CO₂-Enabled Cyanohydrin Synthesis and Facile Homologation Reactions

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ABSTRACT: Thermodynamic and kinetic control of a chemical process is the key to access desired products and states. Changes are made when desired product is not accessible; one may manipulate the reaction with additional reagents, catalysts and/or protecting groups. Here we report the use of carbon dioxide to direct reaction pathways in order to selectively afford desired products in high reaction rates while avoiding the formation of byproducts. The utility of CO₂-mediated selective cyanohydrin synthesis was further showcased by broadening Killiani-Fischer synthesis to offer an easy access to variety of polyols, cyanohydrins, linear alkyl nitriles, by simply starting from alkyl- and arylaldehydes, KCN and atmospheric pressure of CO₂.

A chemical reaction is governed by kinetics and thermodynamics, and a simultaneous control of both parameters is a common practice in designing and optimizing chemical reactions. The manipulation of thermodynamic stability of reactants and products will decide the outcome of a chemical process, while various reaction pathways can lead to undesired products thus reducing overall efficiency of the process.² To circumvent unwanted reaction pathways, chemists have developed selective catalysis, protecting groups (P in Figure 1), trapping reagents and reactivity-altered reactants (A' and B'), which in turn can limit the scope and generality of the original reaction. In our ongoing pursuit to implement CO₂ in the core of organic synthesis, we sought ways in which equilibria can be controlled by the presence and the absence of CO₂ – a mild Lewis and potentially Brønsted acid. Here we demonstrate our strategy by accelerating an organic reaction; nucleophilic 1,2-addition of a carbon nucleophile to carbonyl compounds, namely cyanohydrin formation reaction promoted by CO₂. Facile homologation of aldehydes with cyanide was realized expanding the scope beyond Killiani-Fischer synthesis, under practical reaction conditions, accessing variety of compounds in a modular fashion.

Carbon dioxide is intrinsically stable molecule,²³ however, it can readily and reversibility react with various nucleophiles.²⁴ Recent applications of carbon dioxide in organic synthesis showed fruitful success particularly in CO₂-incorporation,²⁵ CO₂ as a temporal protecting group for C-H activation,⁶ CO₂ for asymmetric catalysis⁷ and oxidation reactions⁸. We recently investigated the role of CO₂ in a cyanation reaction,⁹ where CO₂ can be used in catalytic amounts to facilitate the stereoselective transformation of activated electrophiles via 1,4-conjugate addition reactions. Cyanohydrin synthesis - 1,2-cyanide addition reactions to carbonyls - is one of the oldest C-C bond-forming reactions, reported in 1832 by Winkler using HCN as a cyanide source.¹⁰ Despite the high utility of cyanohydrins in organic synthesis¹¹-¹⁴ the use of HCN may reduce its application potential due to its volatile nature and health risks. Recent activities in cyanohydrin synthesis are mainly performed by using TMSCN¹⁵ and cyanoformate¹⁶ as an HCN surrogate.¹¹,¹²,¹³ These reagents suffer from poor atom economy when un-protected cyanohydrins are desired. Furthermore, the cyanation reactions with in-situ generated HCN (from mixture of TMSCN and an alcohol) are limited by the instability of the cyanide sources thereby limiting the solvent compatibility.¹¹,¹³

It has been a common knowledge that cyanohydrin formation can not be “catalyzed” due to the high nucleophilicity of cyanides although the reaction undergoes strong backward reaction (k_\text{forward} = 1.96 \times 10^4 \text{sec}^{-1}\text{M}^{-1}, k_\text{backward} = 0.87 \times 10^{10} \text{sec}^{-1}) in RCHO + HCN ⇄ RC(OH)CN.¹⁹ Whilst Brønsted acids can generate volatile yet nucleophilic HCN from solid cyanide sources (NaCN or KCN), general and specific acid catalysis can only be operative at exceedingly low concentration of an acid catalyst.²⁰ This has been manifested in total synthesis, which
requires sophisticated cyanide sources and reagents. For example, high selectivity towards cyanohydrin formation was realized assisted by an activating reagent, i.e. Al-based cyanide sources (AlEt₂CN, Nagata’s reagent).²¹²²

At this juncture, the lack of a general and practical method for cyanohydrin formation reaction under neutral conditions led us to investigate the potential utility of CO₂ in cyanohydrin synthesis with alkaline metal cyanides. Under mild conditions, CO₂ can generate slightly acidic medium thus enabling catalysis, while exhibiting Lewis acidic character at the central carbon for trapping and stabilizing anionic species. However, another challenge lays on the side reactions: benzoin- and self-aldol reactions from KCN and aldehydes, generating numerous byproducts (Scheme 1). Based on our previous work, we sought that the use of CO₂ in principle provide a practical method by minimizing side products, while overcoming the limit of Kiliani-Fischer synthesis beyond carbohydrate modification via selective cyanohydrin synthesis.²³

We have recently shown the applicability cyanohydrins as a nucleophile via an umpolung strategy (Scheme 1, α-keto acid synthesis).²⁴ In the absence of Ti(IV) and DBU, we observed facile formation of cyanohydrin in pseudo first order of the aldehyde with KCN under CO₂ atmosphere (1 atm) in ethanol (k = 2.50 x 10⁻⁵). This is approximately 10²-folds rate acceleration compared to the reported values,¹⁹ which is surprising considering that the reaction requires the solubilization of KCN in the organic solvent. We verified that the solubility of KCN was increased in the presence of CO₂ (Figure S6), which can be ascribed to the formation of cyanoformate in solution liberating solubilized cyanide nucleophiles.²⁵ Therefore, we performed various control experiments as summarized in Table 1. Under CO₂ atmosphere (1 atm), full conversion of the starting material (1a) was observed to the desired cyanohydrin affording quantitative isolated yield (99% conversion, 97% yield). When performing the cyanation under a N₂ atmosphere, low conversion to cyanohydrin (7%) was detected within 10 min with no increase in yield of the product after prolonged reaction time (up to 18 h), indicating that the reaction reached fast equilibrium in favor of starting materials. More importantly, in situ generated HCN gave inferior result, (entry 3, 21% yield), while quantitative yield was obtained with KCN/CO₂ combination within 30 minutes (entry 4, 91%). Variety of solvents were found to be compatible to induce desired product (i.e. ethanol, heptane, acetonitrile and water, see supporting information for full optimization, Table S1-13) showing the generality of the use of CO₂ to accelerate cyanohydrin synthesis. The solubility of cyanide is important – a soluble cyanide source, ammonium cyanide, showed good conversion to the product however, the reaction was not efficient under inert N₂ atmosphere (entries 12 and 13). Therefore, we concluded that CO₂ is not innocent in this reaction, and it was evident that the reaction can be promoted by carbon dioxide whereas a strong acid (e.g. HCl) afforded only low yield of the product since HCN (a “slower” nucleophile) generation is favored (entry 14). The use of acetic acid²⁶ showed compatible result (entry 15) confirming that weak acid can indeed catalyze the reaction, by prohibiting the complete protonation of KCN.

Table 1. Optimizing CO₂ Mediated Cyanation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from standard reaction conditions</th>
<th>Yield⁶*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>99% (97%)⁶*</td>
</tr>
<tr>
<td>2</td>
<td>No CO₂ (under N₂)</td>
<td>7%</td>
</tr>
<tr>
<td>3</td>
<td>HCN (2 equiv) instead of KCN</td>
<td>21%</td>
</tr>
<tr>
<td>4</td>
<td>30 min of reaction time</td>
<td>91%</td>
</tr>
<tr>
<td>5</td>
<td>H₂O as a solvent</td>
<td>95%</td>
</tr>
<tr>
<td>6</td>
<td>n-heptane as a solvent</td>
<td>87%</td>
</tr>
<tr>
<td>7</td>
<td>toluene as a solvent</td>
<td>9%</td>
</tr>
<tr>
<td>8</td>
<td>DCM as a solvent</td>
<td>22%</td>
</tr>
<tr>
<td>9</td>
<td>DCM as a solvent + DBU (1 eq)</td>
<td>97%</td>
</tr>
<tr>
<td>10</td>
<td>NaCN, 30 min</td>
<td>57%</td>
</tr>
<tr>
<td>11</td>
<td>NEt₂CN, 30 min</td>
<td>97%</td>
</tr>
<tr>
<td>12</td>
<td>NEt₂CN, 30 min, under N₂</td>
<td>33%</td>
</tr>
<tr>
<td>13</td>
<td>eq. 5M HCl (4 eq.) instead of CO₂</td>
<td>24%</td>
</tr>
<tr>
<td>14</td>
<td>AcOH (4 eq.) instead of CO₂</td>
<td>95%</td>
</tr>
</tbody>
</table>

⁴4-fluorobenzaldehyde (1 mmol) and KCN (2 mmol) were mixed in EtOH (2 mL). The reaction mixture was stirred under CO₂ (1 atm) for 18 h. ⁶Yield was determined by ¹⁹F nuclear magnetic resonance spectroscopy (NMR) (D1; relaxation time = 2 s) of the crude mixture. *Isolated yield.

Figure 2. Cyanohydrin formation using stoichiometric amounts of CO₂. After 10 min was added CO₂ (20 mol%) every 20 min. Cross (X) marks the addition of catalytic amounts of CO₂ (20 mol%).

The role of CO₂ in the cyanohydrin synthesis was further verified by adding catalytic amounts of CO₂ (20 mol%) to a reaction mixture repeatedly (Figure 2). A sharp increase of product formation was immediately observed followed by the addition of CO₂. A near stoichiometric relationship between product formation and the amounts of added CO₂ indicates the added CO₂ was quantitatively consumed as a stoichiometric reagent.
Having demonstrated the feasibility of the CO$_2$ promoted cyanohydrin formation, we explored the scope of the reaction with respect to both aryl and alkyl aldehydes and ketones (Scheme 2). A variety of aryl aldehydes was tested and provided the corresponding cyanohydrins in excellent yields regardless of their substitution in terms of electron donating and withdrawing properties. Cyanohydrins of ortho-substituted benzaldehydes showed increased stability, affording high purity products without purification. When subjecting the α,β-unsaturated aldehydes to the reaction conditions the corresponding cyanohydrins (19 and 20) was isolated in excellent yields, without the formation of byproduct derived from 1,4-conjugate addition reactions. Aliphatic aldehydes were tolerated (20-24) when performed under a CO$_2$ atmosphere, while various aldol condensation products were observed under N$_2$ atmosphere, highlighting the importance of the CO$_2$-mediated cyanohydrin formation conditions. For example, when 3-phenylpropionaldehyde (22) was subjected to the reaction conditions under N$_2$ atmosphere, a complicated reaction mixture was observed due to aldol-reaction related byproducts. Furthermore, the cyanation reaction of sterically hindered free alcohol was achieved (23), which would otherwise not be straightforward by classical means. Despite the reduced reactivity of ketones, both α-keto acids (27-28) and aliphatic ketones (25-26) were smoothly transformed into cyanohydrins in good to excellent yield, with no hemiketal or aldol-reaction related by-products formation. The cyanohydrin formation reaction was operative in the presence of CS$_2$ as a surrogate to carbon dioxide. In this case, we expected that the formation of xanthate would render a synthetic platform to diversify the product.

Both aryl and aliphatic aldehydes were converted into the corresponding cyano methyl xanthate in excellent yields under optimized conditions (29-30, See Tables S15-S17 for more detail), demonstrating, to the best of our knowledge, the first example of α-aryl cyan xanthate. The xanthate formation reaction of aryl aldehydes was also facilitated under carbon dioxide atmosphere, suggesting cyanohydrin formation promoted by CO$_2$. We presumed that the carbonate and dithiocarbonate exchange equilibrium would afford desired products after methylation reaction with MeI.

Cyanohydrin formation: Carbonyl (1 mmol), KCN (2 eq), EtOH (0.5 M) and CO$_2$ (1 atm) was stirred at rt for 18 h. Cyanohydrin formation: Aldehyde (1 mmol), KCN (5 eq), CS$_2$ (10 eq), MeI (5 eq) and MeCN (0.5 M) was stirred at 0 °C for 4 h, then rt for 2 h. Reaction performed on a 100 mmol scale using KCN (1.2 eq). Reaction performed on a 500 mmol scale using KCN (1.2 eq). KCN (3 eq). Performed under a CO$_2$ atmosphere. Performed under a N$_2$ atmosphere.

Scheme 2. Carbon dioxide Mediated Cyanohydrin Synthesis
With these results in our hands, we sought the developed cyanohydrin synthesis demonstrates two different modes for facile and intuitive homologation strategy: 1) CHO homologation by preserving the hydroxy group of cyanohydrin, and 2) CH$_2$ homologation using Barton-McCombie reduction conditions.$^{28}$ These would be allowing for selective elongation via “expanded” Kiliani-Fischer synthesis, which has been restricted to CHO-elongation of carbohydrate-based aldehydes. Additionally, to the best of knowledge, previously reported cyanohydrin formation and elongation sequences are limited to aliphatic aldehyde substrates, which can not undergo aldol and benzoin reactions.$^{29}$ Under optimized reaction conditions, the obtained cyanohydrins were smoothly transformed into the corresponding TBDMS protected cyanohydrin, 31, (91%, 2 steps), and alkyl nitrile, 35, (85%, 2 steps) after protection and reductive deoxygenation reaction, respectively. Each elongation sequence was further repeated to generate α-hydroxy aldehyde for CHO elongation and CH$_2$ elongation to afford 1,2-diols, 32, in 71% yield (3 steps) and β-hydroxy nitrile, 34, in 93% yield. The alkyl nitrile was further functionalized to demonstrate the possibility of CHO elongation and CH$_2$ elongation to generate elongated TBDMS-protected cyanohydrin, 36, in 75% yield (3 steps), and two-carbon elongated linear nitrile, 38, in 92% isolated yield (Scheme 3). All combination of CHO and CH$_2$ elongation displays selective homologation in 3-steps sequence providing a variety of products under practical and simple reaction conditions enabled by CO$_2$ atmosphere.

To shed some lights on the reaction mechanism, we attempted to isolate the carbonate species from the CO$_2$-mediated cyanohydrin formation reaction (Scheme 4). Fortunately, we obtained the Cbz (carboxybenzyl) protected cyanohydrin, 39, in 82% yield by using benzyl bromide under CO$_2$ atmosphere, suggesting the formation of potassium cyanohydrin carbonate. It is noteworthy here that our protocol demonstrates the synthesis of Cbz protected cyanohydrin from carbon dioxide, without the need for reactive reagents such as benzyl cyanoformate or chloroformates.$^{30}$

\[ R'CHO \rightarrow R'CH}_2CN \]

**Scheme 3.** “Expanded” Kiliani-Fischer Homologation and Elongation by CO$_2$- and CS$_2$-mediated Cyanation. (R = 4-F-C$_6$H$_4$)

**Scheme 4.** Synthesis of Cbz Protected Cyanohydrin with CO$_2$

In conclusion, we have developed a synthetic method to access cyanohydrins under practical conditions, which enabled a general method for homologation sequences using potassium cyanide and carbon dioxide. In general, it was found that aldehydes were prone to predominantly form byproducts related to benzoin reaction and aldol condensation reactions in the absence of CO$_2$. These side reactions were prohibited by the action of CO$_2$, acting as a temporary protecting group and providing a broad substrate scope of cyanohydrin and xanthates.

**Figure 3.** (A) Traditional cyanohydrin synthesis and reported equilibrium constants (at room temperature) and (B) A suggested reaction mechanism of CO$_2$-controlled reaction (R$^1$ = 4-F-C$_6$H$_4$, R$^2$ = C$_6$H$_5$)
Thermodynamic analysis of the cyanohydrin synthesis revealed that the desired reaction pathways is not viable with KCN under conventional reaction conditions (Figure 3). The reported equilibrium constant of cyanohydrin synthesis with HCN is in a stark difference with the obtained values in the current study with KCN/CO₂. We therefore believe that CO₂ is not only changing the polarity of the reaction medium, facilitating the reaction, but also affecting the equilibrium of the reaction while forming stable adducts with CO₂. A strong acid is not as efficient as CO₂ since it generates HCN, which shows a slower reaction rate albeit the favored equilibrium to the right side (Figure 3A).

The use of CO₂ is highly practical by simplifying work-up procedures without any remaining protecting groups or reagents after the removal of CO₂. Further investigations in other types of organic reactions and asymmetric cyanohydrin synthesis promoted by CO₂ are underway.

ASSOCIATED CONTENT
Supporting Information. 1H and 13C NMR, optimization tables and mechanistic studies.

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Anslyn, E. V.; Dougherty, D. A. Modern Physical Organic Chemistry; University Science, 2005; pp 537-625


impossible chemical transformations

\[ \text{A} + \text{B} \rightleftharpoons \text{A} \rightarrow \text{B} \]
\[ \Delta G^0 > 0 \]
high activation barrier

\[ \text{A} + \text{B} \rightarrow \text{A-B} \]
\[ \text{A-B} \] (product)

\[ \text{A-B} \rightarrow \text{A-B-CO}_2 \]

\[ \text{CO}_2 \] for Modification of Reaction Coordinate!

\[ \text{A} + \text{B} \rightleftharpoons \text{A} \rightarrow \text{B} \]
lower \[ \Delta G^\ddagger \]. \[ \Delta G^0 < 0 \]