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# Xanthan Sulfuric Acid: An Efficient Bio-supported and Recyclable Solid Acid Catalyst for the Synthesis of 2-Aryl Thiadiazolo Benzimidazoles

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Xanthan sulfuric acid is an efficient solid acid catalyst for the preparation of 2-aryl benzimidazoles in excellent yields. This method is applicable for the reaction of benzo[*c*][1,2,5]thiadiazole-4,5-diamine with aldehydes by simple physical grinding at room temperature. The salient features of the present methodology is cheaper process, easy synthesis of stable catalyst and the catalyst can be easily recycled without significant loss of activity.

**Keywords** benzimidazoles, benzo[*c*][1,2,5]thiadiazole-4,5-diamine, biodegradable, recyclable, xanthan sulfuric acid (XSA)

## Introduction

One of the most challenging tasks in modern organic chemistry is the synthesis of natural products containing heterocyclic ring. Despite the considerable exploration to date within this field, there is still a need for further development of alternative methods for the synthesis of heterocyclic compounds. The benzimidazole ring is a crucial pharmacophore in drug discovery. Benzimidazole derivatives are unique, potent and broad-spectrum class of antirhino/enteroviral agents. They exhibit significant activities such as antihistaminics, antiparasitics, antiulcers, antihypertensives, antivirals, antibacterial, antifungals, anticancers and antitubercular.[1,2] Benzimidazole and its derivatives have been used to act EGFR, VEGFR-2 and PDGFR kinase inhibitors,[3] selective neuropeptide Y Y 1 receptor antagonists,[4] H+/K+-ATP enzyme inhibitors,[5] nitroreductase and aminopeptidase activity in clinically important bacteria.[6] In addition, benzimidazoles are very important intermediates in organic reactions.[7] Therefore, the preparation of benzimidazoles has gained considerable attention in recent years. Despite their importance from pharmacological, industrial, and synthetic point of views, comparatively few methods for the preparation of benzimidazoles have been reported. These include the condensation of *o*-aryldiamines and aldehyde in refluxing nitrobenzene,[8] the condensation of *o*-aryldiamines with carboxylic acids or their derivatives in the presence of strong acids such as polyphosphoric acid[9] or mineral acids,[10] and thermal or acid promoted cyclization of *N*-(*N*-arylbenzimidoyl)-1,4-benzoquinoneimines.[11] Benzimidazoles have also been prepared on a solid phase to provide a combinatorial approach.[12] Various oxidative and catalytic reagents such as sulfamic acid,[13] $I_2$,[14] DDQ,[15] air,[16] oxone,[17] $FeCl_3 \cdot 6H_2O$,[18] $In(OTf)_3$,[19] $Yb(OTf)_3$,[20] $Sc(OTf)_3$,[21] $KHSO_4$,[22] SASPSPE,[23] copper[24] and ionic liquid were used for the synthesis of benzimidazoles.[25] Some of these methods have suffered from the drawbacks such as harsh reaction conditions (*i.e.*, the condensation of *o*-aryldiamines and carboxylic acids carried out by conventional thermal heating, heating under pressure in solvents, using a stoichiometric or excess amount of acid, and very high reaction temperatures), use of hazardous reagents, drastic reaction conditions, prolonged reaction time, tedious work-up procedures, co-occurrence of side reactions, low yields, and expensive reagents/catalysts. Some of the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Furthermore, the disposal of these acids leads to environmental pollution. In view of the pharmaceutical application values of 2-aryl benzimidazoles, it is worthwhile to search continuously for a better catalyst for the synthesis of 2-aryl benzimidazoles in terms of operational simplicity, reusability of catalyst, low cost and greater selectivity.

Xanthan and its derivatives,[26-28] have some unique properties, which make them attractive alternatives for conventional organic or inorganic supports for catalytic applications. Xanthan is the most abundant bacterial

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exopolysaccharide in the world, which is produced through fermentation and it has been widely studied during the past decades, as it is a biodegradable material and a renewable resource. Unlike other gums, it is very stable under a wide range of temperatures and pH values. Recently, xanthan sulfuric acid has emerged as a promising biopolymeric solid support acid catalyst for acid-catalyzed reactions, such as the synthesis of $\alpha$-aminonitriles and 2-amino selenazole-5-carboxylates.[29] Xanthan sulfuric acid can be easily prepared by the reaction of inexpensive xanthan with chlorosulfonic acid.

## Experimental

The progress of the reaction was monitored by TLC. $^1$H NMR spectra were measured on a Varian Gemini 200-MHz spectrometer using TMS as internal standard. The C, H, and N analysis of the compound was done on a Carlo Erba model EA1108. Mass spectra were recorded on a Jeol JMS D-300 spectrometer.

### Preparation of xanthan sulfuric acid

To a magnetically stirred mixture of xanthan (5.00 g) in $CHCl_3$ (15 mL), chlorosulfonic acid (1.00 g) was added dropwise at 0 ℃ during 2 h. After completion of the addition, the mixture was stirred for 3 h. Then, the mixture was filtered and washed with methanol (25 mL) and dried at room temperature to obtain XSA as white powder (5.30 g). Sulfur content of the samples by conventional elemental analysis, was 0.62 mmol/g for XSA. The number of $H^+$ site of xanthan-$SO_3H$ determined by acid-base titration was 0.6 meq/g. This value corresponds to about 92% of the sulfur content, indicating that most of the sulfur species on the sample are in the form of the sulfonic acid groups.

### Procedure for the synthesis of thiadiazolo benzimidazoles

Mixture of xanthan sulfuric acid (0.1 g), aldehyde (3.6 mmol) and benzo[*c*][1,2,5]thiadiazole-4,5-diamine (3.0 mmol) was taken in a mortar, grinding with a pestle at room temperature in the presence of air for the appropriate time, as shown in Table 3. After completion of reaction (progress of the reaction was observed by TLC), $CHCl_3$ (15 mL) was added. The catalyst (XSA) was filtered off, solid was washed with $CHCl_3$ (5 mL), combined $CHCl_3$ solution was concentrated in vacuum to afford the crude product and the crude solid product was further purified by column chromatography [*V*(hexane)/*V*(ethyl acetate)＝8∶2].

## Product characterization data

(Table 3, Entry **3a**): m.p. 185 ℃; $^1$H NMR ($CDCl_3$) $\delta$: 6.11 (s, 1H), 7.07—7.84 (m, 7H); IR (KBr) *v*: 1617, 3419 cm$^{-1}$; EIMS (70 eV) *m*/*z*: 252 ($M^+$). Anal. calcd for $C_{13}H_8N_4S$: C 61.89, H 3. 20, N 22.21; found C 61.83, H 3.21, N 22.24.

(Table 3, Entry **3l**): m.p. 270 ℃; $^1$H NMR ($CDCl_3$) $\delta$: 5.39 (s, 1H), 7.61—8.08 (m, 6H), 9.17 (s, 1H); IR (KBr) *v*: 1622, 3433 cm$^{-1}$; EIMS (70 eV) *m*/*z*: 320 ($M^+$). Anal. calcd for $C_{16}H_8N_4O_2S$: C 59.99, H 2.52, N 17.49; found C 59.83, H 2.64, N 17.37.

(Table 3, Entry **3m**): m.p. 156 ℃; $^1$H NMR ($CDCl_3$) $\delta$: 5.42 (s, 1H), 7.57—8.14 (m, 5H), 9.20 (s, 1H); IR (KBr) *v*: 1625, 3434 cm$^{-1}$; EIMS (70 eV) *m*/*z*: 365 ($M^+$). Anal. calcd for $C_{16}H_7N_5O_4S$: C 52.60, H 1.93, N 19.17; found C 51.72, H 1.51, N 20.21.

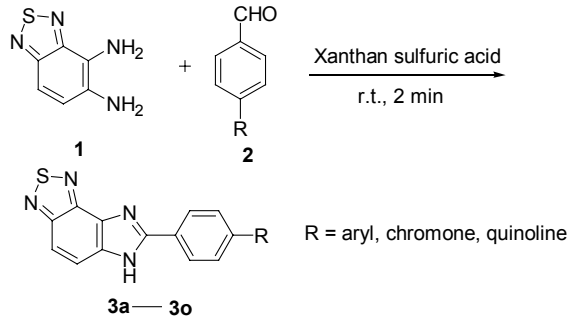
(Table 3, Entry **3n**): m.p. 160 ℃; $^1$H NMR ($CDCl_3$) $\delta$: 5.40 (s, 1H), 7.58—8.12 (m, 7H); IR (KBr) *v*: 1612, 3406 cm$^{-1}$; EIMS (70 eV) *m*/*z*: 337 ($M^+$). Anal. calcd for $C_{16}H_8ClN_5S$: C 56.89, H 2.39, N 20.73; found C 56.09, H 2.22, N 20.13.

(Table 3, Entry **3o**): m.p. 140 ℃; $^1$H NMR ($CDCl_3$) $\delta$: 2.12 (s, 3H), 5.62 (s, 1H), 7.38—7.92 (m, 6H); IR (KBr) *v*: 1653, 3492 cm$^{-1}$; EIMS (70 eV) *m*/*z*: 351 ($M^+$). Anal. calcd for $C_{17}H_{10}ClN_5S$: C 58.04, H 2.86, N 19.91; found C 56.78, H 2.23, N 20.45.

## Results and Discussion

In continuation of our research work on new reagents,[30] we report here the cheaper and recyclable xanthan sulfuric acid as an efficient mild Lewis acid catalyst for the preparation of 2-aryl benzimidazoles in excellent yields (Scheme 1). The plausible mechanism for the formation of benzimidazole by using xanthan sulfuric acid is shown as Scheme 2. The reaction was carried out at room temperature for 2—10 min by simple physical grinding of benzo[*c*][1,2,5]thiadiazole-4,5-diamine with aldehydes in the presence of xanthan sulfuric acid to give the desired benzimidazoles in excellent yields.

**Scheme 1** Synthesis of 2-aryl benzimidazoles with XSA




To illustrate the need of the xanthan sulfuric acid, an experiment was conducted in the absence of xanthan sulfuric acid, and yields obtained were very low, side products were formed and reactants were not involved completely in this reaction. Obviously, the xanthan sulfuric acid is an important component of the reaction.

The efficiency of the xanthan sulfuric acid compared to various sulfur analog acidic catalysts was also examined (Table 1). In this study it was found that xanthan sulfuric acid is a more efficient and superior catalyst

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**Scheme 2** Proposed mechanism

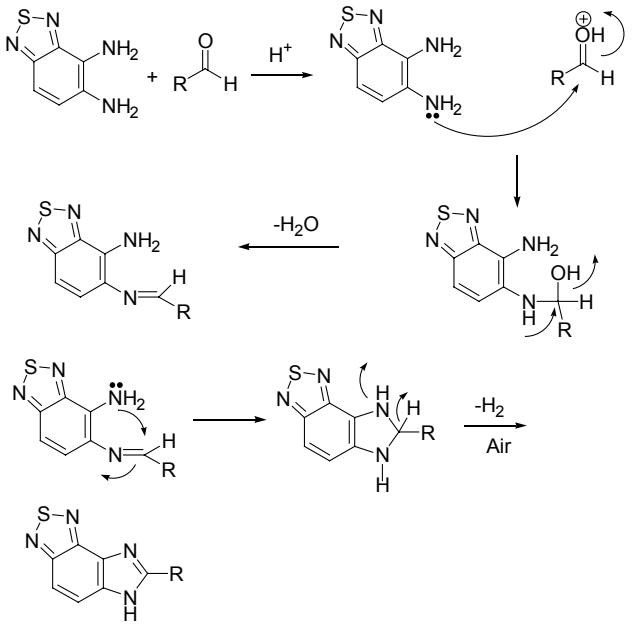

**Table 1** Effect of catalysts on yield

| Entry | Catalyst | Yield[a]/% |
|---|---|---|
| 1 | Xanthan sulfuric acid | 96 |
| 2 | Silica sulfuric acid | 92 |
| 3 | *p*-Toluene sulfonic acid | 85 |
| 4 | Sulfuric acid in acetic acid | 55 |
| 5 | No catalyst | 10 |

[a] Yields refer to the pure isolated product.

over other acidic catalysts with respect to reaction time and yield. It was also observed that the yield was only 10% in the absence of the xanthan sulfuric acid catalyst.

We examined the amount of catalyst in this reaction. The best results were obtained using 0.1 g of catalyst (96%). Using lower amounts of catalyst resulted in lower yields, and in the absence of catalyst the yield of the product was found to be very low (Table 2).

**Table 2** Influence of the catalytic amounts of xanthan sulfuric acid [a]

| Entry | Catalyst/g | Time/min | Yield[b]/% |
|---|---|---|---|
| 1 | None | 20 | Trace |
| 2 | 0.02 | 20 | 25 |
| 3 | 0.04 | 10 | 52 |
| 4 | 0.08 | 10 | 79 |
| 5 | 0.1 | 20 | 96 |
| 6 | 0.1 | 10 | 96 |

[a] Yields refer to the pure isolated product.

The recovered catalyst can be reused at least three additional times in subsequent reactions without significant loss in product yield (Table 4).

**Table 3** Synthesis of benzimidazoles by XSA

| Entry | Aldehyde | Time/min | Yield[a]/% |
|---|---|---|---|
| **3a** | Benzaldehyde | 2 | 96 |
| **3b** | 4-Hydroxybenzaldehyde | 3 | 91 |
| **3c** | 4-Chlorobenzaldehyde | 2 | 95 |
| **3d** | 2-Chlorobenzaldehyde | 3 | 90 |
| **3e** | 4-Methylbenzaldehyde | 3 | 92 |
| **3f** | 4-Methoxybenzaldehyde | 3 | 95 |
| **3g** | 2-Nitrobenzaldehyde | 2 | 83 |
| **3h** | 4-Nitrobenzaldehyde | 2 | 88 |
| **3i** | Naphthaldehyde | 3 | 89 |
| **3j** | 4-Ethoxybenzaldehyde | 3 | 87 |
| **3k** | Furanaldehyde | 2 | 80 |
| **3l** | 4-oxo-4*H*-Chromene-3-carbaldehyde | 3 | 82 |
| **3m** | 6-Nitro-4-oxo-4*H*-chromene-3-carbaldehyde | 5 | 78 |
| **3n** | 2-Chloroquinoline-3-carbaldehyde | 3 | 78 |
| **3o** | 2-Chloro-6-methylquinoline-3-carbaldehyde | 3 | 75 |

[a] Yields refer to isolated pure products.

**Table 4** Results of recyclability of the catalyst[a]

| Run | Cycle | Yield[b]/% |
|---|---|---|
| 1 | 0 | 96 |
| 2 | 1 | 94 |
| 3 | 2 | 88 |
| 4 | 3 | 71 |

[a] Reaction conditions: Mixture of xanthan sulfuric acid (0.1 g), aldehyde (3.6 mmol) and benzo[*c*][1,2,5]thiadiazole-4,5-diamine (3.0 mmol) was ground at room temperature. [b] Yields refer to the pure isolated product.

## Conclusions

In conclusion, xanthan sulfuric acid has proved to be an effective catalyst for the synthesis of benzimidazoles under solid state conditions. The protocol offers several advantages such as catalyst reusability, high yields of product, short reaction time, simple work up procedures and easy isolation, thus making it a viable alternative to the existing methods. Further work is in progress to extrapolate the catalytic activity of xanthan sulfuric acid to other organic transformations

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## References

[1] (a) Zarriumayeh, H.; Zimmerman, D. M.; Cantrell, B. E.; Schober, D.

  

A.; Bruns, R. B.; Gackenheimer, S. L.; Ornstein, P. L.; Hipskind, P. A.; Brittan, T. C.; Gchlert, D. R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 647; (b) Terzioglu, N.; Rijin, R. M. V.; Bakker, R. A.; Desch, I. J.; Lecurs, R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5251.

[2] (a) Erhardt, P. W. *J. Med. Chem.* **1987**, *30*, 231; (b) Ries, U. J.; Mihm, G.; Narr, B.; Hasselbach, K. M.; Wittenben, H.; Entzeroth, M.; Meel, J. C. A. V.; Wienen, W.; Hauel, N. H. *J. Med. Chem.* **1993**, *36*, 4040; (c) Mann, J.; Baron, A.; Opoku-Boahen, Y.; Johansson, E.; Parkinson, G.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **2001**, *44*, 138; (d) Song, X.; Vig, B. S.; Lorenzi, P. L.; Darach, J. C.; Townsend, L. B.; Amiadon, G. L. *J. Med. Chem.* **2005**, *48*, 1274; (e) Ren, X.; Chen, J.; Le, X. *Chin. J. Chem.* **2011**, *29*, 1380; (f) Camacho, J.; Barazarte, A.; Gamboa, N.; Rodrigues, J.; Rojas, R.; Vaisberg, A.; Gilman, R.; Charris, O. *Bioorg. Med. Chem.* **2011**, *19*, 2023.

[3] Li, Y.; Tan, C.; Gao, C.; Zhang, C.; Luan, X.; Chen, X.; Liu, H.; Jiang, Y. E. *Bioorg. Med. Chem.* **2011**, *19*, 4529.

[4] Zarrinmayeh, H.; Zimmerman, D. M.; Cantrell, B. E.; Schober, D. A.; Bruns, R. F. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 647.

[5] Yan, Y.; Liu, Z.; Zhang, J.; Xu, R.; Hu, X.; Liu, G. *Bioorg. Med. Chem. Lett.* **2011**, *21,* 4189.

[6] Cellier, M.; Fabrega, O. J.; Fazackerley, E.; James, A. L.; Orenga, S.; Perry, J. D.; Salwatura, V. L.; Stanforth, S. P. *Bioorg. Med. Chem.* **2011**, *19*, 2903

[7] Hasegawa, E.; Yoneoka, A.; Suzuki, K.; Kato, T.; Kitazume, T.; Yangi, K. *Tetrahedron* **1999**, *55*, 12957.

[8] Sun, Q.; Yan, B. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 361.

[9] Preston, P. N. In *Chemistry of Heterocyclic Compounds*, Part 1, Vol. 40, Eds.: Weissberger, A.; Taylor, E. C., Wiley, New York, **1981**, p. 6.

[10] Grimmet, M. R. In *Comprehensive Hetero cyclic Chemistry*, Vol. 5, Eds.: Kartitzky, A. R.; Ress, C. W., Pergamon, Oxford, **1984**, p. 457.

[11] Benincori, T.; Sannicolo, F. *J. Heterocycl. Chem.* **1998**, *25*, 1029.

[12] (a) Wu, Z.; Rea, P.; Wickam, G. *Tetrahedron Lett.* **2000**, *41*, 9871; (b) Mazurov, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 67.

[13] Chakrabarty, M.; Karmakar, S.; Mukherji, A.; Arima, S.; Harigaya, Y. *Heterocycles* **2006**, *68*, 967.

[14] Gogoi, P.; Konwar, D. *Tetrahedron Lett.* **2006**, *47*, 79.

[15] Lee, K. J.; Janda, K. D. *Can. J. Chem.* **2001**, *79*, 1556.

[16] Lin, S.; Yang, L. *Tetrahedron Lett.* **2005**, *46*, 4315.

[17] Beaulieu, P. L.; Hache, B.; Von Moos, E. *Synthesis* **2003**, 1683.

[18] Singh, M. P.; Sasmal, S.; Lu, W.; Chatterjee, M. N. *Synthesis* **2000**, 1380.

[19] Trivedi, R.; De, S. K.; Gibbs, R. A. *J. Mol. Catal. A: Chem.* **2005**, *245*, 8.

[20] Massimo, C.; Francesco, E.; Francesca, M. *Synlett* **2004**, 1832.

[21] Itoh, T.; Nagata, K.; Ishikawa, H.; Ohsawa, A. *Heterocycles* **2004**, *63*, 2769.

[22] Ma, H. Q.; Wang, Y. L.; Wang, J. Y. *Heterocycles* **2006**, *68*, 1669.

[23] Nasir, I.; Mohammadzade, N. S.; Niknam, K. *Chin. Chem. Lett.* **2011**, *22*, 1151.

[24] Peng, J.; Ye, M.; Zong, C.; Hu, F.; Feng, L.; Wang, X.; Wang, Y.; Chen, C. *J. Org. Chem.* **2011**, *76*, 716.

[25] Ma, H. Q.; Wang, Y. L.; L i, J. P.; Wang, J. Y. *Heterocycles* **2007**, *71*, 135.

[26] Sargent, E. V.; Adolph, J.; Clemmons, M. K.; Kirk, G. D.; Pena, B. M.; Fedoruk, M. J. *J. Occup. Med.* **1990**, *32*, 625.

[27] *Handbook of Water-Soluble Gums and Resins*, Ed.: Davidson, R. L., McGraw-Hill, New York, **1980**.

[28] *Industrial Gums*: *Polysaccharides and Their Derivatives*, Eds.: Whistler, R. L.; BeMiller, J. N., Academic Press, New York, **1973**.

[29] (a) Shaabani, A.; Maleki, A.; Soudi, M. R.; Mofakham, H. *Catal. Commun.* **2009**, *10*, 945; (b) Suresh Kuarm, B.; Venu Madhav, J.; Rajitha, B. *Lett. Org. Chem.***2011***, 8*, 549

[30] (a) Madhav, J. V.; Reddy, Y. T.; Reddy, P. N.; Nikhil, R. M.; Kuarm, S.; Crooks, P. A.; Rajitha, B. *J. Mol. Catal. A* **2009**, *304*, 85; (b) Kuarm, B. S; Reddy, Y. T.; Madhav, J. V.; Crooks, P. A.; Rajitha, B. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 524; (c) Madhav, J. V.; Kuarm, B. S; Rajitha, B. *Arkivoc* **2008**, (xiii), 145; (d) Kuarm, B. S.; Madhav, J. V.; Rajitha, B.; Reddy, Y. T.; Reddy, P. N.; Crooks, P. A. *Synth. Commun.* **2011**, *41*, 662.

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