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Carbon Dioxide-Catalyzed Stereoselective Cyanation Reaction
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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). 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. 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

Figure 1. (a) Effects of cyanoformate in preserving the Fe(III) active center in the ethylene biosynthesis. (b) CCSD(T)-calculated equilibria and potential advantage of CO₂ dissolution in cyanide and water-containing solutions. (c) Conjugate cyanation of coumarins.
HCN are known, but they are based on forming HCN in situ. 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 bioisostere, we envisaged that the cyanofomare may be useful in organic synthesis. Combining cyanide and CO2 in solution affords cyanofomate, as our experiments and calculations confirmed (Figure 1b), where the activities of the cyanofomate and bicarbonate remain uncovered.

To investigate this hypothesis (a synthetic application of cyanofomate 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 carboxyls is particularly interesting and results in β-cyano adducts, which can be further elaborated to γ-aminobutyric acids and 1,2-dicarboxylic acids. However, 1,4-conjugate addition of hydrogen cyanide has been elusive due to competing 1,2-addition reactions. Nagata and co-workers demonstrated that Lewis acids increased selectivity toward 1,4-addition, but addition reactions.14,15

Recently, CO2-mediated organic reactions were re-explored expanding its role beyond the well-known function as a cheap C1 source.21 Fundamentally, adding CO2 to cyanide and using it as a nucleophilic reagent is counterintuitive, as the nucleophilicity of cyanide is reduced upon forming cyanofomate. 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.
The methylation of the β-cyanocarboxylate intermediate was completely chemoselective without dimethylation. A control experiment with 13CO2 strongly suggested no incorporation of atmospheric CO2 in the final product (Figures S2 and S3). Reaction with D2O instead of H2O 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 N2 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 CO2. The use of this solution afforded 82% yield of 2b without additional gaseous CO2, confirming that the cyanation is feasible with dissolved CO2 and water in promoting nucleophilic cyanide addition reactions. To the best of our knowledge, this new reaction protocol employing tetraethylammonium cyanide with CO2 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 β-cyanocarboxylic esters/acids (2a−2s/3n−q) under CO2 without sophisticated purification. The same reactions in the absence of CO2 (under argon or N2), in general, afforded inferior conversion and diastereoselectivity of the cyanination 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 (R2) on the 3-position were tolerated, including free carboxylic acid. For example, 3-carboxycoumarin, 1l, was converted to the corresponding methyl ester (2l) after
calculations, summarized in Figures 2 and S7. In our DFT low barriers for the cyanation reaction, as con
product (G), functional group transformations of \( \beta \)-cyano carboxylate

derivatives 2b. Reaction conditions: (A) 2b (0.2 mmol), TIPSCl (1.5 equiv), imidazole (3 equiv), DMF (1 mL), rt, 3 h; (B) 2b (0.2 mmol),
10 M HCl (2 mL), 70 °C, 16 h; (C) 2b (0.2 mmol), Amberlyst-15 (50 mg), toluene (3 mL), 100 °C, 16 h; (D) 2b (1 mmol), BH₃·Me₂S (2 mmol), THF (10 mL), reflux, 10 h; (E) 2b (1.78 mmol), pyridine
(2 equiv, 3.56 mmol), triflic anhydride (1.2 equiv, 2.14 mmol), 0 °C to rt, 2 h, triflate protected phenol 10 was isolated in 93% yield (30:1 dr); (F) 10 (0.2 mmol) PhB(OH)₂, (1.1 equiv, 0.22 mmol),
Pd(PPh₃)₄ (0.05 equiv, 0.01 mmol), NEt₃ (2 equiv, 0.4 mmol), dioxane (5 mL), H₂ (1 atm), 48 h, (ii) NEt₃ (1.2 equiv), toluene, reflux, 2 h; (H) (i) 2b (0.2 mmol), TIPSCl (1.5
equiv), 2b (0.2 mmol), PhB(OH)₂ (1.1 equiv, 0.22 mmol), Pd(PPh₃)₄ (0.05 equiv, 0.01 mmol), NEt₃ (2 equiv, 0.4 mmol), toluene/ethanol (3:1, 3 mL), microwave, 120 °C, 30 min; (G) 2b (1 mmol), LiBH₄ (2 M in THF, 2 equiv, 2 mmol), THF (10 mL), 30 °C, 2 h; (H) (i) 2b (1 mmol), Pd/C (5 mol %), HCl (0.85 mL), MeOH (5 mL), H₂ (1 atm), 48 h, (ii) NEt₃ (1.2 equiv), toluene, reflux, 12 h.

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-cyanodihydrocoumarin 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 \( \gamma \)-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 triflate 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 enables 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 CO₂ is involved in a stereoselective step. We are currently investigating various (chiral) ammonium and metal salts to expand the scope of CO₂-catalyzed organic transformations.

**ASSOCIATED CONTENT**

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

Methods, procedures, and characterization data; tables of screening data, tested Lewis and Brønsted acids, effects of CO₂ on cyanation, and crystal data; NMR spectra; free energy profiles; XYZ coordinates; ORTEP structures; HPLC chromatogram (PDF)

**REFERENCES**


29. White, D. A. Cyanocarboxylation of Activated Olefins. J. Chem. Soc., Perkin Trans. 1 1976, 1, 1926–1930. Note: Methyl ester 2b was treated under basic conditions, which showed erosion of diastereoselectivity (25:1 dr → 1:1 dr), suggesting the importance of
optimized reaction conditions with CO₂ to induce the highly diastereoselective protonation reaction.


