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A simple, convenient method for the synthesis of maleic anhydrides from α-keto esters and alkanoic acid anhydrides using the $TiCl_4$/*n*-Bu_3N reagent system

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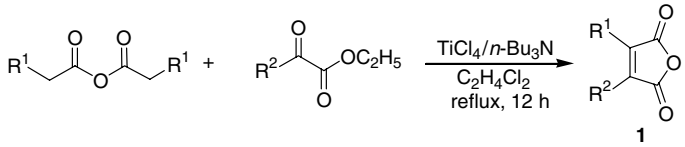
Abstract—Reaction of α-keto esters with alkanoic acid anhydrides using the $TiCl_4$/*n*-Bu_3N reagent system gives the corresponding maleic anhydrides in 62–95% yields.

Maleic anhydrides are important synthons widely used in the construction of new organic skeletons. These cyclic compounds have immense potential for application as dienophiles in Diels–Alder reactions[1] and as monomers in polymerization reactions.[2] Moreover, a large number of substituted maleic anhydrides exhibit a range of biological activities,[3] including antibacterial activity.[4] However, only a very few general methods are available for the synthesis of substituted maleic anhydrides. Previously, palladium catalyzed reagent systems have been reported to yield maleic anhydrides by carbonylation of alk-1-ynes.[5] From this laboratory, oxidative carbonylation of alk-1-ynes has been reported for the synthesis of substituted maleic anhydrides.[6]

During investigations on the synthetic applications of the $TiCl_4/R_3N$ reagent system,[7–9] we have developed a new method for the synthesis of substituted maleic anhydrides from alkanoic acid anhydrides and α-keto esters (Scheme 1).

We observed that the α-keto esters react with alkanoic acid anhydrides in the presence of the $TiCl_4$/*n*-Bu_3N reagent system to give maleic anhydrides.[10] For example, ethyl benzoylformate reacts with acetic anhydride in 1,2-dichloroethane as solvents at reflux to produce phenyl maleic anhydride **1a** in 92% yield. This transformation was found to be general for aryl α-keto esters and alkanoic acid anhydrides using the $TiCl_4$/*n*-Bu_3N regent system. The results are summarized in Table 1.

It was found that use of acetic anhydride gave higher yields (entries 1–3) compared to propionic anhydride (entries 4–6). The reaction of acetic anhydride with *p*-Me and *p*-OMe substituted benzoylformates gave the corresponding anhydrides **1b** and **1c** in 84% and 64% yields, respectively (entries 2 and 3). Similar variation of the yields was observed with substitution of the phenyl ring of α-keto esters on reaction with propionic anhydride (entries 4–6). Diphenyl maleic anhydride **2a** was obtained in 95% yield (entry 7) by the reaction of



Scheme 1.

Keywords: Maleic anhydrides; α-Keto esters; Alkanoic anhydrides; Titanium tetrachloride.
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Table 1. Reaction of α-keto esters with acid anhydrides and $TiCl_4$/n-Bu_3N

Entry	R^1	R^2	Product[a]	Yield (%)[b]
1	H	Ph	**1a**	92
2	H	*p*-MePh	**1b**	84
3	H	*p*-MeOPh	**1c**	64[c]
4	CH_3	Ph	**1d**	81
5	CH_3	*p*-MePh	**1e**	76
6	CH_3	*p*-MeOPh	**1f**	62[c]
7	—[d]	Ph	**2a**	95

[a] The products were identified by ^1H, ^{13}C NMR and mass spectral data[11] and by comparison with the data reported for compounds **1a**, **1b**, **1c**[5g] and **2a**.[12]

[b] Isolated yields are based on the amount of keto ester used.

[c] The reactions were carried out using α-keto ester (5 mmol), anhydride (10 mmol), $TiCl_4$ (3.3 mL of a 1:1 solution of $TiCl_4/CH_2Cl_2$) (15 mmol) and n-Bu_3N (6 mmol).

[d] The reaction was carried out using ethyl benzoylformate (5 mmol), phenyl acetyl chloride (10 mmol), $TiCl_4$ (2.2 mL of a 1:1 solution of $TiCl_4/CH_2Cl_2$) (10 mmol) and n-Bu_3N (6 mmol).

phenyl acetyl chloride and ethyl benzoylformate under the same reaction conditions. However, alkanoic acids and acid chlorides did not react with α-keto esters under the same reaction conditions.

This transformation was carried out using the α-keto ester and alkanoic acid anhydrides in a 1:2 ratio. The reaction gave unidentified more polar products when the α-keto ester and alkanoic acid anhydrides were used in a 1:1 ratio. In the case of –OMe substituted α-keto esters (entries 3 and 6), one further equivalent of $TiCl_4$ was required for the reaction because of its oxygen coordinating ability.

The transformation can be rationalized by the tentative mechanistic pathway outlined in Scheme 2, involving formation of a titanium enolate of the alkanoic acid anhydride and its aldol reaction with the α-keto esters followed by cyclization to give the maleic anhydrides.

Previously, the synthesis of compounds **1a**, **1b** and **1c** has been reported using palladium catalyzed reagent systems by carbonylation of alk-1-ynes.[5] More recently, it was reported that palladium catalyzed and CO_2 promoted oxidative carbonylation of 1-alkynes using PdI_2 in conjunction with excess KI in water/dioxane gave the products **1a**, **1b** and **1c** in 54%, 68% and 70% yields, respectively.[5g] The $TiCl_4$/n-Bu_3N reagent system as well as the substrate alkanoic acid anhydrides and α-keto esters are inexpensive, and are easy to prepare and handle compared to the reagent systems and substrates used previously for the synthesis of these maleic anhydrides.[5] Accordingly, this method offers good synthetic potential.

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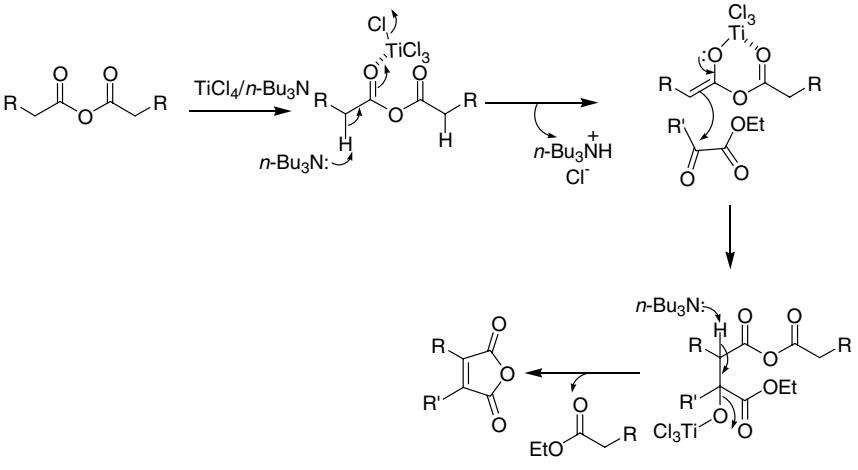

Scheme 2.

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10. Representative procedure for the synthesis of maleic anhydrides: 1,2-Dichloroethane (25 mL), ethyl benzoylformate (0.75 mL, 5 mmol) and acetic anhydride (0.94 mL, 10 mmol) were stirred together at room temperature under N_2. $TiCl_4$ (2.2 mL of a 1:1 solution of $TiCl_4/CH_2Cl_2$, 10 mmol) and n-Bu_3N (1.4 mL, 6 mmol) were added. The reaction mixture was refluxed for 12 h. It was then cooled to 0 °C and a saturated aqueous NH_4Cl solution (10 mL) was added and the contents were stirred for 0.5 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic extract was washed with 2 N HCl (10 mL), water (10 mL), brine solution (10 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was chromatographed on a silica gel column. Phenyl maleic anhydride **1a** (92% yield) was collected using EtOAc/hexane (4:96) mixture as an eluent.
11. Physical constants, ^{13}C NMR and mass spectral data: Compound **1a**: mp: 117–118 °C (lit.[5g] 118–119 °C), ^{13}C NMR δ ppm: 164.5, 163.6, 146.8, 132.7, 129.3, 129.0, 126.9, 124.5. Compound **1b**: mp: 105–106 °C (lit.[5g] 106–108 °C), ^{13}C NMR δ ppm: 164.6, 163.8, 146.6, 143.8, 130.1, 129.0, 124.2, 123.1, 21.6. Compound **1c**: mp: 141–143 °C (lit.[5g] 142–143 °C), ^{13}C NMR δ ppm: 165.2, 163.3, 159.2, 146.4, 131.1, 128.6, 121.0, 114.9, 55.8. Compound **1d**: mp: 98–100 °C, ^{13}C NMR δ ppm: 166.1, 164.8, 139.9, 138.7, 130.9, 129.4, 128.9, 127.5, 10.7, MS (EI): m/z 188 (M^+). Compound **1e**: mp: 108–110 °C, ^{13}C NMR δ ppm: 166.4, 165.0, 141.6, 139.8, 137.6, 129.7, 129.4, 128.7, 21.5, 10.9, MS (EI): m/z 202 (M^+). Compound **1f**: mp 119–120 °C, ^{13}C NMR δ ppm: 172.2, 166.5, 164.7, 161.7, 139.7, 131.3, 128.9, 114.5, 55.4, 10.9, MS (EI): m/z 218 (M^+). Compound **2a**: mp 157–159 °C (lit.[12] 159–162 °C), ^{13}C NMR δ ppm: 164.8, 138.1, 131.1, 129.7, 128.9, 127.1.
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