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[2 + 2] AND [2 + 4] TYPE CYCLOADDITIONS OF ISOCYANATES WITH YNOLATES[#]

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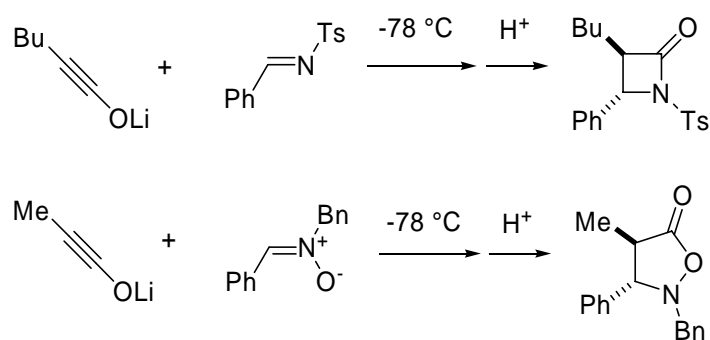
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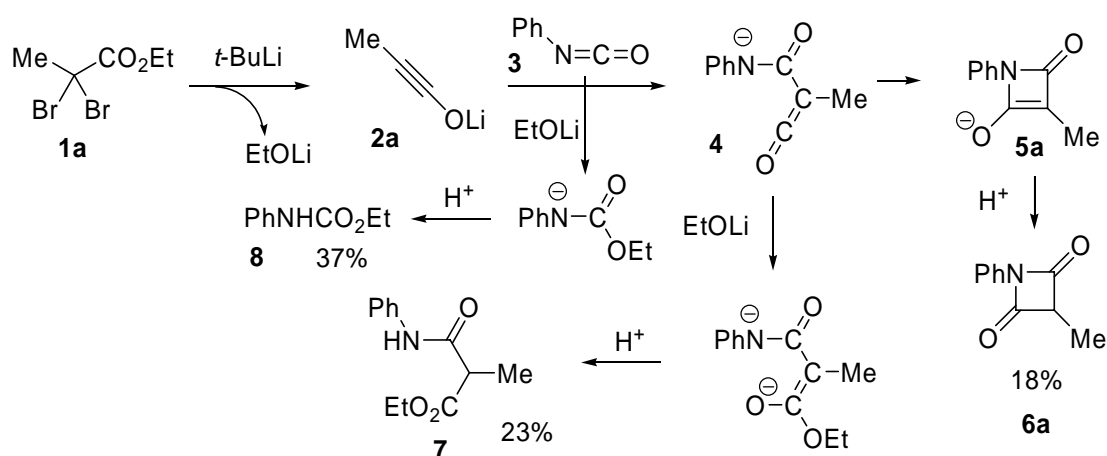
Abstract—Ynolates react with isocyanates to give azetidine-2,4-diones *via* a [2 + 2] type cycloaddition. The [4 + 2] type cycloaddition proceeds in the reactions of vinyl isocyanates with ynolates to provide 2-pyridones.

The cycloaddition of isocyanates, electrophilic heterocumulenes, with double-bond-containing substrates is a valuable method for the synthesis of heterocycles, such as azetidin-2-ones (β -lactams).¹ In many cases, activated isocyanates bearing an electron-withdrawing group have been used in the cycloadditions.² Because ynolates are regarded as having electron-rich triple bond functionality, they are expected to cycloadd to various kinds of dipoles.³ Since our development of a new synthetic method for ynolates,⁴ we have found that the [2 + 2] cycloaddition with aldimines gives β -lactams⁵ and that the [3 + 2] cycloaddition with nitrones furnishes 5-isoxazolidinones⁶ (Scheme 1). Based on the high nucleophilicity of ynolates, we envisioned an efficient cycloaddition of ynolates to isocyanates under mild conditions to provide heterocycles. We now disclose the [2 + 2] and [4 + 2] type cycloadditions of unactivated isocyanates with ynolates furnish azetidine-2,4-diones and 2-pyridones.

The ynoate (**2a**),¹² generated from *ethyl* 2,2-dibromopropionate (**1a**) with *t*-BuLi, was treated with phenyl isocyanate (**3**) at -78 °C, stirred for 5 min, and quenched with acetic acid in THF. After the usual workup, followed by column chromatography, the cyclized product, the azetidine-2,4-dione (**6a**), was isolated in 18% yield, along with the ethyl ester (**7**) (23%) and the ethyl carbamate (**8**) (37%), which would be derived from the addition of lithium ethoxide, released in the preparation of the ynoate (**2a**), to the ketene (**4**) and the isocyanate (**3**), respectively (Scheme 2).

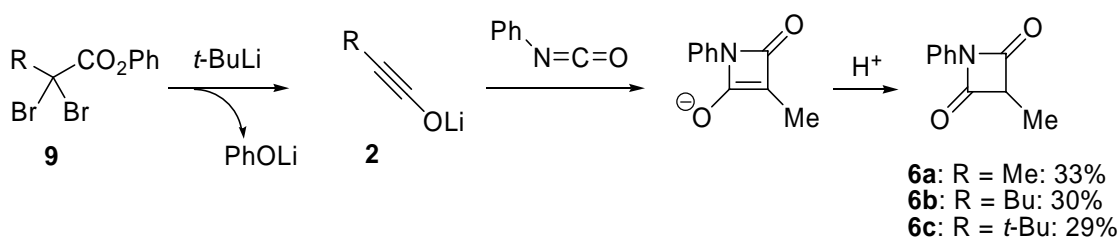


Scheme 1



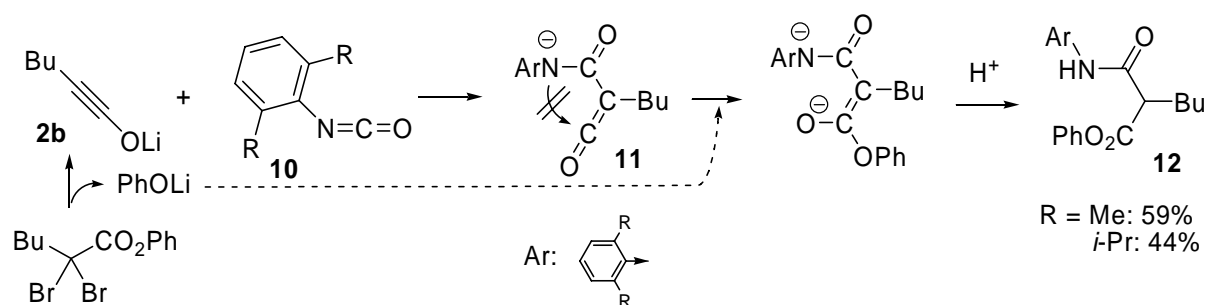
Scheme 2

To circumvent the generation of these side products, *phenyl* esters (**9**) were used as ynone precursors, since phenoxide should be less nucleophilic than ethoxide. Consequently, as shown in Scheme 3, the azetidine-2,4-diones (**6**) were obtained in better yields.^{7,8}



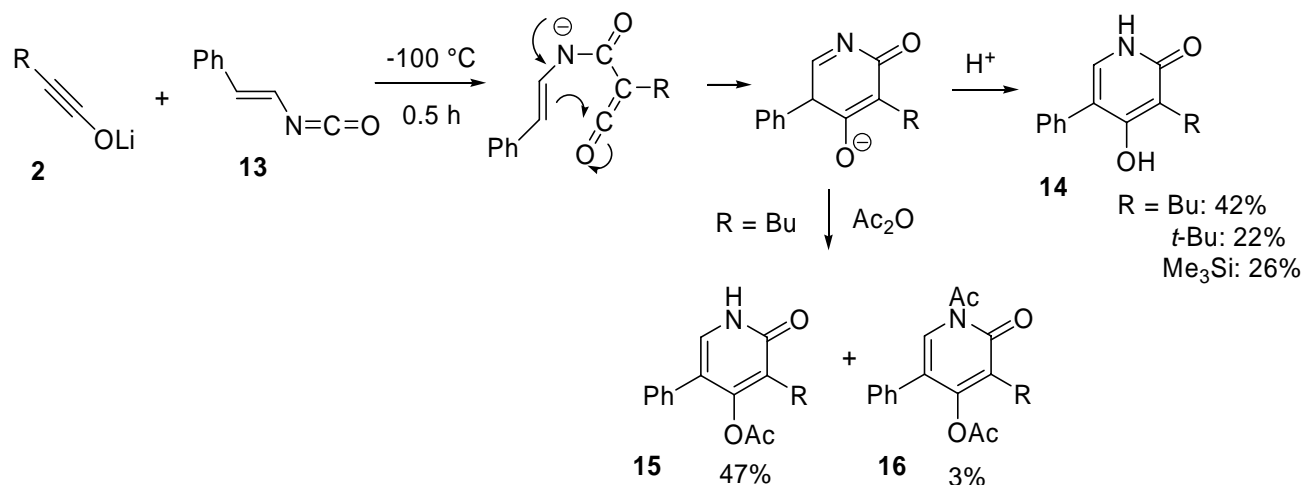
Scheme 3

The sterically hindered 2,6-dialkylphenyl isocyanates (**10**), however, did not give the azetidine-2,4-diones but instead the phenyl esters (**12**), because the cyclization would be inhibited by steric hindrance (Scheme 4). This finding supports the generation of the ketene intermediates (e.g., **4**, **11**) via a stepwise mechanism, and not the concerted mechanism, of the four membered ring formations using ynone.⁹



Scheme 4

We next examined the reaction of ynoles with a vinyl isocyanate (Scheme 5), which is a 1,4-dipole.¹⁰ The ynole (**2b**) reacted with styryl isocyanate (**13**) at $-100\text{ }^{\circ}\text{C}$ to afford 4-hydroxy-2-pyridone (**14**) in 42% yield after quenching with 1 M HCl.¹¹ The use of acetic anhydride in the workup instead of HCl provided 4-acetoxy-2-pyridone (**15**) in slightly better yield, along with a small amount of the diacetate (**16**). The hindered ynoles ($\text{R} = t\text{-Bu}, \text{SiMe}_3$)¹² also provided the pyridones (**14**) in moderate yields. This cyclization can be regarded as a formal [4 + 2] cycloaddition *via* ynoles.¹³



Scheme 5

In conclusion, we have found that formal [2 + 2] and [4 + 2] cycloadditions of ynoles with isocyanates provide 4-membered and 6-membered heterocycles. These new reactions demonstrate the synthetic potential directed towards the synthesis of heterocycles *via* ynoles.

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#Dedicated to the memory of the late Professor Kenji Koga.

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