VERSATILE METHODS OF SYNTHESIS OF 5 TO 8-MEMBERED RING N-HETEROCYCLES VIA INTRAMOLECULAR CYCLOADDITIONS OF ALLYLAMINES[1]

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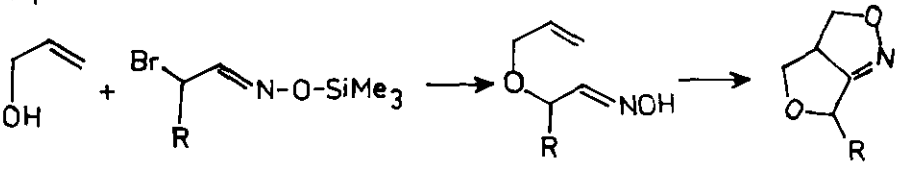
Abstract - N-Tosylallylamines or homoallylamines were monoalkylated with dibromoalkanes to produce bromoalkylamines **3** or **7**. The latter were converted to unsaturated nitro derivatives which, via nitrile oxides, underwent intramolecular cycloaddition to form hetero ring fused isoxazolines. Conversion of the bromo derivatives **3** either via azides to fused triazolines or by free radical reaction to pyrrolidines is also described. These reactions provide an entry into functionalized 5 to 8 membered ring heterocycles.

Introduction

In recent years intramolecular nitrile oxide olefin cycloadditions (INOC) have been of considerable synthetic and mechanistic interest, especially since the resulting isoxazoline ring can serve as a precursor to hydroxy ketones or to other functional groups.[2] We have recently shown that allyl alcohols or allyl amines can be converted by a two carbon chain extension, using an O-silyl-β-bromoaldoxime[3], into α-allyloxy or allylamino substituted aldoximes. Since these oximes were easily oxidized to nitrile oxides, they were suitable precursors for INOC reactions and formation of functionalized tetrahydrofurans or pyrrolidines (Equation 1). The formation of larger rings was hampered by the difficulty to

Equation 1



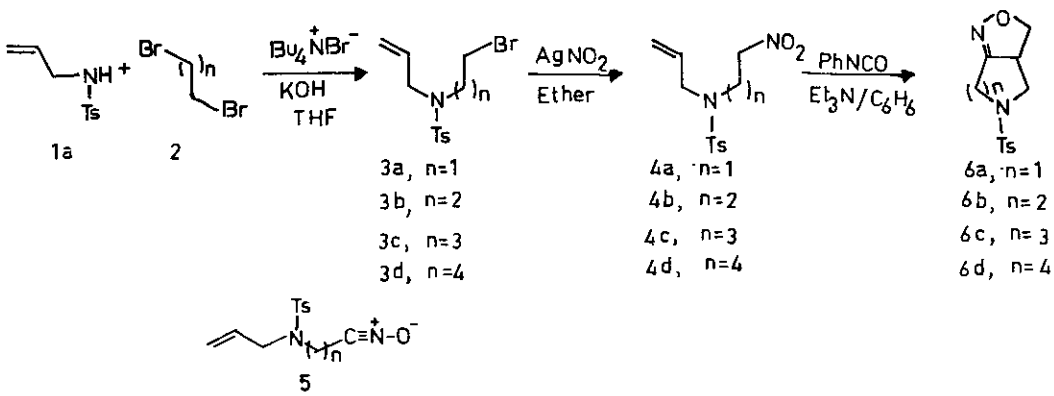
introduce appropriate side chains except in the case of vinyl beta lactams.[4] We now report a general method to convert allylamines through their sulfonamides into a nitrile oxide functionalized system that serves as a method of synthesis of functionalized pyrrolidines, piperidines, hydroazepines, hydroazocines as well

as diaza-heterocycles.

Results and Discussion

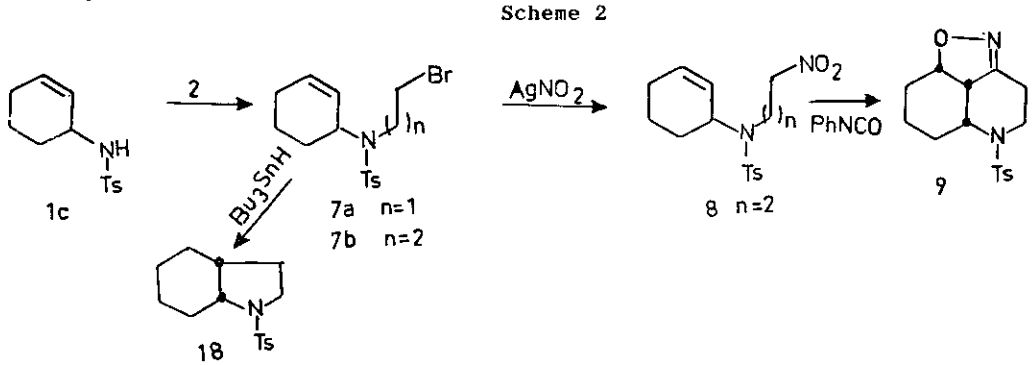
Monoalkylation of simple allylamines with dibromoalkanes was not successful. Since sulfonamides can be desulfonated photochemically[5] or by LAH under mild conditions,[6] we examined N-tosylallylamine **1** as a substrate in the reaction with a dibromoalkane **2** in the presence of solid KOH and a quaternary ammonium salt, a method previously found successful with carboxamides.[4] In this manner we achieved the monoalkylation of **1** to bromoalkylamines **3** in good yield (60-90%). The latters in turn were converted with silver nitrite into nitroalkyl bearing olefins **4** with various size alkyl chains. In situ transformation of **4** into a nitrile oxide **5** was carried out by means of phenyl isocyanate[6] and led to spontaneous cycloaddition with formation of isoxazolines **6** fused to 5-, 6- and 7-membered ring N-heterocycles (Scheme 1).

Scheme 1



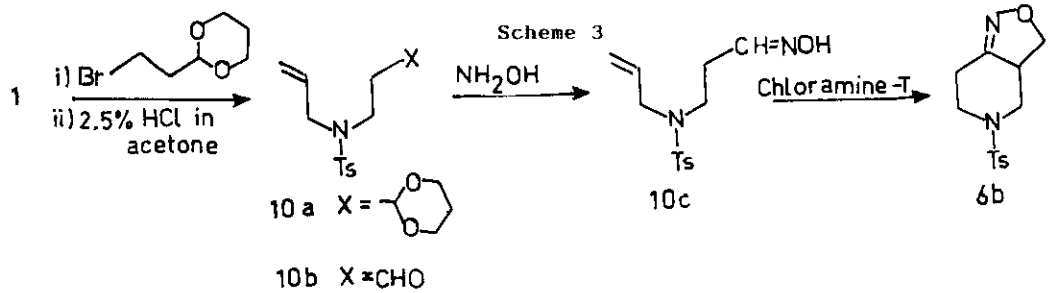
Under very high dilution,[5] we were able to also convert **4d** to **6d**, an isoxazoline fused to 8-membered azocine, in 10% yield. Using the same procedure tricyclic quinolinoisoxazoline **9** was formed on intramolecular cycloaddition starting with aminocyclohexene derivative **1c** via **7** and **8** (Scheme 2).

Scheme 2



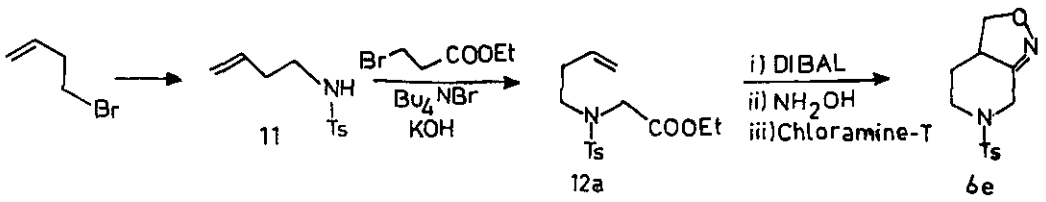
The structures of the acyclic amines were evident from nmr, mass spectra and chemical transformations (see Table). For instance, **3** and **4** showed typical vinyl signals near δ 5.20 and 5.60 ppm, and **4** also exhibited a triplet near δ 4.50 ppm (CH_2-NO_2). The CH_2O absorption in the isoxazolines **6** is dependent upon ring size and is found as a broad doublet at δ 4.16 in the pyrrolidine **6a**, as two doublets of doublets at δ 3.74 and 4.48 in the piperidine **6b**, and similarly at δ 4.03 and 4.47 ppm in the perhydroazepine **6c** and at δ 3.95 and 4.28 ppm in the perhydroazocine **6d**. ^{13}C-Nmr indicated typical vinyl signals near 119 and 134 ppm for **3** and **4** and **4** exhibited its triplet near δ 75 ppm ($\underline{C}H_2$-NO_2). The CH_2O carbon peaks in the isoxazolines **6** are found as a doublet of doublet at δ 70.46 and 71.59 ppm for **6b** and **6c** respectively, and as a triplet at 73.20 for **6a**. The C=N signal in **6** is found between δ 154 and 163 ppm, varying with ring size. An alternative pathway and structure proof for **6b** were provided by conversion of **1a** into the unsaturated acetal **10a**, which was hydrolyzed to the aldehyde **10b**. Oximation of **10b** to **10c** was followed by reaction with chloramine-T,[6] which involves transformation into a nitrile oxide and spontaneous ring closure to **6b** (Scheme 3).

Scheme 3



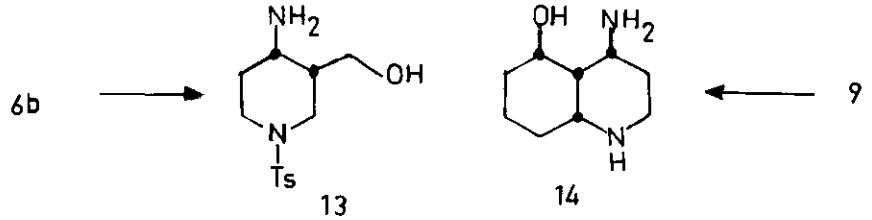
Conversely homoallylamine **11** was prepared from displacement of 4-bromo-1-butene with p-toluenesulfonamide under phase transfer conditions, which was followed by conversion into the unsaturated ester **12** (Scheme 4). Reduction of the latter by DIBAL, oximation and ring closure via a nitrile oxide provided **6e** (CH_2O two doublets of doublets at δ 3.71 and 4.58), regioisomeric with **6b**. The ^{1}H-nmr of **6e** showed a broad doublet at δ 3.98 and 4.75 ppm assignable to the protons alpha to N, whereas in **6b**, these protons are more nearly equivalent and appear as multiplets at δ 4.12 and 4.24 ppm. In ^{13}C-nmr the carbons alpha to N appear at δ 44.70 and 45.97 ppm respectively.

Scheme 4



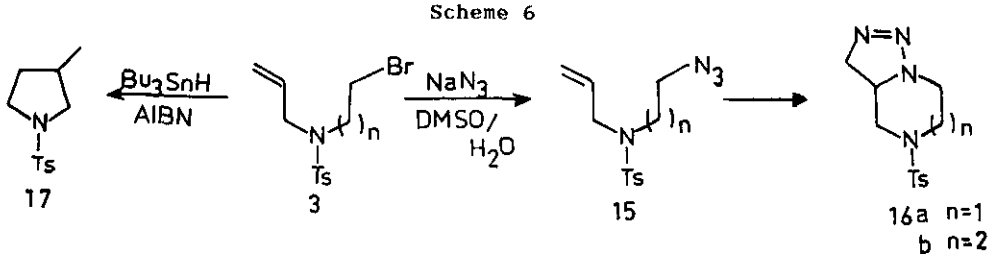
Reductive ring opening of **6b** and **9** with $LiAlH_4$ led in 58% and 60% yield respectively to amino alcohols **13** and **14** (Scheme 5). It is interesting to note that reduction of isoxazoline **6b** occurs without affecting the tosyl group whereas cleavage of the tosyl group was observed in the case of **9**.

Scheme 5



The bromoalkylallylamines **3** also serve as precursors for unsaturated azides **15** which can undergo thermal dipolar cycloadditions to the novel N-heterocycles **16** containing fused 6-, 7- and 8-membered rings, though in low yield. The transformation to **16** was best performed by direct heating of **3** with NaN_3 (Scheme 6) in DMSO-water which in the case of **3b** led directly to triazolinodiazazepine **16b** in 45% yield.[9] The piperazine system **16a** was formed in 25% yield while, the diazocine **16c** was isolated in only 5% yield. As in isoxazolines **6**, the ^{1}H-nmr signal of the $CH_2N{=}N$ group in the triazolines is dependent upon ring size and is found as two doublets of doublet at δ 3.28 and 3.58 ppm in the piperazine **16a**, as two multiplets at δ 3.20 and 3.43 ppm in perhydrodiazepine **16b** and as a multiplet at δ 3.38 ppm in perhydrodiazaocine **16c**. The $\underline{C}H_2N{=}N$ signal in the triazolines **16** a, b, and c is found as triplet at δ 48.90, 48.41 and 50.20 ppm respectively.

Scheme 6



The versatility of the haloalkenylamine building blocks **3** is further indicated by their use as convenient substrates for free radical cyclizations[10] with

Table: Spectral Analysis of the Products

Compound	^{1}H Nmr	^{13}C Nmr
3a	2.45(s, 3H, CH_3), 3.25(t, 2H, CH_2), 3.40(m, 2H,CH_2), 3.80(d, J=6.5 Hz, 2H, CH_2), 5.20(m, 2H, $=CH_2$), 5.60(m, 1H, =CH), 7.30(d, J=8 Hz, 2H, H-3,5), 7.70(d, J=8 Hz, 2H, H-2,6).	21.50(q), 29.28(t), 48.96(t), 51.97(t), 119.59(t), 127.14(d), 129.83(d), 132.88(d), 136.33(s), 143.50(s)
3b	2.20(m, 2H, CH_2), 2.42(s, 3H, CH_3) 3.35(t, J=6.5 Hz, 2H, CH_2), 3.40(t, J=6.5 Hz, 2H, CH_2), 3.80(dm, J=6.5 Hz, 2H, CH_2), 5.20(m,2H, $=CH_2$), 5.60(m, 1H, =CH), 7.30(d, J=8Hz, 2H, H-3,5), 7.70(d, J=8 Hz,2H, H-2,6)	21.49(q), 30.38(t), 31.84(t), 46.12(t), 51.55(t), 119.27(t), 127.17(d), 129.73(d), 132.91(d), 136.54(s), 143.39(s).
3c	1.70(m, 2H, CH_2), 1.90(m, 2H, CH_2), 2.43(s, 3H, CH_3), 3.15(t, J=7 Hz, 2H, CH_2), 3.45(t, J=7 Hz, 2H, CH_2), 3.79 (m, 2H, CH_2), 5.18(m, 2H, $=CH_2$), 5.61(m, 1H, =CH) 7.31(d, J=8 Hz, 2H, H-3,5), 7.70(d, J=8 Hz, 2H, H-2,6).	21.49(q), 26.56(t), 29.52(t), 33.21(t), 46.31(t), 50.66(t), 118.93(t), 127.09(d), 129.67(d), 133.05(s), 136.85(s), 143.25(t).
3d	1.42(m, 2H, CH_2), 1.58(m, 2H, CH_2), 2.00(m, 2H, CH_2), 2.42(s, 3H, CH_3), 3.10(t, J=7 Hz, 2H, CH_2), 3.38(t, J=7 Hz, 2H, CH_2), 3.79 (dm, J=6.5 Hz, 2H, CH_2), 5.15(m, 2H, $=CH_2$), 5.62(m, 1H, =CH), 7.31(d, J=8 Hz, 2H, H-3,5), 7.68(d, J=8 Hz, 2H, H-2,6).	20.90(t), 23.23(q), 26.80(t), 27.50(t), 46.80(t), 50.56(t), 75.36(t), 119.30(t), 127.19(d), 129.85(d), 133.50(d), 136.70(s), 143.30(s).
4a	2.44(s, 3H, CH_3), 3.68(t, J=6.5 Hz, 2H, CH_2),3.79(d, J=6.5 Hz,2H, CH_2), 4.62(t, J=6.5 Hz,2H, CH_2), 5.20(m, 2H, $=CH_2$), 5.61(m, 1H, =CH),7.34(d, J=8 Hz, 2H, H-3,5), 7.70(d, J=8 Hz, 2H, H-2,6).	21.54(q), 44.17(t), 52.39(t), 74.28(t), 120.43(t), 127.30(d), 120.96(d), 132,54(d), 133.54(s), 144.13(s).

4b	2.25(m, 2H, CH_2), 2.45(s, 3H, CH_3), 3.20(t, J=6.5 Hz, 2H, CH_2), 3.79(t, 2H, CH_2),4.49(t, J=6.5 Hz, 2H, CH_2) 5.21(m, 2H, $=CH_2$), 5.63(m, 1H, =CH), 7.32(d, J=8 Hz, 2H, H-3,5), 7.68(d, J=8 Hz, 2H, H-2,6).	21.52(q), 26.41(t), 44.54(t), 51.89(t), 72.48(t), 119.55(t), 127.19(d), 129.88(d), 132.55(d), 135.96(s), 143.72(s).
4c	1.62(m, 2H, CH_2), 2.02(m, 2H, CH_2) 2.43(s, 3H, CH_3), 3.15(t, J=7 Hz, 2H, CH_2), 3.77(t, J=7 Hz, 2H, CH_2), 4.42(t, J=7 Hz, 2H, CH_2), 5.60 (m, 2H, =CH), 7.31(d, J=8 Hz, 2H, H-3,5), 7.68(d, J=8 Hz, 2H, H-2,6).	21.48(q), 24.01(t), 24.85(t), 46.35(t), 50.95(t), 74.94(t), 119.16(t), 127.06(d),129.77(d), 132.92(d), 136.50(s), 143.48(s).
4d	1.42(m, 2H, CH_2), 1.55(m, 2H, CH_2), 1.84(m, 2H, CH_2), 2.42(s, 3H, CH_3), 3.12(m, 2H, CH_2), 3.80(dm, J=6.5 Hz, 2H, CH_2), 4.37(t, J=7 Hz, 2H,CH_2), 5.14 (m, 2H, $-CH_2$), 5.61 (m, 1H, =CH), 7.30(d, J=8 Hz, 2H, H-3.5), 7.70(d, J=8 Hz, 2H, H-2,6).	20.92(t), 22.00(q), 26.80(t), 27.50(t), 46.80(t), 50.86(t), 75.86(t), 119.72(t), 127.19(d), 129.85(d), 137.50(d), 136.73(s), 143.29(s).
6a	2.45,(s, 3H, CH_3), 2.88(m, 1H, CH), 3.81(m, 1H, CH_2), 3.96 (m, 2H, CH_2), 4.16 (b d,J=14 Hz, 1H, OCH_2), 4.53(t, J=8Hz, 1H, OCH_2), 7.36(d, (J=8 Hz, 2H, H-3,5), 7.70(d, J=8 Hz, 2H, H-2,6).	21.60(q), 43.10(d), 51.80(t), 52.70(t), 73.20(t), 127.30(d), 130.10(d), 139.5(s), 144.5(s), 163.72(s).
6b	2.30(t, J=11 Hz, 1H, CH_2), 2.38(dd, J=12,3Hz, 1H, CH_2), 2.43(s, 3H, CH_3) 2.54(m, 1H, CH_2), 2.78(1H, m, CH_2), 3.50(m, 1H, CH), 3.74(dd,J=10,8Hz, 1H, OCH_2), 4.12(ddt, J=11,5,2 Hz, 1H, CH_2), 4.24(ddd, J=9,6,2 Hz, 1H, CH_2), 4.48(dd, J=10,8Hz, 1H, OCH_2), 7.34(dd, 2H, H-3,5), 7.70(d, J=8 Hz, 2H, H-2,6).	21.53(q), 25.08(t), 42.65(t), 47.34(d), 50.87(t), 70.46(dd), 127.29(d), 129.93(d), 133.84(s), 144.10(s), 155.96(s).

6c	1.82(m, 2H, CH_2), 2.02(m, 1H, CH_2), 2.37(m, 1H, CH_2), 2.44(s, 3H, CH_3), 2.85(m, 1H, CH), 3.09(m, 1H, CH_2), 3.19(m, 1H, CH_2), 3.46(m, 1H, CH_2), 3.58(m, 1H, CH_2), 4.03(dd, J=10,8Hz, 1H, OCH_2), 4.47(dd, J=10,8Hz, 1H, OCH_2), 7.31(d, J=8 Hz, 2H, H-3,5), 7.65 (d, J=8 Hz, 2H, H-2,6).	21.47(q), 24.96(t), 26.55(t), 48.69(t), 50.13(t), 52.12(d), 71.59(dd), 126.89(d), 129.89(t), 135.59(s), 143.74(s), 160.43(s).
6d	1.70(m, 2H, CH_2), 1.85(m, 1H, CH_2), 1.95(m, 1H, CH_2), 2.45(s, 3H, CH_3), 2.65(m, 1H, CH_2), 2.75(m, 1H, CH_2), 2.95(m, 1H, CH_2), 3.20(m, 1H, CH), 3.42(m, 1H, CH_2), 3.70(m, 1H, CH_2), 3.80(m, 1H, CH_2), 3.95(m, 1H, OCH_2) 4.28(m, 1H, OCH_2), 7.30(d, J=8 Hz, 2H, H-3,5), 7.65(d, J=8 Hz, 2H, H-2,6).	
6e	1.60(m, 1H, CH_2), 2.13(m, 1H, CH_2), 2.45(s, 3H, CH_3), 2.55(dt, J=12,3 Hz, 1H, CH_2), 3.13(m, 1H, CH_2), 3.22(dd, J=14,1.5 Hz, 1H, CH_2), 3.71(dd, J=11,8Hz, 1H, CH_2), 3.98(dm, J=13 Hz, 1H, CH_2), 4.58(dd, J=10, 8Hz, 1H, CH_2), 4.75(bd, J=13 Hz, 1H, CH_2), 7.35(d, J=8 Hz, 2H, H-3,5), 7.68(d, J=8 Hz, 2H, H-2,6).	21.50(q), 29.9(t), 44.0(d), 44.70(t), 45.97(t), 73.60(dd), 127.70(d), 129.89(d), 133.38(s), 144.15(s), 153.39(s).
7a	1.4-1.8(m, 4H, CH_2), 1.95(m, 2H, CH_2), 2.40(s, 3H, CH_3), 3.13 (m, 2H, CH_2), 3.40(m, 2H, CH_2), 4.50(m, 1H, CH), 5.10(m, 1H =CH), 5.78(m, 1H, =CH), 7.28(d, J=8Hz, 2H, H-3,5), 7.70(d, J=8 Hz, 2H, H-2,6).	

7b	1.4-2.0(m, 8H, CH_2), 2.50(s, 3H, CH_3), 3.40(m, 2H, CH_2), 3.60(m, 2H, CH_2), 4.50(b s, 1H, CH), 4.90(d, J=9 Hz, 1H, =CH), 5.80(m, 1H, =CH), 7.30(d, J=8 Hz, 2H, H-3,5), 7.70 (d, J=8 Hz, 2H, H-2,-6).	21.44(q), 21.65(t), 24.71(t), 30.98(t), 43.03(t), 46.42(t), 55.51(d), 116.45(d), 127.01(d), 127.39(d), 129.56(d), 132.84(d), 137.00(s), 143.16(s).
8	1.4-1.8(m, 6H, CH_2), 1.90(m, 2H, CH_2), 2.42(s, 3H, CH_3),3.70(m, 2H, CH), 4.50(t, J=7 Hz, 2H, CH_2), 5.1(m, 2H, =CH), 5.80(m, 1H, =CH), 7.30(d, J=8 Hz, 2H, H-3,5), 7.70 (d, J=8 Hz, 2H, H-2,6).	21.38(q), 21.58(t), 24.27(t), 28.60(t), 29.05(t), 41.55(t), 55.48(d), 72.89(t), 116.39(d), 126.23(d), 127.38, 129.70(d), 132.90(d), 136.42(s), 143.38(s).
9	1.13(m, 2H, CH_2), 1.30(m, 2H, CH_2), 1.60(m, 2H, CH_2), 2.30(m, 1H, CH_2), 2.43(s, 3H, CH_3), 2.70(dd, J=14, 3 Hz, 1H, CH_2), 3.08(td, J=14, 3 Hz, 1H, CH_2), 3.21(b t, J=8 Hz, 1H, CH_2) 4.08(dd, J=14,6 Hz, 1H, CH), 4.45 (m, 1H, CH), 4.72(m, 1H, CH), 7.30 (d, J=8 Hz, 2H, H-3,5), 7.72(d, J=8 Hz, 2H, H-2,6).	21.38(q), 19.12(t), 24.89(t), 26.49(t), 39.06(d), 32.33(t), 48.15(t), 53.13(d), 78.53(d), 127.70(d), 129.48(d), 138.00(s), 144.30(s), 154.99(s).
13	1.70(m, 2H, CH_2), 2.10(m, 1H, CH), 2.45(s, 3H, CH_3), 3.05(m, 4H, CH_2N), 3.25(m, 1H, $CHNH_2$), 3.80(dd, J=10,4 Hz, 1H, CH_2O), 3.90(dd, J=10, 6 Hz, 1H, CH_2O), 7.30(d, J=8 Hz, 2H, H-3,5), 7.65(d, J=8 Hz, 2H, H-2,6)	
14	1.60(m, 6H, CH_2), 1.95(m, 2H, CH_2), 2.25(m, 1H, CH), 2.85(dt, J=12, 3 Hz, 1H, CH_2N), 3.08(ddd, J= 13,7,1 Hz, 1H, CH_2N), 3.20(t, J=8.5 Hz, 1H, CH_2N), 3.45(m, 1H, CHN), 4.70(m, 1H, CHO)	

16a	2.14(dd, J= 10.5, 8.5 Hz, 1H, CH_2), 2.36(dd, J= 10.5, 4Hz, 1H, CH_2), 2.44(s, 3H, CH_3), 3.00(m, 3H, CH, CH_2), 3.28(dd, J= 13, 7Hz, 1H, $=NCH_2$), 3.4(dd, J=12, 6Hz, 1H, $=NCH_2$), 3.58(m, 2H, CH_2), 7.34(d, J=8 Hz, 2H,H-3,5), 7.62(d, J=8 Hz, 2H, H-2,6).	21.49(q), 44.42(t), 46.34(t), 48.90(t), 53.64(d), 53.83(t), 127.78(d), 129.72(d), 132.63(s), 143.77(s).
16b	1.86(m, 2H, CH_2), 2.43(s,3H, CH_3), 2.78(m, 1H, CH_2), 2.90(dd, J=14, 8 Hz, 1H, CH_2), 3.05(m, 2H, CH_2), 3.20(m,1H, $=NCH_2$), 3.28(dd, J=12, 7 Hz, 1H, CH_2), 3.35(dd, J=12, 5 Hz, 1H, CH_2), 3.43(m, 1H, $=NCH_2$). 3.52(ddd, J=7 3, 1 Hz, 1H, CH), 7.30(d, J=8 Hz, 2H, H-3,5), 7.67(d, J=8 Hz, 2H, H-2,6).	21.48(q), 31.54(t), 44.97(t), 48.41(t), 52.95(t), 53.99(t), 58.41(d), 126.90(d), 129.73(d), 136.17(s), 143.30(s).
16c	1.67(m, 2H, CH_2), 1.80(m, 2H, CH_2), 2.44(s, 3H, CH_3), 2.79(m, 1H, CH_2), 2.94(m, 1H, CH_2),3.02-3.38(m, 7H, CH, CH_2), 7.31(d, J=8 Hz, 2H, H-3,5), 7.61(d, J=8 Hz, 2H, H-2,6).	21.48(q), 25.83(t), 28.04(t), 47.15(t), 50.20(t), 52.40(t), 54.57(t), 57.50(d), 126.89(d), 129.72(d), 136.14(s), 143,31(s).
17	0.92(d, J=6 Hz, 3H, CH_3), 1.35(m, 1H, CH), 1.91(m, 1H, CH_2), 2.12(m 1H, CH_2), 2.43(s ,3H, CH_3),2.74(dd, J=9.5, 7.5 Hz, 1H, CH_2), 3.22(m, 1H, CH_2), 3.33(m, 1H, CH_2), 3.42(dd, J=9.5, 7 Hz, 1H, CH_2), 7.31(d, J=8Hz, H-3,5), 7.71(d, J=8 Hz, 2H, H-2,6).	17.69(q), 21.51(q), 33.32(t), 33.40(d), 47.62(t), 54.81(t), 127.59(d), 129.56(d), 134.38(s), 143.12(s).
18	1.35(m, 2H, CH_2), 1.60(m, 6H, CH_2), 1.85(m, 3H, CH,CH_2), 2.41(s, 3H, CH_3), 3.15(m, 1H, CH), 3.52(m, 2H, CH_2), 7.38(d, J=8 Hz, 2H, H-3,5), 7.70(d, J=8 Hz, 2H, H-2,6).	21.49(q), 25.31(t), 26.31(t), 27.85(t), 29.87(t), 37.74(d), 47.21(t), 59.57(d), 127.28(d), 129.52(d), 135.40(s), 142.94(s)

tributyltin hydride to produce pyrrolidines as illustrated by formation of **17** and **18** from **3a** and **7a** respectively. The ^{1}H-nmr of **17** is almost identical to the one reported with the N-benzenesulfonyl group replacing the tosyl group.[10] Extensions of the scope and synthetic potential of these cyclizations are been investigated.

EXPERIMENTAL

^{1}H-Nmr and ^{13}C-nmr were recorded on a Bruker 300MHz spectrometer. ^{1}H-Nmr and ^{13}C-nmr spectra of the products are shown in the Table. Chemical shifts were recorded in ppm downfield from an internal standared (tetramethylsilane). The following abbreviations were used: s=singlet, d=doublet, t=triplet, q=quartet, p=quintet, b=broad, m=multiplet. Mass spectra were measured on a Finnigan 4021 mass spectrometer. Chromatographic separations were made using a silica gel (70-230mesh, Merck) column. Thin layer chromatography (tlc) was carried out with pre-coated silica gel plates (Kieselgel 60 F_{254}-Merck).

General Procedure for the Preparation of N-(Bromoalkyl)allylamines (**3**) --- A typical procedure is described for N-tosyl-N-(2-bromoethyl)allylamine (**3a**): Freshly powdered KOH (0.33 g, 6 mmol) was added to a mixture of allylamine **1a** (1.3 g, 6 mmol), dibromoethane (**2a**) (1.12 g, 6 mmol) and tetrabutylammonium bromide (0.2 g, 0.6 mmol) in THF (30 ml) followed by stirring at room temperature for 15 h. The solvent was evaporated under reduced pressure, followed by extraction with ether. The organic layer was washed with brine solution, dried over Na_2SO_4 and evaporated. Chromatographic separation using petroleum ether-ethyl acetate (8:2) as a eluant gave **3a** as colourles oil in 82% yield (1.6 g), bp 230-232°C. Ms m/z 320/318 (MH^+), 292/290, 238, 224, 155.

N-Tosyl-N-(3-bromopropyl)allylamine (**3b**)-- Obtained as an oil (95%). Ms m/z: 334/332 (MH^+), 252, 224, 155.

N-Tosyl-N-(4-bromobutyl)allylamine (**3c**)-- Chromatography followed by recrystallization from chloroform-petroleum ether(1:5) give colourless crystals (97%) of 3b, mp 38-40°C. Ms m/z: 348/346 (MH^+), 320/318, 266, 238, 224, 155.

N-Tosyl-N-(5-bromopentyl)allylamine (**3d**)-- Obtained as an oil (55%). Ms m/z: 362/360 (MH^+), 280, 224, 155.

N-Tosyl-N-(2-bromoethyl)-2-cyclohexenylallylamine (**7a**)-- Isolated as an oil (20%). Ms m/z: 360/358 (MH^+), 278, 155.

N-Tosyl-N-(3-bromopropyl)-2-cyclohexenylallylamine (7b)-- Chromatography and recrystallization from chloroform-petroleum ether(1:5) give colourless crystals (70%) of 7b, mp 67-68°C. Ms m/z: 374/372 (MH^+), 292, 264, 212.

General Procedure for Preparation of N-(Nitroalkyl)allylamines (4)---. A typical procedure is described for N-tosyl-N-(2-nitroethyl)allylamine (4a): To a solution of N-(2-bromoethyl)allylamine (3a) (3.3 g, 10 mmol) in dry ether (50 ml) was added $AgNO_2$ (3 g, 18 mmol). After stirring the solution at room temperature for 8 days, the black solid was filtered. Evaporation of the solvent under reduced presure and chromatographic separation of the residue by elution with petroleum ether-ethyl acetate (8:2) gave 4a as a yellow oil in 7.5% yield (0.2 g). Starting material 3a was also isolated. Ms m/z: 285 (MH^+), 267, 155.

N-Tosyl-N-(3-nitropropyl)allylamine (4b) -- Elution with petroleum ether-ethyl acetate (8:2) gave 4b as an oil (20%). High-resolution ms Calcd for $C_{13}H_{16}N_2SO_4$: 297.9800. Found 297.9860. Ms m/z: 299 (MH^+), 281, 270, 252, 241, 224, 155;

N-Tosyl-N-(4-nitrobutyl)allylamine (4c) -- After column chromatography and recrystallization from chloroform-petroleum ether (1:5), 4c was obtained as colourless needles (40%), mp 62-64°C. Ms m/z: 313 (MH^+), 266, 224, 157, 140.

N-Tosyl-N-(5-nitropentyl)allylamine (4d) -- Isolated as an oil (38%). Ms m/z: 327 (MH^+), 280, 224, 155, 137.

N-Tosyl-N-(3-nitropropyl)-2-cyclohexenylallylamine (8) -- After column chromatography and recrystallization from chloroform-petroleum ether(1:5), 8 was obtained as a colourless crystalline solid (35%), mp 87-89°C. Ms m/z: 339 (MH^+), 292, 259, 241, 230, 212, 155.

General Procedure for Preparation of Isoxazolines --- A typical procedure is described for N-tosylpiperidino[4,3-c]-4',5'-dihydroisoxazole (6b): Phenyl isocyanate (0.28 g, 2.3 mmol) was added to a solution of alkylnitroallylamine (4b) (0.2 g, 0.67 mmol) in benzene (25 ml) at room temperature followed by the addition of a catalytic amount of triethylamine. Stirring was continued for 18 h. The reaction mixture was filtered and evaporated under reduced pressure to give a solid mass, which on chromatographic separation using chloroform as eluant and recrystallization from ethanol gave 6c in 80% yield (0.132 g) as a white crystalline solid, mp 168-169°C. High-resolution ms Calcd for $C_{13}H_{13}N_2SO_3$: 279.0977. Found: 279.0802. Ms m/z: 281 (MH^+), 279, 264, 246, 231.

N-Tosylpyrrolidino[4,3-c]-4',5'-dihydroisoxazole (6a) -- After chromatography and crystalization from ethanol 6a was obtained as a white crystalline solid (85%), mp

133-134°C. Ms m/z: 267 (MH^+), 251, 155, 95. Anal. Calcd for $C_{12}H_{14}N_2SO_3$: C, 54.13; H, 5.30; N, 10.52. Found: C, 54.02; H, 5.38; N, 9.96.

N-Tosylperhydroazepino[4,3-c]-4',5'-dihydroisoxazole (**6c**) -- After column chromatography and crystallization from ethanol **6c** was isolated as a white crystalline solid 35% , mp 170-172°C. Ms m/z: 295 (MH^+), 279, 267, 213, 155, 93.

N-Tosylperhydroazocino[4,3-c]-4',5'-dihydroisoxazole (**6d**) --Isolated as an oil (10%). Ms m/z: 309 (MH^+), 278, 240, 224, 184, 155, 124 (100%), 91.

N-Tosylperhydroquinolino[4,6-3',5']-4',5'-dihydroisoxazole (**9**) --Chromatographic separation followed by recrystallization from ethanol gave **9** in 45% yield as a white crystalline solid, mp 140-141°C. Ms m/z: 320 (M^+), 288, 212, 165, 137(100%), 119, 93; High-resolution ms Calcd for $C_{16}H_{20}N_2SO_3$: 320.1362. Found: 320.1056.

Alternative Preparation of N-Tosylpiperidino[4,3-c]-4',5'-dihydroisoxazole (**6b**) -- A solution of N-tosylallylamino-N-propanaldoxime (**10c**) (0.30 g, 1.2 mmol) and chloramine-T.$2H_2O$ (0.30 g, 1.2 mmol) in ethanol (20 ml) was refluxed for 3 h followed by evaporation under reduced pressure. The ethereal extract was washed with 1N NaOH, brine solution and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure, chromatographic separation using chloroform as eluant and recrystallization from ethanol gave 0.19 g of **6b** (65%) as a white crystalline solid, identical to **6b** described above.

N-Tosylpiperidino[3,4-c]-4',5'-dihydroisoxazole (**6e**) --- A solution of unsaturated aldoxime (**12c**) (0.10 g, 0.38 mmol) and chloramine-T.$2H_2O$ (0.13 g, 0.46 mmol) in ethanol (15 ml) was refluxed for 3 h. Evaporation of the solvent under reduced pressure and chromatographic separation using chloroform as eluant and recrystallization from ethanol gave 0.1 g of **6e** (80%) as a white crystalline solid, mp 160-162°C. High-resolution ms Calcd for $C_{13}H_{16}N_2SO_3$: 280.0985. Found: 280.0766. Ms m/z: 281 (MH^+), 280, 263, 194, 184, 155, 125.

General Procedure for Reductive Clevage of Isoxazolines (**6**) --- A typical procedure for preparation of N-tosyl-4-amino-3-hydroxymethylpiperidine (**13**): LAH (0.05 g, 0.13 mmol) was added to a solution of N-tosylpiperidinoisoxazoline (**6b**) (0.1g, 0.35 mmol) in 30 ml of dry ether followed by reflux for 2 h. LAH was decomposed by the addition of ethyl acetate. Evaporation of the solvent under reduce pressure and chromatographic separation of the residue on alumina using chloroform as eluant gave 0.056 g of **13** as a white solid in 58% yield. Ms m/z: 285 (MH^+), 267, 250, 241, 224, 155, 129.

N-Tosyl-4-amino-5-hydroxyperhydroindole derivatives (**14**) -- Chromatographic

separation of the residue on alumina using chloroform as eluant gave (**14**) as white solid in 60% yield. Ms m/z: 171 (MH^+), 153, 139, 122, 111.

General Procedure for Preparation of Triazolines (**16**) --- A typical procedure for preparation of N-tosyltriazolinopiperazine (**16a**): Sodium azide (0.72 g, 10 mmol) was added to a solution of N-(bromoethyl)allyamine (**3a**) (1.1g, 3.5 mmol) in 15 ml dimethyl sulfoxide-water (3:1) followed by heating at 80°C for 6 h. The benzene extract was washed thoroughly with brine solution, dried over Na_2SO_4, and evaporated. Chromatographic separation using chloroform as eluant gave **16a** as an pale yellow oil in 25% (0.25 g) yield. Ms m/z: 281 (MH^+), 253, 155, 91.

N-Tosyltriazolinodiazepine (**16b**) -- Heating of **3b** with NaN_3 at 100°C, followed by chromatographic separation using chloroform as eluant gave **16b** as an pale yellow oil in 45% yield. Ms m/z: 295 (MH^+), 267, 155, 140, 91.

N-Tosyltriazolinodiazocine (**16c**) -- Heating of **3c** with NaN_3 at 120°C, followed by chromatographic separation using chloroform as eluant gave **16c** as an pale yellow oil in 5% yield. Ms m/z: 309 (MH^+), 281, 155, 154.

General Procedure for Radical Cyclization --- A typical procedure for preparation of N-Tosyl-3-methylpyrrolidine (**17**): Tributyltin hydride (0.38 g, 1.4 mmol) was added to a solution of N-(bromoethyl)allyamine (**3a**) (0.44 g, 1.38 mmol) in benzene (15 ml) followed by the addition of a catalytic amount of AIBN. After refluxing for 2 h, solvent was evaporated. Chromatographic separation using petroleum ether-ethyl acetate (8:2) as eluant and recrystallization from chloroform-petroleum ether (1:5) gave **17** in 78% yield (0.26 g) as a white crystalline solid, mp 80-82°C. Ms m/z: 240 (MH^+), 238, 148.

N-Tosylperhydroindole (**18**) -- Chromatographic separation using petroleum ether-ethyl acetate (8:2) as eluant gave **18** in 80% yield as an oil. Ms m/z: 280 (MH^+), 278, 184, 155.

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REFERENCES

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1. Synthetic methods 33. For paper 32 see E.Ghera, R.Maurya, and A. Hassner, Tetrahedron Lett., 1989, **54**, 4741.

2. See for instance A. P. Kozikowski, Accts Chem. Res., 1984, **17**, 410 ; V. Jager, V. Buss, and W. Schwab, Tetrahedron Lett., 1978, 3133; V. Jager and R. Schohe, Tetrahedron, 1984, **40**, 2199; A. P. Kozikowski and P. D. Stein, J. Am. Chem. Soc., 1982, **104**, 4024; D. P. Curran and B. H. Kim, Synthesis, 1986, 312; P. Caramella and P. Grunanger, "1,3-Dipolar Cycloaddition Chemistry", ed. by A. Padwa, Vol 1, Chapter 3, J. Wiley and Sons, 1984, p.337 and references cited; A. Hassner and K. S. K. Murthy , Tetrahedron Lett., 1986, **27**, 1407.

3. A. Hassner and K. S. K. Murthy , Tetrahedron Lett., 1987, **28**, 683, 4097; A. Hassner, K. S. K. Murthy, A. Padwa, W. H. Bullock, and P. D. Stull, J. Org. Chem., 1988, **53**, 5063.

4. K. S. K. Murthy and A. Hassner , Tetrahedron Lett., 1987, **28**, 97.

5. A. Abad, D. Mellier, J. P. Pete, and C. Portella, Tetrahedron Lett., 1971, 4555.

6. T. Fujita and J. M. Lehn, Tetrahedron Lett., 1988, **29**, 1709.

7. T. Mukaiyama and T. Hoshino, J. Am. Chem. Soc., 1960, **82**, 5339.

8. A. Hassner and K. M. L. Rai, Synthesis, 1989, 57.

9. A. G. Hortmann, D. A. Robertson, and B. K. Gillard, J. Org. Chem., 1972, **37**, 322.

10. Y. Ueno, C. Tanaka, and M. Okawara, Chem. Lett., 1983, 795; A. Padwa, H. Nimmesger, and G. S. K. Wong, Tetrahedron Lett., 1985, **26**, 957; Y. Watanabe, Y. Ueno, C. Tanaka, M. Okawara, and T. Endo, Tetrahedron Lett., 1987, **28**, 3953.

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