

A Photochemical Two-Step Formal [5+2] Cycloaddition: A Condensation–Ring-Expansion Approach to Substituted Azepanes

Scott M. Thullen^{a,b}

David M. Rubush^{b,c}

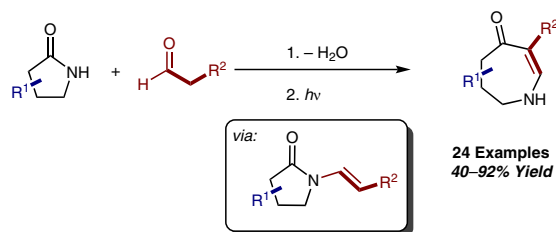
Tomislav Rovis^{*a,b} 

^a Department of Chemistry, Columbia University, New York, NY 10027, USA
tr2504@columbia.edu

^b Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA

^c Current Address: Department of Chemistry, Benedictine University, Lisle, IL 60532, USA

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



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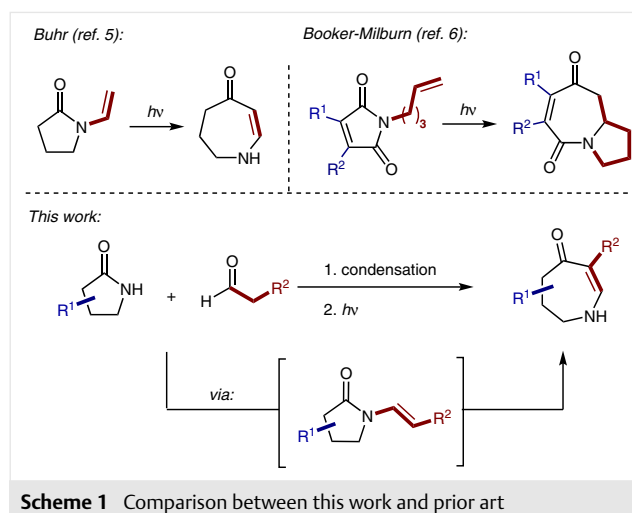
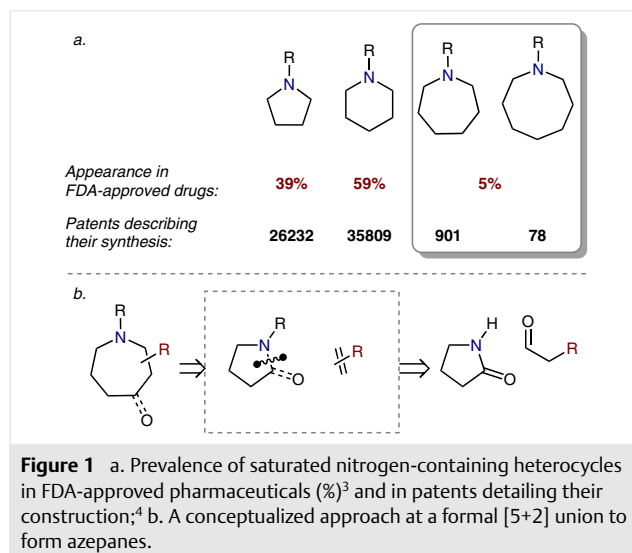
Abstract Seven-membered nitrogen-containing heterocycles are considerably underrepresented in the literature compared to their five- and six-membered analogues. Herein, we report a relatively understudied photochemical rearrangement of *N*-vinylpyrrolidinones to azepin-4-ones in good yields. This transformation 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.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).²

This is particularly evident when considering the incidence of seven- and eight-membered rings in pharmaceuticals approved by the FDA³ compared to their coverage in the patent literature (Figure 1).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 condensa-



tion of pyrrolidinone with aldehydes followed by a photochemical Fries-like rearrangement to form the azepinone. This reaction was first described in the patent literature (Scheme 1);⁵ subsequent studies by Booker-Milburn⁶, Mazzocchi⁷, and others⁸ 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 chemistry⁹ 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.¹⁰



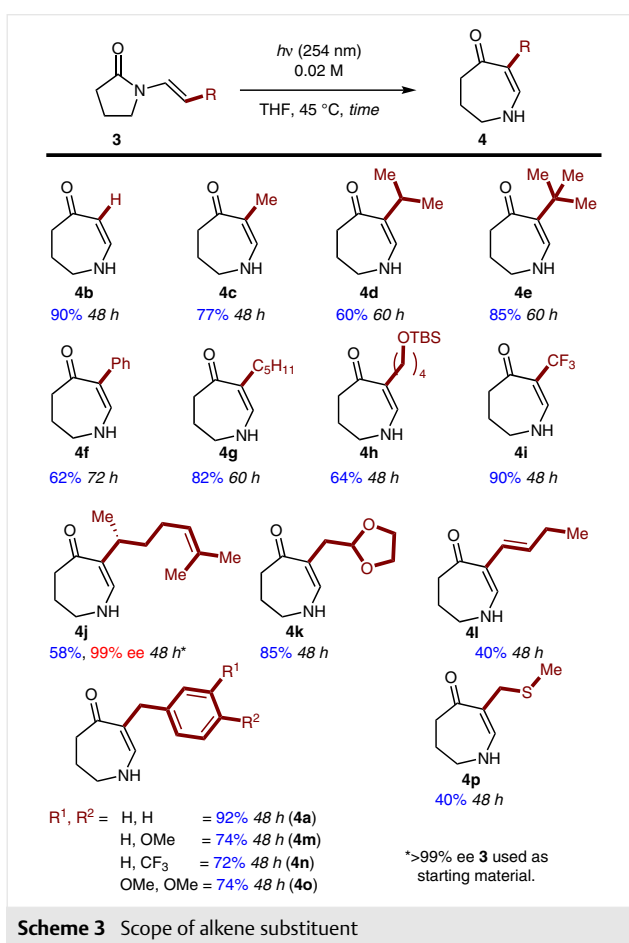
Scheme 2 Formation of *N*-vinylpyrrolidinones

Our investigation into the photochemical¹¹ [5+2] cycloaddition began with optimization of the reaction conditions on **3a**, using the conditions reported in the patent literature⁵ 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 polymerization¹² and dimerization¹³ pathways.

Table 1 Optimization Conditions

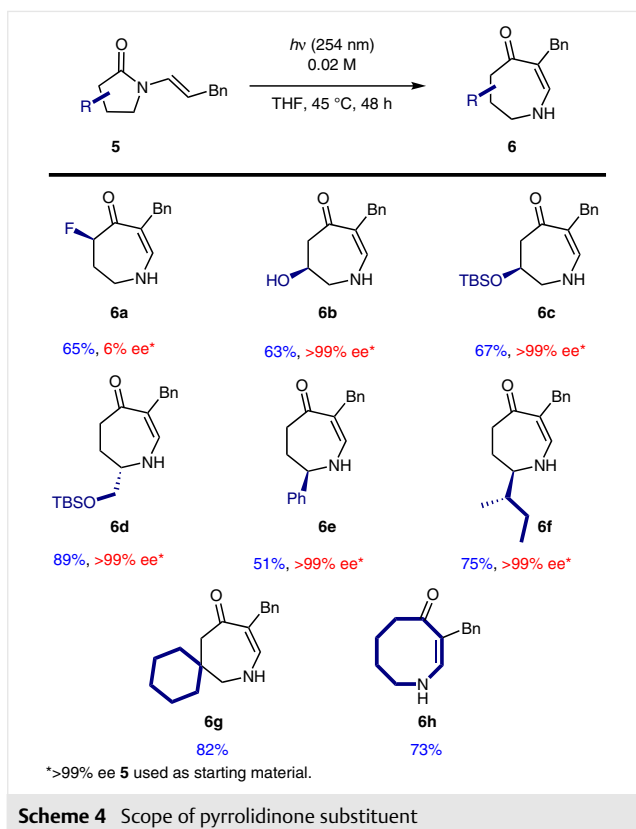
| Entry | Solvent | Concentration (M) | Time (h) | Yield (%) |
|-------|---------|-------------------|----------|-----------|
| 1 | MeOH | 0.2 | 24 | 40 |
| 2 | MeCN | 0.2 | 24 | 22 |
| 3 | THF | 0.2 | 24 | 48 |
| 4 | THF | 0.2 | 48 | 75 |
| 5 | THF | 0.5 | 48 | 67 |
| 6 | THF | 1.0 | 48 | 55 |
| 7 | THF | 0.1 | 48 | 81 |
| 8 | THF | 0.02 | 48 | 92 |

The photochemical rearrangement tolerates a broad range of substitution on the enamine (Scheme 3) including simple alkyl groups (**4c–e**) as well as aryl (**4f**), and electron-rich and electron-poor benzyl substituents (**4m–o**). Di-enamine-substituted pyrrolidinone **3l** participates in the reaction, although in diminished yield. A stereocenter present on the alkene substituent remains intact over the course of the reaction (**4j**). Unfortunately, efforts to create quaternary centers α to the ketone as well as substrates which included carbonyl moieties other than the reactive amide showed no conversion under the irradiative conditions.¹⁴



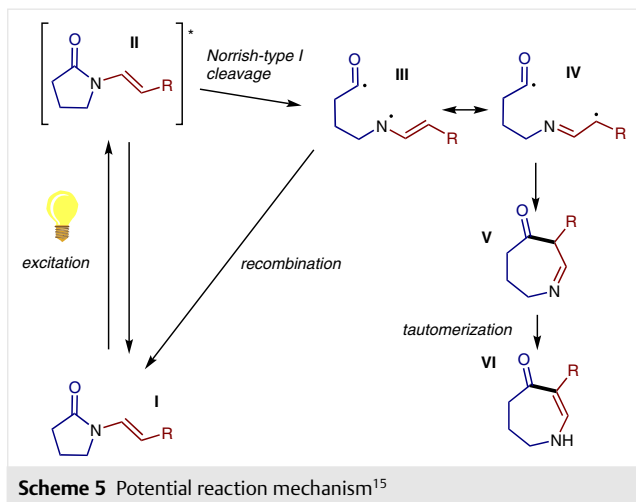
Scheme 3 Scope of alkene substituent

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 α to the amide. It is presumed that this is due to the Norrish Type I cleavage of the C–C bond that does not lead to any productive pathways and recombines, scrambling the stereocenter.



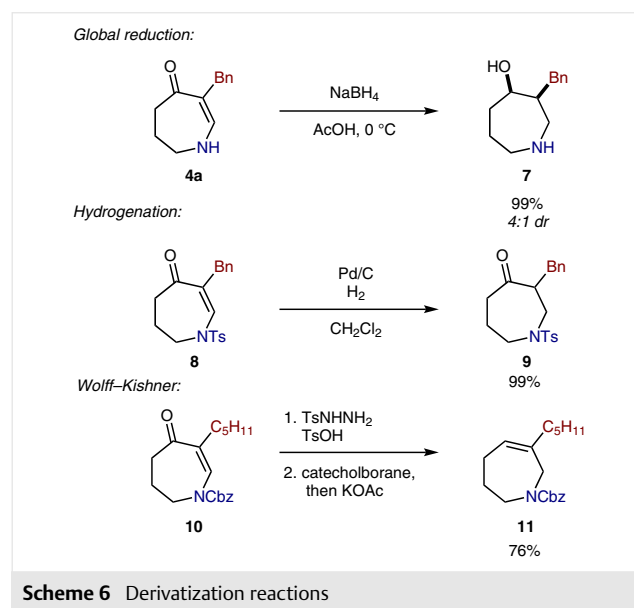
Scheme 4 Scope of pyrrolidinone substituent

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 5 Potential reaction mechanism¹⁵

A potential mechanism for this reactivity, as argued by Shizuka and coworkers¹⁵, involves the Norrish-type I (α) homolytic cleavage of the amide bond after irradiation with 254 nm light (Scheme 5). The resultant biradical **III** can

then either recombine to reform the starting material or combine with the carbon β to the nitrogen to generate imine **V**. Tautomerization of **V** gives the observed product. Investigation of a similar maleimide system by Booker-Milburn and coworkers^{6c} suggests that the reactive biradical intermediate proceeds through an excited singlet state as opposed to an excited triplet state. When directly irradiated, they solely observed the [5+2] cycloaddition product whereas when they irradiated the maleimide in the presence of the triplet sensitizer benzophenone, they solely observed the [2+2] cycloaddition between the alkene and maleimide backbone.¹⁶ In our system, addition of oxygen or catalytic benzophenone as triplet quenchers did not interfere with the outcome of the reaction, supporting the likelihood of a singlet pathway.



Scheme 6 Derivatization reactions

The cyclic vinylogous amide moiety formed in this transformation is easily manipulated to a variety of useful functional handles (Scheme 6). Georg¹⁰ and others¹⁷ 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.¹⁸ 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.^{19,20} 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 azepane derivatives.

Funding Information

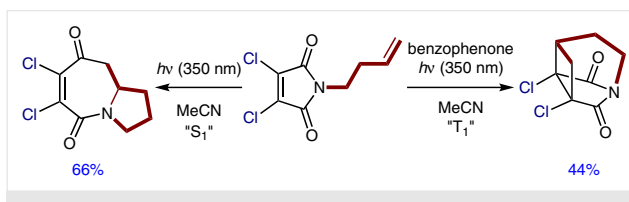
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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1589049>.

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- (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 (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. *R*_f = 0.15 (85:15 EtOAc–hexanes). LRMS (ESI+APCI): *m/z* [M + H]⁺ calcd for [C₁₃H₁₆NO]⁺: 202.28; found: 202.4.