

An Efficient and Convenient Procedure for Preparation of 5-Arylidene Barbituric Acid Catalyzed by ZrO_2/SO_4^{2-} Solid Superacid with Grinding

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An efficient and convenient approach to the condensation reaction of aromatic aldehydes and barbituric acid using ZrO_2/SO_4^{2-} solid superacid as catalyst with grinding at room temperature (without any solvent) is described. This method provides several advantages such as neutral condition, high yields and environment friendly.

Key Words: 5-Arylidene barbituric acid, ZrO_2/SO_4^{2-} , Solid superacid, Aromatic aldehyde, Barbituric acid, Grinding method.

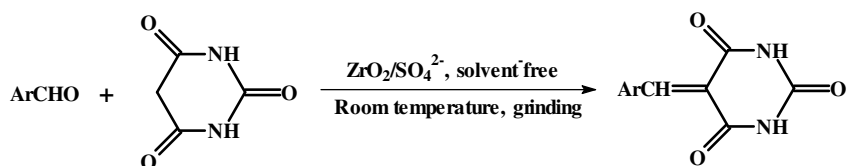
INTRODUCTION

It is known that 5-arylidene barbituric acid and its derivatives are useful compounds. They have attracted strong interest due to their useful biological and pharmacological properties, such as sedative, hypnotic, anticonvulsant, antispasmodic and local anaesthetic agents^{1,2}. Benzylidenebarbituric acids are useful as potential organic oxidizers for the preparation of oxadeazaflavines and for the asymmetrical synthesis of disulfides^{3,4}. Some of them have been recently studied as nonlinear optical materials⁵. In several years, many synthetic methods for preparation of these compounds have been reported⁵⁻¹¹. However, some of these methods have not been entirely satisfactory owing to such drawbacks as cumbersome experimental, in organic solvent, higher temperatures, long reaction times, lower yields and requiring use of a microwave oven.

ZrO_2/SO_4^{2-} is a type of solid acid and has many advantages such as high reactivity, non-toxic, non-corrosive, reusable and environment-friendly. The solid superacid have been used as efficient catalyst for a variety of organic reactions¹²⁻¹⁵.

The grinding method is used more and more frequently in organic synthesis^{16,17}. In comparison with traditional methods, this method is more

convenient and easily controlled. A number of organic reactions can be carried out in higher yields, shorter times or milder conditions by the grinding method. It can even set off some reactions that cannot be carried out under traditional conditions. All of these results prompted us to study the possibility of Knoevenagel condensation of aromatic aldehydes with barbituric acid catalyzed by $\text{ZrO}_2/\text{SO}_4^{2-}$ solid superacid without solvent. Herein, we report the condensation reaction using $\text{ZrO}_2/\text{SO}_4^{2-}$ solid superacid as catalyst under solvent-free conditions by the grinding method at room temperature (**Scheme-I**).



Scheme-I

EXPERIMENTAL

The catalyst $\text{ZrO}_2/\text{SO}_4^{2-}$ solid superacid was prepared as follows. $\text{Zr}(\text{OH})_4$ was infused in H_2SO_4 (1 mol/L) for 4 h, the filtered off, drying at 110°C for 2 h, grind to over 250 mesh, calcined in furnace at 600°C for 4 h and finally stored in a desiccator. Melting points are uncorrected. ^1H NMR spectra were measured on a Bruker Avance (400 MHz) spectrometer using TMS as internal standard and DMSO-d_6 as solvent.

General procedure: Barbituric acid (2 mmol), aromatic aldehyde (2 mmol) and $\text{ZrO}_2/\text{SO}_4^{2-}$ (15 mol %) were added to a mortar. The mixture was grounded by mortar and pestle at room temperature for 15 min and kept at room temperature in a desiccator for a period (12-16 h). The completion of the reaction was monitored by TLC. After completion of the reaction, the mixture was dissolved in DMSO, the catalyst was removed by filtration and washed with DMSO and the solution was poured into H_2O . The precipitate was washed with boiling H_2O and then washed with EtOH, affording the products **3**. Data of some compounds are shown below:

3b: IR (KBr): $\nu_{\text{max}} = 3215, 3080, 1696, 1600, 1377, 1220, 755 \text{ cm}^{-1}$. ^1H NMR (DMSO-d_6): $\delta = 7.04\text{-}7.76$ (m, 4H, ArH), 8.30 (s, 1H, CH=), 11.32 (s, 1H, NH), 11.46 (s, 1H, NH).

3c: IR (KBr): $\nu_{\text{max}} = 3250\text{-}3220, 1740, 1700, 1680, 1580 \text{ cm}^{-1}$. ^1H NMR (DMSO-d_6): $\delta = 7.57\text{-}7.08$ (m, 2H, $\text{ArH}_{4,5}$), 7.84 (d, $J = 8.6 \text{ Hz}$, 1H, ArH_6), 8.15 (s, 1H, ArH_2), 8.22 (s, 1H, HC=), 11.28 (s, 1H, NH), 11.44 (s, 1H, NH).

3d: IR (KBr): ν_{\max} = 3214, 3188, 17566, 1575, 1488, 1443, 1306, 1288, 1202, 1094, 838, 795, 759, 686, 631, 532 cm^{-1} . ^1H NMR (DMSO- d_6): δ = 7.54 (d, J = 8.4 Hz, 2H, ArH), 8.08 (d, J = 8.4 Hz, 2H, ArH), 8.25 (s, 1H, CH=), 11.26 (s, 1H, NH), 11.42 (s, 1H, NH).

3e: IR (KBr): ν_{\max} = 3210-3090, 1730, 1674, 1552, 1435, 1402, 1309, 1216, 1182, 795 cm^{-1} . ^1H NMR (DMSO- d_6): δ = 7.48 (dd, J 1 = 6.75 Hz, J 2 = 1.83 Hz, 1H, ArH₅), 7.74 (d, J = 6.4 Hz, 1H, ArH₆), 7.76 (d, J = 4.14 Hz, 1H, ArH₃), 8.26 (s, 1H, HC=), 11.28 (s, 1H, NH), 11.50 (s, 1H, NH).

3f: IR (KBr): ν_{\max} = 3238, 1750, 1682, 1601, 1519, 1437, 1408, 1371, 1315, 1220, 852, 793, 736, 711 cm^{-1} . ^1H NMR (DMSO- d_6): δ = 7.57 (t, 1H, J = 6.4 Hz, ArH), 7.68 (t, 1H, J = 6.4 Hz, ArH), 7.79 (t, 1H, J = 7.2 Hz, ArH), 8.23 (d, 1H, J = 7.2 Hz, ArH), 8.60 (s, 1H, CH=), 11.22 (s, 1H, NH), 11.47 (s, 1H, NH).

3g: IR (KBr): ν_{\max} = 3293, 3189, 1689, 1627, 1530, 1445, 1402, 1252, 1158, 812, 782, 735, 686, 634, 532 cm^{-1} . ^1H NMR (DMSO- d_6): δ = 7.64-8.32 (m, 4H, ArH), 8.72 (s, 1H, CH=), 11.36 (s, 1H, NH), 11.52 (s, 1H, NH).

3h: IR (KBr): ν_{\max} = 3250-3140, 1750, 1720, 1680, 1530 cm^{-1} . ^1H NMR (DMSO- d_6): δ = 7.98-8.36 (AA'BB' system, 4H, H_{2,3,5,6}), 8.28 (s, 1H, CH=), 11.28 (s, 1H, NH), 11.46 (s, 1H, NH).

3j: IR (KBr): ν_{\max} = 3217-3060, 1720, 1695, 1660, 1560 cm^{-1} . ^1H NMR (DMSO- d_6): δ = 3.88 (s, 3H, MeO), 7.07 (d, J = 4.0 Hz, 2H, ArH_{2,6}), 8.25 (s, 1H, CH=), 8.37 (d, J = 8.0 Hz, 2H, ArH_{3,5}), 11.04 (s, 1H, NH), 11.17 (s, 1H, NH).

3k: IR (KBr): ν_{\max} = 3261-3090, 1730, 1690, 1660, 1560, 1427, 1314, 1268, 894, 841 cm^{-1} . ^1H NMR (DMSO- d_6): δ = 6.22 (s, 2H, OCH₂O), 7.11 (d, J = 8.2 Hz, 1H, H₅), 7.78 (dd, J 1 = 8.2, J 2 = 1.5 Hz, 1H, ArH), 8.23 (s, 1H, CH=), 8.30 (d, J = 1.5 Hz, 1H, ArH), 11.23 (s, 1H, NH), 11.38 (s, 1H, NH).

3m: IR (KBr): ν_{\max} = 3273, 1749, 1699, 1664, 1574, 1539, 1504, 1434, 1413, 1357, 1313, 1281, 1244, 1200, 790 cm^{-1} . ^1H NMR (DMSO- d_6): δ = 3.83 (s, 3H, CH₃O), 6.90 (d, 1H, J = 8.4 Hz, ArH), 7.80 (d, 1H, J = 8.4 Hz, ArH), 8.46 (s, 1H, CH=), 10.50 (s, 1H, OH), 11.10 (1H, s, NH), 11.22 (s, 1H, NH).

3n: IR (KBr): ν_{\max} = 3216, 3073, 2960, 2870, 1610, 1500, 1425, 1365, 1298, 1215, 875, 743 cm^{-1} . ^1H NMR (DMSO- d_6): δ = 7.43-7.67 (m, 5H, ArH), 7.68 (d, 1H, CH=), 7.10 (d, 1H, CH=), 8.42 (m, 1H, CH=), 11.22 (s, 1H, NH), 11.27 (s, 1H, NH).

3o: IR (KBr): ν_{\max} = 3240, 3178, 3033, 2858, 1724, 1651, 1439, 1399, 1309, 1191, 1085, 942, 869, 828, 791, 682, 504 cm^{-1} . ^1H NMR (DMSO- d_6): δ = 3.12 (s, 6H, 2 \times CH₃), 6.80 (d, J = 9.2 Hz, 2H, ArH), 8.15 (s, 1H, CH=), 8.42 (d, J = 9.2 Hz, 2H, ArH), 10.92 (s, 1H, NH), 11.03 (s, 1H, NH).

RESULTS AND DISCUSSION

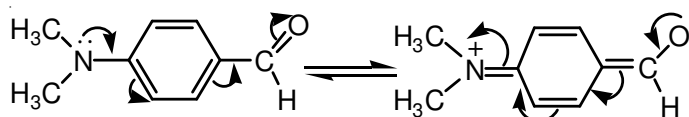
When aromatic aldehyde (**1**) and barbituric acid (**2**) were grounded by mortar and pestle catalyzed by ZrO_2/SO_4^{2-} solid superacid without solvent at room temperature for 15 min and was kept at room temperature in a desiccator, the products **3** were obtained. The results are summarized in Table-1.

TABLE-1
CONDENSATION OF BARBITURIC ACID WITH AROMATIC ALDEHYDES CATALYZED BY ZrO_2/SO_4^{2-} SOLID SUPERACID BY THE GRINDING METHOD

Ar	Product	Colour	Yield (%)	m.p. (°C)	
				Found	Reported ⁶⁻¹¹
C ₆ H ₅ 1a	3a	Milk white	90	269-271	271-272
2-ClC ₆ H ₄ 1b	3b	White	91	220-222	221-222
3-ClC ₆ H ₄ 1c	3c	White	94	274-276	274-278
4-ClC ₆ H ₄ 1d	3d	White	92	296-298	301-302
2,4-Cl ₂ C ₆ H ₃ 1e	3e	White	93	265-267	265-270
2-NO ₂ C ₆ H ₄ 1f	3f	Light yellow	94	260-262	260-261
3-NO ₂ C ₆ H ₄ 1g	3g	Light yellow	90	242-244	242-245
4-NO ₂ C ₆ H ₄ 1h	3h	Light yellow	92	290-293	287-289
4-CH ₃ C ₆ H ₄ 1i	3i	White	86	276-278	278-280
4-CH ₃ OC ₆ H ₄ 1j	3j	Light yellow	88	284-286	296-298
3,4-(OCH ₂ O)C ₆ H ₃ 1k	3k	Light yellow	90	318-320	320
4-HOC ₆ H ₄ 1l	3l	Yellow	86	> 350	> 350
4-HO-3-CH ₃ OC ₆ H ₃ 1m	3m	Yellow	89	292-294	293-294
C ₆ H ₅ CH=CH 1n	3n	Light yellow	87	248-250	250
4-(CH ₃) ₂ NC ₆ H ₄ 1o	3o	Red	74	278-280	277-279

As shown in Table-1, a series of aromatic aldehyde (**1**) and barbituric acid (**2**) on reaction to afford the corresponding 5-arylidene barbituric acid (**3**) in good to excellent yields. No strongly obvious effect of electron and nature of substituents on the aromatic ring was observed. Benzaldehyde, cinnamaldehyde and majority of aromatic aldehydes containing electron-donating groups (such as alkyl group, alkoxy group, hydroxy group) or electron-withdrawing groups (such as halide, nitro group) were employed and reacted well to give the corresponding products **3** in good to excellent yields under this reaction conditions. However, 4-dimethylaminobenzaldehyde and barbituric acid was ground to give 5-(4-dimethylaminobenzylidene)barbituric acid in moderate yield (74 %) under the same conditions. The explanation for this result may be due to the strong electron donating

dimethylamino group in (**1o**) which will reduce the reactivity. A degree of tautomerization may occur in (**1o**) with formation of quinonoid structure and thus decreased reactivity of the aldehyde group (**Scheme-II**).

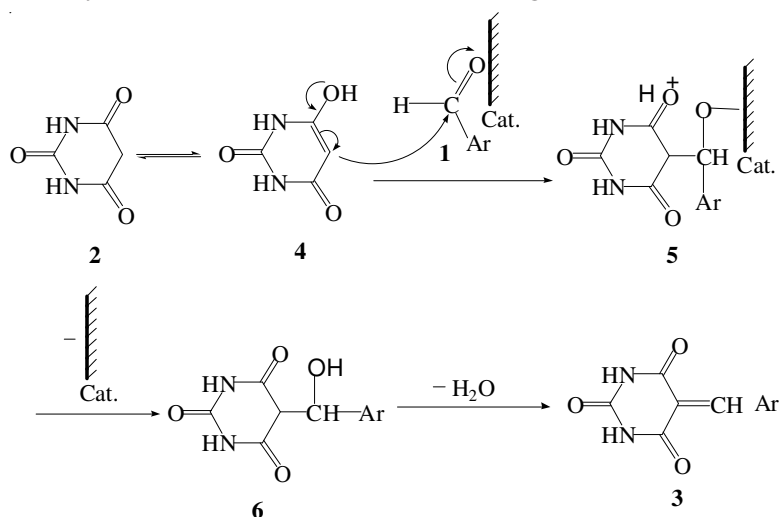


Scheme-II

Considering the reaction of 3-chlorobenzaldehyde as an example, we investigate the effect of the catalyst on the reaction. It was found that increasing the quantity of the catalyst can improve the reaction yields. For example, the reaction could be carried out in the absence of $\text{ZrO}_2/\text{SO}_4^{2-}$ solid superacid when the mixture (**1** and **2**) under solvent-free condition by the grinding at room temperature for 15 min, but obtained in poor yield (28 %). The use and increasing amount of the catalyst to 5, 10 and 15 mol % results in accelerating the reaction yields to 66, 87 and 94 %, respectively. The use of 15 mol % $\text{ZrO}_2/\text{SO}_4^{2-}$ solid superacid is sufficient to push the reaction forward. Higher amounts of the catalyst did not improve the results to a greater extent. Thus, 15 mol % $\text{ZrO}_2/\text{SO}_4^{2-}$ solid superacid was chosen as a quantitative catalyst for these reactions.

It is found that increasing the grinding time can improve the reaction yields. For example, when the grinding time is 5 min, the yield of **3c** is 64 %, whereas when the grinding time is 15 min, the yield increased to 94 %.

The catalyst was easily regenerated by washing with ethanol followed by drying at 120°C for 2 h. The catalyst could be reused 5 times for the synthesis 5-arylidene barbituric acid (**3c**) without significant loss of activity.



Scheme-III

A possible mechanism (**Scheme-III**) to explain for the reaction. Initially barbituric acid (**2**) isomerizes to **4**. The step (**2** → **4** + **1** → **5** → **6**) can be regarded as a fast Knoevenagel addition. Finally, the expected products **3** were afforded by elimination of water (**6** → **3**).

Conclusion

In conclusion, a facile and efficient method for the synthesis of 5-arylidene barbituric acid catalyzed by ZrO₂/SO₄²⁻ solid superacid by the grinding method has been developed. This method possesses these advantages of the operational simplicity, short reaction time, high yields, which uses high reactivity, non-toxic, non-corrosive, non-polluting, recyclable and environment-friendly catalyst.

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