Tetrahedron Letters 52 (2011) 3492–3495

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient and reusable heterogeneous catalyst Animal Bone Meal for facile synthesis of benzimidazoles, benzoxazoles, and benzothiazoles

Yassin Riadi [a,d], Rachid Mamouni [b,*], Rachid Azzalou [a], Mohammadine El Haddad [c], Sylvain Routier [d], Gérald Guillaumet [d,*], Saïd Lazar [a]

[a] Laboratoire de Biochimie, Environnement & Agroalimentaire, URAC 36, Université Hassan II Mohammedia-Casablanca, Mohammedia, Morocco
[b] Laboratoire de Chimie Organique, Equipe de Chimie Bio-Organique Appliquée, Université Ibn Zohr, Agadir, Morocco
[c] Département Sciences de la Matière, Faculté Poly-disciplinaire de Safi, Université Cadi Ayyad, Safi, Morocco
[d] Institut de Chimie Organique & Analytique, Université d'Orléans, UMR CNRS 6005, Orléans, France

ARTICLE INFO

Article history:
Received 31 January 2011
Revised 27 April 2011
Accepted 29 April 2011
Available online 5 May 2011

Keywords:
Animal Bone Meal
Benzimidazoles
Benzoxazoles
Benzothiazoles
Lewis acids
Air

ABSTRACT

A library of benzimidazoles, benzoxazoles, and benzothiazoles was efficiently synthesized by condensation of *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol respectively with aromatic aldehydes in the presence of catalytic amounts of Animal Bone Meal (ABM) and Lewis acids doped ABMs. Reactions were conducted under reflux conditions in air. The remarkable features of this new protocol are high conversion, short reaction times, and cleaner reaction profiles, straightforward procedure, and reduction in catalyst toxicity.

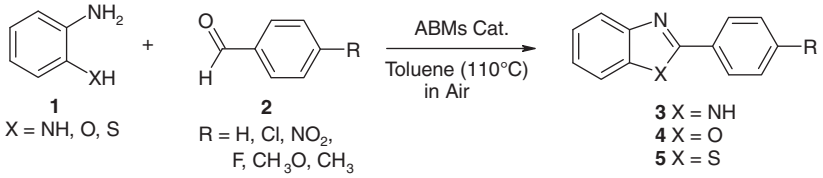
Published by Elsevier Ltd.

1. Introduction

The benzimidazole, benzoxazole, and benzothiazole skeletons may be found in numerous pharmaceutical agents with a diverse spectrum of biological properties.[1–4] Although a wide range of methods are available for synthesizing benzimidazoles,[4–13] benzoxazoles,[14–18] and benzothiazoles,[19–23] a real need exists for new and simple procedures that support many kinds of structural diversity and various substitution patterns in the target library.

Recently, some microwave-assisted methods were reported for the synthesis of 2-substituted benzothiazoles or benzoxazoles.[24] Strong oxidant[25–28] or, more interestingly, catalytic aerobic oxidation involving oxygen as terminal oxidant[29,30] have received considerable attention in the building block construction of benzoxazoles and benzimidazoles.[31–33]

In continuation of our attempts to explore the catalytic activity of Animal Bone Meal (ABM) for useful organic transformations,[34,35] we herein report that Lewis acids doped ABMs catalyzed a simple and environmentally benign synthesis of benzimidazoles, benzoxazoles and benzothiazoles, from the reaction of *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol with aldehydes under reflux conditions (Scheme 1).



Scheme 1. Synthesis of 2-arylbenzimidazoles, benzoxazoles and benzothiazoles catalyzed by ABM, $ZnCl_2$/ABM, $ZnBr_2$/ABM, and $CuCl_2$/ABM.

* Corresponding authors. Tel.: +3 323 841 7073; fax: +3 323 841 7281 (G.G.); tel.: +21 252 822 0267; fax: +21 255 282 20100 (R.M.).
E-mail addresses: mamounirachid@yahoo.fr (R. Mamouni), gerald.guillaumet@univ-orleans.fr (G. Guillaumet).

0040-4039/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2011.04.121

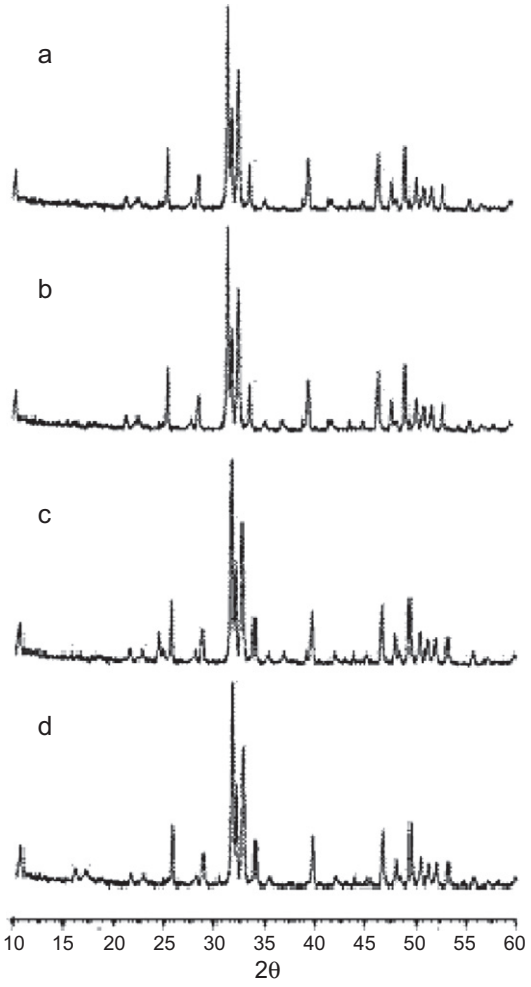


Figure 1. XRD patterns of: (**a**) ABM; (**b**) $ZnBr_2$/ABM; (**c**) $ZnCl_2$/ABM; (**d**) $CuBr_2$/ABM.

2. Preparation of the ABM catalysts

In previous studies we described the preparation of ABM and its KF or $NaNO_3$ doped analogs.[33,34] The modified MX_2/ABMs were obtained by impregnating ABM with an aqueous solution of Lewis acid (MX_2). The resulting suspension was then evaporated to dryness and dried for 2 h at 150 °C prior to characterization and use.[35,36]

The X-ray diffraction (XRD) patterns of MX_2/ABM are similar to those of ABM as shown in Figure 1. The intensity of typical diffraction peaks did not significantly change indicating no disorganization in the crystalline structure of the solid materials. It should be noted that MX_2 specific phases were not detected on the doped materials, indicating that Lewis acids were highly dispersed in the ABM analogs.

3. Optimization of the heterocyclic construction

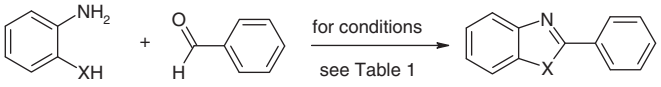
The reaction was first optimized using benzaldehyde **2a** (1.1 equiv) and *o*-phenylenediamine (**1a**), *o*-aminophenol (**1b**), or *o*-aminothiophenol (**1c**) in the presence of $ZnBr_2$/ABM, an inexpensive and readily available catalyst (Table 1).

Without catalyst in refluxing toluene or dioxane, condensation of benzaldehyde **2a** with *o*-phenylenediamine **1a** proceeded smoothly (entries 1, 3). With *o*-aminophenol **1b** and *o*-aminothiophenol **1c** (entries 7, 9, 13, 15) no condensation was observed regardless of the reaction time. Absence of air[33] prevents the required oxidative step and benzimidazole, benzoxazole, and benzothiazole were not detected (entries 6, 12, 18).

In air and in the presence of $ZnBr_2$/ABM, reactions between **2a** and *o*-aminophenol or *o*-aminothiophenol furnished the desired cycloadducts **4a** and **5a** after a few minutes in good (entries 2, 8, 14) to excellent yields (entries 4, 10, 16). In addition, temperature plays a role; reactions performed in refluxing toluene showed a better efficiency (i.e., shorter reaction times and higher yields).

Solvent effects were thus examined using a stoichiometric amount of **1b** with benzaldehyde **2a,** in air, and in the presence

Table 1
Optimization for the synthesis of **3a**, **4a,** and **5a**



1a X = NH
1b X = O
1c X = S

2a

3a X = NH
4a X = O
5a X = S

Entry	Reagent	Solvent	Catalyst	Air	Time	Yield[a] (%)
1	**1a**	Dioxane	No	Yes	16 h	84
2		Dioxane	$ZnBr_2$/ABM	Yes	15 min	79
3		Toluene	No	Yes	24 h	46
4		Toluene	$ZnBr_2$/ABM	Yes	15 min	96
5		Toluene	$ZnBr_2$	Yes	15 min	Trace
6		Toluene	$ZnBr_2$/ABM	No (Ar)	24 h	NR[b]
7	**1b**	Dioxane	No	Yes	24 h	NR[b]
8		Dioxane	$ZnBr_2$/ABM	Yes	15 min	69
9		Toluene	No	Yes	24 h	NR[b]
10		Toluene	$ZnBr_2$/ABM	Yes	15 min	96
11		Toluene	$ZnBr_2$	Yes	15 min	NR[b]
12		Toluene	$ZnBr_2$/ABM	No (Ar)	24 h	NR[b]
13	**1c**	Dioxane	No	Yes	24 h	NR[b]
14		Dioxane	$ZnBr_2$/ABM	Yes	15 min	59
15		Toluene	No	Yes	24 h	NR[b]
16		Toluene	$ZnBr_2$/ABM	Yes	20 min	95
17		Toluene	$ZnBr_2$	Yes	20 min	NR[b]
18		Toluene	$ZnBr_2$/ABM	No (Ar)	24 h	NR[b]

[a] Yields in pure isolated products.
[b] NR: no reaction.

Table 2
Solvent effects on **4a** synthesis catalyzed by $ZnBr_2$/ABM

Entry	Solvent	Reaction temperature (°C)	Reaction time (min)	Yield[a] (%)
1	$CHCl_3$	61	15	28
2	CH_3OH	65	15	12
3	CH_3CN	82	15	45
4	THF	66	15	76
5	Water	100	15	48
6	Dioxane	101	15	69
7	Toluene	61	15	26
8	Toluene	101	15	76
9	Toluene	111	15	96

[a] Yields in pure isolated products.

of $ZnBr_2$/ABM in different solvents (Table 2). After refluxing each assay for 15 min, the reaction was not completed with THF, $CHCl_3$, CH_3CN, dioxane or water.

A mixture of starting materials and final heterocycle was obtained. The best solvent remains toluene, but it should be pointed out that heterocycle construction also requires thermal, aprotic and apolar conditions.

4. Extension of the methodology

For these purpose, two other Lewis acid catalysts were prepared by impregnating ABM with $ZnCl_2$ or $CuCl_2$. Heterocyclic construction efficiency was also performed using ABM alone and three doped ABM analogs.

In air, a slight excess of aldehyde **2a–f** (1.1 equiv) was used in the presence of amino derivatives **1a–c** and ABM catalysts at 111 °C to build a small library of fused heterocycles of type **3**–**5** (Table 3). Reaction progress was monitored by TLC (*n*-hexane/EtOAc 2:1). After completion of the reaction, the crude product was purified by column chromatography and recrystallization to afford pure benzimidazoles **3**, benzoxazoles **4,** and benzothiazoles **5**.[37] Physical and spectral characterization of the products was confirmed by comparison with available literature data.

With ABM alone, the reaction proceeded smoothly throughout heterocycle construction although some degradation was observed. An electro donating group on aldehyde **2** decreased the efficiency of the heterocyclic building. Reaction yields were between 15% and 76%.

Under similar conditions, the use of ABM doped with MX_2 Lewis acids remarkably decreased the reaction time and the products were isolated in good to excellent yields (71–96%). Degradation was always minor and after a few minutes, the heterocycles **3**–**5** were obtained after an easy purification step. Reaction yields and speed slightly decreased when methoxy or methyl benzaldehydes **2d** and **2e** (entries 4 and 5, 10 and 11, and 16 and 17) were employed.

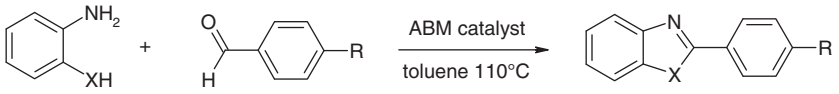
The conversion obtained with ABM, $ZnBr_2$/ABM, $ZnCl_2$/ABM and $CuBr_2$/ABM clearly showed the positive effect of the impregnating process. $ZnCl_2$ doped ABM was systematically 4–10% less efficient than other catalytic systems which led to similar conversions.

$ZnBr_2$/ABM was quantitatively recovered by simple filtration and regenerated by calcination at 400 °C for 2 h and was reused in future reactions. Investigations were performed on benzaldehyde **2a** and *o*-aminophenol **1b** as model substrates (Table 4).

Whatever the assay, completion of the reaction was always achieved in 15 min but a decrease in yield was observed at the fourth round. The catalyst was fully recovered after the first reaction, recovery remained stable till the fifth reaction but the amount of promoter gradually decreased after each assay.

In conclusion, the present method is an efficient and selective procedure for the synthesis of benzimidazoles, benzoxazoles, and benzothiazoles from *o*-phenylenediamine, *o*-aminophenol, or *o*-aminothiophenol, with aromatic aldehydes in refluxing toluene. The MX_2 Lewis acid doped ABMs are new, inexpensive and attractive solid supports which can contribute to the development of

Table 3
Synthesis of benzimidazoles **3**, benzoxazoles **4,** and benzothiazoles **5** under ABM, $ZnBr_2$/ABM, $ZnCl_2$/ABM, and $CuBr_2$/ABM catalysis



1a X = NH
1b X = O
1c X = S

2a-f (1.1 eq.)

3a-f X = NH
4a-f X = O
5a-f X = S

Entry	Product	X	R	Catalyst, yield[a], reaction time				Mp/(lit.) (°C)
				ABM	$ZnBr_2$/ABM	$ZnCl_2$/ABM	$CuBr_2$/ABM	
1	**3a**	NH	H	76%, 35 min	96%, 15 min	86%, 20 min	94%, 10 min	302–304 (301–303)[38]
2	**3b**		Cl	62%, 45 min	93%, 10 min	84%, 10 min	95%, 15 min	292–294 (290–292)[38]
3	**3c**		NO_2	67%, 35 min	92%, 10 min	85%, 10 min	92%, 20 min	324–326 (326–327)[38]
4	**3d**		OCH_3	36%, 45 min	83%, 15 min	78%, 15 min	86%, 20 min	235–237 (234–235)[38]
5	**3e**		CH_3	46%, 1h15	84%, 15 min	79%, 20 min	83%, 30 min	264–266 (263–265)[38]
6	**3f**		F	49%, 45 min	95%, 10 min	82%, 10 min	96%, 20 min	249–251 (250–252)[39]
7	**4a**	O	H	46%, 1h15	96%, 15 min	86%, 20 min	94%, 15 min	102–104 (102–103)[38]
8	**4b**		Cl	76%, 1h15	93%, 15 min	84%, 10 min	95%, 15 min	147–149 (148–150)[39]
9	**4c**		NO_2	62%, 1h15	92%, 20 min	85%, 10 min	92%, 20 min	274–277 (270–272)[39]
10	**4d**		OCH_3	36%, 1h15	83%, 25 min	78%, 25 min	86%, 25 min	102–104 (102–104)[38]
11	**4e**		CH_3	15%, 1h30	84%, 25 min	79%, 20 min	83%, 30 min	113–114 (115–116)[38]
12	**4f**		F	68%, 1h15	95%, 15 min	87%, 10 min	96%, 15 min	99–102 (98–99)[40]
13	**5a**	S	H	69%, 1h15	95%, 20 min	81%, 10 min	96%, 20 min	112–114 (114–115)[41]
14	**5b**		Cl	72%, 1h15	90%, 15 min	82%, 10 min	93%, 15 min	116–117 (116–118)[41]
15	**5c**		NO_2	65%, 1h15	91%, 15 min	82%, 10 min	92%, 15 min	226–228 (226–227)[41]
16	**5d**		OCH_3	36%, 1h30	84%, 25 min	75%, 25 min	84%, 20 min	122–123 (122–124)[41]
17	**5e**		CH_3	22%, 1h15	81%, 25 min	71%, 30 min	87%, 35 min	85–87 (85–86)[41]
18	**5f**		F	53%, 1h15	91%, 15 min	78%, 10 min	90%, 20 min	102–103 (101–103)[41]

[a] Yields in pure isolated products.

Table 4
Studies on the reuse of $ZnBr_2$/ABM

Round	Yield in **4a**[a] (%)	$ZnBr_2$/ABM recovered (%)
1	96	99
2	95	97
3	91	93
4	88	93
5	85	91
6	79	86

[a] Each reaction was carried out as described in reference.[36]

catalytic processes and reduced environmental problems (lower energy, valorization of a waste as natural and reusable catalyst, non-toxicity of the catalyst, reduced amount of solvent).

Acknowledgment

The authors thank the Hubert Curien "Volubilis" Program for financial support.

References and notes

1. Chen, C.; Chen, Y. J. *Tetrahedron Lett.* **2004**, *45*, 113–115.
2. Siddiqui, N.; Rana, A.; Khan, S. A.; Bhat, M. A.; Haque, S. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4178–4182.
3. Lion, C. J.; Matthews, C. S.; Wells, G.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5005–5008.
4. Huang, S. T.; Hsei, I. J.; Chen, C. *Bioorg. Med. Chem.* **2006**, *14*, 6106–6119.
5. Girardet, J.-L.; Townsend, L. B. *J. Org. Chem.* **1999**, *64*, 4169–4172.
6. Yeh, C.-M.; Tung, C.-L.; Sun, C.-M. *J. Comb. Chem.* **2000**, *2*, 341–348.
7. Chen, J. J.; Wei, Y.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2000**, *43*, 2449–2456.
8. Tumelty, D.; Cao, K.; Holmes, C. P. *Org. Lett.* **2001**, *3*, 83–86.
9. Mann, J.; Baron, A.; Opoku-Boahen, Y.; Johansson, E.; Parkinson, G.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **2001**, *44*, 138–144.
10. Raju, B.; Nguyen, N.; Holland, G. W. *J. Comb. Chem.* **2002**, *4*, 320–328.
11. Akamatsu, H.; Fukase, K.; Kusumoto, S. *J. Comb. Chem.* **2002**, *4*, 475–483.
12. Hoesl, C. E.; Nefzi, A.; Houghten, R. A. *J. Comb. Chem.* **2003**, *5*, 155–160.
13. Vourloumis, D.; Takahashi, M.; Simonsen, K. B.; Ayida, B. K.; Barluenga, S.; Winters, G. C.; Hermann, T. *Tetrahedron Lett.* **2003**, *44*, 2807–2811.
14. Shi, D.-F.; Bradshaw, T. D.; Wrigley, S.; McCall, C. J.; Lelieveld, P.; Fichtner, I.; Stevens, M. F. G. *J. Med. Chem.* **1996**, *39*, 3375–3384.
15. Beebe, X.; Wodka, D.; Sowin, T. J. *J. Comb. Chem.* **2001**, *3*, 360–366.
16. Hari, A.; Karan, C.; Rodrigues, W. C.; Miller, B. L. *J. Org. Chem.* **2001**, *66*, 991–996.
17. Pottorf, R. S.; Chadha, N. K.; Katkevics, M.; Ozola, V.; Suna, E.; Ghane, H.; Regberg, T.; Player, M. R. *Tetrahedron Lett.* **2003**, *44*, 175–178.
18. Chen, F.; Shen, C.; Yang, D. *Tetrahedron Lett.* **2011**, *52*, 2128–2131.
19. Chua, M.-S.; Shi, D.-F.; Wrigley, S.; Bradshaw, T. D.; Hutchinson, I.; Shaw, P. N.; Barrett, D. A.; Stanley, L. A.; Stevens, M. F. G. *J. Med. Chem.* **1999**, *42*, 381–392.
20. Kashiyama, E.; Hutchinson, I.; Chua, M.-S.; Stinson, S. F.; Phillips, L. R.; Kaur, G.; Sausville, E. A.; Bradshaw, T. D.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **1999**, *42*, 4172–4184.
21. Hutchinson, I.; Chua, M.-S.; Browne, H. L.; Trapani, V.; Bradshaw, T. D.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2001**, *44*, 1446–1455.
22. Leng, W.; Zhou, Y.; Xu, Q.; Liu, J. *Macromolecules* **2001**, *34*, 4774–4779.
23. Hutchinson, I.; Jennings, S. A.; Vishnuvajjala, B. R.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2002**, *45*, 744–747.
24. Moghaddam, F. M.; Bardajee, G. R.; Ismaili, H.; Dokht Taimoory, S. M. *Synth. Commun.* **2006**, *36*, 2543–2548.
25. Park, K. H.; Jun, K.; Shin, S. R.; Oh, S. W. *Tetrahedron Lett.* **1996**, *37*, 8869–8870.
26. Varma, R. S.; Saini, R. K.; Prakash, O. *Tetrahedron Lett.* **1997**, *38*, 2621–2622.
27. Chang, J.; Zhao, K.; Pan, S. *Tetrahedron Lett.* **2002**, *43*, 951–954.
28. Praveen, C.; Kumar, K. H.; Muralidharan, D.; Perumal, P. T. *Tetrahedron* **2008**, *64*, 2369–2374.
29. Brink, G. J.; Arends, W. C. E., I; Sheldon, R. A. *Chem. Rev.* **2004**, *104*, 4105–4123.
30. Beller, M. *Adv. Synth. Catal.* **2004**, *346*, 107–108.
31. Kawashita, Y.; Nakamichi, N.; Kawabata, H.; Hayashi, M. *Org. Lett.* **2003**, *5*, 3713–3715.
32. Chen, Y. X.; Qian, L. F.; Zhang, W.; Han, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9330–9333.
33. Songnian, L.; Lihu, Y. *Tetrahedron Lett.* **2005**, *46*, 4315–4319.
34. Riadi, Y.; Mamouni, R.; Abrouki, Y.; El Haddad, M.; Saffaj, N.; El Antri, S.; Routier, S.; Guillaumet, G.; Lazar, S. *Lett. Org. Chem.* **2010**, *7*, 269–271.
35. Riadi, Y.; Mamouni, R.; Azzalou, R.; Boulahjar, R.; Abrouki, Y.; El Haddad, M.; Routier, S.; Guillaumet, G.; Lazar, S. *Tetrahedron Lett.* **2010**, *51*, 6715–6717.
36. Sebti, S.; Tahir, R.; Nazih, R.; Boulaajaj, S. *Appl. Catal.* **2001**, *218*, 25–30.
37. *General procedure for the synthesis* ***3–5***: The catalyst (100 mg) was added to a mixture of aldehyde **2** (1.1 mmol) and *o*-phenylenediamine **1a**, *o*-aminophenol **1b** or *o*-aminothiophenol **1c** (1.0 mmol). The mixture was stirred at 111 °C in the presence of 5 mL toluene. Progress of the reaction was monitored by TLC (*n*-hexane/EtOAc 2:1). After complete conversion, the reaction mixture was filtered, the catalyst was washed, and the solvent was removed under reduced pressure. The crude material was purified by column chromatography or recrystallization to afford the pure product **3**, **4** or **5**.
38. Devalla, V. R.; Ethirajulu, K. *J. Chem. Soc.* **1995**, 1497–1501.
39. Bougrin, K.; Loupy, A.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 8055–8064.
40. Naidu, A. B.; Sekar, G. *Synthesis* **2010**, 579–586.
41. Balaji, S. L.; Umesh, R. P.; Jyotirling, R. M.; Ramrao, A. M. *Bull. Korean Chem. Soc.* **2010**, *31*, 2329–2332.