A Novel, One-Pot Synthesis of *α*-*C*-Cyanohydrazines in the Presence of Lithium Perchlorate/Diethylether Solution (5.0 M)

Akbar Heydari,* Robabe Baharfar,[†] Mohsen Rezaie, and Saied M. Aslanzadeh
Chemistry Department, Tarbiat Modarres University, P. O. Box 14155-4838, Tehran, Iran
[†]*Chemistry Department, Mazandaran University, Babolsar, Iran*

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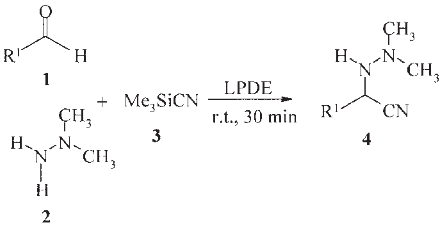
Condensation of *N*,*N*-dimethylhydrazine, an aldehyde in lithium perchlorate/diethylether solution (5.0 M) gave *N*,*N*-dimethylhydrazone, which were treated with trimethylsilylcyanide to afford *α*-*C*-cyanohydrazine. These compounds are important precursors of nitrogen-substituted reagents.

The addition of nucleophilic reagents to the C=N bonds of imines or imine derivatives (iminium salts, acylimines, sulfonimines, nitrones, oximes and hydrazones) is an old and well-known reaction. In comparison to nucleophilic addition to carbonyl compounds, the aza-analogous reaction has been investigated much less. The poor electrophilicity of the imino group, the abstraction of acidic *α*-protons forming an azaenolate, are some general problems. To circumvent these problems, a variety of methods have been developed. For example, activation of the C=N bond of imines or imines derivatives by coordination of Lewis acid with the nitrogen lone pair or by addition of external promoters.[1] It would be difficult to extend the Lewis acids catalyzed nucleophilic addition to imine derivatives. In addition it cannot proceed a one-pot reaction from aldehydes and has to start from imines because the amines and water that exist during imine formation can decompose or deactivate many Lewis acids.[2]

Mannich-type reactions (a three-component condensation reactions) is interesting and important, not only because two bonds are formed in one-pot, but also because the methodology would be useful for making a broad variety of compound libraries.[3] The classical intermolecular three-component Mannich reaction is, however, plagued by a number of serious disadvantages:[4] Due to the drastic reaction conditions unwanted side reactions often take place. Major problems here are deamination and formation of methylene bisketones. If one uses a primary amine, reaction can continue until all the H atoms on the nitrogen are replaced. Additionally, and with very few exceptations, one can only use formaldehyde. Due to the very attractive nature of Mannich bases, there have been many attempts to find alternative synthetic routes to these compounds, which do not suffer the severe drawbacks of the classical procedure. It has been reported that the Mannich-type three-component condensation reactions of aldehydes, *N*,*N*-dimethyltrimethylsilylamine and nucleophiles such as diethylzinc take place in lithium perchlorate/diethylether solution[5] (5.0 M) to yield amines[6] respectively. This method allows, at least in principle, all the limitations of the classical Mannich reaction to be overcome. The level of performance and the versatility of this method has already been powerfully demonstrated in the synthesis of *α*-aminonitriles,[7] *α*-aminophosphonates,[8] *α*-cyanohydroxylamine,[9] *N*-trimethylsilyl-oxy-*α*-aminophosphonates[10] respectively. In this paper, we report the condensation reactions of aldehydes **1**, *N*,*N*-dimethylhydrazine **2** and trimethylsilylcyanide **3** in LPDE (5.0 M) solution, which yield *α*-*C*-cyanohydrazines **4** in a one-pot procedure, within 30 min in high yields.[11] The N-N bond can then be cleaved under reductive conditions to obtain the *α*-aminonitriles. Hydrazones can therefore be regarded as stable equivalents of imines derived from ammonia. *α*-*C*-Cyanohydrazines might be transformed further into *α*-hydrazino carboxylic-acids and *α*-amino acids. To the best of our knowledge, only a few synthesis of *α*-*C*-cyanohydrazines have been reported in the literature: three-component condensation of carbonyl group, sodium cyanide and N_2H_4. sulfate.[12] Without lithium perchlorate/diethylether solution, no product was observed even after 4 h.[13] Several examples of the present three component coupling reactions are summarized in Scheme 1.

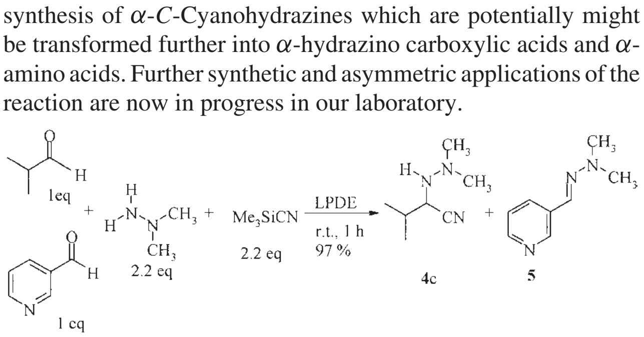


	R^1	Yield 4 %
a	Methyl	94
b	Ethyl	96
c	*i*-Propyl	95
d	*n*-Propyl	92
e	*tert*-Butyl	94
f	*n*-Pentyl	94
g	*c*-Hexyl	96

Scheme 1.

This method seems to be a general synthetic route to *α*-hydrazinonitriles. Unfortunately benzaldehyde, *p*-methoxy benzaldehyde, 3-pyridine carbaldehyde, furfural and cinnamaldehyde are not amerable to the cyanation condition used in the one-pot cyanohydrazination.[14] Additionally, we found that cyanohydrazination of an aliphatic aldehyde rather than an aromatic was performed in more than 99% selectivity. The reaction of isobutyraldehyde, 3-pyridine carbaldehyde with *N*,*N*-dimethylhydrazine and trimethylsilylcyanide in 5.0 M LPDE solution give *α*-*C*-cyanohydrazine **4** and 3-pyridinehydrazone **5**, respectively.

In conclusion, we have observed a three-component condensation reaction that offers an easy and effective one-pot synthesis of *α*-*C*-Cyanohydrazines which are potentially might be transformed further into *α*-hydrazino carboxylic acids and *α*-amino acids. Further synthetic and asymmetric applications of the reaction are now in progress in our laboratory.



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11 A typical experimental procedure, to a mixture of aldehyde (2 mmol) in 5 M LPDE (4 ml) was added *N*,*N*-dimethylhydrazine (2.2 mmol) at room temperature. The mixture was stirred for 15 min. and trimethylsilylcyanide (2.2 mmol) was added. The mixture was stirred for 15 min then water was added and the product was extracted with CH_2Cl_2. The organic phase was collected, dried (Na_2SO_4) and evaporated to afford the crude product. The product was purified by flash chromatography (hexan-ethyl acetate). ^{1}H-NMR, ^{13}C-NMR, IR and MS spectra were entirely consistent with the assigned structures. selected data as follow: **4a** (R^1 = Methyl) ^{1}H-NMR (90 MHz, $CDCl_3$): $\delta = 3.8$ (m, 1H, H1), 3.1 (bs, 1H, NH), 2.6 (s, 6H, NCH_3), 1.4 (d, $J_{\text{H-H}} = 9$ Hz, 3H, CH_3); ^{13}C-NMR (22.5 MHz, $CDCl_3$): $\delta = 121.26$ (CN), 48.17 (NCH_3), 45.64 (CH), 17.54(CH_3); **4b** (R^1 = Ethyl) ^{1}H-NMR (90 MHz, $CDCl_3$): $\delta = 3.7$ (t, $^2J_{\text{H-H}} = 9$ Hz, 1H, H1), 3.0 (bs, 1H, NH), 2.6 (s, 6H, NCH3), 1.8 (q, $J_{\text{H-H}} = 9$ Hz, 2H), 1.1 (t, $J_{\text{H-H}} = 9$ Hz, 3H); ^{13}C-NMR (22.5 MHz, $CDCl_3$): $\delta =$ 120.7 (CN), 52.5 (CH), 48.3 (NCH_3), 25.0 (CH_2), 9.8 (CH_3); **4c** (R^1 = *i*-Propyl): ^{1}H-NMR (90 MHz, $CDCl_3$) $\delta = 3.5$ (d, $J_{\text{H-H}} = 9$ Hz, 1H, H1), 3.1 (bs, 1H, NH), 2.5 (s, 6H, NCH_3), 1.9 (m, 1H, H2), 1.1 (d, $J_{\text{H-H}} = 9$ Hz, 3H, CH_3), 0.9 (d, $J_{\text{H-H}} = 9$ Hz, 3H, CH_3); ^{13}C-NMR (22.5 MHz, $CDCl_3$) $\delta = 119.8$ (CN), 57.6 (CH), 48.0 (NCH_3), 30.0 (CH), 19.1 (CH_3), 18.0 (CH_3).

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13 When a solution of aldehyde and *N*,*N*-dimethylhydrazine was treated with trimethylsilylcyanide in diethyl ether at room temperature for 3 h, the corresponding hydrazone product was obtained with high yield.

14 Cyanohydrazination of aldehydes (R^1 = Phenyl, *p-MeO*-phenyl, 2-Furyl, 3-Pyridyl, trans-PhCH=CH) afforded the corresponding hydrazones in high yield.