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Synthesis of Functionalized Cyclic Imines by Addition of Grignard Reagents to ω-Bromonitriles and γ,δ-Unsaturated Nitriles

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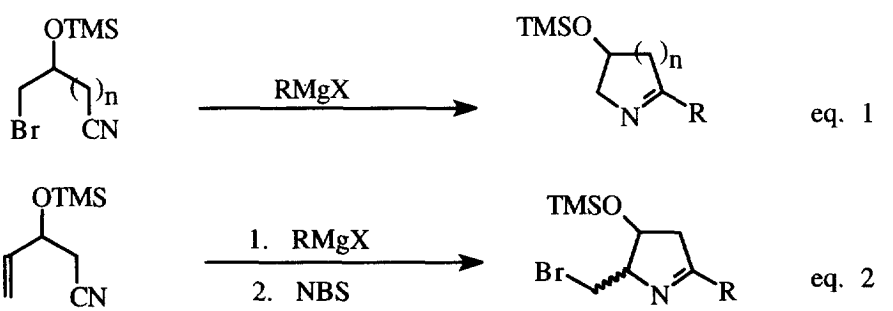
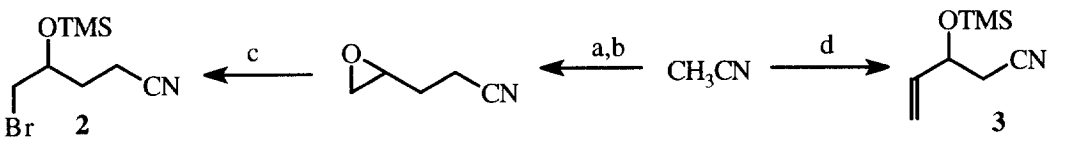
Abstract: Trimethylsilyloxy ω-bromonitriles and trimethylsilyloxy-γ,δ-unsaturated nitriles give clean 1,2-addition products with Grignard reagents that can be induced to undergo subsequent cyclization either directly or by addition of *N*-bromosuccinimide, respectively.

Cyclic imines are potentially versatile synthetic intermediates for alkaloid natural product synthesis and their preparation[1] has attracted renewed synthetic interest. Recently, we reported[2] that 2-alkyl or 2-aryl substituted cyclic imines could be prepared by addition of Grignard reagents to ω-bromonitriles in good overall yields by employing aromatic or hydrocarbon solvents. The utilization of non-polar solvents was essential for the efficient Grignard addition and subsequent cyclization employing α-unsubstituted ω-bromonitriles prone to enolization. Subsequently, two reports appeared on the synthesis of 2-substituted-1-pyrrolines via cyclization of butenyl azides[3] and via addition of γ,δ-unsaturated Grignard reagents to aromatic nitriles[4] followed by bromocyclization. These procedures were all limited to the preparation of simple unfunctionalized cyclic imines or to pyrrolines functionalized with a bromomethyl group. Recognizing that efficient alkaloid syntheses required preparation of functionalized cyclic imines, we set out to develop efficient synthetic routes to silyloxy-substituted ω-bromo- and γ,δ-unsaturated nitriles and to examine their potential utility in the tandem Grignard addition-cyclization reactions (eqs. 1-2).



Regioselective ring opening of ω-epoxynitriles provided a viable path to the requisite ω-bromonitriles. Treatment of epibromohydrin with trimethylsilyl cyanide (TMSCN) in the presence of 18-crown-6/KCN complex afforded bromonitrile **1**[5] in low overall yield (25%). More efficacious conditions (70% yield of **1**) involved the ring opening of epibromohydrin with TMSCN in the presence of a catalytic amount of $Yb(CN)_3$ prepared from $YbCl_3$, *n*-BuLi, and TMSCN.[6] The homologous bromonitrile **2** was prepared by a synthetic sequence involving alkylation of acetonitrile with allyl bromide followed by epoxidation and subsequent ring cleavage of the 2-cyanoethyl oxirane[7] with TMSBr (Scheme I). Intrigued by the possibility of combining Grignard addition to alkyl nitriles with *N*-bromosuccinimide-promoted bromocyclization, we prepared 3-[(trimethylsilyl)oxy]-4-pentenenitrile[5] (**3**) in a single step by addition of the acetonitrile enolate anion to acrolein (Scheme I) follow by quenching with TMSCl.[8]

Scheme I[a]

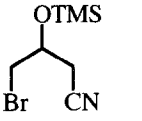
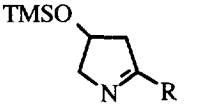
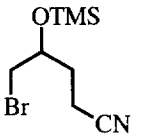
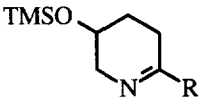
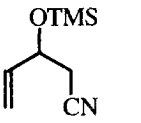
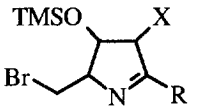


[a] (a) i. *n*-BuLi, THF, -78°C. ii. allyl bromide (75%). (b) *m*-CPBA, CH_2Cl_2, (90%). (c) TMSBr, 0 to 25 °C, (65%). (d) i. *n*-BuLi, THF, -78°C. ii. acrolein. iii. TMSCl (70%).

With the requisite ω-bromosilyloxynitriles or silyloxyalkenyl nitrile in hand, we examined their tandem Grignard addition-cyclization reactions. Treatment of bromonitrile **1** with alkyl or aryl Grignard reagents in benzene cleanly afforded the cyclic imines in good yields (Table 1, entries 1-3). Attempted purification by vacuum distillation resulted in a facile conversion to the corresponding pyrrole which also occurred to a lesser extent on neutral alumina. Purification using activity III basic alumina gave good yields of isolated products which were unstable to elimination of trimethylsilanol in the presence of trace amounts of acid. Reaction of bromonitrile **2** with alkyl and aryl Grignard reagents also gave cyclic imines cleanly and in significantly better yields (Table, entries 4-7). In these reactions, cyclization to the six-membered cyclic imines required addition of THF to the reaction mixture after addition of the Grignard to the nitrile was complete in order to facilitate the cyclization reaction.

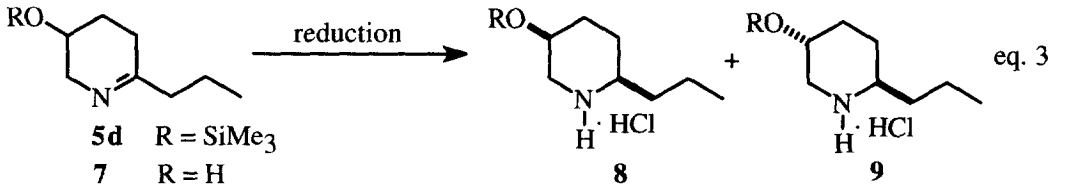
Initially, reaction of alkenylnitrile **3** with PhMgBr followed by treatment with excess *N*-bromosuccinimide (NBS) gave a mixture of **6a** and **6b** in modest yield (**Table 1**, entry 8). Utilizing one equivalent of NBS gave the highly functionalized pyrroline **6a** in good yield (entry 9) largely as a single diastereomer (2:1 *cis* : *trans* as determined by noe measurements). The dibromo compound **6b** was formed as a single diastereomer and appears to arise via NBS bromination of one of the diastereomers of **6a**. Attempted utilization of *n*-BuMgCl or $PhCH_2MgCl$ (entries 10-11) resulted only in a rapid polymerization process yielding material that could not be readily extracted into organic solvents. In this regard, it is interesting to note that the yields of **4a-c** are inversely related to the expected basicities of the Grignard reagents (i.e., *n*-BuMgX > $PhCH_2MgCl$ > PhMgCl in basicity). This suggests that the allylic silyl ether functionality in **3** may undergo elimination of trimethylsilyloxide in the presence of the more basic alkyl Grignard reagents to give 2,4-pentadienenitrile which undergoes base-promoted polymerization.

Table 1. Tandem Grignard addition-cyclization of trimethylsilyloxy ω-bromonitriles and of a γ,δ-alkenylnitrile.

Entry	Substrate	RMgX	Procedure[a]	Product structures	Products	% Yield[b]
1		*n*-Bu	A		**4a**	49
2		Ph	A		**b**	69
3		$PhCH_2$	A		**c**	57
	1			**4**		
4		*n*-Bu	B		**5a**	81
5		Ph	B		**b**	85
6		$PhCH_2$	B		**c**	63
7		*n*-Pr	B	**5**	**d**	74
	2					
8		Ph	C		**6a/6b**	18/9[c]
9			C		**6a**	58
10		*n*-Bu	C			-
11		$PhCH_2$	C			-
	3			**6a** X = H **b** X = Br		

[a] A = i. PhH, 25°C, 2 h. ii. Sat. NH_4Cl / NH_4OH (1:1, v/v). B = i. PhH, 25°C, 2 h. ii. THF, 25°C, 12 h. iii. Sat. NH_4Cl / NH_4OH (1:1, v/v). C = i. PhH, 25°C, 2 h. ii. NBS in THF. iii. Sat. NH_4Cl / NH_4OH (1:1, v/v). [b] Yields are based upon isolated products purified by column chromatography using either activity III basic alumina (for **4** and **6**) or neutral alumina (for **5**). [c] Yields based upon alkenylnitrile with NBS as limiting reagent (1.5 eq).

The synthetic utility of the tandem Grignard addition to ω-bromonitriles or alkenylnitriles is illustrated by an efficient synthesis of (±)-pseudoconhydrine; the (+)-enantiomer isolated from the poison hemlock *Conium matculatium L.* has been synthesized in both racemic[9,10] and homochiral form.[10] Cyclic silyloxy imine **5d**, prepared in four steps and 33% overall yield from acetonitrile and allyl bromide, was reduced to give a mixture of diastereomers isolated as the hydrochloride salts **8** and **9** (eq. 3). In all instances, catalytic hydrogenation (contrary to the implications of an earlier pseudoconhydrine synthesis[9b]) and metal hydride reductions gave the epi-pseudoconhydrine *cis* diastereomer as the major product (Table 2, entries 1-3). The free alcohol **7** also gave predominately the *cis* diastereomer upon hydrogenation (entries 4-5), but metal hydride reduction at low temperatures (entries 6-7) gave reversed selectivity. Intrigued by the increase in *trans* selectivity upon increasing the temperature from 0 °C to room temperature, the reduction was carried out at reflux in THF to afford the desired (±)-pseudoconhydrine with only a trace of the pseudoconhydrine *cis* diastereomer present (entry 8). The pseudoconhydrine was isolated as the hydrochloride salt **9** which gave a ^{13}C spectrum consistent with a literature report but a ^{1}H spectrum not in complete agreement with the reported chemical shifts.[9a] Conversion of the hydrochloride salt **9** to (±)-pseudoconhydronine afforded a sample which gave ^{1}H and ^{13}C spectra consistent with the literature report.[9a]



5d R = $SiMe_3$ **8** **9**

7 R = H

Table 2. Diastereoselectivity in the reduction of cyclic imines **5d** and **7**.

entry	substrate	reduction cond	% yields[a]	ratio **8** / **9**[b]
1	**5d**	H_2/Pt, EtOH, HCl	>95	61 : 39
2		i. H_2/Pt, EtOH ii. conc HCl	>95	90 : 10
3		i. $NaBH_4$, MeOH ii. conc HCl	98	70 : 30
4	**7**	i. H_2/Pt, EtOAc ii. conc HCl	95	60 : 40
5		i. H_2/Pt, hexane ii. conc HCl	>95	59 : 41
6		i. $LiAlH_4$, THF, 0°C ii. conc HCl	38[c]	33 : 67
7		i. $LiAlH_4$, THF, 0°C to rt, 14 h. ii. conc HCl	57[c]	17 : 83
8		i. $LiAlH_4$, THF, reflux, 3 h. ii. conc HCl	86	<5 : 95

[a] Yields are based on crude products > 95% pure by ^1H NMR analysis. [b] Diastereomer ratios were determined by integration ratios of absorptions in the ^1H NMR spectra. [c] Starting cyclic imine present.

In summary, silyloxy functionalized ω-bromonitriles or ω-alkenylnitriles can be efficiently prepared and converted into functionalized cyclic imines via the tandem Grignard addition-cyclization process. Since the cyclization procedure can be effected on either a halide or olefinic center the strategy offers considerable versatility. The commercial availability of both epichlorohydrin and glycidol in both enantiomeric forms provides for a convenient synthetic route to functionalized homochiral five- and six-membered cyclic imines for use in alkaloid natural product syntheses. Studies along these lines are in progress.

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