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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). In many cases, activated isocyanates bearing an electron-withdrawing group have been used in the cycloadditions. Because ynolates are regarded as having electron-rich triple bond functionality, they are expected to cycloadd to various kinds of dipoles. Since our development of a new synthetic method for ynolates, we have found that the [2 + 2] cycloaddition with aldimines gives β-lactams and that the [3 + 2] cycloaddition with nitrones furnishes 5-isoxazolidinones (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 ynolate (2a), 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 ynolate (2a), to the ketene (4) and the isocyanate (3), respectively (Scheme 2).
Bu\text{OLi} + \text{Ph}^+\text{N}^-\text{Ts} \rightarrow_{-78 \ ^\circ\text{C}}^{\text{H}^+} \text{Bu}^+\text{Ph}^\text{N}^-\text{Ts} \\
Me\text{OLi} + \text{Ph}^+\text{N}^-\text{Bn} \rightarrow_{-78 \ ^\circ\text{C}}^{\text{H}^+} \text{Me}^+\text{Ph}^\text{N}^-\text{Bn} \\

\text{Scheme 1}

\begin{align*}
\text{Me}^+\text{CO}_2\text{Et} & \xrightarrow{t-\text{BuLi}} \text{EtOLi} \\
\text{Br} & \rightarrow 2\text{a} \\
\text{PhNCO}_2\text{Et} & \rightarrow_{37\%}^{\text{H}^+} 8 \\
\text{EtOLi} & \rightarrow 4 \\
\text{PhNCO}_2\text{Et} & \rightarrow_{18\%}^{\text{H}^+} 6\text{a} \\
\text{EtO}_2\text{C} & \rightarrow 7 \\
\text{EtO}_2\text{C} & \rightarrow_{23\%}^{\text{H}^+} 7 \\
\end{align*}

\textbf{Scheme 2}

To circumvent the generation of these side products, phenyl esters (9) were used as ynoolate 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.\textsuperscript{7,8}

\begin{align*}
\text{R}^+\text{CO}_2\text{Ph} & \xrightarrow{t-\text{BuLi}} \text{PhOLi} \\
\text{Br} & \rightarrow 2 \\
\text{PhN}=\text{C}=\text{O} & \rightarrow_{6\%}^{\text{H}^+} 5\text{a} \\
\text{PhN}=\text{C}=\text{O} & \rightarrow_{18\%}^{\text{H}^+} 6\text{a} \\
\text{EtO}_2\text{C} & \rightarrow 7 \\
\text{EtO}_2\text{C} & \rightarrow_{23\%}^{\text{H}^+} 7 \\
\end{align*}

\textbf{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) \textit{via} a stepwise mechanism, and not the concerted mechanism, of the four membered ring formations using ynolates.\textsuperscript{9}
Scheme 4

We next examined the reaction of ynolates with a vinyl isocyanate (Scheme 5), which is a 1,4-dipole.\textsuperscript{10} The ynolate (2b) reacted with styryl isocyanate (13) at -100 °C to afford 4-hydroxy-2-pyridone (14) in 42% yield after quenching with 1 M HCl.\textsuperscript{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 ynolates (R = \textit{t}-Bu, SiMe\textsubscript{3})\textsuperscript{12} also provided the pyridones (14) in moderate yields. This cyclization can be regarded as a formal [4 + 2] cycloaddition \textit{via} ynolates.\textsuperscript{13}

Scheme 5

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

**ACKNOWLEDGEMENTS**

Support has been provided in part by a Grant-in-Aid for Scientific Research, the Ministry of Education, Culture, Sports, Science and Technology, Japan.
REFERENCES AND NOTES

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

1. For a review on isocyanates, see: S. Ozaki, Chem. Rev., 1972, 72, 457.


8. A representative procedure: To a solution of phenyl 2,2-dibromopropionate (370 mg, 1.2 mmol) in THF (8 mL) was added a solution of tert-butyllithium (1.52 M in pentane, 3.2 mL, 4.8 mmol) at -78 °C. The reaction was stirred for 3 h then warmed to 0 °C. After 0.5 h, the reaction was cooled to -78 °C, and a solution of phenyl isocyanate (119 mg, 1.0 mmol) in THF (2 mL) was added all at once. After 3~10 min, the reaction was quenched with a solution of acetic acid (0.15 g, 2.5 mmol) in THF (1 mL). After the usual workup and purification by column chromatography, 58 mg (33%) of 3-methyl-1-phenylazetidine-2,4-dione was isolated as colorless prisms; mp 35.2 °C (AcOEt/hexane); 1H-NMR (400 MHz, CDCl3) δ: 1.51 (d, J = 7.6 Hz, 3H), 3.91 (q, J = 7.6 Hz, 1H), 7.27 (t, J = 8 Hz, 1H), 7.41 (t, J = 8 Hz, 2H), 7.83 (d, J = 8 Hz, 2H); 13C-NMR (100 MHz, CDCl3) δ: 9.8, 56.2, 118.9, 126.7, 129.1, 134.1, 168.9; IR (CHCl3): 1860, 1765, 1733 cm⁻¹; MS (EI): m/z 175 (M⁺); Anal. Calcd for C10H9NO2: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.42; H, 5.17; N, 7.98.


10. For a review, see: J. H. Rigby, Synlett, 2000, 1.

12. The ynolates (R = $t$-Bu and SiMe$_3$) were prepared from phenyl 2,2-dibromo-3,3-dimethylbutyrate, and ethyl 2,2-dibromo-2-trimethylsilylacetae, respectively. For the preparation, see: M. Shindo, Y. Sato, R. Koretsune, T. Yoshikawa, K. Matsumoto, K. Itoh, and K. Shishido, *Chem. Pharm. Bull.*, 2003, 51, 477.