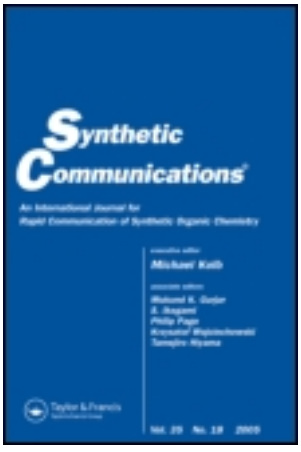


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient Method for Synthesis of the Derivatives of 5-Arylidene Barbituric Acid Catalyzed by Aminosulfonic Acid With Grinding

Ji-Tai Li [a] , Hong-Guang Dai [a] , Da Liu [a] & Tong-Shuang Li [a]
[a] College of Chemistry and Environmental Science, Hebei University, Key Laboratory of Analytical Science and Technology of Hebei Province, Baoding, China
Version of record first published: 16 Aug 2006.

To cite this article: Ji-Tai Li , Hong-Guang Dai , Da Liu & Tong-Shuang Li (2006): Efficient Method for Synthesis of the Derivatives of 5-Arylidene Barbituric Acid Catalyzed by Aminosulfonic Acid With Grinding, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:6, 789-794

To link to this article: http://dx.doi.org/10.1080/00397910500451324

Synthetic Communications®, 36: 789–794, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500451324

Efficient Method for Synthesis of the Derivatives of 5-Arylidene Barbituric Acid Catalyzed by Aminosulfonic Acid With Grinding

Ji-Tai Li, Hong-Guang Dai, Da Liu, and Tong-Shuang Li
College of Chemistry and Environmental Science, Hebei University,
Key Laboratory of Analytical Science and Technology of
Hebei Province, Baoding, China

Abstract: Aminosulfonic acid is an environmentally friendly catalyst. Grinding a mixture of aromatic aldehydes, barbituric acid, and H_2NSO_3H at room temperature (without any solvent) gave 5-arylidene barbituric acid in high yields, providing a simple and efficient route to synthesis of these compounds.

Keywords: Aminosulfonic acid, aromatic aldehyde, 5-arylidene barbituric acid, barbituric acid, grinding method

INTRODUCTION

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 nonlinear optical materials.[3] Over the past few years, many synthetic methods[3–7] for preparation of these compounds have been reported, such as infrared irradiation[3] and

Received in Japan July 15, 2005
Address correspondence to Ji-Tai Li, College of Chemistry and Environmental Science, Hebei University , Hezuo Road No. 88, Baoding 071002, China. Fax: +86-312-5079628; E-mail: lijitai@yahoo.com.cn

microwave irradiation.[4] However, many of these procedures involve expensive reagents, higher temperatures, and lower yields.

Aminosulfonic acid[8] has been extensively used as a catalyst for many organic reactions, such as the esterification of carboxylic acids; the oxidation of aromatic aldehydes to carboxylic acids; the preparation of amines by decarbonylation of carboxamides with sodium hypochlorite; the synthesis of anthroquinonecarboxamides from anthroquinonecarboxylic acids; synthesis of dihydropyrimidinones via condensation of aldehydes, β-keto esters, and urea[9]; and synthesis of bis(indolyl)methanes from indole and aromatic aldehydes[10].

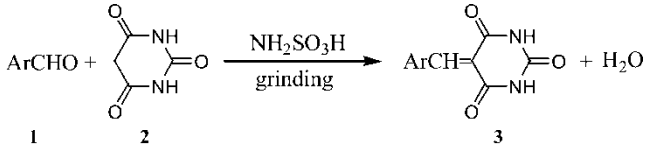
The grinding method is used more and more frequently in organic synthesis in the past three decades. Compared with traditional methods, this method is more convenient and easily controlled. A great number of organic reactions can be carried out in higher yields, shorter times, or milder conditions by the grinding method. It can even set off some reactions that cannot be carried out under traditional conditions.[11]

All of these results spurred us to study the possibility of Knoevenagel condensation of aromatic aldehydes with barbituric acid catalyzed by aminosulfonic acid without solvent. Herein, we report the condensation using aminosulfonic acid as catalyst under solvent-free conditions by the grinding method at room temperature (Scheme 1).

RESULTS AND DISCUSSION

As shown in Table 1, the effects of different catalysts, such as potassium acid phthalate, NH_4Cl, 4-$CH_3C_6H_4SO_3H$, and NH_2SO_3H, on the reaction were examined. Among these catalysts, aminosulfonic acid was found to be an excellent catalyst in terms of yield and cost. So, we chose aminosulfonic acid as the catalyst for synthesis of 5-arylidene barbituric acid by the grinding method.

We studied the influence of the amount of the catalyst on the yield. As shown in Table 2, increasing the quantity of the catalyst can improve the reaction yields. For example, without catalyst the yield is 35%, whereas using 100% mol H_2NSO_3H, the yield of **3i** is 96% for the same period (120 min) using the grinding method.



1 2 3

Scheme 1.

Table 1. Effects of catalysts on the reaction of 4-ClC_6H_4CHO and barbituric acid

Entry	Catalyst[a]	Grinding time, min	Laying time, min	Yield, %
1	Potassium acid phthalate	5	30	23
2	NH_4Cl	5	30	53
3	4-$CH_3C_6H_4SO_3H$	5	30	81
4	NH_2SO_3H	5	30	80

[a]The amount of catalyst is 100% mol. Barbituric acid, 2 mmol (256 mg); aldehyde, 2 mmol (281 mg).

As shown in Table 3, increasing the grinding time can improve the reaction yields. For example, when the grinding time is 1 min, the yield of **3b** is 69%, whereas when the grinding time is 10 min, the yield of **3b** is 86%.

From the results in Table 1, Table 2, and Table 3, the reaction conditions we chose were aromatic aldehyde (2 mmol), barbituric acid (2 mmol), H_2NSO_3H (2 mmol), and grinding the mixture for 10 min. Under these reaction conditions, we did a series of experiments for the condensation of barbituric acid with different aldehydes using the grinding method.

The results are summarized in Table 4. It can easily be seen that the solvent-free grinding method represented a good procedure in terms of the high yield, mild reaction condition, and easy workup. For example, under solvent-free conditions using the grinding method, compounds **3b**, **3f**, **3i**, and **3j** were obtained in high yields (93%, 94%, 96%, 94%). Also, the present procedure also got a good result on a 100-mmol scale for **1b**. The reaction in the absence of solvent has a high concentration of reactants, and the surface area of the catalyst increases greatly upon being ground.

The steric hindrance affects the yields too. As shown in Table 4, when the amount of the catalyst was 100% mol, **3b** was obtained in 93% yield within 190 min, but the reaction of babituric acid with **1a** gave **3a** in only 85% yield within 250 min.

Table 2. Effects of amount of H_2NSO_3H on the reaction of 4-$(CH_3)_2NC_6H_4CHO$ and barbituric acid

Entry	Grinding time, min	Laying time, min	Amount of catalyst, %mol	Yield, %
1	10	120	0	35
2	10	120	10	87
3	10	120	100	96
4	10	120	150	96

Note: Barbituric acid, 2 mmol (256 mg); aldehyde, 2 mmol (298 mg).

Table 3. Effects of grinding time on the reaction of 4-ClC_6H_4CHO and barbituric acid catalyzed by 100% mol NH_2SO_3H

Entry	Grinding time, min	Laying time, min	Yield, %
1	1	30	69
2	5	30	80
3	10	30	86
4	15	30	84

Note: Barbituric acid, 2 mmol (256 mg); aldehyde, 2 mmol (281 mg).

CONCLUSION

In conclusion, we have found a practical Knoevenagel condensation procedure for the preparation of 5-arylidene barbituric acid catalyzed by H_2NSO_3H by the grinding method.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were measured on a Bruker Advance 400 (400-MHz) spectrometer using TMS as internal standard and DMSO as solvent.

Table 4. Condensation of barbituric acid with aromatic aldehydes[a]

Entry	Ar	Laying time, h	mp,°C (lit.)	Yield, %
a	3-ClC_6H_4	4	273–275 (274–278)[12]	85
b	4-ClC_6H_4	3	298–300 (304–308)[12]	93
b[b]	4-ClC_6H_4	3	298–300 (304–308)[12]	96
c	2,4-$Cl_2C_6H_3$	4	269–271 (265–270)[12]	89
d	3-$NO_2C_6H_4$	6	251–253 (248–250)[12]	47
e	4-$CH_3C_6H_4$	4	282–284 (278–280)[12]	65
f	4-$CH_3OC_6H_4$	6	307–309 (298–300)[12]	94
g	3-CH_3O-4-HOC_6H_3	6	309–313 (313)[13]	87
h	$C_6H_5CH{=}CH$	4	274–276 (250)[7]	81
i	4-$(CH_3)_2NC_6H_4$	2	282–284 (278–282)[12]	96
j	4-HOC_6H_4	4	>350	94

[a]The grinding time is 10 min.
[b]The reaction was done on a 100-mmol scale.

General Procedure

Barbituric acid (2 mmol), aromatic aldehyde (2 mmol), and H_2NSO_3H (2 mmol) were added to a mortar. The mixture was ground by mortar and pestle at room temperature for 10 min and was kept at room temperature in a desiccator. The mixture was dissolved in DMSO, and the solution was poured into H_2O. The precipitate was washed with boiling H_2O and then washed with EtOH, affording **3a**–**3j**.The authenticity of the products was established by comparing their melting points and ^{1}H NMR spectra with the data in the literature.

3 h: ^{1}H NMR (400 MHz, DMSO): δ_H 7.49–7.73 (6H, m), 8.015 (1H, d, $J = 12$ Hz), 8.44 (1H, t, $J = 12$ Hz), 11.21 (1H, s, NH), 11.26 (1H, s, NH).

3j: ^{1}H NMR (400 MHz, DMSO): δ_H 6.88 (2H, s), 8.21 (1H, s), 8.33 (2H, s), 10.79 (1H, s, OH), 11.11 (1H, s, NH), 11.24 (1H, s, NH).

ACKNOWLEDGMENTS

Educational Ministry of China, Educational Department of Hebei Province (2001104), and Natural Science Foundation of Hebei Province (203107), China, supported the project.

REFERENCES

1. (a) Bojarski, J. T.; Mokrosz, J. L.; Barton, H. J.; Paluchowska, M. H. Recent progress in barbituric acid chemistry. *Adv. Heterocycl. Chem.* **1985**, *38*, 229–297 and reference therein; (b) Jursic, B. S. A simple method for Knoevenagel condensation of α,β-conjugated and aromatic aldehydes with barbituric acid. *J. Heterocycl. Chem.* **2001**, *38*, 655–657 and reference therein.
2. (a) Figueroa-Villar, J. D.; Rangel, C. E.; Dos Santos, L. N. Synthesis of oxadeaza-flavines from barbituric acid and aromatic aldehydes. *Synth. Commun.* **1992**, *22* (8), 1159–1164; (b) Tanka, K.; Cheng, X.; Yoneda, F. Oxidation of thiol with 5-arylidene-1,3-dimethylbarbituric acids: Application to synthesis of unsymmetrical disulfide. *Tetrahedron* **1988**, *44* (11), 3241.
3. Alcerreca, G.; Sanabria, R.; Miranda, R.; Arroyo, G.; Tamariz, J.; Delgado, F. Preparation of benzylidene barbituric acids promoted by infrared irradiation in absence of solvent. *Synth. Commun.* **2000**, *30*, 1295–1301 and reference therein.
4. Dewan, S. K.; Singh, R. One-pot synthesis of barbiturates on reaction of barbituric acid with aldehydes under microwave irradiation using a variety of catalysts. *Synth. Commun.* **2003**, *33*, 3081–3084.
5. Wan, Y.; Chen, J.; Zhuang, Q. Y.; Shi, D. Q. The condensation of aromatic aldehyde with barbituric acid, 2-thiobarbituric acid in water. *J. Xuzhou Normal Univ.* **2004**, *22*, 47–50.

6. Gao, Y.; Tu, S. J.; Zhou, J. F. Solid phase synthesis of 5-arylidene barbituric acid. *Chin. J. App. Chem.* **2002**, *19*, 499–500.
7. Li, G. S.; Li, J. C.; Wang, C.; Feng, S.; Li, X. L. Study of the solid state reactions of barbituric acid and aromatic aldehyde. *Chem. J. Chin. Univ.* **2001**, *22*, 2042–2044.
8. Wang, B. Sulfamic acid: a very useful catalyst. *Synlett* **2005**, 1342–1343.
9. Li, J. T.; Han, J. F.; Yang, J. H.; Li, T. S. An efficient synthesis of 3,4-dihydropyrimidin-2-ones catalyzed by NH_2SO_3H under ultrasound irradiation. *Ultrason. Sonochem.* **2003**, *10*, 119–122.
10. Li, J. T.; Dai, H. G.; Xu, W. Z.; Li, T. S. An efficient and practical synthesis of bis(indolyl)methanes catalyzed by aminosulfonic acid under ultrasound. *Ultrason. Sonochem.* **2005**, *13*, 24–27.
11. Wang, S. X.; Li, J. T.; Geng, L. J. Synthesis of α,α'-bis(substitutedbenzylidene)-cycloalkanones by a grinding method. *J. Chem. Res.* **2003**, 370–371.
12. Geng, L. J.; Wang, S. X.; Li, J. T.; Liu, C. H. Preparation of the derivatives of 5-arylidene barbituric acid by grinding method. *Chin. J. Org. Chem.* **2002**, *22*, 1047–1049.
13. Kanpp, G.; Naimi-Jamal, M. R.; Schmeyers, J. Solvent-free Knoevenagel condensations and Michael additions in the solid state and in the melt with quantitative yield. *Tetrahedron* **2003**, *59*, 3753–3760.