

# A modified and green Dakin–West reaction: An efficient and convenient method for a one-pot synthesis of $\beta$ -acetamido carbonyl compounds

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Received 7 January 2007; received in revised form 15 February 2007; accepted 16 February 2007

Available online 22 February 2007

## Abstract

An efficient and improved procedure for the synthesis of  $\beta$ -acetamido carbonyl compounds is developed in the presence of trimethylsilyl chloride by a heteropolyacid catalyzed three-component coupling protocol.

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**Keywords:** Multi-component reactions; Dakin–West; Heteropolyacid;  $\beta$ -Acetamido ketones; Trimethylsilyl chloride

## 1. Introduction

Today, with the emergence of high-speed parallel synthesis, the multi-component reaction (MCR) is widely employed for the rapid assembly of arrays with high molecular diversity [1]. Coupled with a post-condensation modification, the power of these reactions is increased even further, giving rise to a plethora of complex, pharmacologically relevant templates for screening purposes [2].

$\beta$ -Acetamido ketones are versatile intermediates because their skeletons exist in a number of biologically important compounds [3,4]. However, despite intensive attempts, only a handful of general methodologies for their construction is available. Among these methods the best known route is the Dakin–West reaction [5], which involves the condensation of an  $\alpha$ -amino acid with acetic anhydride in the presence of a base to afford the  $\alpha$ -acetamido ketones [6]. Iqbal and co-workers proposed another procedure for the formation of these compounds through the condensation of acetophenone, an aryl aldehyde and acetyl chloride in acetonitrile in the presence of  $\text{CoCl}_2$  [7] or montmorillonit K-10 clay [8]. Although, this method is valuable, it has a long reaction time (7 h).

The problems associated with the handling and disposal of the inorganic acids, and their environmental hazards have increased

our interest to develop alternative procedures using solid acid catalysts [9–18]. Because of their super-acidic properties, heteropolyacids, HPAs, can be used in a variety of organic reactions. In continuation of our investigations on the synthesis of  $\beta$ -acetamido ketones [9] and MCRs [10], herein we wish to report a new methodology for the synthesis of  $\beta$ -acetamido ketones using trimethylsilyl chloride instead of acetyl chloride in the presence of a wide range of heteropolyacids, including: Keggin, Wells–Dawson and Preyssler type (Scheme 1).

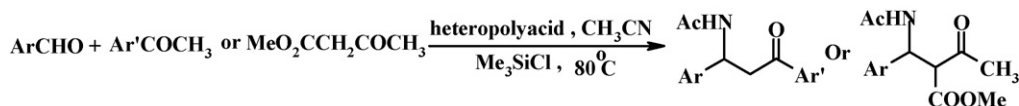
## 2. Experimental

All compounds were known and their physical and spectroscopic data were compared with those of authentic samples and found to be identical [20]. Yields are based on GC analysis.

### 2.1. Synthesis of $\beta$ -acetamido ketone and esters: general procedure

A mixture of Ketone or methyl acetoacetate (5 mmol), aldehyde (5.5 mmol) and trimethylsilyl chloride (15 mmol) in acetonitrile (25 mL) treated with a catalytic amount of  $\text{H}_3[\text{PW}_{12}\text{O}_{40}]$  (1 mol%) at 80 °C. The progress of reaction was monitored by TLC and GC. After completion of the reaction, the mixture was filtered to separate the catalyst and then the solvent was evaporated to dryness under reduced pressure. The pure products could be obtained by crystallization from a mixture of ethanol and water.

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Scheme 1. Synthesis of  $\beta$ -acetamido carbonyl compounds using trimethylsilyl chloride instead of acetyl chloride in the presence of a catalytic amount of a variety of heteropolyacids.

## 2.2. Reusability of catalyst

The recycled catalyst could be washed with dichloromethane and subjected to a second run of the reaction process with the same substrate. The results of the first experiment and subsequent experiments were almost consistent in yields (70, 67 and 65% after three runs).

### 2.2.1. Selected data

Entry 2, Table 3:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.98 (s, 3H), 3.36–3.42 (dd,  $J=6.4, 17.2$  Hz, 1H), 3.69–3.75 (dd,  $J=5.6, 17.2$  Hz, 1H), 3.74 (s, 3H), 5.47–5.51 (m, 1H), 6.64–6.66 (d,  $J=7.2$  Hz, 1H), 6.80–6.84 (m, 2H), 7.23–7.25 (d,  $J=8.8$  Hz, 2H), 7.41–7.45 (t,  $J=7.8$  Hz, 2H), 7.53–7.57 (t,  $J=7.6$  Hz, 1H), 7.88–7.91 (d,  $J=8$  Hz, 2H). IR (KBr): 3310, 1690, 1650, 1550, 1510, 1240, 1030, 760, 690  $\text{cm}^{-1}$ .

Entry 5, Table 3:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.09 (s, 3H), 3.49–3.57 (dd,  $J=5.5, 17.6$  Hz, 1H), 3.78–3.86 (dd,  $J=5, 17.6$  Hz, 1H), 5.64–5.71 (m, 1H), 6.96–6.99 (br d,  $J=8.1$  Hz, 1H), 7.45–7.53 (m, 3H), 7.57–7.62 (t,  $J=7.3$  Hz, 1H), 7.70–7.73 (d,  $J=7.5$  Hz, 1H), 7.89–7.92 (br d,  $J=7.2, 2$  Hz), 8.09–8.12 (d,  $J=8.2$  Hz, 1H), 8.24 (br s, 1H). FT-IR (KBr): 3292, 3068, 2245, 1690, 1647, 1523, 1351, 990, 755, 685  $\text{cm}^{-1}$ .

## 3. Results and discussion

To optimize the catalytic system, the synthesis of  $\beta$ -acetamido- $\beta$ -(4-chlorophenyl) propiophenone was used as a model reaction.

For comparing the progress of reaction at a step wise and a one-pot protocol, a mixture of 4-Cl-benzaldehyde and trimethylsilyl chloride was refluxed in acetonitrile in the presence of a catalytic amount of  $\text{H}_3[\text{PW}_{12}\text{O}_{40}]$ . After 0.5 h acetophenone was added and the mixture refluxed for 3 h. The desired product was obtained in a very low yield in this condition but in the one-pot protocol the product was obtained in a good yield (70%) after 3 h.

The catalytic activity and efficiency of this method can be influenced by various parameters such as the employed catalyst, catalyst amount and temperature.

### 3.1. Effect of catalyst on the model reaction

To study the activity of different catalysts, various heteropolyacids were evaluated in the model reaction at 80  $^\circ\text{C}$  and results are listed in Table 1. In this transformation, Keggin type 12-tungstophosphoric acid,  $\text{H}_3[\text{PW}_{12}\text{O}_{40}]$ , showed higher catalytic activity than  $\text{H}_{14}[\text{NaP}_5\text{W}_{30}\text{O}_{110}]$  as a Preyssler type and  $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}$  as a Wells–Dawson type. It should be added that  $\text{H}_3[\text{PW}_{12}\text{O}_{40}]$  is not soluble in the reaction con-

Table 1

Synthesis of  $\beta$ -acetamido- $\beta$ -(4-chlorophenyl) propiophenone in the presence of various heteropolyacids (1 mol%) in refluxing acetonitrile (80  $^\circ\text{C}$ )

Entry	Heteropolyacid	Time (h)	Yield (%) <sup>a</sup>
1	$\text{H}_3[\text{PW}_{12}\text{O}_{40}]$	3	70
2	$\text{H}_3[\text{PW}_{11}\text{CuO}_{40}]$	6	30
3	$\text{H}_3[\text{PW}_{11}\text{NiO}_{40}]$	8	0
4	$\text{H}_3[\text{PW}_{11}\text{CoO}_{40}]$	6	50
5	$\text{H}_4[\text{SiW}_{12}\text{O}_{40}]$	3.5	65
6	$\text{H}_4[\text{SiMo}_{12}\text{O}_{40}]$	6.5	60
7	$\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}$	3	60
8	$\text{H}_{14}[\text{NaP}_5\text{W}_{30}\text{O}_{110}]$	6	43

<sup>a</sup> Yields are based on GC analysis.

dition but both of  $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}$  and  $\text{H}_{14}[\text{NaP}_5\text{W}_{30}\text{O}_{110}]$  are soluble. We also study the activity of a range of Keggin type heteropolyacids including:  $\text{H}_3[\text{PW}_{11}\text{CuO}_{40}]$ ,  $\text{H}_3[\text{PW}_{11}\text{NiO}_{40}]$ ,  $\text{H}_3[\text{PW}_{11}\text{CoO}_{40}]$ ,  $\text{H}_4[\text{SiW}_{12}\text{O}_{40}]$  and  $\text{H}_4[\text{SiMo}_{12}\text{O}_{40}]$ . Unfortunately, they did not show better results than  $\text{H}_3[\text{PW}_{12}\text{O}_{40}]$  (Table 1). Although it is difficult to offer an explanation for the different activity between these heteropolyacids, there is a complex relationship between the activity and structure of polyanion. By changing the constituent elements of polyanion (both hetero and addenda atoms), the acid strength of HPA as well as its catalytic activity is varied in a wide range [19].

It is worthwhile to mention that the minimum amount of the catalyst was optimized to be 1 mol%.

### 3.2. Effect of temperature on the model reaction

The effect of temperature was studied by carrying out the model reaction in the presence of  $\text{H}_3[\text{PW}_{12}\text{O}_{40}]$  (1 mol%) in acetonitrile at different temperatures (room temperature, 45 and 80  $^\circ\text{C}$ ). It was observed (Table 2) that the yield was increased as the reaction temperature was raised. From these results, 80  $^\circ\text{C}$  is selected as the best temperature for all future studies.

We also tried to use acetic anhydride, benzoylchloride and *p*-nitro-benzoylchloride instead of trimethylsilyl chloride in the model reaction. We can mention unfortunately, our attempts to carry out the reaction in the presence of these reagents failed.

Table 2

Synthesis of  $\beta$ -acetamido- $\beta$ -(4-chlorophenyl) propiophenone in the presence of  $\text{H}_3[\text{PW}_{12}\text{O}_{40}]$  (1 mol%) in acetonitrile at different temperatures

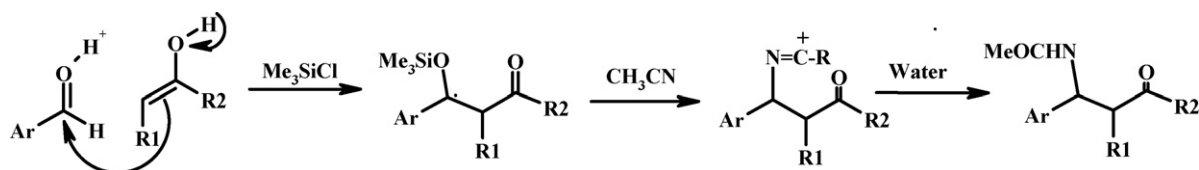
Entry	Temperature ( $^\circ\text{C}$ )	Time (h)	Yield (%) <sup>a</sup>
1	25	3	30
2	45	3	45
3	80	3	70

<sup>a</sup> Yields are based on GC analysis.

Table 3  
Synthesis of  $\beta$ -acetamido ketones and esters using catalytic amount of  $H_3[PW_{12}O_{40}]$

Entry	Aldehyde	Carbonyl compound	Time (h)	Yield (%) <sup>a</sup>	m.p. °C Found reported [Ref.]
1	C <sub>6</sub> H <sub>5</sub> CHO	C <sub>6</sub> H <sub>5</sub> COCH <sub>3</sub>	3.25	65	106 102–104 [20a]
2	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CHO	C <sub>6</sub> H <sub>5</sub> COCH <sub>3</sub>	3	60	109–110 115–117 [20b]
3	4-ClC <sub>6</sub> H <sub>4</sub> CHO	C <sub>6</sub> H <sub>5</sub> COCH <sub>3</sub>	3	70	149–150 146–148 [20c]
5	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CHO	C <sub>6</sub> H <sub>5</sub> COCH <sub>3</sub>	4.25	65	119–121 112–115 [20a]
6	C <sub>6</sub> H <sub>5</sub> CHO	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub>	3	62	73–75 74–76 [20a]
7	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	3.25	67	84–85 83–85 [20a]
8	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CHO	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> COCH <sub>3</sub>	3	63	88–90 87–89 [20a]
9	4-ClC <sub>6</sub> H <sub>4</sub> CHO	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub>	4	66	120 116–118 [20a]
10	C <sub>6</sub> H <sub>5</sub> CHO	CH <sub>3</sub> O <sub>2</sub> CCH <sub>2</sub> COCH <sub>3</sub>	3.10	50	140 129–131 [20d]
11	4-ClC <sub>6</sub> H <sub>4</sub> CHO	CH <sub>3</sub> O <sub>2</sub> CCH <sub>2</sub> COCH <sub>3</sub>	3	52	137–139 130–132 [20d]

<sup>a</sup> Yields are based on GC analysis.



Scheme 2. The suggested mechanism for the reaction.

It is noteworthy to mention that, increasing the amount of trimethylsilyl chloride did not increase the yield of product in the model reaction.

To show the generality of this method the optimized conditions used for the synthesis of other  $\beta$ -acetamido ketones and all results are summarized in Table 3. As shown in Table 3, this method is effective for the preparation of  $\beta$ -acetamido ketones from both acetophenone derivatives as well as ethylacetoacetate. However the catalytic system works best for acetophenone derivatives. The results also showed that the reaction times for the substrates containing electro withdrawing groups are slightly longer. The suggested mechanism for this reaction is patterned in Scheme 2.

The work-up procedure of this reaction is very simple. After completion of reaction the mixture was filtered off to separate the catalyst and then the solvent was evaporated to dryness under reduced pressure. The pure products were obtained by re-crystallization from a mixture of ethanol and water.

In summary, trimethylsilyl chloride is an efficient reagent for the synthesis of  $\beta$ -acetamido ketones.  $H_3[PW_{12}O_{40}]$ , as an example of Keggin-type heteropolyacid, is an inexpensive, reusable and green catalyst for this reaction. In addition, as a non-hygroscopic, non-corrosive and a water stable solid acid, the handling of this catalyst is easy. It makes this catalyst suitable for the large-scale operation. The reaction appears to be heterogeneously catalyzed. High yields, relatively short reaction times, simplicity of operation and easy work-up procedure are some other advantages of this protocol.

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