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SYNTHESIS OF α-AMINONITRILES BY SELF-CATALYZED, STOICHIOMETRIC REACTION OF PRIMARY AMINES, ALDEHYDES, AND TRIMETHYLSILYL CYANIDE

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Abstract: α-Aminonitriles can be prepared at room temperature in good yield by either the addition of a primary amine to a mixture aldehyde/trimethylsilyl cyanide (TMSCN) or by the addition of an aldehyde to a mixture amine/TMSCN. The reaction proceeds via the initial condensation of a minute amount of aldehyde and amine groups to generate azomethine bonds and water. The latter then acts catalytically to rapidly convert the aldehyde into the trimethylsilyl cyanohydrin, which then undergoes nucleophilic attack by the amine. Several new α-aminonitriles and bis(α-aminonitrile)s have been prepared.

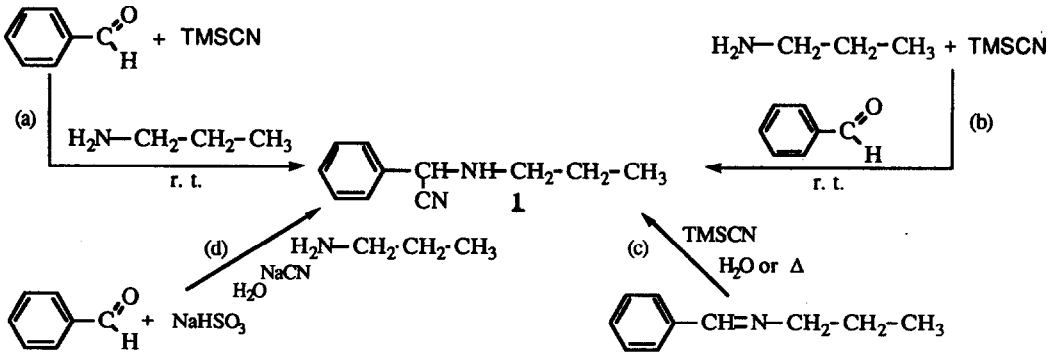
The preparation of α-aminonitriles has recently been reviewed.[1] They are usually prepared in an aqueous solution by reaction of an aldehyde, in the form of its bisulfite salt, an amine, and an inorganic cyanide salt by the well-known Strecker reaction [Scheme 1 - route (d)].[2] This method does, however, not apply to systems where the bisulfite adduct cannot be formed due to a very different solubility behavior between the aldehyde and the inorganic bisulfite, i. e., the aldehyde is insoluble in solvents appropriate for the bisulfite, e. g., water. To counter this problem, aminonitriles can be prepared by first reacting an aldehyde with trimethylsilyl cyanide in the presence of a Lewis acid to form the O-silylated cyanohydrin, which is then reacted with an amine. The method has been used by Mai and Patil to prepare a number of α-aminonitrile salts. When primary amines were used, the reagents were refluxed in methanol for 2 h.[3,4] These same authors developed a non-catalytic method involving several steps.[5] First, two moles of aldehyde or ketone were heated with one mole of amine at 100°C. After cooling, two equivalents of trimethylsilyl cyanide were added and the mixture was eventually heated up again at 100°C. This method, therefore, involves a double stoichiometry of aldehyde or ketone and TMSCN and requires thermal energy. In another communication[6], these same authors report a milder uncatalyzed method involving the condensation of the aldehyde and the amine in refluxing methanol. The resulting solution was then evaporated to near dryness before classic work up. However, this procedure also involves an excess of the aldehyde (33%) and of TMSCN (100%).

We have found that α-aminonitriles can be simply prepared at room temperature by reacting stoichiometric quantities of aldehyde, amine and TMSCN. The reaction can be performed neat (for liquid aldehydes) or in an inert solvent like dichloromethane.

N-propyl-α-cyanobenzylamine (**1**) was prepared when either *n*-propylamine was added to a mixture benzaldehyde/TMSCN [route (a), Scheme 1] or benzaldehyde was added to the mixture *n*-propylamine/TMSCN [route (b), Scheme 1]. It is, however, known, as we have verified by ^{1}H NMR, that in a neat mixture TMSCN does not react with aldehydes unless prolonged heating is applied.[7] Also, it can be shown by the same technique

that TMSCN does not add in a neat mixture to a primary amine. Silylated amines are commonly formed by the reaction of an amine with trimethylchlorosilane either with an excess of amine or in the presence of a tertiary amine. Even with hexamethyldisilazane, a stronger silylating agent, yields of an uncatalyzed reaction are low.[8] However, we have observed that rapid reaction between an aldehyde, a primary amine, and TMSCN occurs when the three reagents are together, leading to the formation of **1**.

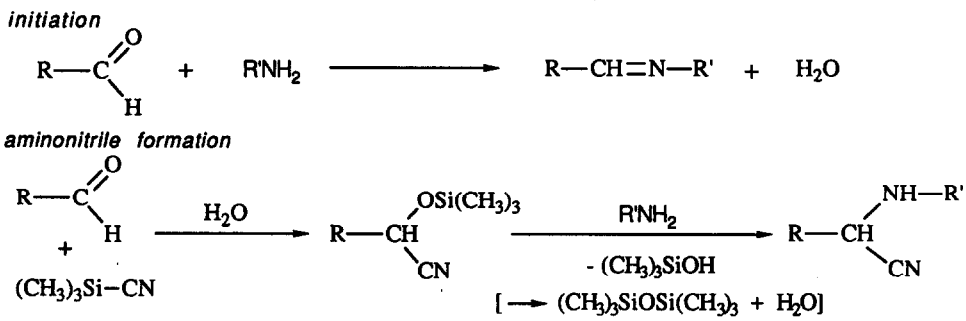
Scheme 1: Selected synthetic routes to N-propyl-α-cyanobenzylamine



What is the mechanism of this process? The condensation of aldehydes and amines is known to proceed to yield imines, with evolution of both heat and water. However, analysis by ^{1}H NMR of the reaction mixture [route (a), neat] after 10 min indicates only a trace amount of N-benzylidenepropylamine but already 34% of the aminonitrile **1** and 64% of the O-silylated cyanohydrin of benzaldehyde.[9] It is clear at this point that the reaction occurs via the intermediate formation of the protected cyanohydrin. We therefore postulate that an initial condensation of a minute amount of the aldehyde and amine occurs, yielding just enough water to catalyze the formation of the protected cyanohydrin (Scheme 2). Water is also generated by condensation of trimethylsilanol, the byproduct of the reaction of the silylated cyanohydrin with the amine, to produce bis(trimethylsilyl ether). Thus water is acting as a true catalyst!

Although water is not involved in the rate-determining step of the reaction (nucleophilic attack by amine, cf above)(Scheme 2), its influence can be demonstrated. Thus, we found by ^{1}H NMR spectroscopy that the amount

Scheme 2: Self-catalyzed condensation of an aldehyde, an amine, and TMSCN



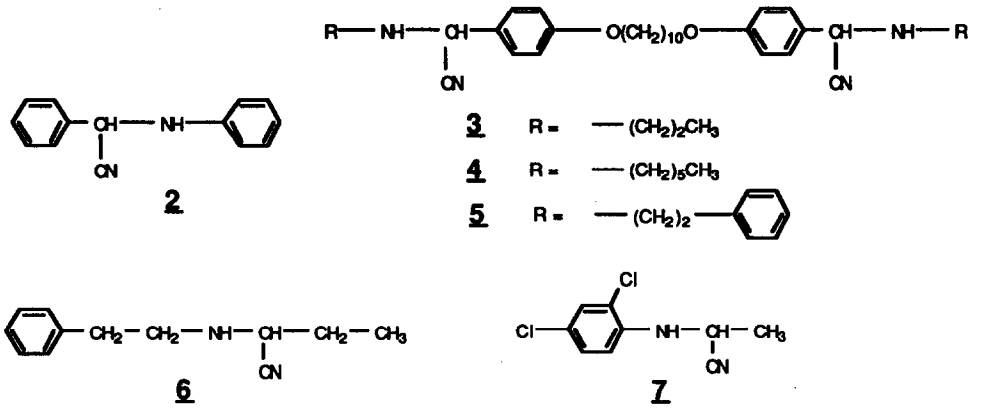


Table 1: Synthesis of mono and bis(α-aminonitrile)s 1-7 by route (a), Scheme 1

α-aminonitrile or bis(α-aminonitrile)	yield (%)	m. p. (°C) (corr.)	elemental analysis calculated (%) C	H	N	found (%) C	H	N
1	100[a]	liquid						
2	96	82.5-83.6[b]						
3	87	71.2-73.5[c]	74.09	8.94	10.80	74.18	8.96	10.70
4	100	76.3-77.6[d]	75.70	9.70	9.29	75.78	9.73	9.30
5	84	93.7-94.4[e]	78.47	7.84	8.72	78.38	8.05	8.64
6	75	liquid[f]	76.55	8.57		76.61	8.59	
7	100	75.0-76.0[g]	50.25	3.75	13.03	50.01	3.76	12.94

a. yield by ^{1}H NMR. Attempts to purify the compound, such as chromatography through a neutral alumina column, resulted in decomposition of the product. Route (b) [Scheme 1] gave 86% yield and route (d) a mixture of 96% 1 and 4% of azomethine.

b. as crystalline precipitate after 1 h reaction, washed with hexanes; lit. 85^{0}C[11], 81-83^{0}C[12], 81^{0}C[13].

c. two day reaction. The resulting suspension was flushed with nitrogen to partly evaporate CH_2Cl_2 and hexanes were added. It was purified by thorough rinsing with hexanes and drying under vacuum. Recrystallization from 3:1 ethyl acetate/hexanes. IR (KBr): 3323 (NH), 2940, 2920, 2858 (aliph. CH), 2223 (CN), 1252 (C-O-C), 1614, 1512, 1478 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.40 (d, 4H, ArH), 6.90 (d, 4H, ArH), 4.70 (s, 2H, CHCN), 3.95 (t, 4H, CH_2O), 2.85-2.65 (m, 4H, $\underline{CH_2}NH$), 1.78 (qn, 4H, $\underline{CH_2}CH_2O$), 1.60-1.30 (m, 18H, CH_2+NH), 0.95 ppm (t, 6H, CH_3).

d. prepared as compound (3) (footnote (c)), with five day reaction (94% after two days). Recrystallized from 10:1 hexanes/ethyl acetate.

e. prepared as compound (3)(footnote (c)), with five hour reaction. Recrystallized from ethyl acetate/hexanes and ethyl acetate.

f. 24 h reaction. Reaction product was chromatographed through neutral alumina column (solvent: dichloromethane).

g. reaction was performed in the presence of a drop of water for one day. The organic phase was dried over sodium sulfate and evaporated at room temperature. The crystals obtained upon standing were recrystallized from ethyl acetate/hexanes. IR (KBr): 3374 (NH), 2992 (ar. CH), 2232 (CN), 1593, 1501 (C=C), 1313, 1172, 859, 809, 757 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.33 (d, J= 2 Hz, 1H, ArH), 7.21 (q, J= 9.5 Hz, 1H, ArH), 6.72 (d, 1H, ArH), 4.4-4.25 (m, 2H, CH + NH), 1.77 (d, J= 7 Hz, 3H, CH_3).

of aminonitrile 1 obtained after 5 min. of reaction of a neat mixture of benzaldehyde, TMSCN, and propylamine was 17% (and 83% O-silylated cyanohydrin). After the same length of time, a reaction conducted over molecular sieves had produced 12% of 1, whereas a reaction catalyzed by a small amount of water already had given 35% of 1. Due to the heat and water evolved in the reaction, the azomethine formed in the initiation step also eventually undergoes TMSCN addition to produce the aminonitrile [route (c) - Scheme 1] via the N-silyl intermediate.[10]

In all, the method, therefore, corresponds to the nucleophilic substitution of a trimethylsilyl cyanohydrin by an amine. It differs from the common procedure in that it is self-catalyzed, therefore avoiding discolorations often found in Lewis acid catalyzed reactions, and requires no thermal energy.

The method was succesfully applied to the synthesis of mono and bis(α-amino-nitrile)s 1-6 (Table 1).

The following is a representative procedure for N-propyl-α-cyanobenzylamine (1). To a mixture of 0.62 g (5.8 mmol) of benzaldehyde and 0.80 ml (6.0 mmol) of TMSCN in 2 ml of dichloromethane was added 0.50 ml (6.1 mmol) of propylamine. A large exothermicity was immediately noted and the mixture was stirred for 16 h. ^{1}H NMR spectroscopy indicated completion after this time.

In the case of 2,4-dichloroaniline, the reaction to form 7 only occured in the presence of a catalytic amount of water as no initiation step had taken place.

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