Nucleophilic Addition to Iminium Ethers in the Preparation of Functionalized *N*-Alkyl Heterocycles

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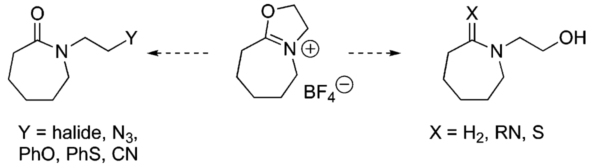

Bicyclic iminium ethers can be synthesized by the reactions of ketones with hydroxyalkyl azides. These cationic species react with a variety of nucleophiles via two possible pathways. The initially formed, kinetic product arises from direct addition to the iminium carbon in the substrate. In some cases, the initial adduct reverts to the starting iminium ether and the ultimate product arises from nucleophilic displacement at the *O*-alkyl group to afford the terminally functionalized *N*-substituted amide. The behavior of a range of nucleophiles was studied by using several iminium ethers. In general, the relevant pathway could be identified by characterization of the product formed. For hydroxide addition, which can afford only one product regardless of mechanism, the reaction was shown to arise by the kinetic pathway, using ^{18}O-labeled hydroxide. A one-pot synthesis of functionalized lactams entailing treatment of ketones first with hydroxyalkyl azides followed by nucleophilic addition was also developed.

Introduction

Iminium ethers exhibit ambident electrophilic character toward nucleophiles.[1] These cationic species are usually formed by *O*-alkylation of amides, but cyclic versions are also directly formed by *N*-alkylation of oxazolines or dihydrooxazines[2] or by the reactions of ketones with hydroxyalkyl azides under Lewis acid promotion.[3] Such *N*-alkyloxazolinium and *N*-alkyldihydrooxazinium salts (**1** or **2**, respectively) are particularly attractive substrates for the preparation of substituted heterocycles (Scheme 1). In most applications of this chemistry, the iminium ethers have been converted to *ω*-hydroxyalkyl amides by base hydrolysis.

Hünig has described two pathways for the addition of nucleophiles to iminium ethers (Scheme 1).[1a] Kinetic attack generally occurs at the carbon bearing the lowest electron density to form a neutral intermediate (path a) that can directly lead to product in certain cases. However, if this intermediate reverts back to the relatively stable iminium ether such that an equilibrium results, attack at the distal ether carbon of the ring may ultimately occur to produce the lactam products as shown in path b. The factors that influence the mechanism are dependent on the relative nature of the nucleophile, the stability

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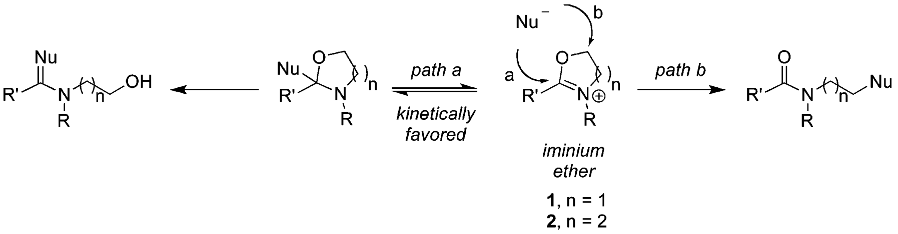
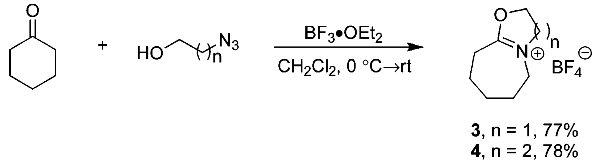
SCHEME 1. Ambident Electrophilicity of Iminium Ethers



SCHEME 2. Preparation of Iminium Ethers



of the ambident iminium ether, the temperature and duration of the reaction, and the solvent. Similar regioselectivity issues arise in the ring-opening chemistry of oxazolines, which is often carried out through *N*-protonated intermediates.[1d−h]

In a preliminary report, we described the preparation of two isolated iminium ethers and their reaction with several nucleophiles.[4] We have recently had occasion to re-examine this chemistry as a tool for library generation. Here, we present a full account that addresses (1) the expansion of the scope of the reaction to encompass a series of substrates related to a recently reported series of γ-turn mimics,[5] (2) the determination of the regiochemistry of hydroxide addition to the iminium ethers, and (3) the development of a one-pot iminium ether synthesis/nucleophilic addition sequence.

Results and Discussion

Survey of the Ambident Electrophilicity of Iminium Ethers. Our initial experiments were carried out with isolated iminium ethers **3** and **4**, which were prepared from cyclohexanone as previously reported.[3a] This involved the treatment of cyclohexanone with the hydroxyethyl or hydroxypropyl azide in the presence of boron trifluoride followed by crystallization of the resulting iminium ether as its tetrafluoroborate salt (Scheme 2). First, reactions that unambiguously arise from either mechanism, as judged by the products formed, were surveyed. We then considered special cases that are either mechanistically ambiguous (hydroxide addition, which would afford the same product by either mechanism) or have a more complex dependency on nucleophilic structure (a related series of stabilized carbon nucleophiles).

Reactions That Proceed via Irreversible Nucleophilic Addition (Path a). Nucleophiles that provide product via path a do so because the initial addition of nucleophile is either irreversible or the initial adduct has another pathway open to it. Examples of these reactions are shown in Scheme 3 and Table 1. Treatment with reducing agents leads to the fully reduced tertiary amine because the addition of hydride to the iminium ether is obviously irreversible. Furthermore, the reduced heterocycle is in equilibrium with the corresponding *N*-hydroxypropyliminium *N*-hydroxybutyliminium ion and so the addition of a second hydride equivalent completes the reaction. This conversion was achievable either under hydrogenation (Table 1, entries 1 and 2) conditions or with sodium borohydride (entries 3 and 4). These mild conditions stand in contrast to the usual reduction of lactams with lithium aluminum hydride or borane reagents. One particularly useful application of this reaction would be the synthesis of D- or T-labeled amines under very mild conditions (entry 5).

Path a adducts can also lead to alternative products when ring opening successfully competes with the ejection of the nucleophile. Two examples are shown in Scheme 3. Thus, when disodium sulfide is added to the iminium ether, the resulting thiolate directly undergoes ring opening to afford the thioamide product in modest yield (Table 1, entry 6). A similar situation was observed with amines (entries 7−10) as well as hydrazines (entry 11), which were found to yield amidines and hydrazones, respectively. The products resulting from amine nucleophiles were found to be unstable to aqueous workup and SiO_2 purification, such that hydrolysis to the corresponding amide occurred when a standard aqueous workup was used. In contrast, immediate silylation of the side chain alkoxy resulted in stable amidines (entries 9−10), suggesting that the hydrolysis step involved intramolecular addition of the terminal hydroxy group to the amidine (Scheme 4). In our preliminary report, we misassigned the product of hydrazine addition as taking place via path b to afford a 3′-(dimethylhydrazino)propyl lactam.[4] Resynthesis and spectroscopic examination of the product of this reaction suggested that it afforded an *N*-guanidinyl lactam **6h**; this compound was isolable by recrystallization from the reaction mixture. Its structure was further supported by *O*-silylation under standard conditions to afford **6i**, which was only consistent with the presence of a hydroxy group (Scheme 4).

Reactions That Proceed via Reversible Nucleophilic Addition (Path b). Some nucleophiles that add to iminium ether **3** via path b are shown in Table 2. In each case, the nucleophile was able to undergo elimination from the first-formed adduct and ultimately attack at the terminal carbon atom (i.e., path b). A number of diverse *N*-alkylated lactams were produced in this way, including azides (entry 1), ethers (entry 2), sulfides (entry 3), and halides (entries 4−5). In a carbon−carbon forming step, cyanide could also be added to yield nitrile derived *N*-alkylated lactams (entry 6).

The applicability of this reaction to peptidomimetic synthesis was demonstrated in the construction of 1,4-diazepin-5-ones.[6] Compounds containing this ring system have recently been shown to exhibit effective inhibition of the lymphocyte function-associate antigen-1 LFA-1 in inflammation and autoimmune

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SCHEME 3. Alternative Pathways for Initial Adducts

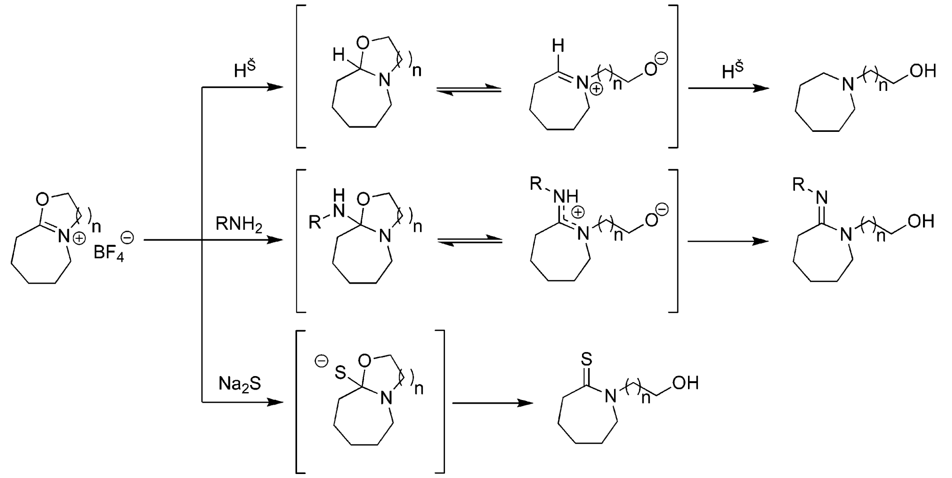
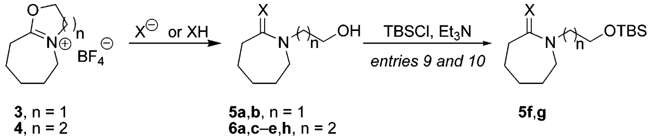


TABLE 1. Nucleophilic Addition Reactions of Iminium Ethers via Path a



entry	iminium ether	reagent	X	product	yield (%)
1	**3**	H_2	H, H	**5a**	87
2	**4**	H_2	H, H	**6a**	52
3	**3**	$NaBH_4$	H, H	**5a**	82
4	**4**	$NaBH_4$	H, H	**6a**	78
5	**3**	$NaBD_4$	D, D	**5b**	78
6	**4**	Na_2S	S	**6c**	57
7	**4**	$H_2NCH_2CH{=}CH_2$	$NCH_2CH{=}CH_2$	**6d**	90^a
8	**4**	$H_2NCH_2CH_2CH_2$	$NCH_2CH_2CH_2$	**6e**	90^a
9	**3**	$H_2NCH_2CH{=}CH_2$	$NCH_2CH{=}CH_2$	**5f**	91^b
10	**3**	H_2NBn	NBn	**5g**	88^b
11	**4**	H_2NNMe_2	$NNMe_2$	**6h**	88

[a] Product yield by crude ^{1}H NMR. [b] Isolated as the *tert*-butyldimethylsilyl ether.

diseases,[7] anticonvulsant activity,[8] and inhibition of reverse transcriptase of HIV-1.[9] In addition, a preliminary report from this laboratory suggested the use of 1,4-diazepinon-5-ones as γ-turn peptidomimetics.[5] In that work, the heterocyclic structure was prepared by using a Schmidt-like nitrogen ring-expansion reaction in which piperidones were treated with hydroxy azides derived from amino acids and the iminium ether intermediates opened with KOH (Scheme 5). The utility of the method would be enhanced if it were possible to diversify the products through reaction of the iminium ether with other nucleophiles. As a first step, 2-azido-1-ethanol **8** was treated with *N*-benzyl-4-piperidone to yield the expected iminium ether **9** (Table 3). The isolated iminium ether was then treated with path b nucleophiles (NaN_3, NaOPh, NaSPh, NaCN, F, and I) to produce lactams **10a**−**f** in good yield.

Isolation of the iminium ether is not always possible and rarely convenient in synthetic contexts. Accordingly, we sought to determine whether this sequence could be performed in one pot, allowing for all three components (piperidone, hydroxy azide, and nucleophile) to be incorporated at once. The exogenous nucleophiles were deliberately chosen to maximize the utility of the resulting 1,4-diazepin-5-ones. Thus, the azide derivatives could in principle be further elaborated to substituted amines by using aza-Wittig chemistry or reductive amination. Nitriles are known as reversible inhibitors of cysteine proteases[10] and the addition of phenoxide and thiophenoxide could lead to further diversification by using aryl-substituted versions. Following considerable experimentation, it was determined that isolation of the iminium ether could be avoided by simply carrying out the ring-expansion reaction under normal conditions in DCM, removing the solvent in vacuo, redissolution in DMF, and finally nucleophile addition. This one-pot sequence was carried out with six amino acid derived hydroxyl azides (**8**, and **11**−**15**) and four path b nucleophiles (NaN_3, NaCN, NaOPh, and NaSPh) as summarized in Table 4.

Elucidation of the Mechanism of Hydroxide Ion Addition. The addition of hydroxide to iminium ethers results in *N*-hydroxyalkyl lactams.[3a] However, this product could be obtained by either of two possible pathways. The use of ^{18}O-labeled hydroxide clearly demonstrated the operation of path a in this case. Addition of potassium hydroxide (98% yield) or saturated sodium bicarbonate (85% yield) prepared from ^{18}O-enriched water (~30%) showed exclusive incorporation of ^{18}O (~30%) at the carbonyl oxygen according to ^{13}C NMR analysis (Scheme 6). Two signals corresponding to the lactam carbonyl (δ = 177.25 and 177.28 ppm) were observed, with the 177.25 ppm signal integrating to approximately 30% assigned to the ^{18}O carbonyl. On the other hand, a single signal was observed for the alcohol carbon (57.82 ppm). Extended treatment of the

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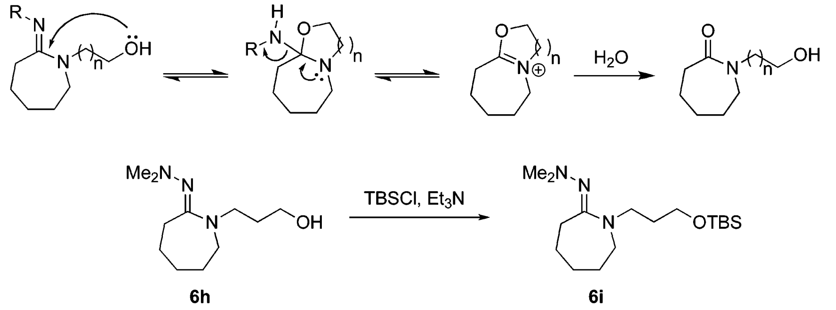
SCHEME 4. Hydrolysis of Amidines to Amides under Aqueous Conditions



SCHEME 5. Modular Synthesis of 1,4-Diazepin-5-ones

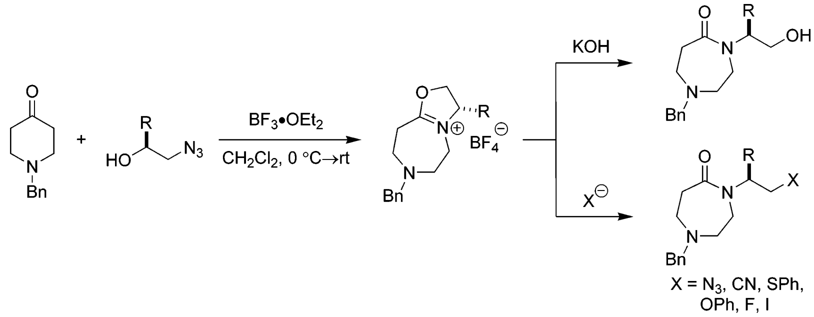
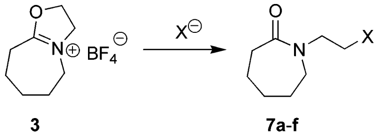
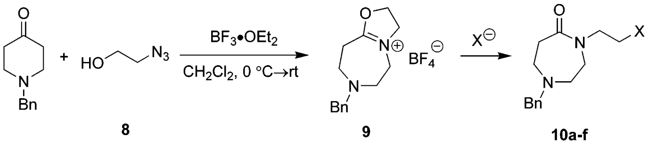


TABLE 2. Nucleophilic Addition Reactions to Iminium Ether 3 via Path b



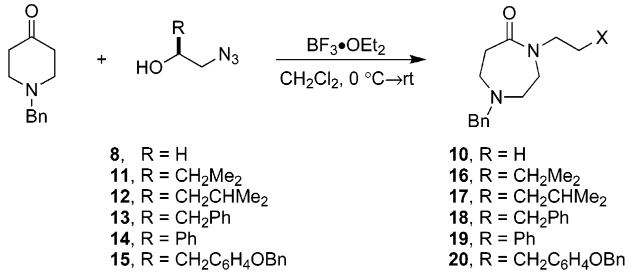
entry	nucleophile	X	product	yield (%)
1	NaN_3	N_3	**7a**	85
2	NaOPh	OPh	**7b**	74
3	NaSPh	SPh	**7c**	95
4	$(n\text{-Bu})_4N^+Ph_3SiF_2^-$	F	**7d**	64
5	$(n\text{-Bu})_4N^+I^-$	I	**7e**	55
6	NaCN	CN	**7f**	82

TABLE 3. Nucleophilic Path b Addition Reaction Yielding 1,4-Diazepin-5-ones



entry	nucleophile	X	product	yield (%)
1	NaN_3	N_3	**10a**	74
2	NaOPh	OPh	**10b**	64
3	NaSPh	SPh	**10c**	80
4	NaCN	CN	**10d**	76
5	$(n\text{-Bu})_4N^+Ph_3SiF_2^-$	F	**10e**	59
6	$(n\text{-Bu})_4N^+I^-$	I	**10f**	50

TABLE 4. One-Pot Nucleophilic Addition Reaction Yielding 1,4-Diazepin-5-ones



entry	hydroxyalkyl azide	product yield (%)			
		N_3	OPh	SPh	CN
1	**8**	**10a** (81)	**10b** (67)	**10c** (80)	**10d** (79)
2	**11**	**16a** (60)	**16b** (55)	**16c** (58)	**16d** (63)
3	**12**	**17a** (66)	**17b** (63)	**17c** (62)	**17d** (69)
4	**13**	**18a** (66)	**18b** (58)	**18c** (60)	**18d** (74)
5	**14**	**19a** (74)	**19b** (62)	**19c** (70)	**19d** (70)
6	**15**	**20a** (55)	**20b** (40)	**20c** (52)	**20d** (52)

labeled product with unlabeled base showed no decrease in the relative amount of isotope incorporation, indicating that exchange was not occurring in the amide product.

Reactions of Stabilized Carbon Nucleophiles. As shown in Table 5, the mechanistic pathways taken by a small group of stabilized carbon nucleophiles differed according to the nature of the nucleophile. Sodium dimethyl malonate (entry 1) and the sodium anion of bis(phenylsulfonyl)methane (entry 2) provide reversible path b addition products **23a** and **23b**, respectively, although the *O*-alkylation product was obtained in the case of **23a**. Alternatively, the addition of $NaCH(CN)_2$ produced **24** (entry 3) via base-promoted elimination. Our results show that the nature of the anion-stabilizing group determines whether path a or path b predominates in the reactions of $NaCH(CO_2Me)_2$, $NaCH(SO_2Ph)_2$, or $NaCH(CN)_2$.[11] In each of these adducts, the presence of an acidic proton allows for the possibility of elimination following the initial addition. The slightly higher acidity of malononitrile ($pK_a = 11.1$)[12] relative

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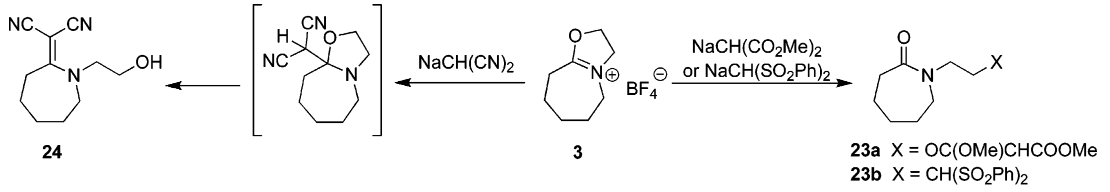
TABLE 5. Nucleophilic Carbon Addition Reactions of Iminium Ethers



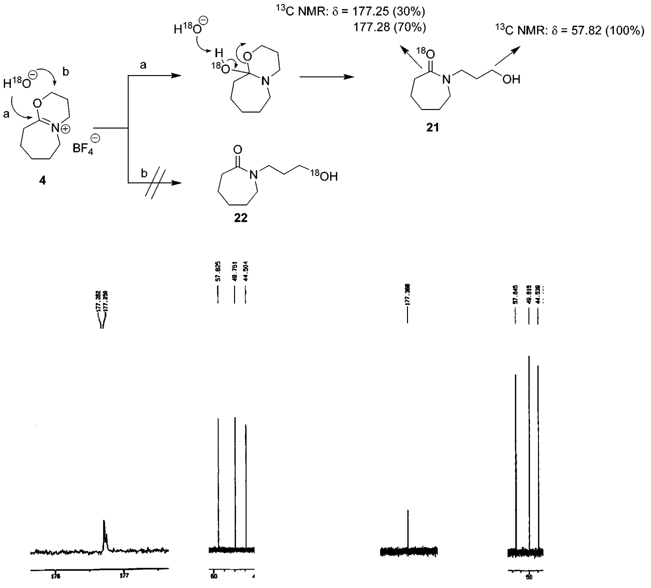
24

3

23a X = OC(OMe)CHCOOMe
23b X = $CH(SO_2Ph)_2$

entry	Nu	X	product	yield (%)
1	$NaCH(CO_2Me)_2$	OC(OMe)CHCOOMe	**23a**	34
2	$NaCH(SO_2Ph)_2$	$CH(SO_2Ph)_2$	**23b**	54
3	$NaCH(CN)_2$	$C(CN)_2$	**24**	71

SCHEME 6. Addition of ^{18}O-Labeled Hydroxides to Iminium Ethers



^{13}C NMR spectrum of **21** ^{13}C NMR spectrum of unlabelled **21**

to bis(phenylsufonyl)methane (pK_a = 12.2)[13] and dimethyl malonate (pK_a = 16.4)[14] might explain the exclusive observation of **24** (by in situ deprotonation of the bracketed intermediate shown in Table 5), although it is also possible that this is the only nucleophile in this series small enough to add to the iminium ether in the first place. At present, we cannot distinguish between these possibilities.

Conclusion. The regioselective addition of various heteroatom and carbon nucleophiles to *N*-alkyloxazolinium and *N*-alkyldihydrooxazinium ions has been surveyed. The ambident nature of iminium ethers toward these additions allows for the preparation of either *N*-substituted lactams or other nitrogen heterocycles via two different pathways. Taken together, these results greatly extend the kinds of functionalized lactams or lactam derivatives that can be synthesized from iminium ether intermediates.

Experimental Section

Previously Reported Procedures. Iminium ethers **3** and **4** and hydroxy azides **8** and **11**−**15** were prepared as previously reported.[3a,5]

General Procedure for the Reaction of *N*-Alkyloxazolinium and *N*-Alkyldihydrooxazinium Salts with Nucleophiles: Hexahydro-1-(2′-azidoethyl)-2*H*-azepin-2-one (7a). Sodium azide (216 mg, 3.32 mmol) was added to a solution of iminium ether **3** (300 mg, 1.33 mmol) in DMF (5 mL) and the reaction mixture was stirred at 70 °C for 24 h. Water (20 mL) was added and the reaction mixture was extracted with ether (3 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo to afford a clear yellow liquid. The crude liquid was purified by chromatography (2/1 ethyl acetate−hexane) to yield 206 mg (85%) of **7a** as a clear colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60−1.80 (m, 6H), 2.51 (m, 2H), 3.40−3.53 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 28.4, 29.7, 37.1, 48.1, 49.8, 50.9, 176.0; IR (neat) 2100, 1630 cm^{-1}; MS (EI) *m/e* 183 ($M^+ + 1$), 155, 126, 44; HRMS calcd for $C_8H_{15}N_4O$ ($M^+ + 1$) 183.1246, found 183.1248.

General Procedure for the One-Pot Preparation of Functionalized 1,4-Diazepin-5-ones from Piperidone and Hydroxy Azides: Hexahydro-4-(2′-azidoethyl)-1-benzyl-5*H*-1,4-diazepan-5-one (10a). Boron trifluoride diethyl etherate (0.335 mL, 2.64 mmol) was added dropwise to a solution of 1-benzyl-4-piperidone (100 mg, 0.528 mmol) and 2-azidoethanol (69.0 mg, 0.792 mmol) in methylene chloride (2 mL) at 0 °C and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo and the residue was dissolved in DMF (2 mL). Sodium azide (85.9 mg, 1.32 mmol) was added and the reaction mixture was stirred at 70 °C for 24 h. H_2O (10 mL) was added and the reaction mixture was extracted with ether (3 × 30 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo to afford a clear yellow liquid. The crude liquid was purified by chromatography (ethyl acetate) to yield 117 mg (81%) of **10a** as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58−2.65 (m, 2H), 2.65−2.72 (m, 4H), 3.43−3.48 (m, 2H), 3.49−3.55 (m, 4H), 3.57 (s, 2H), 7.23−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.6, 48.5, 50.2, 50.8, 51.4, 56.1, 63.0, 127.4, 128.5, 129.0, 138.1, 175.2; IR (neat) 2931, 2814, 2101, 1651 cm^{-1}; MS (ESI) *m/e* 274 ($M^+ +$ 1), 272, 224; HRMS calcd for $C_{14}H_{20}N_5O$ ($M^+ + 1$) 274.1668, found 274.1691.

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Supporting Information Available: Additional experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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