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Reaction of 2-Methoxy-3*H*-azepine with NBS: Efficient Synthesis of 2-Substituted 2*H*-Azepines

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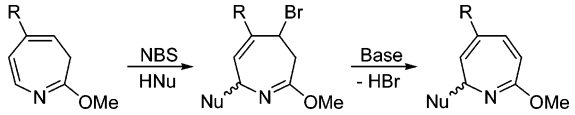


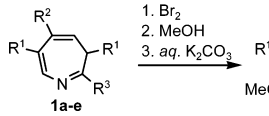
The reaction of 2-methoxy-3*H*-azepines, in the presence or absence of a nucleophile, with *N*-bromosuccinimide (NBS) gave a regioselective 1,4-adduct from which the corresponding 2*H*-azepine derivatives were formed via base-promoted hydrogen bromide elimination, generally in moderate to quantitative yield. Competitive formation of 4-bromo-2-methoxy-3*H*-azepine by electrophilic substitutuion or 3*H*-azepin-2-yl 2*H*-azepin-2-yl ether by transetherification was minimized at lower reaction temperatures. Quantitative substitution of 2-(2′,4′,6′-trichlorophenoxy)-2*H*-azepine derivatives, formed in moderate yield from the respective 3*H*-azepine and NBS in the presence of 2,4,6-trichlorophenol (TCP), by various nucleophiles gave the corresponding 2-substituted 2*H*-azepine. Among these nucleophiles were alkanethiol and alkylamine that are not tolerated in the reaction of 3*H*-azepine and NBS.

Introduction

Synthesis of 2*H*-azepine derivatives as naturally occurring alkaloids[1] was initiated upon isolation of chalciporone and norchalciporyl propionate.[2] As well, synthetic value of 2*H*-azepine has been generated from the purpose of studying the characteristic thermal [1,5]-hydrogen shift to the more thermally stable 3*H*-azepine,[3] which consequently provides a challenge in synthesis.[1] Recently 2-methoxy-2*H*-azepine derivatives have also been realized as an indispensable precursor in the synthesis of azatropylium ions in solution by demethoxylation using $TiCl_4$.[4]

In previous work, from the more thermally stable 3*H*-azepine substrates, we reported the first synthesis of 2*H*-azepines where 2,7-dimethoxy-2*H*-azepines **2a**−**c** were formed specifically by adding methanol to the reaction mixture of the corresponding 2-methoxy-3*H*-azepines **1a**−**c**[5] and bromine followed by workup with aq alkaline (Scheme 1).[6] Similar treatment of 2,5- and 3,6-di-*tert*-butyl-3*H*-azepines (**1d**,**e**)[3a] also gave 2-methoxy-2*H*-azepines **2d**,**e**, respectively.[7] Formation of 2-methoxy-2*H*-azepine can be paralleled to trapping tropylium bromide,

SCHEME 1. Conversion of 3*H*-Azepine to 2*H*-Azepine with Bromine



	yield (%)
a: R^1 = R^2 = H, R^3 = OMe	46
b: R^1 = H, R^2 = ^{t}Bu, R^3 = OMe	52
c: R^1 = H, R^2 = Me, R^3 = OMe	30
d: R^1 = ^{t}Bu, R^2 = R^3 = H	43
e: R^1 = H, R^2 = R^3 = ^{t}Bu	52

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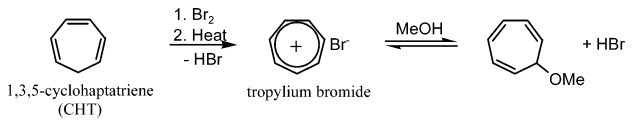
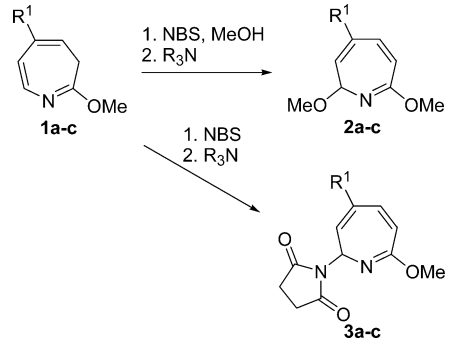
SCHEME 2. Formation and Substitution of Tropylium



SCHEME 3. Conversion of 3*H*-Azepine to 2*H*-Azepine with NBS



formed from bromine and 1,3,5-cycloheptatriene (CHT),[8] with methanol[9] (Scheme 2). Regioselective substitution at the C2 position by methanol has been predicted based on frontier molecular orbital consideration of the interaction between a nucleophile and the previously hypothesized azepinium ion intermediates, for which the π-LUMO coefficients were largest at the C2 position.[3,7] While azatropylium is theoretically predicted to be a relatively stable aromatic cation,[10] azepine is expected to be more susceptible to oxidation than CHT leading to azatropylium because of an electronegative nitrogen atom in the triene conjugation.[11]

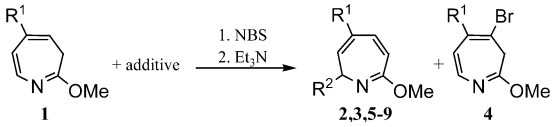
Although the reaction conditions are similar to those of CHT and bromine, even in situ by NMR spectral measurement of the reaction mixture, evidence of an azepinium ion intermediate has not been observed. To explore the reaction mechanism including the reason for regioselective introduction of the methoxy group at the C2 position, attempts were made to determine the structure of any reaction products without adding methanol to the 3*H*-azepine and NBS reaction mixture prior to and after treatment with alkaline.[6]

Results and Discussion

Reaction of 3*H*-Azepine and NBS. An alternative attempt to understand the mechanism of the previously reported 3*H*-azepine to 2*H*-azepine conversion in Scheme 1[6,7] by replacing bromine with NBS (Scheme 3) resulted in quantitative conversion of 3*H*-azepines **1a**,**b** to 2-methoxy-2*H*-azepines **2a**,**b** (Table 1, entries 8 and 9). Reaction of **1c** in the presence of methanol produced both 2-methoxy-2*H*-azepine **2c** in 66% yield and 2-succinimido-2*H*-azepine **3c** in 33% yield (Table 1, entry 10). In the absence of methanol (Scheme 3) reaction of 3*H*-azepines **1a**−**c** efficiently gave 2-succinimido-2*H*-azepines **3a**−**c** in 81%, quantitative, and 73% yield, respectively (Table 1, entries 1, 3, and 4). Formation of **3a** and **3c** was accompanied by formation of the corresponding regioselectively brominated products, 4-bromo-2-methoxy-3*H*-azepine (**4a**) in 19% yield and 4-bromo-2-methoxy-5-methyl-3*H*-azepine (**4c**) in 22% yield, for which the MS and NMR spectral data of each supports the structure. Replacing bromine with NBS led to a new efficient method for converting 3*H*-azepine to 2*H*-azepine.[6] In contrast to the conversion with bromine, the chemoselectivity of NBS as well as a significantly lower concentration of HBr in the reaction environment are factors attributable to improved yields. Results for the conversion of **1a**−**c** in the presence of other nucleophiles are listed in Table 1.

In the presence of methylamine or diethylamine the starting material was almost completely recovered with no evidence of 2-amino-2*H*-azepine formation. In the presence of *N*-methylacetamide both succinimide and amide substituted products **3a**,**b** and **5a**,**b** were formed (Table 1, entries 6 and 7). Similar to *N*,*N*-dimethylacetamide,[12] due to restricted rotation about the C−N bonds, at room temperature the 2-(*N*-methylacetamido)-

TABLE 1. Conversion of 3*H*-Azepine to 2-Substituted 2*H*-Azepine with NBS[a]



entry	starting compd	reaction temp (°C)	additive	R^1	R^3	product	yield (%)
1	**1a**	−41	none	H	$C_4H_4O_2N$	**3a**	81
				H		**4a**	19
2	**1a**	25	none	H	$C_4H_4O_2N$	**3a**	27
				H		**4a**	68
3	**1b**	−98	none	^{t}Bu	$C_4H_4O_2N$	**3b**	100
4	**1c**	−98	none	Me	$C_4H_4O_2N$	**3c**	73
				Me		**4c**	22
5	**1c**	25	none	Me	$C_4H_4O_2N$	**3c**	
				Me		**4c**	97
6	**1a**	−41	AcNHMe	H	AcNMe	**5a**	53
				H	$C_4H_4O_2N$	**3a**	37
7	**1b**	−98	AcNHMe	^{t}Bu	AcNMe	**5b**	77
	1a	−41		^{t}Bu	$C_4H_4O_2N$	**3b**	21
8			MeOH	H	MeO	**2a**	99
9	**1b**	−98	MeOH	^{t}Bu	MeO	**2b**	100
10	**1c**	−98	MeOH	Me	MeO	**2c**	66
				Me	$C_6H_2O_2N$	**3c**	33
11	**1b**	−98	^{t}BuOH	^{t}Bu	^{t}BuO	**6**	91
12	**1a**	−41	TCP	H	$C_6H_2Cl_3O$	**7a**	47
13	**1b**	−98	TCP	^{t}Bu	$C_6H_2Cl_3O$	**7b**	64
14	**1a**	−41	AcOH	H	AcO	**8**	80
15	**1a**	−41	PrSH	H		**1a**	74
				H	PrS	**9a**	21
16	**1b**	−98	PrSH	^{t}Bu		**1b**	>95
17	**1c**	−98	PrSH	Me		**1c**	>95

[a] Reactions of 3*H*-azepine (1 mmol), an additive (2 mmol), and NBS (1.1 mmol) were carried out in CH_2Cl_2 under a nitrogen atmosphere at the specified temperature for 10 h, then an excess of triethylamine was introduced, and the solution was stirred at room temperature for 5 h. Yields are based on the crude isolated products.

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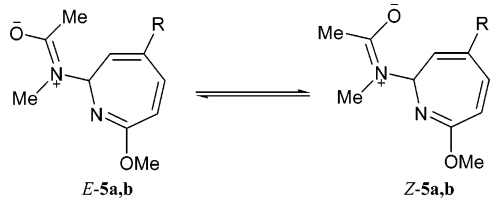


FIGURE 1. The *E* and *Z* structures of **5** observed in the NMR spectra due to restricted rotation about the amide C−N bond.

2*H*-azepines **5a** and **5b** were respectively found to exist in 55:45 and 58:42 molar ratios of *Z* and *E* conformers (Figure 1) for which chemical exchange was confirmed by observation of positive signals in the 2D NOESY spectra between corresponding proton signals. Assignment of the signals to the corresponding isomer in the ^{1}H and ^{13}C NMR spectrum of the isomeric mixture was accomplished with ^{1}H−^{1}H COSY, HMQC, and HMBC techniques. *Z* and *E* geometry was concluded based on the difference in peak width and relative chemical shift of the *N*-methyl NMR signals (*Z*-**5a**: δ_H 3.18, $\omega_{1/2} = 1.32 \pm 0.24$ Hz; *E*-**5a**: δ_H 3.11, $\omega_{1/2} = 1.90 \pm 0.24$ Hz; *Z*-**5b**: δ_H 3.21, $\omega_{1/2} = 1.53 \pm 0.24$ Hz; *E*-**5b**: δ_H 3.14, $\omega_{1/2} = 1.95 \pm 0.24$ Hz) due to cis and trans long-range coupling and anisotropic shift due to shielding by the C=O bond in comparison to dimethylacetamide.[12]

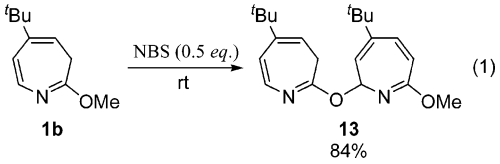
Similar to the conversion in the presence of methanol, even in the presence of sterically hindered *tert*-butyl alcohol or 2,4,6-trichlorophenol (TCP), which is a comparatively weak nucleophile, the corresponding 2-*tert*-butoxy-2*H*-azepine **6** and 2-TCP-2*H*-azepines **7a**,**b** (Table 1, entries 11, 12, and 13) were formed in good and moderate yields. Use of TCP as an example of a phenol derivative in this reaction was 2-fold. First, TCP is relatively resistant to bromination whereas unsubstituted phenols react competitively with NBS under the reaction conditions to give complex mixtures of brominated phenol derivatives and unreacted 3*H*-azepine. Second, based on the results of Table 1, oxygen nucleophiles generally react efficiently under these conditions, thus although the TCP group is a relatively weak nucleophile TCP should nonetheless react to give the corresponding 2*H*-azepine. Unfortunately due to the exceptional ability of TCP as a leaving group, isolation of **7a**,**b** by the standard procedure of extracting byproducts with water (triethylammonium bromide) and aqueous base (succinimide) led to hydrolysis of **7a**,**b** and attempted isolation by medium-pressure liquid chromatography (MPLC) on silica gel or alumina even at 0 °C led to complete decomposition. Although separation of **7a**,**b** from **3a**,**b**, triethylammonium bromide and succinimide was accomplished to a good degree by extraction of **7a**,**b** from the crude reaction mixture with hexane, triethylammonium trichlorophenoxide and **7a**,**b** could not be completely separated thus characterization was limited to NMR and MS spectroscopy.

2-Acetoxy-7-methoxy-2*H*-azepine **8** was formed in good yield from **1a** in the presence of acetic acid (Table 1, entry 14). Similar to the TCP derivatives, the acetoxy group was also easily substituted by stronger nucleophiles. Attempts to isolate the acetoxy derivatives from the reaction mixtures of **1b** and **1c** in the presence of acetic acid failed but by qualitative analysis of the ^{1}H NMR spectra of the crude reaction mixtures, the corresponding 2-acetoxy-2*H*-azepines were formed in moderate yield. Although a large loss through decomposition on silica gel occurred, pure **8** was isolated by MPLC at 0 °C.

In the presence of propane thiol, NBS favorably reacted with propane thiol to give propyl disulfide as the major product along with the unreacted starting material. Despite reaction of 3*H*-azepine being the minor reaction pathway, the 2-propylthio-2*H*-azepine **9a** was nonetheless formed in low yield from **1a** although no 2-propylthio-2*H*-azepine was isolated from the reaction of **1b** or **1c** (Table 1, entries 15, 16, and 17).

The reaction temperatures were determined by maximization of monocyclic 2*H*-azepine formation, which were also found to be the minimum temperatures at which the 3*H*-azepines would react within a reasonable amount of time. Predominance of **4a** increased in the reaction of **1a** and NBS as the temperature increased from −41 °C, and at room temperature **3a** and **4a** were formed in 27% and 68% yields, respectively (Table 1, entry 2). Reaction of **1c** and NBS at room temperature gave 4-bromo-2-methoxy-5-methyl-3*H*-azepine (**4c**) in near quantitative yield (Table 1, entry 5). Unexpected formation of bisazepinyl ethers **10**−**12** from the reaction of **1b** and NBS occurred at temperatures above −63 °C and became predominant above 0 °C. The temperature-dependent product distribution is summarized in Table 2. Although not discussed here, it should be noted that the product distribution is also dependent on the solvent system. Generally a 0.1−0.3 M solution of 3*H*-azepine in dichloromethane gave good results.

Reaction of **1b** and NBS in a 2:1 molar ratio at room temperature (eq 1) gave 5-*tert*-butyl-3*H*-azepin-2-yl 4-*tert*-



butyl-7-methoxy-2*H*-azepin-2-yl ether (**13**) in 84% yield. Peculiar formation of bisazepinyl ethers is an unprecedented transesterification of the imidate oxygen in **1b**, replacing the methyl group with a 2*H*-azepinyl group or vice versa substitution of a 2*H*-azepine at C2 by the oxygen of a 2-methoxy-3*H*-azepine. There are no parallel transesterifications or transetherifications of any form that have been reported in the literature to our knowledge and out of the 3*H*-azepines examined here, only **1b** led to formation of bisazepinyl ethers.

Structure Determination of Bisazepinyl Ethers. The structure of bisazepinyl ether **13** was substantiated by MS (FAB) *m/z* 343 $(M + H)^+$. The structures of each ring linked by oxygen were determined to be a 5-*tert*-butyl-3*H*-azepin-2-yl and a 4-*tert*-butyl-7-methoxy-2*H*-azepin-2-yl group based on ^{1}H and ^{13}C NMR spectral data, which shows nearly superimposable signals to those of **1b** and **2b** in the region of olefinic ring protons. Structures of **10**−**12** were concluded similarly.

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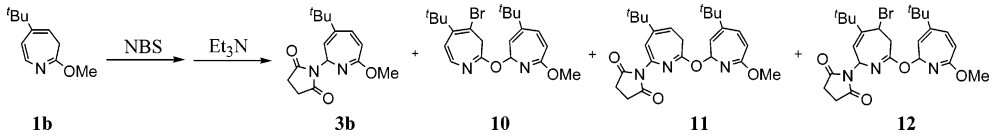
TABLE 2. Temperature-Dependent Product Distribution of the Reaction of 1b and NBS[a]



temp (°C)	time (h)	crude yield (%) 3b	10	11	12
−98	10	95			
−63	8	89	2		
−23	6	66	13	5	7
−13	6	62	15	5	9
0	5	27	22	6	15
5	4	18	23	7	40
rt	2	10	25	10	43
40	0.5	5	58	3	28

[a] Reactions of **1b** (1 mmol) and NBS (1.1 mmol) were carried out in CH_2Cl_2. Yields were determined based on the ^1H NMR spectra of the reaction mixture.

Two isomers of **12** were separated by MPLC on silica gel. The NMR spectra and incapacity for chemical exchange suggests they are stereoisomers. Although clear evidence is insufficient, the cis and trans geometry of the bromine atom and succinimido group in the two isomers was estimated by comparing GIAO chemical shift calculation[13] (HF/6-311+G (2d,p)) results based on the optimized cis and trans structures (B3LYP/6-31G*)[14] of **14b** (Figure 2a,b), calculated using the Gaussian98[15] program, with the ^1H NMR spectra of **12** (Figure 2c,d). The assignments were made based on the extreme variation in chemical shift of the C2 proton on the adduct ring, observed in both the experimental spectral data (7.40 and 6.74 ppm) and theoretically calculated spectral values (6.94 and 6.18 ppm for trans and cis **14b**). The exceptionally low field shift of the C2 proton resonating at 7.40 ppm and that estimated to resonate at 6.94 ppm in the calculated trans structure can be expected from contact deshielding by the bromine atom[16] on C5. Close proximity of the C2 proton and the C5 bromine atom is predicted for the trans structure (2.770 Å). Thus by consideration of this theoretical and experimental coherence, assignment of the stereoisomer with the proton resonating at 7.40 ppm to the trans adduct and that resonating at 6.74 ppm to the cis adduct was made. Calculated chemical shifts for C2 protons of the optimized structures of cis and trans **14b** and observed chemical shifts for the stereoisomers of **12** are shown in Figure 2.

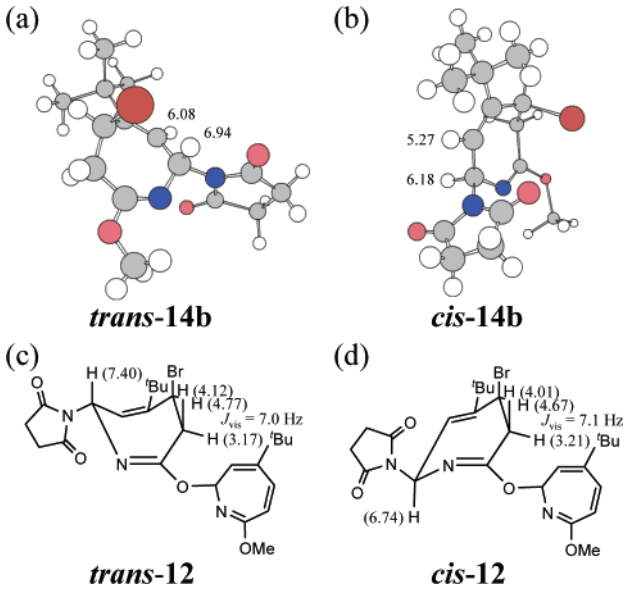


FIGURE 2. A comparison of the calculated chemical shifts (HF/6-311+G (2d,p)) of the optimized structures (B3LYP/6-31G*) of the (a) trans and (b) cis 1,4-adducts of **14b** with the chemical shifts of the stereoisomers of **12** (c and d). Chemical shift values are expressed in ppm.

1,4-Addition of NBS. The reaction intermediates responsible for this conversion were elucidated by NMR observation of the reaction product(s) of 3*H*-azepine and NBS in the presence or absence of methanol. Regioselective formation of NBS 1,4-adduct 5-bromo-5,6-dihydro-2-succinimido-2*H*-azepines **14a**,**b** was confirmed by signals corresponding to a single compound with coupling constants that distinguish the ring structure (**14a**: J_{2-3} = 2.7 Hz, J_{3-4} = 11.7 Hz, J_{4-5} = 2.7 Hz, J_{5-6} = 4.9 Hz, $J_{5-6'}$ = 12.5 Hz, $J_{6,gem}$ = 13.7 Hz; and **14b**: J_{2-3} = 3.4 Hz, J_{5-6} = 3.7 Hz, $J_{5-6'}$ = 4.0 Hz, $J_{6,gem}$ = 18.6 Hz) in the NMR spectral data upon completion of the reaction of 3*H*-azepines **1a**,**b** with NBS in CD_2Cl_2 (Table 3, entries 1 and 2) and observation of the $(M + H)^+$ signal in the FAB-MS and FAB-HRMS spectra of the crude reaction mixtures. In the presence of methanol regioselective formation of bromomethoxy 1,4-adduct 5-bromo-5,6-dihydro-2-methoxy-2*H*-azepines **15a**,**b** was similarly con-

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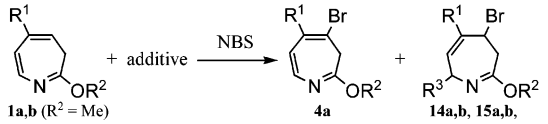
(16) Yonemoto, T. *Can. J. Chem.* **1966**, *44*, 223−231.

TABLE 3. 1,4-Addition of Bromine and a Nucleophile to 3*H*-Azepines[a]

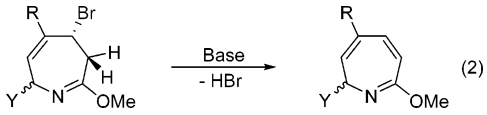


entry	starting compd	reaction temp (°C)	additive	R^1	R^3	product	yield (%)
1	**1a**	−41		H		**4a**	20
				H	$C_4H_4O_2N$	**14a**	80
2	**1b**	−98		*t*Bu	$C_4H_4O_2N$	**14b**	100
3	**1a**	−41	MeOH	H	MeO	**15a**	99
4	**1b**	−98	MeOH	*t*Bu	MeO	**15b**	100
5	**13**	0		*t*Bu		**10**	1
				*t*Bu	$C_4H_4O_2N$	**12**	88
6	**13**	0	MeOH	*t*Bu	MeO	**16**	100

[a] Reactions of 3*H*-azepine (1 mmol), an additive (2 mmol), and NBS (1 mmol) were carried out in CD_2Cl_2. Yields were determined based on the ^{1}H NMR spectra of the reaction mixture.

firmed (Table 3, entries 3 and 4, **15a**: $J_{2-3} = 2.2$ Hz, $J_{3-4} = 11.8$ Hz, $J_{4-5} = 4.9$ Hz, $J_{5-6} = 3.4$ Hz, $J_{5-6'} = 12.0$ Hz, $J_{6,gem} = 13.4$ Hz; and **15b**: $J_{2-3} = 3.1$ Hz, $J_{5-6} = 3.7$ Hz, $J_{5-6'} = 4.0$ Hz, $J_{6,gem} = 18.9$ Hz). Upon precipitation from acetone 1,4-adduct **14b** was stable and pure enough for complete spectroscopic characterization but unfortunately, due to instability, clear observation of **14a**, **15a**, and **15b** was limited to the crude reaction mixture within a few hours of formation. Complete ^{1}H and ^{13}C NMR spectral data of adducts **14a**,**b** and **15a**,**b** were attained for which assignment of the signals to the structures was accomplished by using HMQC and ^{1}H−^{1}H COSY techniques (Table 4). Similarity between the calculated ^{1}H NMR shifts for the trans structure of **14b** opposed to the cis structure (Figure 2a,b) and the ^{1}H NMR spectra of **14b** (Table 4), in particular at the C2 proton (δ 7.00 ppm), suggests **14b** is the trans adduct, which was also predicted to be more stable than the cis adduct by 0.0049 au (3.1 kcal/mol) by comparison of the B3LYP/6-31G*[14] optimized structures. Electrophilic addition of bromine occurred selectively at C4 with concurrent nucleophilic addition selectively at C7 of the 3*H*-azepine ring. Formation of other stereoisomers has not been observed.

The 1,4-adducts **14b**, **15a**, and **15b** were quantitatively formed as sole products but **14a** was formed along with **4a** in a 4 to 1 molar ratio (Table 3, entries 1−4), which is the same molar ratio as **3a** to **4a** suggesting competition between 1,4-addition and electrophilic substitution. Treatment of the 1,4-adducts with triethylamine gave quantitative conversion to the respective 2*H*-azepines and triethylamine hydrobromide via 1,2-elimination of HBr (eq 2). Although there are examples of ionic 1,4-

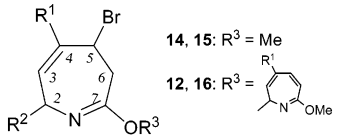


addition of bromine and a nucleophile in the literature,[17] this is the first report of ionic 1,4-addition of NBS to a conjugated diene to give the 1-bromo-4-succinimido adduct as far as we know. Typical yields of 1,4-addition to 1,3-butadiene derivatives using NBS in the presence of water, alcohol, or carboxylic acid are around 50%.[17] In comparison to other π-electron-rich conjugated dienes, the 1,3-butadiene function in the 3*H*-azepine ring shows exceptionally high reactivity and reaction regioselectivity. The reasons for the difference are not yet fully understood but it is thought to be due to the rigid geometry of the conjugated imino-diene structure in the azepine ring.

Reaction of Bisazepinyl Ether 13 with NBS. There are two unique features of bisazepinyl ethers. One, a molecule possessing both a 2*H*- and a 3*H*-azepine ring provides a system where the relative reactivity of both isomers can be compared. The other, the steric effect from close proximity of two azepine rings renders bisazepinyl ethers thermally stable relative to the monoring analogues. Consequences of the thermal stability are observed in the 1,5-hydrogen isomerization rate of the 2*H*-ring of **13** ($\tau_{1/2} = 2150$ min at 80 °C) compared to **2b** ($\tau_{1/2} = 210$ min at 80 °C) and in the NMR signals for the C3 methylene protons at room temperature of the 3*H*-ring of **13**, 2.62 (1H, dd) and 3.16 ppm (1H, dd), show distinct geminal coupling ($J_{gem} = 12.2$ Hz) compared to **1b**, 2.59 ppm, (2H, d). The latter implies the ring inversion of the 3*H*-azepine moiety of **13** is sterically hindered. The thermal stability of **13** afforded an opportunity for isolation and examination of stable 1,4-adducts of the 3*H*-azepine ring.

Reaction of **13** and NBS at 0 °C gave a <1% yield of **10** and a 88% yield of a 24:76 molar ratio of *trans*- and *cis*-**12**. The 1,4-adduct **16** was formed quantitatively in

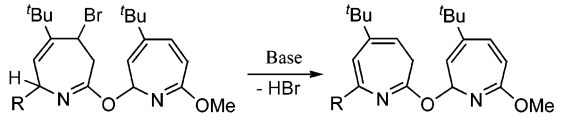
TABLE 4. NMR Resonances of 1,4-Adducts[a]



compd	R1	R2	C2	C3	C4	C5	C6	H2	H3	H4	H5	H6ax	H6eq
14a	H	$C_4H_4O_2N$	62.0	131.3	131.7	42.0	40.8	6.45	5.90	5.75	4.90	3.05	3.56
14b	*t*Bu	$C_4H_4O_2N$	60.5	129.2	149.1	41.9	39.7	7.00	5.84		4.85	3.05	3.16
15a	H	MeO	86.4	134.6	131.1	42.6	40.8	5.44	5.76	5.80	4.81	3.08	3.33
15b	*t*Bu	MeO	84.8	133.4	147.9	43.1	40.3	5.75	5.86		4.86	3.03	3.09
syn−**12**	*t*Bu	$C_4H_4O_2N$	62.7	121.5	151.8	39.8	47.0	6.74	5.53		4.76	4.01	3.21
anti−**12**	*t*Bu	$C_4H_4O_2N$	61.0	121.6	150.8	40.1	47.0	7.40	5.37		4.77	4.12	3.17
16	*t*Bu	MeO	80.4	124.8	152.9	42.3	44.2	5.65	6.10		4.83	3.95	2.95
16	*t*Bu	MeO	82.7	124.7	152.1	41.8	44.8	5.59	6.06		4.79	3.81	2.89

[a] Resonance values are displayed in ppm.

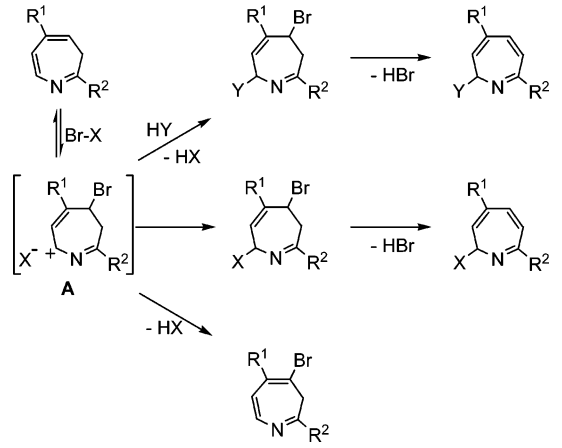
TABLE 5. 1,4-Elimination of HBr from the 1,4-Adducts 12 and 13[a]



entry	substrate	R	product	yield (%)
1	**12**	$C_4H_4O_2N$	**11**	92
2	**16**	MeO	**17**	68

[a] Yields are based on isolated products.

SCHEME 4. Conversion Mechanism



the presence of methanol again as a mixture of two stereoisomers in a 1:4 molar ratio (Table 3, entries 5 and 6). Treatment of adduct **12** with DBU and **16** with Bu_4-NOH did not afford the corresponding 2*H*-azepines by 1,2-elimination of hydrogen bromide but instead the substituted 3*H*-azepines **11** and **17** by 1,4-elimination (Table 5). Elimination occurred at room temperature, ruling out the likelihood of 1,5-hydrogen shift[3] of a 2*H*-azepine intermediate. Logically, 1,4-elimination as opposed to 1,2-elimination is a consequence of steric interference at C6 by the azepinoxy substituent at C7 of the dihydroazepine ring.

Conversion Mechanism of 3*H*-Azepine to 2-Substituted-2*H*-azepine. The reaction system for the conversion of 3*H*-azepine to 2*H*-azepine in Scheme 4 was concluded by observation of regioselective 1,4-addition of electrophilic bromine to C4 and a nucleophile to C7 of the 3*H*-azepine ring followed by 1,2-elimination of HBr. The regioselectivity of C4 toward electrophilic attack can be explained in terms of the resulting intermediate cation stability. Figure 3 shows the theoretical stabilities calculated by AM1[18] and ab initio (B3LYP/6-31G*) methods[14] for the cations potentially formed from 3*H*-azepine. Concurrent with the experimental result, the cation in Figure 3c is the most stable, which clearly supports the proposed mechanism. The largest LUMO coefficient in the intermediate cation A, shown in Figure 4, is on the carbon that was C7 of the parent 3*H*-azepine and therefore concurs with the experimental result that this is the most reactive location toward a nucleophile. Theoretical agreement with unambiguous experimental results provides strong evidence that the 3*H*- to 2*H*-azepine conversion mechanism is electrophilic + nucleophilic 1,4-addition followed by 1,2-elimination. Competition of electrophilic substitution by bromine selectively at C4 with regioselective 1,4-addition and the observation that 4-bromo-2-methoxy-3*H*-azepines are not formed from 1,4-adducts under the reaction conditions further suggest the conjugated cation intermediate **A** that is common to both reaction pathways, proposed in Scheme 4, as the first reaction intermediate. Similarly, the observation that methanol does not displace the succinimide moiety of 1,4-adducts **14a**,**b** also supports the reaction pathway via cation intermediate **A**. Although the methoxy moiety in the conjugation is expected to enhance reactivity and regioselectivity by π-electron donation to the conjugation, 2-alkyl-substituted 3*H*-azepines (i.e. **1d**,**e**) show similar regioselectivity[7] suggesting the reactivity is general.

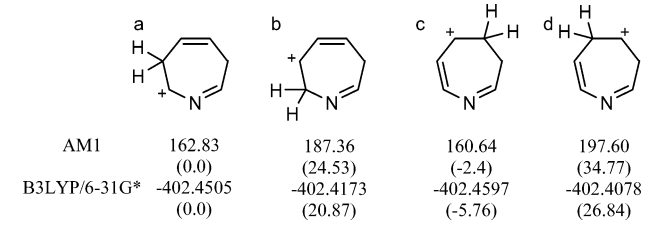


FIGURE 3. Relative stabilities of dihydroazepinium isomers, representative of the cation intermediate **A**, arising from electrophilic attack on the available positions of the 3*H*-azepine ring. AM1 energies are in kcal/mol and B3LYP/6-31G* energies are in au.

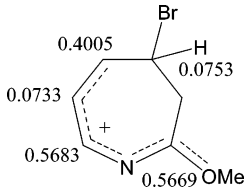


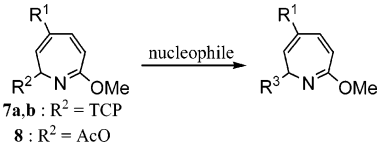
FIGURE 4. LUMO coefficients of the proposed reaction intermediate **A** for R^1 = H, R^2 = OMe calculated by AM1.[18]

The formation mechanism of bisazepinyl ethers from **1b** remains unclear. A likely mechanism could be nucleophilic attack of the oxygen lone pair electrons of one azepine molecule on the initially formed conjugated cation intermediate **A** that was proposed in Scheme 4. Removal of the methyl group from the new ether link may occur via bromide substitution to give methyl bromide. Careful observation of the ^{1}H NMR spectrum of the reaction mixture arising from **1b** and NBS at room temperature suggests formation of methyl bromide by a singlet peak at 2.57 ppm. At higher temperatures formation of bisazepinyl ether from **1b**, as opposed to electrophilic bromination observed with **1a** and **1c**, can most reasonably be considered due to steric interaction between the C4 position and the *tert*-butyl group in the conjugated cation intermediate **A**.

(17) (a) Konya, N.; Seko, S. Eur. Patent 1072589 (20010131), 2001. (b) Van, T. N.; Kimpe, N. *Tetrahedron* **2000**, *56*, 7969−7973. (c) Deagostino, A.; Tivola, P. B.; Prandi, C.; Venturello, P. *Synlett* **1999**, 1841−1843. (d) Wakamatsu, K.; Kigoshi, H.; Niiyama, K.; Niwa, H.; Yamada, K. *Tetrahedron* **1986**, *42*, 5551−5558. (e) Pearson, A. J.; Ray, T. *Tetrahedron Lett.* **1986**, *27*, 3111−3114.

(18) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909.

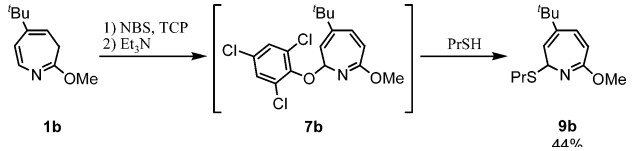
TABLE 6. Nucleophilic Substitution of 2-TCP- and 2-AcO-2*H*-Azepines[a]



entry	starting compd	reaction time at 30 °C	half-life	nucleophile	R^1	R^3	product	yield (%)
1	**7b**	5 h	3 min	$PrNH_2$	^{t}Bu	PrNH	**18**	100
2	**7a**	30 min	45 s	MeOH	H	MeO	**2a**	100
3	**8**	10 h	10 min	MeOH	H	MeO	**2a**	100
4	**7b**	30 min	35 s	MeOH	^{t}Bu	MeO	**2b**	100
5	**7b**	25 h0	36 min	^{t}BuOH	^{t}Bu	^{t}BuO	**6**	100
6	**7a**	25 h	14 min	AcOH	H	AcO	**8**	37
7	**7a**	25 h	260 min	PrSH	H	PrS	**9a**	100
8	**8**	25 h	90 min	PrSH	H	PrS	**9a**	100
9	**7b**	25 h	8 min	PrSH	^{t}Bu	PrS	**9b**	100

[a] Reactions were carried out in $CDCl_3$ with the specified nucleophile in excess of 2*H*-azepine. Reaction times were determined by the time required for change in the ^{1}H NMR spectra of the reaction mixture to become unobservable. Half-life values were extrapolated from the time-dependent ^{1}H NMR spectra. Yields were determined based on the ^{1}H NMR spectra of the reaction mixture.

SCHEME 5. Substitution via 2-TCP-2*H*-Azepine



Nucleophilic Substitution of 7a,b and 8. TCP is best known for its function as a leaving group in peroxyoxalate chemiluminescent reactions.[19] Similarly, as a substituent on the azepine ring, TCP also functioned as a good leaving group. 2-TCP-2*H*-azepines **7a**,**b** were quantitatively *ipso*-substituted by various nucleophiles to give the corresponding 2*H*-azepines (Table 6). Among the nucleophiles that successfully substituted the TCP group were propylamine and propane thiol, which failed to react efficiently under the 3*H*-azepine to 2*H*-azepine conversion protocol. An efficient sequential one-pot synthesis of 2-propylthio-2*H*-azepine **9b** using the TCP derivative as an intermediate was developed (Scheme 5), which extends the range of nucleophiles that can be substituted into the 2 position of the 2*H*-azepine ring. In this process most of the TCP is recovered and can be reused.

The kinetic properties, mechanism, and range of the substitution reaction of, as well as thermal properties of, **7** and **8** will be examined in detail in future papers. Substitution of 2-TCP-2*H*-azepines by carbon nucleophiles will also be investigated.

Conclusions. Improved efficiency in the conversion of 3*H*-azepines to 2*H*-azepines was accomplished by the use of NBS for which a variety of nucleophiles were substituted at the 2 position. For nucleophiles not tolerated by NBS, indirect substitution was effected with TCP. The alcohol, carboxylic acid, phenol, amide, amine, and sulfide nucleophiles examined here represent general examples of oxygen, nitrogen, and sulfur nucleophiles, thus elucidating the flexibility of one aspect of this novel reaction. This reaction may be general to a variety of 3*H*-azepine derivatives providing an efficient method for generating thermally less stable 2*H*-azepine derivatives.

(19) (a) Stevani, C. V.; Silva, S. M.; Baader, W. J. *Eur. J. Org. Chem.* **2000**, 4037−4046. (b) Rauhut, M. M. *Acc. Chem. Res.* **1969**, *2*, 80−87.

Experimental Section

2-Methoxy-3*H*-azepines **1a** and **1b** were prepared according to the established method[5] and structures were confirmed by identical ^{1}H NMR spectra to those previously reported.

2-Methoxy-5-methyl-3*H*-azepine (1c). 4-Nitrotoluene (30.0 g, 219 mmol), tri-*n*-butylphosphine (97.4 g, 481 mmol), and 50 mL of methanol were heated in an autoclave at 150 °C for 25 h. Excess methanol was then removed and the reaction mixture distilled. The fraction from 24 to 26 °C at 4 Torr contained **1c** (18.3 g, 61%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81 (3H, s), 2.51 (2H, d, J = 6.5 Hz), 3.65 (3H, s), 5.01 (1H, td, J = 6.5, 1.0 Hz), 5.82 (1H, dd, J = 8.5, 1.0 Hz), 6.81 (1H, d, J = 8.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.9 (q), 32.6 (t), 54.2 (q), 113.1 (d), 118.0 (d), 135.8 (s), 136.6 (d), 153.5 (s). IR (film) ν_{max} 1626, 1545, 1439, 1251, 1197, 1025 cm^{-1}; UV−vis (EtOH) λ_{max} 257 nm (log ϵ 3.68); MS (FAB) *m/z* 138 $(M + H)^+$. Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.58; H, 8.07; N, 10.20.

General Procedure A for Conversion of 3*H*-Azepines to 2*H*-Azepines with Use of NBS. NBS (0−10% molar excess) was dropped into a solution of 2-methoxy-3*H*-azepine **1** and an additive (200−500% molar excess) in CH_2Cl_2 (0.1−0.3 M solution of **1**) stirred under a nitrogen atmosphere at the specified reaction temperature then the solution was stirred at the specified reaction temperature for 10 h before triethylamine or dimethylethylamine (300% molar excess) was introduced and then the solution was then stirred at room temperature for 5 h, unless otherwise specified. Volatile components were then removed under reduced pressure then the remaining material was redissolved in CH_2Cl_2, washed once with water then twice with aq K_2CO_3, then dried over $MgSO_4$. Volatile components were then removed under reduced pressure.

General Procedure B for Conversion of 3*H*-Azepines to 2*H*-Azepines with Use of NBS. NBS (0−10% molar excess) was dropped into a solution of 2-methoxy-3*H*-azepine **1** and an additive (200−500% molar excess) in CH_2Cl_2 (0.1−0.3 M solution of 1) stirred under a nitrogen atmosphere at the specified reaction temperature then the solution was stirred at the specified reaction temperature for 10 h before triethylamine or dimethylethylamine (300% molar excess) was introduced with additional stirring at room temperature for 5 h. Volatile components were then removed under reduced pressure and the soluble 2*H*-azepine derivatives were extracted from the remaining material with hexane.

Reaction of 1a at −41 °C. According to procedure A, NBS (400 mg, 2.25 mmol) was reacted with **1a** (250 mg, 2.03 mmol) at −41 °C, which gave a mixture of **3a** and **4a**. Hexane extraction of the residue gave **4a** (79 mg, 19%) as a brown oil. The remaining insoluble **3a** (360 mg, 81%) upon recrystallization from AcOEt and hexane gave colorless prisms. Purification of **4a** performed by medium-pressure liquid chromatography (MPLC) on ICN 32-63 silica gel at 0 °C eluted by 1:9 v/v AcOEt−hexane gave a colorless oil (70 mg, 17%).

7-Methoxy-2-succinimido-2*H*-azepine (3a): mp 169−170 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.78 (4H, s), 3.60 (3H, s), 5.35 (1H, dd, J = 4.6, 1.7 Hz), 6.20 (1H, ddd, J = 10.0, 5.3, 1.7 Hz), 6.23 (1H, dd, J = 10.0, 4.6 Hz), 6.52 (1H, d, J = 11.7 Hz), 6.75 (1H, dd, J = 11.7, 5.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.2 (t), 54.1 (q), 62.7 (d), 126.2 (d), 126.3 (d), 131.4 (d), 137.6 (d), 161.6 (s), 176.8 (s); IR (KBr) ν_{max} 1711, 1626, 1444, 1396, 1253, 1214, 1176 cm^{-1}; UV−vis (EtOH) λ_{max} 273 nm (log ϵ 2.82); MS (FAB) m/z 221 $(M + H)^+$. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.02; H, 5.54; N, 12.54.

4-Bromo-2-methoxy-3*H*-azepine (4a): colorless liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.10 (2H, s), 3.74 (3H, s), 5.76 (1H, dd, J = 8.1, 6.1 Hz), 6.50 (1H, d, J = 6.1 Hz), 6.94 (1H, d, J = 8.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 43.8 (t), 55.2 (q), 104.3 (s), 113.9 (d), 128.9 (d), 137.2 (d), 149.4 (s); IR (film) ν_{max} 1624, 1531, 1439, 1249, 1189, 1029 cm^{-1}; UV−vis (EtOH) λ_{max} 266 nm (log ϵ 3.84); MS (FAB) m/z 202 $(M + H)^+$; HRMS (FAB) m/z found 201.9883, calcd for C_7H_9NOBr $(M + H)^+$ 201.9868.

Reaction of 1a at 25 °C. According to procedure A, NBS (400 mg, 2.25 mmol) was reacted with **1a** (250 mg, 2.03 mmol) at 25 °C, which gave a mixture of **3a** and **4a**. Hexane extraction of the nonvolatile component gave **4a** (280 mg, 68%) as a brown oil. The remaining insoluble **3a** (120 mg, 27%) upon recrystallization from AcOEt and hexane gave colorless prisms. Purification of **4a** performed by MPLC on ICN 32-63 silica gel at 0 °C eluted by 1:9 v/v AcOEt−hexane gave a colorless oil (250 mg, 61%).

Reaction of 1b at −98 °C. According to procedure A, NBS (1.00 g, 5.62 mmol) was reacted with **1b** (1.00 g, 5.58 mmol) at −98 °C, which gave **3b** (1.54 g, 100%) as a slightly yellow solid. Recrystallization of **3b** from AcOEt and hexane gave colorless prisms.

4-*tert*-Butyl-7-methoxy-2-succinimido-2*H*-azepine (3b): mp 121−122 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (9H, s), 2.75 (4H, s), 3.58 (3H, s), 5.21 (1H, d, J = 5.2 Hz), 5.95 (1H, d, J = 5.2 Hz), 6.47 (1H, d, J = 12.4 Hz), 6.93 (1H, d, J = 12.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3 (t), 29.4 (q), 34.8 (s), 54.0 (q), 63.2 (d), 123.3 (d), 124.9 (d), 138.9 (d), 147.6 (s), 161.3 (s), 176.8 (s); IR (KBr) ν_{max} 1705, 1644, 1444, 1404, 1251, 1210, 1187 cm^{-1}; UV−vis (EtOH) λ_{max} 276 nm (log ϵ 3.18); MS (FAB) m/z 277 $(M + H)^+$. Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 65.26; H, 7.32; N, 10.02.

Temperature-Dependent Reaction of 1b. NBS (200 mg, 1.12 mmol) was reacted with **1b** (200 mg, 1.12 mmol) in CH_2Cl_2 at the temperature and for the length of time specified in Table 2. Volatile components were then removed. The crude yields given in Table 2 were measured based on the mass of the product mixture and component ratios determined by integration of the ^{1}H NMR spectra of the crude reaction mixtures. Yields were reconfirmed by comparison to a benzene internal standard in the ^{1}H NMR spectra. The products were isolated from the reaction mixtures by MPLC on ICN 32-63 silica gel at 0 °C eluted by 1:3 v/v AcOEt−hexane. Recrystallization of **10** from THF and hexane gave colorless plates. Recrystallization of **11** from hexane gave colorless plates. Recrystallization of *cis*-**12** from AcOEt and ether gave colorless plates. Recrystallization of *trans*-**12** from AcOEt and ether gave colorless plates.

4-Bromo-5-*tert*-butyl-3*H*-azepin-2-yl 4-*tert*-butyl-7-methoxy-2*H*-azepin-2-yl ether (10): colorless plates; mp 174−175 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (9H, s), 1.35 (9H, s), 3.28 (1H, d, J = 13.0 Hz), 3.53 (1H, d, J = 13.0 Hz), 3.66 (3H, s), 5.27 (1H, d, J = 5.0 Hz), 5.71 (1H, d, J = 5.0 Hz), 6.17 (1H, d, J = 9.2 Hz), 6.49 (1H, d, J = 11.8 Hz), 6.94 (1H, d, J = 11.8 Hz), 7.05 (1H, d, J = 9.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.3 (q), 29.3 (q), 34.7 (s), 36.0 (s), 51.4 (t), 53.8 (q), 65.3 (d), 107.1 (d), 118.3 (d), 124.7 (d), 126.4 (d), 127.2 (d), 139.0 (d), 142.7 (s), 146.9 (s), 160.4 (s), 165.5 (s); IR (KBr) ν_{max} 1676, 1639, 1446, 1390, 1367, 1270, 1249, 1183 cm^{-1}; UV−vis (EtOH) λ_{max} 264 nm (log ϵ 3.77); MS (FAB) m/z 421 $(M + 1)^+$. Anal. Calcd for $C_{21}H_{29}BrN_2O_2$: C, 59.86; H, 6.94; N, 6.65. Found: C, 59.87; H, 6.99; N, 6.45.

5-*tert*-Butyl-7-succinimido-3*H*-azepin-2-yl 4-*tert*-butyl-7-methoxy-2*H*-azepin-2-yl ether (11): colorless plates; mp 88−91 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.16 (9H, s), 2.70 (4H, br s), 2.98 (1H, ddd, J = 12.5, 5.6, 1.5 Hz), 3.31 (1H, dd, J = 12.5, 7.8 Hz), 3.57 (3H, s), 5.64 (1H, d, J = 5.6 Hz), 5.71 (1H, dd, J = 7.8, 5.6 Hz), 5.83 (1H, d, J = 5.6 Hz), 6.40 (1H, d, J = 1.5 Hz), 6.44 (1H, d, J = 12.0 Hz), 6.89 (1H, d, J = 12.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.0 (t), 28.9 (t), 29.4 (q), 29.6 (q), 34.6 (s), 34.9 (s), 37.4 (t), 53.5 (q), 65.8 (d), 120.2 (d), 124.5 (d), 125.0 (d), 125.6 (d), 128.3 (s), 139.4 (d), 146.6 (s), 146.8 (s), 160.8 (s), 171.5 (s), 174.4 (s), 175.6 (s); IR (KBr) ν_{max} 1719, 1686, 1630, 1446, 1379, 1321, 1251, 1189 cm^{-1}; UV−vis (EtOH) λ_{max} 254 nm (log ϵ 3.82); MS (FAB) m/z 440 $(M + H)^+$; HRMS (FAB) m/z found 440.2549, calcd for $C_{25}H_{34}N_3O_4$ $(M + H)^+$ 440.2549. Anal. Calcd for $C_{25}H_{33}N_3O_4$: C, 68.31; H, 7.57; N, 9.56. Found: C, 67.92; H, 7.40; N, 10.19.

***cis*-5-Bromo-4-*tert*-butyl-5,6-dihydro-2-succinimido-2*H*-azepin-7-yl 4-*tert*-butyl-7-methoxy-2*H*-azepin-2-yl ether (*cis*-12):** colorless plates; mp 124−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (9H, s), 1.20 (9H, s), 2.61−2.67 (2H, m), 2.68−2.74 (2H, m), 3.21 (1H, dd, J = 15.0, 7.1 Hz), 3.48 (3H, s), 4.01 (1H, dd, J = 15.0, 1.3 Hz), 4.76 (1H, d, J = 7.1 Hz), 5.53 (1H, dd, J = 5.8, 1.0 Hz), 5.74 (2H, s), 6.40 (1H, d, J = 11.9 Hz), 6.74 (1H, d, J = 5.8 Hz), 6.92 (1H, ddd, J = 11.9, 1.3, 1.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.3 (t), 29.6 (q), 29.7 (q), 34.8 (s), 37.0 (s), 39.8 (d), 47.0 (t), 53.2 (q), 62.7 (d), 68.7 (d), 121.5 (d), 124.1 (d), 127.7 (d), 139.1 (d), 146.7 (s), 151.8 (s), 160.2 (s), 172.8 (s), 176.0 (s); IR (KBr) ν_{max} 1702, 1669, 1634, 1452, 1328, 1265, 1201 cm^{-1}; UV−vis (EtOH) λ_{max} 262 nm (log ϵ 3.41); MS (FAB) m/z 520 $(M + H)^+$. Anal. Calcd for $C_{25}H_{34}BrN_3O_4$: C, 57.69; H, 6.58; N, 8.07. Found: C, 57.44; H, 6.62; N, 7.89.

***trans*-5-Bromo-4-*tert*-butyl-5,6-dihydro-2-succinimido-2*H*-azepin-7-yl 4-*tert*-butyl-7-methoxy-2*H*-azepin-2-yl ether (*trans*-12):** colorless plates; mp 145−146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.17 (9H, s), 2.67 (4H, s), 3.17 (1H, dd, J = 15.0, 7.0 Hz), 3.72 (3H, s), 4.12 (1H, dd, J = 15.0, 0.5 Hz), 4.77 (1H, d, J = 7.0 Hz), 5.23 (1H, d, J = 4.5 Hz), 5.37 (1H, dd, J = 5.0, 0.5 Hz), 5.40 (1H, d, J = 4.5 Hz), 6.42 (1H, d, J = 12.0 Hz), 6.91 (1H, d, J = 12.0 Hz), 7.40 (1H, d, J = 5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3 (t), 29.5 (q), 29.6 (q), 34.5 (s), 37.1 (s), 40.1 (d), 47.0 (t), 54.0 (q), 61.0 (d), 69.6 (d), 121.6 (d), 123.9 (d), 128.4 (d), 138.9 (d), 145.8 (s), 150.8 (s), 159.2 (s), 172.4 (s), 175.7 (s); IR (KBr) ν_{max} 1713, 1655, 1450, 1342, 1323, 1263, 1199 cm^{-1}; UV−vis (EtOH) λ_{max} 268 nm (log ϵ 3.29); MS (FAB) m/z 520 $(M + H)^+$. Anal. Calcd for $C_{25}H_{34}BrN_3O_4$: C, 57.69; H, 6.58; N, 8.07. Found: C, 57.30; H, 6.55; N, 7.83.

Reaction of 1c at −98 °C. According to procedure A, NBS (280 mg, 1.57 mmol) was reacted with **1c** (200 mg, 1.46 mmol) at −98 °C for 10 h, which gave a mixture of **3c** and **4c**. Separation of the reaction mixture by MPLC on silica gel at 0 °C eluted by 1:1 v/v AcOEt−hexane gave **3c** (250 mg, 73%) and **4c** (70 mg, 22%) as a colorless oil. Recrystallization of **3c** from AcOEt and hexane gave colorless prisms.

7-Methoxy-4-methyl-2-succinimido-2*H*-azepine (3c): colorless prisms; mp 134.5−135.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.87 (3H, s), 2.78 (4H, s), 3.61 (3H, s), 5.33 (1H, d, J = 5.1 Hz), 5.96 (1H, d, J = 5.1 Hz), 6.44 (1H, d, J = 11.7 Hz), 6.50 (1H, d, J = 11.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.7 (q), 28.2 (t), 54.0 (q), 62.8 (d), 124.9 (d), 127.1 (d), 135.2 (s), 141.1 (d), 161.3 (s), 176.8 (s); IR (KBr) ν_{max} 1702, 1628, 1446, 1390, 1253, 1205, 1160 cm^{-1}; UV−vis (EtOH) λ_{max} 282 nm (log ϵ

3.15); MS (FAB) *m/z* 315 $(M + H)^+$. Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.55; H, 6.02; N, 11.77.

4-Bromo-2-methoxy-5-methyl-3*H*-azepine (4c): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (3H, s), 3.12 (2H, s), 3.74 (3H, s), 5.83 (1H, d, J = 8.2 Hz), 6.84 (1H, d, J = 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1 (q), 43.7 (t), 55.0 (q), 102.4 (s), 117.6 (d), 133.9 (s), 136.3 (d), 151.5 (s); IR (film) ν_{max} 1618, 1535, 1439, 1259, 1191, 1027 cm^{-1}; UV−vis (EtOH) λ_{max} 261 nm (log ϵ 3.79); MS (FAB) *m/z* 216 $(M + H)^+$. Anal. Calcd for $C_8H_{10}BrNO$: C, 44.47; H, 4.66; N, 6.48. Found: C, 44.38; H, 4.48; N, 6.44.

Reaction of 1c at 25 °C. According to procedure A, NBS (280 mg, 1.57 mmol) was reacted with **1c** (200 mg, 1.46 mmol) at 25 °C for 1 h, which gave **4c** (305 mg, 97%) as a yellow oil. Purification of **4c** performed by MPLC on ICN 32-63 silica gel eluted by 1:9 v/v AcOEt−hexane gave a colorless oil (290 mg, 92%).

Reaction of 1a in the Presence of *N*-Methylacetamide. According to procedure A, NBS (800 mg, 4.49 mmol) was reacted with **1a** (500 mg, 4.06 mmol) in the presence of *N*-methylacetamide (600 mg, 8.21 mmol) at −41 °C, which gave a mixture of **3a**, **4a**, and **5a**. Separation of the reaction mixture by MPLC on alumina at 0 °C eluted by 1:1 v/v THF−hexane gave **3a** (330 mg, 37%), **4a** (60 mg, 7%), and **5a** (420 mg, 53%). Recrystallization of **5a** from AcOEt and hexane gave colorless prisms.

2-(*N*-Methylacetamido)-7-methoxy-2*H*-azepine (5a): colorless prisms; mp 69−70 °C.; *E*-**5a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.02 (3H, s), 3.10 (3H, s), 3.63 (3H, s), 4.84 (1H, d, J = 4.4 Hz), 5.90 (1H, dd, J = 9.8, 4.4 Hz), 6.15 (1H, dd, J = 9.8, 5.6 Hz), 6.54 (1H, d, J = 11.5 Hz), 6.75 (1H, dd, J = 11.5, 5.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7 (q), 28.6 (q), 53.7 (q), 70.0 (d), 125.9 (d), 126.3 (d), 133.4 (d), 137.6 (d), 160.0 (s), 170.1 (s). *Z*-**5a**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.12 (3H, s), 3.18 (3H, s), 3.62 (3H, s), 5.75 (1H, dd, J = 9.8, 4.4 Hz), 5.78 (1H, d, J = 4.4 Hz), 6.12 (1H, dd, J = 9.8, 5.6 Hz), 6.47 (1H, d, J = 11.5 Hz), 6.70 (1H, dd, J = 11.5, 5.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.3 (q), 31.1 (q), 53.6 (q), 64.8 (d), 126.0 (d), 126.2 (d), 133.9 (d), 137.7 (d), 160.2 (s), 170.9 (s); IR (KBr) ν_{max} 1653, 1630, 1446, 1404, 1265, 1241, 1226, 1201, 1052, 1011 cm^{-1}; UV−vis (EtOH) λ_{max} 276 nm (log ϵ 3.20); MS (FAB) *m/z* 195 $(M + H)^+$; HRMS (FAB) *m/z* found 195.1167, calcd for $C_{10}H_{15}N_2O_2$ $(M + H)^+$ 195.1134. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.88; H, 7.39; N, 14.36.

Reaction of 1b in the Presence of *N*-Methylacetamide. According to procedure A, NBS (540 mg, 3.03 mmol) was reacted with **1b** (500 mg, 2.79 mmol) in the presence of *N*-methylacetamide (410 mg, 5.61 mmol) at −98 °C, which gave a mixture of **3b** and **5b**. Separation of the reaction mixture by MPLC on alumina at 0 °C eluted by 1:1 v/v THF−hexane gave **3b** (160 mg, 21%) and **5b** (540 mg, 77%). Recrystallization of **5b** from AcOEt and hexane gave colorless prisms.

4-*tert*-Butyl-7-methoxy-2-(*N*-methylacetamido)-2*H*-azepine (5b): colorless prisms; mp 113−116 °C. *E*-**5b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.10 (9H, s), 2.01 (3H, s), 3.14 (3H, s), 3.64 (3H, s), 4.74 (1H, d, J = 4.6 Hz), 5.65 (1H, d, J = 4.6 Hz), 6.52 (1H, d, J = 12.0 Hz), 6.96 (1H, d, J = 12.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8 (q), 28.8 (q), 29.5 (q), 34.7 (s), 53.6 (q), 70.4 (d), 125.0 (d), 125.4 (d), 138.9 (d), 147.2 (s), 159.7 (s), 170.1 (s). *Z*-**5b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.08 (9H, s), 2.13 (3H, s), 3.21 (3H, s), 3.64 (3H, s), 5.51 (1H, d, J = 4.9 Hz), 5.70 (1H, d, J = 4.9 Hz), 6.46 (1H, d, J = 12.0 Hz), 6.91 (1H, d, J = 12.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.5 (q), 29.5 (q), 31.3 (q), 34.6 (s), 53.4 (q), 65.1 (d), 124.9 (d), 125.6 (d), 138.7 (d), 147.2 (s), 160.0 (s), 170.8 (s); IR (KBr) ν_{max} 1650, 1634, 1446, 1400, 1255, 1214, 1017, 996 cm^{-1}; UV−vis (EtOH) λ_{max} 278 nm (log ϵ = 3.14); MS (FAB) *m/z* 251 $(M + H)^+$. Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.09; H, 9.00; N, 11.27.

Reaction of 1a in the Presence of Methanol. According to procedure A, NBS (400 mg, 2.25 mmol) was reacted with **1a** (250 mg, 2.03 mmol) in the presence of methanol (165 μL, 4.07 mmol) at −41 °C, which gave **2a** (308 mg, 99%) as a yellow oil. Purification of **2a** performed by MPLC on ICN 32-63 silica gel at 0 °C eluted by 1:9 v/v AcOEt−hexane gave a colorless oil (250 mg, 80%).

2,7-Dimethoxy-2*H*-azepine (2a): colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.47 (3H, s), 3.68 (3H, s), 4.31 (1H, dd, J = 3.9, 1.7 Hz), 5.96 (1H, dd, J = 10.0, 3.9 Hz), 6.05 (1H, ddd, J = 10.0, 5.4, 1.7 Hz), 6.47 (1H, d, J = 11.5 Hz), 6.72 (1H, dd, J = 11.5, 5.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 53.7 (q), 54.7 (q), 87.4 (d), 124.0 (d), 125.6 (d), 135.6 (d), 138.1 (d), 158.9 (s); IR (film) ν_{max} 1634, 1448, 1251, 1207, 1125 cm^{-1}; UV−vis (EtOH) λ_{max} 274 nm (log ϵ 3.28); MS (EI) *m/z* 153 (M^+, 15). Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 61.76; H, 7.23; N, 9.07. Instability of **2a** results in unsatisfactory elemental analysis data.

Reaction of 1b in the Presence of Methanol. According to procedure A, NBS (1.07 g, 6.01 mmol) was reacted with **1b** (1.00 g, 5.58 mmol) in the presence of methanol (1.2 mL, 29.6 mmol) at −98 °C, which gave **2b** (1.17 g, 100%) as a slightly yellow solid. Recrystallization of **2b** from hexane gave colorless prisms.

4-*tert*-Butyl-2,7-dimethoxy-2*H*-azepine (2b): colorless prisms; mp 37−37.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (9H, s), 3.48 (3H, s), 3.71 (3H, s), 4.23 (1H, d, J = 3.8 Hz), 5.77 (1H, dd, J = 3.8, 1.2 Hz), 6.46 (1H, d, J = 12.4 Hz), 6.94 (1H, dd, J = 12.4, 1.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.5 (q), 34.5 (s), 53.6 (q), 54.8 (q), 87.9 (d), 124.5 (d), 128.1 (d), 139.2 (d), 145.1 (s), 158.6 (s); IR (KBr) ν_{max} 1640, 1448, 1261, 1199, 1112 cm^{-1}; UV−vis (EtOH) λ_{max} 276 nm (log ϵ 3.19); MS (FAB) *m/z* 210 $(M + H)^+$. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.87; H, 9.11; N, 6.56.

Reaction of 1c in the Presence of Methanol. According to procedure A, NBS (2.85 g, 16.0 mmol) was reacted with **1c** (2.00 g, 14.6 mmol) in the presence of methanol (0.94 g, 29.3 mmol) at −98 °C for 3 h, which gave a mixture of **2c** and **3c**. Hexane extraction of the residue gave **2c** (1.60 g, 66%) as a yellow solid that upon recrystallization from hexane gave colorless prisms. The remaining insoluble **3c** (1.12 g, 33%) upon recrystallization from AcOEt and hexane gave colorless prisms.

2,7-Dimethoxy-4-methyl-2*H*-azepine (2c): colorless prisms; mp 38.5−40.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (3H, s), 3.47 (3H, s), 3.71 (3H, s), 4.30 (1H, br d, J = 4.0 Hz), 5.71 (1H, br d, J = 4.0 Hz), 6.45 (1H, d, J = 11.5 Hz), 6.63 (1H, d, J = 11.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (q), 53.8 (q), 54.9 (q), 87.5 (d), 124.1 (d), 131.4 (d), 132.4 (s), 141.5 (d), 158.5 (s); IR (KBr) ν_{max} 1638, 1444, 1247, 1205, 1087 cm^{-1}; UV−vis (EtOH) λ_{max} 280 nm (log ϵ 3.08); MS (FAB) *m/z* 168 $(M + H)^+$. Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 63.87; H, 7.71; N, 8.68. Instability of **2c** results in unsatisfactory elemental analysis data.

Reaction of 1b in the Presence of *tert*-Butyl Alcohol. According to procedure A, NBS (540 mg, 3.03 mmol) was reacted with **1b** (500 mg, 2.79 mmol) in the presence of *tert*-butyl alcohol (410 mg, 5.53 mmol) at −98 °C, which gave a mixture of **3b** and **6**. Hexane extraction of the nonvolatile component gave **6** (640 mg, 91%) as a slightly yellow solid. The remaining insoluble **3b** (60 mg, 8%) upon recrystallization from AcOEt and hexane gave colorless prisms. Purification of **6** by MPLC on ICN 32-63 silica gel eluted by 1:9 v/v AcOEt−hexane gave a white solid (470 mg, 67%). Recrystallization of **6** from hexane gave colorless plates.

2-*tert*-Butoxy-4-*tert*-butyl-7-methoxy-2*H*-azepine (6): colorless prisms; mp 70.5−71.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.06 (9H, s), 1.24 (9H, s), 3.64 (3H, s), 4.47 (1H, d, J = 4.2 Hz), 5.71 (1H, dd, J = 4.2, 1.0 Hz), 6.44 (1H, d, J = 12.0 Hz), 6.91 (1H, dd, J = 12.0, 1.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.0 (q), 29.6 (q), 34.2 (s), 53.5 (q), 74.0 (s), 81.3 (d), 124.4 (d), 130.5 (d), 139.1 (d), 143.5 (s), 157.2 (s); IR (KBr) ν_{max} 1632, 1468, 1446, 1247, 1205, 1096 cm^{-1}; UV−vis (EtOH) λ_{max} 278 nm (log ϵ 3.22); MS (FAB) *m/z* 252 $(M + 1)^+$. Anal. Calcd for

$C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.51; H, 10.03; N, 5.77.

Reaction of 1a in the Presence of 2,4,6-Trichlorophenol. According to procedure B, NBS (760 mg, 4.27 mmol) was reacted with **1a** (500 mg, 4.06 mmol) in the presence of 2,4,6-trichlorophenol (1.50 g, 7.60 mmol) at −98 °C, which prior to extraction gave 3.88 g of a brown viscous oil that was estimated to contain **3a** (430 mg, 48%) and **7a** (610 mg, 47%) by the ^{1}H NMR spectrum. The remaining components of the oil were triethylammonium bromide, succinimide, and TCP. The 920 mg nonvolatile component from the hexane extract was estimated to contain **7a** (480 mg, 37%) determined by the ^{1}H NMR spectrum.

7-Methoxy-2-(2′,4′,6′-trichlorophenoxy)-2*H*-azepine (7a): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.53 (3H, s), 5.33 (1H, dd, J = 3.7, 2.0 Hz), 6.15 (1H, ddd, J = 10.0, 5.6, 2.0 Hz), 6.30 (1H, dd, J = 10.0, 3.7 Hz), 6.44 (1H, d, J = 11.5 Hz), 6.74 (1H, dd, J = 11.5, 5.6 Hz), 7.30 (2H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 53.9 (q), 89.1 (d), 124.3 (d), 125.6 (d), 128.4 (d), 129.4 (s), 131.2 (s), 134.7 (d), 138.3 (d), 148.4 (s), 158.2 (s); MS (FAB) *m/z* 317 $(M)^+$; HRMS (FAB) *m/z* found 316.9774, calcd for $C_{13}H_{10}NO_2Cl_3$ (M) 316.9777.

Reaction of 1b in the Presence of 2,4,6-Trichlorophenol. According to procedure B, NBS (540 mg, 3.03 mmol) was reacted with **1b** (500 mg, 2.79 mmol) in the presence of 2,4,6-trichlorophenol (1.10 g, 5.57 mmol) at −98 °C, which gave 1.65 g of an amber oil that was estimated to contain **3b** (50 mg, 6%) and **7b** (670 mg, 64%) by the ^{1}H NMR spectrum.

2-(2′,4′,6′-Trichlorophenoxy)-4-*tert*-butyl-7-methoxy-2*H*-azepine (7b): ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.13 (9H, s), 3.53 (3H, s), 5.20 (1H, d, J = 4.0 Hz), 6.10 (1H, dd, J = 4.0, 1.5 Hz), 6.41 (1H, d, J = 12.0 Hz), 6.94 (1H, dd, J = 12.0, 1.5 Hz), 7.29 (2H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.4 (q), 34.7 (s), 53.7 (q), 89.7 (d), 124.5 (d), 127.1 (d), 128.4 (d), 129.3 (s), 131.2 (s), 139.5 (d), 145.4 (s), 148.5 (s), 158.1 (s); MS (FAB) *m/z* 374 $(M + H)^+$.

Reaction of 1a in the Presence of Acetic Acid. According to procedure B, NBS (800 mg, 4.49 mmol) was reacted with **1a** (500 mg, 4.06 mmol) in the presence of acetic acid (490 mg, 8.16 mmol) at −41 °C, which gave a mixture of **3a** and **8**. Hexane extraction of the nonvolatile component gave **8** (590 mg, 80%) as a brown oil. Further purification of the hexane extract by MPLC on ICN 32-63 silica gel at 0 °C eluted by 1:4 v/v AcOEt−hexane gave **8** (380 mg, 52%) as a colorless oil. The remaining insoluble material was redissolved in CH_2Cl_2, washed once with water and twice with aq K_2CO_3, then dried over $MgSO_4$. Removal of the solvent gave **3a** (160 mg, 18%) as a brown solid that upon recrystallization from AcOEt and hexane gave colorless prisms. Throughout the procedure, care was taken not to expose **8** to temperatures above 20 °C.

2-Acetoxy-7-methoxy-2*H*-azepine (8): colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.12 (3H, s), 3.62 (3H, s), 5.66 (1H, dd, J = 4.2, 2.0 Hz), 5.89 (1H, dd, J = 10.0, 4.2 Hz), 6.08 (1H, ddd, J = 10.0, 5.4, 2.0 Hz), 6.48 (1H, d, J = 11.5 Hz), 6.72 (1H, dd, J = 11.5, 5.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3 (q), 53.9 (q), 81.5 (d), 124.6 (d), 126.1 (d), 133.6 (d), 138.0 (d), 159.2 (s), 170.2 (s); IR (film) ν_{max} 1744, 1634, 1446, 1253, 1203, 1044 cm^{-1}; UV−vis (EtOH) λ_{max} 271 nm (log ϵ 3.31); MS (FAB) *m/z* 182 $(M + H)^+$; HRMS (FAB) *m/z* found 182.0826, calcd for $C_9H_{12}NO_3$ $(M + H)^+$ 182.0817.

Reaction of 1a in the Presence of Propane Thiol. According to procedure A, NBS (800 mg, 4.49 mmol) was reacted with **1a** (500 mg, 4.06 mmol) in the presence of propane thiol (620 mg, 8.14 mmol) at −41 °C, which gave a mixture of unreacted **1a**, **9a**, and propyl disulfide. Separation of the reaction mixture by MPLC on ICN 32-63 silica gel at 0 °C eluted by 1:9 v/v AcOEt−hexane gave **1a** (370 mg, 3.00 mmol), **9a** (170 mg, 21%) as a colorless oil, and propyl disulfide (500 mg, 3.33 mmol).

7-Methoxy-2-propylthio-2*H*-azepine (9a): colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.99 (3H, dd, J = 7.6, 7.3 Hz), 1.65 (2H, m, J = 8.1, 7.8, 7.6, 7.3, 6.8, 6.6 Hz), 2.64 (1H, ddd, J = 12.7, 8.1, 6.8 Hz), 2.72 (1H, ddd, J = 12.7, 7.8, 6.6 Hz), 3.68 (3H, s), 4.54 (1H, d, J = 5.9 Hz), 5.90 (1H, dd, J = 9.8, 5.9 Hz), 6.13 (1H, dd, J = 9.8, 5.4 Hz), 6.48 (1H, d, J = 11.7 Hz), 6.70 (1H, dd, J = 11.7, 5.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.6 (q), 23.1 (t), 32.5 (t), 53.9 (q), 59.7 (d), 126.0 (d), 126.5 (d), 134.8 (d), 137.7 (d), 162.1 (s); IR (film) ν_{max} 1624, 1444, 1245, 1197 cm^{-1}; UV−vis (EtOH) λ_{max} 279 nm (log ϵ 3.15); MS (FAB) *m/z* 198 $(M + H)^+$; HRMS (FAB) *m/z* found 198.0919, calcd for $C_{10}H_{16}NOS$ $(M + 1)^+$ 198.0953. Anal. Calcd for $C_{10}H_{15}NOS$: C, 60.88; H, 7.66; N, 7.10. Found: C, 60.57; H, 7.18; N, 7.32.

Reaction of 1b in the Presence of Propane Thiol. According to procedure A, NBS (540 mg, 3.03 mmol) was reacted with **1b** (500 mg, 2.79 mmol) in the presence of propane thiol (420 mg, 5.51 mmol) at −98 °C, which gave a mixture of unreacted **1b** and propyl disulfide.

Reaction of 1c in the Presence of Propane Thiol. According to procedure A, NBS (710 mg, 3.99 mmol) was reacted with **1c** (500 mg, 3.64 mmol) in the presence of propane thiol (550 mg, 7.22 mmol) at −98 °C, which gave a mixture of unreacted **1c** and propyl disulfide.

General Procedure for Preparation of 1,4-Adducts of 3*H*-Azepines. NBS (2 mmol) was dropped into a solution of **1** (2 mmol) and additive (4 mmol) in CD_2Cl_2 (5 mL) stirred under a nitrogen atmosphere at the specified reaction temperature then the solution was stirred at the specified reaction temperature for 10 h. A portion of the solution was then transferred to an NMR sample tube for spectral analysis. Excess additive and CD_2Cl_2 were then removed. The nonvolatile component was then analyzed by FAB-MS and FAB-HRMS spectroscopy.

Preparation of 5-Bromo-5,6-dihydro-7-methoxy-2-succinimido-2*H*-azepine (14a). 14a was prepared from **1a** at −41 °C. ^{1}H NMR (600 MHz, CD_2Cl_2) δ 2.70 (4H, s), 3.05 (1H, ddd, J = 13.7, 4.9, 2.0 Hz), 3.56 (1H, dd, J = 13.7, 12.5 Hz), 3.57 (3H, s), 4.90 (1H, dddd, J = 12.5, 4.9, 3.2, 2.7 Hz), 5.75 (1H, ddd, J = 11.7, 2.7, 1.7 Hz), 5.90 (1H, dddd, J = 11.7, 3.2, 2.7, 2.0 Hz), 6.45 (1H, dt, J = 2.9, 2.7 Hz); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 29.9 (t), 40.8 (t), 42.0 (d), 53.9 (q), 62.0 (d), 131.3 (d), 131.7 (d), 163.1 (s), 176.6 (s).

Preparation of 5-Bromo-4-*tert*-butyl-5,6-dihydro-7-methoxy-2-succinimido-2*H*-azepine (14b). 14b was prepared from **1b** at −98 °C. Extraction of impurities and decomposition products from the residue with acetone gave insoluble **14b** as a colorless solid: mp 140−141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (9H, s), 2.76 (4H, s), 3.05 (1H, ddd, J = 18.6, 3.7, 2.8 Hz), 3.16 (1H, ddd, J = 18.6, 4.0, 2.8 Hz), 3.52 (3H, s), 4.85 (1H, ddd, J = 4.0, 3.7, 2.1 Hz), 5.84 (1H, dd, J = 3.4, 2.1 Hz), 7.00 (1H, dt, J = 3.4, 2.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0 (q), 28.3 (t), 37.1 (s), 39.7 (t), 41.9 (d), 52.7 (q), 60.5 (d), 129.2 (d), 149.1 (s), 158.5 (s), 176.2 (s); IR (KBr) ν_{max} 1711, 1692, 1400, 1373. 1207, 1187 cm^{-1}; UV−vis (*n*-hexane) λ_{max} 222 nm (log ϵ 3.41); MS (FAB) *m/z* 357 $(M + H)^+$; HRMS (FAB) *m/z* found 357.0853, calcd for $C_{15}H_{22}BrN_2O_3$ $(M + H)^+$ 357.0814.

Preparation of 5-Bromo-5,6-dihydro-2,7-dimethoxy-2*H*-azepine (15a). 15a was prepared from **1a** in the presence of methanol at −41 °C. ^{1}H NMR (600 MHz, CD_2Cl_2) δ 3.08 (1H, dd, J = 13.4, 3.4 Hz), 3.33 (1H, dd, J = 13.4, 12.0 Hz), 3.36 (3H, s), 3.69 (3H, s), 4.81 (1H, ddddd, J = 12.0, 4.9, 4.4, 3.4, 1.2 Hz), 5.44 (1H, dd, J = 4.4, 2.2 Hz), 5.76 (1H, ddd, J = 11.8, 2.2, 1.2 Hz), 5.80 (1H, dd, J = 11.8, 4.9 Hz); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 40.8 (t), 42.6 (d), 53.4 (q), 54.5 (q), 86.4 (d), 131.1 (d), 134.6 (d), 161.2 (s); MS (FAB) *m/z* 234 $(M + H)^+$; HRMS (FAB) *m/z* found 234.0091, calcd for $C_8H_{13}NO_2Br$ $(M + H)^+$ 234.0130.

Preparation of 5-Bromo-4-*tert*-butyl-5,6-dihydro-2,7-dimethoxy-2*H*-azepine (15b). 15b was prepared from **1b** in the presence of methanol at −98 °C. ^{1}H NMR (500 MHz, CD_2-

Cl_2) δ 1.09 (9H, s), 3.03 (1H, ddd, J = 18.9, 3.7, 2.7 Hz), 3.09 (1H, ddd, J = 18.9, 4.0, 2.4 Hz), 3.48 (3H, s), 3.61 (3H, s), 4.86 (1H, ddd, J = 4.0, 3.7, 2.1 Hz), 5.75 (1H, ddd, J = 3.1, 2.7, 2.4 Hz), 5.86 (1H, dd, J = 3.1, 2.1 Hz); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 28.2 (q), 37.0 (s), 40.3 (t), 43.1 (d), 52.5 (q), 54.6 (q), 84.8 (d), 133.4 (d), 147.9 (s), 162.1 (s).

Reaction of 1b with 0.5 equiv of NBS. NBS (100 mg, 0.56 mmol) was dropped into a solution of 2-methoxy-3*H*-azepine **1b** (200 mg, 1.12 mmol) in CH_2Cl_2 (10 mL) stirred under a nitrogen atmosphere at room temperature then the solution was stirred for 5 h at room temperature before treatment with aq K_2CO_3. The organic phase was separated and dried over $MgSO_4$. Separation of the reaction mixture by MPLC on Woelm 32-63 silica gel eluted with 1:4 v/v AcOEt−hexane at 0 °C gave unreacted **1b** (50 mg, 0.28 mmol) and **13** (120 mg, 63%, 84% yield based on converted **1b**). Recrystallization of **13** from AcOEt and hexane gave colorless plates.

5-*tert*-Butyl-3*H*-azepin-2-yl 4-*tert*-butyl-7-methoxy-2*H*-azepin-2-yl ether (13): colorless plates; mp 115−116 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.13 (9H, s), 2.62 (1H, dd, J = 12.2, 6.1 Hz), 3.16 (1H, dd, J = 12.2, 7.9 Hz), 3.67 (3H, s), 5.29 (1H, d, J = 4.9 Hz), 5.53 (1H, dd, J = 7.9, 6.1 Hz), 5.73 (1H, d, J = 4.9 Hz), 6.23 (1H, d, J = 9.3 Hz), 6.48 (1H, d, J = 12.0 Hz), 6.93 (1H, d, J = 12.0 Hz), 7.03 (1H, d, J = 9.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.3 (q), 29.6 (q), 34.4 (s), 34.6 (s), 37.5 (t), 53.6 (q), 65.4 (d), 115.4 (d), 117.4 (d), 124.8 (d), 127.1 (d), 127.8 (d), 139.0 (d), 146.7 (s), 147.8 (s), 160.3 (s), 168.3 (s); IR (KBr) ν_{max} 1678, 1630, 1446, 1394, 1367, 1267, 1241, 1216, 1181 cm^{-1}; UV−vis (EtOH) λ_{max} 252 nm (log ϵ 3.90); MS (FAB) *m/z* 343 $(M + H)^+$. Anal. Calcd for $C_{21}H_{30}N_2O_2$: C, 73.65; H, 8.83; N, 8.18. Found: C, 73.82; H, 8.97; N, 8.47.

Reaction of 13 with NBS. NBS (110 mg, 0.62 mmol) was dropped into a solution of **13** (200 mg, 0.58 mmol) in CH_2Cl_2 (5 mL) stirred under a nitrogen atmosphere at 0 °C then the solution was stirred for 2 h. Separation of the reaction mixture by MPLC on Woelm 32-63 silica gel at 0 °C eluted with 1:1 v/v AcOEt−hexane gave **10** (1.8 mg, 0.7%), *cis*-**12** (203 mg, 67%), and *trans*-**12** (63 mg, 21%).

Elimination of HBr from 12. A solution of isomeric **12** (280 mg, 0.538 mmol) and DBU (1.00 g, 6.57 mmol) in CH_2Cl_2 was stirred at room temperature for 2.5 days (reaction progress monitored by TLC). Volatile components were removed under vacuum, and isolation by column chromatography on silica gel eluted with 1:4 v/v AcOEt−hexane gave **11** (220 mg, 93%). Recrystallization from hexane gave **11** as colorless plates.

Reaction of 13 with NBS in the Presence of Methanol. NBS (140 mg, 0.79 mmol) was dropped into a solution of **13** (250 mg, 0.73 mmol) and methanol (1 mL, 24.7 mmol) in CH_2Cl_2 (5 mL) stirred under a nitrogen atmosphere at 0 °C then the solution was stirred for 2 h before treatment with aq K_2CO_3. The organic phase was separated and dried over $MgSO_4$. Removal of volatile components gave an isomeric mixture of **16** (330 mg, 100%) with a 4:1 molar ratio as a colorless solid.

5-Bromo-4-*tert*-butyl-5,6-dihydro-2-methoxy-2*H*-azepin-7-yl 4-*tert*-butyl-7-methoxy-2*H*-azepin-2-yl ether (16): colorless solid; mp 75−78 °C. Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.09 (9H, s), 1.27 (9H, s), 2.85 (1H, dd, J = 13.9, 6.8 Hz), 3.50 (3H, s), 3.64 (3H, s), 3.95 (1H, dd, J = 13.9, 1.5 Hz), 4.83 (1H, d, J = 6.8, 1.5 Hz), 5.40 (1H, d, J = 4.9 Hz), 5.65 (1H, d, J = 7.1 Hz), 5.74 (1H, d, J = 4.9 Hz), 6.10 (1H, d, J = 7.1 Hz), 6.47 (1H, d, J = 12.0 Hz), 6.92 (1H, d, J = 12.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.4 (q), 30.9 (q), 34.6 (s), 36.4 (s), 42.3 (d), 44.2 (t), 53.8 (q), 56.1 (q), 66.2 (d), 80.4 (d), 124.5 (d), 124.8 (d), 128.5 (d), 139.1 (d), 146.5 (s), 152.9 (s), 160.3 (s), 171.4 (s). Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.04 (9H, s), 1.25 (9H, s), 2.89 (1H, dd, J = 13.9, 6.8 Hz), 3.46 (3H, s), 3.61 (3H, s), 3.81 (1H, dd, J = 13.9, 1.5 Hz), 4.79 (1H, d, J = 6.8, 1.5 Hz), 5.38 (1H, d, J = 4.9 Hz), 5.59 (1H, d, J = 7.1 Hz), 5.83 (1H, d, J = 4.9 Hz), 6.06 (1H, d, J = 7.1 Hz), 6.44 (1H, d, J = 12.0 Hz), 6.92 (1H, d, J = 12.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.5 (q), 30.8 (q), 34.6 (s), 36.5 (s), 41.8 (d), 44.8 (t), 53.4 (q), 56.0 (q), 67.7 (d), 82.7 (d), 124.4 (d), 124.7 (d), 127.9 (d), 139.7 (d), 146.6 (s), 152.1 (s), 159.6 (s), 171.3 (s). IR (KBr) ν_{max} 1671, 1636, 1466, 1448, 1267, 1201 cm^{-1}; UV−vis (EtOH) λ_{max} 265 nm (log ϵ 3.10); MS (FAB) *m/z* 453 $(M + H)^+$; HRMS (FAB) *m/z* found 453.1757, calcd for $C_{22}H_{34}BrN_2O_3$ $(M + 1)^+$ 453.1752.

Elimination of HBr from 16. A solution of **16** (270 mg, 0.60 mmol) in 5 mL of 1.0 M methanolic tetrabutylammonium hydroxide was stirred at room temperature for 2.5 days (reaction progress monitored by TLC). The mixture was then concentrated under vacuum, diluted with water, extracted with CH_2Cl_2, then dried over $MgSO_4$. Purification by MPLC on Woelm 32-63 silica gel eluted with 3:7 v/v AcOEt−hexane gave a 20:47 molar ratio isomeric mixture of **17** (150 mg, 68%). Recrystallization of the isomeric mixture of **17** from AcOEt and hexane gave colorless plates with no change in molar ratio of the isomers.

5-*tert*-Butyl-7-methoxy-3*H*-azepin-2-yl 4-*tert*-butyl-7-methoxy-2*H*-azepin-2-yl ether (17): colorless plates; mp 140.5−141.0 °C. Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.09 (9H, s), 1.11 (9H, s), 2.71 (1H, dd, J = 12.1, 5.6 Hz), 3.14 (1H, dd, J = 12.1, 7.6 Hz), 3.53 (3H, s), 3.72 (3H, s), 5.40 (1H, dd, J = 7.6, 5.6 Hz), 5.47 (1H, s), 5.59 (1H, d, J = 4.4 Hz), 5.88 (1H, d, J = 4.4 Hz), 6.35 (1H, d, J = 12.0 Hz), 6.90 (1H, d, J = 12.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.6 (q), 29.6 (q), 34.4 (s), 34.7 (s), 37.4 (t), 53.3 (q), 55.8 (q), 67.8 (d), 94.0 (d), 112.9 (d), 123.8 (d), 131.2 (d), 139.1 (d), 144.7 (s), 147.4 (s), 154.2 (s), 159.4 (s), 169.1 (s). Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.06 (9H, s), 1.11 (9H, s), 2.79 (1H, dd, J = 11.7, 4.9 Hz), 3.19 (1H, dd, J = 11.7, 7.8 Hz), 3.68 (3H, s), 3.77 (3H, s), 5.44 (1H, dd, J = 7.8, 4.9 Hz), 5.58 (2H, s), 5.61 (1H, s), 6.47 (1H, d, J = 12.0 Hz), 6.86 (1H, d, J = 12.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.5 (q), 29.6 (q), 34.4 (s), 34.7 (s), 37.4 (t), 53.9 (q), 56.4 (q), 66.5 (d), 95.9 (d), 114.2 (d), 124.7 (d), 125.3 (d), 138.5 (d), 146.4 (s), 146.9 (s), 152.7 (s), 160.0 (s), 170.4 (s). IR (KBr) ν_{max} 1673, 1642, 1462, 1439, 1412, 1367, 1255, 1220, 1151 cm^{-1}; UV−vis (EtOH) λ_{max} 247 nm (log ϵ 4.00); MS (FAB) *m/z* 373 $(M + H)^+$. Anal. Calcd for $C_{22}H_{32}N_2O_3$: C, 70.94; H, 8.66; N, 7.52. Found: C, 71.08; H, 8.76; N, 7.70.

Qualitative Nucleophilic Substitution of 7a, 7b, and 8. To a $CDCl_3$ solution of **7a**, **7b**, or **8** (10 mg) in an NMR sample tube, a nucleophile was introduced in molar excess. The mixture was periodically observed by ^{1}H NMR spectroscopy until no further change in the spectra could be detected. The results are displayed in Table 6. The products were purified by MPLC on silica gel at 0 °C.

4-*tert*-Butyl-7-methoxy-2-propylthio-2*H*-azepine (9b): colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (3H, t, J = 7.4 Hz), 1.09 (9H, s), 1.66 (2H, hext, J = 7.4 Hz), 2.54−2.83 (2H, m), 3.70 (3H, s), 4.35 (1H, d, J = 5.8 Hz), 5.66 (1H, d, J = 5.8 Hz), 6.46 (1H, d, J = 12.0 Hz), 6.93 (1H, d, J = 12.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6 (q), 23.0 (t), 29.4 (q), 32.3 (t), 34.6 (s), 53.6 (q), 60.2 (d), 124.6 (d), 127.0 (d), 138.9 (d), 147.5 (s), 161.4 (s); IR (film) ν_{max} 1628, 1444, 1243, 1203 cm^{-1}; UV−vis (EtOH) λ_{max} 277 nm (log ϵ 3.36); MS (FAB) *m/z* 254 $(M + H)^+$; HRMS (FAB) *m/z* calcd for $C_{14}H_{23}NOS$ $(M)^+$ 253.1500, found 253.1464. Anal. Calcd for $C_{14}H_{23}NOS$: C, 66.36; H, 9.15; N, 5.53. Found: C, 66.17; H, 9.24; N, 5.73.

4-*tert*-Butyl-7-methoxy-2-propylamino-2*H*-azepine (18): colorless solid; mp 75.5−77.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7.2 Hz), 1.07 (9H, s), 1.50−1.60 (2H, m), 1.70 (1H, br s), 2.51−2.57 (1H, m), 2.93−2.99 (1H, m), 3.66 (3H, s), 3.75 (1H, d, J = 4.8 Hz), 5.62 (1H, d, J = 4.8 Hz), 6.46 (1H, d, J = 12.0 Hz), 6.92 (1H, d, J = 12.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.0 (q), 23.4 (t), 29.6 (q), 34.5 (s), 48.0 (t), 53.4 (q), 70.3 (d), 124.5 (d), 128.9 (d), 139.0 (d), 145.8 (s), 159.5 (s); IR (KBr) ν_{max} 3260, 1624, 1441, 1241 cm^{-1}; UV−vis (EtOH) λ_{max} 276 nm (log ϵ 3.07); MS (FAB) *m/z* 237 $(M + H)^+$; HRMS (FAB) *m/z* calcd for $C_{14}H_{25}N_2O$ $(M + H)^+$ 237.1967, found 237.1989.

Preparation of 9b. NBS (220 mg, 1.24 mmol) was dropped into a solution of **1b** (210 mg, 1.17 mmol) in the presence of 2,4,6-trichlorophenol (450 mg, 2.28 mmol) in CH_2Cl_2 (20 mL) stirred under a nitrogen atmosphere at −98 °C then the solution was stirred at −98 °C for 10 h before triethylamine (360 mg, 3.56 mmol) was introduced and stirring was continued at room temperature for 5 h. Propane thiol (900 mg, 11.8 mmol) was then added to the reaction mixture and stirring was continued for 6 h. Excess triethylamine, propane thiol and CH_2Cl_2 were then removed under reduced pressure then the nonvolatile component redissolved in CH_2Cl_2, washed once with water then twice with aq K_2CO_3, then dried over $MgSO_4$. Volatile components were then removed under reduced pressure and separation of the remaining material by column chromatography on silica gel eluted by 1:9 v/v AcOEt−hexane gave **9b** (130 mg, 44%) as a colorless oil.

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