APROTIC CHLORIDE AND BROMIDE-PROMOTED ALKYNE–IMINIUM ION CYCLIZATIONS**

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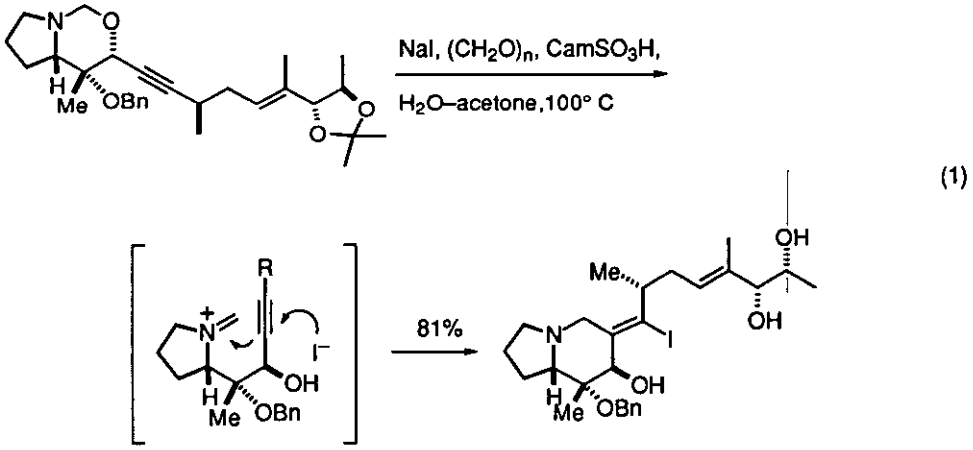
Abstract- The title cyclizations of 4-alkynyl- and 3-alkynyl-*N*-(methoxymethyl)-amines occur under milder conditions, and in the case of chloride in higher yields, than direct cyclizations of the corresponding secondary amine with formaldehyde and a halide salt.

The discovery that simple iminium ions react with tethered alkynes in the presence of external nucleophiles broadened the scope of Mannich cyclization chemistry.[2] Iodide has proven to be the most useful promoter and cyclizations with this nucleophile can be carried out in a wide variety of solvents including water. Aqueous NaI-promoted alkyne–formaldiminium ion cyclizations are the central steps in efficient syntheses of the pumiliotoxin A and allopumiliotoxin alkaloids developed recently in our laboratories (e.g., eq 1).[3] In order to extend the range of nucleophiles that can be employed in these cyclizations,[4] we have examined related cyclizations of formaldehyde *N,O*-acetals. We now report that under strictly anhydrous conditions nucleophiles as weak as chloride are effective cyclization promoters.[6]

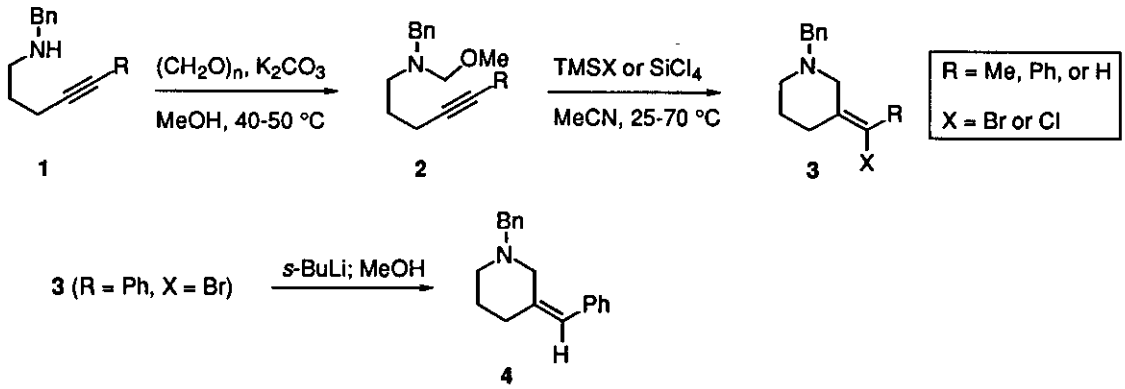


(1)

According to established precedents,[7] 4-alkynyl-*N*-(methoxymethyl)amines (2) were prepared from the corresponding secondary 4-alkynylamines (1)[2] in yields of 90-95% (Scheme 1). Since these *N,O*-acetals decomposed gradually upon storage at room temperature, freshly prepared crude acetals were azeotropically dried with toluene under vacuum (twice) and, in most cases, used without further purification. Treatment of

** Dedicated to the memory of the scientific accomplishments and character of Professor Yoshio Ban.

Scheme 1



4-alkynyl-*N*,*O*-acetals (**2**) with TMSCl[8], $SiCl_4$,[8] or TMSBr[9] at 25-70 °C in MeCN (0.05-0.1 M) gave 3-(1-haloalkylidene)piperidines (**3**) in good yields (Scheme 1 and Table 1).[11]

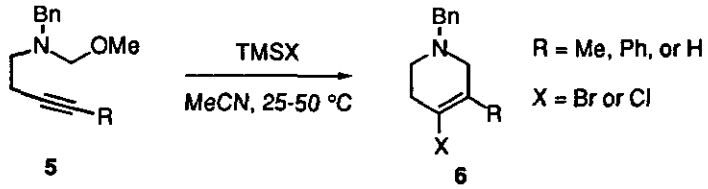
Cyclizations of the more nucleophilic internal alkynes (**2**) (R = Me or Ph) took place at 25-50 °C , while 70 °C was required for cyclizations of the terminal alkynyl substrate. Cyclization occurred exclusively in the 6-exo mode with high stereoselectivity to form the (*E*)-1-haloalkylidene stereoisomer (**3**): no trace of the (*Z*)-alkylidene stereoisomer was seen by ^{13}C nmr analysis of the crude cyclization product when the terminal substituent was Me or H (Table 1, entries 1-3 and 6-8), while 6-7% of the (*Z*)-alkylidene stereoisomer was observed in the phenyl series (Table 1, entries 4 and 5).[13] Stereochemical assignments for **3** (R = H or Me) are based on ^1H nOes detected between the vinylic substituent and the C-2 methylene hydrogens, while assignments for **3** (R = Ph) followed from the large ^1H nOe observed between the vinylic hydrogen and the C-4 methylene hydrogens of the reduction product (**4**) (Scheme 1).

Table 1. Preparation of 3-(1-haloalkylidene)piperidines (**3**).[a]

			reaction conditions			alkylidenepiperidine (**3**)
entry	R	X	promoter (equiv)	temp (°C)	time (h)	yield (%)
1	Me	Cl	TMSCl (4)	25	4	69
2	Me	Cl	TMSCl (4)	25	6	78
3	Me	Br	TMSBr (4)	25	17	83
4	Ph	Cl	TMSCl (4)	50	4	93[b]
5	Ph	Br	TMSBr (4)	25	19	81[c]
6	H	Cl	TMSCl (4)	70	13	44
7	H	Cl	$SiCl_4$ (2)	70	8	64
8	H	Br	TMSBr (4)[d]	70	3	60

[a] Cyclizations were performed at 0.1 M in MeCN; CH_2Cl_2 was used as the solvent in entry 2. [b] *E*/*Z* ratio was 93:7 by glc analysis. [c] *E*/*Z* ratio was 94:6 by glc analysis. [d] TMSBr was prepared in situ from hexamethyldisilane and Br_2 and the substrate concentration was 0.05 M.

Identical treatment of 3-alkynyl-*N,O*-acetals (**5**) afforded 4-halo-1,2,5,6-tetrahydropyridines (**6**) (eq 2, Table 2). Yields of **6** (R = Me or H) were good, while cyclizations in the phenyl series proceeded in lower efficiency. Purification of *N,O*-acetal (**5**) (R = Me) by bulb-to-bulb distillation from K_2CO_3 immediately prior to cyclization resulted in some improvement in the chemical yield (Table 2, compare entries 1-4).



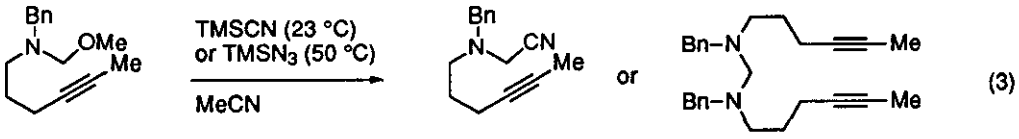
5 **6**

Table 2. Preparation of 4-halo-1,2,5,6-tetrahydropyridines (**6**).[a]

			reaction conditions			tetrahydropyridine (6)
entry	R	X	promoter (equiv)	temp (°C)	time (h)	yield (%)
1	Me	Cl	TMSCl (4)	40	1	58
2[b]	Me	Cl	TMSCl (4)	50	3	71
3	Me	Br	TMSBr (4)	25	7	77
4[b]	H	Br	TMSBr (4)	50	3	82
5	Ph	Cl	TMSCl (4)	50	1	47
6	Ph	Br	TMSBr (4)	40	1	50

[a] Cyclizations were performed at 0.1 M. [b] Freshly distilled *N,O*-acetal was used.

Attempts to extend these aprotic cyclizations to non-halide nucleophiles such as TMSCN, $TMSN_3$, TMSOAc, TMSOTf were unsuccessful. For example, treatment of **2** (R = Me) with TMSCN provided the cyanomethylamine (**7**) in 81% yield, while diaminomethane (**8**) was the major product (82%) formed from reaction of this substrate with $TMSN_3$.



2 (R = Me) **7** **8**

In summary, (*E*)-3-(1-haloalkylidene)piperidines and 4-halo-1,2,5,6-tetrahydropyridines can be prepared by halide-promoted Mannich cyclizations of 4-alkynyl- and 3-alkynyl-*N,O*-acetals, respectively.[14] These aprotic cyclizations occur under milder conditions and in higher yields than related direct cyclizations of the corresponding secondary amine with formaldehyde and a halide salt.[3]

ACKNOWLEDGMENTS

This work was supported by NIH grant HL-25854. Nmr and mass spectra were determined at UCI using instruments purchased with the assistance of NSF Shared Instrumentation Grants.

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4. Under our previous protic conditions, nonbasic nucleophiles with nucleophilic constants[5] η-MeI>5.8 are useful cyclization promoters.

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9. Use of TMSBr prepared in situ from $(TMS)_2$ and Br_2[10] gave results similar to those obtained with TMSBr purchased from Aldrich Chemical Co.

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11. Halide-promoted cyclizations can also be accomplished with $MeSiCl_3$, ZnX_2 (X = Cl, Br), or a mixture of TiX_4/*n*-Bu_4NX (X = Cl, Br). However, $TiCl_4$ and $SnCl_4$ were ineffective.[12]

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13. We were unable to obtain this minor product in pure form, therefore the structural assignment is provisional. That this material was likely the (Z)-stereoisomer was consistent with the MS fragmentation pattern (from GC-MS analysis), which was identical to that of **3** (R = Ph).

14. *Representative Experimental Procedure. Preparation of (E)-1-Benzyl-3-(1-bromoethylidene)-piperidine. (3, R = Me, X = Br)* A solution of TMSBr (0.26 ml, 2.0 mmol) and *N,O*-acetal (**2**) (R = Me, 114 mg, 0.50 mmol) in dry MeCN (8 ml) was maintained in a sealed tube at 25 °C for 17 h. The reaction then was partitioned between 1 M NaOH (10 ml) and Et_2O (10 ml). The aqueous layer was extracted with Et_2O (2 x 10 ml) and the combined organic layers were washed with brine (10 ml), dried ($MgSO_4$), and filtered. Concentration followed by purification of the residue by column

chromatography (SiO_2, 9-7:1 hexanes-Et_2O, 5 % Et_3N) gave 115 mg (83 %) of **3** (R = Me, X = Br) as a nearly colorless oil: Ir (film) 2923, 1661, 1454, 1243, 1141, 1121, 1070, 736 cm^{-1}; ^1H nmr (250 MHz, $CDCl_3$) δ 7.20-7.40 (m, 5H, Ph), 3.56 (s, 2H, CH_2Ph), 3.03 (s, 2H, $NCH_2C{=}C$), 2.55 (t, J = 5.2 Hz, 2H, NCH_2CH_2), 2.42 (t, J = 6.1 Hz, 2H, $CH_2C{=}C$), 2.21 (s, 3H, CH_3), 1.65-1.72 (m, 2H, NCH_2CH_2); ^{13}C nmr (75 MHz, $CDCl_3$) δ 138.0, 132.9, 129.0, 128.2, 127.1, 116.5, 62.2, 54.9, 53.6, 32.9, 25.1, 24.6; ms (EI) *m/z* 281.0575, 279.0607 (281.0601, 279.0622 calcd for $C_{14}H_{18}N^{81}Br$, $C_{14}H_{18}NBr$). Oxalate salt: mp 183-184 °C (EtOAc); Anal. Calcd for $C_{16}H_{20}NO_4Br$: C, 51.90; H, 5.45; N, 3.78. Found: C, 51.83; H, 5.48; N, 3.79.

Received, 16th August, 1995