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On the preparation of azepinones

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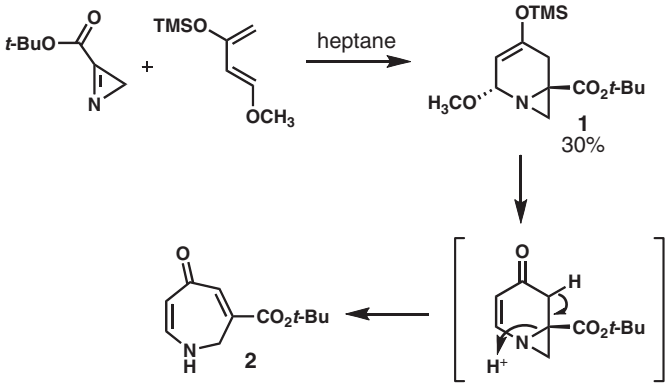
ABSTRACT

We report here a simple and efficient preparation of 1*H*-azepin-5(2*H*)-ones and their unexpectedly facile isomerization to 1*H*-azepin-5(4*H*)-ones under mildly basic reaction conditions.

During the course of the total synthesis of a complex alkaloid, we had need of a substituted 1*H*-azepin-5(2*H*)-one. Azepinones are accessible via the Diels–Alder cycloaddition of electron rich dienes and 2*H*-azirine-3-carboxylic acid esters (Scheme 1).[1,2] These reactions proceed under relatively mild conditions and owe their remarkable success to the combined effects of a highly strained carbon–nitrogen double bond and an electron-withdrawing carboxylate group.

In the case of unsubstituted 2*H*-azirine-3-carboxylic acid esters, it was reported that some cycloadducts underwent a strain-relieving scission of a carbon–nitrogen bond to produce mixtures of pyridones and azepinones.[2] For example, treatment of *t*-butyl 2*H*-azirine-3-carboxylate with 1-methoxy-3-trimethylsilyloxybutadiene[3] (Danishefsky's diene) afforded the silyl enol ether cycloadduct **1**. Upon prolonged standing at ambient temperature, the silyl enol ether decomposed to afford the corresponding azepinone-3-carboxylate ester **2**, presumably via the pathway depicted in Scheme 1. It was later reported by the same group that treatment of analogous cycloadducts with solutions of tetra-*n*-butylammonium fluoride (TBAF, 1 M in tetrahydrofuran, 0.3 equiv) afforded the same products.[1]

We wished to take advantage of this strain-relieving ring-expansion to generate azepinones like **6** and **7** (Scheme 2). After much experimentation, we found it most convenient to work with ethyl 2*H*-azirine-3-carboxylate (**3**), which we generated by heating dilute (0.07 M) solutions of ethyl 2-azidoacrylate[2b,4] in dichloromethane to 150 °C in a sealed vessel for just over one hour (see Supplementary data for details).[5] The resultant solution of ethyl



Scheme 1. Diels–Alder cycloaddition of 2*H*-azirine-3-carboxylate *t*-butyl ester (Alves and Gilchrist, 1998).

2*H*-azirine-3-carboxylate (**3**) was charged directly with 1-methoxy-3-trimethylsilyloxybutadiene (0.75 equiv) and heated to 80 °C for 40 min to afford the desired cycloadduct **4** in good yield.

We sought a means of inducing the strain-relieving bond scission (**4** → **6**) as part of a one-pot cycloaddition-ring expansion sequence to access the azepinone directly. We were surprised to find that treatment of crude or purified cycloadducts **4** and **5** with commercial solutions of TBAF (conditions previously described by Alves)[2d] yielded mixtures of isomeric azepinones. For example, when we treated the crude cycloadduct **4** with TBAF (1 M in THF, 0.3 equiv), we observed formation of a mixture of the desired 1*H*-azepin-5(2*H*)-one **6**, the isomerized 1*H*-azepin-5(4*H*)-one **8** (in which the

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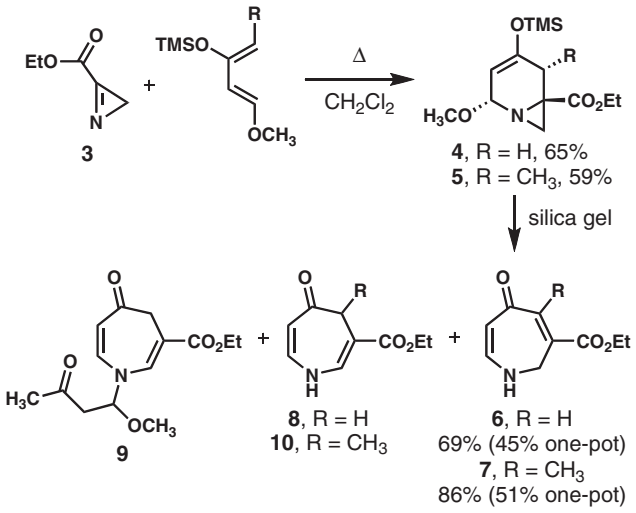


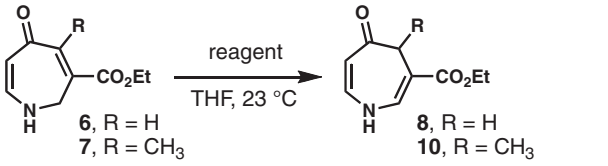
Scheme 2. Diels–Alder cycloaddition of 2*H*-azirine-3-carboxylate ethyl ester (this work).

double bond has migrated from C3–C4 to C2–C3), and the Michael adduct **9** incorporating 4-methoxy-3-buten-2-one in a 1:1:1.3 ratio (^{1}H NMR analysis).[6] We have evidence to suggest the Michael adduct arises from the conjugate addition of the cycloadduct at nitrogen to 4-methoxy-3-buten-2-one, followed by the strain-releasing bond-scission of the resultant cation.[7] Separating each component of this mixture by column chromatography proved quite tedious, thus precluding the use of this procedure for a one-pot azepinone synthesis.

Treatment of the purified cycloadduct **4** with TBAF (0.3 equiv) yielded the desired 1*H* azepin-5(2*H*)-one **6** (17%), and the isomerized 1*H*-azepin-5(4*H*)-one **8** as the major product (60%). In the presence of TBAF in any amount, mixtures of products were observed, however we found the stoichiometry was critical to our success. The desired azepinone isomer **6** was observed and isolated upon treatment of the cycloadduct **4** with 0.3 equiv TBAF, provided the reaction was closely monitored by TLC and purified immediately upon consumption of the starting material. However, when the same reaction was conducted with 1.0 equiv TBAF under otherwise identical conditions, it was difficult to obtain any of the desired isomer. The rate of fluoride-mediated azepinone isomerization is competitive with fluoride-mediated ring expansion; complete consumption of the cycloadduct was observed after approximately 3 h at room temperature, which is sufficient time for nearly complete azepinone isomerization to occur. We cannot rule out the possibility that trace amounts of hydroxide in our TBAF solutions were responsible for the isomerization, and under otherwise identical reaction conditions, other milder sources of fluoride (e.g., TBAF/AcOH, $Et_3N{\cdot}3HF$, HF·pyridine, HF·acetonitrile, CsF) did not efficiently induce the desired ring expansion (<10% conversion was observed in all cases).

After careful study, we noted that the isomerization of **6** and **7** to **8** and **10**, respectively, occurred under a variety of basic conditions. Our results are summarized in Table 1. Conversion of **6** to **8** was complete within 3.5 h in the presence of 1 equiv TBAF. Conversion of **6** to **8** in the presence of stoichiometric sodium ethoxide proceeded at a much slower rate (complete conversion after ~20 h). Azepinone **7** bearing a C4 methyl group is generally more resistant to isomerization under the conditions we examined, and required much longer reaction times to achieve full conversion. Both **6** and **7** proved stable to acidic conditions; very little isomerization was observed upon treatment of **6** with PPTS or *p*-TsOH for several hours.[8] We have not observed conversion of **8** and **10** back to **6** and **7** under any conditions we have examined. It is also noteworthy that thermal isomerization of **6** or **7** does

Table 1
Isomerization of azepinones



Entry	Substrate	R	Reagent[a]	Conversion[b] (%)
1	6	H	TBAF[c]	100
2	7	CH_3	TBAF	100
3	6	H	NaOEt	100
4	7	CH_3	NaOEt	70
5	6	H	NEt_3[d]	50
6	7	CH_3	NEt_3[d]	<5
7	6	H	PPTS	15
8	7	CH_3	PPTS	0
9	6	H	TsOH	11[e]
10	7	CH_3	TsOH	0
11	6	H	TsOH[f]	20
12	7	CH_3	TsOH[f]	Decomp.

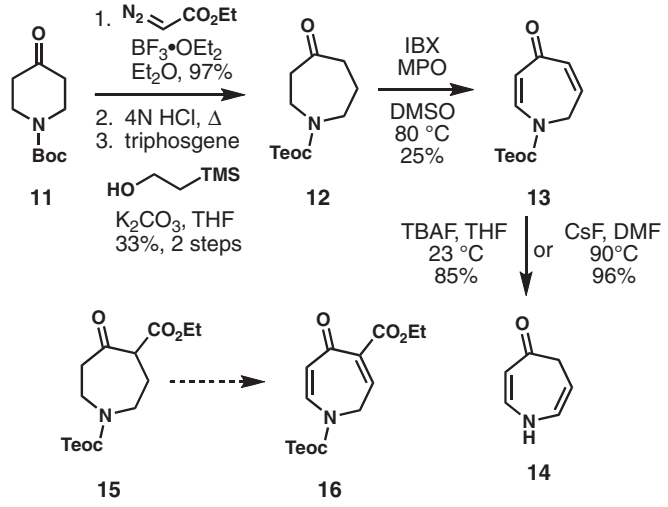
[a] Experiments conducted on 0.1 mmol scale in 1 mL THF with 1 equiv reagent. See Supplemental data for details.
[b] Determined by ^{1}H NMR analysis after 20 h reaction time.
[c] Determined by ^{1}H NMR analysis after 3.5 h reaction time.
[d] Two equivalent NEt_3 employed.
[e] Determined by ^{1}H NMR analysis after 15 h reaction time.
[f] Experiment conducted at 60 °C for 6 h.

not occur at an appreciable rate in the absence of base, though we did observe isomerization of **6** to **8** after prolonged storage on the bench at ambient temperature.

We chose to use the stability of the azepinones to acidic reaction conditions to our advantage to achieve our goal of a one-pot azepinone synthesis. While the cycloadducts are indeed isolable by careful column chromatography (see Supplementary data for details), we found that prolonged exposure to silica gel cleanly and efficiently induced the ring expansion.[9] After the cycloaddition was observed to be complete (TLC analysis) in our optimized procedure, silica gel was added directly to the crude reaction mixture. The resultant suspension was stirred at ambient temperature (23 °C) and then filtered to afford the 1*H*-azepin-5(2*H*)-one **6** in good yield (45%) as a single isomer (determined by ^{1}H NMR analysis of the crude product). This strategy worked well for the cycloaddition-ring expansion sequence of both 1-methoxy-3-trimethylsilyloxybutadiene and 1-methoxy-3-trimethylsilyloxypenta-1,3-diene[3a,10] with ethyl 2*H*-azirine-3-carboxylate.

We reasoned that removing the C3-carboxylate might affect the position of the double bond. To that end, we prepared the azepanone **12**[11] (Scheme 3) from the commercially available *N*-Boc-4-piperidone (**11**). We were able to introduce the desired unsaturation via oxidation of **12** with 2-iodoxybenzoic acid (IBX) in the presence of 4-methoxypyridine *N*-oxide to afford the azepinone **13**.[12] However, treatment of this substrate with either of two different fluoride sources induced complete isomerization of the double bond in addition to removal of the 2-(trimethylsilyl)ethyl carbamate protecting group to give azepinone **14**. The C3–C4 double bond isomer was not detected. We prepared the corresponding azepanone-4-carboxylate **15** utilizing the same strategy but we were unable to introduce the desired unsaturation selectively to give **16**.

In summary, we have developed an efficient one-pot preparation of 1*H*-azepin-5(2*H*)-ones and noted an unexpectedly facile isomerization of the C3–C4 double bond to C2–C3. The isomerization occurs readily under basic reaction conditions, regardless of substitution, and appears to be irreversible. We are currently studying the synthesis of new azepinones with a variety of substitution patterns, the effects of basic and acidic reaction conditions,



Scheme 3. Preparation of azepinones by unsaturation.

and the use of azepinones as nucleophiles at nitrogen and at carbon. These studies will be disclosed in due course.

Acknowledgments

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Supplementary data

Supplementary data (detailed experimental procedures and spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.003.

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5. The thermal electrocyclic ring closure of vinyl azides to azirines is often accompanied by dimerization to give pyrroles, polymerization, and other unproductive decomposition. Generating the azirine quickly at high temperature and high dilution minimizes these issues and provides material sufficient for use without further purification or isolation.
6. 4-Methoxy-3-buten-2-one is present in small amounts in either commercially available or freshly prepared 1-methoxy-3-trimethylsilyloxybutadiene, and is undoubtedly produced upon treatment of our crude reaction mixtures with TBAF.
7. Treatment of either the azepinones **6** or **8** with 4-methoxy-3-buten-2-one in the presence of TBAF produces Michael adduct **9** in only trace amounts. Formation of this side product is completely suppressed by employing the azirine in excess and the diene as limiting reagent in the cycloaddition reaction.
8. Direct treatment of the cycloadducts with *p*-TsOH resulted in ring opening products incorporating tosylate. See Supplementary data. An analogous reaction was reported with hydrochloric acid. See Ref. 2c
9. Silica gel is mentioned once in the discussion of a prior report as inducing the desired transformation, but no experimental procedure was provided. See Ref. 2d. *General procedure for the one-pot cycloaddition-ring expansion—ethyl 5-oxo-2,5-dihydro-1H-azepine-3-carboxylate* (**6**)*:* A solution of ethyl 2-azidoacrylate.[2b,4] (1.41 g, 10.0 mmol, 1 equiv) in dichloromethane (150 mL, 0.07 M) was heated to 150 °C in a sealed tube for 75 min, then was cooled to 23 °C whereupon 1-methoxy-3-trimethylsilyloxybutadiene.[3] (1.30 g, 7.50 mmol, 0.75 equiv) was added. The resultant orange solution was heated to 80 °C for 40 min, then was cooled to 23 °C whereupon 10 g silica gel was added. The resultant suspension was stirred at 23 °C for 18 h, then was filtered. The silica gel was washed with ethyl acetate (2 × 30 mL) and the combined filtrates were concentrated. The residue was purified by flash column chromatography (50% ethyl acetate–hexanes) to give the azepinone **6** (610 mg, 45% yield) as a yellow semisolid. TLC (ethyl acetate): R_f = 0.23 (UV, $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.13 (d, J = 2.0 Hz, 1H), 7.07 (dd, J_1 = 8.1 Hz, J_2 = 6.8 Hz, 1H), 5.97 (br, 1H), 5.30 (d, J = 8.4 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 4.14 (d, J = 5.0 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 189.8, 165.7, 147.8, 142.1, 129.8, 104.6, 61.8, 42.7, 14.1. FTIR (NaCl, thin film), cm^{-1}: 3221, 2985, 1712, 1639. HRMS (EI$^+$): Calcd for $C_9H_{11}NO_3$ [M+H]$^+$: 181.0739. Found: 181.0736.
10. We prepared 1-methoxypent-1-en-3-one by a one-step procedure: Burger, M. T.; Still, W. C. *J. Org. Chem.* **1996**, *61*, 775–777.
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