Layered Double Hydroxides (LDHs): An Efficient Catalyst System for the Synthesis of Chiral Aminonitriles

F. Tahooria,b*, M. Moradinejadb, R. Tondfekr and F. Karbasi

aRazi Vaccine and Serum Research Institute, Agricultural Research and Extension Organization (AREEO), Karaj, Iran
bDepartment of Chemistry, Tehran East branch, Islamic Azad University, Tehran, Iran
cDepartment of Chemistry, Iran University of Science and Technology, Tehran, Iran

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Strecker reaction is one of the simplest multicomponent reactions. It used for synthesis of chiral α-amino nitriles. This reaction was carried out in the presence of catalytic amount of layered double hydroxides (LDHs). In this study, simple and practical method for the synthesis of this class of catalysts is provided. The results shown that LDH is the good heterogen catalyst for synthesis of chiral α-amino nitriles.

Keywords: Layered double hydroxide (LDHs), Strecker reaction, α-Amino acids, Diastereoselectivity

INTRODUCTION

To use multicomponent reactions, is a good way to synthesis many components. Application of these reactions because of the simplicity, compatibility with the environment, reducing the synthesis steps, the less chemical waste and so on has always been [1]. According to Tietze, these reactions have high bond forming efficiency [2]. So many chemists make use of these reactions to produce various products.

One of the oldest and most widely used multicomponent reactions is Strecker that reported by Strecker for synthesis of α-amino acids in 1850. Accurate reaction between aldehyde and amine in the first step to form the imine followed by the addition of hydrogen cyanidetoform α-aminonitriles as an intermediate necessary for synthesis of α-amino acids [3]. The highly used compounds in these reactions, they usually try to improve the reaction efficiency by charging the reaction conditions, such as solvent, temperature, catalyst concentration and type of the reagent and formation of side products are minimized. Among the various catalysts that have been used so far like Lewis acid such as chlorides [4,5], transition metals such as Indium [6], Rhodium [7], Ruthenium [5], Cerium [8], Nickel [4], Palladium [9], etc. oxides such as Aluminum, Silicon, Titanium and Manganese [10], complex compounds such as montmorillonite-KSF [11], phosphotungstic acid [12] and nanocatalyst [13] and magnetic catalysts [14] can be mentioned. Using lewis acid catalysts containing chiral ligands or chiral organic compounds, pure enantiomer α-amino acids have been synthesized [15-17].

However, this reaction due to the formation of new chiral center is also take into consideration. For selective synthesis of chiral center, chiral primary substance, chiral media or catalysts helping chiral center can be used according to the reaction mechanism which goes through via attaching of cyanide anion to imine bond, if the media ionic the possibility of selective formation of an enantiomer will enhance.

Layered Double Hydroxide/LDH) are a class of compounds that are formed by repetition of layers with positive ion and also the zone between a layer containing negative ions and solvent molecules that cause neutralization. More studies of these class of compounds has been done with di- and tri-valentations. These classes of compounds have the general formula...
Typical powder XRD patterns of the Mg
the range of 400
transformation infrared spectroscope in reflectance mode, at
were recorded on a D/max
IR spectra of the
products contain some CO
absorption peak at 1365 cm
In these reactions the efficiency
of reactions is improved usually by changing the reaction
conditions such as solvent, temperature, catalyst
concentration and type of reagent and the formation of side
product is minimized subsequently.

EXPERIMENTAL

All the substances used in reaction are purchased from
Fluka and Merck companies. To identify the products
formed by 
and 
spectra taken by Bruker
DRX 300 Avance spectrometers, respectively at 300 and 75
MHz and are used in CDCl
solvent improving reaction
condition. For separation of catalyst are used from Eppendorf
centrifuge

Synthesis of Mg-Al-Cu-NO
LDHs
Magnesium hydroxide (5.80 g, 0.10 mol) was added to
aluminum hydroxide (1.30 g, 0.017 mol) and milled for 1 h
in room temperature using a planetary ball mill. The mixture
was removed in Teflon-lined stainless-steel autoclave
containing 30 ml of 0.078 M Cu(NO
) solution. Then, it was heated in an oven and treated hydrothermally at
80 °C. The mixture was centrifuged. Product was washed
with water and dried.

X-Ray diffraction (XRD) patterns of the prepared samples
were recorded on a D/Max-rA model diffractometer with
Cu Kα radiation in the 20 range of 10-70 with a
scanning rate of 0.08° min
. FT-IR spectra of the samples
were collected using KBr pellets on a Vector 22 Fourier
transformation infrared spectroscope in reflectance mode, at
the range of 400-4000 cm
, with a resolution of 2 cm
Typical powder XRD patterns of the Mg-Al-Cu-LDH
shown in Fig. 1.

The characteristic diffraction peaks of the LDH-phase
could be clearly observed which is in good agreement with
that reported in the literature [28]. According to the JCPDS
37-0630, the characteristic diffractions around 20
11.4°, 22.6°, 34.5°, 38.7°, 45°, 60.3° and 61.5° can be
assigned to the typical (003), (006), (012), (015), (018),
(110) and (113) face of Mg-containing Cu-Al-LDH.

Figure 2 shows the FT-IR spectra of the Mg-Al-Cu-
LDH. The strong and broad band centered on 3450 cm
was assigned to the OH stretching and be
peaks from 400 to
around
1500 cm
The peaks from 400 to 1000 cm
were attributed to the
stretching and bending vibrations of M-O and M-OH [30].

General Procedure for the Synthesis of Methyalted
Amino Acids
1 mmol amino acid was mixed with 3 ml methanol in
balloon. The balloon was placed in a bath of water and
acetone until the temperature of balloon contents reached to
-5 °C, then 3 mmol thionyl chloride was slowly added to
reaction vessel. After thionyl chloride is increased, all the
amino acids become soluble and the environment pH
decreased to 1. The reaction mixture is being mixed at room
temperature for 5 h and the progress of the reaction using
TLC with a mixture of H
: MeOH:EtOH (10:2:1) and the
detector ninhydrine followed. After completion of the
reaction, methanol was evaporated by hot water bath, and
solid product was dried. In the following, for purification,
the resulting precipitate was dissolved in the minimum
amount of methanol and diethyl ether was added as
antisolvent finally, pure precipitate obtained was filtered.

General Procedure for the Synthesis of α-Amino
Nitriles (4a-h)
mol resulting methylated amino acid was dried and
dissolved with 5 ml methanol. 20 mg catalyst was added to
reaction vessel and after being mixed for 5 min. 1 mmol
benzaldehyde was added to the balloon content reaction
progress was followed by TLC (hexane:ethylacetate
Fig. 1. XRD patterns of Mg-Al-Cu-LDH.

Fig. 2. IR Spectra of Mg-Al-Cu-LDH.
Progress was followed and after 3 h, the contents of the balloon were transferred to the special centrifuge container (room temperature, 3000 rpm, 10 min) and the catalyst was removed by decantation.

The remaining solution was purified by plate chromatography and the product was isolated.

**Spectral Data for Compounds**

**Methyl-2-((cyano(p-tolyl)methyl)amino)-3-(1H-indol-3-yl)propanoate (4a).** (mixture of two diastereomers (58:42)). 1H NMR (300 MHz, CDCl3) δ 2.35 (s, 6H, Me, mixture of two diastereomers), 3.20 (dd, 2H, J = 11.7, 4.16, CH2, mixture of two diastereomers), 3.29-3.30 (m, 2H, CH2, mixture of two diastereomers), 3.68 (s, 3H, -OMe, diastereomer A), 3.74 (s, 3H, -OMe, diastereomer B), 3.97-4.01 (m, 1H, CHα, diastereomer A), 4.24-4.26 (m, 1H, CHα, diastereomer B), 4.61 (s, 1H, CHCN, diastereomer A), 4.82 (s, 1H, CHCN, diastereomer B), 7.01 (d, 1H, J = 2.1, 2H, CH Ar, diastereomer A), 7.05 (d, 1H, J = 2.0, 2H, CH Ar, diastereomer B), 7.12-7.20 (m, 4H, CH Ar, mixture of two diastereomers), 7.21 (s, 1H, -CH indole, diastereomer A), 7.26 (s, 1H, -CH indole, diastereomer B), 7.32 (d, 2H, J = 8.0, CH Ar, mixture of two diastereomers), 7.53 (t, 2H, J = 8.2, CH Ar, mixture of two diastereomers), 7.60 (d, 2H, J = 7.3, CH Ar, mixture of two diastereomers), 7.84 (d, 1H, J = 1.3, CH Ar, diastereomer A), 7.85-7.87 (m, 1H, CH Ar, diastereomer B).

13C NMR (75 MHz, CDCl3) δ 29.1, 29.2, 31.4, 31.9, 52.1, 52.2, 52.8, 52.9, 54.6, 59.0, 59.4, 110.1, 110.4, 111.3, 118.6, 118.8, 118.9, 119.5, 121.9, 122.1, 122.9, 123.1, 127.4, 128.3, 129.5, 129.6, 130.1, 131.4, 131.5, 136.1, 136.2, 139.1, 147.2, 174.0, 174.1.

**Scheme 1. General reaction of preparation amino nitrils in optimized condition**

3:1) after formation of imine, 1 mmol trimethyl silyl cyanide was added (Scheme 1). Reaction progress was followed and after 3 h, the contents of the balloon were transferred to the special centrifuge container (room temperature, 3000 rpm, 10 min) and the catalyst was removed by decantation.

The remaining solution was purified by plate chromatography and the product was isolated.

Ar, diastereomer B), 7.57 (d, 2H, J = 5.9, CH Arindole, diastereomer A), 7.62 (d, 2H, J = 6.7, CH Ar, diastereomer B), 8.11-8.17 (m, 2H, CH Ar, mixture of two diastereomers), 8.19-8.21 (m, 2H, CH Ar, mixture of two diastereomers).

13C NMR (75 MHz, CDCl3) δ 29.3, 29.7, 52.6, 54.1, 56.6, 58.0, 58.5, 60.4, 108.7, 109.5, 111.0, 118.4, 119.7, 119.8, 122.2, 122.3, 123.0, 123.1, 123.3, 123.6, 126.8, 126.9, 129.9, 131.8, 133.1, 134.9, 136.3, 136.4, 143.2, 144.4, 172.9, 173.8, 174.0.

**Methyl-2-[(cyano(p-tolyly)methyl)amino]-3-(4-hydroxyphenyl) propanoate (4e).** (mixture of two diastereomers (55:45)). 1H NMR (300 MHz, CDCl3) δ 2.61-2.89 (m, 1H, CH2, mixture of two diastereomers), 2.98-3.11 (m, 2H, CH2, mixture of two diastereomers), 3.29 (dd, 1H, J = 13.6, 5.1, CHα, diastereomer A), 3.75 (s, 6H, -OMe, mixture of two diastereomers), 4.14 (dd, 1H, J = 8.5, 1H, CHα, diastereomer B), 4.59 (s, 1H, CHCN, diastereomer A), 4.83 (s, 1H, CHCN, diastereomer B), 6.67 (d, 2H, J = 6.3, CH Ar, diastereomer A), 6.70 (d, 2H, J = 5.9, CH Ar, diastereomer B), 6.75 (d, 2H, J = 9.4, CH Ar, mixture of two diastereomers), 6.97 (dd, 2H, J = 6.0, 2.1, CH Ar, mixture of two diastereomers), 7.02 (t, 2H, J = 2.6, CH Ar, CH Ar, mixture of two diastereomers), 7.05 (brs, 1H, CH Ar, diastereomer A), 7.34-7.42 (m, 6H, CH Ar, mixture of two diastereomers), 7.68 (dd, 2H, J = 8.0-1.6, CH Ar, mixture of two diastereomers).

13C NMR (75 MHz, CDCl3) δ 29.7, 30.1, 38.5, 38.9, 52.3, 52.9, 59.8, 60.5, 115.3, 115.5, 115.6, 115.7, 127.4, 127.6, 128.1, 128.5, 128.7, 129.2, 130.3, 130.4, 130.8, 1313.2, 131.4, 134.2, 154.7, 155.2, 172.4, 173.8.

**Methyl-2-[(cyano(3-nitrophcnyl)methyl)amino]-3-(4-hydroxyphenyl) propanoate (4f).** (mixture of two diastereomers (63:37)). 1H NMR (300 MHz, CDCl3) δ 2.78-2.85 (m, 1H, CH2, one of diastereomers), 2.99-3.07 (m, 2H, CH2, mixture of two diastereomers), 3.27 (dd, 1H, J = 5.1, 4.7, CH2, one of diastereomers), 3.70 (s, 3H, -OMe, diastereomer A), 3.77 (s, 3H, -OMe, diastereomer B), 4.12 (q, 1H, J = 7.2, CHα, diastereomer A), 4.19 (dd, 1H, J = 9.0, 4.8, CHα, diastereomer B), 4.62 (s, 1H, CHCN, diastereomer A), 4.99 (s, 1H, CHCN, diastereomer B), 6.69 (dd, 3H, J = 8.5, 2.7, CH Ar, mixture of two diastereomers), 6.77 (d, 1H, J = 8.5, CH Ar, diastereomer A), 6.95 (td, 3H, J = 8.8, 2.4, CH Ar, mixture of two diastereomers), 7.04 (d, 1H, J = 8.5, CH Ar, diastereomer B), 7.54 (t, 2H, J = 8.1, CH Ar, mixture of two diastereomers), 7.72-7.74 (m, 1H, CH Ar, diastereomer A), 7.94 (s, 1H, CH Ar, diastereomer B), 8.01 (dt, 1H, J = 7.7, 1.1, CH Ar, diastereomer A). 8.18-8.24 (m, 3H, CH Ar, mixture of two diastereomers), 8.47 (t, 1H, J = 1.7, CH Ar, diastereomer A).

13C NMR (75 MHz, CDCl3) δ 29.6, 38.5, 38.8, 52.5, 52.6, 55.1, 59.5, 60.6, 115.4, 115.6, 115.7, 117.4, 122.7, 127.4, 128.0, 128.4, 129.6, 130.2, 130.3, 130.4, 130.8, 133.9, 136.4, 136.9, 154.8, 155.1, 173.6, 173.8.

**Methyl-2-[(cyano(phenyl)methyl)amino]-3-phenylpropanoate (4g).** (mixture of two diastereomers (71:29)). 1H NMR (300 MHz, CDCl3) δ 2.88-2.97 (m, 2H, CH2, mixture of two diastereomers), 3.10-3.19 (m, 2H, CH2, mixture of two diastereomers), 3.75 (s, 3H, -OMe, diastereomer A), 3.78 (s, 3H, -OMe, diastereomer B), 3.86 (dd, 1H, J = 7.7, 5.5, CHα, diastereomer A), 3.99 (dd, 1H, J = 5.8, CHα, diastereomer B), 4.55 (s, 1H, CHCN, diastereomer A), 4.84 (s, 1H, CHCN, diastereomer B), 7.11-7.28 (m, 4H, CH Ar, mixture of two diastereomers), 7.30-7.32 (m, 2H, CH Ar, mixture of two diastereomers), 7.36-7.39 (m, 2H, CH Ar, mixture of two diastereomers), 7.40 (dd, 1H, J = 7.7, 5.1, CH Ar, mixture of two diastereomers), 7.57 (d, 2H, J = 5.9, CH Arindole, diastereomer A), 7.62 (d, 2H, J = 6.7, CH Ar, diastereomer B), 8.11-8.17 (m, 2H, CH Ar, mixture of two diastereomers), 8.19-8.21 (m, 2H, CH Ar, mixture of two diastereomers).
7.49-7.62 (m, 3H, CH Ar, mixture of two diastereomers), 7.68-7.75 (m, 2H, CH Ar, mixture of two diastereomers), 7.82 (dd, 2H, J = 8.3 Hz, J = 1.2, CH Ar, mixture of two diastereomers), 13C NMR (75 MHz, CDCl₃) δ 39.4, 39.7, 52.2, 52.9, 53.0, 53.3, 59.6, 60.4, 110.1, 116.7, 117.0, 118.4, 118.6, 127.0, 127.1, 127.4, 127.5, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.1, 129.3, 129.4, 129.7, 131.6, 132.8, 132.9, 133.2, 135.6, 136.1, 136.4, 136.8, 173.5, 173.6.

**RESULTS AND DISCUSSION**

Initially, to determine the optimum conditions of synthesis, reaction of methylated phenylalanine with benzaldehyde was selected as a model and reaction parameters were studied (Scheme 2). To do this, the effect of catalyst used in synthesis of derivative was evaluated that the catalyst used was evaluated. After determining LDH catalyst as the best catalyst, in order to optimized the reaction solvent, protic polar solvents such as methanol and aprotic solvent such as dichloromethane and also a solvent such as acetonitrile and solvent free condition were used. The final results are given in Table 2.

First, 1 mmol methylated phenylalanine and 5 ml solvent, followed by 20 mg catalyst were mixed together, after 5 min, 1 mmol benzaldehyde was added to the contents of the flask. After 30 min, the reaction progress was followed by TLC. When the imine structure was confirmed, the value of 1 mmol trimethylsilylcyanide was added and TLC taken again.

TLC showed that imine formation in acetonitrile is harder and slower. Methylated amino acid was dissolved in methanol better. Progress was followed by TLC. The results showed that the best imines were formed in methanol and dichloromethane. It should be noted that in term of solvent free, gridding materials in crucible was used to raise the chances of molecules colliding. In solvent free, reaction was progress but slow. The results show that methanol was selected as the optimal solvent.

After determining methanol as a solvent, amount of catalyst used in reaction at room temperature was evaluated. The intended reaction (methylated phenyl alanine reaction with benzaldehyde) was done with different levels of LDH catalyst, after 30 min, the intensity of the spots on the TLC showed that all of them have produced imine at the same ratio. 1 mmol trimethylsilylcyanide was added and reaction progress was followed by the TLC. (As there has been no molecular structure set for this catalyst, molar mass and M percent of catalyst consumption can't be reported) (Table 3).

After optimization of reaction condition, derivatives of α-amino nitriles were synthesized and diastereoselectivity of new chiral center were determined by the comparison of the integral of singlet peaks in σ = 4-5.5 ppm (CHCN) (Table 4).

Scheme 2. The model reaction

![Scheme 2: The model reaction](image)

**Table 1. Effect of Catalyst for the Model Reaction**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>H₃[P(W₃O₁₀)₆].H₂O</td>
<td>80</td>
</tr>
<tr>
<td>(S)- (+)-1,1'-Binaphthyl-2-2'diyl hydrogen phosphate</td>
<td>39</td>
</tr>
<tr>
<td>S-Proline</td>
<td>78</td>
</tr>
<tr>
<td>LDH</td>
<td>82</td>
</tr>
</tbody>
</table>

**Table 2. Effect of Solvent for the Model Reaction**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>Methanol</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>Dichloromethan</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>Acetonitril</td>
<td>76</td>
</tr>
</tbody>
</table>

**Table 3. Effect of amount of LDH for the Model Reaction**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mg)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>63</td>
</tr>
</tbody>
</table>
CONCLUSIONS

The results show that in presence of catalytic amount of Layered double hydroxides (LDH), the strecker reaction proceeds selectively. This can be due the ionic environment. It is also concluded that selectivity increases when using smaller side chain amino acids.

REFERENCES