

Light-Driven Carboxylation of *o*-Alkylphenyl Ketones with CO₂

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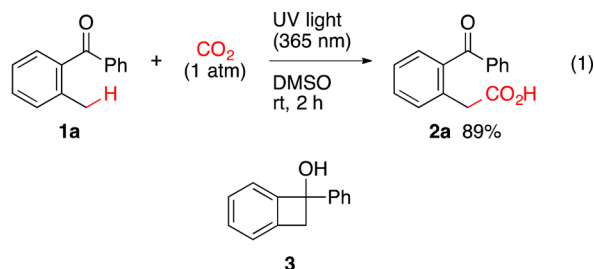
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S Supporting Information

ABSTRACT: *o*-Alkylphenyl ketones undergo a C–C bond forming carboxylation reaction with CO₂ simply upon irradiation with UV light or even solar light. The reaction presents a clean process exploiting light energy as the driving force for carboxylation of organic molecules with CO₂.

C–C bond forming carboxylation reactions of organic molecules with carbon dioxide (CO₂) have gained considerable attention in organic synthesis.¹ Most conventional methods including Grignard reactions and transition metal catalysis use stoichiometric amounts of reducing agents or bases.^{2–4} The major driving force of these carboxylation reactions derives from the chemical reagents. Alternatively, electro-⁵ or photo-assisted⁶ reductive carboxylation reactions have been devised. Electron donors like triethylamine were used as the sacrificial reducing agents in most cases. Herein, we report a unique and clean carboxylation reaction that uses no sacrificial reagent but light energy as the driving force; simply upon UV irradiation of a DMSO solution of *o*-alkylphenyl ketones, CO₂ is efficiently incorporated to produce *o*-acylphenylacetic acids.

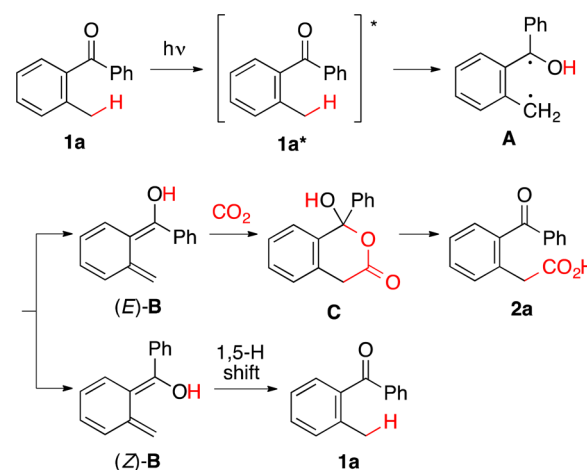
Photoirradiation of *o*-alkylphenyl ketones induces an endergonic isomerization to highly energetic *o*-quinodimethanes through the Norrish Type II photoreaction (referred to as “photoenolization”).⁷ The resulting *o*-quinodimethanes are highly reactive 1,3-dienes, which readily participate in a [4 + 2] cycloaddition reaction with various dienophiles like acrylates and aldehydes.⁸ We questioned whether the *o*-quinodimethanes might react with CO₂. Such a photoreaction-based process would present a clean carboxylation reaction driven by light.⁹ With this idea in mind, a reaction of *o*-methylbenzophenone (**1a**) with CO₂ was examined using an LED lamp (365 nm) as the light source under various reaction conditions. We discovered that the carboxylation reaction was effected by a remarkably simple operation. When a DMSO solution of **1a** (0.04 M) was irradiated under an atmospheric pressure of CO₂, carboxylic acid **2a** was cleanly produced (eq 1). Simple acid–base extraction of the



reaction mixture afforded **2a** in a pure form in 89% yield. Whereas *N,N*-dimethylacetamide (DMA) was also effective for the production of **2a**, less polar solvents like benzene and acetonitrile failed to afford **2a** and produced benzocyclobutenol **3** instead.¹⁰

Shown in Scheme 1 is a probable mechanistic scenario for the photochemical carboxylation reaction of **1a**. First, **1a**

Scheme 1. Proposed Mechanism

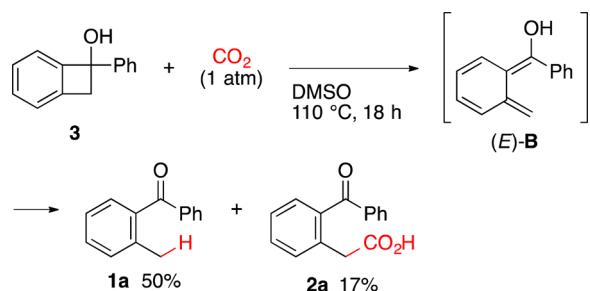


absorbs a photon to produce the excited state. The oxygen of the excited carbonyl group abstracts a hydrogen of the *ortho*-methyl group to furnish a 1,4-biradical species **A**, which possesses a phenylene linker inbetween. Such a biradical species spontaneously generates the *o*-quinodimethane **B**. Whereas the (*Z*)-isomer rapidly undergoes 1,5-hydrogen shift to revert to the starting ketone **1a**, the (*E*)-isomer possesses a lifetime long enough to react with CO₂. The 1,3-diene moiety of (*E*)-**B** undergoes a [4 + 2] cycloaddition reaction with the C–O double bond of CO₂ to afford the six-membered cycloadduct **C**. Finally, a ring-opening reaction gives the carboxylic acid **2a**.

It is possible to generate the assumed *o*-quinodimethane intermediate (*E*)-**B** from benzocyclobutenol **3** by a thermal torquoselective¹¹ ring-opening reaction with outward rotation of the hydroxy group.¹² We thus examined a thermal reaction of **3** with CO₂ in the absence of light to gain a mechanistic insight (Scheme 2). When a DMSO solution of **3** was simply heated at 110 °C under an atmospheric pressure of CO₂, the carboxylated product **2a** was produced in 17% yield

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Scheme 2. Thermal Reaction of 3 with CO₂

together with the ring-opening product **1a** (50%). This result indicates that *o*-quinodimethane (*E*)-**B** thermally reacts with CO₂. Although the simple yield of trapping of (*E*)-**B** with CO₂ is low, the isomerization of **1a** back to (*E*)-**B** repeats under photoirradiation conditions until **1a** is fully carboxylated.

A wide variety of dienophiles including aldehydes and ketones undergo a [4 + 2] cycloaddition reaction with 1,3-dienes.¹³ To the best of our knowledge, however, a [4 + 2] cycloaddition reaction in which CO₂ acts as the dienophile is unprecedented in literature¹⁴ probably due to the much lower reactivity of CO₂. Therefore, we next investigated the energetics of the cycloaddition step using DFT calculations¹⁵ to assess the validity of the proposed [4 + 2] cycloaddition pathway (Figure 1a).

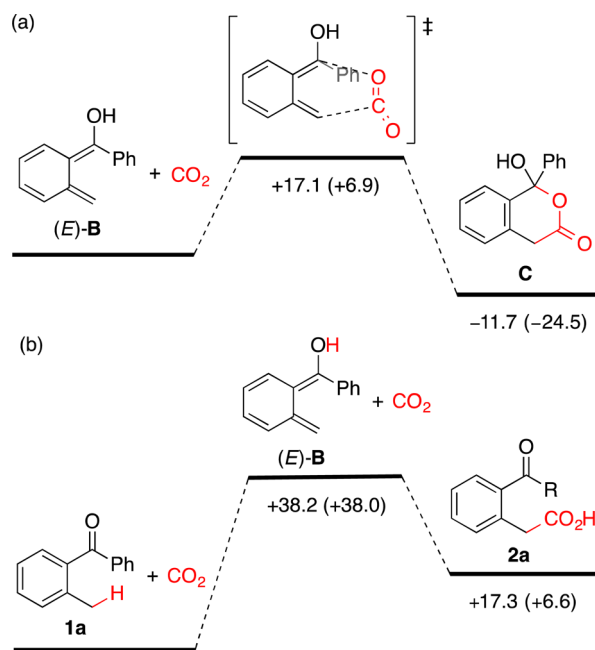


Figure 1. (a) Energy diagram of [4 + 2] cycloaddition between (*E*)-**B** and CO₂. (b) Energy diagram of **1a**, (*E*)-**B**, and **2a**. These structures are optimized with the B3LYP-D/6-311+G(d,p) level of theory using polarizable continuum model (PCM, solvent = DMSO). The numbers are Gibbs' energy (kcal/mol, at 298 K, 1 atm), and the numbers in parentheses are enthalpies (kcal/mol).

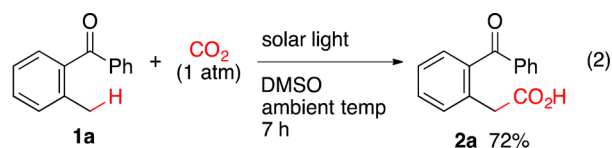
The six-membered transition state could be located with the reasonable activation energy ($\Delta G^\ddagger = +17.1$, $\Delta H^\ddagger = +6.9$ kcal/mol) and the transition state connected to the cycloadduct **C** at the local minimum, which was thermodynamically more stable than the *o*-quinodimethane (*E*)-**B** and CO₂ ($\Delta G = -11.7$, $\Delta H = -24.5$ kcal/mol). These results demonstrate the thermal [4 + 2]

cycloaddition reaction of *o*-quinodimethane (*E*)-**B** with CO₂ is energetically feasible.

The whole process from **1a** to **2a** is a formal insertion reaction of CO₂ into the benzylic C–H bond. It should be noted that DFT calculations suggest the insertion process is energetically uphill ($\Delta G = +17.3$, $\Delta H = +6.6$ kcal/mol, Figure 1b). Nevertheless, intervention of the considerably endergonic photoisomerization of **1a** to (*E*)-**B** ($\Delta G = +38.2$, $\Delta H = +38.0$ kcal/mol) energetically allows the incorporation of CO₂ without any additional reagents. Light energy gained in the photoenolization step serves as the driving force for the whole process.

Various *o*-alkylphenyl ketones **1** underwent the carboxylation reaction with an atmospheric pressure of CO₂ at room temperature (Table 1).¹⁶ Alkyl *o*-tolyl ketones **1b** and **1c** (R¹ = alkyl) afforded the carboxylic acid **2b** and **2c** in good yields. Functional groups like chloro, fluoro, hydroxy, and acetal groups were tolerated on the aromatic ring (2f–i). Bis(*o*-tolyl) ketone (**1j**) underwent monocarboxylation selectively (**2j**). In the case of substrate **1k** having a methyl group at the benzylic position, a ring-closing reaction forming the corresponding benzocyclobutenol competed with the [4 + 2] cycloaddition with CO₂, lowering the yield of the carboxylated product **2k** (33%). Nonetheless, addition of KOH (10 mol %) promoted the reversion of the benzocyclobutenol to the starting ketone,¹⁷ improving the yield of the carboxylated product **2k** to 71%. Sterically more congested ketones like 2-isopropylphenyl ketone and 2,4,6-trimethylphenyl ketone failed to give the carboxylated products. The 2,5-dimethylphenyl ketone **1l** underwent site-selective carboxylation at the 2-position (ortho to the carbonyl group) (**2l**). The methoxy-substituted ketone **1m** and the trifluoromethyl-substituted ketone **1n** also afforded the carboxylated products, although a longer reaction time (4 h) was required for **1n**.

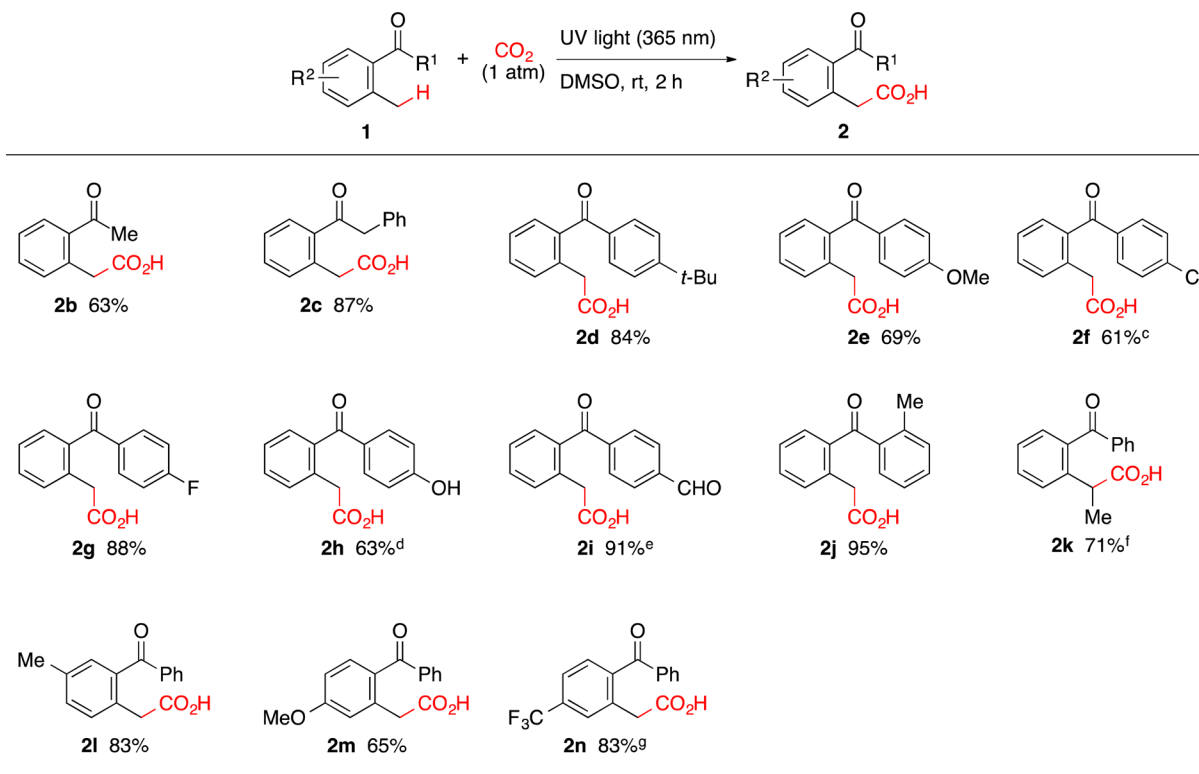
Solar light also effected the present carboxylation reaction (eq 2). A DMSO solution (5 mL) of ketone **1a** (0.20 mmol) was



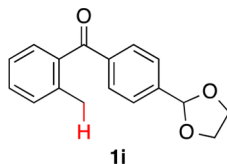
placed in an ordinary Pyrex Erlenmeyer flask (100 mL) filled with CO₂ (1 atm). The flask was then put on a rooftop on a sunny day to be irradiated with solar light. After 7 h (total amount of solar radiation was 4.2 kWh/m²), acid–base extraction of the reaction mixture was conducted to isolate analytically pure carboxylic acid **2a** in 72% yield.

The present carboxylation reaction provides a simple and straightforward access from readily available materials (*o*-alkylphenyl ketones, CO₂, and hydrazine) to 2,3-benzodiazepines, which constitute a versatile pharmacophore of various biologically active compounds including Tofisopam and Girisopam.¹⁸ Initially, carboxylation of **1a** was conducted under the standard reaction conditions, and then hydrazine was added to the reaction mixture directly (Scheme 3). Subsequent treatment with an aqueous HCl solution (2 N) induced condensation to furnish 2,3-benzodiazepine **4** in 72% yield.

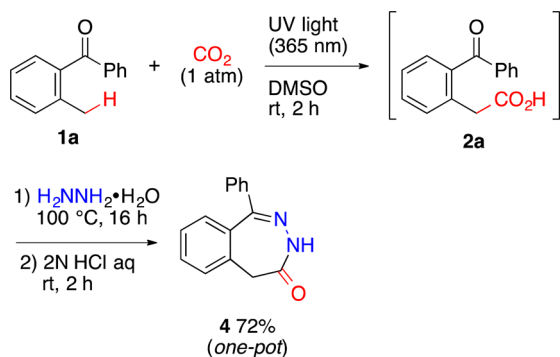
In conclusion, *o*-alkylphenyl ketones undergo a C–C bond forming carboxylation reaction with CO₂ by exploiting UV light or even solar light as the driving force. The reaction presents an

Table 1. Photocarboxylation of **1** with CO₂^{a,b}

^aReaction conditions: **1** (0.20 mmol), CO₂ (1 atm), DMSO (5 mL), UV light (365 nm, LED lamp), rt, 2 h. ^bIsolated yield. ^c1 mL of DMSO was used. ^d10 mL of DMSO was used. ^eAcetal **1i** was used as the substrate. The crude reaction mixture was treated with an aqueous H₂SO₄ solution (2M) at rt for 1.5 h.



^fKOH (10 mol %) was added and the reaction was conducted for 5 h. ^gReaction time = 4 h.

Scheme 3. Synthesis of 2,3-Benzodiazepine **4**

interesting example of usage of light energy for carboxylation of organic molecules with CO₂.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10032.

Experimental procedures, computational details, and spectra data (PDF)

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Notes

The authors declare no competing financial interest.

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