

## Synthesis of Symmetrical Carboxylic Acid Anhydrides from Acyl Chlorides in the Presence of In Metal and DMF

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Symmetrical carboxylic acid anhydrides are valuable reagents for preparing carboxylic acid derivatives owing to their highly reactive electrophilic character.<sup>1</sup> Carboxylic acid anhydrides are typically prepared by the reaction of an acyl halide with a carboxylate metal salt,<sup>2</sup> or with a carboxylic acid in the presence of a base.<sup>3</sup> Alternatively, carboxylic acid anhydrides are made by the reaction of a carboxylic acid with a powerful dehydrative coupling agent such as thionyl chloride,<sup>4</sup> phosgene,<sup>5</sup> carbodiimides,<sup>6</sup> phosphoranes,<sup>7</sup> isocyanate,<sup>8</sup> ethoxyacetylene,<sup>9</sup> 1, 3, 5-triazines<sup>10</sup> and trichloroacetonitrile/PPh<sub>3</sub>.<sup>11</sup> Many of these methods, however, suffer from drawbacks including use of expensive and/or toxic reagents, low yields, tedious workup procedures, harsh reaction conditions and incompatibility with poly-functionalized substrates. Therefore, mild and efficient methods for preparing carboxylic acid anhydrides are still in great demand.

Organic reactions employing indium metal have gained considerable attention because indium-mediated reactions show high reactivity and unique properties in organic or aqueous medium.<sup>12</sup> Indium is non-hazardous and inert towards air and water. Moreover, pretreatment is unnecessary to activate in-

dium metal. These inherited merits of indium prompted us to investigate indium-mediated reactions.<sup>13</sup> We herein report on an indium metal-mediated synthesis of symmetrical carboxylic acid anhydrides from acyl chlorides in the presence of DMF.<sup>14</sup>

When a solution of benzoyl chloride, DMF and indium powder in hexane was stirred at room temperature for 3 h, benzoic anhydride was obtained in 79% yield (Table 1, entry 1). The amount of indium powder could be reduced to 0.6 equiv without a detrimental effect on the yields of benzoic anhydride (entries 2-4). The efficiency of the reaction drastically decreased with less than 0.3 equiv of indium powder, showing that the reaction is not catalytic (entry 5). Controlled experiments revealed that the reaction did not proceed without indium powder or DMF (entries 6 and 7). These results imply that indium and DMF play a crucial role in the reaction. The solvent effects on the reaction were also examined. The reactions carried out in hydrocarbon or chlorinated hydrocarbon solvents afforded benzoic anhydride in good yields (entries 8-12). The reactions performed in ethers such as THF, dioxane and diethyl ether gave somewhat lower yields (entries 13-15). Among the solvents examined, the best choice was acetonitrile (entry 16).

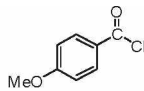
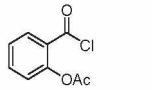
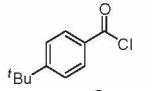
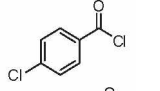
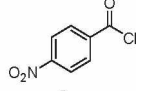
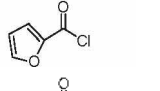
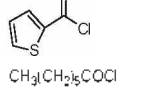
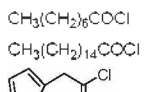
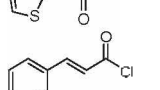
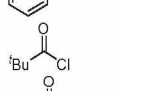
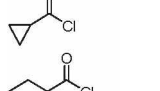
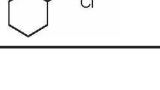
We applied the optimal reaction conditions to preparation of structurally diverse anhydrides.<sup>15</sup> The results are presented in Table 2. The reaction shows the generality for a wide range of acyl chlorides. Aromatic and aliphatic acyl chlorides afforded the corresponding anhydrides in high isolated yields. Compared with electron-rich aromatic acyl chlorides, electron-deficient aromatic acyl chlorides gave the products in higher yields (entries 1-5). The reaction with heteroaromatic acyl chlorides proceeded to give high yields of the corresponding carboxylic acid anhydrides (entries 6 and 7). The reaction with aliphatic acyl chlorides required longer reaction times to be completed than the reaction with aromatic acyl chlorides (entries 8-11). Sterically hindered acyl chloride such as pivaloyl chloride was also converted smoothly into the corresponding carboxylic acid anhydride in high yield (entry 13). Interestingly, the reaction times for cyclic aliphatic acyl chlorides were shorter than those of acyclic aliphatic acyl chlorides under the reaction conditions (entries 14-15).

It is assumed that indium metal promotes the formation of Vilsmeier-type iminium salt with a carboxylate anion as counter anion, which reacts with an acyl chloride to give the corresponding carboxylic acid anhydride via a typical nucleophilic acyl substitution reaction process.<sup>16</sup>

**Table 1.** Optimizing reaction conditions.

Entry	In (equiv)	DMF (equiv)	Solvent	Isolated yield (%)
1	1.1	2.0	hexane	79
2	0.6	2.0	hexane	79
3	0.6	3.0	hexane	78
4	0.6	1.0	hexane	75
5	0.3	2.0	hexane	45
6	0	2.0	hexane	0
7	0.6	0	hexane	0
8	0.6	2.0	cyclohexane	78
9	0.6	2.0	pentane	76
10	0.6	2.0	benzene	68
11	0.6	2.0	CH <sub>2</sub> Cl <sub>2</sub>	78
12	0.6	2.0	ClCH <sub>2</sub> CH <sub>2</sub> Cl	77
13	0.6	2.0	THF	70
14	0.6	2.0	dioxane	71
15	0.6	2.0	diethyl ether	69
16	0.6	2.0	CH <sub>3</sub> CN	89

**Table 2.** Synthesis of symmetrical carboxylic acid anhydrides from acyl chlorides in the presence of In powder and DMF.

Entry	Acid chloride	Time (h)	Isolated yield (%)
1		3	77
2		3	88
3		3	79
4		2	96
5		2	97
6		3	82
7		3	79
8	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> COCl	18	75
9	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>6</sub> COCl	18	79
10	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>14</sub> COCl	15	81
11		12	80
12		12	81
13		12	90
14		3	80
15		3	93

In conclusion, we have developed a simple, mild and efficient method for synthesizing symmetrical carboxylic acid anhydrides from acyl chlorides. The method shows the generality for a wide range of sterically diverse acyl chlorides.

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- For examples on zinc-mediated reactions, see: Serieys, A.; Botuha, C.; Chemla, F.; Ferreira, F.; Pérez-Luna, A. *Tetrahedron Lett.* **2008**, *49*, 5322.
- General procedure: To a suspension of indium powder (344 mg, 3.0 mmol) and DMF (0.78 mL, 10 mmol) in CH<sub>3</sub>CN (5 mL) was added acyl chloride (5 mmol) dropwise for 5 min at 0 °C under argon. The reaction was allowed to be stirred for 2-18 h at room temperature. The reaction was monitored with TLC. After completion of the reaction, the solvent was evaporated. The residue was purified with column chromatography on silica gel affording the corresponding carboxylic acid anhydride.
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