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Novel Synthesis of α-Amino Acids *via* Cyanosilylation of Schiff Bases

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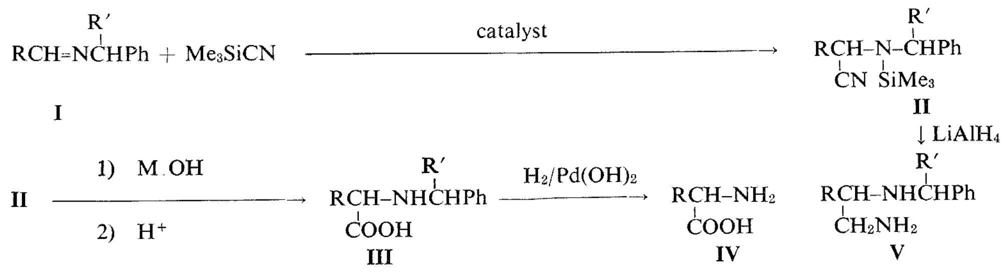
Trimethylsilyl cyanide (TMSCN) has recently been exploited and has received growing interest in synthetic utility because of its potential reactivity towards carbonyl and other functions. Thus, TMSCN adds to aldehydes and ketones[1)] under thermal and anionic catalysis to give the corresponding cyanohydrin derivatives which are inaccessible by conventional means. In addition, this reagent has been shown to provide a useful means of selective protection of carbonyl groups.[2)] More recently, reactions of TMSCN with epoxides,[3)] acyl halides[3)] and isocyanates[4)] have been developed, but to our knowledge, no attempt has been made on the addition reaction of TMSCN to Schiff bases.

Extension of the concept of Lewis acid-catalyzed cyanosilylation of carbonyl group to azomethine function reasonably suggests a successful synthesis of the corresponding α-amino nitrile derivatives, the potential precursors of α-amino acids.



In accordance with the expectation, the cyanosilylation of Schiff bases (**I**) with an equimolar TMSCN was easily effected at room temperature under Lewis acid catalysis to give the corresponding *N*-trimethylsilyl-amino nitriles (**II**) in moderate yields.

We wish, at this time, to describe the regiospecific addition of TMSCN to several Schiff bases, to give α-amino acids (**IV**) after methanolysis, hydrolysis and hydrogenolysis of the cyanosilylation intermediates (**II**).

Since the choice of catalyst seemed of utmost importance in effecting cyanosilylation, several Lewis acids were tested in a model reaction leading to alanine (**IV**, R=Me) as the end product, and zinc iodide was found to be the most effective catalyst in the present system (Table I), as was the case with carbonyl cyanosilylation.[1,2)]

TABLE I. EFFECT OF LEWIS ACIDS ON THE YIELD OF ALANINE

Catalyst	% Yield of alanine
ZnI_2	37.3
HgI_2	26.4
$AlCl_3$	14.0
BF_3 etherate	34.7

With this Lewis acid used as catalyst, the general synthetic procedure is exemplified by a typical run for alanine synthesis. TMSCN[1)] (1.0 g, 0.01 mole) was added to a solution of the Schiff base,[5)] prepared from acetaldehyde and α-phenethylamine, (1.47 g, 0.01 mole) and zinc iodide (300 mg) in dry ether (20 ml) at room temperature under nitrogen atmosphere for 48 hr. After the period, methanol (10 ml) was added to the reaction mixture and the insoluble substance was removed by filtration. The filtrate was condensed under reduced pressure and the remaining syrup was further hydrolyzed in 6 N-hydrochloric acid (30 ml) for 12 hr. The hydrolyzate was extracted with ether to remove colored substance and the aqueous layer was again evaporated to dryness under reduced pressure. *N*-Phenethylalanine was taken up in absolute ethanol (20 ml) free from salt and was purified on an Amberlite IR–120 column. The identity of the product was obtained by comparison with an authentic specimen prepared from the reductive amination[6] of pyruvic acid with α-phenethylamine. Yield 720 mg (37.3%). The hydrogenolysis over palladium hydroxide in the usual manner[7] afforded alanine, isolated and characterized, in nearly quantitative yield.

Experimental results of the cyanosilylation of various Schiff bases with TMSCN under the condition illustrated above were summarized in Table II.

Table II. Zinc Iodide-catalyzed Cyanosilylation of Schiff Bases[a]

Schiff base (I) R	R′	Solvent	% Yield of α-amino acid (IV)
Me	Me	ether (20 ml)	37.3[b]
Et	Me	ether (20 ml)	20.0[c]
i-Pr	H	neat	5.4[d]
i-Bu	Me	neat	11.9[e]
Ph	H	neat	20.7[f]

[a] In a 0.01 mole scale, [b] alanine, [c] butyrine, [d] valine, [e] leucine, [f] phenylglycine.

The mixture which resulted from zinc iodide-catalyzed reaction of the Schiff base (**I**, R=R′=Me: 1.47 g, 0.01 mole) with TMSCN in dry ether (20 ml) was reduced with a slight excess of lithium aluminum hydride (0.4 g, 10.6 mmole). The basic fraction of the ether extract contained 3 components as indicated by TLC. The diamine (**V**, R=R′=Me) was isolated and purified on a silica gel column with ethanol-28% aqueous ammonia (30:1) used as eluent. Viscous liquid, yield 710 mg (39.8%), n_D^{22} 1.5248; PMR ($CDCl_3$) δ 7.34 (5H, phenyl proton), 3.90 (1H, methine proton), 1.35 (d–d, 3H, methyl proton), 1.00 (3H, methyl proton).

For the present, the reaction yields found for the cyanosilylation of Schiff bases are not satisfactory, but we have every reason to believe that much improvement will be feasible by setting up appropriate reaction parameters other than those arbitrarily adopted here.

It is also worthy of note that the present cyanosilylation is capable of effecting asymmetric synthesis by the introduction of chiral benzylic amines in Schiff bases, which is currently in progress and will be the subject of our paper in the near future.

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