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Light-Driven Carboxylation of o-Alkylphenyl Ketones with CO₂

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ABSTRACT: *o*-Alkylphenyl ketones undergo a C–C bond forming carboxylation reaction with CO_2 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 CO_2 .

C-C bond forming carboxylation reactions of organic molecules with carbon dioxide (CO₂) have gained considerable attention in organic synthesis.¹ Most of 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 Alternatively, electro-⁵ or photo⁶-assisted reagents. 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 which uses no sacrificial reagent but light energy as the driving force; simply upon UV irradiation of a DMSO solution of oalkylphenyl ketones, CO₂ is efficiently incorporated to produce o-acylphenylacetic acids.

Photoirradiation of *o*-alkylphenyl ketones induces an endergonic isomerization to highly energetic oquinodimethanes through the Norrish Type II photoreaction (referred to as "photoenolization").⁷ The resulting o-quinodimethanes are highly reactive 1,3-dienes which facilely 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 omethylbenzophenone (1a) with CO_2 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**. Firstly, **1a** 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 1,4biradical 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 CO_2 . The 1,3-diene moiety of (E)-**B** undergoes a [4+2] cycloaddition reaction with the

Scheme 1. Proposed Mechanism



C–O double bond of CO_2 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 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.

Scheme 2. A thermal reaction of 3 with CO₂



A wide variety of dienophiles including aldehydes and ketones undergo a [4+2] cycloaddition reaction with 1,3dienes.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). The sixmembered 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.



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).

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** (\mathbf{R}^1 = alkyl) afforded the carboxylic acid **2b** and 2c in good yields. Functional groups like chloro, fluoro, hydroxyl and acetal groups were tolerated on the aromatic ring (2f-i). Bis(o-tolyl) ketone (1j) underwent monocarboxylation selectively (2j). In 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% (entry 10). Sterically more congested ketones like 2-isopropylphenyl ketone and 2,4,6trimethylphenyl ketone failed to give the carboxylated products. The 2,5-dimethylphenyl ketone 11 underwent site-selective carboxylation at the 2-position (ortho to the carbonyl group) (21). 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**.



^a Reaction conditions: **1** (0.20 mmol), CO₂ (1 atm), DMSO (5 mL), UV light (365 nm, LED lamp), rt, 2 h. ^b Isolated yield. ^c 1 mL DMSO was used. ^d 10 mL DMSO was used. ^e Acetal **1i** was used as the substrate. The crude reaction mixture was treated with an aqueous H_2SO_4 solution (2M) at rt for 1.5 h. ^f KOH (10 mol %) was added and the reaction was conducted for 5 h. ^g Reaction time = 4 h.



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 CO_2 (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, CO_2 , and hydrazine) to 2,3benzodiazepines, 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 (2N) in-

duced condensation to furnish 2,3-benzodiazepine **4** in 72% yield.

Scheme 3. Synthesis of 2,3-benzodiazepine 4



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

ASSOCIATED CONTENT

Experimental procedures, computational details and spectra data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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