mer B, 42968-09-2; **5** picrate, 42968-10-5; **6a**, 42968-11-6; **6b**, 42968-12-7; **6b** picrate, 42968-13-8; benzaldehyde, 100-52-7; 2-butanone, 78-93-3; *tert*-butylamine, 78-81-9; piperidine, 110-89-4; morpholine, 110-91-8.

Supplementary Material Available. Full nmr data in Figures 1 and 2 will appear following this article in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-911.

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Synthetic Applications of Trimethylsilyl Cyanide. An Efficient Synthesis of β-Aminomethyl Alcohols

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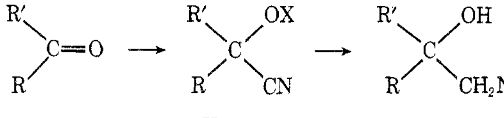
Received September 17, 1973

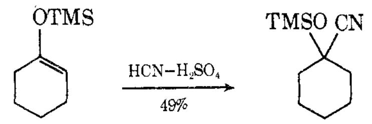
The use of trimethylsilyl cyanide (TMSCN) as a reagent for the direct formation of trimethylsilyl cyanohydrin ethers **3** from ketones is reported. The advantages in using TMSCN as opposed to hydrogen cyanide are illustrated by the formation of cyanohydrin ethers of ketones that do not form stable cyanohydrins. The reduction of derivatives **3** with lithium aluminum hydride is reported to afford β-aminomethyl alcohols **4** in good yield. The combined carbonyl derivatization–reduction sequence should afford a general synthesis of **4** useful in executing ring expansion reactions.

A great deal of attention has been devoted to the conversion of ketones to β-aminomethyl alcohols **4**. Interest in these derivatives has largely centered around their use in the Tiffeneau-Demjanov ring expansion of cycloalkanones.[2] The major difficulty in this general homologation process has been associated with the lack of reliable routes to β-aminomethyl alcohols.

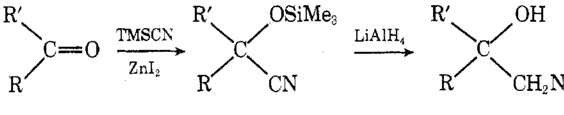


1 2, X = H 3, X = SiMe$_3$ 4

The two classical methods for effecting this transformation have involved the formation and subsequent reduction of either ketone cyanohydrins[3] **2** or β-nitromethyl alcohols.[4] Both procedures have suffered from lack of generality and low overall yields for the desired transformation.[5] For the more widely used homologation sequence proceeding through ketone cyanohydrins, the yield of β-amino alcohol **4** is directly dependent upon the stability of the cyanohydrin **2**, the formation of which is highly dependent upon the steric and strain factors in the ketone.[6] Recently Parham and coworkers have shown that cyanohydrin ethers can be prepared by the acid-catalyzed addition of HCN to both alkyl[7a] and trimethylsilyl enol ethers,[7b,c] and that the resultant cyanohydrin derivatives can be reduced with LiAlH$_4$ to the desired β-amino ethers or alcohols. Although this approach results in the synthesis of derivatives of unstable cyanohydrins, the sequence requires the synthesis of the appropriate enol derivative, thus lengthening as well as restricting the homologation sequence to those systems for which enol ethers are easily prepared.



In conjunction with our interest[8] in exploring the utility of trimethylsilyl cyanide (TMSCN)[9] as a useful reagent in organic synthesis, we would like to report on its advantages in effecting carbonyl aminomethylation *via* the α-silyloxy nitriles **3** (eq 1).

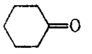
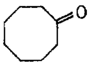
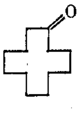
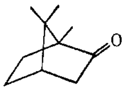
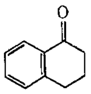
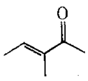


(1)

1 3 4

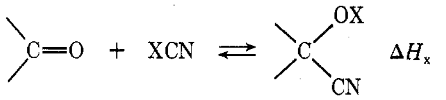
Our previous studies have shown that, in contrast to the substrate sensitivity of HCN–carbonyl addition reactions, the addition of TMSCN to both ketones and aldehydes is a general, high-yield process.[8] Apparently this is a consequence *of the alteration in the* ΔH *for the carbonyl addi-*

Table I
Synthesis of β-Aminomethyl Alcohols 4

1			3			4			
Registry no.	Structure	Identification	Registry no.	Yield, %[a]	Bp, °C (mm)	Registry no.	Yield, %[b]	Mp or bp,[d] °C (mm)	Ref
.108-94-1		**a**	24731-36-0	94	72 (1.0)	19968-85-5	86	206–208	3e
502-49-8		**b**	50361-50-7	94.5	47 (0.03)	50361-56-3	55	217	3a, 3f
830-13-7		**c**	50361-51-8	94.5	80 (0.03)	50361-57-4 832-29-1	59.4	199–200 (124–126)[c]	3h
76-22-2		**d**[14]	50361-52-9	>95[e]		50361-59-6	89.2	258–261	
529-34-0		**e**	50361-53-0	>95[e]		50361-60-9	64[c]	100 (0.003)	
565-62-8		**f**	40326-22-5	91.5	69 (2.0)	50529-56-1	57.2[c]	30 (0.03)	
98-86-2	PhCOCH₃	**g**	25438-38-4	>95[e]		50361-61-0	84.4	138–140	20

[a] Yields were of isolated product except where noted. [b] Amine isolated as the hydrochloride salt except where noted. [c] Isolated as the free amine. [d] Melting points are those of amine hydrochloride; boiling points are for the amino alcohols. [e] Yield determined by glc.

tion reaction when changing from proton to silicon (X = H, SiR_3; eq 2).



$$>C{=}O + XCN \rightleftarrows >C(OX)(CN) \quad \Delta H_x \qquad (2)$$

Although calculations of ΔH_{Si} *vs.* ΔH_H for eq 2 are quite inaccurate owing to the unknown value of the Si-CN bond dissociation energy and the apparent discrepancies in the reported H-C bond dissociation energy in hydrogen cyanide (111 kcal/mol,[10a] 129 kcal/mol[10b]), one may calculate a $\Delta H_{Si} - \Delta H_H$ value of −31 to −49 kcal/mol if a Si-CN bond energy value of 76 kcal.mol is used.[11] Although this calculation is optimistic,[12,13] it is suggestive that the addition of silyl cyanides to carbonyl groups should be energetically more favorable than the corresponding addition reactions of HCN. This prediction has been clearly borne out by experiment.

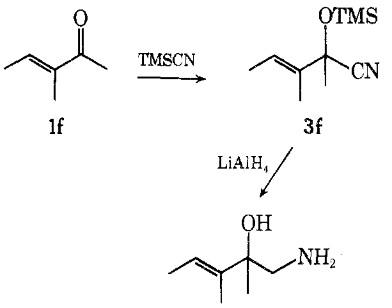
As shown in Table I, the advantage of employing TMSCN in the direct formation of cyanohydrin derivatives 3 is evident. In spite of the reported inability to form cyanohydrins of both camphor[14] and α-tetralone,[6a] we have found that the corresponding trimethylsilyl cyanohydrins 4 may be formed in excellent yields. These results are not surprising in light of our similar observations[8a] with other systems such as benzophenone and 1-indanone, which are also resistant to cyanohydrin formation.[6a] Another unusual property of TMSCN is its regiospecificity in reactions with α,β-unsaturated carbonyl derivatives.[8a,b] For example, 3-methyl-3-penten-2-one (**f**) reacts with TMSCN to give *exclusively* the 1,2 adduct. Direct carbonyl insertion has also been observed to be the exclusive mode of reaction of TMSCN with *p*-quinones.[8b] These observations are in marked contrast to the base-catalyzed addition of hydrogen cyanide with similar substrates. With the exception of the TMSCN–camphor adduct **30**, which exhibited partial reversion to starting materials on distillation, the trimethylsilyl cyanohydrins could be readily distilled without decomposition.

As we have previously reported, the addition of TMSCN to ketones and aldehydes is dramatically catalyzed by both Lewis acids as well as nucleophiles such as cyanide ion.[8c] The choice of zinc iodide as a cyanosilylation catalyst in the present study was arbitrary, and, in systems that are particularly acid labile, other modes of catalysis should work equally well.

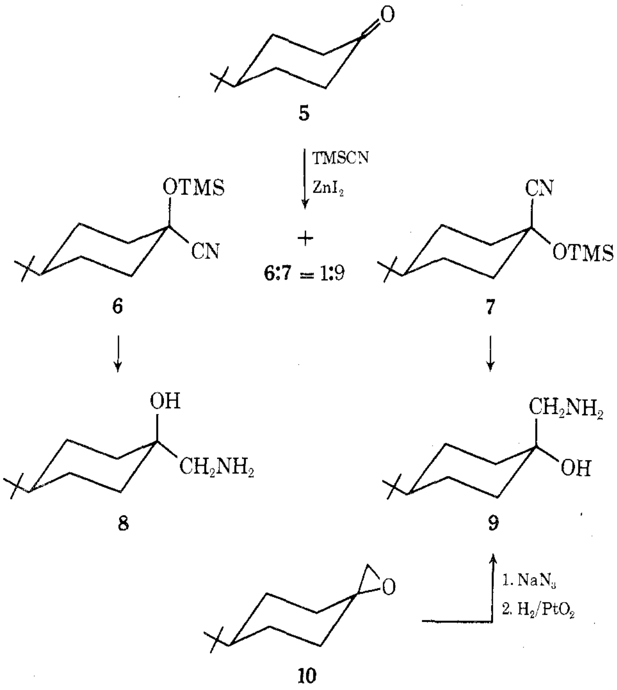
Reduction of the trimethylsilyl cyanohydrins 3 to the desired β-aminomethyl alcohols was carried out with lithium aluminum hydride according to the procedure of Amundsen and Nelson.[15] In most routine ketone aminomethylations the ketone may be simply mixed with 1–1.2 equiv of TMSCN in the presence of a small amount (*ca.* 1–3 mg) of anhydrous zinc iodide in the absence of solvent. With the exception of highly hindered ketones such as camphor where heating (100°, 2 hr) is required, the reaction to form the trimethylsilyl cyanohydrin 3 is exothermic. The cyanohydrin derivatives may be reduced directly to the amino alcohols 4 without purification. For the cases cited in Table I the ketones were cyanosilylated and reduced without isolation of the trimethylsilyl cyanohydrin.

The use of TMSCN for the aminomethylation of α,β-unsaturated ketones should be particularly useful. The desired transformation, illustrated by the conversion of enone **1f** to amino alcohol **4f**, is not possible *via* either the classical cyanohydrin[3] or nitromethane[4] procedures owing to the problems associated with preferential 1,4 addition.

To ascertain the stereochemical course of TMSCN addition to a relatively unhindered but conformationally locked ketone, 4-*tert*-butylcyclohexanone (**5**) was treated with 1.05 equiv of TMSCN in the presence of zinc iodide. The mixture of adducts **6** and **7** formed in a ratio of 1:9 in



97% yield was reduced to the amino alcohols **8** and **9** in 96% yield.[16] Proof that the major diastereoisomer was **9** was confirmed by independent synthesis from the epoxide **10** of known stereochemistry.[17] It appears that the observed isomer ratio of 90:10 for **7**:**6** is a consequence of kinetic rather than thermodynamic control. Although the ratio of **7**:**6** remains unchanged after 24 hr at 25° in the presence of the zinc iodide catalyst, equilibrium can be established at this tempterature with a catalytic amount of potassium cyanide 18-crown-6 complex.[8c] The observed equilibrium ratio of **7**:**6** of 78:22 is in accord with the calculated equilibrium ratio of approximately 72:28 based on the conformational *A* values reported for $-OSiMe_3$[18] and -CN.[19]



Conclusions

Trimethylsilyl cyanide is an excellent reagent for the direct formation of ketone cyanohydrin ethers. The transformation proceeds in excellent yield in a variety of systems. Even hindered ketones which prove to be unreactive toward hydrogen cyanide addition readily form adducts. The reduction of cyanohydrin ethers can be carried out efficiently with lithium aluminum hydride, affording good yields of β-aminomethyl alcohols.

Experimental Section[21]

Trimethylsilyl Cyanide (TMSCN). Procedure A is a modification of that reported by MacDiarmid and coworkers.[9] Procedure B was developed by us as a more economical route for large-scale preparations.

A. A dry, foil-wrapped, 1-l, round-bottom flask, equipped with a mechanical stirrer, was charged with 269.8 g (2.01 mol) of silver cyanide followed by 730 ml (6 mol) of chlorotrimethylsilane.[22] The mixture was mechanically stirred for 3 days. The solution was filtered, yielding a clear organic layer and solid, which was subsequently washed with anhydrous ether and the filtrate and ether washes were combined. Careful distillation using a 60-cm vacuum-jacketed fractionating column produced 158.5 g (1.60 mol, 79.6%) of trimethylsilyl cyanide: bp 114–117° (760 mm); nmr (CCl_4, with $CHCl_3$ as an internal standard) δ 0.4 [s, $Si(CH_3)_3$]; ir (neat) 2210 cm^{-1} (-CN).

B. A dry, 1-l, three-necked reaction vessel equipped with a mechanical stirrer, a spiral reflux condenser, and a Dry Ice condenser protected with a NaOH trap was charged with 500 ml of anhydrous ether and 15.9 g (2.0 mol) of granular lithium hydride. Approximately 150 ml (3.8 mol) of hydrogen cyanide,[23] distilled slowly through a calcium chloride trap maintained at 50–60°, was introduced into the stirred reaction vessel through the spiral condenser inlet over a 2-hr period. The reaction mixture was externally cooled with an ice bath sufficiently to maintain a slow steady reflux at the Dry Ice condenser. Upon completion of the hydrogen cyanide addition, the light brown reaction mixture was stirred for 1 hr at 25°, the spiral reflux condenser was removed, and 250 ml of technical (98%) chlorotrimethylsilane[22] was added over a 30-min period. Stirring was continued for 18 hr at 25°, the Dry Ice condenser was removed, and the solution was heated at reflux (1 hr) to remove excess hydrogen cyanide. The reaction mixture was filtered, the solid residue was rinsed with anhydrous ether, and the combined filtrate was distilled as in procedure A to give 153 g of trimethylsilyl cyanide, bp 117–118°. In several different runs yields of 71–84% based on lithium hydride were obtained.

General Synthesis of Trimethylsilyl Cyanohydrins 3. To 1 equiv of ketone, contained in a dry, one-necked reaction vessel fitted with a serum cap, a static nitrogen head for pressure equilibration, and a magnetic stirring bar, was added *via* syringe 1.1 equiv of trimethylsilyl cyanide containing a catalytic amount of anhydrous zinc iodide with stirring. Approximately 1–10 mg of catalyst is ample for reactions carried out on a 0.1-*M* scale. For unhindered ketones the reaction is exothermic and external cooling may be necessary, while for hindered ketones warming may be required. Although solvents were not used in this study even with solid ketones, the option of employing solvents such as chloroform or benzene has been exercised with no change in yield. The crude yields of adduct are nearly quantitative. In the present study the cyanohydrin ether was either distilled directly from the reaction flask through a 6-in. Vigreux column or used without further purification.

Cyclohexanone cyanohydrin ether (3a)[24] (94%) had bp 72–74° (1 mm); ir (neat) 1246, 838, 750 cm^{-1} ($SiCH_3$); nmr (CCl_4) δ 0.15 (s, 9, CH_3).

Anal. Calcd for $C_{10}H_{19}NOSi$: C, 60.86; H, 9.70. Found: C, 60.78; H, 9.61.

Cyclooctanone cyanohydrin ether (3b) (94.5%) had bp 47° (0.03 mm, molecular distillation); nmr (CCl_4) δ 0.1 [s, 9, $Si(CH_3)_3$], 1.5 (m, 14, CH_2).

Anal. Calcd for $C_{12}H_{23}NOSi$: C, 63.94; H, 10.29. Found: C, 63.76; H, 10.44.

Cyclododecanone cyanohydrin ether (3c) (94.5%) had bp 80° (0.03 mm, molecular distillation); nmr (CCl_4) δ 0.1 [s, 9, $Si(CH_3)_3$], 1.3 (s, 22, ring CH_2); ir (neat) no CN.

Anal. Calcd for $C_{16}H_{31}NOSi$: C, 68.29; H, 11.10. Found: C, 68.39; H, 10.95.

3-Methyl-3-penten-2-one cyanohydrin ether (3f) (91.5%) had bp 68–70° (2 mm); ir (neat) 1665 cm^{-1} (no CN); nmr (CCl_4) δ 0.1 [s, 9, $Si(CH_3)_3$], 1.4, 1.48 (broad s, 9, 3 CH_3), 5.66 (m, 1, $=CH$).

Anal. Calcd for $C_{10}H_{19}NOSi$: C, 60.86; H, 9.70. Found: C, 61.01; H, 9.90.

β-Aminomethyl Alcohols 4a–g. The general conditions for reduction are similar to that reported by Amundsen.[15] A dry, nitrogen-purged, 100-ml, three-necked flask equipped with a mechanical stirrer, reflux condenser, and Hershberg addition funnel was charged with a suspension of 1.53 g (40.4 mmol) of lithium aluminum hydride in 30 ml of anhydrous ether. To this suspension was added a solution of 36 mmol of unpurified cyanohydrin ether **3** in 10 ml of ether dropwise at a rate which maintained gentle reflux of the reaction mixture. Stirring was continued for 1 hr after the addition had been completed. Destruction of the excess lithium aluminum hydride was completed by cautious dropwise addition of 1.5 ml of water followed by dropwise addition of 1.5 ml of 15% NaOH and subsequent addition of 4.5 ml of water. Stirring was continued until a granular white precipitate was formed. Filtration yielded a clear ether solution which was dried over anhydrous sodium sulfate. The amino alcohol 4 may be isolated as the free amine by removing the ether under reduced pressure or, as the amine hydrochloride salt, by bubbling HCl gas through the ether solution to precipitate the amine hydrochloride salt.

1-Aminomethyl-1-cyclohexanol (4a) was isolated as the amine hydrochloride (86%), mp 206–208° (reported[3c] mp 211°).

Anal. Calcd for $C_7H_{16}NOCl$: C, 50.75; H, 9.74. Found: C, 50.84; H, 9.59.

1-Aminomethyl-1-cyclooctanol (4b) was isolated as the amine hydrochloride (55.3%), mp 217° (reported[3a] mp 230°), nmr (DMSO-d_6) δ 1.5 (s, 14, ring CH_2), 2.7 (m, 2, NCH_2), 3.4 (m, 1, OH), 8.0 (m, 3, NH_3).

1-Aminomethyl-1-cyclododecanol (4c) was isolated as the amine hydrochloride (59.4%), mp 199–200° (reported[3h] mp 217°), or as the amine, mp 124–125° (reported[3h] mp 126.6–127.7°), nmr (DMSO-d_6) on amine salt δ 1.30 (s, 22, CH_2), 2.64 (s, 2, CH_2N), 8.04 (m, 3, NH_3).

2-(Aminomethyl)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (4d) was isolated as the amine hydrochloride salt (89.2%), mp 258–261°, nmr (DMSO-d_6) δ 2.8 (s, 2, CH_2N), 4.74 (s, 1, OH), 8.0 (m, 3, NH_3).

Anal. Calcd for $C_{11}H_{22}NOCl$: C, 60.12; H, 10.09. Found: C, 59.96; H, 9.80.

1-(Aminomethyl)-1,2,3,4-tetrahydro-1-naphthol (4e) was isolated as the amine (64%), bp 100° (0.003 mm, molecular distillation), nmr ($CDCl_3$) δ 2.0, 2.2, 2.87, 2.97 (s, CH_2N), 7.2 (m, 4, aromatic H).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.53; H, 8.56.

2-(Aminomethyl)-3-methyl-3-penten-2-ol (4f) was isolated as the amine (57.2%), bp 30° (0.03 mm), nmr ($CDCl_3$) δ 1.2 (s, 3, CH_3), 1.6 (m, 6, CH_3), 1.7 (m, 3, NH_2, OH), 2.6 (q, J = 12 Hz, 2, CH_2N), 5.6 (m, 1, C=CH).

Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70. Found: C, 65.22; H, 11.59.

α-(Aminomethyl)-α-methyl benzyl alcohol (4g) was isolated as the amine hydrochloride salt (84.8%), mp 138–140°, nmr (DMSO-d_6) δ 1.5 (s, 3, CH_3), 3.0 (s, 2, CH_2N), 5.9 (m, 1, OH), 7.4 (m, 5, aromatic H), 8.05 (m, 3, NH_3).

Anal. Calcd for $C_9H_{14}NOCl$: C, 57.60; H, 7.52. Found: C, 57.50; H, 7.40.

Acknowledgment. The authors are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation for support of this research.

Registry No.—TMSCN, 7677-24-9.

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