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tert-BuOK-Catalyzed condensation of ethyl diazoacetate to aldehydes and palladium-catalyzed 1,2-hydrogen migration for the synthesis of β-ketoesters under solvent-free conditions

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www.rsc.org/advances A mild and convenient method for the condensation of ethyl diazoacetate (EDA) with aldehydes catalyzed by *tert*-BuOK under solvent-free conditions was developed. The corresponding a-diazo- β -hydroxy esters were further converted into β -ketoesters through palladium-catalyzed 1,2-hydrogen migration under neat conditions. The two-step transformation exemplifies a simple method for the efficient and green synthesis of β -ketoesters.

Introduction

The development of environmentally benign and cost-efficient protocols for the purpose of green, sustainable chemistry has been in demand in both academic and industrial research.¹ A generally desirable process is the catalytic transformation of neat reactants with the least waste under mild reaction conditions with simplicity and cost-efficiency. Moreover, because of the increasing public concern regarding the harmful effects of organic solvents on the environment and human body, solvent-free organic reactions have been receiving more attention for many years due to their clean and environmentally friendly protocols as well as convenient product purification.² It is often claimed that 'the best solvent is no solvent' in modern organic chemistry.

α-Diazo-β-hydroxy esters are a class of versatile compounds endowed with a wealth of potential synthetic applications.³ For example, a variety of β-substituted α-diazo carbonyl compounds can be synthesized from them just through simple nucleophilic substitution, and can then undergo various reactions through transition metal-catalyzed diazo decomposition.⁴ Among those, 1,2-migration to an electrophilic carbon center is a common transformation.^{5,6} It has been demonstrated that hydride,⁵ alkyl, aryl, vinyl, acetylenyl and even thiol groups can act as 1,2migration groups under specific reaction conditions.⁶ Although various Lewis acids including Rh₂(OAc)₄, ZnCl₂, ZnBr₂, SnCl₂, BF₃, GeCl₂, AlCl₃ and SnCl₄ have been reported to effect the 1,2migration transformation,^{3,7} the corresponding reaction using palladium as the catalyst is unknown to the best of our knowledge. Moreover, most of these reactions were performed in organic solvents under anhydrous conditions. According to the demands of green chemistry, further development of more efficient and environmentally friendly methodologies in this area continues to be desirable. Herein, we wish to report (1) the *tert*-BuOK-catalyzed condensation of ethyl diazoacetate (EDA) with aldehydes under solvent-free conditions, and (2) the palladium-catalyzed 1,2hydrogen migration of corresponding α -diazo- β -hydroxy esters under neat conditions. This two-step transformation exemplifies a simple method for the efficient and green synthesis of β -ketoesters (Scheme 1).

Results and discussion

A common method for the preparation of α -diazo- β -hydroxy esters is the nucleophilic addition of EDA to carbonyl compounds, for which deprotonation of EDA is needed. This is usually achieved by treating the diazo compound with excess strong base, such as butyllithium, lithium diisopropylamide and sodium hydride under absolutely anhydrous conditions.⁸ Wang and his co-workers have developed a mild DBU-catalyzed condensation of acyldiazomethanes to aldehydes affording β -hydroxy α -diazo carbonyl compounds in CH₃CN⁹ and also in water.¹⁰ However, the efficiency of this transformation in water is not satisfactory, because a long reaction time (24–168 h) is necessary in order to complete the reactions. Here, we describe an efficient *tert*-BuOKcatalyzed condensation of EDA with aldehydes under solvent-free conditions.

Firstly, we employed EDA **1** and benzaldehyde **2a** as substrates to investigate this solvent-free condensation reaction. The effectiveness of various bases was carefully examined for this process.



Scheme 1 The synthesis of β-ketoesters under solvent-free conditions.

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N₂ H ^{⊥⊥} CO	D ₂ Et +	base r.t., neat	OH CO ₂ Et
1	2a		3a
Entry	Base (mol%)	Time $(h)^a$	Yield $(\%)^b$
1	tert-BuOK (20)	2	87
2	KOH (20)	6	53
3	$K_2 CO_3 (20)$	18	50
4	Cs_2CO_3 (20)	6	75
5	KOAc (20)	18	0
6	$Et_3N(20)$	18	0
7	DBU (20)	2	60
8	tert-BuOK (10)	2	70
9	tert-BuOK (30)	2	84

Table 1 The effect of the base on the condensation reaction of EDA 1 with benzaldehyde 2a under solvent-free conditions $^{\rm a}$

 a Reactions were carried out with 0.6 mmol of 1, 0.5 mmol of 2a at room temperature. b Yield of isolated pure products.

The results are summarized in Table 1. *tert*-BuOK was found to be the most suitable base for this transformation, giving the corresponding α -diazo- β -hydroxy ester **3a** in 87% yield after reaction at room temperature for 2 h (Table 1, entry 1). Other bases, such as KOH, K₂CO₃ and Cs₂CO₃, could also afford the condensation product **3a**, albeit with slightly lower yields (Table 1, entries 2–4). However, when KOAc and Et₃N were used in this reaction, no product was obtained (Table 1, entries 5 and 6). It was noted that DBU was also suitable for this solvent-free reaction, giving product **3a** in 60% yield (Table 1, entry 7). Encouraged by these results, we carefully examined the effect of the catalyst loading on this solvent-free reaction (Table 1, entries 8 and 9). The results indicate that 20 mol% of *tert*-BuOK gave the best yield of the product under solvent-free conditions at ambient temperature.

To evaluate the scope of this new method, the optimized conditions were then applied to the synthesis of α -diazo- β -hydroxy esters by condensation of various aldehydes with EDA and without any solvent, as shown in Table 2. Most aromatic aldehydes reacted efficiently to afford the corresponding α -diazo- β -hydroxy esters in moderate to good yields (Table 2, entries 1-13). As anticipated, the reaction of an aromatic aldehyde bearing a strong electronwithdrawing substituent, such as a m-nitro group, gave the product 3i in 88% yield (Table 2, entry 9), while an aromatic aldehyde with a strong electron-donating substituent, such as a *p*-methoxy group, could only provide the product 3k in 39% yield (Table 2, entry 11). Moreover, this approach was also applicable to heteroaromatic aldehydes to give the condensation products in high yields (Table 2, entries 12 and 13). Importantly, aliphatic aldehydes were also tolerated, although the yields were lower compared to the reaction with aromatic aldehydes (Table 2, entries 14-17).

Having prepared a variety of α -diazo- β -hydroxy esters, we conceived of this solvent-free method being applied to metalcatalyzed diazo decomposition reactions. Although metal-catalyzed

 Table 2 tert-BuOK-Catalyzed condensation reactions of EDA 1 with various aldehydes 2a-q under solvent-free conditions^a

N₂ H ^{⊥⊥} C 1	CO₂Et + 0 2 a-q	<i>tert</i> -BuOK (20 mol%) r.t., neat	OH R CO ₂ Et N ₂ 3a-q
Entry	2, R	Reaction time (h)	3, Yield $(\%)^{b}$
1 2 3 4 5 6 6 7 8 9 10 11 12 13	2a, Ph 2b, p -ClC ₆ H ₄ 2c, p -BrC ₆ H ₄ 2d, p -FC ₆ H ₄ 2e, o -ClC ₆ H ₄ 2e, o -ClC ₆ H ₄ 2g, m_ip -Cl ₂ C ₆ H ₄ 2g, m_ip -Cl ₂ C ₆ H ₄ 2i, m -NO ₂ C ₆ H ₄ 2i, m -NO ₂ C ₆ H ₄ 2i, p -CH ₃ C ₆ H ₄ 2k, p -CH ₃ OC ₆ H ₄ 2l, 2 -Pyridyl 2m, 2 -Thienyl 2m, CH CH	2 2 0.5 0.5 0.5 0.5 2 0.5 2 1.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0	3a, 87 3b, 80 3c, 72 3d, 82 3e, 92 3f, 94 3g, 90 3h, 77 3i, 88 3j, 67 3k, 39 3l, 73 3m, 75 2n, 56
14 15 16 17	20 , $CH_3CH_2CH_2$ 20 , $CH_3CH_2CH_2$ 2p , $(CH_3)_2CH$ 2q , $PhCH_2CH_2$	0.5 0.5 0.5	30, 50 30, 69 3p, 70 3q, 87

^{*a*} Reactions were carried out with 0.6 mmol of **1** and 0.5 mmol of aldehydes **2a–q** at room temperature under neat conditions. ^{*b*} Yield of isolated pure products.

1,2-hydrogen migration of α -diazo- β -hydroxy esters has been studied in detail to afford synthetically useful β -keto esters, there are only two reports of this transformation using water as a green medium.¹¹ Moreover, to the best of our knowledge, metalcatalyzed diazo decomposition of α -diazo- β -hydroxy esters under solvent-free conditions has not been reported. Encouraged by these findings and as a continuation of our research interest in green chemistry, we herein report a palladium-catalyzed reaction of α -diazo- β -hydroxy esters under neat conditions.

	OH CO ₂ Et <u>catalys</u> N ₂ r.	st, neat	O O OEt
Entry	Catalyst (mol%)	Reaction time	Yield $(\%)^b$
1	$Rh_2(OAc)_4(2)$	20 min	88
2	$CuSO_4(2)$	2 h	65
3	$Pd(OAc)_2(2)$	0.5 h	67
4	$PdCl_2(2)$	2.5 h	79
5	$Pd_2(dba)_3$ (2)	0.5 h	67
6	$PdCl_2(PhCN)_2$ (2)	0.5 h	81
7	$PdCl_2(PPh_3)_2(2)$	5 h	96

Table 3 Metal-catalyzed diazo decomposition under solvent-free conditions^a

^{*a*} Reactions were carried out with 0.5 mmol of **3a** at room temperature under neat conditions. ^{*b*} Yield of isolated pure products.

Ethyl 2-diazo-3-hydroxy-3-phenylpropanoate 3a was first chosen as the substrate to investigate the diazo decomposition reaction under solvent-free conditions (Table 3). When we treated 3a in the presence of Rh₂(OAc)₄ at room temperature without any solvent, the reaction was completed within 20 min. As expected, 1,2hydrogen migration product 4a was isolated in 88% yield accompanied with a trace of the 1,2-phenyl migration product (Table 3, entry 1). Next, other metal salts were carefully tested in this solvent-free reaction to find a cheaper and more easily available catalyst. It was found that CuSO4 was also suitable for this transformation, giving the β -keto ester 4a in moderate yield (Table 3, entry 2). Interestingly, when $Pd(OAc)_2$ was used as the catalyst in this reaction, the 1,2-hydrogen migration product 4a was isolated with 67% yield (Table 3, entry 3). A further screening of palladium catalysts revealed that other rare earth metal salts, such as PdCl₂, Pd₂(dba)₃, and PdCl₂(PhCN)₂, behaved similarly, giving the desired product in 79, 67, and 81% yield, respectively (Table 3, entries 4-6). However, the most effective catalyst turned out to be $PdCl_2(PPh_3)_2$ (2 mol%), furnishing the product in 96% vield (Table 3, entry 7).

Subsequently, we examined the scope of this palladiumcatalyzed diazo decomposition reaction of various α -diazo- β -hydroxy esters under solvent-free conditions, as shown in Table 4. It was found that substrates with a phenyl ring bearing a halogen atom generally gave excellent yields of the β -keto ester products, regardless of the position of the substituent on the phenyl ring (Table 4, entries 1–7). However, it should be noted that the above reaction conditions did not work for solid substrates

Table 4 Palladium-catalyzed diazo decomposition reaction of various α -diazo- β -hydroxy esters under solvent-free conditions^a



^{*a*} Reactions were carried out with 1 equiv. of α-diazo-β-hydroxy esters **3a-p** and 0.02 equiv. of $PdCl_2(PPh_3)_2$ at room temperature under neat conditions. ^{*b*} Yield of isolated pure products. ^{*c*} The reactant and catalyst could not be mixed effectively.



Scheme 2 Two-step one-pot reaction under solvent-free conditions.

such as β -(2-nitrophenyl) and β -(3-nitrophenyl) substituted α -diazo- β -hydroxy esters (Table 4, entries 8 and 9). Moreover, this method worked well even with β -2-pyridyl and β -2-thienyl substituted substrates, giving the desired products in high yields (Table 4, entries 12 and 13). Surprisingly, when β -ethyl substituted substrate **3n** was subjected to this reaction, only a trace of product was formed (Table 4, entry 14), while other β -aliphatic substituted substrates reacted smoothly to produce β -keto esters in moderate yields (Table 4, entries 15 and 16).

Finally, the transformation of the two-step reaction to a direct one-pot conversion of aldehydes to β -keto esters was explored. Thus, aldehydes **2a** and **2k** were treated with EDA in the presence of 20 mol% *tert*-BuOK at room temperature. After completion of the condensation, 2 mol% PdCl₂(PPh₃)₂ was added directly to the resulting mixture and stirred for several hours. After the workup procedure, β -keto esters **4a** and **4k** were isolated in 60% and 37% overall yields, respectively (Scheme 2).

On the basis of the results presented above and the previous understanding of this type of transition-metal-catalyzed diazo decomposition reaction,^{5,6} we conceived that this Pd-catalyzed 1,2-hydrogen migration reaction may proceed *via* a Pd carbene intermediate, as shown in Scheme 3. It has been noted that the long reaction time of the 1,2-hydrogen migration using a palladium catalyst can be attributed to the electron-donating effect of triphenylphosphine in PdCl₂(PPh₃)₂, which decelerates the formation progress of the Pd carbene intermediate.

Conclusions

In summary, we have developed a mild and convenient method for the condensation of EDA with aldehydes catalyzed by *tert*-BuOK under solvent-free conditions. The corresponding α -diazo- β -hydroxy esters were further converted into β -ketoesters through palladium-catalyzed 1,2-hydrogen migration under neat condi-



Scheme 3 Possible reaction pathway of the Pd-catalyzed 1,2-hydrogen migration reaction.

tions. The two-step transformation exemplifies a simple method for the efficient and green synthesis of β -ketoesters.

Experimental

General procedure for the *tert*-BuOK-catalyzed condensation reaction of EDA with aldehydes

To a 10 mL flask with a stir bar were added aldehyde 2 (0.5 mmol), EDA 1 (0.6 mmol) and *tert*-BuOK (0.1 mmol), and the mixture was stirred vigorously at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting mixture was separated directly by flash column chromatography over silica gel to afford corresponding α -diazo- β -hydroxy ester 3.

General procedure for the palladium-catalyzed diazo decomposition reaction of α -diazo- β -hydroxy esters under solvent-free conditions

To a 10 mL flask with a stir bar were added α -diazo- β -hydroxyester 3 (0.5 mmol) and PdCl₂(PPh₃)₂ (0.01 mmol), and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting mixture was isolated by flash column chromatography on silica gel to give corresponding β -keto ester 4.

All of these α -diazo- β -hydroxy esters 3 and β -keto esters 4 are known compounds and were easily identified by comparison of their spectroscopic data with those previously reported.^{10–12}

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