Synthetic Methods

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Transition-Metal-Free Aerobic Oxidative Cleavage of C–C Bonds in α-Hydroxy Ketones and Mechanistic Insight to the Reaction Pathway**

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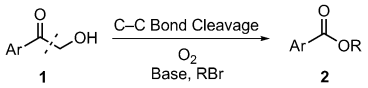
The cleavage of C–C bonds is an attracting and challenging field in modern organic chemistry, and has attracted considerable interest in the past decade.[1] Recently, numerous unique and useful carbon–carbon bond cleavage procedures have been developed,[2] most of which are catalyzed by transition metals.[3] Despite great achievements having been made in the oxidative cleavage of C–C bonds, the use of expensive and toxic metals in combination with oxidants, which may produce a large amount of byproduct, limits its applications greatly. Therefore, the discovery of a transition-metal-free method to achieve carbon–carbon bond cleavage is still desirable for these synthetic transformations, especially for acyclic structures. Herein, we demonstrate a transition-metal-free aerobic oxidative C–C bond cleavage and esterification of acyclic α-hydroxy ketones (Scheme 1).

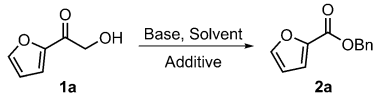


1 2

Scheme 1. Oxidative cleavage and esterification of C–C bonds.

Our research commenced with the reactions of 1-(furan-2-yl)-2-hydroxyethanone (**1a**) and BnBr in the presence of K_2CO_3 refluxed in acetone in air (Table 1, entry 1). An unpredicted product, benzyl-furan-2-carboxylate (**2a**) was obtained in 35% yield. The extensive screening of conditions was carried out subsequently. For the initial screening, we examined the reaction between 1-(furan-2-yl)-2-hydroxyethanone (**1a**) and BnBr with the addition of H_2O (1.0 equiv), which improved the yield to 42% (Table 1, entry 2). By increasing the amount of H_2O to 20 equiv, the yield was elevated to 55%. [18]-Crown-6 ([18]-C-6) proved to be effective for this transformation, and 61% yield was obtained (Table 1, entry 6). To our delight, THF was found to be the best choice for this reaction after solvent screening and afforded 78% yield (Table 1, entries 7–13). When the quantity of BnBr was reduced to 2.0 equiv, the yield was decreased to 62% (Table 1, entry 14). There was no improvement after the addition of TBAB, TBAI, and TBAC (Table 1, entries 15–17). When the reaction was carried out in O_2 atmosphere, the yield of isolated **2a** increased to 80% (Table 1, entry 18). Foreseeably, when nitrogen replaced oxygen, only trace amount of product could be observed by GC/MS (Table 1, entry 19). These results implied that O_2 played a key role in this transformation, therby helping us to gain insight into the mechanism. Several bases were also screened, and the results showed that K_2CO_3 was still the best base (Table 1, entries 20–24). In the absence of base, no products were delivered and the starting material **1a** was recovered almost quantitatively (Table 1, entry 25). Finally, K_2CO_3 (2.0 equiv) and [18]-C-6

Table 1: Optimization of reaction conditions.[a]



1a 2a

Entry	Base	Solvent	Additive (equiv)	Yield [%][b]
1	K_2CO_3	acetone	none	35
2	K_2CO_3	acetone	H_2O (1.0)	42
3	K_2CO_3	acetone	H_2O (10)	48
4	K_2CO_3	acetone	H_2O (20)	55
5	K_2CO_3	acetone	H_2O (50)	47
6	K_2CO_3	acetone	–[c]	61
7	K_2CO_3	butan-2-one	–[c]	51
8	K_2CO_3	toluene	–[c]	NR[d,e]
9	K_2CO_3	DMF	–[c]	ND[d,e]
10	K_2CO_3	DCE	–[c]	64[d]
11	K_2CO_3	MeCN	–[c]	trace[d]
12	K_2CO_3	dioxane	–[c]	35[d]
13	K_2CO_3	THF	–[c]	78
14	K_2CO_3	THF	–[c]	62[f]
15	K_2CO_3	THF	H_2O (20)/TBAB (0.2)	48
16	K_2CO_3	THF	H_2O (20)/TBAI (0.2)	36
17	K_2CO_3	THF	H_2O (20)/TBAC (0.2)	48
18	**K_2CO_3**	**THF**	**–[c]/O_2 (1 atm)**	**80**
19	K_2CO_3	THF	–[c]/N_2 (1 atm)	trace
20	K_3PO_4	THF	–[c]/O_2 (1 atm)	46
21	Cs_2CO_3	THF	–[c]/O_2 (1 atm)	52
22	Na_2CO_3	THF	–[c]/O_2 (1 atm)	32
23	$KHCO_3$	THF	–[c]/O_2 (1 atm)	51
24	Et_3N	THF	–[c]/O_2 (1 atm)	trace
25	none	THF	–[c]/O_2 (1 atm)	NR

[a] Reaction Conditions: **1a** (0.5 mmol), BnBr (4.0 equiv), and base (2.0 equiv) were heated to reflux in solvent (5 mL) in air for 24 h; DCE = 1,2-dichloroethane, DMF = *N*,*N*-dimethylformamide, TBAB = tetrabutylammonium bromide, TBAI = tetrabutylammonium iodide, TBAC = tetrabutylammonium chloride. [b] Yield of isolated product; [c] H_2O (20 equiv) and [18]-crown-6 (0.2 equiv) were added; [d] 70°C; [e] ND = No detection, NR = no reaction; [f] BnBr (2.0 equiv).

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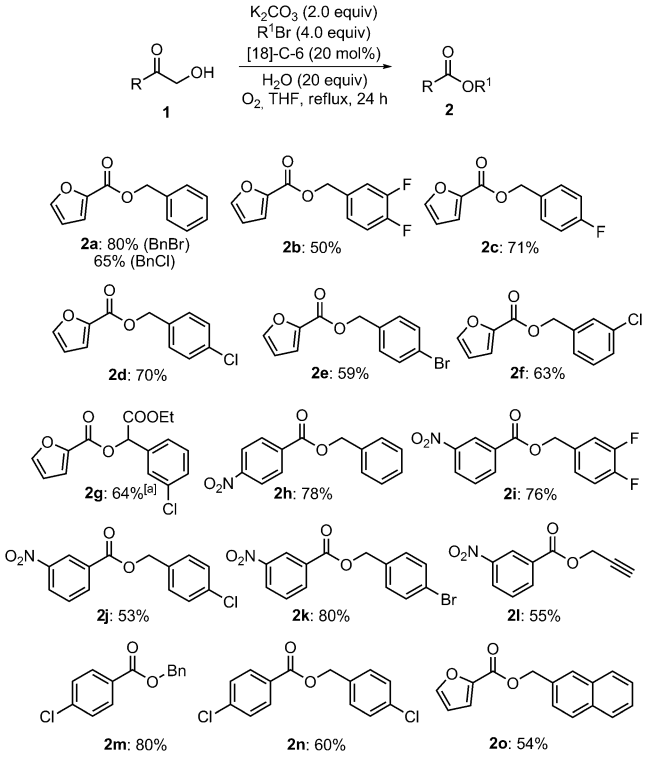
(20 mol%) in THF with H_2O (20 equiv) under O_2 (1.0 atm) were chosen as the optimized conditions A.

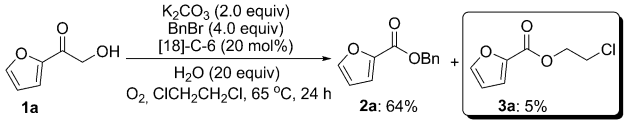
With the optimized conditions A in hand, a series of α-hydroxy ketones and halides were investigated (Scheme 2). On the basis of 1-(furan-2-yl)-2-hydroxyethanone (**1a**),



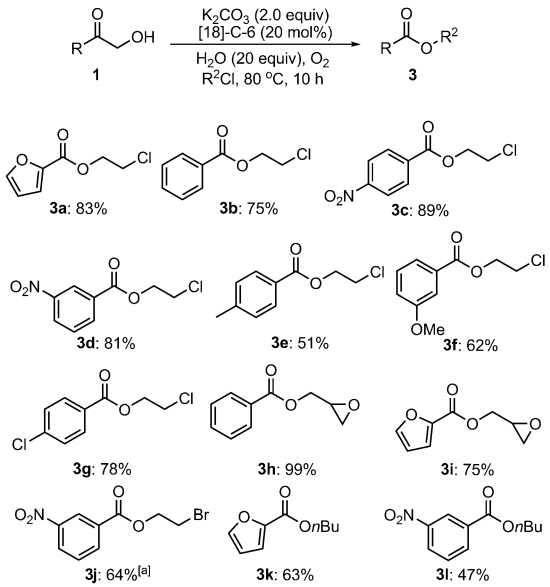
Scheme 2. Scope of the oxidative cleavage and esterification of α-hydroxy ketones with halides. Standard reaction conditions A: **1** (0.5 mmol), R^1Br (2.0 mmol), K_2CO_3 (1.0 mmol), [18]-C-6 (0.1 mmol, 0.2 equiv), THF (5 mL), H_2O (10 mmol, 20 equiv), O_2 (1.0 atm), reflux, 24 h. [a] Reaction time: 36 h.

benzyl halides substituted with both electron-donating and electron-withdrawing groups could be successfully converted to the corresponding esters in moderate to good yields (Scheme 2, **2a**–**2g**). It is noteworthy that the secondary bromides could also afford the desired ester **2g** in good yield. α-Hydroxy ketones bearing electron-withdrawing groups on phenyl groups exhibited higher reactivity, affording products in better yields (Scheme 2, **2h**–**2l**). When 1-(4-chlorophenyl)-2-hydroxyethanone was employed, **2m** and **2n** were obtained in good yields. 2-(Bromomethyl)naphthalene was also an effective halide and gave the desired product **2o** in 54% yield.

Notably, when DCE was used as solvent in this transformation (Table 1, entry 10), next to 64% of **2a**, 2-chloroethyl-furan-2-carboxylate (**3a**) was obtained as byproduct in 5% yield (Scheme 3). This result inspired us to test the reaction in the absence of activated halides. As expected, 2-chloroethyl-furan-2-carboxylate (**3a**) was directly produced in 83% yield at 80°C (Scheme 4, **3a**).The scope of this reaction with unactivated halides was further investigated (Scheme 4). Notably, both electron-rich- and electron-defi-



Scheme 3. Reaction in unactivated halide solvent.

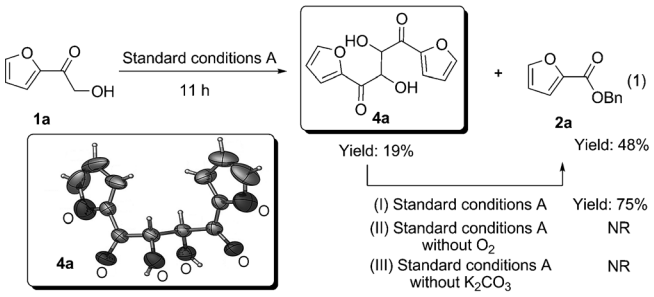


Scheme 4. Scope of the oxidative cleavage and esterification of α-hydroxy ketones with unactivated halides. Standard reaction conditions B: **1** (0.5 mmol), R^2Cl (5.0 mL), K_2CO_3 (1.0 mmol), [18]-C-6 (0.1 mmol, 0.2 equiv), H_2O (10 mmol, 20 equiv), O_2 (1.0 atm), reflux, 10 h. [a] DBE was used as solvent.

cient- substituted phenyl groups on α-hydroxy ketones could be transformed into the desired products in moderate to excellent yields (Scheme 4, **3b**–**3g**). Both 2-(chloromethyl)-oxirane and 1,2-dibromoethane (DBE) proved to be effective in this transformation (Scheme 4, **3h**–**3j**). It was worth mentioning that *n*BuCl could also afford desired products in moderate yields (Scheme 4, **3k** and **3l**).

With these results in hand, we tried to explore the mechanism of this reaction system. On the basis of the reaction condition, we envisioned that this transformation involved an oxidative cleavage process promoted by O_2. As mentioned in the optimization section, the desired **2a** was formed in 80% yield in an O_2 atmosphere (Table 1, entry 18). But when the reaction was protected with N_2, a trace of **2a** (4.5%) was isolated (Table 1, entry 19). These results strongly indicate that O_2 is a key factor to this transformation.

Notably, we detected an intermediate **4a** that formed during the process and disappeared at the end of this transformation and that was isolated in 19% yield at 11 h [Eq. (1) in Scheme 5]; **4a** was unambiguously established to be the dimer of **1a** by X-ray crystal structure analysis (Scheme 5). Then the isolated dimer **4a** was subjected to the standard conditions A (Scheme 5, I). To our delight, **4a** was converted to **2a** in 75% yield, thereby demonstrating that

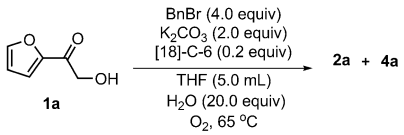


Scheme 5. Isolation, transformation, and X-ray crystal structure of the key intermediate **4a**. Thermal ellipsoids are set at 50% probability.[8]

4a was a key intermediate in this transformation (Scheme 5, I). Two control experiments without either K_2CO_3 or O_2 were performed. However, no product **2a** was detected (Scheme 5, II and III), and **4a** was recovered totally. These results strongly indicated that both K_2CO_3 and O_2 are necessary for the conversion of dimer intermediate **4a** to the final product **2a**.

Since the dimer **4a** was a key intermediate, we presumed that **1a** should be converted to **4a** without BnBr. To our surprise, no desired product **4a** was detected without BnBr, and substrate **1a** was decomposed completely (Table 2, entry 1). Obviously, BnBr is essential to form dimer **4a**.

Table 2: Effects of halides in the transformation of **1a** to **4a**.[a]

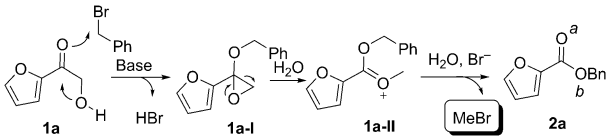


Entry	Change from the "standard conditions"[a]	Results[b]
1	without BnBr	decomposed
2	KI (4.0 equiv) instead of BnBr	decomposed
3	KBr (4.0 equiv) instead of BnBr	decomposed
4	BnCl (4.0 equiv) instead of BnBr	**2a**: 65%
4	with TEMPO (2.0 equiv)	**2a**: 47%

[a] For the reaction conditions: Table 1, entry 18. TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxyl. [b] Yields of isolated products.

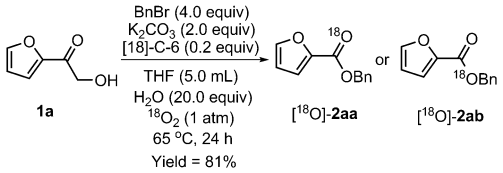
Subsequently, KI and KBr also proved to be ineffective to this transformation (Table 2, entries 2 and 3). However, when BnCl was used, **4a** could be observed by GC/MS, and **2a** could be isolated in 65% yield (Table 2, entry 4). Hence, we conclude that not only K_2CO_3 and O_2, but also organic halides are necessary for this transformation to dimer intermediate **4a**. By using the radical scavenger TEMPO (2.0 equiv), the yield of **2a** was sharply decreased from 80% to 47%, thus indicating that this transformation may involve a radical process.

The origination of the two oxygen atoms in ester **2a** is a crucial question for understanding the mechanism of C–C bond cleavage. First of all, a C–C bond cleavage that occurs through intramolecular oxygen atom rearrangement is suggested in Scheme 6. Both atoms O^a and O^b are from substrate **1a**, and MeBr is considered to be the byproduct. However,



Scheme 6. Suggested C–C bond cleavage through intramolecular oxygen atom rearrangement.

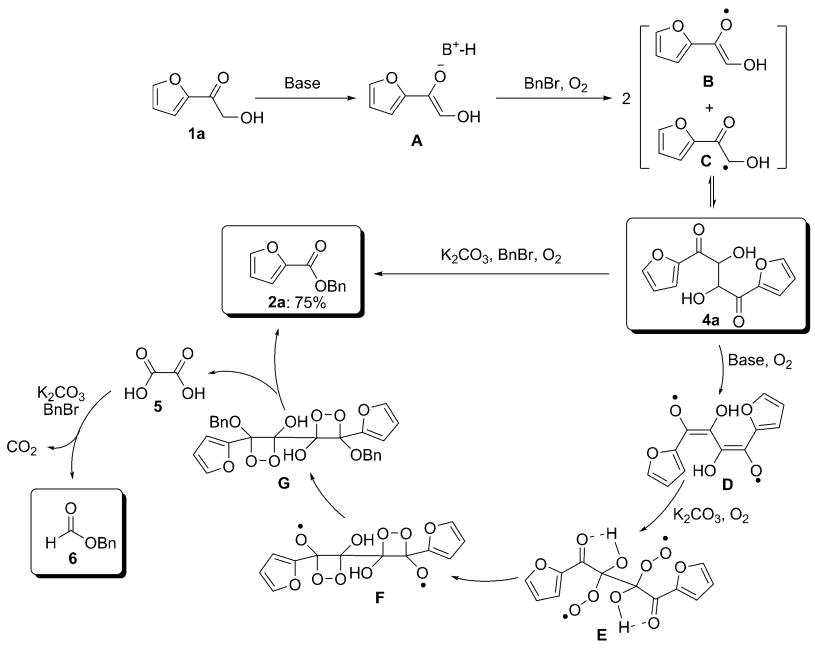
MeBr could not be found by GC/MS. To examine this hypothesis, the reaction was further investigated in $^{18}O_2$ atmosphere. ^{18}O-labeled products [^{18}O]-**2aa** or [^{18}O]-**2ab** were detected, thereby indicating that one of the oxygen atoms of the ester originated from molecular dioxygen (Scheme 7). At the same time, the suggested pathway shown in Scheme 6 is excluded.



Scheme 7. Isotopic labeling experiment with ^{18}O.

Subsequently, a plausible pathway through [4+2] and [2+2] cycloaddition of O_2 was taken into consideration (see the Supporting Information, Part V). Since singlet oxygen could perform the [4+2] and [2+2] cycloaddition,[4] reaction of **1a** with singlet oxygen (generated from triplet oxygen and light in the presence of TPP (tetraphenylporphyrin) as a sensitizer) was carried out (see the Supporting Information, Part V).[4d] The reaction performed with singlet oxygen showed no improvement in both yield and reaction time compared to that performed in triplet oxygen, thus inspiring us to consider another pathway.

On the basis of the above results, a superoxide radical mechanism for this transformation is illustrated in Scheme 8.[5] In this transformation, substrate **1a** could form the dimeric intermediate **4a** in the presence of halide and base in an aerobic atmosphere via radicals **B** and **C**.[6] Also a peroxyl radical of THF as a radical initiator has been thought over (see the Supporting Information, Part VI), but it was excluded, because the formation of **4a** in this route must be involved with BnBr according to entry 1 in Table 2. The conjugated diene intermediate **D** was easily formed under basic conditions and O_2. Then auto-oxidation through reaction of radical **D** with O_2 could generate superoxide radical **E**.[5] Further intramolecular cycloaddition to the ketone would form the corresponding oxygenic radical **F**. Intermediate **F** would then capture a benzyl radical to give intermediate **G**, and subsequent fragmentation of **G** would produce the desired ester **2a** and byproduct **5**, which resulted in benzyl formate **6**.[7] To our delight, when the reaction was monitored by GC/MS, the byproduct benzyl formate was unambiguously detected, thus solidly indicating **6** was the byproduct of oxidative cleavage of α-hydroxy ketone (Figure 1). Though



Scheme 8. Proposed reaction mechanism for oxidative cleavage and esterification of α-hydroxy ketones.

most of the intermediates were not isolated, the proposed mechanism could explain the experimental results appropriately.

In conclusion, we have developed a transition-metal-free aerobic oxidative C–C bond cleavage method. The use of molecular oxygen (1 atm) as the oxidant under mild conditions makes this chemistry relatively environmentally friendly and practical. The dimer of an α-hydroxy ketone was proved to be a key intermediate for this transformation. Labeling experiments with ^{18}O indicated that one of the oxygen atoms of the ester is derived from molecular dioxygen. We also found that halides were not only the source of the organic substrate, but also an initiator of this transformation. Further studies to clearly understand the reaction mechanism of C–C bond cleavage and esterification and the synthetic applications are ongoing.

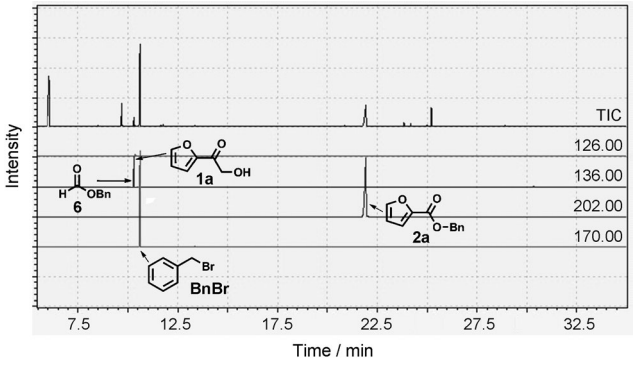


Figure 1. GC/MS spectra at 24 h. The top trace shows the total ion current (TIC), and the lower traces show the traces corresponding to the individual masses (see labels).

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[8] CCDC-896120 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

