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Palladium-catalyzed formation of phenolic compounds by reaction of carbonyl compounds with carbon dioxide†

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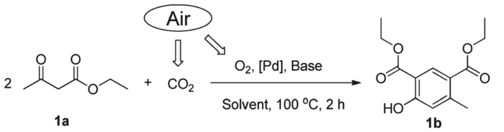
The use of carbon dioxide as a renewable and environmentally friendly source of carbon is highly attractive. A novel and efficient protocol for the synthesis of phenolic compounds from carbonyl compounds and carbon dioxide in the presence of a catalytic amount of Pd(OAc)$_2$ has been developed. This reaction is appealing for industries and is a tool for the sequestration of carbon dioxide.

Carbon dioxide (CO$_2$), as the main culprit in global warming, is an inexhaustible source of carbon on earth. If CO$_2$ can be captured and used in industrial production, it can not only reduce the worsening greenhouse effect, but also resolve the energy crisis. Therefore, the investigation of efficient catalytic processes for CO$_2$ transformation into useful chemical feedstock is a highly attractive field.[1] In the past decade, lots of chemical reactions utilizing CO$_2$ as raw material have been reported,[2] which have aroused our considerable interest in CO$_2$. Herein, we present our independent finding that palladium-catalyzed reaction of carbonyl compounds proceeded smoothly with CO$_2$ to give the corresponding phenolic compounds in good yields, which are well known for their anti-allergenic, anti-atherogenic, anti-inflammatory, anti-microbial, antioxidant, anti-thrombotic, cardioprotective and vasodilatory effects.[3]

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Base	Solvent	Yield[b] [%]
1	PdCl$_2$	K$_2$CO$_3$	DMF	83
2	Pd(dba)$_2$	K$_2$CO$_3$	DMF	85
3	Pd(OAc)$_2$	K$_2$CO$_3$	DMF	91
4[c]	—	K$_2$CO$_3$	DMF	Trace
5	Pd(OAc)$_2$	Na$_2$CO$_3$	DMF	44
6	Pd(OAc)$_2$	K$_3$PO$_4$	DMF	56
7	Pd(OAc)$_2$	NaOH	DMF	None
8	Pd(OAc)$_2$	Et$_3$N	DMF	None
9	Pd(OAc)$_2$	(*i*-Pr)$_2$NH	DMF	None
10[d]	Pd(OAc)$_2$	—	DMF	None
11	Pd(OAc)$_2$	K$_2$CO$_3$	DMAC	78
12	Pd(OAc)$_2$	K$_2$CO$_3$	MFM	69
13	Pd(OAc)$_2$	K$_2$CO$_3$	DMB	81
14	Pd(OAc)$_2$	K$_2$CO$_3$	DMSO	82
15	Pd(OAc)$_2$	K$_2$CO$_3$	CH$_3$COCH$_3$	None
16	Pd(OAc)$_2$	K$_2$CO$_3$	CH$_3$CN	None

[a] Reaction conditions: **1a** (0.6 mmol), air (1 atm), [Pd] (5 mol%), base (0.5 equiv.), solvent (1 mL), 100 °C, 2 h. [b] Isolated yield of the pure product based on **1a**. [c] In the absence of catalyst. [d] In the absence of base.

Initially, the reaction conditions were optimized starting from ethyl acetoacetate (**1a**) and air (1 atm) in the presence of K$_2$CO$_3$ in DMF at 100 °C with various palladium catalysts, as summarized in Table 1. It was observed that Pd(OAc)$_2$ gave the best result (Table 1, entry 3). Then, in order to prove that the CO$_2$ comes from the air, a series of control experiments have been done (for details, see the ESI†). PdCl$_2$ and Pd(dba)$_2$ were also effective, albeit affording the products with slightly diminished yields (Table 1, entries 1 and 2). In the absence of a palladium source, only a trace amount of the desired product was observed under the same reaction conditions (Table 1, entry 4). Base also plays an important role in the catalyst systems. When K$_2$CO$_3$ was replaced by Na$_2$CO$_3$ or K$_3$PO$_4$, a moderate yield was achieved. Other bases like NaOH, Et$_3$N, and (*i*-Pr)$_2$NH were found to be ineffective (Table 1, entries 7–9). A control experiment confirmed that in the absence of K$_2$CO$_3$ the reaction led to recovery of materials (Table 1, entry 10). Further inspection of the reaction conditions revealed that this reaction also proceeded efficiently in solvents such as DMAC (dimethylacetamide), MFM (*N*-methylformamide), DMB (*N*,*N*-dimethylbenzamide), and DMSO (dimethyl sulfoxide) (Table 1, entries 11–14), whereas CH$_3$COCH$_3$ and CH$_3$CN were found to be unfavorable (Table 1, entries 15 and 16). On the basis of the above experiments, the optimized reaction conditions are summarized as follows: Pd(OAc)$_2$, K$_2$CO$_3$, and DMF.

With the optimized reaction conditions in hands, we started to investigate the scope and limitation of this reaction, and the results are summarized in Table 2. Methyl, ethyl,[4] isopropyl,

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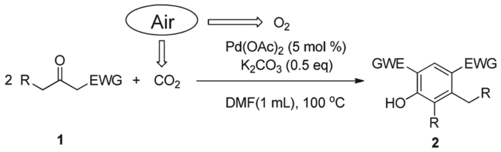
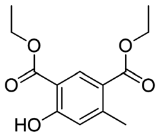
† Electronic supplementary information (ESI) available: Experimental section and NMR data for the prepared compounds. CCDC 904546. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc37194d

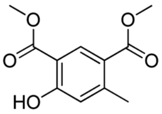
Table 2 Synthesis of phenolic compounds **2** catalyzed by Pd(OAc)$_2$/K$_2$CO$_3$[a]



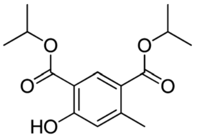
R = H, alkyl
EWG = carbonyl, ester group, sulfonic acid groups



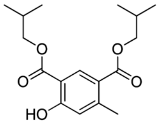
1b, 2 h, 91%



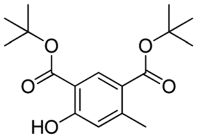
2b, 2 h, 92%



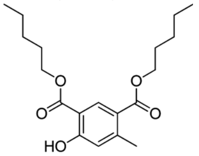
3b, 2.5 h, 88%



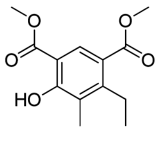
4b, 3 h, 89%



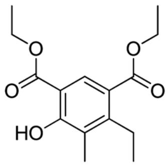
5b, 4 h, 86%



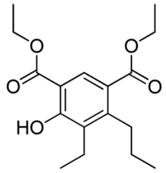
6b, 3.5 h, 89%



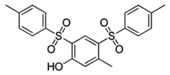
7b, 2.5 h, 83%



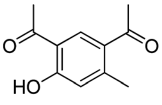
8b, 3 h, 81%



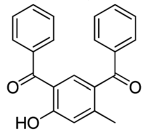
9b, 3.6 h, 79%



10b, 5 h, 80%



11b, 4.8 h, 66%



12b, 5 h, 63%

[a] Reaction conditions: **1** (0.6 mmol), air (1 atm), Pd(OAc)$_2$ (5 mol%), K$_2$CO$_3$ (0.5 equiv.), DMF (1 mL), 100 °C.

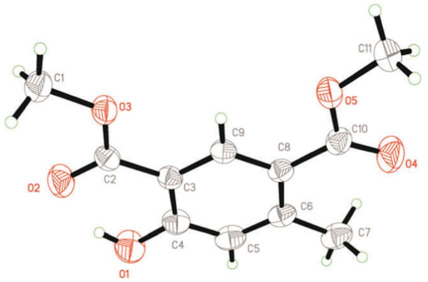


Fig. 1 X-ray crystal structure of **2b**. The thermal ellipsoids are at the 50% probability level.

isobutyl, *tert*-butyl, and *n*-pentyl acetoacetates all reacted smoothly affording the target products in good to excellent yields (Table 2, **1b–6b**). The crystallization of compound **2b** from ethanol gave single crystals suitable for X-ray analysis. Fig. 1 illustrates the molecular structure of phenolic compound **2b**. In addition, methyl 3-oxopentanoate, ethyl 3-oxopentanoate, and ethyl 3-oxohexanoate could also participate in the reaction and give the desirable results (Table 2, **7b–9b**). It was particularly noteworthy that 4-toluenesulfonylacetone was also suitable for this reaction (Table 2, **10b**). Gratifying, acetylacetone and benzoylacetone could be readily introduced in the reaction, providing the corresponding phenolic compounds **11b** and **12b**, but the yields were lower. However, 1,3-diphenylpropane-1,3-dione and diethyl malonate failed to afford the desired products and led to recovery of starting materials.

In summary, we have identified a novel protocol for the synthesis of phenolic compounds by reaction of carbonyl compounds with carbon dioxide. This method has the unique advantages of employing CO$_2$ as a carbon source and simple carbonyl compounds as substrates. Thus, this method constitutes an economical and environmentally benign process for the synthesis of phenolic compounds. Further studies to broaden the substrate scope of the process are underway in our laboratory.

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Notes and references

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4 The yield of the large-scale synthesis of diethyl 4-hydroxy-6-methylisophthalate **1b** from ethyl acetoacetate (**1a**) (60 mmol, 7.8 g) was 87%.