Not surprisingly, the [2+1] adducts, stemming from reaction at the more electron-rich unsaturation and, presumably reflecting the electrophilic nature of these carbenes, prevailed in each case.[9.10] Next, the corresponding *p*-methoxyphenylhalodiazirines were prepared and heated with the generic isocyanate. Once again both the chloro- and fluorocarbenes[9,10] behaved as electrophiles providing the cyclopropane products as mixtures of diastereomers (Eq. (2)). There was no evidence of [4+1] cycloadducts being produced, which was assumed to be reflective of the absence of sufficient nucleophilic character in these particular carbenes. This reactivity pattern is fully consistent with the positioning of these two carbenes on the Moss scale (m_{cxy} 1.1 and 1.3).[6]



(2)

5, X=Cl, 68%
6, X=F, 13%

The corresponding dimethoxyphenylchloro- and fluorodiazirines were then prepared in the usual fashion and reacted with the isocyanate partner. To our delight, a substantial quantity of the hydroindolone adduct (**7**)[9,10] was produced along with smaller amounts of the corresponding [2+1] adduct (**8**).[9,10] Based on this result it would appear that the presence of two electron donating groups on the arene moiety is sufficient to allow the carbene to exhibit enough nucleophilic character to give rise to the [4+1] adduct. Again this pattern appears to conform to the Carbene Philicity Scale in which $(MeO)_2C_6H_3CC1$ has a m_{cxy}=1.9 ($(MeO)_2C$=2.4).[6] It is noteworthy that only 1:1 adducts were produced in this case. This result contrasts with the 2:1 adducts (carbene:isocyanate) that prevail with more nucleophilic carbene partners and may be reflective of the reduced basicity of arylhalocarbenes.

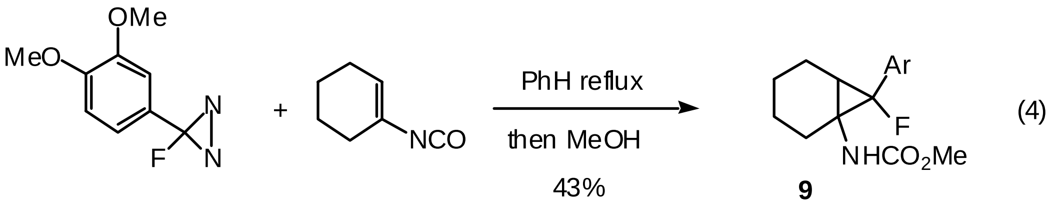


(3)

7, 51%

8, 20%

Interestingly, the corresponding fluoro derivative (m_{cxy}=1.6) provided cyclopropane product (**9**)[9,10] derived from the [2+1] cycloaddition lane.

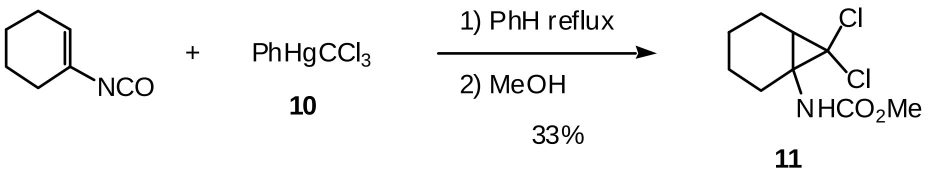


43%

(4)

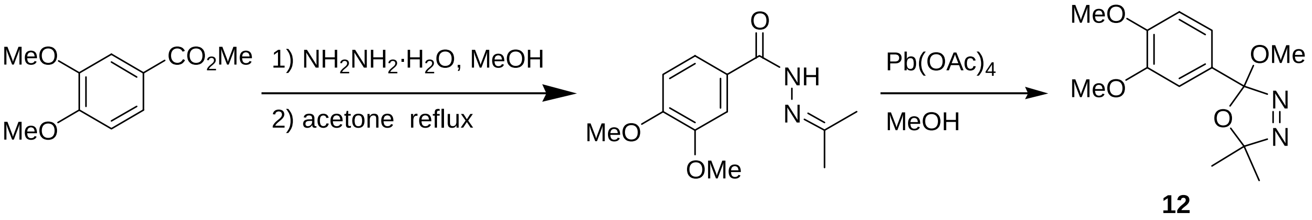
9

To help calibrate the reactivity profile of the various arylhalocarbenes on the carbene philicity scale, a reaction of the strongly electrophilic dichlorocarbene (m_{cxy}=1.0) with the vinyl isocyanate was carried out. In this case the Seyferth reagent (**10**)[11] was selected as the source of the carbene due to its expected compatibility with the rather fragile isocyanate function. In this instance a 33% yield of the anticipated cyclopropane product (**11**)[9] was obtained after quenching with methanol.

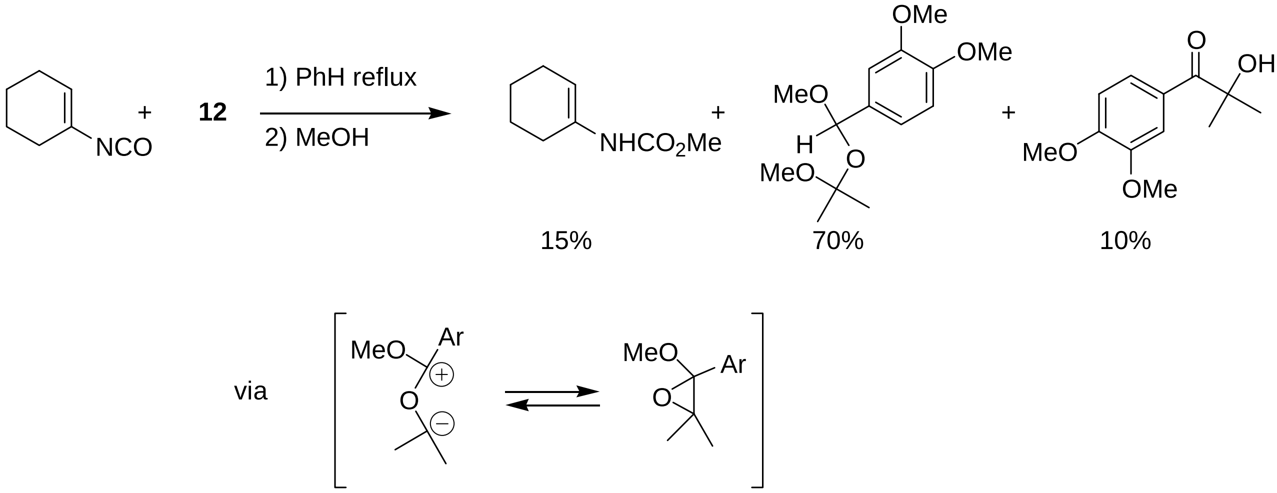


(5)

Finally, it was reasoned that replacing the halogen with a methoxy group would serve to enhance the nucleophilic character of the aryl-substituted carbene species and, in turn, increase the amount of [4+1] adduct obtained in reaction with cyclohexene-1-isocyanate. To that end, the corresponding oxadiazoline (**12**)[12] was prepared as shown in equation (6). Thermal decomposition of these interesting heterocycles has proven to be the method of choice for producing nucleophilic carbenes suitable for undergoing cycloaddition with sensitive reaction partners.[1,12] Surprisingly, heating excess oxadiazoline (**12**) in the presence of the generic vinyl isocyanate afforded no discernable products derived from either a [2+1] or a [4+1] reaction channel (Eq. (7)). Instead, only a somewhat modest yield of a number of products suggesting that the heterocycle, in fact, did not decompose to the carbene as expected, but followed an alternative course that involved a 1,3-dipolar intermediate, a pathway not without precedent in the thermochemistry of oxadiazolines.[13]



(6)



(7)

Further work is currently underway to attempt to modify the reactivity of oxadiazoline **12** so that formation of the desired arylmethoxycarbene will prevail and to optimize the formation of the hydroindolone (**7**) and related heterocycles.

ACKNOWLEDGEMENTS

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