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Note

$H_3PW_{12}O_{40}/SiO_2$: An Eco-friendly Alternative for the Stereo-, Regio- and Chemoselective Claisen-Schmidt Condensation

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$H_3PW_{12}O_{40}/SiO_2$ or (PW/SiO_2) promotes the regio-, stereo- and chemoselective Claisen-Schmidt condensation with improved yields.

Keywords: Dodecatungstophosphoric acid; $H_3PW_{12}O_{40}/SiO_2$; Aldol condensation; Claisen-Schmidt condensation; α,β-Unsaturated ketones; Heteropoly acids.

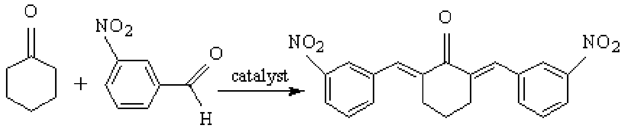
INTRODUCTION

Claisen-Schmidt condensation as a type of crossed aldol condensation is an effective pathway for the preparation of α,β-bis(substituted benzylidene)cycloalkanones as precursors for the synthesis of bioactive pyrimidine derivaties or nikkomycine.[1] Crossed aldol condensation is always carried out in the presence of acids or bases such as silica sulfuric acid,[2] $Mg(HSO_4)_2$,[3] TiO_2,[4] $RuCl_3$,[5] $TiCl_3(SO_2CF_3)$,[6] $KHSO_4$,[7] $[Cp^*Rh(\eta^6\text{-}C_6H_6)](BF_4)_2$,[8] NaOAc/HOAc,[9] $ZrCl_4$,[10] $FeCl_3.6H_2O$,[11] $LiOH.H_2O$,[12] I_2,[13] Al_2O_3-MgO[14] acid-base functionalized catalyst[15] and polymer supported sulphonic acid,[16] among others. The use of toxic and expensive reagents, low yields, long reaction times and formation of a mixture of products are among the drawbacks of the reported procedures. Recently, more attention has been paid to Claisen-Schmidt condensation.

RESULTS AND DISCUSSION

In continuation of our studies on the application of solid acids in organic synthesis[17-22] we report a simple, efficient and selective protocol for the Claisen-Schmidt condensation in the presence of ($H_3PW_{12}O_{40}$) or (PW). It is obvious that bulk PW has a low surface area. The high surface area can be achieved by dispersing the PW on some solid supports with high surface areas. Thus, we have used silica, titania or zirconia supported $H_3PW_{12}O_{40}$ for Claisen-Schmidt condensation (Table 1).

Table 1. Claisen-Schmidt condensation of 2 mmol of 3-nitrobenzaldehyde and 1 mmol of cyclohexanone in various conditions[a]



Entry	Catalyst	Condition/solvent	Yield[a] (%)
1	PW(0.06 g)	Reflux/toluene	65
2	PW(0.06 g)	Reflux/acetonitrile	52
3	PW(0.06 g)	Reflux/THF	50
4	PW(0.06 g)	Reflux/HOAc	70
5	PW(0.06 g)	Reflux/EtOH	75
6	PW(0.06 g)	Reflux/CH_2Cl_2	80
7	PW(0.06 g)	50-60 °C/-	75
8	PW(0.06 g)	Ultrasound/CH_2Cl_2	35
9	SiO_2	50-60 °C/-	-
10	60% PW/SiO_2(0.06 g)	50-60 °C/-	90
11	60% PW/TiO_2(0.06 g)	50-60 °C/-	62
12	60% PW/ZrO_2(0.06 g)	50-60 °C/-	85
13	40% PW/SiO_2(0.06 g)	50-60 °C/-	80
14	50% PW/SiO_2(0.06 g)	50-60 °C/-	85
15	70% PW/SiO_2(0.06 g)	50-60 °C/-	90
16	60% PW/SiO_2(0.04 g)	50-60 °C/-	82
17	60% PW/SiO_2(0.05 g)	50-60 °C/-	85
18	60% PW/SiO_2(0.08 g)	50-60 °C/-	90
19	60% PW/SiO_2(0.06 g)[b]	50-60 °C/-	88
20	60% PW/SiO_2(0.06 g)[b]	50-60 °C/-	82

[a] Isolated yield.
[b] Catalyst reused in three successive runs; the catalyst was filtered, washed with dry acetone and dried in a domestic microwave oven for 20 min at a power of 100.

The results have indicated that the PW/SiO_2 was the best one among others. In the preparation of PW/SiO_2, we have used 0.2 mL of HCl (0.5 M) to prevent the PW disso-

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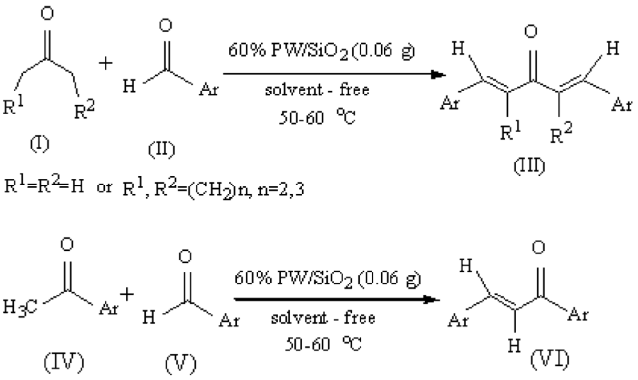
ciation. Meanwhile, we found that solid matrices which were prepared from similar HCl solutions succeeded in Claisen-Schmidt condensation in a very low yield (10-15%) in the absence of PW. Various types of ketones were subjected to aromatic aldehydes in the presence of 60% PW/SiO_2 under solvent-free conditions at 50-60 °C with improved yields of only di-aldol products (Scheme I, Table 2).

Scheme I



The stereoselectivity of this method was confirmed by the formation of a trans double bond in the Claisen-Schmidt condensation of methyl ketones (Table 2, entries 13-18). Regioselectivity of this method was examined by crossed aldol condensation of 2-butanone and 4-methyl-2-pentanone with 4-chlorobenzaldehyde (Scheme II). Because of the preference for acid catalyzed enolization to give more substituted enol, under PW/SiO_2-catalyzed condensation, the branched-chain ketol was formed with high yield (Scheme II).

Additionally, the chemoselectivity of the reaction was evaluated via a competitive PW/SiO_2 catalyzed reaction of 4-chlorobenzaldehyde (2 mmol) with a mixture of cyclohexanone (1 mmol) and acetone (1 mmol). It was found that cyclohexanone reacted with benzaldehyde in a high yield. No chemoselectivity was observed for cyclohexanone versus acetophenone or 4-nitrobenzaldehyde versus 4-methyl benzaldehyde. Due to confirmation of the reusability of catalyst, after reaction, PW/SiO_2 was recovered by filtration and washed with acetone several times. The catalyst activity gradually declined in successive runs (Table 1, entries 19-20), which indicated that loss of cata-

Table 2. Claisen-Schmidt condensation of ketones with aldehydes promoted 60% $PW-SiO_2$ under solvent-free conditions at 50-60 °C[a]

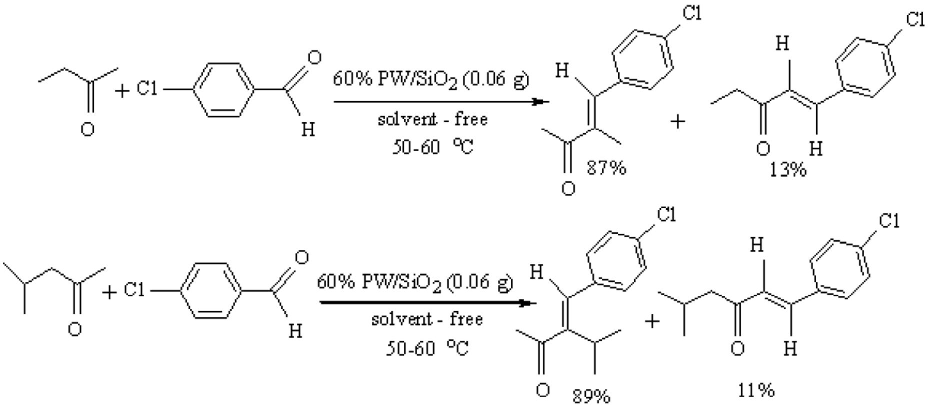
Entry	Product	Yield (%)[b]	Ref.[c]	M.P. °C
1	III: $R_1,R_2 = (CH_2)_3$, Ar = 3-NO_2-C_6H_4	92	11	89-90
2	III: $R_1,R_2 = (CH_2)_3$, Ar = 4-CH_3-C_6H_4	84	11	165-166
3	III: $R_1,R_2 = (CH_2)_3$, Ar = -C_6H_5	80	11	116-117
4	III: $R_1,R_2 = (CH_2)_3$, Ar = 3-OCH_3, 4-OH-C_6H_3	45	13	168-170
5	III: $R_1,R_2 = (CH_2)_3$, Ar = 2-Cl-C_6H_4	87	12	88-89
6	III: $R_1,R_2 = (CH_2)_3$, Ar = 4-OCH_3-C_6H_4	85	13	202-204
7	III: $R_1,R_2 = (CH_2)_2$, Ar = 4-OCH_3-C_6H_4	75	13	215-216
8	III: $R_1,R_2 = (CH_2)_2$, Ar = 2,4-Di-Cl, -C_6H_3	75	13	217-219
9	III: $R_1,R_2 = (CH_2)_2$, Ar = 4-CH_3-C_6H_4	73	11	245-246
10	III: $R_1,R_2 = (CH_2)_2$, Ar = 2-Cl-C_6H_4	87	11	152-153
11	III: $R_1,R_2 = (CH_2)_2$, Ar = 4-NO_2-C_6H_4	71	2	230-231
12	VI: Ar′ = Ph, Ar = 4-NO_2-C_6H_4	75	10	159-160
13	VI: Ar′ = Ph, Ar = 3-NO_2-C_6H_4	74	10	144-145
14	VI: Ar′ = Ph, Ar = 4-Cl-C_6H_4	82	2	108-109
15	VI: Ar′ = Ph, Ar = 4-OMe-C_6H_4	81	2	75-76
16	VI: Ar′ = Ph, Ar = 4-CH_3-C_6H_4	76	2	97-98
17	VI: Ar′ = 4-Cl-C_6H_4-C = C-, Ar = 4-Cl-C_6H_4	75	11	192-194

[a] The molar ratio of aldehyde(mmol): ketone(mmol): catalyst(g) is 2: 2(1): 0.06 and the time of reaction is 60 minutes.

[b] Isolated yield.

[c] All products are known and were identified by their melting points, TR and ^1H NMR spectra.

Scheme II



lyst activity was very low.

In sum, PW/SiO$_2$ as a solid acid has a high efficiency and has catalyzed the Claisen-Schmidt condensation reaction in solvent-free conditions. This plain methodology offers several advantages including a simple work up, scale up, improved yields, regio-, stereo- and chemoselectivity, and a recyclable catalyst with a very clean reaction.

EXPERIMENTAL

General

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. Yields refer to isolated products. The products were characterized by comparison of their spectral (IR and ^{1}H-NMR) and physical data with authentic data.

Preparation of various supported 12-tungstophosphoric acids (60%w/w)

The mixtures of 0.6 g of 12-tungstophosphoric acid and 0.4 g of silicagel, TiO$_2$ or ZrO$_2$ were separately ground into fine particles. A suspension of each mixture and 0.2 mL of HCl 0.5 M and 1 mL of methanol were stirred for 20 min at room temperature. The solvent of each suspension was evaporated at about 80-90 °C until dryness. The obtained solids were dried in a domestic microwave oven for 20 min at a power of 100.

Synthesis of 4-chlorobenzylidene acetophenone, a typical procedure

A mixture of 0.28 g (2 mmol) of 4-chlorobenzaldehyde, 0.24 g (2 mmol) of acetophenone and 0.06 g of 60% PW/SiO$_2$ was stirred at 50-60 °C for 60 min. The progress of the reaction was monitored by TLC (eluent, dichloromethane : ether, 80:20). After the completion of the reaction, CH$_2$Cl$_2$ was added to the mixture and filtered. The solvent of the filtrate was then evaporated and the crude product was crystallized from ethanol and consequently the pure product was obtained in a 82% yield; m.p.: 108-109 °C, (Lit: 107-109 °C).[2]

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