Double-Carboxylation of Two C–H Bonds in 2-Alkylheteroarenes Using LiO-t-Bu/CsF

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S Supporting Information

ABSTRACT: We describe the double-carboxylation of two C-H bonds (i.e., at the benzylic and the β -positions) in 2-alkylheteroarenes using a combination of LiO-t-Bu and CsF. A diverse range of substrates, namely benzothiophene, thiophene, benzofuran, furan, and indole derivatives, are efficiently converted into the doubly carboxylated products. A variety of functionalities (i.e., methyl, methoxy, halogen, cyano, ester, ketone, and amide moieties) are well tolerated.



he development of carboxylation reactions using CO₂ to form C-C bonds has long received significant interest due to the abundance, nontoxicity, and low cost of CO₂ as a C1 source since the pioneering works using organolithium, organomagnesium,² and sodium phenoxide³ were reported. Indeed, the development of monocarboxylation reactions of a variety of functionalized σ -bonds (i.e., C–Sn, C–B, C–Si, C– Zn, C-Al, and C-halogen), unfunctionalized C-H bonds, and unsaturated bonds has been reported in which one CO₂ molecule couples with one substance.⁴ In contrast, the studies of the corresponding double-carboxylation reactions, wherein two CO₂ molecules are captured by one substance, have not been advanced, despite the fact that they can efficiently provide dicarboxylic acids.⁵ So far, the double-carboxylation reactions of unsaturated bonds, such as those present in acetylenes, allenes, alkenes, and dienes, have been achieved using either a catalytic or a stoichiometric amount of transition metals with a reducing reagent or Brønsted base or upon electrochemical reduction.⁶ The direct double-carboxylation of two C-H bonds is also of great interest due to the abundance of C-H bonds in organic substances (Figure 1a). Although several examples have been demonstrated by employing transition-metal catalysts and Brønsted bases, $^{7-13}$ these examples are limited to specific substrates, such as acetonitrile,⁷ acetylene,⁸ benzene,⁹ phenol,¹⁰ phenylpyrazole,¹¹ and 1,2,4,5-tetrafluoroand -chlorobenzenes.^{12,13} This is due to a drop in the nucleophilicity of the molecule following the first carboxylation, in addition to the increased steric hindrance, both of which significantly affect the reactivities of C-H bonds close to the introduced carboxylic moiety. The stepwise operation, involving the deprotonation of two C-H bonds followed by subsequent coupling with CO2, also results in doublecarboxylation (Figure 1b). This protocol, however, requires the use of very strong Brønsted bases, such as n-BuLi, s-BuLi, t-BuLi, or 2,2,6,6-tetramethylpiperidide base, to generate unstable dicarbanionic species, which significantly limits the

(a) Direct double-carboxylation of two C-H bonds $\rm CO_2H$ CO₂H CO₂ x 2 СНСК Limited substrates (b) Stepwise double-carboxylation of two C-H bonds J. ⊕ м⊕ CO₂H CO₂H c[⊖] c $^{\Theta}$ Unstable dicarbanion Strong base $CO_{2} \times 2$ Limited substrates/functional group tolerance (c) This work: Double-carboxylation of 2-alkylheteroarenes O₂H LiO-t-Bu, CsF CO₂H CO₂ (1 atm) H_2 DMI, 150 °C (X = S, O, NR) Various 2-alkylheteroarenes: (Benzo)thiophene, (benzo)furan, and indole derivatives High functional group tolerance. Me, OMe, halogen, CN, ester, amide, and ketone

Figure 1. Double carboxylation of two C-H bonds.

substrate scope and functional group tolerance.¹⁴ As such, no system applicable to a diverse range of substrates has been established.¹⁵ We recently reported that the carboxylation of electron-rich heteroarenes proceeds smoothly using the

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Brønsted base system LiO-*t*-Bu/CsF/18-crown-6.^{16,17} Thus, we herein report the use of LiO-*t*-Bu and CsF to promote the double-carboxylation of 2-alkylheteroarenes (i.e., benzothiophene, thiophene, benzofuran, furan, and indole derivatives) at the benzylic $C(sp^3)$ -H and the β -C(sp²)-H bonds (Figure 1c). The tolerance of this system to a wide range of functional groups will also be examined.

Initially, the reaction of 2-methylbenzothiophene (1a) was carried out using the various Brønsted bases in 1,3-dimethyl-2imidazolidinone (DMI) at 130 °C under ambient CO_2 pressure (Table 1). The reaction of LiO-*t*-Bu provided the

Table 1. Effects of the Alkoxide Bases and Additives on the Reaction^a

\bigcirc		CO ₂ Base DMI, 13	(5.0 eq) (s) (5.0 eq) 30 °C, 13 h		
	1a (†	1 atm) CO_2H CO_2H CO_2H CO_2H	+	CO₂H +	
		2а-Н	3		4
entry	base	additive(s)	yield of 2a- H ^b (%)	yield of 3^b (%)	yield of 4 ^b (%)
1	LiO-t-Bu		12	0	0
2	LiO-t-Bu	LiF	6	0	0
3	LiO-t-Bu	RbF	24	5	0
4	LiO-t-Bu	CsF	83	2	0
5	LiO-t-Bu	CsCl	14	0	0
6	LiO-t-Bu	CsI	5	1	0
7		CsF	0	0	0
8	LiO-t-Bu	CsF + 18-crown-6	77	6	10
9	NaO-t-Bu		27	7	2
10	NaO-t-Bu	CsF	77	3	3
11	KO-t-Bu		53	5	2
12	KO-t-Bu	CsF	57	7	2
13	LiOMe	CsF	0	0	0
14 ^c	LiO-t-Bu	CsF	94	1	3

^{*a*}Conditions: **1a** (0.30 mmol), CO_2 (1 atm), alkoxide base (1.50 mmol), additive(s) (1.50 mmol), DMI (1.5 mL), 130 °C, 13 h. ^{*b*}Yields were determined by ¹H NMR spectroscopy using 1,1,2-trichloroethane as an internal standard. ^{*c*}Reaction was conducted at 150 °C.

desired product **2a-H** in 12% yield (entry 1). The effects of additives were then evaluated based on our previous studies into the monocarboxylation of heteroarenes.^{16a} Among the examined alkali-metal salts, CsF was the most effective, furnishing **2a-H** in 83% yield (entries 2–6). In the absence of LiO-*t*-Bu, **2a-H** was not obtained (entry 7). The addition of 18-crown-6 did not increase the yield of **2a-H**, and **3** and **4** were also formed in yields of 6% and 10%, respectively (entry 8). In addition, NaO-*t*-Bu/CsF and KO-*t*-Bu/CsF gave yields of 77% and 57%, respectively, while LiOMe/CsF was ineffective (entries 9–13). When the reaction of LiO-*t*-Bu and CsF was carried out at 150 °C, **2a-H** was obtained in 94% yield (entry 14).^{18,19} Finally, the product obtained using these conditions was isolated as the dimethyl ester form of **2a** in 83% yield following treatment with TMSCH₂N₂ (Figure 2).

With the optimized reaction conditions in hand, they were then applied to the double carboxylation of a variety of 2alkylbenzothiophenes (Figure 2). 2-Methylbenzothiophenes



Figure 2. Substrate scope: 2-alkylbenzothiophenes. (a) Reactions were conducted on a 0.3 mmol scale. (b) Isolated yields. (c) Reaction was conducted on a 1.2 mmol scale. (d) Reaction was conducted at 160 $^{\circ}$ C. (e) Reaction was conducted at 140 $^{\circ}$ C. (f) Reaction was conducted at 100 $^{\circ}$ C.

1b and 1c, bearing electron-donating methyl and methoxy groups at the 5-position, afforded the desired products 2b and 2c in yields of 84% and 75%, respectively. The reactions of 1d and 1e, which contained methoxy substituents at the 6- and 7positions, respectively, formed 2d and 2e in yields of 71% and 82%. In addition, halogen atoms (i.e., F, Cl, and Br) were tolerated to give the corresponding products 2f-h in yields of 87%, 83%, and 82%, respectively. The tolerance of the relatively weak $C(sp^2)$ -Br bond is due to the in situ generation of the relatively weak tert-butyl carbonate base from tertbutoxide and CO₂, which can prevent the one-electron transfer reaction of the tert-butoxide to cleave the bond, as noted in our previous study.^{16a} Actually, we confirmed that the combination of [t-BuOCO₂Li] with CsF resulted in the double-carboxvlation of 1h under an argon atmosphere (Scheme S1). The dimethyl ester structure of the benzothiophene derivative was confirmed by X-ray crystal analysis of 2h (see the Supporting Information). Furthermore, 1i and 1j, which contain electronwithdrawing cyano and ester moieties, were also suitable substrates, giving 2i and 2j in yields of 82% and 74%, respectively. 2-Ethylbenzothiophene (1k) and 2-propylbenzothiophene (11) were also efficiently converted to the desired products 2k and 2l in 81% and 76% yields, respectively. Finally, the reaction of substrate 1m bearing two benzothiophene moieties was examined; the triple-carboxylated product 2m was obtained in 31% yield along with the doublecarboxylated product 2m' in 26% yield.

To broaden the substrate scope, the current system was then applied to the double carboxylation of 2-methylheteroarenes other than 2-methylbenzothiophenes (Figure 3). Thus, the



Figure 3. Substrate scope: 2-methylheteroarenes with the exception of 2-methylbenzothiophenes. (a) Reactions were conducted on a 0.3 mmol scale. (b) Isolated yields. (c) Reaction was conducted at 130 $^{\circ}$ C. (d) Reaction was conducted at 180 $^{\circ}$ C. (e) DMI (2.0 mL) was used.

reactions of 2-methylthiophenes **5a** and **5b**, bearing phenyl and *p*-cyanophenyl moieties at the 5-position, proceeded to form **6a** and **6b** in yields of 80% and 88%, respectively. The regioselectivity of the double-carboxylation in the thiophene derivative was confirmed by X-ray crystal analysis of **6b** (see the Supporting Information). It was found that electrophilic keto and amide substituents were well tolerated on the thiophene ring to provide the desired products **6c** and **6d** in 67% and 82% yields, respectively. In addition, 2-methylbenzo-furan (**5e**) and 2-methyl-5-phenylfuran (**5f**) were also smoothly converted to their corresponding products in yields of 92% and 77%, respectively, while 2-methylindoles **5g**–**i**, bearing methyl, phenyl, and pyridyl groups on their nitrogen atom, gave diesters **6g**–**i** in yields of 77%, 90%, and 70%, respectively.

On the basis of the above results, a mechanism for the double-carboxylation process was proposed (Scheme 1). In this mechanism, an equilibrium exists between the tertbutoxide base, [t-BuOM] (M = Li or Cs), and the carbonate, [t-BuOCO₂M], under a CO_2 atmosphere.^{20,21} The increased reactivity obtained by the combined Brønsted bases of LiO-t-Bu and CsF is considered to be due to the generation of the cesium base, a stronger base than the corresponding lithium base, with the formation of stable LiF salt.²² The base initially deprotonates the benzylic $C(sp^3)$ -H bond of 1a to generate the anionic species 7,²³ which then reacts with CO₂ at the benzylic position to form 8. Subsequently, deprotonation of the benzylic position and coupling with CO_2 at the β -position occur to form 10, which is further deprotonated to give 11 (path a). Alternatively, 7 undergoes the first carboxylation at the β -position and the second at the benzylic position (path b).

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Scheme 1. Proposed Mechanism

Equilibrium of Brønsted bases under an CO2 atmosphere



To gain insight into the reaction pathway of the proposed double-carboxylation, additional experiments were carried out (Figures 4 and 5). Initially, monocarboxylated substrates 3 and



Figure 4. Conversion of monocarboxylated substrates 3 and 4 to 2a. (a) Reactions were conducted on a 0.3 mmol scale. (b) Isolated yields.

4 were subjected to the carboxylation reaction, and both provided dicarboxylated product 2a. This result suggests that both types of monocarboxylated intermediate may be involved in the present system and that both paths a and b can be involved. The reaction of 2-isopropylbenzothiophene (15) was then carried out to give the monocarboxylated product 16 at



Figure 5. Monocarboxylation of 15 and 17 at the benzylic $C(sp^3)$ -H bonds. (a) Reactions were conducted on a 0.3 mmol scale. (b) Isolated yields.

the benzylic position and not at the β -position.²⁴ The benzylic carboxylation of 2,3-dimethylbenzothiophene (17) also occurred, thereby indicating that the carboxylation reaction takes place at the benzylic position prior to the β -position. This result appeared to favor pathway a.²⁵

In summary, we successfully demonstrated that the Brønsted base system LiO-*t*-Bu/CsF opened the door for the efficient direct double-carboxylation of two C–H bonds in 2alkylheteroarenes. Indeed, this system facilitated the doublecarboxylation of various substrates, namely benzothiophene, thiophene, benzofuran, furan, and indole derivatives. The reaction was also found to be compatible with a wide range of functional groups, such as methyl, methoxy, halogen, cyano, ester, ketone, amide, and pyridyl moieties.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b01386.

Experimental details of synthetic procedures, effects of amounts of reagents and solvents (Table S1), double carboxylation of **1h** with [*t*-BuOCO₂Li] and CsF under an Ar atmosphere (Scheme S1), spectra data for obtained products, and X-ray crystallographic data for **2h** and **6b** (PDF)

Accession Codes

CCDC 1898070–1898071 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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(18) For more details regarding the reaction optimization (quantities of reagents and solvents), see Table S1.

(19) The reaction under high-pressure conditions was also examined as follows, but it did not improve the yield of **2a-H**. **2a-H** was obtained in the same yield of 11% when the reaction of **1a** with LiO-*t*-Bu (5 equiv) and CsF (5 equiv) in DMI at 110 °C was conducted under either 1.0 or 6.0 atm of CO₂ (results not shown).

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(25) In a related study, we recently found that the deprotonative coupling reaction of 1a with carbonyl compounds takes place at the benzylic position using an in situ generated amide base; see ref 16f.