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Efficient Synthesis of α-Hydroxy-β-Ketoesters from Methyl Phenylglyoxalate and Acid Chlorides mediated by Titanium Trichloride

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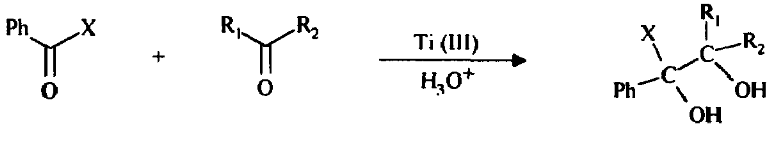
Summary *Methyl phenylglyoxalate and acid chlorides undergo rapid condensation reactions on treatment with a* $TiCl_3$*-THF/*CH_2Cl_2 *solution, in the presence of pyridine, at room temperature.*

We recently reported that an aqueous solution of $TiCl_3$ induces reductive coupling reactions of α-X-carbonyls (X= $COOCH_3$,[1] COR,[2] CN[3]) with aldehydes or ketones (Scheme).

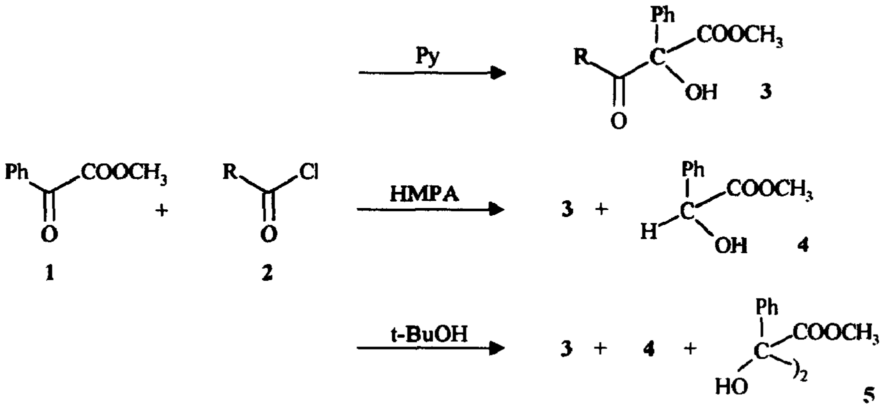
Scheme



It was of interest to extend the above series of reactions to acid chlorides, but it became crucial to work under anhydrous conditions. Solutions of $TiCl_3$ in THF/CH_2Cl_2 (1:2) are stable for long periods (provided air and moisture are excluded) and, now, commercially available.

Here, we wish to report a new and facile synthesis of α-hydroxy-β-ketoesters **3** from methyl phenylglyoxalate **1** and acid chlorides **2**, promoted by $TiCl_3$-THF/CH_2Cl_2 solution, in the presence of pyridine.

Table. Reactions of Methyl phenylglyoxalate and acid chlorides in THF with Ti(III) chloride under various conditions.



Entry	Acid chloride	Additive (equiv.)	Products (isolated yield, %)[a]		mp °C (lit.)
			3[b]	4	
1	PhCOCl	Py (3)	86	-	94 (91-2)[6]
2	PhCOCl	HMPA (4)	44	41	
3	p-MeC_6H_4COCl	Py (3)	90	-	105
4	p-MeC_6H_4COCl	HMPA (4)	55	36	
5	p-MeC_6H_4COCl	none	42	34	
6	p-MeC_6H_4COCl	t-BuOH (5)	6	11[c]	
7	p-$MeOC_6H_4COCl$	Py (3)	74	-	110-1
8	p-$MeOC_6H_4COCl$	HMPA (4)	traces	75	
9	p-ClC_6H_4COCl	Py (3)	70	-	98-100
10	p-ClC_6H_4COCl	HMPA (4)	40	43	
11	CH_3COCl	Py (3)	72	-	liquid
12	CH_3COCl	HMPA (4)	21	25	

[a] Yields (%) are based on the starting 1. [b] All products 3 have spectral characteristics (^1H NMR, IR and MS) in agreement with the structures proposed. [c] 63% of 5 (*meso*) is formed.

The following procedure is typical: a 1M $TiCl_3$-THF/CH_2Cl_2 solution (5 mmol) was added, at once, to a well stirred solution of **1** (2.5 mmol), **2** (2.5 mmol) and pyridine (3 mmol) in anhydrous THF (10 ml), under nitrogen, at room temperature. The blue colour of $TiCl_3$ immediately turned to green, and a yellow precipitate[4] appeared in less than one minute. After 15 min[5] stirring, the solution was quenched with water and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to dryness. The crude product was recrystallized from the appropriate solvent or purified on a silica gel column (hexane/ether/chloroform, 2:1:1) to give **3** in 70-90% yield, based on the starting **1**. Some representative results are collected in Table.

The yield of **3**, based on the converted **1**, were always quantitative, neither self-reductive coupling of **1** (*e.g.* **5**) nor the alcohol **4** were found.[7] The use of pyridine was essential to obtain **3** in useful yield. Repeating the reaction in the absence of pyridine or in the presence of other additive, such as hexamethylphosphoroamide (HMPA),[8] a drastic decrease of **3** and the concomitant formation of **4** was observed.

Much to our surprise,[9] in the presence of a protic additive, such as t-BuOH (entry 6), a high yield (63%) of the *meso* dimer **5** was obtained, along with minute amounts of **3** and **4**. The nature of the additive undoubtedly influences the equilibria involved in these reactions and affects important parameters of the metal ion, such as its electronic property and Lewis acidity.

According to our previous reports,[1,2,3] the reaction starts by an electron transfer from Ti(III) to **1**. At this stage the radical anion formed has many options open to it: it can dimerize into **5**, it may add to **2** or it can be further reduced into an organometallic species which, in turn, may give **3** or **4**.[10] Additional experiments will be necessary to distinguish between a radical or an organometallic mechanism of addition.

The precise role of pyridine is not clear in these reactions: at first glance, the formation of an acylpyridinium ion intermediate[11] ($RCOCl + Py \leftrightarrows RCOPy^+Cl^-$) could explain the high yield of **3**, though from preliminary studies it emerges that pyridine acts as a proper ligand at the metal ion. In fact, the yield of 1,2-diols, formed when ketones or aldehydes are used instead of **2** under analogous experimental conditions, are strongly increased by the addition of pyridine.

In conclusion, our method is very attractive for the synthesis of **3** because of the high yields and its rapidity (titration at room temperature) and it compares favourably with the few literature methods available which require multi-step and low-yielding reactions.[6,12]

We are further investigating the scope of this reaction with the aim to extend it to other acid derivatives and to achieve a more detailed knowledge of the mechanism involved.

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References and Notes

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2. Clerici, A.; Porta, O. *J. Org. Chem.* **1988**, *54*, 3872.
3. Clerici, A.; Porta, O. *J. Org. Chem.* **1993**, *58*, 2889.
4. The yellow precipitate is an adduct of Ti(IV). Its ^1H NMR (DMSO) spectrum evidences the presence of THF and pyridine in the ratio 1:4. Probably the adduct is a six coordinated octahedric complex, Ti(IV)ClTHFPy$_4$. It is very sensitive to moisture and is completely destroyed when the reaction is quenched with H_2O.
5. Control experiments revealed that the reaction is over in less than 5 min.
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7. Control experiments confirmed that **2** is not reduced by Ti(III).
8. It is well known that HMPA increases the reduction potential of SmI_2 and of low-valent metals. Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485.
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10. The formation of **5**, instead of **4**, in the presence of t-BuOH, as an additive, makes questionable the presence of an organometallic species.
11. The efficient nucleophilic catalysis of acylation reactions by pyridine ha long been known. March J. in "*Advanced Organic Chemistry*", 3rd Edition, J. Wiley and Sons Editor: New York, **1985**, p 333.
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