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Synthesis and Isolation of 5,6-Dihydro-4*H*-1,3-Oxazine Hydrobromides by Autocyclization of *N*-(3-Bromopropyl)amides

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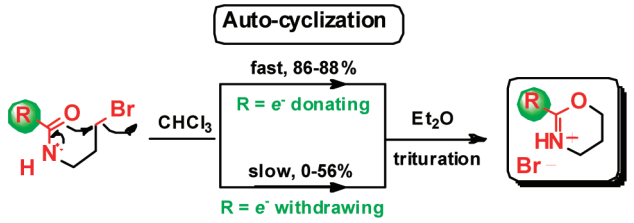

5,6-Dihydro-4*H*-1,3-oxazine hydrobromides have been synthesized by the nucleophilic autocyclo-*O*-alkylation of *N*-(3-bromopropyl)amides under neutral conditions in chloroform. It is found that electron-donating amide α-substituents influence the autocyclization efficiency.

5,6-Dihydro-4*H*-1,3-oxazines (**1**) are important intermediates for the synthesis of a broad range of synthons[1] such as bicyclic heterocycles,[2] and pyrroles,[3] ring-opened products such as 3-aminopropylester,[4] aldehydes,[5] α-amido aldehydes,[6] ketimines,[7]and olefins,[3] and polymers[8] such as pendant-type and main-chain polyamides and polyamines.[9] There has been considerable interest in this motif due to its presence in several biologically active compounds such as acetylcholine esterase inhibitors,[10] choline acetyl transferase inhibitors,[11] and cardenolide analogues.[12] Recently, 1,3-benzoxazines have also found applications as stimulus responsive quantum dots,[13] molecular switches,[14] and detectors.[15]

The 5,6-dihydro-4*H*-1,3-oxazine hydrobromide salts **2**, on the other hand, have received much lesser attention as electrophilic synthons in organic transformations. This is mainly because, unlike the relatively stable 1,3-oxazines (**1**) which can be synthesized from a variety of starting materials such as ketones,[16] nitriles,[17] azides,[18] olefins,[19] ketimines,[20] amido alcohols,[21] amido propylbromides,[22] and amino alcohols,[23] the highly reactive salts **2** can only be synthesized in situ by reacting oxazines **1** with the desired acids (Scheme 1 A). Under these conditions however, the yields of the salts **2** are poor and they ring open to yield 3-hydroxypropylamide and 3-aminopropylesters (**3**).[1] Hence, a method to synthesize and isolate the salts **2** will have several applications.

We envisioned that, if the amide carbonyl in amides **4** is rendered sufficiently nucleophilic to undergo an autocyclo-*O*-alkylation reaction (Scheme 1 B) under neutral conditions, then the in situ generated hydrobromic acid can be trapped by the resulting 1,3-oxazines (**1**) to yield the desired salts **2**. This may be best achieved in a nonpolar solvent such as chloroform. In this endeavor, we synthesized the benzamide **4g** (Table 1) and monitored its ^{1}H NMR in $CDCl_3$ (60 mM) as a function of time. Indeed, **4g** was converted exclusively to **2g** (Scheme 2), following first-order kinetics as expected for an intramolecular nucleophilic cyclization reaction.

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(24) $T_{1/2}$ were determined by following the time-dependent disappearance of the triplet for -CH_2-Br (in **4**) at $\delta \approx 3.40 \pm 0.2$ ppm and the simultaneous growth of the triplet for -CH_2-O- (in **2**) at $\delta \approx 4.60 \pm 0.2$ ppm in the ^{1}H NMR spectra.
(25) There is a dead time error of 20−30 min due to the time taken to prepare the sample and acquire the FID.

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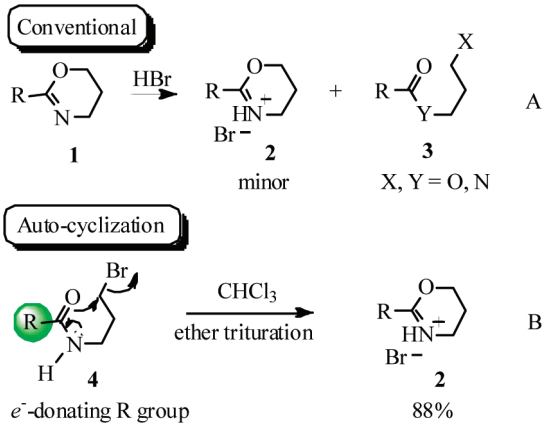
SCHEME 1. Synthesis of 1,3-Oxazine Hydrobromides 2



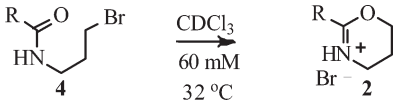
The reaction had a half-life ($t_{1/2}$)[24] of 97 h[25] (32 °C). Notably, the moisture-sensitive hydrobromide **2g**, which was insoluble in ether, was isolated from a mixture (56:44) of **2g** and **4g** by simple trituration of the concentrated mixture with dry ether.

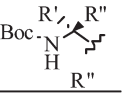
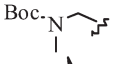
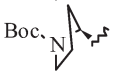
There are no reports of such autocyclization of **4** to **2** under neutral conditions,[26] although the bromooxazinization[27] of amido γ-olefins have been reported. In fact, several benzamides (**4**) are known to be very stable in the absence of base in solvents such as THF, acetonitrile, and ether. Hence, generalization of the current method will provide direct access to a variety of synthons, **2**, which are otherwise difficult to isolate.[1] In the current work we report the propensity of the *N*-(3-bromopropyl)acetamides (**4a**−**e**, **i**), the benzamides (**4f**−**h**), and the peptidylamides (**4j**−**r**), with electronically varying amide α-substituents, to undergo autocyclo-*O*-alkylation and form the salts **2a**−**r** under neutral conditions in chloroform.

The starting materials, amides (**4a**−**r**), were synthesized in good yields by coupling the corresponding carboxylic acids and anhydrides with 3-bromopropylamine[28] **5** (Scheme 3). Time-dependent ^{1}H NMR of the acetamides **4b**−**e** revealed that they underwent clean autocyclization to form the corresponding 2-alkyl-5,6-dihydro-4*H*-1,3-oxazine hydrobromides (**2b**−**e**, Table 1). The salts were easily isolated by trituration of the mixtures with ether.

The $t_{1/2}$ of autocycliation of **4b**−**e** (Table 1) decreased in the order (**4b** > **4c** > **4d** > **4e**) of increase in electron density on the α-carbon. Notably, **4e** with the *tert*-butyl substituent cyclized significantly faster than **4a**−**c** which have enolizable hydrogens at the α-carbon. Thus, the cyclization rate is affected predominantly by the inductive effect of the α-carbon substituents. The benzamides **4f**−**h** cyclize more slowly than the acetamides, but the electronic effects are similar (Table 1). The formamide **4a** remained stable and unchanged due to the poor electron-donating ability of hydrogen. Surprisingly, the autocyclization of the peptides,

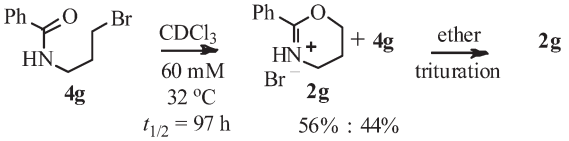
TABLE 1. Autocyclization of *N*-(3-Bromopropyl)amides 4



Entry	R	4	2	$t_{1/2}$[a]	yield[d] %	time (h)
1	H^-	**4a**	**2a**	-[b]	0	100
2	CH_3^-	**4b**	**2b**	34	86	141
3	CH_3-CH_2-	**4c**	**2c**	25	88	170
4	$(CH_3)_2$-CH-	**4d**	**2d**	23	87	122
5	$(CH_3)_3$-C-	**4e**	**2e**	19	87	127
6	*p*-NO_2-Ph-	**4f**	**2f**	>400	5[e]	179
7	Ph^-	**4g**	**2g**	97	56	196
8	*p*-MeO-Ph	**4h**	**2h**	28	84	93
9	Ph-CH_2-	**4i**	**2i**	175	53	198
						
10	H^- H^-	**4j**	**2j**	325[c]	41[e]	218
11	H^- CH_3^-	**4k**	**2k**	>400	12[e]	160
12	CH_3^- CH_3^-	**4l**	**2l**	>400	16[e]	160
13	H^- $(CH_3)_2$-CH-	**4m**	**2m**	>400	9[e]	119
14	H^- $(CH_3)_2CH$-CH_2-	**4n**	**2n**	>400	14[e]	145
15		**4o**	**2o**	-[b]	0[e]	152
16		**4p**	**2p**	>400	4[e]	100

[a] $T_{1/2}$'s were calculated from time-dependent ^{1}H NMR studies. [b] Amide **4** is unchanged after > 100 h. [c] Estimated $t_{1/2}$. [d] Isolated yields after ether wash. [e] Yield based on ^{1}H NMR.

SCHEME 2. Synthesis of 2g by Autocyclization of 4g



including the α-disubstituted, α,β-bis(disubstituted) and cyclic amides (**4j**−**p**) was extremely slow. Their rates decreased significantly with time, as the concentration of the hydrobromide salts (**2j**−**p**) increased, implying the poor nucleophilicity of their amide carbonyl oxygens. The α-(Boc-NH-) substituent seems to be sufficiently electron withdrawing to significantly decrease the autocyclization rates of the peptidyl amides **4j**−**p**. Hence, electron-donating α-substituents on the amide are essential for the nucleophilic autocyclo-*O*-alkylation of **4** to proceed at a reasonable rate.

Solution FTIR ($CHCl_3$, 10 mM) spectral analysis of the amides showed that the amide C=O stretch bands of **4j**−**p**

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SCHEME 3. Synthesis of *N*-(3-Bromopropyl)amides 4

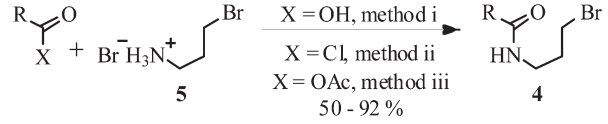
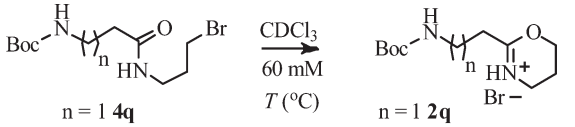


TABLE 2. Effect of Temperature on Autocyclization of 4q,r



Entry	4	2	T (°C)	$t_{1/2}$[a]	yield[b] (%)	time (h)
1	**4q**	**2q**	32	148	83	384
2	**4q**	**2q**	40	64	50	64
3	**4q**	**2q**	50	36	44	28
4	**4r**	**2r**	32	68	76	133
5	**4r**	**2r**	40	30	36	13
6	**4r**	**2r**	50	18	47	13

[a]Determined by time-dependent ^{1}H NMR analysis. [b]Yield based on ^{1}H NMR.

appear at higher values (> 1683 cm^{-1}), similar to that for the unreactive formamide **4a** (1689 cm^{-1}), than that for the acetamides **4b**−**e** (∼1672−1654 cm^{-1}). The lower bond order of the amide C=O in **4b**−**e** than in peptides **4j**−**p** suggested that the electron-donating α-susbstituents probably facilitate the stabilization of the amide in the more nucleophilic enolate resonance form than do the electron-withdrawing substituents.

The β- and γ-(Boc-NH-)-substituted amides **4q** and **4r**, however, underwent faster autocyclization reactions (Table 2, entries 1, 4). The $t_{1/2}$ of these reactions were halved upon increasing the reaction temperature from 32 to 40 °C and to 50 °C (Table 2). Thus, the rates of the autocyclization reactions can be controlled by varying the reaction temperature. The temperature dependence of the $t_{1/2}$ and the significant difference in rates of autocyclization between **4i**−**p** and **4q**, **r**, can have advantages for the design of peptides that can undergo residue-selective cyclizations along the chain length.[29]

In summary, we have identified that *N*-(3-bromopropyl)-amides undergo clean autocyclization reaction in chloroform, following first-order kinetics, to yield the 5,6-dihydro-4*H*-1,3-oxazine hydrobromides. The progress of the reaction can be easily monitored in real time by ^{1}H NMR. The moisture-sensitive hydrobromide salts can be isolated simply by trituration with dry ether. Electron-donating α-substituents on the amide facilitate the progress of the autocyclization reaction. The scope of the reaction has been expanded by the synthesis of β- and γ-peptide-derived 1,3-oxazine hydrobromides.

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Experimental Section

General Procedure for Synthesis of *N*-(3-Bromopropyl)-amides. Method i. Under N_2 atmosphere was added ethylchloroformate (ECF) (1.03 mmol) to a cold (−20 °C) solution of the carboxylic acid (1 mmol) and *N*-methyl morpholine (NMM) (1.5 mmol) in tetrahydrofuran (THF) (6 mL), and this mixture was vigorously stirred. After 2 min of stirring, a solution of 3-bromopropylamine hydrobromide (1 mmol) in a mixture of THF/DMF (1:4 - v/v) was added to the mixture followed by NMM (2.5 mmol) and stirred. After 10 min the mixture was warmed to 25 °C and stirred further until TLC indicated complete consumption of the starting acid. THF was removed under reduced pressure, and the resulting viscous solution was diluted with water (5 mL) and thoroughly extracted with ethyl acetate (15 mL). The combined organic extracts were washed with saturated aqueous citric acid (5 mL) and saturated aqueous sodium bicarbonate ($NaHCO_3$) (5 mL) and were dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated to give a residue, which was purified by silica gel (100−200 mesh) flash column chromatograph using ethyl acetate/hexanes as eluting solvents.

Method ii. To a cooled (0 °C) suspension of 3-bromopropylamine hydrobromide (1 mmol) and the acylchloride (1 mmol) in methylene chloride (DCM) (5 mL) was slowly added triethylamine (2 mmol), such that the temperature was maintained at 0 °C. After 10 min the mixture was warmed to 25 °C and stirred further until TLC indicated the complete consumption of the acylchloride. The mixture was diluted with DCM (5 mL) and washed with water (5 mL), 1N HCl (5 mL), saturated $NaHCO_3$ (5 mL) and dried over Na_2SO_4 and concentrated under vacuum to give a residue, which was purified by silica gel flash column chromatograph.

Method iii. To a cooled (5 °C) solution of 3-bromopropylamine hydrobromide (1 mmol) and acetic anhydride (1 mmol) in distilled water (1 mL) was slowly added sodiumbicarbonate (2.5 mmol). The mixture was stirred at 5 °C for 10 min, extracted with ethyl acetate (15 mL), dried over Na_2SO_4 and concentrated to give a residue, which was purified by silica gel flash column chromatograph.

***N*-(3-Bromopropyl)formamide (4a).** Amide **4a** was synthesized by following the procedure in method i. Purification by silica gel flash column chromatograph (EtOAc/hexane, 1:1) yielded the desired product as a viscous oil (253 mg, 1.5 mmol, 50% yield). (TLC - EtOAc, R_f = 0.27). IR (NaCl, neat): 3282, 3055, 2943, 2876, 1668, 1540, 1386, 1260 cm^{-1}; IR (NaCl, 10 mM in $CHCl_3$): 3445, 3014, 2866, 1689, 1509, 1392, 1216, 805, 786, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (s, 1H), 5.95 (bs, 1H), 3.49−3.43 (m, 4H), 2.15−2.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.5, 36.8, 31.9, 30.5; HRMS *m*/*z* Calcd for $C_4H_8BrNONa$ 187.9687, Found 187.9709.

***N*-(3-Bromopropyl)acetamide (4b).** Amide **4b** was synthesized by following the procedure in method iii. Purification by silica gel flash column chromatograph (EtOAc/hexane, 1:1) yielded the desired product as a viscous oil (135 mg, 0.8 mmol, 76% yield). (TLC - EtOAc, R_f = 0.33). IR (NaCl, neat): 3416, 3287, 3086, 2966, 2936, 2878, 1756 (weak), 1652, 1557, 1436, 1370, 1296, 1261 cm^{-1}; IR (NaCl, 10 mM in $CHCl_3$): 3455, 3014, 1672, 1602, 1520, 1437, 1368, 1221, 762, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.01 (bs, 1H), 3.41 (t, J = 6.6 Hz, 2H), 3.37 (q, J = 6.6 Hz, 2H), 2.05 (quin, J = .6 Hz, 2H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.8, 37.8, 32.0, 30.8, 22.9; HRMS *m*/*z* Calcd for $C_5H_{10}BrNONa$ 201.9843, Found 201.9849.

***N*-(3′-Bromopropyl)-2,2-dimethylpropionamide (4e).** Amide **4e** was synthesized by following the procedure in method ii. Purification by silica gel flash column chromatography (EtOAc/hexane, 1:5) yielded the desired product as a viscous oil (234 mg, 1.2 mmol, 64% yield). (TLC - EtOAc, R_f = 0.71). IR (NaCl, neat): 3345,

2964, 2931, 2871, 1640, 1534, 1481, 1438, 1367, 1298, 1211 cm^{-1}. IR (NaCl, 10 mM in $CHCl_3$): 3472, 3013, 2970, 1654, 1602, 1515, 1213, 795, 698, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.88 (bs, 1H), 3.41 (t, J = 6.4 Hz, 2H), 3.38 (q, J = 6.4 Hz, 2H), 2.08 (quin, J = 6.4 Hz, 2H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.7, 38.9, 38.1, 32.1, 31.0, 27.5; HRMS m/z Calcd for C_8H_{16}-BrNONa 244.0313, Found 244.0316.

General Procedure for the Autocyclization and Purification of 2-Substituted-5,6-dihydro-4*H*-1,3-oxazine Hydrobromides. A solution of the amide (**4**) in $CHCl_3$ (60 mM) in a clean, dry, round-bottomed flask was shaken in a constant temperature incubator at 32 °C. The progress of the reaction was periodically monitored (^1H NMR). After completion of the reaction, $CHCl_3$ was removed under reduced pressure to get a thick residue, which was triturated with cold, dry diethylether (3 × 4 mL). The resulting insoluble precipitate was dried under vacuum to get the desired 2-substituted-5,6-dihydro-4*H*-1,3-oxazine hydrobromides (**2**).

2-Ethyl-5,6-dihydro-4*H*-1,3-oxazine Hydrobromide (2c). Following the general ether-wash procedure, **2c** was isolated from a mixture of **4c** (5%) and **2c** (95%), as an oil (88 mg, 0.46 mmol, 88% yield). IR (NaCl, neat): 3447, 2984, 2948, 2925, 1671, 1655, 1541, 1288, 1275, 1084, 829 cm^{-1}; IR (NaCl, 10 mM in $CHCl_3$): 3019, 2968, 2654 (br), 2434, 1672, 1602, 1529, 1217, 1086, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 12.81 (bs, 1H), 4.63 (t, J = 5.7 Hz, 2H), 3.66 (t, J = 5.7 Hz, 2H), 2.84 (q, J = 7.8 Hz, 2H), 2.21 (quin, J = 5.7 Hz, 2H), 1.24 (t, J = 7.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.7, 69.3, 38.1, 27.0, 18.8, 9.5; HRMS m/z Calcd for $C_6H_{12}NO$ 114.0919, Found 114.0937.

2-(*tert*-Butyl)-5,6-dihydro-4*H*-1,3-oxazine hydrobromide (2e). Following the general ether-wash procedure, **2e** was isolated from a mixture of **4e** (10%) and **2e** (90%), as a hygroscopic solid (86 mg, 0.39 mmol, 87% yield); mp = 145−146 °C. IR (NaCl, neat): 3468, 3418, 2977, 2941, 1656, 1510, 1297, 1191, 1050, 836 cm^{-1}; IR (NaCl, 10 mM in $CHCl_3$): 3018, 2961, 2820, 1652, 1499, 1293, 1049, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 13.12 (bs, 1H), 4.68 (t, J = 5.4 Hz, 2H), 3.86 (q, J = 5.9 Hz, 2H), 2.23 (quin, J = 5.7 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 181.2, 69.6, 39.3, 39.0, 27.1, 18.8; HRMS m/z Calcd for $C_8H_{16}NO$ 142.1232, Found 142.1232.

2-Phenyl-5,6-dihydro-4*H*-1,3-oxazine Hydrobromide (2g). Following the general ether-wash procedure, **2g** was isolated from a mixture of **2g** and **4g** (53: 47%), to get **2g** (56 mg, 56% yield) as a hygroscopic solid; mp = 136−137 °C. IR (KBr, neat): 3061, 2918, 1651, 1602, 1512, 1489, 1376, 1298, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 13.08 (bs, 1H), 8.34−8.30 (m, 2H), 7.70−7.63 (m, 1H), 7.56−7.50 (m, 2H), 4.87 (t, J = 5.3 Hz, 2H), 3.95−3.94 (m, 2H), 2.35−2.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.8, 135.7, 129.3, 129.0, 124.8, 69.8, 38.9, 19.1; HRMS m/z Calcd for $C_{10}H_{12}NO$ 162.0919, Found 162.0912.

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Supporting Information Available: Experimental methods and spectral data for all the amides **4** and the oxazine hydrobromides **2**; time-dependent ^1H NMR spectra of the amides; kinetic data for the autocyclization reactions. This material is available free of charge via the Internet at http://pubs.acs.org.