Article

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Synthesis of Tetraketones Using ZnS Nanoparticles as an Efficient Catalyst

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An efficient pseudo-three-component synthesis of tetraketones is described by one-pot condensation of 5,5-dimethylcyclohexane-1,3-dione and aldehydes using ZnS nanoparticles at room temperature. This method provides several advantages such as mild reaction conditions, applicability to a wide range of substrates, reusability of the catalyst, and low catalyst loading.

Keywords: Pseudo-three-component; Tetraketones; ZnS nanoparticles; Nanocatalyst; One-pot.

INTRODUCTION

Tetraketones show significant biological activities including as tyrosinase inhibitors,[1] lipoxygenase inhibitors, and antioxidants.[2] These attributes make tetraketones noteworthy targets in organic synthesis for future considerations. A number of improved procedures have been reported for the synthesis of tetraketones in the presence of catalysts including cetyltrimethyl ammonium bromide (CTMAB),[3] L-proline,[4] Fe/NaY zeolite,[5] urea,[6] $(NH_4)_2HPO_4$,[7] BiOCl.[8] nickel nanoparticles (NPs),[9] and ionic liquids.[10] Each of these methods has its own advantages but also suffers from certain disadvantages such as prolonged reaction time, tedious work-up processes, low yield, high action temperature, and hazardous reaction conditions. Despite the availability of these methods, there remains enough space for a capable and reusable catalyst with high catalytic activity for the preparation of tetraketones. The use of environmentally friendly and green catalysts that can be easily recycled at the end of reactions has attracted great attention in recent years.[11–14] ZnS NPs have emerged as a suitable class of heterogeneous catalysts owing to their numerous applications in synthesis and catalysis.[15–18] Since these NPs can often be recovered simply by an easy work-up, which prevents contamination of the products, they may be considered as promising, safe, and reusable catalysts as well as greener compared to traditional catalysts.[19,20] Here we reported the use of ZnS NPs as an efficient catalyst for the preparation of tetraketones by a one-pot condensation of 5,5-dimethylcyclohexane-1,3-dione and aldehydes (Scheme 1).

RESULTS AND DISCUSSION

The morphology and particle size of ZnS NPs were investigated by scanning electron microscopy (SEM) as shown in Figure 1. The SEM images show particles with diameters in the range of nanometers. The crystalline nature of the synthesized ZnS NP samples was further verified by X-ray diffraction (XRD) patterns. The crystallite diameter (D) of the ZnS NPs was calculated by the Debye–Scherrer equation ($D = K\lambda/\beta \cos\theta$). The results show that the obtained ZnS NPs had an average diameter of 25–30 nm (Figure 2).

Initially, we explored and optimized different reaction parameters for the synthesis of tetraketones by one-pot condensation of 5,5-dimethylcyclohexane-1,3-dione and 4-chlorobenzaldehydeas a model reaction (Table 1). These reactions were carried out in the presence of various catalysts, such as $(NH_4)_2Ce(NO_3)_6$, $FeCl_3$, nano-Fe_3O_4, nano-ZnO, and nano-ZnS. The best results were obtained in water, and the reaction gave satisfactory results in the presence nano-ZnS. In order to optimize the reaction conditions, we performed the reaction using different quantities of the catalyst. There was no difference in yield and reaction time when catalyst loading was enhanced to 6 mol%.

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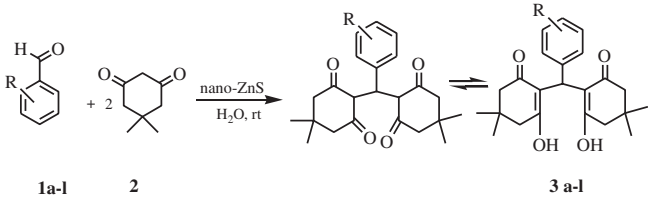

Scheme 1. Synthesis of tetraketones.

To investigate the scope and limitation of this catalytic process, aromatic aldehydes were chosen as substrates (Table 2). Investigations of the reaction scope revealed that various aromatic aldehydes (bearing electron-withdrawing and electron-donating groups) could be utilized in this protocol.

We also investigated the reusability of the nano-ZnS catalyst at room temperature in water for the synthesis of product **3i**, and it was found that product yields decreased only slightly on each reuse (run 1, 97%; run 2, 97%; run 3, 96%; run 4, 96%; run 5, 95%). After completion of the reaction, $CHCl_3$ was added. The catalyst was insoluble in $CHCl_3$ and it could therefore be recovered by simple filtration. The

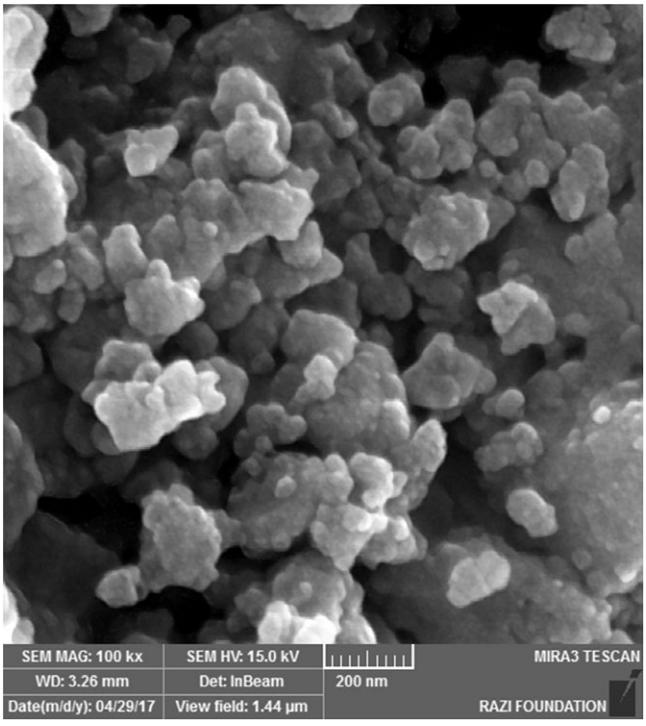

Fig. 1. Scanning electron microscopy images of the catalyst.

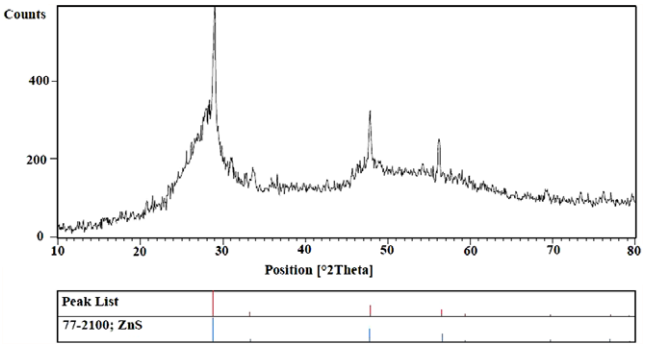

Fig. 2. X-ray diffraction pattern of the catalyst.

NPs were then washed 3–4 times with ethanol and dried at 40°C for 10 h.

EXPERIMENTAL

The products were isolated and characterized by physical methods and spectral data. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer with tetramethylsilane as internal standard. The IR spectra were recorded on an FT-IR Magna 550 apparatus using KBr plates. Melting points were determined on an Electro-Thermal 9200 instrument, and are not corrected. The elemental analyses (C, H, N) were carried out on a Carlo ERBA Model EA 1108 analyzer. Powder XRD was carried out on a Philips diffractometer (X'pert) with monochromatized Cu Kα radiation (λ = 1.5406 Å). Microscopic morphology of the products was visualized by SEM (MIRA3 TESCAN).

Preparation of ZnS nanoparticles

ZnS NPs were prepared by dropping simultaneously 50 mL of a 1 M solution of $ZnSO_4$ and 50 mL of a 1 M solution of Na_2S into 200 mL of distilled water containing 50 mL of 0.1 M solution of EDTA, which was vigorously stirred using a magnetic stirrer under Ar atmosphere. The high insolubility of ZnS formed out of the chemical reaction resulted in the formation of a number of new nuclei while preventing the growth of the already existing ones, thus limiting the particle size. The role of EDTA was to stabilize the particles against aggregation, which may lead to an increase in the particle size. The precipitate was separated from the reaction mixture and was dried at room temperature. After sufficient drying, the precipitate was

Table 1. Optimization of reaction conditions using different catalysts[a]

Entry	Solvent	Catalyst (mol%)	Time (min)	Yield (%)[b]
1	H_2O	—	120	50
2	CH_3CN	$(NH_4)_2Ce(NO_3)_6$ (6)	60	58
3	EtOH	$FeCl_3$ (7)	60	64
4	EtOH	nano-Fe_3O_4 (6)	60	69
5	EtOH	nano-ZnO (6)	60	72
6	H_2O/EtOH (5:5)	nano-ZnS (4)	30	85
7	$CHCl_3$	nano-ZnS (4)	30	62
8	CH_3CN	nano-ZnS (4)	30	75
9	EtOH	nano-ZnS (4)	30	80
10	H_2O	nano-ZnS (2)	30	86
11	H_2O	nano-ZnS (4)	30	97
12	H_2O	nano-ZnS (6)	30	97

[a] 4-Chlorobenzaldehyde (1 mmol) and 5,5-dimethylcyclohexane-1,3-dione (2 mmol).
[b] Isolated yield.

crushed to fine powder with the help of a mortar and pestle.[18,19]

General procedure for the preparation of tetraketones

In a 20-mL flask was placed benzaldehydes (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (2 mmol), and ZnS NPs (4 mol%) in water (5 mL). The resulting yellow solution was stirred at room temperature for 30 min (TLC-monitored). A white precipitate formed, which was filtered and $CHCl_3$ was added to it. The catalyst was insoluble in $CHCl_3$, so it could be recovered by a simple filtration. The solvent was evaporated and the solid obtained was recrystallized from ethanol to afford the tetraketones.

Spectral data

*2,2′-(2,4-Dichlorophenyl)methylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3a**)*. White powder; m.p. 200–202°C, IR (KBr) cm^{-1}: 3352, 2958, 1722, 1611, 1468; ^1H NMR (400 MHz, $CDCl_3$): δ 1.10 (6H, s, 2 CH_3), 1.12 (6H, s, 2 CH_3), 2.21–2.46 (8H, m, 4 CH_2), 5.57 (1H, s, CH), 7.19–7.30 (3H, m, Ar), 11.87 (2H, brs, OH) ppm; Anal. Calcd for $C_{23}H_{26}Cl_2O_4$: C, 63.16; H, 5.99; Found: C, 63.12; H, 5.90.

*2,2′-(2-Chlorophenyl)methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3b**)*. White powder; m.p. 202–204°C, IR (KBr) cm^{-1}: 3393, 2956, 1720, 1611, 1468; ^1H NMR (400 MHz, $CDCl_3$): δ 1.10 (6H, s, 2 CH_3), 1.14 (6H, s, 2 CH_3), 2.21–2.47 (8H, m,

Table 2. Synthesis of tetraketones using ZnS nanoparticles

Entry	Aldehydes (R)	Product	Time (min)	Yield (%)[a]	m.p. (°C)[Ref]	m.p. (°C) (found)
1	2,4-Dichloro	**3a**	30	97	197–199[7]	200–202
2	2-Cl	**3b**	30	94	199–200[5]	202–204
3	2-NO_2	**3c**	30	94	188–189[6]	194–196
4	3-OH	**3d**	40	90	243–244[21]	245–246
5	3-NO_2	**3e**	30	92	190–191[6]	194–196
6	4-$CH(CH_3)_2$	**3f**	45	90	—	167–169
7	4-Br	**3g**	30	97	154–156[5]	170–172
8	4-CH_3	**3h**	40	90	142–143[6]	140–142
9	4-Cl	**3i**	30	97	143–145[5]	144–146
10	4-$N(CH_3)_2$	**3g**	50	85	194–195[22]	196–198
11	4-NO_2	**3k**	30	97	188–190[5]	185–187
12	4-OH	**3l**	45	87	182–184[5]	189–191

[a] Isolated yield.

4 CH_2), 5.62 (1H, s, CH), 7.11–7.41 (4H, m, Ar), 11.87 (2H, brs, OH) ppm; Anal. Calcd for $C_{23}H_{27}ClO_4$: C, 68.56; H, 6.75; Found: C, 68.48; H, 6.65.

*2,2′-(2-Nitrophenyl)methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3c**)*. White powder; m.p. 194–196°C, IR (KBr) cm^{-1}: 3421, 3390, 2956, 1722, 1615, 1467; ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (12 H, s, $4CH_3$), 2.29 (8H, s, $4CH_2$), 6.20 (1H, s, CH), 7.24–7.56 (4H, m, Ar), 11.89 (2H, brs, OH) ppm; Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39; Found: C, 66.79; H, 6.50; N, 3.27.

*2,2′-(3-Hydroxyphenyl)methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3d**)*. White powder; m.p. 245–246°C, IR (KBr) cm^{-1}: 3419, 3387, 2947, 1718, 1609, 1456; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.09 (12H, s, $4CH_3$), 2.29 (8H, s, $4CH_2$), 5.43 (1H, s, CH), 6.58–7.27 (4H, m, Ar), 11.95 (3H, brs, OH) ppm; Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34; Found: C, 71.78; H, 7.28.

*2,2′-(3-Nitrophenyl)methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3e**)*. White powder; m.p. 194–196°C, IR (KBr) cm^{-1}: 3414, 3385, 2943, 1715, 1605; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.12 (12H, s, $4CH_3$), 2.36 (8H, s, $4CH_2$), 5.54 (1H, s, CH) 7.26–8.05 (4H, m, Ar), 11.87 (2H, brs, OH) ppm; Anal. Calcd for C, 66.81; H, 6.58; N, 3.39; Found: C, 66.75; H, 6.48; N, 3.28.

*2,2′-(4-isopropylphenyl)methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3f**)*. White powder; m.p. 167–169°C, IR (KBr) cm^{-1}: 3399, 2942, 1710, 1608; ^1H NMR (400 MHz, $CDCl_3$): δ 1.17 (12H, s, $4CH_3$), 1.23 (6H, s, $2CH_3$), 2.34 (8H, s, $4CH_2$), 2.86 (1H, s, CH), 5.51 (1H, s, CH), 7.00–7.26 (4H, m, Ar), 11.91 (2H, brs, OH) ppm; Anal. Calcd for C, 76.06; H, 8.35; Found: C, 75.95; H, 8.29.

*2,2′-(4-Bromophenyl)methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3g**)*. White powder; m.p. 170–172°C, IR (KBr) cm^{-1}: 3398, 2939, 1703, 1647; ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (12H, s, 4 CH_3), 2.40 (8H, s, $4CH_2$), 5.45 (1H, s, CH), 6.95–7.63 (4H, m, Ar), 11.90 (2H, brs, OH) ppm; Anal. Calcd for C, 61.75; H, 6.08; Found: C, 61.70; H, 6.15.

*2,2′-(4-Methylphenyl)methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3h**)*. White powder; m.p. 140–142°C, IR (KBr) cm^{-1}: 3390, 2934, 1705, 1645; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.27 (12H, s, $4CH_3$), 2.05 (3H, s, CH_3), 2.30 (8H, s, $4CH_2$), 5.53 (1H, s, CH), 6.97–7.26 (4H, m, Ar), 11.92 (2H, brs, OH) ppm; Anal. Calcd for C, 75.36; H, 7.91; Found: C, 75.30; H, 7.87.

*2,2′-(4-chlorophenyl)methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3i**)*. White powder; m.p. 144–146°C, IR (KBr) cm^{-1}: 3397, 2930, 1703, 1644; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.59 (12H, s, $4CH_3$), 2.35 (8H, s, $4CH_2$), 5.47 (1H, s, CH), 7.0–7.38 (4H, m, Ar), 11.37 (2H,brs,OH) ppm; Anal. Calcd for C, 68.56; H, 6.75; Found: C, 68.48; H, 6.63.

*2,2′-(4-N,N-Dimethylaminophenyl)methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3j**)*. White powder; m.p. 196–198°C, IR (KBr) cm^{-1}: 3129, 1628, 1611, 1506, 1311, 850; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm)1.12 (12H, s, $4CH_3$), 2.28 (8H,s,$4CH_3$), 2.91 (6H, s, $N(CH_3)_2$) 5.26 (1H, s, CH), 6.55–8.04 (4H, m, Ar), 11.88 (2H,s,OH) ppm; Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40; Found: C, 72.87; H, 7.78; N, 3.37.

*2,2′-(4-Nitrophenyl)methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3k**)*. White powder; m.p. 185–187°C, IR (KBr) cm^{-1}: 3123, 1674, 1622, 1510, 1363, 1340, 1463, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (12H, s,$4CH_3$), 2.36 (8H, s, $4CH_2$), 5.55 (1H, s, CH), 7.24–8.15 (4H, m, Ar), 11.81 (2H, brs, 2OH) ppm; Anal. Calcd for C, 66.81; H, 6.58; N, 3.39; Found: C, 66.75; H, 6.46; N, 3.28.

*2,2′-(4-Hydroxyphenyl)methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3l**)*. White powder; m.p. 189–191°C, IR (KBr) cm^{-1}: 3120, 1673, 1621, 1514, 1360, 1342; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.16 (12H, s, $4CH_3$), 2.29 (8H, s, $4CH_2$), 5.47 (1H, s, CH), 6.69–7.26 (4H, m, Ar), 11.89 (3H, brs, OH) ppm; Anal. Calcd for C, 71.85; H, 7.34; Found: C, 71.75; H, 7.28.

CONCLUSIONS

In conclusion, we have developed a simple and highly efficient protocol for the synthesis of tetraketones by a one-pot condensation of 5,5-dimethylcyclohexane-1,3-dione and aldehydes using ZnS NPs at room temperature. The salient features of this protocol are short reaction times, high yields, and the absence of any hazardous organic solvent.

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Supporting information

1H NMR spectra of tetraketones are available in the online version of this article.

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