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Short communication

Temperature-controlled NaI-mediated α-oxybenzoylation or oxyacylation–decarboxylation reactions of dimethyl malonate with carboxylic acids

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ABSTRACT

A NaI-mediated α-functionalization of dimethyl malonate and its derivatives with carboxylic acids has been developed. Two different reaction routes based on the same substrates and reaction conditions by simply altering the reaction temperature have been observed, which led to the synthesis of two types of products in good to high yields. The scope of substrates was investigated for both types of reactions, respectively, and possible reaction mechanisms were suggested.

1. Introduction

β-Dicarbonyl compounds are crucial structural units that have found widespread applications in synthetic chemistry [1–3]. The functionalization of β-dicarbonyl compounds at the α-position with heteroatomic groups, in particular α-oxygen functionalization, is one of the most promising transformations for this type of compounds, as it provides key intermediates for the synthesis of a variety of heterocyclic and natural products that adopt unique interests in medicinal chemistry [4–10]. Recently, a range of α-oxygen functionalizations of β-dicarbonyl compounds including the oxyacylation, oxybenzoylation, oxytosylation, oxyphosphorylation and oxyalkylation have been approached by stoichiometric or catalytic reactions [11–23]. However, the majority of the reported protocols utilized stoichiometric polyvalent iodine reagents which are considered environmentally unfriendly [24–29].

To develop a 'greener' and atom-economic methodology for the α-carboxyl functionalizations of a class of important β-dicarbonyl compounds, malonate esters, we investigated the reaction between dimethyl malonate and carboxylic acid mediated by a catalytic amount of iodide salt in the presence of an oxidant, and report herein our results on the NaI-catalyzed α-oxybenzoylation of dimethyl malonate with a variety of carboxylic acids in high yield under mild conditions. Interestingly, an oxyacylation–decarboxylation product, α-carboxylic ester resulting from the same reaction, yet at higher temperature was observed and its substrate scope was preliminarily explored.

2. Experimental

2.1. General procedure for preparation of α-oxybenzoylative products through the reaction between dimethyl malonate and carboxylic acids at 60 °C

To a reaction tube equipped with a magnetic stir bar cinnamic acid (0.3 mmol), dimethyl malonate (0.9 mmol), NaI (20 mol%) TBHP (1.5 equiv.) in DMF (2 mL). The resulting reaction mixture was kept stirring at 60 °C for 12 h. At the end of the reaction, the reaction mixture was

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cooled to room temperature. After the removal of the solvent, the residue was subjected to column chromatography on silica gel using ethyl acetate and petroleum ether mixtures to afford the desired product in high purity.

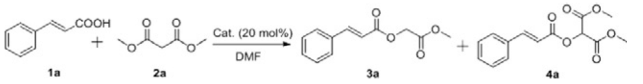
2.2. General procedure for preparation of oxyacylation–decarboxylation products through the addition reaction between dimethyl malonate and carboxylic acids at 120 °C

To a reaction tube equipped with a magnetic stir bar cinnamic acid (0.3 mmol), dimethyl malonate (0.9 mmol), NaI (20 mol%), TBHP (1.5 equiv.) and DMF (2 mL) was added under air. The resulting reaction mixture was kept stirring at 120 °C for 12 h. At the end of the reaction, the reaction mixture was cooled to room temperature. After the removal of the solvent, the residue was subjected to column chromatography on silica gel using ethyl acetate and petroleum ether mixtures to afford the desired product in high purity.

3. Results and discussions

Our initial studies began with a model reaction between cinnamic acid and dimethyl malonate. It was interesting to note when the mixture of cinnamic acid and dimethyl malonate (1.0 equiv.) was heated in the presence of catalytic amount of sodium iodide and a common oxidant TBHP in DMF at 120 °C for 12 h (TBHP = *tert*-butyl hydroperoxide), the product **3a**, resulting from the sequential oxidative coupling and decarboxylation reaction, was isolated in 43% yield (entry 1, Table 1). Although the formation of **3a** was deviated from our goal of gaining a direct oxidative coupling of dimethyl malonate with cinnamic acid at the α-position, the fact that the α-oxygen functionalization of dimethyl malonate did occur certainly warrants further investigation. Therefore, a thorough screening on the reaction conditions was carried out in order to suppress the production of **3a**, while pursuing the desired **4a** from the direct oxidative coupling without decarboxylation. Increasing the loading amount of dimethyl malonate resulted in the isolation of **3a** in moderate yields, whereas **4a** was still not obtained (entry 2, Table 1). It was found that **3a** could be isolated in 70% yield when the amount of dimethyl malonate was increased to 3.0 equiv. (entry 3, Table 1). Other oxidants such as DCP and DTBP were examined, yet none of them led to the formation of **4a**, although product **3a** was unfavorable as well (entries 4 and 5, Table 1). Attempts to replace NaI with other catalysts such as KI, iodine, TBAI (*tert*-butylammonium iodide) or TBAB (*tert*-butylammonium bromide) were unsuccessful, providing either **3a** as the only product in low to moderate yields (entries 6–9, Table 1). Increasing the loading of catalyst NaI to 50 mol% did not improve the results (entry 10, Table 1). However, shortening the reaction time to 1 h favored the formation of **4a** in 28% yield (entry 11, Table 1). Finally, temperature was found to be a determining factor for controlling the formation of **3a** and **4a** in this reaction. Although the temperature above 100 °C has a little influence on the reaction, a lower reaction temperature (60 °C) completely inhibited the decarboxylation process and pleasingly, the α-oxybenzoylation product **4a** was isolated as the only product in 94% yield, which drastically dropped to 50% when the reaction was run at 40 °C (entries 12–15, Table 1). As it was known that a decarboxylation process might occur from β-diesters with heat, we performed an additional experiment to ascertain whether or not **3a** was formed following decarboxylation from **4a**. Interestingly, heating pure **4a** in DMF to 120 °C for 12 h led to the isolation of **3a** in 43% yield, indicating that **3a** was probably generated from **4a**.

Table 1
Screening of reaction conditions.[a]



Entry	Catalyst (equiv.)	Oxidant	Temp. (°C)	Time (h)	Yield[b] (%, **3a**)	Yield[b] (%, **4a**)
1[c]	NaI (0.2)	TBHP	120	12	43	Trace
2[d]	NaI (0.2)	TBHP	120	12	58	Trace
3	NaI (0.2)	TBHP	120	12	70	Trace
4	NaI (0.2)	DCP	120	12	20	Trace
5	NaI (0.2)	DTBP	120	12	62	Trace
6	TBAI (0.2)	TBHP	120	12	65	Trace
7	KI (0.2)	TBHP	120	12	52	Trace
8	I_2 (0.2)	TBHP	120	12	<5	Trace
9	TBAB (0.2)	TBHP	120	12	<5	Trace
10	NaI (0.5)	TBHP	120	12	71	Trace
11	NaI (0.2)	TBHP	120	1	52	28
12	NaI (0.2)	TBHP	130	12	55	Trace
13	NaI (0.2)	TBHP	100	12	50	30
14	NaI (0.2)	TBHP	60	12	N.D.	94
15	NaI (0.2)	TBHP	40	12	N.D.	50

N.D.: Not detected. DCP: dicumyl peroxide; DTBP: di-*t*-butyl peroxide.

[a] Unless otherwise stated, all reactions were carried out with **1a** (0.3 mmol), **2a** (0.9 mmol), a catalyst (0.2–0.5 mol%) and an oxidant (0.45 mmol) in DMF in the air.

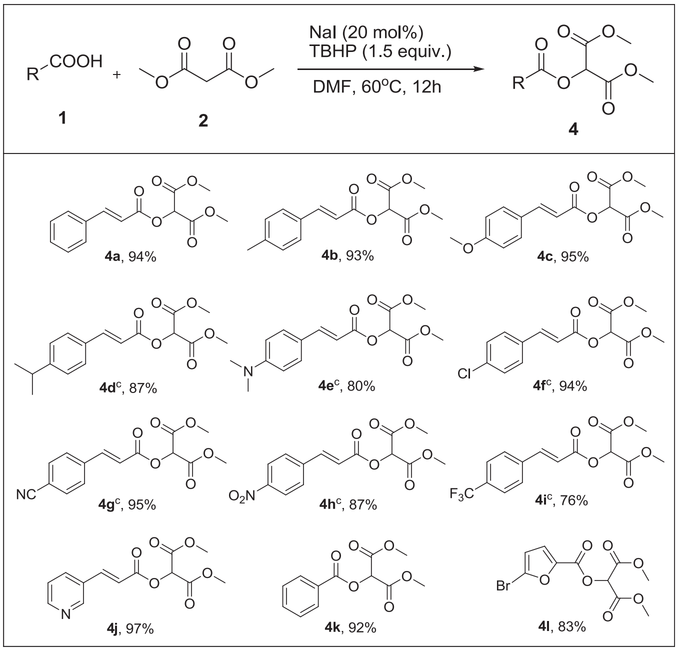
[b] Isolated yield.

[c] 0.3 mmol of **2a** was used.

[d] 0.6 mmol of **2a** was used.

With the above optimized reaction conditions for **4a** in hand, the scope of substrates was further examined and the results were listed in Table 2. First, a variety of cinnamic acid derivatives with substituents on the aromatic ring were tested. Cinnamic acids with electron-donating groups including methyl, methoxyl, isopropyl, or *N,N′*-dimethylamino units reacted with dimethyl malonate (3.0 equiv.) smoothly at 60 °C in the presence of NaI (20 mol%) and TBHP (1.5 equiv.), affording the corresponding products **4b**–**4e** in 80–95% yields. The reactions were equally efficient when some cinnamic acids having electron-withdrawing substituents were employed. In addition, the heterocyclic analogue of cinnamic acid, 3-(3-pyridyl)acrylic acid also furnished the reaction, giving **4j** in 97% yield. At this end, several general carboxylic acids including benzoic acid and 5-bromo-2-furoic acid were utilized for the reactions with dimethyl malonate under the optimal

Table 2
α-Oxybenzoylation of dimethyl malonate[a].



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.9 mmol), NaI (0.2 mol%) and TBHP (0.45 mmol) in DMF at 60 °C in the air.

[b]Isolated yield.

[c]16 h.