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$SiO_2 \cdot 12WO_3 \cdot 24H_2O$: a Highly Efficient Catalyst for the Synthesis of 5-Arylidene Barbituric Acid in the Presence of Water

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The condensation of aromatic aldehydes and barbituric acid catalyzed by $SiO_2 \cdot 12WO_3 \cdot 24H_2O$ in aqueous media at room temperature gave 5-arylidene barbituric acid in high yields with or without the use of ultrasound, providing a simple and efficient route to synthesis of these compounds.

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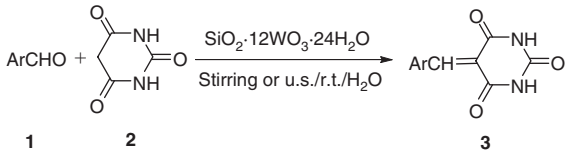
Some barbituric acid derivatives have been widely used as sedative, hypnotic, anticonvulsant, antispasmodic, and local anaesthetic agents.[1] Benzylidene barbituric acids are useful as potential organic oxidizers, for the preparation of oxadeazaflavines, and for the asymmetrical synthesis of disulfides.[2] Some of them have been recently studied as non-linear optical materials.[3] Over the past few years many synthetic methods[3–10] for preparation of these compounds have been reported, such as infrared irradiation[3] and microwave irradiation.[4] However, in spite of their potential utility, some of these procedures involve expensive catalysts, a long reaction time and lower yields.

Heteropolyacids have been found to act as outstanding catalysts in electrophilic transformations.[11] Silicotungstic acid is a solid heteropolyacid which has been used for the synthesis of trioxanes,[12] alkylation of benzene with olefins,[13] preparation of acrolein from glycerol,[14] synthesis of novel indolyl crown ethers and di(indolyl)pyrazolyl methanes, and cyclodehydration of 1,4-butanediol to tetrahydrofuran.[15] It has been previously reported that silicotungstic acid has high catalytic activity and good stability, and is an environmentally friendly catalyst.

Organic reactions in aqueous media are attracting increasing interest due to environmental issues and the understanding of biochemical processes. Water offers many practical and economic advantages as a reaction solvent including low cost, safe handling, and environmental compatibility. Recently, many organic reactions in aqueous media have been described in the literature.[16] To the best of our knowledge, however, there are no literature examples of the synthesis of 5-arylidene barbituric acid in aqueous media using silicotungstic acids as catalysts, especially at room temperature with stirring or the use of ultrasound irradiation. Herein, we wish to report an efficient and simple procedure for the room temperature synthesis of 5-arylidene barbituric acid in the presence of water, catalyzed by $SiO_2 \cdot 12WO_3 \cdot 24H_2O$, both with and without the use of ultrasound irradiation (Scheme 1).

We studied the influence of the amount of catalyst on the reaction. As shown in Table 1, increasing the amount of catalyst



1 2 3

Scheme 1. Synthesis of 5-arylidene barbituric acid.

Table 1. Effect of reaction conditions on the reaction of 4-$CH_3OC_6H_4CHO$ with barbituric acid

Barbituric acid, 1 mmol; 4-$CH_3OC_6H_4CHO$, 1 mmol; A: stirring without ultrasound; B: ultrasound irradiation, 25 kHz

Entry	Molar ratio of 1:2:catalyst	Time [min]		Yield [%]	
		A	B	A	B
1	1:1:0	20	5	40	50
2	1:1:0.0025	20	5	86	88
3	1:1:0.005	20	5	98	99
4	1:1:0.01	20	5	98	99
5	1:1:0.05	30	10	99	99

can improve the reaction yields. For example, in the absence of silicotungstic acid the yield of arylidene barbituric acid was 40%, whereas using 0.005 mmol silicotungstic acid with stirring the yield was 98% (Table 1, entry 3) for the same period.

The effect of ultrasound irradiation on the reaction was observed. As shown in Table 1 and Table 2, condensation of 4-methoxybenzaldehyde with barbituric acid catalyzed by silicotungstic acid in the absence of ultrasound offered 5-(4-methoxybenzylidene)-barbituric acid (Table 2, **3a**) at 98% yield within 20 min. The use of ultrasound irradiation allowed a similar yield to be obtained within 5 min. Additionally the reaction of 4-methylbenzaldehyde (**1g**) with barbituric acid with stirring for 25 min gave **3g** at 88% yield, whereas the use of ultrasound

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Table 2. Condensation of barbituric acid with aromatic aldehydes with and without the use of ultrasound
A, stirring without ultrasound; B, ultrasound irradiation

Compound	Ar	Time [min]		Yield [%]		mp [°C]	mp [°C] (Lit.)
		A	B	A	B		
3a	4-$CH_3OC_6H_4$	20	5	98	99	296–298	298–300[8]
3b	2-$CH_3OC_6H_4$	25	5	98	97	266–268	270–272[7]
3c	4-HOC_6H_4	25	5	97	98	>350	>350[9]
3d	3-CH_3O-4-HOC_6H_3	20	4	93	98	307–310	309–313[9]
3e	4-ClC_6H_4	40	10	96	94	300–301	301–302[6]
3f	3-ClC_6H_4	40	10	41	68	267–268	274–278[8]
3g	4-$CH_3C_6H_4$	25	10	88	95	277–279	278–280[8]
3h	C_6H_5	30	10	62	61	267–268	270–272[8]
3i	4-$(CH_3)_2NC_6H_4$	30	5	92	98	280–283	282–284[9]
3j	2-HO-3-$CH_3OC_6H_3$	20	5	91	99	>350	>350[10]
3k	3,4-$(OCH_2O)C_6H_3$	20	5	96	97	326	320[3]
3l	4-$NO_2C_6H_4$	40	15	15	20	306–308	307–310[8]

gave a 95% yield of the same product within 10 nm. It is clear that ultrasound can accelerate the condensation of some aromatic aldehydes with barbituric acid.

From the results above the optimum reaction conditions were chosen: aromatic aldehyde (**1**, 1 mmol), barbituric acid (**2**, 1 mmol), silicotungstic acid (0.005 mmol), and water (3 mL). Under these reaction conditions, a series of experiments for the synthesis of 5-arylidene barbituric acids was carried out. Good yields were obtained for all systems, except for **3f** and **3l**, within 20–40 min (Table 2).

When 4-aminoacetophenone, 4-nitroacetophenone, or 4-methoxyacetophenone was used as a substrate, no product was obtained despite the use of stirring, ultrasonic irradiation or extending the reaction time. This indicates that the method has some limitations with respect to some aromatic ketones, possibly due to steric hindrance around the carbonyl group which inhibits the condensation.

The condensation of barbituric acid with aliphatic (cyclic) ketones such as acetone, butanone, and cyclohexanone was also carried out using either ultrasound radiation or stirring. In both cases no reaction product was obtained.

We have shown that the method presented here represents an efficient procedure in terms of high yield, mild reaction conditions, and easy workup. In addition, compared with the use of stirring, ultrasonic irradiation can reduce the reaction time.

In conclusion, we have found a practical procedure for the preparation of 5-arylidene barbituric acids from some aromatic aldehydes and barbituric acid, catalyzed by silicotungstic acid ($SiO_2 \cdot 12WO_3 \cdot 24H_2O$).

Experimental

Materials and Measurements

Liquid aldehydes were purified by distillation before use. Melting points were uncorrected. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ^1H NMR spectra were measured on a Bruker AVANCE-400 (400 MHz) spectrometer using TMS as internal standard and DMSO as solvent. Mass spectra were determined on a VG-7070E spectrometer (EI, 70 eV). Sonication was performed in a Shanghai Branson-BUG25–06 ultrasonic cleaner (with a frequency of 25 kHz and a nominal power of 250 W). The reaction flask was located in the cleaner, where the surface of the reactant solution is slightly lower than the level of the water. Observation of the surface of the reaction solution during vertical adjustment of vessel depth will show the optimum position by the point at which maximum surface disturbance occurs. The reaction temperature was controlled by the addition or removal of water from the ultrasonic bath.

General Procedure

Aldehyde (**1**, 1 mmol), barbituric acid (**2**, 1 mmol), $SiO_2 \cdot 12WO_3 \cdot 24H_2O$ (0.005 mmol), and water (3 mL) were mixed in a 25 mL round-bottomed flask. The reaction mixture was either stirred, or irradiated in the water bath of an ultrasonic cleaner, at room temperature for the period as indicated in Table 2. After completion of the reaction, the reaction mixture was filtered, washed with boiling H_2O and then washed with EtOH, affording the known products (**3a**–**3l**). The authenticity of the products was established by spectroscopic data and by comparing their melting points with literature values.[3,5–10]

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