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$CuSO_4$-catalyzed diazo decomposition in water: a practical synthesis of β-keto esters

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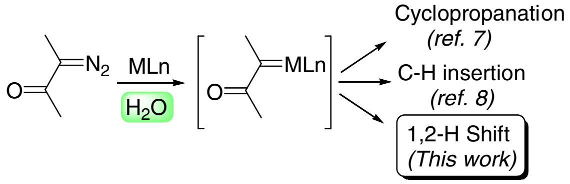
Abstract—$CuSO_4$ was found to be an efficient catalyst for the diazo decomposition of β-hydroxy α-diazoesters in water. 1,2-H shift occurred efficiently to give β-keto esters in high yields. No O–H bond insertion products were identified.

β-Keto esters are multicoupling reagents having both electrophilic carbonyl and nucleophilic carbon, which make them valuable intermediates for the synthesis of complex molecules. This type of compound is one of the basic building blocks in total synthesis.[1] Therefore, many methods have been developed to synthesize β-keto esters. Among these methods, the condensation of ethyl diazoacetate (EDA) with aldehydes catalyzed by acids is a facile and efficient way.[2,3] This reaction has been catalyzed by a variety of Lewis acids and Brønsted acids such as BF_3, $ZnCl_2$, $ZnBr_2$, $AlCl_3$, $SnCl_2$, $GeCl_2$, $SnCl_4$, $NbCl_5$, HBF_4, zeolite and montmorillonite.[3] Another approach to prepare the β-keto esters from aldehydes and EDA involved a two-step procedure.[4] First, the aldol-type condensation of aldehydes and EDA formed α-diazo-β-hydroxyesters. Then, metal-catalyzed decomposition of α-diazo-β-hydroxyesters afforded β-keto esters. However, these reactions were all performed in organic solvent under an anhydrous condition. Recently, Nishida and co-workers have reported the PTC-promoted one-pot synthesis of α-diazo-β-hydroxyesters from NaN_3 under aqueous basic conditions.[5]

Metal-catalyzed diazo decomposition is usually performed in dry organic solvent due to the high reactivity of the metal carbene intermediate, which could react with water to give O–H insertion product. Water as the most inexpensive and environmentally benign solvent has been widely used for organic reactions over the past decade.[6] Recently, several groups have been exploring the transition metal-catalyzed reaction of α-diazocarbonyl compounds in water. Charette and Wurz demonstrated that cyclopropanation reactions involving ethyl diazoacetate and olefins proceeded with a high efficiency in water using Rh(II) carboxylates.[7] Later Afonso and co-workers reported that $Rh_2(OAc)_4$-catalyzed intramolecular C–H insertion of diazo substrates could be efficiently performed in water.[8] More recently Francis and Antos found that metallocarbenoids derived from stabilized vinyl diazo compounds can react with 3-methylindole in a highly efficient manner in an aqueous solution. This reaction has been used to modify tryptophan residues on protein substrates.[9] However, to the best of our knowledge, metal-catalyzed decomposition of the α-diazo-β-hydroxyesters in water has not been reported. Encouraged by these results and as a continuation of our research interest in 1,2-migration of metal carbene,[10] we report here the $CuSO_4$-catalyzed reaction of α-diazo-β-hydroxyesters in water.



Initially, we chose ethyl 2-diazo-3-hydroxy-3-phenylpropanoate **1a** as the substrate to investigate the reaction in water (Table 1). The decomposition of **1a** could

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Keywords: Diazo compounds; Carbenoids; 1,2-H shift; β-Keto esters; Water as solvent.

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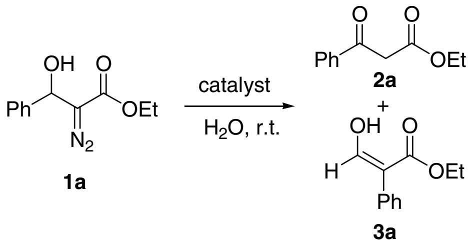
afford two products: 1,2-hydrogen migration to give β-keto ester **2a**, and 1,2-phenyl migration to afford **3a**. In most cases 1,2-hydrogen migration was predominant.[4] When we treated **1a** in 5 mL water in the presence of $Rh_2(OAc)_4$, the reaction finished within 20 min. As expected, **2a** was isolated in a 91% yield (Table 1, entry 1). No water insertion product was obtained. However, it should be noted that rhodium(II) catalyst is a very expensive catalyst. Consequently, we next aim to find a cheaper and more easily available catalyst.

We were delighted to find that the decomposition of **1a** catalyzed by 10 mol % $CuSO_4$ gave **2a** in a 79% yield in 16 h (Table 1, entry 2). The catalyst loading could be reduced to 1 mol % (entries 3 and 4). Other catalysts were also examined. Using 10 mol % $MgSO_4$ or $ZnCl_2$ led to very low conversions of the starting materials even after 24 h (entries 5 and 6). Surprisingly, when catalyzed by 5 mol % $FeCl_3{\cdot}6H_2O$, 1,2-phenyl migration product **3a** was obtained as a major product. Considering the easy hydrolysis of $FeCl_3$ to generate HCl in water, we speculated that protonic acid might be the real catalyst in this case. As expected, when 15 mol % HCl was used as a catalyst similar result was observed (Table 1, entries 7 and 8). More recently, Fructos and co-workers described the first example of a gold-based catalyst for the decomposition of ethyl diazoacetate.[11] Hence, gold catalysts were also explored in our system. The reaction was completed within 20 min when 2 mol % AuCl was used, whereas longer reaction times (20 h) were required when $AuCl_3$ was involved. In both cases **2a** was separated as the major product (Table 1, entries 9 and 10).

Table 1. Diazo decomposition in water



Entry	Catalyst (mol %)	Reaction time[a]	Yield[b] (%)	
			2a	3a
1	$Rh_2(OAc)_4$ (0.5)	20 min	91	—[c]
2	$CuSO_4{\cdot}5H_2O$ (10)	16 h	79	—
3	$CuSO_4{\cdot}5H_2O$ (5)	16 h	96	—
4	$CuSO_4{\cdot}5H_2O$ (1)	24 h	91	—
5	$MgSO_4$	24 h	<10[d]	—
6	$ZnCl_2$	24 h	<10[d]	—
7	$FeCl_3{\cdot}6H_2O$ (5)	16 h	29	58
8	HCl (15)	3 h	28	56
9	AuCl (2)	20 min	79	Trace
10	$AuCl_3$ (2)	20 h	69	Trace
11[e]	$CuSO_4$ (10)	72 h	78	—

[a] Reaction conditions: Diazo substrate **1a** (0.3 mmol) was stirred with catalyst in 5 mL water.
[b] Isolated yields after column chromatography.
[c] Not observed in TLC.
[d] Estimated by TLC.
[e] The reaction performed in CH_2Cl_2 at room temperature.

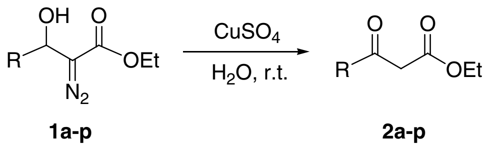
For comparison, the decomposition of **1a** catalyzed by $CuSO_4$ in CH_2Cl_2 was also tested. The reaction proceeded much slower than in water (Table 1, entry 11).

Subsequently, with 1 or 5 mol % $CuSO_4$ as the catalyst, various α-diazo-β-hydroxyesters were decomposed in water to afford β-keto esters in good to excellent yields (Table 2).[12] A range of β-aryl substituted substrates were suitable for this reaction, regardless of the position and electronic property of the substituent in the phenyl ring (Table 2, entries 1–9). β-Aliphatic substituted substrates also reacted smoothly to generate β-keto esters in high yields (Table 2, entries 11–14). This method even worked with β-2-furanyl, alkenyl and alkynyl substituted substrates though the yields were moderate (Table 2, entries 10, 15 and 16). The reaction time ranged from 30 min to 39 h, which were also affected to some extent by the situation of stirring, as well as the solubility of the substrate in water. For example, **1k** can totally dissolve in water, and the reaction was completed in 1 h. For diazo compounds **1d–f** and **1n**, 5 mol % $CuSO_4$ was used instead because the reaction was too slow when carried out with 1 mol % catalyst loading.

It should be noted that the above reaction conditions did not work well for the solid substrates such as β-(4-methoxyphenyl), β-(2,4-dichlorophenyl) and β-(2,6-dichlorophenyl) substituted α-diazo-β-hydroxyesters. Moreover, this approach was not suitable for β,β-disubstituted α-diazo-β-hydroxyesters.

In summary, we have demonstrated that the decomposition of α-diazo-β-hydroxyesters catalyzed by $CuSO_4$ can be efficiently performed in water to afford β-keto esters in high yields. This method has the following advanta-

Table 2. $CuSO_4$-catalyzed diazo decomposition in water[12]



Entry	Diazo compounds (R =)	Reaction time	Yield[a] (%)
1	**1a**, C_6H_5	24 h	91
2	**1b**, *o*-$CH_3C_6H_4$	39 h	88
3	**1c**, *m*-BrC_6H_4	39 h	90
4[b]	**1d**, *m*-CNC_6H_4	4 h	84
5[b]	**1e**, *m*-$CF_3C_6H_4$	36 h	81
6[b]	**1f**, *p*-$CH_3C_6H_4$	4 h	84
7	**1g**, *p*-FC_6H_4	30 min	92
8	**1h**, *p*-ClC_6H_4	21 h	86
9	**1i**, 3,5-$(MeO)_2C_6H_3$	1 h	89
10	**1j**, 2-Furanyl	14 h	41
11	**1k**, CH_3CH_2	1 h	72
12	**1l**, $CH_3(CH_2)_5$	5 h	92
13	**1m**, $(CH_3)_2CHCH_2$	24 h	90
14[b]	**1n**, cyclopentyl	3 h	91
15	**1o**, *trans*-$C_6H_5CH{=}CH$	5 h	69
16	**1p**, $C_6H_5C{\equiv}C$	20 h	53

[a] Isolated yields after column chromatography.
[b] 5 mol % $CuSO_4{\cdot}5H_2O$ was used in these cases. For other substrates, 1 mol % $CuSO_4{\cdot}5H_2O$ was applied.

ges: (1) water (the most 'green' solvent) as solvent; (2) an inexpensive and easily available catalyst; (3) low catalyst loading; (4) the only byproduct is nitrogen. These advantages should enable this reaction to become a useful preparative method of β-keto esters. Other metallocarbenoid reactions in water are under investigation in our group.

Acknowledgements

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12. General procedure. *Caution*: All diazo compounds are highly toxic or presumed to be toxic. Diazo compounds are potentially explosive. They should be handled with care in a well-ventilated fumehood. α-Diazo-β-hydroxyesters **1a**–**p** (0.3 mmol) was charged in a 25 mL round-bottomed flask, 5 mL water was added followed by $CuSO_4\cdot 5H_2O$ (0.003 or 0.015 mmol), the mixture was stirred at room temperature until complete disappearance of the diazo substrate. The reaction mixture was then extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column (petroleum ether–EtOAc = 5:1–10:1) to afford β-keto esters **2a**–**p**.