

## ZnO mediated a cheap, efficient, and mild synthesis of unsymmetrical carboxylic acid anhydrides

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### Abstract

The treatment equimolar quantities of carboxylic acids with acid chlorides in the presence of ZnO brings about highly efficient unsymmetrical anhydrides at room temperature in solvent-free condition. Reactivity trends favored formation of the product using both electron deficient and rich aryl acids and acid chlorides.

**Keywords:** ZnO; Unsymmetrical anhydrides; Solvent-free conditions; Carboxylic acid

### 1. Introduction

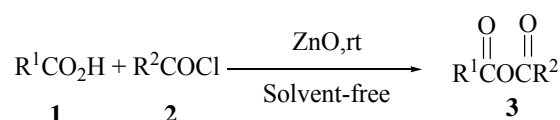
Because of the wide applications of carboxylic acid anhydrides for the preparation of many other functional groups such as amides, esters, peptides [1] and as acylating agents, the development of highly selective and environmental friendly synthetic methods of carboxylic acid anhydrides has been of interest. Many useful methods have been reported in the literature for the synthesis of symmetrical carboxylic acid anhydrides [2-17].

However, to our knowledge only a few methods have been reported for the synthesis of asymmetrical carboxylic acid anhydrides by the reaction of an acyl halide and a carboxylic acid [18]. The synthesis of asymmetrical anhydrides needs reagents, which are unstable, not commercially available, not easy to handle, not reusable or else need lengthy workup. Srivastava and Kabalka [18c] reported the use of  $\text{CoCl}_2$  as a catalyst for synthesis of anhydrides. Although this catalyst removes the need for difficult reagents, at the end of the reaction the separation of the cobalt salt proves a problem. Recently, Leadbeater and co-workers [18b] reported the use of a polymer-supported cobalt phosphine complex catalyst for anhydride formation. This catalyst can be reused and appears to be a good procedure, but there are several factors limiting its applications, for example, no commercially available catalyst, use of toxic organic solvent, using a nitrogen bubble flow, and long reaction time. Metal oxide catalysts have rapidly become an area of intense research activity.

catalysts is the ease of separation from the product mixture at the end of a reaction. As well as allowing for more rapid purification of the product mixture, this means that the metal oxides can be reused in subsequent reactions.

### 2. Results and discussion

In continuation of our interest in the application of metal oxides as catalysts in organic synthesis [19], in this paper, we would like to report the ZnO as an effective catalyst for the synthesis of unsymmetrical carboxylic acid anhydrides rapidly at room temperature, in high yield under solvent-free conditions (Scheme 1).



Scheme 1.

To exploit a simple and suitable condition for synthesis of anhydrides, the reaction of benzoyl chloride with benzoic acid was studied under a variety of conditions via TLC and  $^1\text{H}$  NMR spectroscopy (Table 1).

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**Table 1.** Synthesis of benzoic anhydride **3a** using a reaction between 1 mmol of benzoyl chloride and 1mmol of benzoic acid under various reaction conditions using ZnO

Entry	Amount of ZnO (mmol)	Solvent	Time (min)	Yield <sup>a</sup> (%)
1	0.05	None	5	30
2	0.1	None	5	50
3	0.5	None	5	85
4	1	None	5	95
5	1	CH <sub>3</sub> CN	5	95
6	1	THF	5	95
7	1	PEG-300	5	95
8	1	Toluene	5	80
9	1	CH <sub>2</sub> Cl <sub>2</sub>	5	95

a) Isolated yields

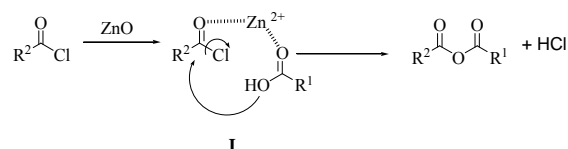
According to Table 1, initially a mixture of benzoic acid **1a** (1mmol) and benzoyl chloride **2a** (1mmol) was stirred at room temperature for 5 min. in the presence of ZnO (5 mol %) in solvent-free conditions. The reaction occurred to generate corresponding benzoic anhydride **3a** in 30% yield. Further, the amount of the catalyst versus reaction yields of product was studied. An increase in the amount of ZnO to 100 mol% led to an increase in the yield of product without significantly affecting reaction times. Then, to find safe reaction conditions, various solvents were studied. As shown in Table 1, entries 5-9, using several organic solvents did not affect either reaction time or yields. So, the best reaction conditions are using 100 mol% of the catalyst, at room temperature and no solvent. To illustrate the need for catalyst for these reactions, an experiment was conducted in which the reaction of benzoyl chloride and benzoic acid was studied in the absence of ZnO, the reaction did not occur, even after 24h. Obviously, ZnO is an essential component of the reaction.

On the basis of these optimization results, the application of this procedure to various carboxylic acids and acid chlorides were investigated. The results are summarized in Table 2.

As shown in Table 2, in all cases, unsymmetrical carboxylic acid anhydrides **3a-r** was obtained in excellent yields. The method is suitable for

preparation of unsymmetrical anhydrides since a variety of aliphatic and aromatic acid chlorides and acids can be utilized. All the acids and acid chlorides reacted very rapidly within 5-20 min. The reaction of benzoyl chloride **2a** with electron withdrawing substituted benzoic acids (entries 2-6), as well as of electron donating substituted benzoic acid (entry 7) showed good results. It was very exciting to find that fatty acids such as stearic acid and 11-aminoundecanoic acid (entries 10, 11) reacted very rapidly in the presence of ZnO to afford the corresponding anhydride in high yields. This procedure is also good enough for the preparation of anhydride from dicarboxylic acids, diacid chlorides, and cyclic acid or acid chlorides (entries 12-15). It is interesting to note that benzene sulfonic acid **1n** reacted with benzoyl chloride to afford the corresponding sulfonic acid anhydride in good yield (entry 18). However, this method was not suitable for the conversion of phosphonic acids or thiocarboxylic acids. As shown in Table 2, the reactions are remarkably clean, and no chromatographic separation is necessary to get the spectra-pure compounds except in some cases (Table 2, entries 5, 6, 8, 9, and 13-16) where some starting materials remained, the conversion being less than 90%.

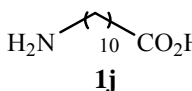
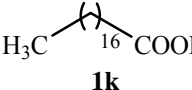
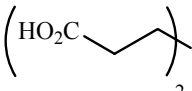
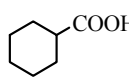
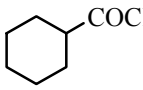
A mechanistic proposal for the role of ZnO as the catalyst is shown in scheme 2. The ZnO has Lewis acid sites (Zn<sup>+2</sup>) and Lewis basic sites (O<sup>-2</sup>) [20]. Lewis acid sites (Zn<sup>+2</sup>) of ZnO are coordinated to the oxygen of the carbonyl groups in both acid and acid chloride, resulting in the increased reactivity to give intermediate I. After losing a molecule of HCl the product was obtained.



**Scheme 2.**

Finally, In order to show the accessibility of the present work in comparison with some other catalysts reported previously, we summarized some of the results for the preparation of benzoic anhydride **3a** in Table 3. This shows that ZnO is the most efficient catalyst with respect to the reaction time and temperature and exhibits broad applicability in terms of yield.

**Table 2.** Synthesis of unsymmetrical carboxylic acid anhydrides, using ZnO under solvent-free condition

Entry	Acid	Acid Chloride	product	Time (min)	Yield <sup>a</sup> (%)
1	PhCO <sub>2</sub> H <b>1a</b>	PhCOCl <b>2a</b>	<b>3a</b>	5	95
2	2,6-diClC <sub>6</sub> H <sub>3</sub> CO <sub>2</sub> H <b>1b</b>	<b>2a</b>	<b>3b</b>	5	90
3	2-ClC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H <b>1c</b>	<b>2a</b>	<b>3c</b>	5	90
4	3-ClC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H <b>1d</b>	<b>2a</b>	<b>3d</b>	5	85
5	4-ClC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H <b>1e</b>	<b>2a</b>	<b>3e</b>	5	75
6	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H <b>1f</b>	<b>2a</b>	<b>3f</b>	5	70
7	4-MeC <sub>6</sub> H <sub>4</sub> <b>1g</b>	<b>2a</b>	<b>3g</b>	5	85
8	2-naphtyl <b>1h</b>	<b>2a</b>	<b>3h</b>	5	80
9	1-naphtyl <b>1i</b>	<b>2a</b>	<b>3i</b>	5	80
10	 <b>1j</b>	<b>2a</b>	<b>3j</b>	10	90
11	 <b>1k</b>	<b>2a</b>	<b>3k</b>	10	85
12	 <b>1l</b>	<b>2a</b>	<b>3l</b>	10	85
13	<b>1a</b>	ClCO(CH <sub>2</sub> ) <sub>8</sub> COCl <b>2b</b>	<b>3m</b>	10	50
14	 <b>1m</b>	<b>2a</b>	<b>3n</b>	10	70
15	<b>1a</b>	 <b>2e</b>	<b>3o</b>	5	70
16	<b>1a</b>	4-ClC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H <b>2d</b>	<b>3p</b>	5	70
17	<b>1a</b>	2-ClC <sub>6</sub> H <sub>4</sub> COCl <b>2c</b>	<b>3q</b>	5	90
18	PhSO <sub>3</sub> H <b>1n</b>	<b>2a</b>	<b>3r</b>	20	85

a) Isolated yields

**Table 3.** Synthesis of benzoic acid anhydride **3a** from benzoic acid and benzoyl chloride under various reaction conditions

Entry	Catalyst / Temp.°C	Solvent	Time (min)	Yield (%) <sup>a</sup>
1	ZnO/rt	none	5	95
2	CO(II)Cl <sub>2</sub> /40°C [18c]	CH <sub>2</sub> Cl <sub>2</sub>	300	91
3	Polymer supported CoCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> /40°C [18b]	CH <sub>2</sub> Cl <sub>2</sub>	240	87
4	polymer of 4- vinylpyridine/rt [18a]	CH <sub>2</sub> Cl <sub>2</sub>	360	90

a) Isolated yields

### 3. Experimental

Starting materials were obtained from Fluka Company. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were measured on Bruker Advance DPX FT 250 and 62.9 MHz spectrometry with TMS as an internal standard. IR spectra were obtained on a Perkin-Elmer or FTIR-800 instruments. Mass spectra were obtained on a Shimadzu GCMS0QP 1000EX at 20 and/or 70 eV. Elemental analyses were performed on Thermo Finnigan, Flash EA 1112 series micro analyzer by the head of the CHN lab.

#### 3.1. General procedure

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Carboxylic acids **1** (1 mmol) were added to ZnO which had been dried in an oven overnight at 100 °C (powder 0.08 g, 1mmol); after a few minutes, carboxylic acid chloride **2** (1 mmol) was added dropwise at room temperature and stirred with a magnetic stirrer. The progress of the reaction was monitored by TLC. The solid mass was then eluted with dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>) or EtOAc. The organic solvent was then washed with H<sub>2</sub>O (2×10 mL) and a saturated solution of NaHCO<sub>3</sub> and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent, the pure products **3a-d**, **3g**, **3j-l**, **3q**, and **3r** were obtained. In the case of compounds **3e**, **3f**, **3h**, **3i**, and **3m-p**, the crude product was purified by silica gel column chromatography (n-hexane:EtOAc, 4:1). The structure of the products was confirmed by <sup>1</sup>H NMR, IR, and compared with authentic samples obtained commercially or prepared by reported methods.

**10-Aminodecanoic benzoic anhydride (3k)** White solid; m.p: 59 C ;IR (KBr): ν 1720, 1778 (C=O), 987 (C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):δ 8.02-8.10 (m, 2H, Ar-H ), 7.48 (m, 1H, Ar-H), 7.31-7.45 (m, 2H, Ar-H), 6.14 (bs, 2H, -NH<sub>2</sub>), 3.34-3.42 (m, 2H, -CH<sub>2</sub>-NH<sub>2</sub>), 2.22-2.57 (m, 2H,-

CH<sub>2</sub>CO-), 1.50-1.72 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO-), 1.21 (m, 12H, -CH<sub>2</sub>-C<sub>6</sub>H<sub>12</sub>CO-); <sup>13</sup>C NMR (62.89 MHz, CDCl<sub>3</sub>): δ 171.0, 162.3, 134.5, 131.2, 130.5, 128.8, 128.5, 126.8, 40.1, 35.5, 29.6, 29.3, 29.2, 29.12, 28.8, 26.9, 24.2. GC-MS /EI: m/z 305 (M<sup>+</sup>). Anal. Calcd. For C<sub>18</sub>H<sub>27</sub>NO<sub>3</sub>: C, 70.79; H, 8.91: Found: C, 70.93; H, 8.65.

**Benzoic stearic anhydride (3l)** White solid; m.p: 63 °C; IR (KBr): ν 1697, 1752 (C=O), 1099 (C-O); <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>): δ 8.09 (d, J=7.25 Hz, 2H, Ar-H), 7.58-7.63 (m, 1H, Ar-H), 7.43-7.49 (m, 2H, Ar-H ), 2.28-2.47 (m, 2H, -CH<sub>2</sub>CO-), 1.61-1.66 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO-), 1.25(m, 26H, CH<sub>3</sub>-C<sub>13</sub>H<sub>26</sub>-CH<sub>2</sub>), 0.85-0.9 (m, 3H, -Me); <sup>13</sup>C NMR (62.89 MHz, CDCl<sub>3</sub>):δ 169.6, 162.3, 134.5, 133.7, 130.1, 129.4, 128.4, 35.5, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.27, 29.22, 29.0, 28.9, 28.8, 24.6, 24.3, 24.2, 22.7, 14.11. GC-MS /EI: m/z 388 (M<sup>+</sup>). Anal. Calcd. For C<sub>25</sub>H<sub>40</sub>O<sub>3</sub>: C, 77.27; H, 10.38: Found: C, 77.25; H, 10.48.

**Benzoic 3-(3, 4, 5-trioxo-5-phenyl pentyl thio) propanoic anhydride (3m)** White solid; m.p: 95 C; IR (KBr): ν 1720, 1782 (C=O), 995(C-O) cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>): δ 8.03-8.16 (m, 4H, Ar-H), 7.57-7.67 (m, 2H, Ar-H), 7.25-7.55 (m, 4H, Ar-H), 2.93-2.99 (m, 4H, -CH<sub>2</sub>-CH<sub>2</sub>-S-CH<sub>2</sub>-CH<sub>2</sub>-), 2.81-2.90 (m, 4H, -CH<sub>2</sub>-S-CH<sub>2</sub>-); <sup>13</sup>C NMR (62.89 MHz, CDCl<sub>3</sub>): 172.2, 133.8, 130.5, 130.2, 129.2, 128.8, 128.4, 34.5, 26.6. Anal. Calcd. For C<sub>20</sub>H<sub>18</sub>O<sub>6</sub>S: C, 62.16; H, 4.70: Found: C, 62.25; H, 4.13.

### 4. Conclusion

In conclusion, we have described a novel and highly efficient solvent-free protocol for synthesis of unsymmetrical anhydride using non toxic and inexpensive ZnO powder. The advantages of this environmentally benign and safe protocol include a simple reaction setup, not requiring specialized equipment, very mild reaction conditions, high product yields, very short reaction times, and the elimination of solvents.

### Acknowledgments

We gratefully acknowledge the support of this work by Shiraz University.

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