Lithium Perchlorate as an Efficient Catalyst for Selective Transesterification of β-Keto Esters Essentially Under Neutral Conditions

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Abstract: Lithium perchlorate catalysed efficient transesterification of β -keto esters has been carried out, which affords various esters under almost neutral conditions.

Key words: transesterification, β -keto ester, lithium perchlorate, catalyst

β-Keto esters represent an important class of organic building blocks¹ and are used for efficient synthesis of a number of complex natural products. Transesterification, one of the useful and important methods of ester synthesis has wide applications both in academic and industrial research² and in general, it is accelerated by protic acids,³ Lewis acids³ and basic catalysts.³ More recently, various catalysts have been reported to effect transesterification.^{3,4} Most of the reported methods of transesterification of β -keto esters are not general and are equilibrium driven reactions where usage of an excess of one of the reactants is mandatory to obtain good yields. Toxic and expensive DMAP⁵ catalyzed transesterification required a large amount of catalyst whereas tertiaryl butyl acetoacetate⁶ is restricted to tertiary butyl esters, thus lacking generality. Distannoxanes⁷ gave good yields of β -keto esters; however the catalysts are difficult to prepare. Although many methods are available for the preparation of alkyl benzoylacetates, there are few reports^{4a,4d} on the synthesis of β -keto esters which are required for the synthesis of lignans including podophyllotoxin. α-Disubstituted β -keto ester enolates underwent efficient 1,3-ester shift under basic conditions.8 Very few examples are reported on transesterification of β -keto esters with propargylic alcohols^{2,9} even though several of the reported methods were effective with allylic alcohols. Transesterification of simple esters with stoichiometric amounts of iron(III) perchlorate¹⁰ is also reported without selectivity towards β-keto esters.

In recent years lithium perchlorate and lithium perchlorate in diethyl ether (LPDE) have gained a lot of importance as versatile reagents for effecting organic transformations under neutral conditions.¹¹ Thus, the development of a new method which allows transesterification under essentially neutral conditions should heighten the synthetic potentiality of the reaction. We report here lithium perchlorate as a neutral catalyst for selective and practical transesterification of β -keto esters (Scheme).

After scanning through different catalysts (Table 2), we found that lithium perchlorate worked remarkably well. Treatment of butyl/ ethyl/ methyl β -keto ester with alcohols along with a catalytic amount of lithium perchlorate in toluene at 100 °C afforded β -keto esters in excellent to good yields. Various alcohols (primary, secondary, tertiary, benzylic, allylic and propargylic) underwent smooth transesterification reactions. Even less reactive trityl alcohol afforded the corresponding β -keto ester in moderate yield (Table 1, entry 7) which is otherwise often problematic in acid catalyzed reactions or failed to undergo transesterification with Ti(OEt)₄.^{4e} It should be pointed out that transesterification of β -keto esters with unsaturated alcohols is rather difficult as it is offset by facile decarboxylated rearrangement.¹² The superiority of this procedure can be clearly visualized in transesterifications leading to the synthesis of β -keto esters with an aromatic moiety in good yields (Table 1, entries 9-12). In this connection it should be mentioned that a recent literature report¹³ which describes the synthesis of alkyl β -keto esters employing a tin based super acid catalyst, failed with aromatic substrates. It is also clear from Table 1 that the conversion of ethyl ester to higher homologue appears to be efficient by this procedure (Table 1, entry 1) in excellent yield. It is important to note that chiral integrity of (-)-menthol is maintained under these reaction conditions (chiral alcohol is recovered by base hydrolysis of ester and its optical rotation is checked, Table 1, entry 5). It is noteworthy to mention that the reaction appears to be specific only for transformation of β -keto esters. Other esters like α -keto esters, γ -keto esters as well as normal esters failed to undergo the reaction (Table 1, entries 13-17).

In conclusion we have demonstrated that lithium perchlorate is an excellent catalyst for transestrification of β -keto esters essentially under neutral conditions besides enabling an easy work-up. The effectiveness of this protocol is manifested in its selectivity towards β -keto esters whereas other esters are found to be unreactive under these reaction conditions.



Scheme

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Entry	Ester	Alcohol	Product	Reaction Time (h)	Yield ^{a,b} (%)
1	O O OEt	CH ₃ (CH ₂) ₂ OH	O O Pr	2	93
2	O O OPr	CH ₃ (CH ₂) ₃ OH	OBu	2	88
3	O O OEt	PhCH ₂ OH	OCH ₂ Ph	2	94
4	O O OMe	он-		2.5	89
5	O O O OEt	С	O O OMn	3.5	79
6	O O O O O O O O O O O O O O O O O O O	HOCHC≡CH I CH(CH ₃) ₂	O O O O O O O O O O O O O O O O O O O	3	73
7	O O OEt	Ph ₃ COH	O O O O O O O CPh3	8	57
8	O O OEt			3	65
9	OEt	ОН		6	82
10	CH_2CO_2Me CO O O O	ОН		6	77
11	CH_2CO_2Me CO O O O O	ОН		6	71
12	COCH ₂ CO ₂ Et	ОН	CH_2CO_2 Ph CO	7	76
			UCH ₂ CU ₂ Me		

 $\begin{tabular}{ll} Table 1 & Lithium perchlorate catalyzed transesterification of β-keto esters $\end{tabular}$

Entry	Ester	Alcohol	Product	Reaction Time (h)	Yield ^{a,b} (%)
13	CH ₃ (CH ₂) ₄ CO ₂ Me	BuOH	No Reaction	10	
14	CH ₃ COCO ₂ Me	BuOH	No Reaction	10	
15	CH ₃ CO(CH ₂) ₂ CO ₂ Me	BuOH	No Reaction	10	
16	CNCH ₂ CO ₂ Me	BuOH	No Reaction	10	
17	Ph CO ₂ Me	BuOH	No Reaction	10	

 Table 1
 continued

a) Yields of pure isolated products. b) Products are characterised by their spectral analysis.

Table 2 Catalytic effect on transesterification of ethyl acetoacetate (5 mmol) with n-butanol (5 mmol)

Entry	Catalyst (mmol)	Reaction Time (h)	Yield ^{a,b} (%)	Entry	Catalyst (mmol)	Reaction Time (h)	Yield ^{a,b} (%)
1	None	2		6	NaClO ₄ (1.0)	6	60
2	LiClO ₄ (0.5)	2	60	7	FeClO ₄ (1.0)	2	30
3	LiClO ₄ (1.0)	2	93	8	FeClO ₄ (5.0)	2	80
4	LiClO ₄ (2.0)	2	93	9	LiBr (1.0)	2	50
5	NaClO ₄ (1.0)	2	30	10	LiBr (1.0)	6	90

a) Yields of pure isolated products. b) Products are characterised by their spectral analysis.

Typical procedure: Methyl 3-(3,4,5-trimethoxyphenyl)-3-oxo propionate (5 mmol), cinnamyl alcohol (5 mmol) and lithium perchlorate (1 mmol) in toluene (20 mL) was heated to 100 °C in a round bottom flask with distillation condenser to remove methanol. After completion (TLC) the reaction mixture was cooled, filtered and the filtrate was concentrated and chromatographed on SiO₂ (hexane-ethyl acetate, 9:1) to afford (*E*)-3-phenyl-2-propenyl 3-(3,4,5-trimethoxyphenyl)-3-oxopropanoate as a colourless liquid in excellent yield.

Yield: (77%); **IR** (neat) cm⁻¹: 3322, 1734, 1699; ¹**H NMR:** δ = (200 MHz, CDCl₃): 7.5-7.3 (m, 5H), 7.39 (s, 1H), 7.23 (s, 1H), 6.75 (d, J = 15 Hz, 1H), 6.30-6.20 (m, 1H) 4.8 (dd, J = 6 and 1.2 Hz, 2H), 4.05, 3.89 (s, 9H), [3.88, 5.5, 12.1] (s, 2H); ¹³**C NMR** : δ = (50 MHz, CDCl₃): 191, 167, 153, 143, 135, 134, 130, 128, 128, 126, 122, 106, 86, 65, 60, 56, 45; Anal. Calcd. for C₂₁H₂₂O₆(370.41): C, 68.10; H, 5.99. Found: C, 67. 90; H, 5.55

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