Base controlled diastereoselective synthesis of either **anti**- or **syn**-β-aminonitriles

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Supporting Information Placeholder

**ABSTRACT:** Deprotonation of secondary alkane nitriles with nBuLi and addition to aryl imines gives kinetic anti-β-aminonitriles. Use of LHMDS allows reversible protonation of the reaction intermediate to give syn-β-aminonitriles. The pure diastereoisomers can be isolated in good yields and the mechanism was elucidated.

The nitrile functional group is ubiquitous in synthesis due to its ease of incorporation, ability to facilitate the formation of new bonds and interconversion into a myriad of other functional groups. It is present in biologically active natural products and its use as a pharmacophore has also been recognised. The β-aminonitrile functional group is an under investigated subset of alkanenitriles. There are many naturally occurring β-aminonitriles and pharmaceuticals. The β-aminonitrile is also a precursor to 1,3-diamines and β-amino acid derivatives.

Routes to the β-aminonitrile functional group include ring opening of aziridines with cyanide, conjugate addition of amines to acrylonitriles, hydrocyanation of nitroalkenes and Thorpe-Ziegler reaction between two nitriles followed by conjugate addition. The most efficient method and that which has led to many enantioselective syntheses through asymmetric transition metal catalysis, is the addition of alkanenitriles to imines. Deprotonation of alkyl nitriles (CHCN, pK½ 31.3, PhCHCN, pK½ 21.9 in DMSO) and subsequent reaction with electrophiles requires strong bases, such as LDA and diisopropylamine, which can trigger undesired side reactions, such as epimerisation or elimination. Increasing the acidity of alkenenitriles through coordination with catalytic transition metal complexes has allowed the use of weaker bases for this reaction. Examples of alkenenitriles other than acetonitrile often give poor diastereoselectivities. Good enantioselectivities and in some cases good diastereoselectivities have been obtained in asymmetric catalysed reactions, the major diastereoisomer isolated from these can be either **anti**- or **syn**- depending upon the type of nitrile and catalyst used. A rare and recent example of the addition of a lithio nitrile anion, generated by treatment with LHMDS, to an imine as part of a complex natural product synthesis gave no diastereoselectivity. The same reaction using Ellman’s auxiliary on the imine gave a diastereoselectivity ~15:85 **anti**:**syn for the product β-aminonitrile. There is a clear need to be able to synthesise β-aminonitriles from longer alkanenitriles than acetonitrile and to understand how to access either **anti**- or **syn**- diastereoisomers to complement existing stereoselective methodology. We communicate here a synthesis of β-aminonitriles which by judicious choice of base can give either **anti**- or **syn**-β-aminonitriles with alkanenitriles and offer some mechanistic understanding of this.

We recently developed conjugate addition nitro-Mannich reactions where a nitronate anion generated by conjugate addition to a nitroalkene, underwent addition to an imine. We attempted an analogous reaction with cyanoalkenes. Although conjugate reduction using Superhydrine® proceeded cleanly, disappointingly no 1,2-addition to the imine was observed with or without Brønsted or Lewis acids in a range of solvents.

Scheme 1. 1,2-addition of alkane nitriles to aldimines

To confirm that 1,2-addition could occur we generated the corresponding α-cyano carbazide from 3-phenylpropanenitrile with a range of bases and then added imine (Scheme 1, R1=Bn, R2=2-Br-C6H4). The 2-bromophenyl imine was used in preparation for a possible Pd catalysed intramolecular amination. We observed that the diastereomeric ratio of the product β-aminonitrile was dependent on the nature of the base and temperature (Table 1). With the base ‘BuLi the **anti**-β-aminonitrile was observed with a diastereomeric ratio (dr) = 85:15 at -78 °C (entry 1). A repeat reaction with warming to rt for 5 min switched the diastereoselectivity to favour the **syn**-β-aminonitrile 15:85 (entry 2). In the case of LHMDS the
syn-β-aminonitrile was observed with $d_r = 90:10$ at -78 °C (entry 3). Warming to room temperature as before gave no change in the sense or extent of diastereoselectivity (entry 4). LDA gave essentially the same results as BuLi (compare entries 1 and 2 with 5 and 6). This similarity of BuLi and LDA had been noted before in the reaction of α-amidoalkyphenyl sulfones (generating the corresponding N-Boc-imine in situ) with lithiated nitriles, and gave variable yields and diastereoselectivities of the anti-β-aminonitrile.

Table 2. Scope of diastereoselectivity

<table>
<thead>
<tr>
<th>entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>base</th>
<th>yield of major (%)&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-Br-Ph</td>
<td>Ph</td>
<td>BuLi</td>
<td>85:15</td>
</tr>
<tr>
<td>2</td>
<td>2-Br-Py</td>
<td>Py</td>
<td>BuLi</td>
<td>85:15</td>
</tr>
<tr>
<td>3</td>
<td>2-Br-Py</td>
<td>Py</td>
<td>BuLi</td>
<td>85:15</td>
</tr>
<tr>
<td>4</td>
<td>2-Br-Py</td>
<td>Py</td>
<td>BuLi</td>
<td>85:15</td>
</tr>
<tr>
<td>5</td>
<td>2-Br-Py</td>
<td>Py</td>
<td>BuLi</td>
<td>85:15</td>
</tr>
<tr>
<td>6</td>
<td>2-Br-Py</td>
<td>Py</td>
<td>BuLi</td>
<td>85:15</td>
</tr>
</tbody>
</table>

We were intrigued by the fact that the judicious choice of base could prepare either anti- or syn-β-aminonitriles. A survey of the reaction of different lithiated alkane nitriles (from 1), generated with either BuLi or LHMDS at -78 °C for 1 h, with a variety of imines 2 was performed (Scheme 1, Table 2). A reaction with a secondary alkyl nitrile iso-butynitrile with either base gave only ~7% yield and was not further optimised. With primary alkyl nitriles the base controlled diastereoselectivity was observed across a range of substrates. There was a marginal gain in diastereoselectivity with aromatic imines if there was an ortho-substituent (compare entries 1, 2, 5-11 with entries 3 and 4). The beneficial effect of ortho-substituents was only replicated on the nitrile partner 3-(2-chlorophenyl)propynitrile for the syn-diastereoisomer generated with LHMDS (entries 21, 90% yield). Other nitriles of simple alkyl derivatives gave no clear trend in diastereoselectivities.
but gave some examples of good selectivity (entries 13, 14 and 21) and many others where the major isomers could be isolated diastereomerically pure. Alkyl imines derived from cyclohexanecarboxaldehyde and n-hexanal both gave the same diastereoselection with each base favouring the anti-diastereoisomer (entries 30-33). Other aromatic imines gave moderate to good yields of pure major diastereoisomers (entries 24-29).

To elucidate the mechanism for this diastereoselectivity the reaction (Scheme 1, R1=Br and R2=Br-C6H5) was performed at -78 °C at varying reaction times and the crude material analysed by 1H NMR (Table 3). The results suggest that the initial 2-3 min equilibration favours the anti-diastereoisomer in an 85:15 ratio after 1 min at -78 °C with both BuLi and LHMDS. The initial anti-selectivity for LHMDS was quickly eroded over time (<30 min) and as the conversion increased with time, the selectivity for the syn-diastereoisomer also increased to a maximum 10:90 (~60 min). For BuLi the initial and rapid anti-selectivity (85:15) was maintained and did not start to be eroded until after 1 h. After 6 h the BuLi reaction was syn-selective, but only to the extent of 25:75. These results suggest that the anti-diastereoisomer is the kinetic product and the syn-diastereoisomer is the thermodynamic product. Quite why the syn-diastereoisomer is the thermodynamically more stable product is not obvious to us.

Table 3. Effect of base and temperature on diastereoselectivity

<table>
<thead>
<tr>
<th>time at -78 °C</th>
<th>BuLi anti: syn</th>
<th>conversion (%)</th>
<th>LHMDS anti: syn</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 min</td>
<td>85:15</td>
<td>80</td>
<td>85:15</td>
<td>30</td>
</tr>
<tr>
<td>5 min</td>
<td>85:15</td>
<td>90</td>
<td>70:30</td>
<td>50</td>
</tr>
<tr>
<td>30 min</td>
<td>85:15</td>
<td>90</td>
<td>25:75</td>
<td>90</td>
</tr>
<tr>
<td>1 h</td>
<td>85:15</td>
<td>90</td>
<td>10:90</td>
<td>100</td>
</tr>
<tr>
<td>3 h</td>
<td>50:50</td>
<td>&gt;95</td>
<td>10:90</td>
<td>100</td>
</tr>
<tr>
<td>6 h</td>
<td>25:75</td>
<td>&gt;95</td>
<td>10:90</td>
<td>100</td>
</tr>
</tbody>
</table>

All reactions were carried out on a 0.5 mmol scale, nitrile (1.0 equiv), Base (1.1 equiv in hexane), imine (1.1 equiv) in THF (6 mL) at -78 °C for 1 h. Determined by comparison of the 1H NMR signals for the CH:CHCN protons (~2.5-3.5 ppm) of the crude reaction mixture (to nearest 5). By 1H NMR.

To probe the mechanism of isomerisation a crossover experiment was conducted. The initial product 3 (R1=Br, R2=Br-C6H5), formed in situ from addition to PMP protected imine 2 (R1=Br-C6H5) after 1 h at -78 °C, was treated with an equivalent of the corresponding N-para-ethoxyphenyl protected imine 4 and left to stir for a further 1 h at -78 °C (Scheme 2). The crude 1H NMR did not show any incorporation of the second imine with either base. Repeating the crossover experiment, but warming to rt for 5 min directly after the addition of an equivalent of 4, showed a statistical 50:50 mixture of both β-aminonitriles, again for both bases. As there is no crossover at -78 °C, we can conclude that the equilibration of the LHMDS system at -78 °C is not due to a retro-then re-addition pathway.

A key control experiment was treatment of anti-3 (R1=Br, R2=Br-C6H5) with LHMDS (1.1 equiv) in the presence of 4 at -78 °C. After 1 h, there was again no incorporation of imine 4, but the original anti-diastereoselectivity (85:15) had eroded to 70:30 (Scheme 2). Using LHMDS as base the original kinetic anti-3 (R1=Br, R2=Br-C6H5) with either BuLi or LHMDS at -78 °C for 1 h also led to no change in diastereoselectivity. This enables the conversion of anti-β-aminonitriles to syn-β-aminonitriles.

The pKa of HMDS (26) is similar to that of HCCN (22-31). We propose that BuLi deprotonation occurs by deprotonation and reprotonation of the HCCN of 3 by HMDS (Scheme 2). Using LHMDS as base the original kinetic anti-3 rich mixture is reprotonated by HMDS and the regenerated LHMDS equilibrates the HCCN centre to the thermodynamic mixture, with syn-3 as the major diastereoisomer. With BuLi the initial kinetic anti-3 rich mixture is stable at -78 °C for at least 1 h. Additional proof was provided by a series of other experiments (R1=Br, R2=2-Br-C6H5). Addition of an equimolar quantity of HMDS to an BuLi deprotonation directly before or after addition of imine favoured the thermodynamic syn-3 (25:75). Addition of an equimolar quantity of BuLi to a LHMDS deprotonation, followed by imine favoured the kinetic anti-3 (75:25). Allowing a LHMDS experiment to stir...
for 30 min after addition of imine and then adding an equimolar quantity of 1BuLi favoured the thermodynamic syn-3 (20:80), implying that the equilibration was interrupted by irreversible deprotonation with 1BuLi. Circumstantially commercial LHMDS led to the formation of syn-3 more efficiently than freshly prepared LHMDS.24 This explanation (Scheme 3) satisfactorily accounts for the diastereoselectivities of all the aromatic imines investigated, but an anomaly is the two examples of alkyl imines derived from cyclohexane carboxaldehyde and n-hexanal (entries 30-33). An equal amount of anti-diastereoisomer prevailed with both bases in each case, suggesting that the initial kinetic diastereoisomer does not undergo equilibration.

A previous literature report of lithium cyanate additions to benzaldehyde imines using LDA suggests some epimerisation via both retro-re-addition and deprotonation/reprotonation of HCCN.15 The paper also goes on to show that addition of a variety of alkyl halides gives good to moderate yields of quaternary nitriles. In our case, it would not be unreasonable to assume that a small equilibrium exists between aza-anion 3 and 6 (Scheme 3) and that this is only significantly perturbed in the presence of a suitable reversible proton donor, such as HMDS.

To show the synthetic versatility of the β-aminonitrites syn-3 (R1=Br, R2=2-Br-C6H5) was reduced to the corresponding 1,3-diamine with LiAlH4/H2SO4 in 92% yield and hydrolysed with basic hydrogen peroxide to the β-amino acid in 65% yield, with no erosion in diastereoselectivity (see Supporting Information (SI)).

The judicious choice of either irreversible conditions with 1BuLi to give anti-diastereoselectivity or reversible conditions with LHMDS to give syn-diastereoselectivity provides an operationally simple method for the isolation of diastereomERICALLY pure β-aminonitrites derived from substituted primary acetonitriles and aryl imines. The characterisation of the thermodynamic equilibration process with HMDS offers the opportunity for the products from enantioselective syntheses that are anti-diastereoselective to be converted into syn-diastereoisomers. The methodology described provides a direct method for the stereoselective synthesis of β-aminonitriles which will widen their use as chiral building blocks in target synthesis.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterisation data and NMR spectra for all compounds. Representation of X-ray structure for syn-3 R1=Br, R2=2-Br-C6H5 (PDF)

Crystallographic data for syn-3 R1=Br, R2=2-Br-C6H5 (CIF)

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Notes
The authors declare no competing interest.

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REFERENCES

(8) For example: Saika, M.; Deka, D. C.; Karmakar, S. Current Microwave Chemistry 2016, 3, 47 and references therein.
(23) Unambiguous assignment of relative stereochemistry was achieved through single crystal X-ray crystallography of the prevailing syn-diastereoisomer (syn-3 \( R^1 = \text{Bn}, \ R^2 = 2\text{-Br-C}_6\text{H}_5 \)) from a reaction using LHMDS. See SI and CCDC 1531946

(24) Possible quenching of LHMDS by adventitious water over time during use could increase the concentration of HMDS.