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Communication

## Dichloromethane as a methylene synthon for regioselective linkage of diverse carboxylic acids: direct access to methylene diesters under metal-free conditions

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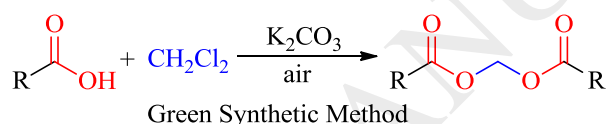
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## Graphical Abstract



- |                            |                            |
|----------------------------|----------------------------|
| ☑ various carboxylic acids | ☑ under air conditions     |
| ☑ metal-free conditions    | ☑ cost-effective synthesis |

This simple protocol is a convenient and cost-effective route to synthesize methylene diesters from a wide scope of carboxylic acids substrates with good functional group tolerance. Several gram-scale reactions have been performed to evaluate the effectiveness and practicality of this protocol.

## ABSTRACT

A metal-free cross coupling between common CH<sub>2</sub>Cl<sub>2</sub> and carboxylic acids has been achieved with K<sub>2</sub>CO<sub>3</sub> as the sole additive. This simple protocol is a convenient and cost-effective route to synthesize methylene diesters from a wide scope of carboxylic acids substrates with good functional group tolerance. Several gram-scale reactions have been performed to evaluate the effectiveness and practicality of this protocol.

## Keywords:

Carboxylic acids

Dichloromethane

Methylene synthon

Methylene diesters

Metal-free conditions

Carboxylic acids are widely found in nature, which are a kind of nontoxic and inexpensive compounds. As a result, one of the current research interests is the transition-metal catalyzed carboxylate-directed C-H transformation or decarboxylative conversion to form new C-C and C-Hetero bonds [1]. Along this line, we have gained extensive knowledge in the realm of Pd-mediated decarboxylative *ortho*-halogenation of aromatic carboxylic acids using carboxyl as traceless directing group and Cu-promoted decarboxylative *ipso*-functionalization of aryl carboxylic acids [2], including decarboxylative methylthiolation [3a], arylation [3b], protonation [2c], cyanation and halogenation [2d-f]. In addition, carboxylic acids can also be employed to synthesize esters, it is worth to note ester scaffolds serve as value intermediates in organic synthesis and key structural units in a variety of natural products, pharmaceuticals and polymers [3]. As a consequence, the development of efficient methods for facile construction of organic esters

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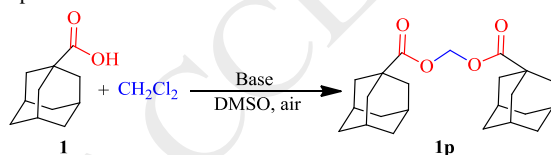
molecules has attracted considerable attention in the past several decades. The traditional method toward the condensation of carboxylic acids or their derivatives with alcohols represents one of the most conventional methods to synthesize corresponding esters, although the drawbacks associated with incomplete transformation and/or generation of a large amounts of unwanted by-products [3]. Moreover, great progress has been made to prepare esters *via* catalytic coupling of carboxylic acids with various partners including aryl organometallic reagents [4], aldehydes [5], and arenes [6]. More recently, significant attention has been paid to esterification conversion *via* cross coupling of carboxylic acids with aryl halides C-Halo bond activation, in this regard, McCusker and MacMillan firstly reported the coupling of carboxylic acids with aryl bromides to provide aryl esters under excited-state organometallic catalysis *via* direct photoexcitation [7a], whereas Itami described carboxylic acids and aryl iodides underwent a transition-metal Pd-catalyzed coupling reaction to furnish the desired aryl esters [7b].

Compared to aryl halides, dichloromethane (DCM) is one of the simplest and cheapest halogenated hydrocarbon molecules that widely used as solvent in laboratory, in addition, methylene chloride can also be employed as reagent to build new C-C bond and C-Hetero bond. On this point, with double C-Cl activation of dichloromethane, Kozak [8a] and Zhang [8b] disclosed the insertion of methylene fragment of DCM into two equivalents of Grignard reagents or oxazolidin-2-ones partner using iron or NaH as promoter respectively. To the best of our knowledge, it is seldom used DCM as C1 synthon in the synthesis of methylene-bridged acylals [9], which are important starting material for the preparation of dienes and chiral allylic esters in organic synthesis [10]. As one part of our continuous efforts to develop efficient functionalization transformation of cheap and abundant carboxylic acids [3], herein we reveal a simple, effective, metal-free and scalable approach for the synthesis of methylene diesters *via* cross coupling of dichloromethane with various carboxylic acids using  $K_2CO_3$  as the sole additive.

Unless otherwise noted, the reagents used for experiments were commercially available and were used as received. All reactions were performed in dried glass reaction tube equipped with a magnetic stir bar under air atmosphere. Column chromatography was performed on silica gel 300-400 mesh. The yields reported are the isolated yields and the average of two runs.  $^1H$ ,  $^{13}C$  and  $^{19}F$  NMR spectra of compounds were recorded at 400, 100 and 377 MHz with  $CDCl_3$  as solvent respectively. All coupling constants ( $J$  values) were reported in Hertz (Hz). HRMS were performed by Center of Analysis and Testing, Nanchang University.

The research was commenced by performing the coupling of 1-adamantanecarboxylic acid **1** (1-AdCOOH) with  $CH_2Cl_2$  as the model reaction for the optimization studies, in which  $CH_2Cl_2$  was used as a solvent and stoichiometric methylene source. Table 1 presented some selected results from the optimization studies, which illustrated the effects of the additive, temperature, reaction time and other reaction parameters on the transformation outcome. As our recently developed decarboxylative *ipso*-functionalization reactions have been performed at 140 °C [2a-d], initially, in the presence of 1 equivalent of  $Li_2CO_3$  as additive, the model reaction between  $CH_2Cl_2$  and 1-AdCOOH **1** was performed at 130 °C without metal mediator under an air atmosphere to provide desired methylene diadamantanecarboxylate **1p** in 28% yield (Table 1, entry 1). To improve conversion of the reaction, a careful examination of different alkali carbonates was next performed, which revealed that  $K_2CO_3$  gave superior yield than that of  $Li_2CO_3$  and  $Na_2CO_3$  under otherwise identical conditions (entries 1-3), furthermore, upon evaluating the effect of the counterion of potassium salt compound on the transformation, it's found  $K_2CO_3$  was a much better choice than either  $K_3PO_4$  or  $KOtBu$  (entries 3-5). Nevertheless, lower yields were obtained when employing organic base instead of  $K_2CO_3$  as additive for the model reaction (entry 6). It's noteworthy that doubling of  $K_2CO_3$  inputs resulted into enhanced reaction efficiency in synthetically useful levels (88%) (entry 7). To our delight, reaction temperature was an important factor to affect the conversion efficiency, since lowering temperature to 100 °C exerted a detrimental effect on the reaction and delivered the corresponding product **1p** in 75% yield (entry 8). It is gratifying to obtain as high as 93% yield of the desired product **1p** when the reaction time was reduced to 5 h (entry 9), unfortunately, both switching mixed solvent  $CH_2Cl_2$ /DMSO to  $CH_2Cl_2$ /NMP and  $CH_2Cl_2$ /DMF and changing reaction atmosphere to aerobic conditions led to inferior reaction conversion under the same reaction time (5 h, entries 10 and 11).

Table 1

Optimization of the reaction conditions.<sup>a</sup>

Entry	Base (equiv.)	Temp. (°C)	Yield (%) <sup>b</sup>
1	$Li_2CO_3$ (1)	130	28
2	$Na_2CO_3$ (1)	130	37
3	$K_2CO_3$ (1)	130	77
4	$K_3PO_4$ (1)	130	22
5	$KOtBu$ (1)	130	39
6	$Et_3N$ (1)	130	25
7	$K_2CO_3$ (2)	130	88
8	$K_2CO_3$ (2)	100	75
9	$K_2CO_3$ (2)	130	93
10	$K_2CO_3$ (2)	130	84
11	$K_2CO_3$ (2)	130	89
12	$K_2CO_3$ (0)	130	0

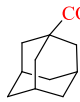
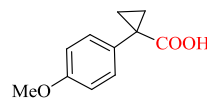
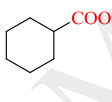
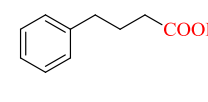
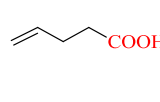
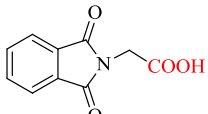
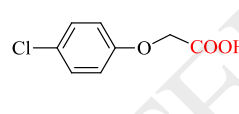
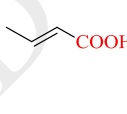
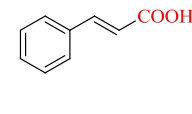
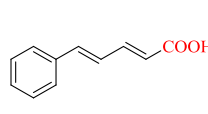
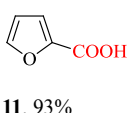
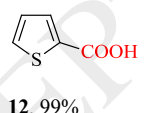
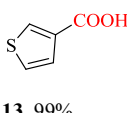
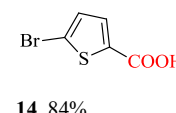
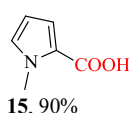
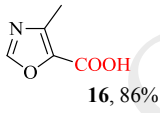
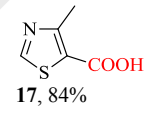
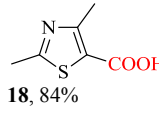
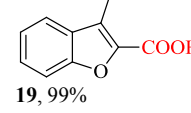
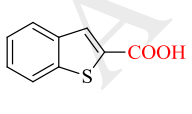
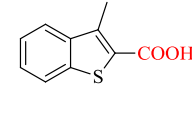
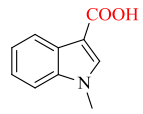
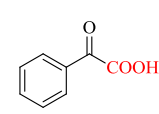
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<sup>a</sup> Conditions: **1** (0.2 mmol), CH<sub>2</sub>Cl<sub>2</sub> (1 mL), DMSO (1 mL), air, 20 h.<sup>b</sup> Yield of the isolated product. <sup>c</sup> 5 h. <sup>d</sup> NMP instead of DMSO. <sup>e</sup> DMF instead of DMSO.

Finally, controlled experiment showed that none of target product **1p** could be detected in the absence of K<sub>2</sub>CO<sub>3</sub>, suggesting that the base is essential for this conversion (entry 12). Weighing the pros and cons, the coupling of dichloromethane with carboxylic acids using 2 equivalent of K<sub>2</sub>CO<sub>3</sub> as the sole additive at 130 °C for 5 hours under an air atmosphere was employed as standard conditions to synthesize methylene diesters.

Subsequently, the obtained optimality conditions (entry 9, Table 1) to achieve methylene diadamantanecarboxylate **1p** encouraged us to evaluate the scope of this metal-free coupling of methylene chloride with respect to carboxylic acids, as illustrated in Table 2, the transformation was shown to be an effective strategy for a diverse array of alkyl carboxylic acids **1-7**,  $\alpha,\beta$ -unsaturated carboxylic acids **8-10**, heteroaryl carboxylic acids **11-22** and  $\alpha$ -oxobenzeneacetic acid **23**. Besides tertiary aliphatic carboxylic acids **1** and **2** provided the desired products in good to excellent yields in this protocol, cyclohexanecarboxylic acid **3** also proceeded straightforward with DCM to give product **3p** in nearly quantitative yield. Remarkably, primary carboxylic acids including aminoacetic and oxyacetic acid **6-7** as well as the substrates **4-5** tolerated carbon-carbon double bond and aryl functional groups, which were well carried out with CH<sub>2</sub>Cl<sub>2</sub> under the standard conditions. For the substrates  $\alpha,\beta$ -unsaturated carboxylic acids, crotonic acid **8** and cinnamic acid **9** successfully furnished desired products in nearly quantitative yield, cinnamalacetic acid **10** comprised a conjugated diene unit also generated the end product, albeit with mild conversion. Gratifyingly, *O*-, *S*- and *N*-containing heteroaryl carboxylic acids **11-22** were proved to be suitable starting materials to afford hoped-for products. Significantly, it is no matter whether carboxyl group at the position *ortho* or *meta* to the sulfur, thiophenic acids **12-13** were also quantitatively transformed to corresponding products. Even though a methyl substituent presented on the position *ortho* to the carboxyl, the substrates **16-19** and **21** gave expected products in good to excellent yields without being affected by the steric effect. Finally,  $\alpha$ -oxobenzeneacetic acid **23** delivered the desired product in moderate yield, and it's failed to improve conversion efficiency through increasing reaction temperature or enhancing the amount of K<sub>2</sub>CO<sub>3</sub> additive.

**Table 2**Scope of carboxylic acids in the transformation.<sup>a</sup>

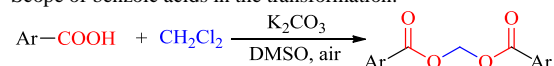
R-COOH + CH <sub>2</sub> Cl <sub>2</sub>		$\xrightarrow[\text{DMSO, air}]{\text{K}_2\text{CO}_3}$		R-COO-CH <sub>2</sub> -O-COO-R	
1 - 23				1p - 23p	
	<b>1</b> , 93%		<b>2</b> , 79%		<b>3</b> , 99%
	<b>4</b> , 80%		<b>5</b> , 99%		<b>6</b> , 55%
	<b>7</b> , 72%		<b>8</b> , 97%		<b>9</b> , 99%
	<b>10</b> , 38%		<b>11</b> , 93%		<b>12</b> , 99%
	<b>13</b> , 99%		<b>14</b> , 84%		<b>15</b> , 90%
	<b>16</b> , 86%		<b>17</b> , 84%		<b>18</b> , 84%
	<b>19</b> , 99%		<b>20</b> , 61%		<b>21</b> , 96%
	<b>22</b> , 99%		<b>23</b> , 42%		

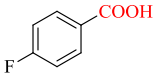
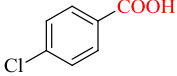
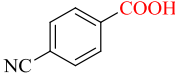
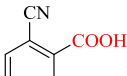
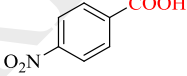
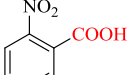
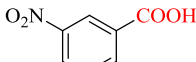
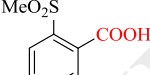
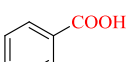
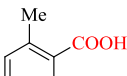
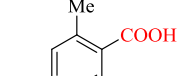
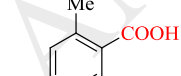
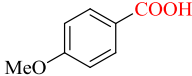
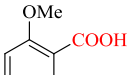
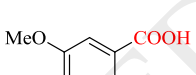
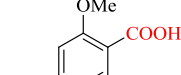
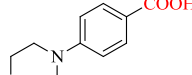
<sup>a</sup> Reaction conditions: acid (0.2 mmol), K<sub>2</sub>CO<sub>3</sub> (2 equiv.), CH<sub>2</sub>Cl<sub>2</sub> (1 mL), DMSO (1 mL), air, 130 °C, 5 h.

The feasibility of coupling of dichloromethane with alkyl and heteroaryl carboxylic acids inspired us to further explore the generality of other aromatic carboxylic acids with different substituents. As illustrated in Table 3, a wealth of benzoic acids **24-40** were favorably carried out with CH<sub>2</sub>Cl<sub>2</sub> under the standard conditions. It's observed that benzoic acid **32** was a viable substrate to afford

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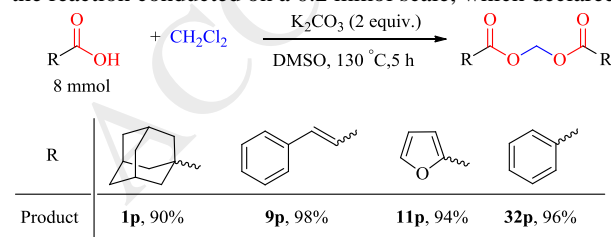
desired methylene dibenzoate **32p** with  $\text{CH}_2\text{Cl}_2$  in quantitative yield, which was the divide between electron-withdrawing (fluoro, chloro, cyano, nitro and sulfonyl) **24-31** and electron-donating (methyl, methoxy and morpholinyl) substituents **33-40** on the benzoic acid substrate, thus, the substituent groups were found to be broad and well-tolerated in this protocol. Apart from the substrates **24**, **26**, **28** and **29**, the conversion efficiency of benzoic acids bearing electron-donating groups was superior to that of benzoic acids with electron-withdrawing groups in this protocol, which could be explained as a result of enhanced electron density of aryl carboxylate through electron-donating substituent on the aromatic ring in the presence of  $\text{K}_2\text{CO}_3$ . Moreover, steric hindrance did not significantly affect the efficiency of the reaction, compared with their isomers, benzoic acids (**27**, **29**, **31**, **34-35**, **37** and **39**) with *ortho* group gave target products in good to excellent yields. No matter where the nitro or methoxy substituent was in the carboxyl group, nitrobenzoic acids **28-30** and methoxybenzoic acids **36-38** were effective substrates to conveniently provided corresponding products in good yields. Notably, the substituent of halo-moiety in substrate **25** survived well in the reaction, which offered the possibility for late-stage functionalization *via* the activation of carbon-halogen bond.

**Table 3**Scope of benzoic acids in the transformation.<sup>a</sup>

24 - 40		24p - 40p	
	<b>24</b> , 99%		<b>25</b> , 86%
	<b>26</b> , 98% <sup>b</sup>		<b>27</b> , 74%
	<b>28</b> , 99%		<b>29</b> , 98%
	<b>30</b> , 94%		<b>31</b> , 87% <sup>b</sup>
	<b>32</b> , 99%		<b>33</b> , 98%
	<b>34</b> , 96%		<b>35</b> , 99%
	<b>36</b> , 94%		<b>37</b> , 95%
	<b>38</b> , 97%		<b>39</b> , 99%
	<b>40</b> , 93%		

<sup>a</sup> Reaction conditions: acid (0.2 mmol),  $\text{K}_2\text{CO}_3$  (2 equiv.),  $\text{CH}_2\text{Cl}_2$  (1 mL), DMSO (1 mL), air, 130 °C, 5 h. <sup>b</sup> 140 °C, 8 h.

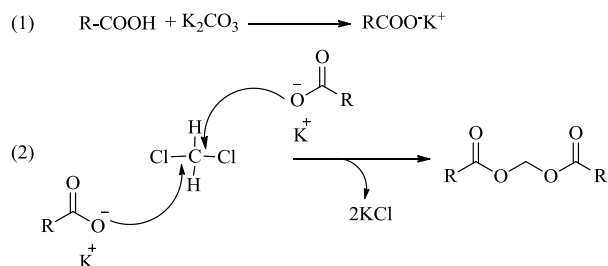
To prove the effectiveness and practicality of this method, a 40-fold scale-up of the metal-free synthesis was performed under the optimized conditions. As shown in Scheme 1, employing 8 mmol of carboxylic acid as starting material with  $\text{K}_2\text{CO}_3$  (2 equiv.) in DMSO under an air atmosphere, as a result, no matter what type of carboxylic acid successfully reached nearly the same efficiency as the reaction conducted on a 0.2 mmol scale, which declared a great potential of the method on large-scale synthesis.

**Scheme 1.** Gram-scale synthesis of products **1p**, **9p**, **11p** and **32p**.

Basing on the above results, though the proposal of a detailed mechanism should be awaited further investigation, a plausible mechanism for this transformation was hypothesized in Scheme 2. Initially, the carboxylic acid substrate was easily transformed to potassium carboxylate salt in the presence of stoichiometric amounts of  $\text{K}_2\text{CO}_3$ , subsequently, the carboxylate anion's negatively charged oxygen nucleophilic attacked the considerably electrophilic methylene chloride's carbon. As a result, the final methylene

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diester was generated with the liberation of KCl product. Due in part to the decreased electron density of carboxylate by induced effect of heteroatom, the transformation yields with using benzoic acids were generally better than that employing heteroaryl carboxylic acids. Since  $K_2CO_3$  was unable to regenerate during the process, that is why stoichiometric amounts of additive were needed in the reaction.



**Scheme 2.** Proposed mechanism for the transformation.

In summary, we have established a simple and practical method for the metal-free coupling reaction between easily available  $CH_2Cl_2$  and carboxylic acids with  $K_2CO_3$  as the sole additive. The transformation demonstrated an efficient protocol to synthesize methylene diesters in fair to excellent results with several distinguishing features: extensive substrate scope including readily available carboxylic acids with good functional group tolerance; a simple reaction system to efficiently offer corresponding esters products with cheap  $K_2CO_3$  as the sole additive under metal-free conditions. Further synthetic application of the protocol is currently in progress.

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