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Published in:
ACS Catalysis

DOI:
10.1021/acscatal.9b01087

Publication date:
2019

Document version
Publisher's PDF, also known as Version of record

Document license:
Other

Citation for published version (APA):
Carbon Dioxide-Catalyzed Stereoselective Cyanation Reaction

Tamal Roy,† Myungjo J. Kim,‡,§,∥ Yang Yang,†,∥ Suyeon Kim,‡,§ Gyumin Kang,‡,§ Xinyi Ren,† Anders Kadziola,† Hee-Yoon Lee,*‡ Mu-Hyun Baik,*‡,§ and Ji-Woong Lee,*†

†Department of Chemistry, University of Copenhagen, Universitetsparken 5, Copenhagen Ø 2100, Denmark
‡Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Korea
§Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 34141, Korea

Supporting Information

ABSTRACT: We report a Michael-type cyanation reaction of coumarins by using CO2 as a catalyst. The delivery of the nucleophilic cyanide was realized by catalytic amounts of CO2, which forms cyanoformate and bicarbonate in the presence of water. Under ambient conditions, CO2-catalyzed reactions afforded high chemo- and diastereoselectivity of β-nitrile carbonyls, whereas only low reactivities were observed under argon or N2. Computational and experimental data suggest the catalytic role of CO2, which functions as a Lewis acid, and a protecting group to mask the reactivity of the product, suppressing byproducts and polymerization. The utility of this convenient method was demonstrated by preparing biologically relevant heterocyclic compounds with ease.

KEYWORDS: carbon dioxide, cyanation, cyanoformate, DFT calculation, coumarins

The cyanoformate ion (NC–CO2−) is involved in the biological synthesis of ethylene at an Fe-containing enzyme (Figure 1a).1,2 The formation of the cyanoformate ion from 1-aminocyclopropane-1-carboxylic acid is thought to protect the catalytically active Fe(III) center, which may be poisoned by cyanide ligation.3−5 Although it is thermodynamically unstable, cyanoformate formed by combining cyanide and CO2 may present a new opportunity in synthesis as a convenient source of highly nucleophilic cyanides avoiding the direct use of toxic hydrogen cyanide. Various surrogates of Scheme 1. (A) Hydrocyanation and Ring-Opening Reaction of Coumarin 1a under CO2 and (B) a Comparison of Reactivities of 1a under CO2 (Red) and Argon (Brown) as a Function of Time

Received: March 15, 2019
Revised: May 1, 2019
Published: May 1, 2019

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HCN are known, but they are based on forming HCN in sili. Recently, “shuttle” catalysis was introduced to deliver cyanide from less toxic alkyl nitriles. Nonetheless, cyanides are indispensable as reagents for many reactions. Inspired by the ethylene biosynthesis, we envisaged that the cyanoformate may be useful in organic synthesis. Combining cyanide and CO₂ in solution affords cyanoformate, as our experiments and calculations confirmed (Figure 1b), where the activities of the cyanoformate and bicarbonate remain uncovered.

To investigate this hypothesis (a synthetic application of cyanoformate in chemical reaction), we chose coumarin derivatives. There are currently no convenient procedures for accessing nitrile derivatives of coumarins, which represent densely functionalized synthons for organic synthesis. Owing to the divergent reactivity of alkyl nitriles to amines, carboxylic acids, aldehydes/ketones, and amides, cyanation is ubiquitous in natural products syntheses, pharmaceuticals, and polymers.

Hydrocyanation of unsaturated carbonyls is particularly interesting and results in β-cyano adducts, which can be further elaborated to γ-amino butyric acids and 1,2-dicarboxylic acids. However, 1,4-conjugate addition of hydrogen cyanide has been elusive due to competing 1,2-addition reactions.

Herein, we report an operationally simple 1,4-cyanation reaction of activated substrates, namely coumarins, to afford β-cyano carboxylates using CO₂ and cyanide (Figure 1c). The presented reactions were highly chemo- and stereoselective even in the presence of water. A larger scale synthesis of α-aryl-β-cyano esters demonstrates the utility of the protocol for preparing heterocyclic compounds. In-depth computational analysis supports the proposed catalytic role of CO₂, bicarbonate, and carbonic acid as Lewis and Brønsted acids to selectively activate electrophiles.

Recently, CO₂-mediated organic reactions were reported expanding its role beyond the well-known function as a cheap C₁ source. Fundamentally, adding CO₂ to cyanide and using it as a nucleophilic reagent is counter-intuitive, as the nucleophilicity of cyanide is reduced upon formation of cyanoformate. Nevertheless, we were surprised to obtain high isolated yield (90%) of 2a starting from coumarin 1a with high diastereoselectivity (20:1 dr) under CO₂ atmosphere, whereas negligible reactivity was observed under N₂ or argon atmosphere (Scheme 1).

Table 1 summarizes the optimization of reaction conditions based on the methyl ester of the ring-opened product (2b) in the presence of an internal standard. The structure of 2b was unambiguously confirmed by X-ray single crystal analysis.

**Table 1. Optimization of the Reaction Conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from Standard Reaction Condition</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>without additional water</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>argon or N₂ instead of CO₂</td>
<td>&lt;10</td>
</tr>
<tr>
<td>4</td>
<td>Prestatement with CO₂</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>20–40 mol % of CO₂</td>
<td>67–81%</td>
</tr>
<tr>
<td>6</td>
<td>MeCN as a solvent</td>
<td>99%</td>
</tr>
<tr>
<td>7</td>
<td>at 25 °C</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>KCN instead of NEt₄CN</td>
<td>n.d.</td>
</tr>
<tr>
<td>9</td>
<td>3 equiv NaCN + NBu₄Cl (10 mol %)</td>
<td>n.d.</td>
</tr>
<tr>
<td>10</td>
<td>3 equiv NaCN + 1.2 equiv NBu₄Cl</td>
<td>72%</td>
</tr>
<tr>
<td>11</td>
<td>Lewis, Brønsted acids instead of CO₂</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

**Scheme 2. Substrate Scope of the CO₂-Catalyzed Cyanation of Coumarins**

HCN are known, but they are based on forming HCN in situ. After 3 h. Lewis acid and Brønsted acids (2 equiv): Ti(OEt)₄, BF₃·OEt₂, Cu(OAc)₂·H₂O, FeCl₃, NH₄Cl, and p-nitrophenol were added instead of CO₂. MeCN was used as a solvent.

**Supporting Information**

See Supporting Information section 11 for more details.
The methylation of the \( \beta \)-cyano carboxylate intermediate was completely chemoselective without dimethylation. A control experiment with \(^{13}\)CO\(_2\) strongly suggested no incorporation of atmospheric CO\(_2\) in the final product (Figures S2 and S3). Reaction with D\(_2\)O instead of H\(_2\)O gave identical results (99% NMR yield, >15:1 dr) with >75% H\(^-\)D exchange at both acidic protons on stereogenic carbons (Figure S6).

Interestingly, small amounts of water (∼1 vol %) improved the reaction rate, yield, and selectivity toward the syn-product (entries 1 and 2), which may be due to water promoting the decomposition of cyanocarboxylate and faster release of cyanide. When the same reaction was carried out under N\(_2\) or argon atmosphere, only a trace amount (<10%) of 2b was found with the majority of substrate remaining unreacted (entry 3). As a control experiment, a saturated solution was prepared by purging a solution of tetraethylammonium cyanide with CO\(_2\). The use of this solution afforded 82% yield of 2b without additional gaseous CO\(_2\), confirming that the cyanation is feasible with dissolved CO\(_2\) (entry 4). Moreover, we tested reactions with reduced CO\(_2\) amounts (20−40 mol % with respect to coumarin 1b) and found up to 81% conversion of 1b to the desired product, suggesting a potential turnover of CO\(_2\) (up to 3 TON, entry 5). Acetonitrile was a compatible solvent; however, the diastereoselectivity was reduced to 6:1, while lower conversion was observed at room temperature (entries 6 and 7). Various insoluble cyanide sources were inferior to soluble ammonium cyanide (entry 8 and Table S1).

Catalytic amounts of NBu\(_4\)Cl (10 mol %) were employed to evaluate a potential phase-transfer catalysis, but excess stoichiometric amounts of NBu\(_4\)Cl (1.2 equiv) were necessary to mediate the cyanation reaction (entries 9 and 10). Various Lewis and Brønsted acids, such as BF\(_3\)·OEt\(_2\), Ti(O\(_i\)Pr)\(_4\), Sc(OTf)\(_3\), Fe(III), Cu(II), NH\(_4\)Cl, and HCl, with and without water showed negligible activity, implying a superior performance of CO\(_2\) and water in promoting nucleophilic cyanide addition reactions. To the best of our knowledge, this new reaction protocol employing tetraethylammonium cyanide with CO\(_2\) is the only method to selectively deliver cyanide for the conjugate addition reaction of coumarins.

With the optimized reaction conditions in our hands, we verified the generality of the cyanation reaction by varying the electronic properties of coumarins. The relative stereochemistry of products was unambiguously determined by X-ray single crystallography of products 2a, 2b, and 2f (Scheme 2). High diastereoselectivity and isolated yield were obtained with corresponding \( \beta \)-cyano carboxylic esters/acids (2a–2s/3n–q) under CO\(_2\) without sophisticated purification. The same reactions in the absence of CO\(_2\) (under argon or N\(_2\)), in general, afforded inferior conversion and diastereoselectivity of the cyanation products. Practical reaction conditions allowed us to smoothly convert coumarin 1b to carboxylic acid product 3b (0.96 g) after a single crystallization step. Various substituents (R\(_2\)) on the 3-position were tolerated, including free carboxylic acid. For example, 3-carboxycoumarin, 1l, was converted to the corresponding methyl ester (2l) after

(Scheme 2). DFT calculated free energy profiles for the CO\(_2\)-catalyzed cyanation of coumarin. The black trace represents the pathway to the major diastereomer. The blue trace represents the pathway to the minor diastereomer. All of the H atoms are removed for clarity at the ORTEP view.

Figure 2. DFT calculated free energy profiles for the CO\(_2\)-catalyzed cyanation of coumarin. The black trace represents the pathway to the major diastereomer. The blue trace represents the pathway to the minor diastereomer. All of the H atoms are removed for clarity at the ORTEP view.
Several mechanistic scenarios involving the ketene were examined to shed light on the diastereoselective protonation, as detailed in the Supporting Information. As shown in Figure 2, the carbonate addition to the C=O bond is most plausible traversing D-TS at 25.1 kcal/mol to afford intermediate E, which quickly rearranges to form the proton exchange product F. On the basis of the experimental observations, the involvement of CO₂ and related equilibria is plausible at the diastereoselective protonation step. With carbon dioxide not fully dissociated, the decarboxylation step is estimated to be downhill in energy by 9.4 kcal/mol. Notably, two major rotational isomers (G and G') were identified to undergo facile intramolecular protonation with the barrier of only 2.3 kcal/mol, in the presence of weakly bound CO₂. The energy difference between the rotamers were maintained for the corresponding transition states leading to a differentiation for the si- and re-face protonation. The observed transition states G-TS and G'-TS showed a remarkable energy difference (2.7 kcal/mol), consistent with the experimental diastereoselectivity. In the absence of CO₂ binding, as illustrated in Supporting Information, the gap between two proton transfer barriers was reduced significantly, which results in the reduced diastereoselectivity, confirmed by experiments.

The utility of this highly stereoselective processes was demonstrated in a larger scale reaction (22.5 mmol) of 1b. Owing to the high crystallinity of the product, methyl ester 2b and carboxylic acid 3b were precipitated in high yield and selectivity (80–90%, >25:1 dr, Figure 3). The employed ammonium cation can be recycled in high purity as tetraethylammonium iodide after methylation (see section 12, Supporting Information), avoiding HCN generation.

Obtained product 2a was subjected to functional group transformations to demonstrate the application potential of cyanated coumarins (Figure 3). The phenolic –OH group on 2a was protected to triisopropylsilyl ether 4 in high yield and diastereoselectivity. The hydrolysis of nitrile groups (2b and 3b) under acidic conditions resulted in the same cyclic 1,4-dicarbonyl 5 with good yield and diastereoselectivity (80%, 20:1 dr). Acid-catalyzed reaction afforded 4-cyano hydroucoumarin derivative 6 (62% 20:1 dr) starting from methyl ester 2b. A borane reduction of methyl ester 2b smoothly afforded pyrrolidine derivative 7 (59%, 30:1 dr) upon reduction of the nitrile group to a primary amine and in situ cyclization. A selective reduction of methyl ester 2b over the nitrile group was performed with LiBH₄ to furnish γ-cyano alcohol 8 (71% yield, >20:1 dr). Biologically important five-membered lactam derivative 9 was synthesized via the reduction of nitrile functional group with H₂ over Pd/C, followed by cyclization in toluene under reflux (50% yield in two steps, 2.5:1 dr). Further structural diversification in the ortho-position of the aromatic substituent was achieved via Suzuki coupling of corresponding triolate derivative 10 to produce biaryl derivative 11 in high isolated yield (90%) with slightly diminished dr (4:1) due to the basic reagents in the reaction.

In conclusion, a catalytic application of CO₂ and its equilibria with water and cyanide (to form cyanoformate) were demonstrated by a 1,4-conjugate cyanation reaction of coumarins. This new and practical synthetic methodology enabled us to access various heterocycles of biological relevance. The role of CO₂ was confirmed by mechanistic studies and computational analysis, pinpointing the critical involvement of CO₂ in the product determining step and while affecting the reaction rate. The proposed mechanism showed...
a potential asymmetric catalysis where CO$_2$ is involved in a stereoselective step. We are currently investigating various (chiral) ammonium and metal salts to expand the scope of CO$_2$-catalyzed organic transformations.

**ASSOCIATED CONTENT**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b01087.

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The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

The generous support from the Department of Chemistry, University of Copenhagen, the Novo Nordisk Fonden (NNF17OC0027598), and the Villum Fonden (00019062) is gratefully acknowledged. The authors thank Christian Cortzen for his support in NMR spectroscopy. We thank the National Research Foundation (2018R1A2B2005585) and the Institute for Basic Science in Korea (IBS-R010-A1) for financial support.

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(29) White, D. A. Cyanocarboxylation of Activated Olefins. Chem. Soc., Perkin Trans. 1 1976, 1, 1926–1930. Note: Methyl ester 2b was treated under basic conditions, which showed erosion of diaster-eoselectivity (25:1 dr → 1:1 dr), suggesting the importance of
optimized reaction conditions with CO$_2$ to induce the highly diastereoselective protonation reaction.


