Received: 19 October 2011

(wileyonlinelibrary.com) DOI 10.1002/aoc.2826

Applied Organometallic

hemistry

AgOTf-catalyzed transesterification of β -keto esters

Accepted: 11 January 2012

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AgOTf proved to be an effective catalyst for the transesterification of β -keto esters with primary, secondary and tertiary alcohols. The products were obtained in high yield within a reasonable reaction time period. The kinetics of the transesterification reaction were also studied and the reaction was found to follow second-order kinetics. Copyright © 2012 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: transesterification; β -keto esters; AgOTf; Lewis acid; kinetics

Introduction

Among the various classical organic reactions, transesterification has enormous use in the laboratory and in industry. Transesterification of β -keto esters is a routinely utilized transformation in organic chemistry. The classical method for the synthesis of β -keto esters is by Claisen condensation between two esters or one ester and another carbonyl compound.^[1,2] Esters can also be synthesized from carboxylic acids and alcohols, but sometimes carboxylic acids are less soluble and difficult to subject to esterification. When the parent carboxylic acids are labile and difficult to isolate then transesterification becomes more advantageous.^[3] Among the esters, β -keto esters are of special interest because of their electrophilic and nucleophilic centers, making them a valuable synthon for the synthesis of natural products such as karrikinolide (KAR1), tetrahydrozerumbone, serricornine and trichodiene.^[4]

It is reported that the chelate complex of β -keto esters suppresses the activity of some pathogenic viruses through the formation of a coordinate bond to metal ions at the active site of the virus enzyme responsible for virus replication.^[5,6] Besides this, metal chelates of β -diketones find application in oils of biological origin, lubricating compositions and potential antiviral drugs.^[7]

Recently, transesterification has been affected by various transition metal catalysts such as NiCl₂, CuCl₂ and CoCl₂.^[3] Iron-based catalysts such as [Bu₄N][Fe(CO)₃(NO)]^[8] and Fe(acac)₃^[9] are also reported. Solid acid catalysts such as S-SnO₂,^[10] CuSO₄,^[11] montorillonite K-10,^[12] B₂O₃/ZrO₂,^[13] Nb₂O₅,^[14] zeolites^[15–18] and Amberlyst-15^[19] have also been used. Recent literature shows the application of ionic liquids^[20,21] and enzymes.^[22] Use of molecular sieves alone is also effective in transesterification of *β*-keto esters with higher alcohols.^[5,6] Recently, molecular iodine had been explored as a powerful catalyst for esterification and transesterification reactions, with good yields.^[23] Recently, Singh and Nolan have reported the synthesis of phosphorous esters by transesterification with NHC catalyst.^[24] Again, NaBH₄ is a common reducing reagent and alcoholic solutions of sodium borohydride are neither strongly acidic nor basic, which makes it suitable for transesterification of acid- and base-labile esters.^[25] Several Lewis acid catalysts such as

 $BF_3.OEt_2$,^[4] $BiCl_3$ ^[26] and $Bi(NO_3)_5$ ^[3] have also been reported for the transesterification of β -keto esters with alcohol.

Recently, we have used AgOTf as a mild Lewis acid catalyst in acylation reactions.^[27] Our continued success with a silver-based catalytic process^[28,29] prompted us to study the AgOTf-catalyzed transesterification of β -keto esters.

Results and Discussion

Transesterification of β -Keto Esters

Since transesterification is an equilibrium process, the reaction was performed with the aid of Dean–Stark apparatus to drive the reaction in the forward direction. As a model reaction, we used readily available ethyl acetoacetate and benzyl alcohol in the presence of a catalytic amount of Ag(I) salt.

Our next aim was to optimize the reaction conditions with various readily available Ag(I) salts in different solvents (Table 1). With AgOTf as catalyst, the reaction proceeds smoothly in boiling toluene to give the product in 90% isolated yield in 7 h. Highly polar solvents such as DMF, DMSO and 1,4-dioxane (Table 1, entries 3–5) give only 40%, 30% and 10% yield of product, respectively, with long reaction time. Under similar conditions, a low boiling solvent such as THF (Table 1, entry 1) at 80 °C gives 20% yield in 15 h and CH₃NO₂ (Table 1, entry 6) at 110 °C gave 70% yield in 10 h. Among the various Ag(I) salts, AgCl, AgBr and AgNO₃ (Table 1, entries 7–9) gave 5–30% yield in 24 h, whereas AgI and AgOAc (Table 1, entries 10 and 11) gave 50–70% yield in 15–20 h in boiling toluene. The reaction performed in toluene with AgOTf under ambient conditions took much longer and without AgOTf no product formation was observed (Table 1,

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Table 1.	Transesterification of ethy	yl acetoacetate with benz	yl alcohol in different solvents ar	d Ag(I) salts
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	+ F			
	0	solvent (10 ml)	V O Ph	
		110 °C		
Entry	Solvent	Ag(I) salt	Time (h) ^a	Yield (%) ^b
1	THF (80 °C)	AgOTf	15	20
2	Toluene	AgOTf	7	90
3	1,4-Dioxane	AgOTf	24	10
4	DMSO	AgOTf	12	30
5	DMF	AgOTf	15	40
6	CH ₃ NO ₂	AgOTf	10	70
7	Toluene	AgNO₃	24	5
8	Toluene	AgCl	24	5
9	Toluene	AgBr	24	30
10	Toluene	Agl	20	50
11	Toluene	AgOAc	15	70
12	Toluene	_	24	5
13	Toluene	AgOTf (RT)	24	30
14	Toluene	AgOTf (5 mol%)	10	80
15	Toluene	AgOTf (20 mol%)	6.5	89

^bIsolated yield after column chromatography of the crude product.

entries 12 and 13). A large amount of catalyst decreased the reaction time slightly but yield did not improve (Table 1, entry 15).

Having realized the optimized conditions, we investigated the transesterification of ethyl acetoacetate with various alcohols using AgOTf as catalyst. Several aromatic and aliphatic alcohols were subjected to the transesterification reaction (Table 2). The expected products were obtained in high yield. Aromatic alcohols containing electron-donating substituents (Table 2, entries 2–4) gave the corresponding acetoacetates in 6–8 h with around 90% yield, whereas alcohols containing electron-withdrawing substituent (Table 3, entry 5) took a much longer time.

In the case of allylic alcohols (Table 2, entries 7 and 8), it is known that allylic acetoacetates are difficult to prepare because there is a chance of their undergoing Carroll rearrangement,^[30,31] but here expected β -keto esters are obtained with good yield. In the case of aliphatic alcohols, going from primary to secondary to tertiary the bulkiness of carbon skeleton increases, reaction time increases and the yield of desired keto esters decreases in the same order (Table 2, entries 9–13). Thus tertiary alcohols are less active as the rate of reaction is greatly affected by steric effects.

Besides this, we have performed transesterification by varying the substituent on β -keto esters (Table 3).

The transesterification reaction is highly effected by the steric factor; thus *t*-butyl acetoacetates (Table 3, entry 4) become more active than the secondary and primary (Table 3, entries 1–3) in order to relieve the strain by transesterification. The proposed mechanism is shown in Scheme 1.

Coordination of Ag(I) to the oxygen increases the electrophilicity of the carbonyl carbon. When R' is CH_2COCH_3 , due to the electron-withdrawing effect of this group electrophilicity of the carbonyl carbon increases and attack by the alcohol becomes faster, so the reaction becomes faster as compared to when R' is the electron-donating group such as in normal esters.

Next, we decided to explore the kinetic studies of transesterification. Thus the transesterification of benzyl alcohol and *i*-butyl alcohol with ethyl acetoacetate (Table 2) and *t*-butyl acetoacetate with benzyl alcohol (Table 3) have been subjected to highperformance liquid chromatographic analysis to determine the starting materials and product present as a function of time. Kinetics were studied by monitoring the disappearance of ester and appearance of the corresponding product (Fig. 1).

Using Van't Hoff differential method, the order (*n*) and rate constant (*k*) have been determined. The rates of the reaction at different concentrations have been estimated by evaluating the slope of the tangent at each point on the curve (Fig. 1). With these data \log_{10} (rate) vs. \log_{10} (concentration) were plotted (Fig. 2). The order (*n*) and rate constant (*k*) were obtained from the slope of the line and its intercept on the \log_{10} (rate) axis. From Fig. 2, the rate of the reaction was found to be second order (n = 2.05) and the rate constant was $k = 9.18 \times 10^{-4} \, \text{Lmol}^{-1} \, \text{s}^{-1}$. Similarly, for the transesterification of *i*-butyl alcohol and ethyl acetoacetate; *t*-butyl acetoacetate and benzyl alcohol showed second-order kinetics ($n \approx 2$) with rate constant $3.9 \times 10^{-4} \, \text{Lmol}^{-1} \, \text{s}^{-1}$ and $9.09 \times 10^{-4} \, \text{Lmol}^{-1} \, \text{s}^{-1}$ respectively (see supporting information for details).

Conclusions

We have found that AgOTf is a versatile and mild Lewis acid catalyst for the transesterification of various β -keto esters. Various functionalized alcohols as well as β -keto esters undergo transesterification smoothly. Further studies to extend the scope of the Ag(I)-based catalytic system are in progress in our laboratory.

Table 2.	Transesterification of ethyl acetoacetate with va	arious alcohols ^a		
	0 0 	OH 10 mol % AgOTf 0 0 toluene 110 °C	O R + EtOH	
Entry	Alcohol	Product	Time (h) ^b	Yield (%) ^c
1	СН ₂ ОН		7	90
2	MeO-CH2OH	OMe	6.5	92
3	MeO CH ₂ OH	OMe	6	90
4	СІСН2ОН	O O OMe	8	84
5		O O NO2	19	70
6	ОН		10	80
7	ОН		9	85
8	Ph	0 0 O Ph	8	87
9	ОН		6	81
10	ОН		9	79
11	→он		15	78
12	Он		10	77
13	ОН		12	78
^a Reactior ^b Monitor	ed using thin-layer chromatography.	der reflux conditions.		

^clsolated yield after column chromatography of the crude product.

Experimental

Typical procedure for Transesterification of β -Keto Esters

A mixture of β -keto ester (for ethyl acetoacetate, 1.26 ml, 10 mmol), alcohol (for benzyl alcohol, 2.16 ml, 20 mmol) and the catalyst AgOTf (10 mol%, 0.256 g) in toluene (10 ml) was heated to reflux. The reaction mixture was connected to a Dean–Stark apparatus to remove the newly formed alcohol. After consumption of ester, the reaction mixture was concentrated and

extracted in dichloromethane. The residue was concentrated and purified by column chromatography using hexane and ethyl acetate as eluents. The spectroscopic characterization of all the compounds matches well with the literature.^[32-38] (see supporting information).

Acknowledgments

This work was supported by the Department of Science and Technology and the Council of Scientific and Industrial Research,

Table 3. Transesterification of benzyl alcohol with β -keto esters				
Entry	β -Keto ester	Product	Time (h) ^b	Yield (%) ^c
1	O O CH3	O O O Ph	10	79
2		O O U O Ph	7	83
3		O O O Ph	8	82
4	<u>i</u> i o	O O O Ph	6	85

^aReactions performed in toluene with 10 mol% AgOTf under reflux conditions.

^bMonitored using thin-layer chromatography.

^cIsolated yield after column chromatography of the crude product.



Scheme 1. Proposed mechanism of transesterification.



Figure 1. Concentration versus time in the conversion of ethylacetoacetate to benzylacetoacetate by AgOTf at 110 $^\circ\text{C}.$

New Delhi. The services of the NMR facility purchased under the FIST program, sponsored by the Department of Science and Technology, New Delhi, are gratefully acknowledged. R. D. thanks



Figure 2. Van't Hoff differential plot for the conversion of ethylacetoacetate to benzylacetoacetate by AgOTf at 110 °C.

the Council of Scientific and Industrial Research, New Delhi, for a research fellowship.

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