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Rate Accelerations in AgNO₃ Mediated Transesterification of β -Keto esters

Thummala Raja Mania^a, Yelike Hemanth Sriram^a, KuthathiBhaskara^a, Addula Kiran Kumar^a*, Kudle Karunakar Rao^b

^a Department of Chemistry, Osmania University, Telangana State, Hyderabad 500007, India

^b Department of Bio-Chemistry, Osmania University, Telangana State, Hyderabad 500007, India

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KEYWORDS

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Conventional

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ABSTRACT

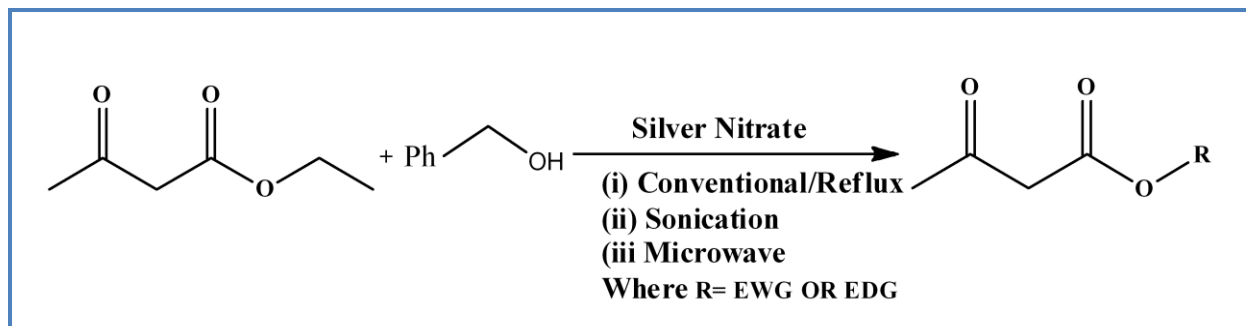
In the present study, AgNO₃ is employed as an effective catalyst for transesterification of β -keto esters with various alcohols under conventional and non-conventional conditions. The alcohols are easily converted into corresponding acetates in very good yields and less reaction times. However, a decrease in reaction times as well as moderate yields were observed when performed under non-conventional conditions such as Sonication and Microwave irradiation. Contrary to many other silver salts catalysts, AgNO₃ has shown remarkable levels of activity and stability towards transesterification reaction. The tendency in reaction rates was found to be MWAS (3-6 min) <<< Sonication (30-45 min) <<< Conventional (8-12 hrs).

*Corresponding author, email: kirankumaroucs@gmail.com

Department of Chemistry, Osmania University, Telangana State, Hyderabad 500007, India

Tel.: +91 9912483629

Graphical Abstract



Introduction

Transesterification is an organic reaction, has immense use in both laboratory and industry among all the classical organic reactions for the synthesis of pharmaceutical products, polymers and several other organic esters [1]. It is generally facilitated by the exchange of an organic group of an ester and the organic group of an alcohol. These reactions are mainly catalysed using acid catalysts [2]. They act as electrophile due to donation of proton to carbonyl group or base catalysts [3] and as nucleophile due to proton removal. Biocatalysts such as enzymes [4] are also used in some cases. Several protic acids [5] are also used as catalysts which are highly corrosive and are not eco-friendly, it is due to the fact that a large amount of unspent acid is sent out in the form of industrial waste which is not environmental friendly.

Transesterification of β -keto esters is a well-known transformation in synthetic organic Chemistry [6]. β -Keto esters were prepared by condensation reaction between an ester and another carbonyl compound [7]. β -Keto esters provide a substantial source for the production of natural products [8-11] with their electrophilic and nucleophilic centres.

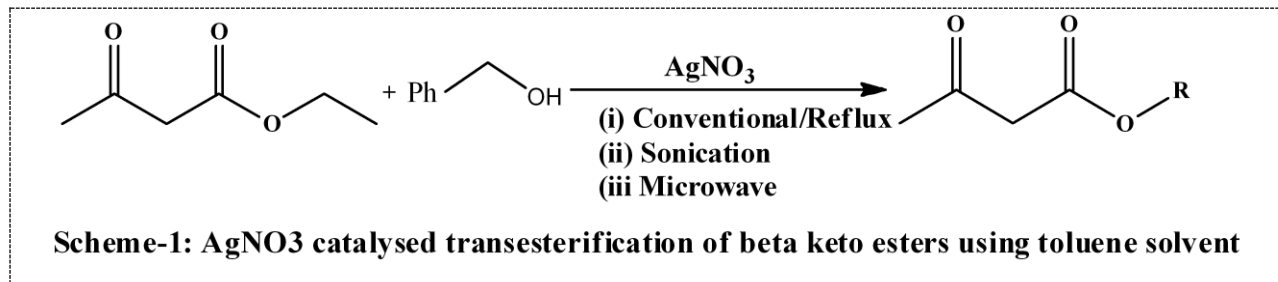
Several transformations have been reported showing the use of several solid acid catalysts such as zeolite H-FER [12], amberlyst-15 [13], Zinc-I₂[14] and several heterogeneous catalysts [15]. Recently, transesterification has also been carried out by certain iron based catalysts such as [Bu₄N][Fe(CO)₃(NO)] and Fe(acac)₃ [16, 17] which were also reported. In Ionic liquids [18, 19], molecular iodine [20] catalysed transesterification is also well established. However, many catalysts that are derived from heavy or rare metals could not serve the purpose for large-scale applications due to their drawbacks such as toxicity and extortionate prices.

As a result there has been an ever increasing demand for metal ions or metal-based species as reaction promoters which can serve the purpose in small amounts. Over the years, transition metals have been the source for exploring suitable catalysts because many of them are easily available, environmentally safe and economically viable. Transition metals can both lend and take

electrons from other molecules. By giving and taking electrons so easily, transition metal catalysts speed up reactions. Numerous metal complexes such as Ni, Cu, Co [21] have also been used as catalysts for transesterification.

Reactions which have been catalysed using silver salts with alcohols are well-known phenomenon in aqueous media. Very little work has been reported with the analogous reactions in non-aqueous media. Recently, acetylation reactions using AgOTf as a mild Lewis acid catalyst has been studied [22]. Encouraged by the earlier investigations and the obtained results [23, 24], we have characterized the use of AgNO₃ as efficient catalyst for β- Keto esters transesterification reactions using different alcohols under conventional, sonication and solvent free microwave conditions.

The obtained results were accumulated in Table 2. The resultant products were characterized by IR, ¹H, and ¹³C NMR Spectroscopy.



Experimental

All the chemicals were purchased from Aldrich or Arcos Organics and used without further purification. Analytical TLC was carried out using Merck aluminium-backed 0.2 mm silica gel 60 F-254 plates. Column chromatography was conducted using Merck silica gel 60 (230-400mesh). For Ultrasonically assisted reactions, a Sonicated bath (KQ-250B, China) was used. A flat transducer with a frequency of 40 kHz and voltage of 220V (with an output of 100 W electric power rating) was mounted at the bottom of the Sonication bath. The reaction vessel was placed inside the ultrasonic bath containing water. CEM laboratory microwave oven is used in this study for microwave assisted reactions.

General procedure for the transesterification under conventional Condition:

For condensation, the contents such as benzyl alcohol (10mmol), ethyl acetoacetate (10mmol), catalytic amount of AgNO₃ (5mmol) and solvent (toluene, 20mL) were taken in a previously cleaned in a round bottom flask and is subjected to reflux at 70°C-80°C for about 8 to 12 hours. After complete conversion as indicated by TLC, the reaction mixture was quenched with water, treated with dilute NaHCO₃ solution and followed by the addition of ethyl acetate. The organic layer was

separated, dried over Na_2SO_4 , concentrated under vacuum and purified with column chromatography using hexane: ethyl acetate as eluent to get pure product. Obtained product is characterized by NMR Spectroscopy studies.

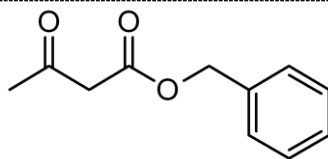
Oxo butanoates of certain aromatic alcohols such as benzyl, 4-methyl benzyl, Methoxy benzyl 3, 4-dimethoxy benzyl, 4-Chloro benzyl, 2-nitro benzyl Oxo butanoates are obtained respectively from the $AgNO_3$ (Silver nitrate) catalysed transesterification of benzyl, 4-methyl, Methoxy benzyl and 3, 4-dimethoxy benzyl, 4-chloro benzyl, 2-nitro benzyl alcohols according to the procedures described above under conventional and non-conventional conditions.

Benzyl 3-oxobutanoate: 1H NMR (300MHz, $CDCl_3$): 7.41(m, 5H, Ar-H), 7.32(s, 3H, $-CH_3$)

5.06(m, 2H, CH_2), 3.18(m, 2H, $-CH_2-$), 2.11(t, 3H, CH_3)

^{13}C NMR (75 MHz, $CDCl_3$): δ 200.4, 168.1, 136.1, 128.9, 127.6, 127.1, 66.1, 50.0, 30.3

BP=276 $^{\circ}C$; HRMS (EI) Calc. M: 192.2112, Found: 192.0786



(a)

The spectral data of the obtained products are demonstrated as the supplementary data in a different document.

Procedure for Ultrasonically assisted method:

For ultrasonically assisted reaction, the contents of the reaction such as benzyl alcohol (10mmol), ethyl acetoacetate (10mmol), catalytic amount of $AgNO_3$ (5mmol) and solvent (toluene, 20mL) were taken in a boiling tube placed in a sonication bath. A high energy sound wave of about 40 kHz frequency and voltage of 220V was mounted at the bottom of the Sonication bath. The mechanism of the reaction is discussed in the above section. The progress of the reaction is monitored by TLC. The work up procedure and characterization is the same as discussed in conventional method.

Procedure for Microwave assisted reaction:

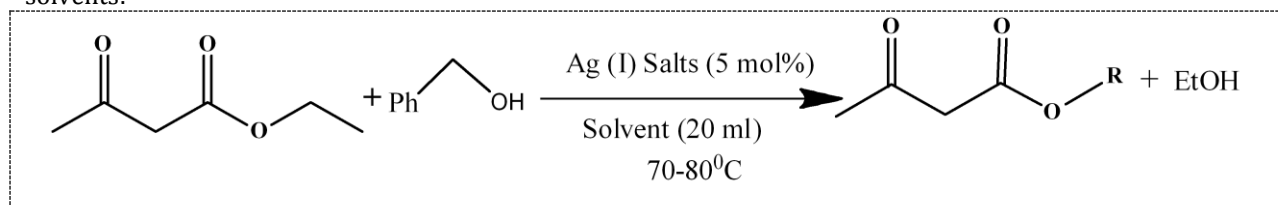
This is a solvent free technique in which the contents of the reaction such as benzyl alcohol (10mmol), ethyl acetoacetate (10mmol), catalytic amount of $AgNO_3$ (5mmol) are taken in a 50 mL beaker and mixed thoroughly. About 500 mg of silica gel was added to the mixture and heated (320 Watt) in a controlled microwave synthesizer. The progress of the reaction is monitored by TLC. The work up procedure and characterization is the same as discussed in conventional method.

Results and Discussion:

For AgNO₃ catalysed transesterification reaction, we took readily available ethyl acetoacetate with different alcohols (primary, secondary and tertiary) in toluene media.

Initially, we optimized the reaction conditions by taking the readily available silver salts in different solvents such as DCM, DCE, Methanol, Acetone, ACN, Nitro Methane, 1, 4-Dioxane, Carbon tetra fluoride and toluene. However, in boiling toluene, the reaction shown a yield of about 88% in just 8 hrs (entry 3), where as more polar solvents such as DCM, DCE, Methanol, Acetone (entries 1, 2 and 4, 5,) and 1, 4-Dioxane and nitro methane (entry 6 and 7) has shown 30%, 38%, 45%, 51%, 55%, 5% yields respectively. Under similar conditions, Low boiling solvent such as DCM (Table 1, entry 1) at 90°C gave 30% yield in 14 h and 1, 4-Dioxane (Table 1, entry 6) at 100 °C gave 38% yield in 12 h. Among the various Ag(I) salts, AgCl, AgBr (Table 1, entries 8 and 9) gave 55%, 61% yield in 24 h, where as AgI and AgOAc (Table 1, entries 10 and 11) gave 50–60% yield in 14–18 h in boiling toluene. Based on these transformations, we concluded that AgNO₃ is a suitable catalyst for transesterification of alcohols with reduced reaction times with two to five fold yield. The reaction is also performed when no AgNO₃ is added. This resulted in no further processing of the reaction. Observed data is shown in Table 1.

Table-1: Transesterification of ethyl acetoacetate with benzyl alcohol using Ag (I) salts and different solvents:



Entry	Solvent	Ag(I) Salt	R.T.(hrs)	Yield (%)
1	DCM	AgNO ₃	14	30
2	DCE	AgNO ₃	13	38
3	Toluene	AgNO ₃	8	88
4	Methanol	AgNO ₃	10	45
5	Acetone	AgNO ₃	10	51
6	1, 4-Dioxane	AgNO ₃	12	55
7	Nitro Methane	AgNO ₃	11	52
8	Toluene	AgCl	18	55
9	Toluene	AgBr	18	61
10	Toluene	AgI	14	50
11	Toluene	AgOAc	16	60

From the earlier investigation, we had performed transesterification reaction with $AgNO_3$ catalyst in toluene media using β -keto esters, ethyl acetoacetate and different alcohols in conventional condition (8-12hrs) at 70-80°C. Several aromatic and aliphatic alcohols have been imperilled to transesterification. All the data were compiled in Table 2.

Transesterification takes place by enhancing the electrophilic character of the carbonyl group. β -Keto esters esterify an alcohol in toluene media in order to form the desired keto ester derivatives. Acetoacetates of alcohols easily crystallize and are more soluble in organic solvents. All electron donating substituents (entry 2-5) have shown less reaction time with good yield where as in electron withdrawing substituents (entry 6) the reaction time was a little bit higher with quite stumpy yield. Aliphatic substituent alcohols experienced a bit lower yield and higher reaction time. This is because of the fact that as the size of the ring increases, bulkiness of the carbon skeleton increases. As a result, yield of the desired keto ester decreases with increased reaction time. So, lesser the ring size, greater is the yield of the product.

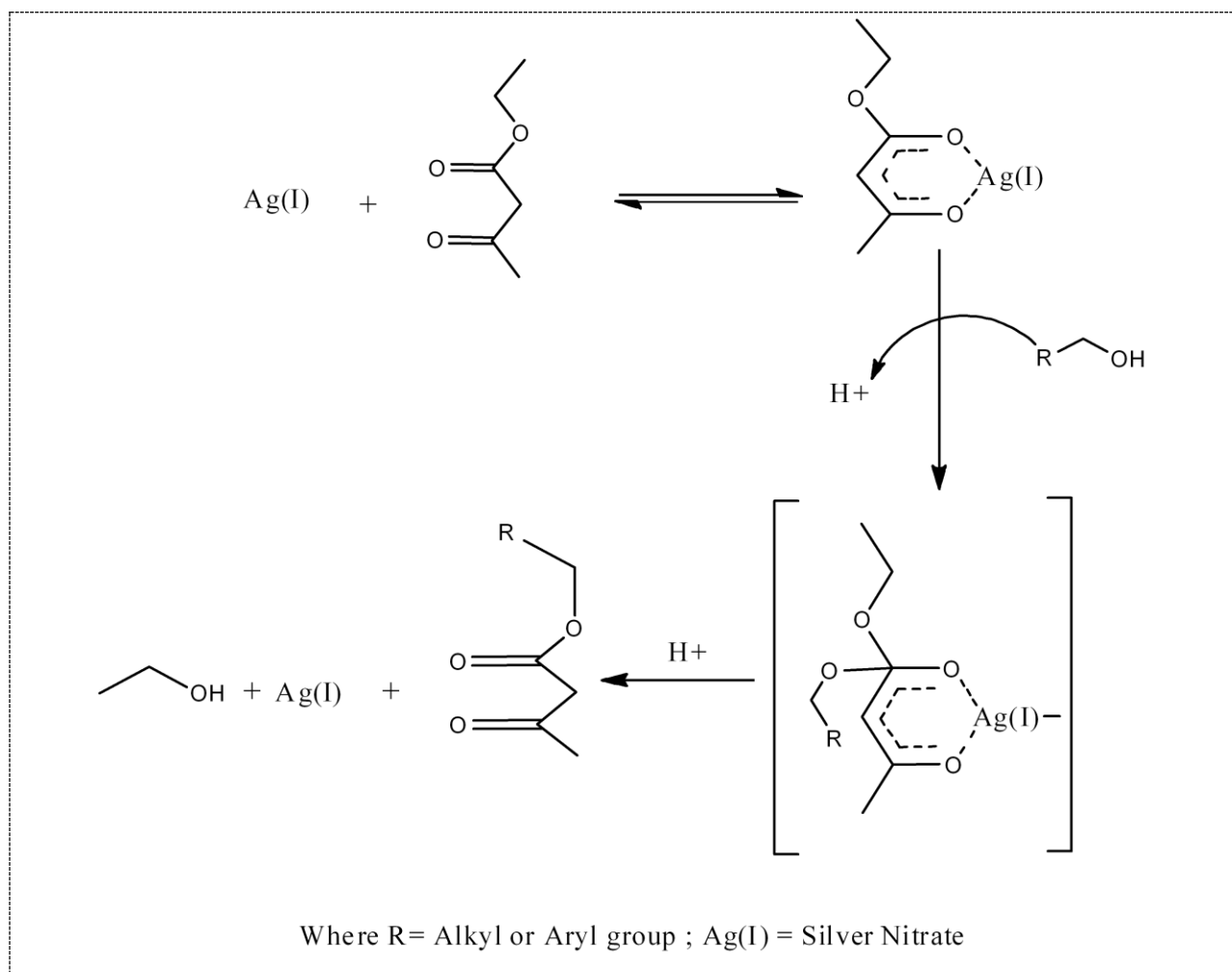
Similarly, as a comparative study, $AgNO_3$ catalysed transesterification is also carried out in sonication condition, the yields were found to be high and good as compared to conventional condition, the reaction occurred within 30-45 minutes [25, 26]. This is due to the fact that the reaction mixture is subjected to high energy sound waves when placed in a Sonication bath. Due to cavitation phenomenon, large amount of energy and pressure is released which destroys the attractive forces of molecules in the liquid phase, as a result, the reaction time gets reduced producing moderate yields. When transesterification was carried out in solvent free condition such as microwave [27], the reaction time is so far reduced to just 3-6 min depicting from good to excellent yields. During this phenomenon, Bulk activation of molecules in reaction mixture occurs as the reaction contents are heated directly without external heating. This also reduces the reaction time far better than conventional and sonication and many fold yield is observed.

The trend in reaction rate is shown as:

MWAS (3-6min) <<< Sonication (30-45 min) <<< Conventional

The proposed mechanism for transesterification is shown in the form of scheme-2.

All the resultant products were shown below in Table 2.



Scheme2. Mechanism of AgNO_3 catalysed transesterification of β - Ketoesters

S.No	Substrate	Product	Conventional		Sonication		Microwave	
			RT (hrs)	Yield (%)	RT (min)	Yield (%)	RT (min)	Yield (%)
1			8	89	30	90	3	91
2			9	82	35	83	3.5	83
3			11	83	39	85	4	86

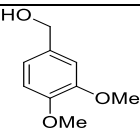
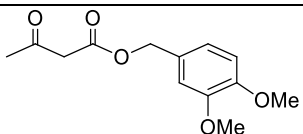
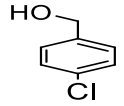
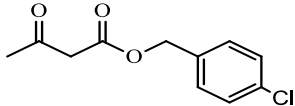
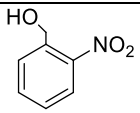
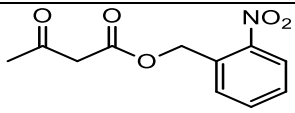
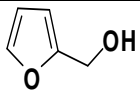
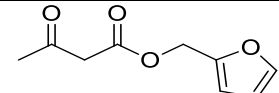
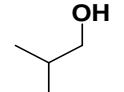
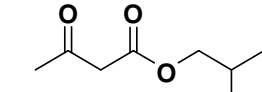
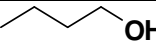
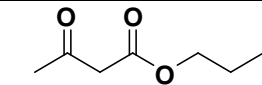
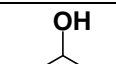
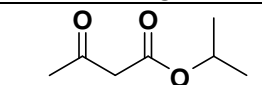
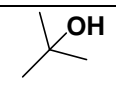
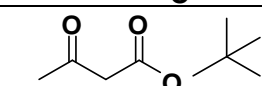
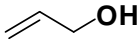
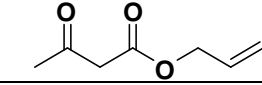
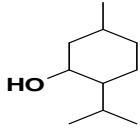
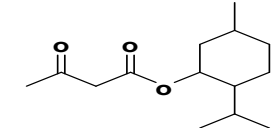
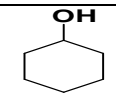
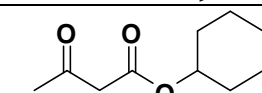
4			11.5	83	40	84	4	86
5			9	80	40	83	5	84
6			13	71	45	72	6	74
7			12	80	36	83	5.5	84
8			10	76	45	77	5	79
9			11	76	44	77	5	78
10			12	75	43	77	5	79
11			10.5	78	45	79	5.5	81
12			11.5	79	43	81	6	81
13			10.5	81	38	83	4.5	84
14			8.5	81	40	82	5	85

Table 2. AgNO_3 catalysed transesterification of β -keto esters with various Alcohols in

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