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Cu-catalyzed debrominative cyanation of *gem*-dibromoolefins: a facile access to α,β-unsaturated nitriles

Brij Bhushan Ahuja* and Arumugam Sudalai*

An efficient catalytic route for the synthesis of α,β-unsaturated nitriles from easily accessible *gem*-dibromoolefins has been developed. The method utilized inexpensive reagents such as Cu$_2$O as catalyst, L-proline as ligand and NaN$\text{CN}$ as cyanide source to afford α,β-unsaturated nitriles in high yields (62-86%). Deuterium exchange study has shown that one of the bromide atoms of *gem*-dibromoolefins exchanges with cyanide while the other with deuterium atom.

α,β-Unsaturated nitriles are a ubiquitous structural unit frequently found in natural products and act as a valuable synthetic intermediates for pharmaceuticals, agrochemicals, dyes and functional materials.$^1$ They also serve as a synthetic precursor for the transformation to a variety of functional group such as amides, ester, ketone, amine and alcohols.$^2$ The compact nature of the nitrile moiety, as well as its hydrogen bond accepting ability, and metabolic stability has made it an important functional group in medicinal chemistry research. Some of the representative examples of pharmaceutical agents which comprise a α,β-unsaturated nitrile group includes IDX899 and rilpivirine, the potent anti-HIV nonnucleoside reverse transcriptase inhibitors; entacapone, a drug for Parkinson’s disease; and CC-5079, the anticancer agent (Fig. 1).$^3$ Therefore, the development of newer methods for their facile access is of significant interest among organic chemists. A number of synthetic routes to α,β-unsaturated nitriles are known such as amide dehydrogenation reaction,$^4$ Wittig/Homer-Wadsworth-Emmons$^5$ or Peterson olefination,$^6$ carbocyanation of alkynes,$^7$ cyanation of alkynyl halides$^8$ and oxidative transformation of the corresponding aldehydes,$^9$ amines,$^{10}$ amides,$^{11}$ alcohols,$^{12}$ azides,$^{13}$ and hydrazones.$^{14}$ Although some of these methods are attractive, they suffer from certain limitations of using extreme conditions, poor yields and expensive reagents. Therefore, the development of convenient and user-friendly procedure for the synthesis of α,β-unsaturated nitriles by using inexpensive reagents and from easily accessible starting material is highly desirable.

The chemistry of *gem*-dibromoolefins (1a-r), was almost confined to the synthesis of terminal alkynes through Corey-Fuchs reaction.$^{15}$ Recently, versatility of *gem*-dibromoolefins have been exploited in the synthesis of various carbocycles and heterocycles such as indoles,$^{16}$ benzofuran,$^{17}$ benzothiophenes,$^{18}$ isocoumarins$^{19}$ and other heterocycles$^{20}$ through metal catalyzed tandem coupling reaction (Suzuki, Sonogashira, Heck or Ullmann type) or C-H activation. In addition the versatility of *gem*-dibromoolefins in metal catalyzed cross coupling reactions with alkynes, vinylalanes and organoboranes, tin, magnesium and zinc compounds to give highly stereoselective synthesis of trisubstituted alkenes$^{21}$ by prudent selection of coupling partner has been exploited. To the best of our knowledge, a direct method of synthesis of α,β-unsaturated nitriles from *gem*-dibromoolefins has not been reported.

![Scheme 1. Cu$_2$O catalyzed synthesis of α,β-unsaturated nitriles from *gem*-dibromoolefins](image-url)

**Fig. 1** Representative examples of pharmaceuticals containing α,β-unsaturated nitrile group.

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National Chemical Laboratory, Chemical Engineering & Process Development Division, Pune-411008, Maharashtra, India e-mail: a.sudalai@ncl.res.in; Tel.: +91 20 25902174; fax: +91 20 25902676.

†Electronic supplementary information (ESI) available: Experimental procedure, characterization data, $^1$H and $^{13}$C NMR spectra.

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utilizing gem-dibromomolefins as precursor remains elusive in literature. In continuation of our studies on Cu-mediated catalyzed development of newer synthetic methodologies, herein we report a novel Cu\textsubscript{2}O catalyzed synthesis of α,β-unsaturated nitriles from gem-dibromomolefins (Scheme 1).

In our initial study, (2,2-dibromomethyl)benzene (1a) was treated with CuCN (3 equiv) in DMF at 150 °C, which gave the corresponding cinnamonitrile (2a) in 21% yield with E/Z ratio 4.5:1 (Table 1, entry 1). The yield of 2a was, however, significantly improved to 57% when L-proline (L1) was used as promoter in combination with CuCN in DMF at 120 °C (entry 2).\textsuperscript{25} In order to provide a catalytic process, we have carried out the cyanation reaction with copper (I) oxide as a catalyst, NaCN as CN source. Thus, by using Cu\textsubscript{2}O (10 mol%) along with NaCN (1.1 equiv), 2a was obtained in low yield (24%, entry 3). In order to improve the yield and selectivity, a series of N-based ligands [L-proline (L1), 1,10-phenanthroline (L2), N,N-dimethylethylene diamine (L3) and 1,2-ethylenediamine (L4)] were screened along with Cu\textsubscript{2}O (entry 4-7). After several experimentations, it was thus found that a combination of (2,2-dibromomethyl)benzene, NaCN, copper (I) oxide (10 mol%), L-proline (L1, 10 mol%) in DMF at 110 °C for 12 h was the best optimized condition in achieving 2a in high yield (81%, entry 4), however, significant improvement in selectivity was not observed. Replacing the solvent (dioxane, toluene) or CN source (K\textsubscript{3}[Fe(CN)\textsubscript{6}], or TMSCN) had a deleterious effect on the conversion (entry 4,8). Also lowering Cu\textsubscript{2}O concentration (5 mol%) afforded 2a in low yields (43%). The result was also inferior when the catalyst was changed to CuX (X = Br, Cl, I or CN) (entry 10-13).

With the optimized conditions in hand [Cu\textsubscript{2}O (10 mol%), L-proline (10 mol%), NaCN (1.2 equiv, DMF, 110 °C), we then investigated the generality of this copper (I) oxide catalyzed debrominative cyanation of gem-dibromomolefins 1a-r (Table 2). The starting materials 1a-r are readily prepared from the corresponding commercially available aldehydes via the

![Scheme 1](image_url)

**Table 1: Cu\textsubscript{2}O-catalyzed synthesis of cinnamonitrile 2a: optimization studies\textsuperscript{a}**

<table>
<thead>
<tr>
<th>No.</th>
<th>Catalyst</th>
<th>ligand/additive</th>
<th>CN source (equiv)</th>
<th>yield (%)\textsuperscript{b}</th>
<th>temp. (°C)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>--</td>
<td>CuCN (3)</td>
<td>21\textsuperscript{c}</td>
<td>150</td>
</tr>
<tr>
<td>2</td>
<td>--</td>
<td>L1 (1 equiv)</td>
<td>CuCN (2.2)</td>
<td>57\textsuperscript{d}</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>Cu\textsubscript{2}O</td>
<td>--</td>
<td>NaCN (1.1)</td>
<td>24</td>
<td>110</td>
</tr>
<tr>
<td>4</td>
<td>Cu\textsubscript{2}O</td>
<td>L1</td>
<td>NaCN (1.1)</td>
<td>81\textsuperscript{e}trace\textsuperscript{f}</td>
<td>110</td>
</tr>
<tr>
<td>5</td>
<td>Cu\textsubscript{2}O</td>
<td>L2</td>
<td>NaCN (1.1)</td>
<td>68</td>
<td>110</td>
</tr>
<tr>
<td>6</td>
<td>Cu\textsubscript{2}O</td>
<td>L3</td>
<td>NaCN (1.1)</td>
<td>41</td>
<td>110</td>
</tr>
<tr>
<td>7</td>
<td>Cu\textsubscript{2}O</td>
<td>L4</td>
<td>NaCN (1.1)</td>
<td>26</td>
<td>110</td>
</tr>
<tr>
<td>8</td>
<td>Cu\textsubscript{2}O</td>
<td>KI</td>
<td>K\textsubscript{4}[Fe(CN)\textsubscript{6}] (0.5)</td>
<td>trace\textsuperscript{g}</td>
<td>110</td>
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<td>9</td>
<td>Cu\textsubscript{2}O</td>
<td>L1</td>
<td>TMSCN</td>
<td>trace</td>
<td>110</td>
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<tr>
<td>13</td>
<td>CuCN</td>
<td>L1</td>
<td>NaCN (1.1)</td>
<td>54</td>
<td>110</td>
</tr>
</tbody>
</table>

\textsuperscript{a}2a-phenyl and 1,2-ethylenediamine were screened along with Cu\textsubscript{2}O (10 mol%).

\textsuperscript{b}reaction conditions: gem-dibromomolefin (3 mmol), NaCN (3.3 mmol), Cu\textsubscript{2}O (10 mol%), L-proline (10 mol%), DMF, 110 °C, 12 h; \textsuperscript{c}isolated yield after column chromatographic purification; \textsuperscript{d}temp. 150 °C; \textsuperscript{e}temp. 120 °C; \textsuperscript{f}5 mol% Cu\textsubscript{2}O was used. Toluene and dioxane were used separately.

\textsuperscript{g}DMF/H\textsubscript{2}O was used (1:1).

\textsuperscript{h}2a-r: yield (%); E/Z

\textsuperscript{i}2,2-dibromomethyl)benzene (3 mmol), catalyst (10 mol%), ligand (10 mol%), solvent 10 mL, 12 h. \textsuperscript{j}isolated yield after column chromatographic purification. \textsuperscript{k}temp. 150 °C; \textsuperscript{l}temp. 120 °C. \textsuperscript{m}Cu\textsubscript{2}O was used. Toluene and dioxane were used separately.

\textsuperscript{n}DMF/H\textsubscript{2}O was used (1:1).

With the optimized conditions in hand [Cu\textsubscript{2}O (10 mol%), L-proline (10 mol%), NaCN (1.2 equiv, DMF, 110 °C), we then investigated the generality of this copper (I) oxide catalyzed debrominative cyanation of gem-dibromomolefins 1a-r (Table 2).
Ramirez procedure. The substrates bearing different substitutions like halogen, alkyl, alkoxy, nitro, thio etc group on the aromatic nucleus were well tolerated under the reaction conditions and the E and Z substituted a,b-unsaturated nitriles (2a-r) were isolated in good yields. In case of p-chlorocinnaminitrile 2d we observed as a single E isomer. In addition to the aryl group, the reaction also proceeded equally well with different gem-dibromoolefins including heteroaryl- and alkynyl substituted alkenes. Interestingly, when 4-(3,3-dibromoallyl)-1,2-dimethoxybenzene 1m was subjected under standardized condition we observed the isomerized product i.e. β,γ-unsaturated nitrile as a single E isomer. Intriguingly, (2,2-dibromovinyl)ferrocene (1n) performed well, under the optimized condition to generate the expected product in 71% yield. In all cases we observed thermodynamic stable E as the major product with ratio varying from 1.2:1 to 100:0. However, in case of aliphatic gem-dibromoolefins we observed the complex reaction mixture, which may be a limitation of this catalytic process.

In order to gain insight into the mechanistic details of the reaction, p-nitrodibromoalkene 1g was treated with Cu(O (10 mol %), L-proline (10 mol %), NaCN (1.2 equiv), D₂O (2 equiv) in DMF at 110 °C for 12 h that resulted in α-deuterated p-nitrocinnaminitrile 3 (Scheme 2). Based on this deuterated study, a probable mechanism for debrominative coupling reaction has been proposed. First L-proline interacts with Cu₂O to generate a proline-Cu (I) complex A. The oxidative addition of dibromoolefins to Cu (I) species then produces intermediate B which subsequently undergoes nucleophilic displacement with NaCN to generate intermediate C. Reductive elimination of intermediate C produces bromo cyano olefin D with the liberation of catalytic complex A. Bromo cyano olefin D again undergoes subsequent oxidative addition with Cu (I) complex A to generate intermediate E which on protonation facilitates the formation of α,β-unsaturated nitriles (Figure 2).

In conclusion, we have developed an efficient catalytic process for the synthesis of α,β-unsaturated nitriles from gem-dibromoolefins using Cu (I) oxide as catalyst, L-proline as ligand, and NaCN as cyanide source. The easy accessible starting materials, broad reaction scope and using cheap commercially available reagents makes this method of high significance in organic synthesis.

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Experimental Section
1. General
Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80 °C was used. Melting points are uncorrected. Infrared spectra were recorded on Shimadzu FTIR-8400 spectrometer. The wave numbers (n) of recorded IR-signals are quoted in cm⁻¹. ¹H and ¹³C NMR were recorded on Bruker AV-200, AV-400 and AV-500 NMR spectrometers, respectively. Purification was done using column chromatography (230–400 mesh).

Note: sodium cyanide is “highly toxic” and must be handled with care.

2. General experimental procedure for the preparation of α,β-unsaturated nitriles (2a-r):
To a stirred solution of gem-dibromoolefins 1a-r (3 mmol) in dry DMF (15 mL) was added NaCN (3.3 mmol), Cu₂O (0.3 mmol) and L-proline (0.3 mmol). The entire reaction mixture was heated to 110 °C while being stirred under N₂ for 12 h (monitored by TLC). The reaction mixture was then cooled to room temperature and excess cyanide was quenched with aq. NaClO₂, diluted with water (10 mL) and EtOAc (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The aqueous layer after extraction was poured into aq. KMnO₄ solution to quench excess NaCN and then disposed off. The combined organic extracts were washed with brine, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give crude products which were purified by column chromatography [silica gel (230-400 mesh) and petroleum ether: EtOAc (7:3) as an eluent]
to afford the corresponding α,β-unsaturated nitriles (2a–r) in 62-89% yield.

3. General experimental procedure for the preparation of α-deuterated p-nitro cinnamaldehyde 3:

To a stirred solution of 1-(2,2-dibromovinyl)-4-nitrobenzene (1 mmol) in dry DMF (5 mL) was added NaCN (1.1 mmol), CuO (0.1 mmol), L-proline (0.1 mmol) and D₂O (1 mmol). The entire reaction mixture was heated to 120 °C while being stirred under N₂ for 12 h (monitored by TLC). The reaction mixture was then cooled to room temperature and excess cyanide was quenched withaq. NaClO₂, diluted with water (10 mL) and EtOAc (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The aqueous layer after extraction was poured into aq. KMnO₄ solution to quench excess NaCN and then disposed off. The combined organic extracts were washed with brine, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give crude products which were purified by column chromatography [silica gel (230–400 mesh) and petroleum ether: EtOAc (7:3) as eluent to afford the corresponding α-deuterated p-nitro cinnamaldehyde 3 in 20% yield.

4. Spectroscopic Data:

Cinnamaldehyde (2a): Yield: 84% (0.325 g, 2.52 mmol); Colourless liquid; IR (CHCl₃, cm⁻¹): υmax 856, 1247, 1560, 1591, 2111; unseparable mixture of E/Z (4:5:1) isomers; α-deuterated: IR (CHCl₃, cm⁻¹): 856, 1247, 1560, 1591, 2111; unseparable mixture of E/Z (4:5:1) isomers; α-deuterated.

4.1. Spectroscopic Data for 3

4.1.1. (4-Methoxyphenyl)cinnamaldehyde (2b): Yield: 86% (0.410 g, 2.56 mmol); White solid; mp 83–84°C; α-deuterated: IR (CHCl₃, cm⁻¹): 856, 1247, 1560, 1591, 2111; unseparable mixture of E/Z (4:5:1) isomers; α-deuterated.

4.1.2. (4-Methylthiophenyl)cinnamaldehyde (2c): Yield: 86% (0.484 g, 2.48 mmol); White solid; mp 88–89°C; α-deuterated: IR (CHCl₃, cm⁻¹): 856, 1247, 1560, 1591, 2111; unseparable mixture of E/Z (4:5:1) isomers; α-deuterated.

4.1.3. (4-Fluorophenyl)cinnamaldehyde (2d): Yield: 80% (0.353 g, 2.4 mmol); White solid; mp 40–42°C; α-deuterated: IR (CHCl₃, cm⁻¹): 856, 1247, 1560, 1591, 2111; unseparable mixture of E/Z (4:5:1) isomers; α-deuterated.

4.1.4. (4-Chlorophenyl)cinnamaldehyde (2e): Yield: 86% (0.369 g, 2.58 mmol); White solid; mp 83–84°C; α-deuterated: IR (CHCl₃, cm⁻¹): 856, 1247, 1560, 1591, 2111; unseparable mixture of E/Z (4:5:1) isomers; α-deuterated.
3-(thiophen-2-yl)acrylonitrile (2j): Yield: 79% (0.320 g, 2.37 mmol); IR (CHCl$_3$, cm$^{-1}$): $\nu_{max}$ 975, 1117, 1234, 1601, 1623, 2217; unseparable mixture of E/Z (2/1) isomers; E distinct signals; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 5.65 (d, $J = 16.4$ Hz, 1H), 7.04-7.07 (m, 1H), 7.24-7.26 (m, 1H), 7.39-7.42 (m, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 94.4, 117.7, 128.3, 129.1, 131.1, 138.3, 142.5; Z distinct signals; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 5.26 (d, $J = 11.7$ Hz, 1H), 7.03-7.07 (m, 1H), 7.23 (d, $J = 23.1$ Hz, 1H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 91.7, 117.3, 120.1, 133.1, 137.6, 140.5; Analysis: C$_8$H$_7$NS requires C, 80.54; H, 6.34; N, 10.16%.  

3-(furan-2-yl)acrylonitrile (2k): Yield: 84% (0.300 g, 2.52 mmol); Pale yellow oil; IR (CHCl$_3$, cm$^{-1}$): $\nu_{max}$ 975, 1117, 1235, 1601, 1623, 2217; unseparable mixture of E/Z (2/1) isomers; E distinct signals; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 5.76 (d, $J = 15.8$ Hz, 1H), 7.99 (d, $J = 15.8$ Hz, 1H), 7.91 (d, $J = 2$ Hz, 1H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 39.3, 99.2, 116.4, 117.4, 117.2, 135.9, 145.3, 150.1; Z distinct signals; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 5.24 (d, $J = 10.5$ Hz, 1H), 6.90-7.01 (m, 2H), 7.19-7.29 (m, 1H), 7.34-7.42 (m, 3H), 7.44-7.52 (m, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 96.7, 116.4, 124.2, 124.7, 128.9, 129.6, 129.7, 132.5, 141.3, 141.9; Analysis: C$_8$H$_7$NS requires C, 79.49; H, 6.45; N, 4.23; N, 10.13; Found: C, 79.73; H, 6.45; N, 4.63%.

References


26 Melting point is reported for E and Z mixture.