

An Effective Method for the Construction of Esters Using Cs_2CO_3 as Oxygen Source

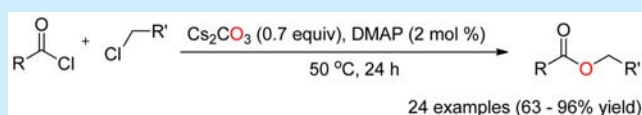
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S Supporting Information

ABSTRACT: An effective method for the construction of esters from acyl chloride and haloalkane using Cs_2CO_3 as an oxygen source was achieved for the first time. The methodology has a wide scope of substrates and can be scaled up. The study of a preliminary reaction mechanism demonstrated that the O in the products comes from Cs_2CO_3 and this esterification proceeds through a free radical reaction. It was also found that CO_2 can also be used in this esterification reaction as an oxygen source.

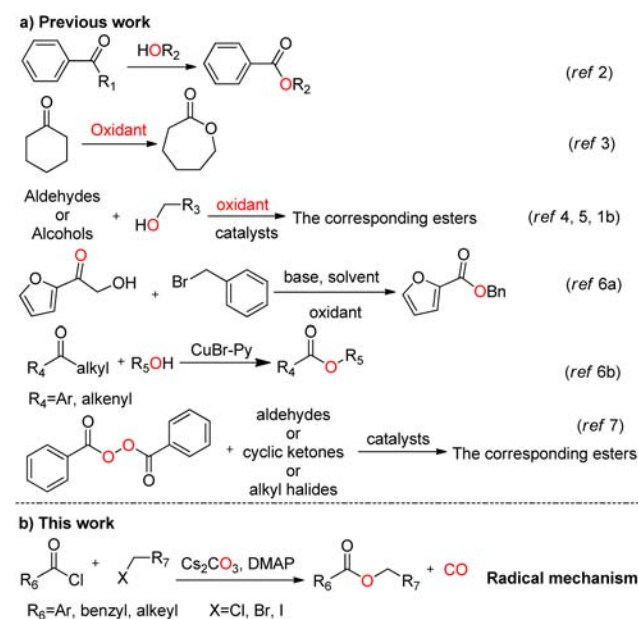


The esterification reaction is one of the most useful and important transformations in organic chemistry. Esters are used in the synthesis of fine chemicals as well as natural and pharmacological compounds.¹ In this context, a tremendous number of approaches for ester synthesis have been developed. Traditionally, activated acid derivatives and alcohols were used in the esterification reaction producing large amounts of unwanted byproducts.² Additional methods for the synthesis of esters involving the oxidation process have also been reported, for example, the Baeyer–Villiger oxidation reaction,³ the oxidative esterification of aldehydes or alcohols with alcohols,^{4,5,1b} and the oxidative cleavage of C–C bonds.⁶ Organic peroxides were also used in the esterification reaction by reacting with aldehydes,^{7a,b} cyclic ketones,^{7c,d} and alkyl halides.^{7e} In previous reports, the O in the ester products comes from an oxidant, alcohol, or other organic substrates (Scheme 1a).

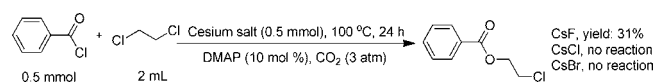
We subsequently attempted to develop a new esterification method using a novel oxygen source. We devised a strategy for the construction of esters using acyl chloride and haloalkane as substrates with Cs_2CO_3 as the oxygen source (Scheme 1b). To our knowledge, this reaction process is reported for the first time. We proved that the O in the ester products comes from Cs_2CO_3 . We also proved that this reaction may proceed through an unusual radical reaction mechanism. The successful demonstration of this strategy will be presented herein.

At first, we would like to use CO_2 as an oxidant in the esterification because CO_2 can oxidize methane⁸ and was reduced to CO. We found that benzoyl chloride can react with 1,2-dichloroethane forming 2-chloroethyl benzoate in the presence of CsF, DMAP, and CO_2 , and we obtained the product in 31% yield. When we replaced CsF with CsCl or CsI, no esterification occurred (Scheme 2). Since CO_2 and CsF could be used in this esterification reaction and carbonate was a form of immobilized carbon dioxide, we screened a series of

Scheme 1. Strategies for the Construction of Esters



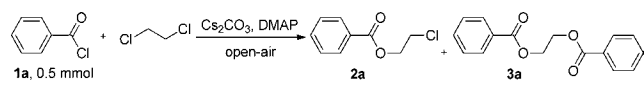
Scheme 2. Esterification Reaction Using CO_2



carbonates. First, we made an attempt with benzoyl chloride (0.5 mmol), Cs_2CO_3 (0.5 mmol), and DMAP (10 mol %) in 1,2-dichloroethane (2 mL) at 100 °C for 24 h. We obtained the product **2a** in 99% yield (Table 1, entry 1). When we removed

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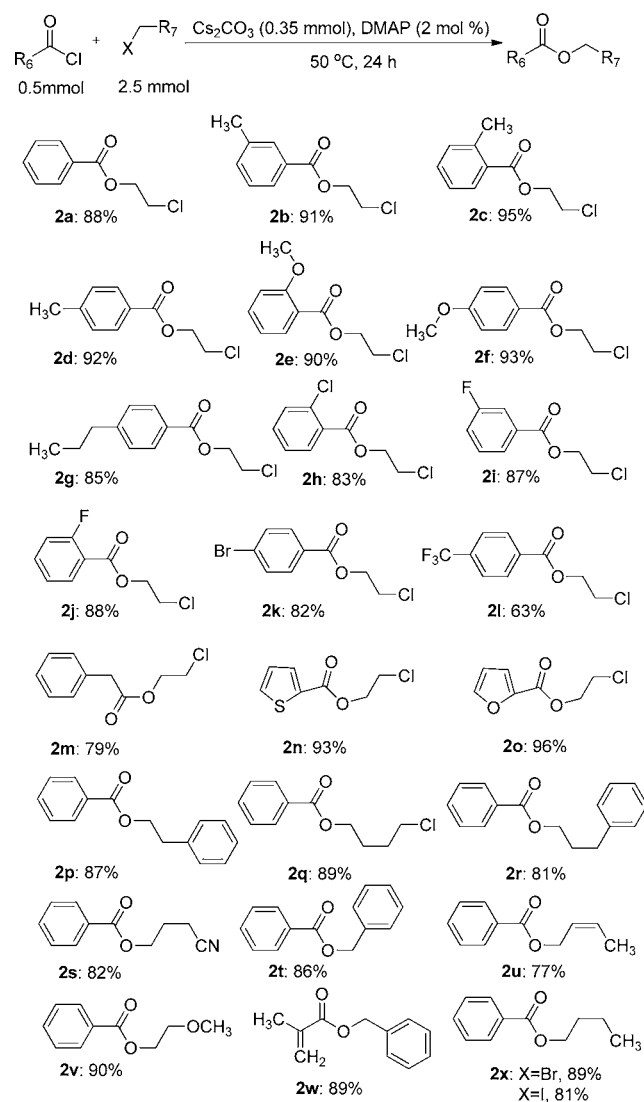
Table 1. Optimization of the Reaction Conditions^a


entry	Cs ₂ CO ₃ (mmol)	DMAP (mol %)	ClCH ₂ CH ₂ Cl (mL)	temperature (°C)	yield ^c (%)
1	0.5	10	2	100	2a:99
2	0.5	—	2	100	2a:66
3	—	10	2	100	NR
4	K ₂ CO ₃ 0.5	10	2	100	2a:38
5	Na ₂ CO ₃ 0.5	10	2	100	2a:10
6	Li ₂ CO ₃ 0.5	10	2	100	NR
7 ^b	0.5	10	2	100	2a:99
8	0.45	6	2	100	2a:98
9	0.45	6	1	100	2a:98
10	0.45	6	0.5	100	2a:96
11	0.45	6	0.2	100	2a:95
12	0.45	6	0.1	100	2a:61 3a:15
13	0.45	6	0.2	60	2a:94
14	0.45	6	0.2	50	2a:95
15	0.45	6	0.2	40	2a:83
16	0.35	6	0.2	50	2a:98
17	0.25	6	0.2	50	2a:65
18	0.35	2	0.2	50	2a:97 (88 ^d)

^aReaction time: 24 h. ^bIn argon atmosphere. ^cGC-MS yield based on the amount of **1a** used. ^dIsolated yield.

DMAP, we only obtained the product **2a** only in 66% yield (Table 1, entry 2). The reaction could not occur without Cs₂CO₃ (Table 1, entry 3). So Cs₂CO₃ and DMAP were all necessary to achieve this reaction. Next, the K₂CO₃, Na₂CO₃, and Li₂CO₃ were also tested. The experiment results showed that Cs₂CO₃ was the best choice (Table 1, entries 4–6). We also undertook the experiment in an argon atmosphere, and the product **2a** was obtained in 99% yield (Table 1, entry 7). This experiment proved that the O in the product **2a** came from Cs₂CO₃, not air. Then we studied the amount of 1,2-dichloroethane and found that 0.2 mL (5 equiv) was the best choice (Table 1, entries 8–12). After a series of experiments under different reaction temperature, we chose 50 °C as the optimum reaction temperature (Table 1, entries 13–15). The influences of the amounts of Cs₂CO₃ and DMAP were investigated, and an 88% isolated yield was obtained when the amount of Cs₂CO₃ was 0.35 mmol and the amount of DMAP was 2 mol % (Table 1, entries 16–18). Finally, entry 18 was chosen as the standard conditions (0.5 mmol of acyl chloride, 0.35 mmol of Cs₂CO₃, 2 mol % DMAP, 5 equiv of 1,2-dichloroethane, 50 °C, 24 h).

Having identified the standard reaction conditions, we studied the scope of the substrates. A variety of substituted benzoyl chlorides which have electron-donating and electron-withdrawing groups in the arene were subjected to our esterification protocol. The corresponding esters were obtained in moderate to good yields; thus, our esterification protocol has a wide scope of substrates (Scheme 3, **2a–2l**). Para, meta, and ortho substitution of the arene groups were tolerated (Scheme 3, **2b–2d**, **2e**, **2f**, **2i**, **2j**). The acyl chloride compounds containing other heterocycles were also tested and produced

Scheme 3. Esterification Reaction Using Acyl Chloride and Halohydrocarbon^{a,b}

^aIsolated yield. ^bX = Cl (**2a–2w**).

good yields (Scheme 3, **2n**, **2o**). We also investigated the compound 2-phenylacetyl chloride and obtained a good yield (Scheme 3, **2m**). Different halohydrocarbons were also subjected to our esterification protocol, and good yields were obtained (Scheme 3, **2p–2v**). The methacryloyl chloride and benzyl chloride were also investigated, and an 89% yield was obtained (Scheme 3, **2w**). The *n*-butyl bromide and *n*-iodobutane were used as substrates, and good yields were obtained (Scheme 3, **2x**).

Finally, the practical applicability of the esterification protocol was demonstrated. We used methacryloyl chloride and benzyl chloride as the test substrates, working on a gram scale. A 12.5 mmol (1.3 g) reaction of methacryloyl chloride was performed with 8.75 mmol of Cs₂CO₃, 2 mol % DMAP, and 62.5 mmol of benzyl chloride at 50 °C. The desired product **2w** was obtained in 83% isolated yield within 72 h. This result suggested that our esterification protocol is a practical process for the preparation of benzyl methacrylate **2w**. Although a stoichiometric amount of expensive Cs₂CO₃ was used, we found a new method for the esterification reaction.

The CsCl byproduct can be easily separated from the reaction system and can be used for other purposes resulting in reduced costs for our esterification methodology.

We tried to study the mechanism of the esterification of acyl chloride and haloalkane. Having established that O comes from Cs₂CO₃, not air (Table 1, entry 7), we studied the type of gases produced by this esterification reaction, and CO is the main ingredient (Figure 1). When TEMPO was added to

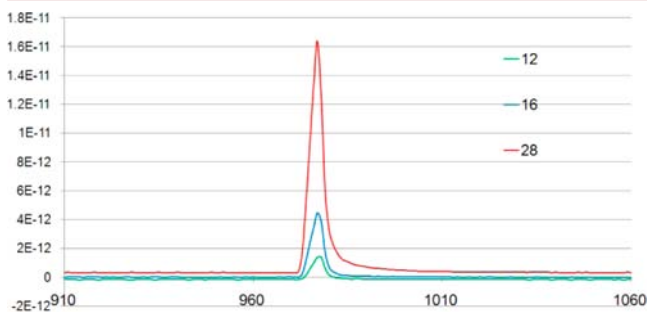


Figure 1. Gas mass spectra of the esterification reaction using acyl chloride and haloalkane.

the reaction system, no product **2a** was obtained. So the esterification of an acyl chloride and a haloalkane may proceed through a free radical. To further confirm this result, we utilized electron paramagnetic resonance (EPR) spectroscopy and obtained an EPR spectrum which displayed a resonance characteristic of an oxygen radical (Figure 2).

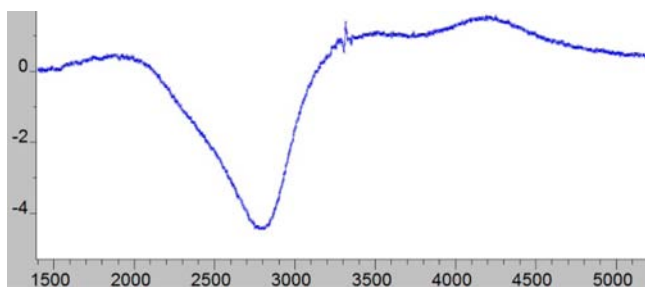
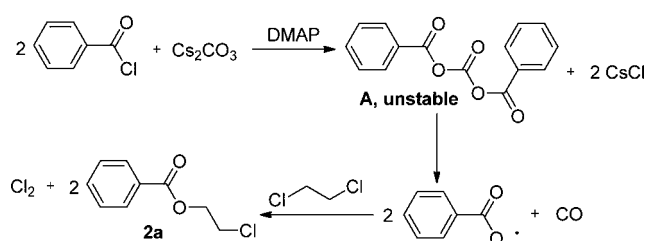


Figure 2. Electron paramagnetic resonance (EPR) spectra (X band, 9.3 GHz, 99.1 K).

On the basis of the above-mentioned results and pertinent literature, we proposed a possible reaction pathway (Scheme 4). First, benzoyl chloride reacted with Cs₂CO₃ forming intermediate **A** which was unstable and decomposed forming free radical **B** and CO gas. Finally, the free radical **B** reacted with 1,2-dichloroethane forming product **2a**.

In summary, we report the first effective method for the construction of esters from acyl chloride and haloalkane

Scheme 4. Possible Reaction Pathway



using Cs₂CO₃ as the oxygen source. Twenty-four substrates were tested, and good yields were obtained. The controlled experiments demonstrated that the O in the ester products comes from Cs₂CO₃ and this esterification may proceed through a free radical pathway. Further studies will be aimed at further investigations into the reaction mechanism.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02479.

Experimental procedure, control experiments, experiment on a gram scale, compound characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Otera, J. *Esterification: methods, reactions, and applications*; Wiley-VCH: Weinheim, 2003. (b) Wang, L. Y.; Li, J.; Dai, W.; Lv, Y.; Zhang, Y.; Gao, S. *Green Chem.* **2014**, *16*, 2164–2173.
- (2) (a) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed.; Wiley-VCH: New York, 1999. (b) Iranpoor, N.; Firouzabadi, H.; Khalili, D. *Org. Biomol. Chem.* **2010**, *8*, 4436–4443. (c) Nowrouzi, N.; Mehranpour, A. M.; Rad, J. A. *Tetrahedron* **2010**, *66*, 9596–9601. (d) Otera, J. *Acc. Chem. Res.* **2004**, *37*, 288–296. (e) Hatano, M.; Furuya, Y.; Shimmura, T.; Moriyama, K.; Kamiya, S.; Maki, T.; Ishihara, K. *Org. Lett.* **2011**, *13*, 426–429.
- (3) (a) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105–4124. (b) Ochiai, M.; Yoshimura, A.; Miyamoto, K.; Hayashi, S. *J. Am. Chem. Soc.* **2010**, *132*, 9236–9239.
- (4) (a) Ekoue-Kovi, K.; Wolf, C. *Chem. - Eur. J.* **2008**, *14*, 6302–6315. (b) Yoo, W. J.; Li, C. J. *Tetrahedron Lett.* **2007**, *48*, 1033–1035. (c) Yoo, W. J.; Li, C. J. *J. Org. Chem.* **2006**, *71*, 6266–6268. (d) Xu, B.; Liu, X.; Haubrich, J.; Friend, C. M. *Nat. Chem.* **2010**, *2*, 61–65. (e) Wu, X. F.; Darcel, C. *Eur. J. Org. Chem.* **2009**, 1144–1147.
- (5) (a) Taarning, E.; Madsen, A. T.; Marchetti, J. M.; Egeblad, K.; Christensen, C. H. *Green Chem.* **2008**, *10*, 408–414. (b) Taarning, E.; Nielsen, I. S.; Egeblad, K.; Madsen, R.; Christensen, C. H. *ChemSusChem* **2008**, *1*, 75–78. (c) Ishida, T.; Nagaoka, M.; Akita, T.; Haruta, M. *Chem. - Eur. J.* **2008**, *14*, 8456–8460. (d) Su, F. Z.; Ni, J.; Sun, H.; Cao, Y.; He, H. Y.; Fan, K. N. *Chem. - Eur. J.* **2008**, *14*, 7131–7135. (e) Oliveira, R. L.; Kiyohara, P. K.; Rossi, L. M. *Green Chem.* **2009**, *11*, 1366–1370. (f) Miyamura, H.; Yasukawa, T.; Kobayashi, S. *Green Chem.* **2010**, *12*, 776–778. (g) Wang, X.; Zhao, G.; Zou, H.; Cao, Y.; Zhang, Y.; Zhang, R.; Zhang, F.; Xian, M. *Green Chem.* **2011**, *13*, 2690–2695. (h) Liu, P.; Li, C.; Hensen, E. J. M. *Chem. - Eur. J.* **2012**, *18*, 12122–12129. (i) Gowrisankar, S.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5139–5143. (j) Liu, C.; Wang, J.; Meng, L.; Deng, Y.; Li, Y.; Lei, A. W. *Angew. Chem., Int. Ed.* **2011**, *50*, 5144–5148.
- (6) (a) Liu, H.; Dong, C.; Zhang, Z. G.; Wu, P. Y.; Jiang, X. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 12570–12574. (b) Huang, X. Q.; Li, X. Y.;

Zou, M. C.; Song, S.; Tang, C. H.; Yuan, Y. Z.; Jiao, N. *J. Am. Chem. Soc.* **2014**, *136*, 14858–14865.

(7) (a) Kano, T.; Mii, H.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 3450–3451. (b) Gotoh, H.; Hayashi, Y. *Chem. Commun.* **2009**, 3083–3085. (c) Lifchits, O.; Demoulin, N.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9680–9683. (d) Jadhav, M. S.; Righi, P.; Marcantoni, E.; Bencivenni, G. *J. Org. Chem.* **2012**, *77*, 2667–2674. (e) Chen, H. H.; Wang, G. Z.; Han, J.; Xu, M. Y.; Zhao, Y. Q.; Xu, H. J. *Tetrahedron* **2014**, *70*, 212–217.

(8) (a) Shimamura, T.; Okumura, K.; Nakagawa, K. *J. Mol. Catal. A: Chem.* **2004**, *211*, 97–102. (b) Mimura, N.; Takahara, I.; Inaba, M. *Catal. Commun.* **2002**, *3*, 257–262.