



## One-pot synthesis of $\alpha$ -aminonitriles from alkyl and aryl cyanides: a Strecker reaction via aldimine alanes

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### ABSTRACT

A one-pot Strecker reaction using various alkyl, arylalkyl and aryl nitriles is developed. Aldimine alanes were generated in situ from nitriles by the addition of diisobutylaluminum hydride, and were converted into the corresponding imines on reaction with (*S*)-(–)-1-phenylethylamine. Nucleophilic addition to the imines in the presence of catalytic triethylamine, using acetone cyanohydrin as a cyanide source, provided  $\alpha$ -aminonitriles.

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$\alpha$ -Aminonitriles are important intermediates of the Strecker reaction for preparing  $\alpha$ -amino acids. The classic Strecker reaction is a three-component reaction involving condensation of an aldehyde, an ammonia and a cyanide followed by subsequent hydrolysis of the resulting  $\alpha$ -aminonitrile. In addition,  $\alpha$ -aminonitriles have been applied in many organic transformations. Reduction of the nitrile group provides a convenient method for the preparation of 1,2-diamines.<sup>1</sup>  $\alpha$ -Aminonitriles can undergo loss of cyanide to form stable iminium ions from which variously substituted amines have been synthesized.<sup>2</sup>  $\alpha$ -Aminonitriles possessing an  $\alpha$ -hydrogen can be deprotonated and the carbanions formed are able to react with various electrophiles.<sup>3</sup>

Typically,  $\alpha$ -aminonitriles are prepared by the reaction of aldehydes with amines using various cyanides such as HCN, KCN, TMS-CN, (EtO)<sub>2</sub>P(O)CN, Et<sub>2</sub>AlCN, Bu<sub>3</sub>SnCN, acetone cyanohydrin or acyl cyanides.<sup>4,5</sup> Preformed imines which are intermediates of  $\alpha$ -aminonitrile formation during the Strecker synthesis are widely used starting materials in catalytic asymmetric Strecker syntheses.<sup>6</sup> Treatment of  $\alpha$ -hydroxynitriles with amines also yields  $\alpha$ -aminonitriles.<sup>7</sup> RuCl<sub>3</sub>-catalyzed oxidative cyanation of tertiary amines with sodium cyanide results in the corresponding  $\alpha$ -aminonitriles.<sup>8</sup> However, no examples of Strecker reactions using nitriles as starting materials have been published despite the fact that the nitriles can serve as aldehyde equivalents following their reductive hydrolysis using DIBAL-H. Organoaluminum imine complexes formed by the reduction of nitriles with dialkylaluminum hydrides are common intermediates in organic synthesis.<sup>9</sup> The preparation and characterization of stable dialkylaluminum aldimine complexes have been reported.<sup>10,11</sup> Various dialkylaluminum aldimine complexes were found to react

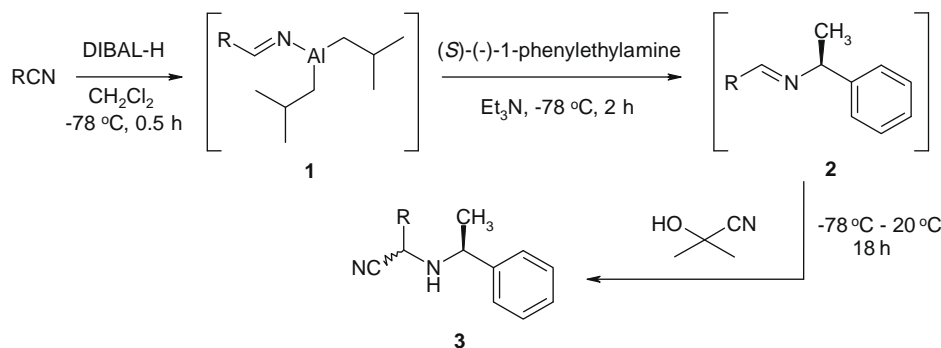
with ammonia or primary amines yielding Schiff bases.<sup>12,13</sup> Based on these findings, it was conceivable to prepare  $\alpha$ -aminonitriles by reacting nitriles with DIBAL-H and then convert the resulting alane complexes to imines by adding an amine followed by nucleophilic addition of a cyanide to the intermediate imine.

Our objective was to develop a simple and efficient one-pot method for the synthesis of  $\alpha$ -aminonitriles starting from various alkyl, aryl and arylalkyl cyanides, chiral amines and acetone cyanohydrin as the cyanide source. (*S*)-(–)-1-Phenylethylamine, which is reported to induce asymmetry in Strecker reactions, was used as a chiral inducing agent.<sup>14</sup> Catalytic triethylamine was added since it has been reported<sup>4</sup> to catalyze the Strecker reaction in the presence of acetone cyanohydrin.

A series of nitriles were reacted with an excess of DIBAL-H in dichloromethane at –78 °C to afford aldimine alane complexes **1** on 0.5–2.0 mmol scale (Scheme 1).<sup>15</sup> The alanes were formed in 30 min and were not isolated. After quenching the excess of hydride with ethyl acetate, (*S*)-(–)-1-phenylethylamine and catalytic triethylamine were added to generate the respective imines **2**. Finally, addition of excess acetone cyanohydrin gave  $\alpha$ -aminonitriles **3** in an overnight reaction at room temperature. The diastereomeric mixture of  $\alpha$ -aminonitrile was isolated by standard silica gel chromatography. The by-product, 2-methyl-2-(1-phenylethylamino)propane-nitrile, formed in the reaction of acetone cyanohydrin and (*S*)-(–)-1-phenylethylamine,<sup>16</sup> was also isolated.

In the alane-Strecker reaction, the majority of the nitriles were converted into the required  $\alpha$ -aminonitriles **3** in good yields (Table 1). The lowest yield (20%) was obtained for ethoxypropionitrile (entry 6). Starting from 1,5-dicyanopentane (entry 5), in addition to the diamionitrile (43%), monoaminonitrile (30%) was also isolated. Interestingly, no aminonitrile formation was detected with 2-tolunitrile, while a moderate yield (53%) was obtained from the *para*-substituted analogue (entry 10). Starting from phthalonitrile,

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**Scheme 1.** One-pot preparation of  $\alpha$ -aminonitriles **3** via intermediate diisobutylaluminium aldimines **1**.

**Table 1**

Structures of the nitriles, isolated yields of  $\alpha$ -aminonitriles **3** and the diastereomeric ratios

Entry	R-CN	Yield of <b>3</b> (%)	dr
1	CH <sub>3</sub> -	92	1.80
2	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> -	82	2.05
3	(CH <sub>3</sub> ) <sub>3</sub> C-	91	1.85
4	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>16</sub> -	67	1.95
5	NC-(CH <sub>2</sub> ) <sub>5</sub> -	43	2.32
6	CH <sub>3</sub> CH <sub>2</sub> -O-CH <sub>2</sub> CH <sub>2</sub> -	20	2.99
7		52	3.41
8		92	1.90
9		75	3.06
10		53	2.32
11		80	1.44
12		87	1.41
13		45	2.19
14		60	2.39
15		94	1.52

a tar-like crude product was obtained which did not contain the expected di- or monoaminonitrile according to mass spectrometry. These findings indicate the importance of steric factors in aminonitrile formation. Reactions carried out with allyl cyanide, acrylonitrile and cinnamonitrile resulted in no aminonitrile formation. Since the diastereomers were not separable, the diastereomeric ratios (dr) of the alane-Strecker reactions were determined from the integral values of the RCH-CN protons of the new stereogenic centre in the product <sup>1</sup>H NMR spectra. The signals due to the methine

proton of the major isomers always appeared at a higher field than that of the minor isomers. The structures of the aminonitriles prepared in a previous study from (*R*)-(+)-1-phenylethylamine and acetaldehyde as well as pivalaldehyde were confirmed, and a predominance of (*R,R*) diastereomers over (*R,S*) was found.<sup>17</sup> Since the chemical shifts of the diastereomers of the  $\alpha$ -aminonitriles derived from entries **1** and **3** with (*S*)-(-)-1-phenylethylamine (**Table 1**) were exactly the same as reported for the aforementioned analogues we can presume that the (*S,S*)-conformer is the predominant product in the alane-Strecker synthesis. The diastereomeric ratios ranged from 1.41 to 3.41.

The effect of reaction conditions on the yields and diastereomer ratios was further studied using pivalonitrile (**Table 2**, entry 3). When the reaction was carried out at room temperature, the yield was decreased significantly without significantly affecting the ratio of the diastereomers. The reduced yield (37%) in the absence of triethylamine is probably due to the decreased degree of dissociation of the cyanohydrin into acetone and HCN which therefore slows the hydrocyanation of the imine. The dissociation of acetone cyanohydrin was previously shown to be catalyzed by triethylamine.<sup>18</sup> Since the dissociation was extremely slow in dioxane,<sup>18</sup> we can assume that the dramatically lowered yield in tetrahydrofuran can also be explained by the repressed dissociation of the cyanohydrin in this solvent. The alane-Strecker reaction also proceeded excellently in toluene. The effect of commercially available Jacobsen's thiourea catalyst **4** (**Fig. 1**), which was applied successfully in the asymmetric Strecker reaction of preformed imines and HCN,<sup>19</sup> on the diastereoselectivity of the reaction was studied briefly. In the presence of 2 mol % of organocatalyst **4** added after imine formation, a poor yield (18%) and only a slightly higher diastereomer ratio was detected. When triethylamine and the catalyst **4** (4 mol %)

**Table 2**

Effect of the reaction conditions on the yields and diastereomeric ratios in the alane-Strecker reaction carried out with pivalonitrile

Solvent	Amine <sup>a</sup>	Et <sub>3</sub> N	Catalyst <sup>b</sup>	Temperature (°C)	Yield (%)	dr
CH <sub>2</sub> Cl <sub>2</sub>	S	+	-	20	59	1.99
CH <sub>2</sub> Cl <sub>2</sub>	S	-	-	-78	37	2.08
CH <sub>2</sub> Cl <sub>2</sub>	S	-	+	-78	18	2.17
CH <sub>2</sub> Cl <sub>2</sub>	S	+	+ <sup>c</sup>	-78	33	1.80
CH <sub>2</sub> Cl <sub>2</sub>	S <sup>d</sup>	+	-	-78	22	2.20
CH <sub>2</sub> Cl <sub>2</sub>	R	+	-	-78	90	1.79
CH <sub>2</sub> Cl <sub>2</sub>	R	+	+	-78	43	2.04
THF	S	+	-	-78	2	1.33
Toluene	S	+	-	-78	92	1.96

<sup>a</sup> S: (*S*)-(-)-1-phenylethylamine, R: (*R*)-(+)-1-phenylethylamine.

<sup>b</sup> 2 mol % of catalyst **4**, see Ref. 19.

<sup>c</sup> 4 mol % of catalyst **4**, see Ref. 19.

<sup>d</sup> 2 equiv of (*S*)-(-)-1-phenylethylamine and 5 equiv of acetone cyanohydrin were applied.

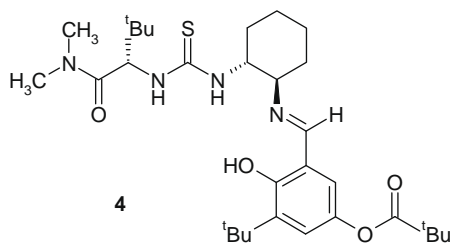


Figure 1. Jacobsen's thiourea catalyst.

were added together the yield was somewhat improved but the diastereoselectivity was reduced slightly. When (*R*)-(+)-1-phenylethylamine was employed as the chiral inducer the presence of the thiourea catalyst **4** decreased the yield without any significant effect on the diastereoselectivity.

The results obtained when using catalyst **4** were consistent with our anticipations. The Jacobsen catalyst was shown to catalyze the highly enantioselective hydrocyanation of imines by activation of the electrophile with H-bonding between the acidic NH protons of **4** and the imine lone pair.<sup>20</sup> In our system, the excess of the chiral amine and the catalytic Et<sub>3</sub>N can neutralize the acidity of the catalyst therefore preventing it binding to the substrate. Also, the acidic catalyst can decrease the dissociation of the acetone cyanohydrin. In order to improve the diastereoselectivity of the alane-Strecker reaction a change of the cyanide source is necessary when a chiral H-bond donor catalyst is employed.

In conclusion, we have reported a convenient one-pot transformation of a variety of alkyl and aryl cyanides to diastereomeric  $\alpha$ -aminonitriles. The transformation is achieved through in situ generation of the corresponding aldimine alanes using DIBAL-H followed by reaction with a chiral amine to generate an imine, which subsequently undergoes cyanide addition with acetone cyanohydrin. Although the yields of the reactions were satisfactory, the general lack of significant diastereoselectivity requires further study to access more diastereo-enriched  $\alpha$ -aminonitriles as valuable intermediates of N-substituted  $\alpha$ -amino acid building blocks.

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## References and notes

- Hassan, N. A.; Bayer, E.; Jochims, J. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3747–3757.
- Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, 29, 359–373.
- Enders, D.; Kirchoff, J.; Gerdes, P.; Mannes, D.; Raabe, G.; Runsink, J.; Boche, G.; Marsch, M.; Ahlbrecht, H.; Sommer, H. *Eur. J. Org. Chem.* **1998**, 63–72.
- Paraskar, A. S.; Sudalai, A. *Tetrahedron Lett.* **2006**, 47, 5759–5762.
- Pan, S. C.; List, B. *Synlett* **2007**, 318–320.
- Groger, H. *Chem. Rev.* **2003**, 103, 2795–2827.
- Besidsky, Y.; Luthman, K.; Hacksell, U. *J. Heterocycl. Chem.* **1994**, 31, 1497–1502.
- Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, 125, 15312–15313.
- Cainelli, G.; Panunzio, M.; Andreoli, P.; Martelli, G.; Spunta, G.; Giacomini, D.; Bandini, E. *Pure Appl. Chem.* **1990**, 62, 605–612.
- Jensen, J. A. *J. Organomet. Chem.* **1993**, 456, 161–166.
- Gilbertson, R. D.; Haley, M. M.; Weakley, T. J. R.; Weiss, H.-C.; Boese, R. *Organometallics* **1998**, 17, 3105–3107.
- Bogdanovic, B.; Konstantinovic, S. *Liebigs Ann. Chem.* **1970**, 738, 202–205.
- Zandbergen, P.; Van den Nieuwendijk, A. M. C. H.; Brussee, J.; Van der Gen, A.; Kruse, C. G. *Tetrahedron* **1992**, 48, 3977–3982.
- Stout, D. M.; Black, L. A.; Matier, W. L. *J. Org. Chem.* **1983**, 48, 5369–5373.
- General procedure for the preparation of 3*: Diisobutylaluminum hydride (1.4 equiv, 2.8 mmol, 1 M in dichloromethane) was added to the nitrile (1 mmol) in dichloromethane (5 mL) under argon at  $-78^\circ\text{C}$ . The mixture was stirred for 30 min and the excess DIBAL-H was quenched by the addition of ethyl acetate (0.4 mmol) at  $-78^\circ\text{C}$ . After 5 min, catalytic triethylamine (0.1 equiv, 0.1 mmol) and (*S*)-(-)-1-phenylethylamine (5 equiv, 5 mmol) were added, and the mixture was stirred for 2 h at dry ice temperature. Next, acetone cyanohydrin (10 equiv, 10 mmol) was added via syringe and the temperature was allowed to warm to  $20^\circ\text{C}$  and the mixture was stirred overnight. After dilution with dichloromethane (10 mL), the solution was washed with 1 N sodium hydroxide (10 mL). The organic layer was dried over magnesium sulfate and the solvent was removed in vacuum. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent (93/7–9/1).
- Jacobson, R. A. *J. Am. Chem. Soc.* **1945**, 67, 1996–1998.
- Inaba, T.; Fujita, M.; Ogura, K. *J. Org. Chem.* **1991**, 56, 1274–1279.
- Stewart, T. D.; Fontana, J. J. *J. Am. Chem. Soc.* **1940**, 62, 3281–3285.
- Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, 124, 10012–10014.
- Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, 45, 1520–1543.