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Reactions of azepinones with electrophiles

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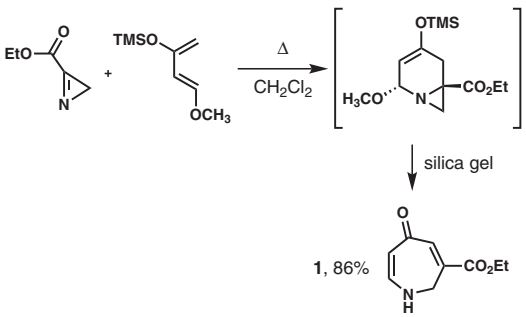
ABSTRACT

Azepinones are available via a one-pot cycloaddition-ring expansion reaction sequence in good yield. The reactions of azepinones with alkyl halides and epoxides were studied. We report herein protocols for the alkylation of azepinones at nitrogen with alkyl halides and epoxides and the isomerizations that occur in the presence of a base. We also report an unexpected ring contraction under oxidative conditions.

Azepinones are important heterocycles embedded in the structures of many biologically-relevant alkaloids, and can serve as intermediates in the synthesis of a variety of complex nitrogen-containing molecules. Thus, methods for the generation and manipulation of azepinones are of interest to the synthetic community.

We recently reported a one-pot synthesis of 1*H*-azepin-5(2*H*)-ones and noted their sensitivity to base;[1] 1*H*-azepin-5(2*H*)-ones undergo an unexpectedly facile isomerization to the corresponding 1*H*-azepin-5(4*H*)-ones under conditions that were previously described for their synthesis.[2] The 1*H*-azepin-5(2*H*)-ones are robust toward acid, an observation we used to our advantage in developing an efficient synthetic protocol. The 1*H*-azepin-5(2*H*)-one **1** is obtained in high yield in a one-pot procedure via the cycloaddition of Danishefsky's diene[3] to 2*H*-azirine-3-carboxylate ethyl ester,[2] followed by a ring expansion in the presence of silica gel (Scheme 1). The previously described synthetic protocol[3] for azepinones of this type is problematic due to base-induced isomerizations of the desired products, however, this issue is completely avoided by employing the one-pot reaction sequence. During the course of our studies, we demonstrated that bases as mild as fluoride anion (conjugate acid HF pK_a ~3 in water) are sufficient to induce the undesired (and effectively irreversible) isomerization, so we anticipated that transformations as trivial as alkylation of azepinones at nitrogen would be problematic. We report herein conditions for the further elaboration of 1*H*-azepin-5(2*H*)-ones and 1*H*-azepin-5(4*H*)-ones, and the unexpected reactivity of the alkylated azepinones toward oxidants.

In the absence of exogenous base, alkylation of 1*H*-azepin-5(2*H*)-one **1** at nitrogen with reactive electrophiles such as benzyl bromide does not proceed at any appreciable rate (Table 1, entry 1), even in the presence of mild amine bases (Table 1, entry 2). However, addition of sodium hydride is sufficient to induce alkylation (51% yield, Table 1, entry 3) at the cost of a significant amount of isomerization to give the corresponding *N*-benzyl-aze-



Scheme 1. One-pot preparation of 1*H*-azepin-5(2*H*)-ones.

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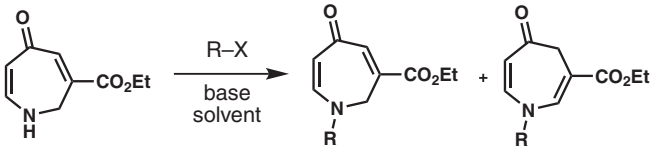
Table 1
Reaction of 1*H*-azepin-5(2*H*)-one **1** with alkyl halides



1 **2-5a** **2-5b**

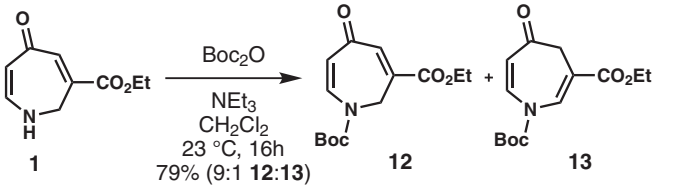
Entry	R–X	Base	Solvent	Temp (°C)	Product	Yield **a**/**b** (%)
1	BnBr	—	THF	66	**2**	—
2	BnBr	*i*-Pr_2NEt	THF	23	**2**	—
3	BnBr	NaH	THF	23	**2**	51/18
4	BnBr	LDA	THF	40	**2**	45/—
5	BnBr	K_2CO_3	DMSO	60	**2**	75/5
6	Allyl-Br	K_2CO_3	DMSO	60	**3**	70/6
7	*n*-BuBr	*i*-Pr_2NEt	THF	66	**4**	—
8	*n*-BuBr	*i*-Pr_2NEt	CH_2Cl_2	40	**4**	—
9	*n*-BuBr	K_2CO_3	THF	66	**4**	—
10	*n*-BuBr	K_2CO_3	DMSO	60	**4**	58/30
11	*i*-PrI	K_2CO_3	DMSO	60	**5**	21/26

Reactions were conducted at 0.07 M in the indicated solvent for 24 h, with 1.5 equiv alkyl halide and bases as follows: *i*-Pr_2NEt (1.3 equiv), NaH (1.3 equiv), LDA (1.1 equiv), K_2CO_3 (3 equiv).

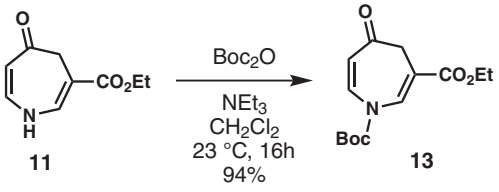
pin-5(4*H*)-one **2b** (18% yield). After some experimentation, we found that employing a more polar, aprotic solvent (DMSO) and employing solid potassium carbonate as the base cleanly afforded the desired *N*-benzyl-azepin-5(2*H*)-one **2a** (75% yield, Table 1, entry 5).[4] The isomeric alkylation product was barely detectable by ^{1}H NMR analysis of the crude product mixture. We found these conditions to be general; the 1*H*-azepin-5(2*H*)-one **1** undergoes alkylation with activated, unactivated, and even hindered unactivated electrophiles such as 2-iodopropane (Table 1, entries 6, 10, and 11), though less active electrophiles result in isomeric product mixtures. We have evidence to suggest that the *N*-alkyl-azepin-5(4*H*)-one products **2b**–**5b** arise via isomerization of the starting material followed by alkylation; exposure of *N*-alkyl-azepin-5(2*H*)-ones **2a**–**5a** to the alkylation reaction conditions for extended periods of time does not appear to induce any detectable isomerization.

We also found that 1*H*-azepin-5(2*H*)-ones are sufficiently nucleophilic to open terminal epoxides (Table 2). Again, the addition of exogenous base was necessary, with the DMSO/K_2CO_3 reaction conditions proving most efficient (Table 2, entries 6, 7, and 9). Unfortunately, we found that the epoxide opening reactions gave *N*-alkyl-azepin-5(4*H*)-ones exclusively, presumably due to the presence of alkoxide intermediates. We attempted several epoxide opening reactions under typical acidic conditions in order to avoid this issue, with little success (e.g., Table 2, entries 1–3).

We examined analogous alkylation and epoxide opening reactions using the isomeric 1*H*-azepin-5(4*H*)-one **11** and found that it is also a competent nitrogen nucleophile (Table 3). We have also been able to acylate both azepinone isomers efficiently to afford the corresponding *N*-Boc compounds in high yield (Eqs. 1 and 2).

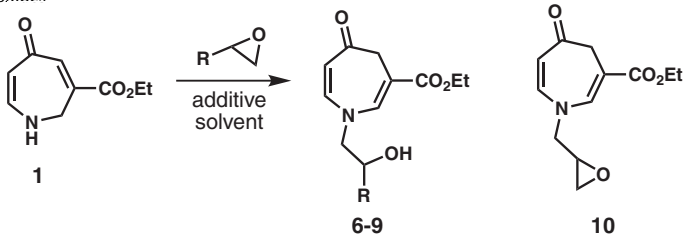


(1)



(2)

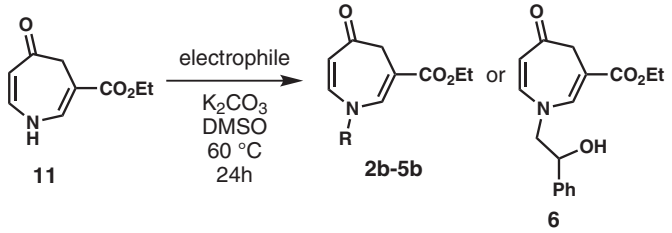
Table 2
Reaction of 1*H*-azepin-5(2*H*)-one **1** with epoxides



Entry	Epoxide	Additive	Solvent	Temp (°C)	Product	Yield (%)
1	Ph	$TsOH·H_2O$	CH_2Cl_2	23→40	**6**	—
2	Ph	$BF_3·OEt_2$	CH_2Cl_2	23→40	**6**	—
3	Ph	—	CH_2Cl_2	23→40	**6**	—
4	Ph	NaH	THF	66	**6**	—
5	Ph	K_2CO_3	THF	66	**6**	37
6	Ph	K_2CO_3	DMSO	60	**6**	65
7	*n*-Hex	K_2CO_3	DMSO	60	**7**	19
8		K_2CO_3	DMSO	60	**8**	—
9	Cl	K_2CO_3	DMSO	60	**9**	34 (17% **10**)

Reactions were conducted at 0.07 M in the indicated solvent for 24 h, with 1.5 equiv epoxide and additives as follows: $TsOH·H_2O$ (0.1 equiv), $BF_3·OEt_2$ (0.2 equiv), $Yb(OTf)_3$ (0.1 equiv), NaH (1.1 equiv), K_2CO_3 (3 equiv).

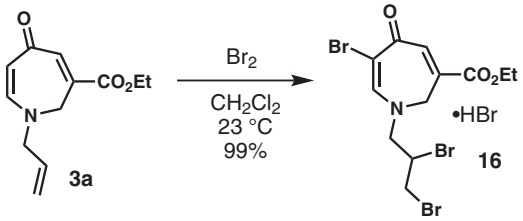
Table 3
Reaction of 1*H*-azepin-5(4*H*)-one **11** with alkyl halides and epoxides



Entry	Electrophile	Product	Yield (%)
1	BnBr	**2b**	98
2	Allyl bromide	**3b**	87
3	*n*-BuBr	**4b**	87
4	*i*-PrI	**5b**	57
5		**6**	62

Reactions were conducted at 0.07 M for 24 h with 1.5 equiv electrophile and 3 equiv K_2CO_3.

We attempted to further elaborate the *N*-alkyl azepinones as part of our studies in total synthesis and made some surprising observations. For example, we observed no oxidation of the *N*-allyl azepinone **3a** upon treatment with osmium tetroxide (up to 10 mol %) and *N*-methylmorpholine *N*-oxide (NMO) even after a prolonged reaction time. We also treated **3a** with *m*-chloroperbenzoic acid (*m*CPBA) in the presence of sodium bicarbonate in aqueous dichloromethane in an attempt to obtain the epoxide, but we were surprised to observe clean formation of the ring-contracted product, the *N*-allyl 2-pyrrolidinone **14** in 75% yield, with no evidence of epoxidation of the allyl sidechain (Scheme 2). No epoxide formation was observed even in the presence of excess *m*CPBA. The *N*-benzyl azepinone **2a** undergoes an analogous transformation as well upon treatment with *m*CPBA.[5] We are in the process of elucidating the mechanism of this reaction, however, to date we have not isolated or rigorously characterized any intermediates. We propose the ring contraction proceeds via epoxidation of the vinylogous amide, followed by a ring closure to give a hemiaminal (see Scheme 2). Isomerization of the hemiaminal epoxide moiety and ring-opening affords an epoxy aldehyde that can undergo attack by water and retro-aldol to give a 2-pyrrolidinone. Isomerization of the double bond leads to the observed product. We have not been successful in observing or isolating any glyoxaldehyde that might lend support to this proposed mechanism. We noted that the *N*-alkyl 1*H*-azepin-5(4*H*)-ones (**2b** and **3b**) do not undergo this ring contraction in the presence of *m*CPBA, presumably due to the decreased nucleophilicity of the isomeric vinylogous amide. This might suggest that the isomerization of the double bond occurs after formation of 2-pyrrolidinone if the reaction proceeds by the proposed mechanism.



(3)

We have also observed that treatment of the *N*-allyl 1*H*-azepin-5(2*H*)-one **3a** with molecular bromine affords a tribrominated product **16** in which the allyl sidechain and the vinylogous amide have both undergone electrophilic attack (Eq. 3). This tribrominated product dominates regardless of the stoichiometry of bromine, but is formed cleanly and in good yield when 2 equiv of bromine is employed. This result may lend some support to our proposed mechanism above wherein the vinylogous amide acts as a carbon nucleophile but is by no means conclusive.

We have developed conditions for the alkylation of 1*H*-azepin-5(2*H*)-ones with alkyl halides with minimal isomerization to the corresponding 1*H*-azepin-5(4*H*)-ones. Analogous alkylations with terminal epoxides afford 1*H*-azepin-5(4*H*)-one products exclusively, presumably due to basic alkoxides in the reaction mixtures. We have documented the unexpected nucleophilicity of the vinylogous amide moiety of the azepinones, and an unexpected ring contraction of *N*-alkyl 1*H*-azepin-5(2*H*)-ones in the presence of an oxidizing peracid. We are continuing to study the unusual behavior and synthetic potential of these important heterocycles, and we are working toward rigorously establishing the mechanism of the *m*CPBA-induced oxidative ring contraction.

Acknowledgments

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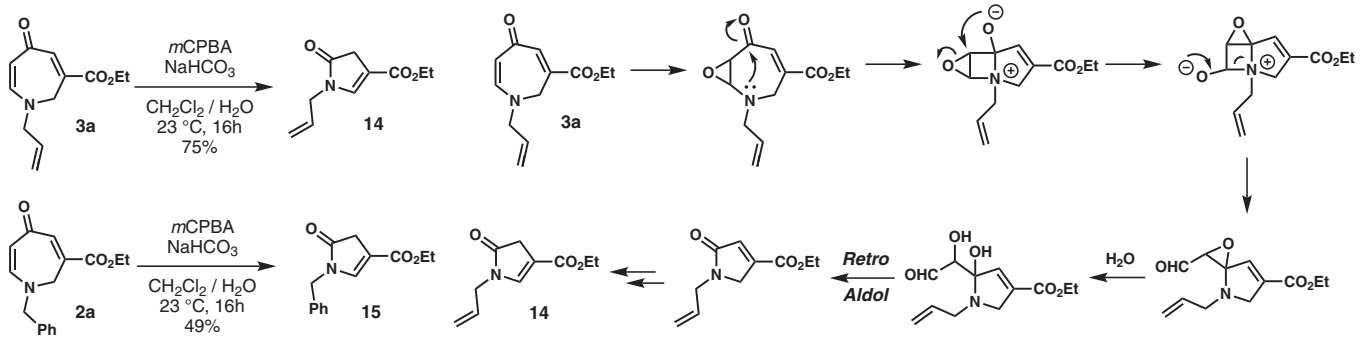
Supplementary data

Supplementary data (detailed experimental procedures, spectral data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.091.



Scheme 2. An unexpected oxidative ring contraction.

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4. General procedure for alkylation and epoxide opening reactions with azepinone **1**: anhydrous potassium carbonate (207 mg, 1.50 mmol, 3.00 equiv) and an electrophile (0.75 mmol, 1.50 equiv) were added sequentially to a stirred solution of azepinone **1** (91 mg, 0.50 mmol, 1 equiv) in 7 mL dimethylsulfoxide (0.07 M) at 23 °C. The resultant suspension was placed in an oil bath preheated to 60 °C and stirred at that temperature for 24 h, then was cooled and partitioned between saturated aqueous sodium chloride solution (20 mL) and ethyl acetate (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and the dried solution was concentrated. The residue was purified by flash column chromatography (80% ethyl acetate–hexanes) to afford the alkylated product.
5. The ring contraction occurs with or without the inclusion of sodium bicarbonate.