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Dedicated to our friend and colleague Victor Snieckus on the occasion of his 80th birthday.

Abstract
Seven-membered nitrogen-containing heterocycles are considerably underrepresented in the literature compared to their five- and six-membered analogues. Herein, we report a relatively understudied photochemical rearrangement of \(N\)-vinylpyrrolidinones to azepin-4-ones in good yields. This transformation allows for the conversion of readily available pyrrolidinones and aldehydes to densely functionalized azepane derivatives in a facile two-step procedure.

Key words azepane, photochemistry, photo-Fries rearrangement, heterocycles, [5+2] cycloaddition

Seven-membered nitrogen-containing rings present an intriguing challenge compared to their five- and six-membered analogues. Although they occur with less frequency than these other ‘common’ rings, their appearance in molecules of biological interest provides significant motivation to construct these frameworks efficiently and effectively.\textsuperscript{1} Additionally, five- and six-membered heterocycles have been heavily explored, while substantially less work has been done on the construction of seven-membered (and larger) nitrogen-containing rings (Figure 1).\textsuperscript{2}

This is particularly evident when considering the incidence of seven- and eight-membered rings in pharmaceuticals approved by the FDA\textsuperscript{3} compared to their coverage in the patent literature (Figure 1).\textsuperscript{4}

While cyclization strategies dominate azepane and azocane synthesis, we felt that two component-coupling approaches were fundamentally more powerful and considered various disconnections. A \([5+2]\) approach proved alluring since the two-atom unit may be an alkene or surrogate, trivially accessed and abundant, while the five-atom unit is pyrrolidinone. Such a union could be realized by condensation–ring-expansion.

Scheme 1 Comparison between this work and prior art

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme1.png}
\caption{Comparison between this work and prior art}
\end{figure}

Buhr (ref. 5): Booker-Milburn (ref. 6):

This work:
The reaction was first described in the patent literature (Scheme 1); subsequent studies by Booker-Milburn, Mazzocchi, and others have shown similar photochemical \([5+2]\)-ring-expansion chemistry with the maleimide and phthalimide frameworks, respectively. Stimulated by the conviction that this photo-Fries-like chemistry could be a powerful reaction for the synthesis of azepanes, we sought to develop the method.

The \(N\)-vinylpyrrolidinones are readily accessible through the condensation of a desired aldehyde and pyrrolidinone (Scheme 2). Unlike the chemistry of the maleimides, this method allows for the facile and diverse structural modification and functionalization around the azepane motif. Additionally, the resultant vinylogous amide moiety formed during the reaction is an exemplary functional group for further manipulation.

Our investigation into the photochemical \([5+2]\) cycloaddition began with optimization of the reaction conditions on \(3a\), using the conditions reported in the patent literature as a starting point (Table 1, entry 1). The use of THF as solvent increases the yield of the reaction to 48% over 24 hours (Table 1, entry 8). Dilution of the reaction to 0.02 M further increases the yield, presumably due to disfavored competitive polymerization and dimerization pathways.

Functionalization at any of the positions on the pyrrolidinone ring is also possible (Scheme 4). Interestingly, heteroatoms are often tolerated, even in the case of unprotected alcohols. Pre-existing stereocenters on the pyrrolidinone ring do not racemize in the rearrangement chemistry with the exception of stereocenters \(\alpha\) to the amide. It is presumed that this is due to the Norrish Type I cleavage of the \(\text{C}–\text{C}\) bond that does not lead to any productive pathways and recombines, scrambling the stereocenter.
The transformation also allows us to access larger rings (6h). A further increase in ring size leads to difficulty in purification due to competitive polymerization, despite diluting the samples to 0.001 M.

Scheme 4 Scope of pyrrolidinone substituent

The cyclic vinylogous amide moiety formed in this transformation is easily manipulated to a variety of useful functional handles (Scheme 6). Georg and others have extensively studied the modification of the six-membered vinylogous amide analogues; however, the comparable reactivity with seven-membered azepin-4-ones is relatively rare. We found that these scaffolds easily convert into other useful seven-membered heterocycles. Global reduction of the vinylogous amide, as well as semireduction by hydrogenation to the ketone each proceed uneventfully; a Wolff–Kishner protocol results in deoxygenation with alkene migration to deliver 11.

In conclusion, we have developed a formal two-step [5+2] cycloaddition to form azepinones exploiting a relatively understudied photochemical rearrangement. This facile approach allows for the construction of synthetically useful functionalized azepin-4-ones in good yields from
readily available aldehydes and pyrrolidinones. Modification of these substrates allows for the access to a diverse set of substituted azepeane derivatives.

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Supporting Information
Supporting information for this article is available online at https://doi.org/10.1038/s-0036-1589049.

References and Notes
(4) Based on Scifinder search of patents containing synthesis of 'pyrrolidines', 'piperidines', 'azepanes', and 'azocanes'.
(10) For a recent review on the reactivity of cyclic vinylogous amides as well as other applicable references, see: Seki, H.; Georg, G. J. Synlett 2014, 25, 2536.
(14) Compounds that do not show reactivity in the photochemical rearrangement chemistry are listed in the Supporting Information. Generally speaking, other carbonyl moieties or other UV-reactive moieties seem to be detrimental to the reaction.
(16) Specifically (from ref. 6c) see Scheme 7.


(19) General Procedure
An N-vinyl pyrrolidinone was charged in a quartz reaction vessel, under an argon atmosphere, and degassed THF was added (0.01 M) via cannula. The quartz reaction vessel was irradiated in a Rayonet reactor (internal temp. ca. 45 °C) using 254 nm mercury arc lamps until completion. The reaction was then passed through a short silica plug and concentrated in vacuo. The crude product was purified using flash chromatography on silica gel (EtOAc–hexanes or MeOH–CH2Cl2).

(20) Representative Product 3-Benzyl-1,5,6,7-tetrahydro-4H-azepin-4-one (4a)
Compound 4a was obtained using general procedure from vinyl lactam 3a. White solid; 92% yield. 1H NMR (400 MHz, CDCl3): δ = 7.31–7.08 (m, 5 H), 6.76 (d, J = 7.3 Hz, 1 H), 5.61 (s, 1 H), 3.53 (s, 2 H), 3.46–3.36 (3 m, 2 H), 2.78–2.68 (m, 2 H), 1.99 (m, 2 H). 13C NMR (101 MHz, CDCl3): δ = 198.76, 142.55, 128.61, 128.17, 125.60, 109.74, 47.18, 42.62, 37.00, 22.94. IR (ATR): 3278, 3075, 2929, 1617, 1544, 1405, 1367, 1325, 1234, 1159, 1108, 1066 cm−1. Rf = 0.15 (85:15 EtOAc–hexanes). LRMS (ESI+APCI): m/z [M + H]+ calcd for [C13H16NO]+: 202.28; found: 202.4.