

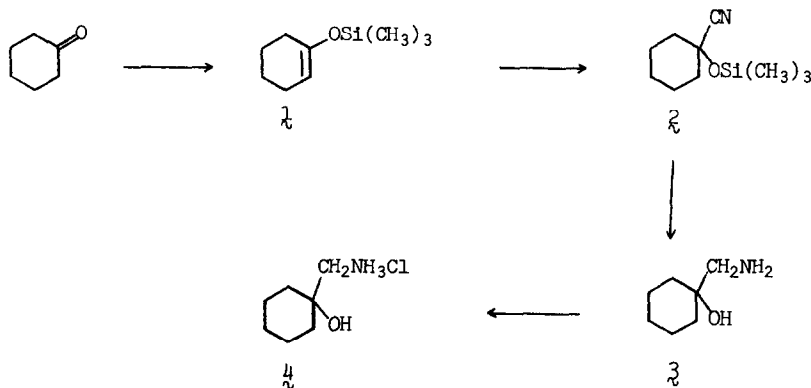
A NEW SYNTHESIS OF β -AMINO ALCOHOLS

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The usual pathways¹ for preparing β -amino alcohols for use in the Tiffeneau-Demjanov reaction involve either preparation of cyanohydrins or β -nitroalcohols from ketones, followed by reduction. Difficulty is encountered with some conjugated and sterically hindered ketones with the initial addition reaction. Recently we have described the synthesis of β -amino ethers from ketones for use in a modified Tiffeneau-Demjanov reaction,² and now wish to report a new synthetic procedure for β -amino alcohols.

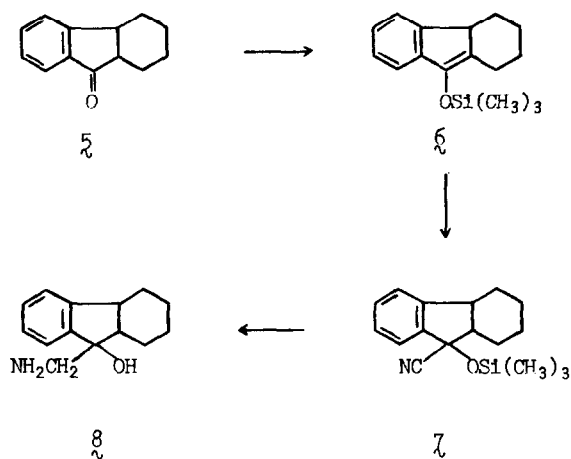
Preliminary work was done with the cyclohexane system. Cyclohexanone was converted to the



known trimethylsilyl enol ether **1** by alternate procedures reported by House³ and by Stork.⁴ Addition of **1** to excess, liquid, anhydrous hydrogen cyanide containing a drop of sulfuric acid (four hours at 0°, then twelve hours at 20°) yielded 49% α -cyanocyclohexyl trimethylsilyl ether **2** as a clear, colorless oil [bp₁₃ 102-105°; ir (neat): ν 2210 w (-C \equiv N), ν 1247 s, 836 s, 742 m (-Si-CH₃);

$n_D^{22.5}$ 1.4421; analysis: C, 60.99; H, 9.82; N, 7.31]. Reduction of the nitrile and hydrolysis of the ether was accomplished by treatment of **4** with lithium aluminum known amino alcohol was purified and characterized⁵ as the hydrochloride **4** (white plates; known amino alcohol was purified and characterized⁵ as the hydrochloride **4** (white plates; mp: 220-220.5°).

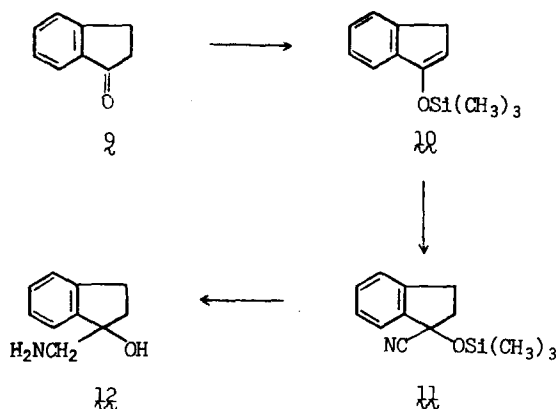
1,2,3,4,4a,9a-Hexahydrofluoren-9-one (**5**) provided a good test of the usefulness of the method as it forms neither a cyanhydrin nor an adduct with nitromethane in ethoxide-ethanol.⁶ Reaction of **5** with sodium hydride in glyme followed by treatment with chlorotrimethylsilane (method of



Stork) gave the silyl enol ether **6** in 75% yield as a yellow oil [bp_{1.1} 128-132.5°; ir (neat): ν 1642 s (C=C), ν 1248 s, 839 s, 750 s (-Si-CH₃); nmr (30% in CCl₄): aromatic H (m, 4, τ 2.4-3.1), aliphatic H (m, 18, τ 6.7-10.0); n_D^{30} 1.5337; analysis: C, 74.13; H, 8.66]. Reaction of **5** with chlorotrimethylsilane and trimethylamine in dimethylformamide (House method) gave only 22% yield of **6**. Addition of **6** to hydrogen cyanide as described above, gave a 59% yield of the desired cyanoether **7** as a yellow oil [isolated by preparative GC (3% SE 30 on Chromasorb W, 168°); ir (neat): ν 2201 w (-C≡N), ν 1245 s, 835 s, 742 s (-Si-CH₃); nmr (CCl₄): aromatic H (m, 4, τ 2.4-3.1), aliphatic methine and methylene H (m, 10, τ 6.6-9.3), methyl H (s, 9, τ 9.75); n_D^{22} 1.5162; analysis: C, 71.26; H, 8.36; N, 4.72]. Lithium aluminum hydride, followed by water,

reduced the nitrile and cleaved the ether bond of **7** to give the β -amino alcohol **8**, which was obtained in 96% yield as the hydrochloride (mp 202-203 $^{\circ}$; analysis: C, 66.29; H, 7.77; N, 5.26; Cl, 14.06).

1-Indanone (**9**) gave similar results. In the preparation of the silyl enol ether **10**, sodium hydride reacted vigorously under Stork's conditions with 1-indanone to effect an apparent conden-



sation reaction; the House method gave 74% of **10** as a clear, colorless oil [bp_{0.50} 82-83.5 $^{\circ}$; ir (neat): ν 1610 s ($\text{C}=\text{C}$), ν 1245 s, 835 s, 743 s ($-\text{Si}-\text{CH}_3$); nmr (18% in CCl_4): aromatic H (m, 4, τ 2.5-3.0), olefinic H (t, 1, τ 4.7, $J = 2.5$), CH_2 (d, 2, τ 6.9, $J = 2.5$), CH_3 (s, 9, τ 9.7); uv ($\lambda_{\text{max}}^{95\% \text{ EtOH}}$ ϵ): 257 (12400); n_D^{23} 1.5220]. Addition of hydrogen cyanide to **10** gave the cyanoether **11** as a clear, colorless oil [bp_{0.35} 90.5-94 $^{\circ}$; ir (neat) ν 2210 w ($-\text{C}\equiv\text{N}$), ν 1250 s, 837 s, 750 s ($-\text{Si}-\text{CH}_3$); nmr (15% in CCl_4): aromatic H (m, 4, τ 2.4-2.9), CH_2 (m, 4, τ 6.7-7.9), CH_3 (s, 9, τ 9.8); n_D^{22} 1.4996]. Reaction of **11** with lithium aluminum hydride, then water, gave the β -amino alcohol **12**, obtained as the hydrochloride in 63% yield (mp: 160-245 $^{\circ}$ with decomposition; analysis: C, 60.12; H, 6.83; N, 6.78).

The two methods used for preparing the silyl enol ethers show distinct differences depending upon the starting ketone. In our work, Stork's method appears more suitable for hindered ketones that undergo condensation with difficulty, and House's method is best for less hindered, easily condensable ketones. The α -cyanoalkyl trimethylsilyl ethers decompose slowly on standing and

quickly in the presence of base, but are stable enough for vacuum distillation. The cyano-ether γ was stable on the gas chromatograph at 168°.

The reaction sequence seems to be a general method for preparing β -amino alcohols and is especially valuable for ketones which do not form cyanohydrins or condense with nitromethane.

References

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