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Synthesis of Ortho-Functionalized 1,4-Cubanedicarboxylate Derivatives through Photochemical Chlorocarbonylation

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ABSTRACT: The cubane ring has received intense attention as a 3D benzene isostere and scaffold. Mono- and 1,4-disubstituted cubanes are well-described. Here we report a practical procedure for a direct radical-mediated chlorocarbonylation process initially reported by Bashir-Hashemi, to access a range of 2-substituted 1,4-cubanedicarboxylic ester derivatives. A subsequent regioselective ester hydrolysis to give fully differentiated 1,2,4-trisubstituted cubanes is demonstrated.

Whether drug-like molecules with substantial sp³-rich substructures could improve clinical success by modulating their pharmacokinetics properties is a subject of debate.^{1,2} However, sp³-rich sphere-like fragments are underrepresented in drug screening libraries,³ and 1,4-substituted cubanes have received great interest as non-classical bio-isosteres for *para*-substituted benzene structures in medicinal chemistry.^{4–6} Further exciting opportunities to enter unexplored areas of chemical space can be envisaged with 1,2- and 1,3-substituted cubanes to replace *ortho-* and *meta*-substituted benzenes (Figure 1A).⁵ In addition to bioisosteric applications, cubanes could also be considered as a 3D benzene-like scaffold, offering an opportunity to introduce substituents perpendicular to the aromatic plane.^{6,7} However, accessing these cubane motifs is still hampered by non-trivial synthetic access.

Eaton et al. pioneered *ortho*-lithiation of amidocubanes (Figure 1B).⁸ While this requires the introduction of a directing group and the use of strong bases, it is a versatile methodology to introduce cubane substitution.⁹ Subsequently, transmetalation, typically with Zn, enhances the nucleophilicity and was shown to facilitate reaction with electrophiles.¹⁰

Direct C–H to C–C bond formation can also be achieved using radical-based strategies, despite the strong cubane C–H bond (Figure 1C).¹¹ The C–H bond dissociation enthalpy of 1 is expected to be even higher than 104.7 kcal·mol⁻¹ due to the presence of electron-withdrawing groups.^{12,13} Indeed, while *tert*-butoxyl radicals abstract hydrogen atoms from cubane or mono-substituted cubanes, no cubyl radical formation could be observed for 1.¹⁴ Nevertheless, based on the work of Kharasch and Brown, Bashir-Hashemi reported a photochemical radical chlorocarbonylation of dimethyl 1,4cubanedicarboxylate 1 with oxalyl chloride under light irradiation.^{15–17} Radical-mediated cubane trifluoromethylation using oxone with (bipy)Cu(CF₃)₃ under blue light irradiation was recently reported to allow direct CF₃ introduction, albeit in low yield (14%) despite using 6 equiv of $1.^{18}$

Radical-mediated halogenation has also been reported to subsequently enable C–C bond formation.^{10b,d} Here, regioselective hydrogen abstraction of monosubstituted cubanes was shown to be challenging due to the small BDE differences between the *para-, meta-,* and *ortho*-hydrogens.

Direct introduction of a carboxylic acid group in the archetypical cubane starting material **1** is of high interest due to the rich cubane decarboxylative functionalization chemistry developed in recent years.¹⁹

Most of the reported aliphatic C–H bond carboxylations rely on the use of transition metal complexes, photoredox catalysis process, or both, usually in the presence of carbon dioxide, and remain limited to allylic, benzylic, α -amino weak C–H bonds.²⁰ With the challenging cubyl radical formation in mind, Bashir-Hashemi's chlorine radical mediated cubane C– H chlorocarbonylation remains of great interest despite the use of the toxic and corrosive oxalyl chloride in very large excess, and the use of a high-powered halogen lamp (\geq 275 W) operating at very high temperatures.¹⁶ This method has previously shown high potential to access molecular diversity in the field of combinatorial chemistry.²¹ Recently, several milder conditions for the generation of chlorine radical have

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been reported (for nickel mediated C_{sp}^{3} -H cross-coupling or Minisci-type reactions);²² however, a large excess of substrates (5 to 20 equiv) is required, rendering these approaches unattractive with the use of expensive 1.

Herein, we describe our efforts to develop safer, milder, practical, and more efficient conditions to achieve the powerful C-H chlorocarbonylation of 1 (Figure 1D) to give access to a wide variety of 1,2,4-substituted cubane derivatives, exemplify the synthetic opportunities offered by the introduction of the corresponding carboxylic acid, and fully differentiate the three substituents.

Key considerations involved the excess of oxalyl chloride and the irradiation source. Instead of using oxalyl chloride as the solvent, dichloromethane was chosen, given the hydrocarbons and ethers, the only other solvents compatible with oxalyl chloride, are expected to undergo H-atom transfer (HAT) with the cubyl radical. According to the reported photodissociation mechanism of oxalyl chloride,²³ we considered that a large part of the emission spectrum of the previously used halogen or mercury-vapor lamps remained unused, leading us to select UV-irradiation to increase the energy efficiency. In addition, the use of a microreactor was employed as a safe and more efficient means for photochemical reactions, envisioning to enable a drastic reduction in lamp power. A previously reported²⁴ home-made reactor setup using commercially available parts and a low-powered 9 W bulb was used.

Our synthetic study began with UV-B irradiation of a 0.05 M solution of 1 in a continuous manner. However, the formation of carbon monoxide gas bubbles led to an uncontrolled flow rate, and consequently a low conversion toward the formation of chlorocarbonylated cubane **2**. The use of a back pressure

regulator led to clogging and was therefore abandoned. Therefore, in order to keep the inherent benefits of the photomicroreactor such as better light penetration, mixing, and heat transfer²⁵ despite the excessive gas generation, the microreactor was used in a recirculating mode, enabling the formed carbon monoxide to escape from the setup (Figure 2). In this case, an ice–water bath was used in order to cool the solution during the process.



Figure 2. Schematic representation and picture of the recirculating flow microphotoreactor.

After some experimentation toward reducing the amount of oxalyl chloride, irradiation of dimethyl 1,4-cubanedicarboxylate 1 with 20 equiv of oxalyl chloride for 3 h under a recirculating flow rate of 0.2 mL·min⁻¹, followed by quenching with methanol, gave trimethyl 1,2,4-cubanetricarboxylate 3 in 23% yield along with unreacted 1 (Table 1, entry 1). When the flow rate was increased to 3 mL·min⁻¹, the yield increased to 49% and increasing the irradiation time to 4 h led to a 62% yield with 7% of unreacted 1 (entries 2 and 3). Under similar

Table 1. Optimization for the *Ortho*-Carboxylation of Dimethyl-1,4-cubanedicarboxylate 1^a

MeO₂C∕	CO ₂ M	$\begin{array}{c} Lamp\\ e & (COCI)_2\\ (20 \text{ equiv.})\\ \hline\\ CH_2CI_2, time, rt\\ Flow rate\\ V_i = 2 \text{ mL}\\ (recirculating \ \mu R) \end{array}$		DH MeO₂C	CO ₂ Me O OMe
Entry	Light	(COCl) ₂ [equiv]	Flow rate [mL·min ⁻¹]	Time [h]	Yield [%] ^b
1	UV-B	20	0.2	3	23 ^c
2	UV-B	20	3	3	49 ^c
3	UV-B	20	3	4	62 ^c
4	UV-B	20	3	4	60 ^d
5	UV-C	20	3	4	32 ^{<i>d</i>,<i>e</i>}
6	UV-A	20	3	4	49 ^c
7	Blue LED	20	3	8	0 ^f
8	UV-B	40	3	4	61
9	UV-B	10	3	4	55
10	UV-B	20 ^g	3	4	8
11	None	20	3	3	0

^{*a*}Reaction conditions: Optimized on 0.6 mmol of 1 Internal Volume $(V_i) = 2 \text{ mL}$. ^{*b*1}H NMR yield with 1,4-dimethyl terephthalate as internal standard. ^{*c*}c = 0.05 M, CH₂Cl₂ (10.95 mL), (COCl)₂ (20.0 equiv). ^{*d*}c = 0.1 M, CH₂Cl₂ (5.0 mL), (COCl)₂ (20.0 equiv). ^{*e*}Reactor fouling was observed (see Supporting Information for details). ^{*f*}Kessil A160WE Tuna Blue (40 W) lamp. ^{*g*}Methyl chlorooxoacetate (20.0 equiv).

irradiation conditions, doubling the concentration of 1 does not improve the yield (entry 4).

The use of UV-C and UV-A lamps was then investigated. With a UV-C (λ = 100–280 nm) lamp, the yield was decreased to 32% (entry 5). Considering reactor fouling was also observed, no further optimizations were carried out with UV-C (see Supporting Information for details). Under similar conditions, replacing UV-B with UV-A ($\lambda = 340-400$ nm) also led to a lower yield (49%) for the same irradiation time. Under 40 W blue LED (λ = 450 nm) light, no product could be observed after 8 h of irradiation (Table 1, entry 7) demonstrating that the visible region ($\lambda = 400-700$ nm) of the emitted spectrum by halogen or mercury-vapor lamps initially reported^{16,17} is not optimal. With regard to the large excess of oxalyl chloride used originally, doubling the concentration did not significantly increase the yield of 1 whereas decreasing the concentration 2-fold still gave trimethyl 1,2,4-cubanetricarboxylate 3 in 55% yield (entries 8 and 9). Using the optimized conditions, replacing oxalyl chloride with methyl chlorooxoacetate led to the desired product 3 in 8% yield (entry 10). Finally, as expected, a control experiment performed in the absence of light gave no product (entry 11).

Using the optimized conditions, the formed acid chloride intermediate 2 was then trapped with various nucleophiles to demonstrate further in situ derivatization while keeping the two original ester groups intact. Several 1,2,4-tricarbonyl cubane derivatives have been prepared (Scheme 1). Hydrolysis of 2 gave the crude carboxylic acid 4 in 56% yield, similar to that obtained by Irngartinger¹⁷ (cf. Figure 1). Doubling the amount of 1 and increasing the reaction time to 8 h led to isolation of 4 in 44% yield (Scheme 1). While 3 was obtained subsequently by the addition of methanol after concentration of the acyl chloride intermediate 2, attempting to trap the acyl chloride similarly with more complex and bulkier alcohols at room temperature did not lead to isolation of the corresponding 1,2,4-triester cubanes, illustrating the hindered nature of this acid chloride group. However, refluxing 2 in toluene in the presence of 1 equiv or a slight excess of (-)-menthol and bile acid methyl ester led to the corresponding desired product 5 and 6 in 30% and 37% yield respectively (Scheme 1). The use of hydroxyphthalamide at room temperature enabled us to obtain the redox active ester 7 in low yield. In most cases, excess triethylamine (5.0 equiv) was added in order to avoid protonation and precipitation of the nucleophiles due to the formation of hydrochloric acid during the photochemical step. Changing alcohol for cyclohexyl mercaptan afforded 8 in 43% yield. Trapping the acyl chloride 2 with ammonium chloride in the presence of triethylamine led to the isolation of the corresponding amide 9 in 22% yield. Primary amines such as p-fluorobenzylamine and the bulky tert-butyl amine gave the amides in 43-47% yield. Amide bond formation using the para-anisidine cubane isostere^{19d} led to 12 in reasonable yield. Because aminocubanes are unstable,⁴ it was added as the hydrochloric acid salt. Electron-poor and -rich anilines and ampyrone gave the corresponding amides 13-15 in moderate and good yields, respectively. Finally, secondary amides 16 and 17 obtained with morpholine and piperidine, which are abundant drug substructures, were synthesized. Unfortunately, attempts to form a carbonyl-carbon bond through Friedel-Craft acylation in the presence of N-methyl-indole did not lead to the corresponding ketone 19, probably due to the unlikely

Scheme 1. In Situ Derivatization of Acyl Chloride Intermediate 2^{a}



"Isolated yield based on 0.6 mmol of 1; 7-10% of 1 was recovered after the reaction.

formation or stabilization of the corresponding cubyl acylium ion.

With these 1,2,4-trisubstituted cubane derivatives in hand, further transformations were explored. Starting from the *ortho*-carboxylic acid **4**, the redox-active ester 7 was obtained in 92%

yield (Scheme 2). This can now be used for a range of decarboxylative coupling methodologies²⁶ to establish C_{cub} -

Scheme 2. Nickel-Catalyzed *Ortho*-Functionalization of RAE 1,2,4-Cubane Diester 7



 $C_{sp^{3}/sp^{2}}$ ortho-cubane functionalization without the need to introduce a directing amide group as previously reported.^{10c}

By applying the Senge nickel catalyzed decarboxylative procedure without further optimization, *ortho*-phenyl cubane diester **20** was obtained in 32% yield from 7 in the presence of 4 equiv of phenyl zincate chloride.¹⁹ Similarly, Giese-type reaction using benzyl acrylate as a Michael acceptor gave **21** in 20% isolated yield.²⁷

The presence of the substituent at the 2-position leads to a differentiation of the two ester groups. Selective ester hydrolysis will allow fully differentiated functionalization³ and can be used to further functionalize this position or, through decarboxylation, give access to 1,2- or 1,3-substituted cubane derivatives. Selective hydrolysis of the least hindered ester group was achieved: by starting with **13**, saponification with 1 equiv of sodium hydroxide led to the isolation of the corresponding carboxylic acid **22** in 84% yield in a 10:1 ratio (¹H NMR analysis) of the regiosiomers (Scheme 3). Saponification of **15** enabled isolation of **23** with complete regioselectivity (¹H NMR analysis) in 74% isolated yield.

In conclusion, we have successfully developed a modified protocol for the radical-mediated C-H chlorocarbonylation of dimethyl 1,4-cubanedicarboxylate 1 using oxalyl chloride under light irradiation. Key improvements include the use of an adequate emission low-powered UV source, the use of a

Scheme 3. Regioselective Saponification



recirculating microreactor to enable continuous-flow conditions despite excessive gas formation, and the significant reduction in excess of oxalyl chloride by using a solvent, leading to a safe and accessible platform. This allows for convenient installation of the chlorocarbonyl group and, through its hydrolysis, of the versatile carboxylic acid group, with both exemplifying utility by ester and amide formations and by *ortho*-arylation and alkylation via nickel catalysis, showing their potential for the synthesis of diverse 1,2,4trisubstituted cubanes and, by extension, for cubane-derived derivatives such as cyclooctatetraenes.²⁸ In addition, regioselective ester hydrolysis to access fully differentiated trisubstituted cubane derivatives is demonstrated.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01702.

Experimental procedures and compound characterization, instructions for instrument setup, copies of NMR spectra, X-ray crystallographic data (PDF)

Accession Codes

CCDC 1977608, 1986355, and 2057837 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/ data_request/cif, or by emailing data_request@ccdc.cam.ac. uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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