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ORIGINAL PAPER

1,3-Dibromo-5,5-dimethylhydantoin as an efficient homogeneous catalyst for synthesis of benzoxazoles, benzimidazoles, and oxazolo[4,5-*b*]pyridines

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Abstract A simple and highly efficient method for synthesis of benzoxazoles, benzimidazoles, and oxazolo-[4,5-*b*]pyridines is described. Condensation of orthoesters with *o*-substituted anilines or 2-amino-3-hydroxypyridine was performed in the presence of catalytic amounts of commercially available, inexpensive, and moisture-stable 1,3-dibromo-5,5-dimethylhydantoin under solvent-free conditions. The corresponding heterocycles were obtained in good to excellent yields. The main advantages of the present procedure are mild reaction conditions, short reaction times, high yields of products, easy work-up, and absence of solvent.

Keywords 1,3-Dibromo-5,5-dimethylhydantoin · Benzoxazole · Benzimidazole · Oxazolo[4,5-*b*]pyridine · Orthoester

Introduction

Benzoxazoles, benzimidazoles, and oxazolopyridines are of great interest in diverse areas of chemistry [1–6] because of their different pharmacological activities such as antiviral [7], antibacterial [8], antifungal [9], antiparkinson [10], anticancer [11], and antibiotic [12] properties. They have been also used as ligands in asymmetric transformations [13]. Numerous methods have been reported for synthesis of these heterocycles, including condensations of carboxylic acids [14], orthoesters [15–20], acid chlorides [21], nitriles [22], amides [23], aldehydes [24], and esters [25] with *o*-substituted anilines, Beckmann rearrangement of *o*-acylphenol oximes [26], and photocyclization of phenolic Schiff bases [27]. However, some of these methods suffer from one or more drawbacks such as strong acidic conditions, long reaction times, low yields of the products, tedious work-up, need for excess amounts of reagent, and use of toxic reagents, catalysts, and/or solvents.

Hence, development of new catalytic methods for synthesis of benzoxazoles, benzimidazoles, and oxazolo[4,5-*b*]pyridines in terms of operational simplicity, nontoxicity, and economical acceptability of the catalyst is of interest. 1,3-Dibromo-5,5-dimethylhydantoin (DBDMH) is a five-membered heterocycle which has been extensively used as a brominating and oxidating agent in organic synthesis. During the last decade, DBDMH has attracted special attention as an efficient homogeneous catalyst in organic transformation, because this compound is relatively nontoxic, commercially available, inexpensive, and insensitive to air and moisture. Therefore, in continuation of our studies on preparation of benzoxazoles, benzimidazoles, and oxazolo[4,5-*b*]pyridines [28, 29], we were interested in examining the catalytic ability of DBDMH in the synthesis of these biologically active heterocycles.

Results and discussion

For optimization of reaction conditions, first, triethyl orthoacetate (**2b**) was reacted with *o*-aminophenol (**1a**) in the presence of DBDMH (Scheme 1). Different molar ratios of substrate and catalyst, different solvents, absence of solvent, and various temperatures were examined in the model reaction. The best result was obtained in the reaction of 1 mmol *o*-aminophenol with 1.1 mmol triethyl orthoacetate in the presence 2 mol% of DBDMH at room

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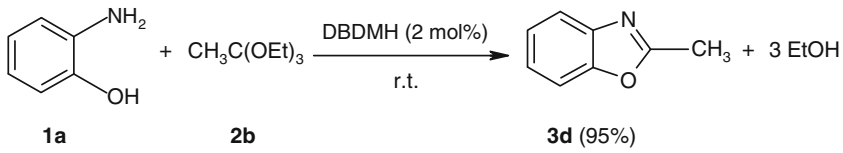
Scheme 1



1a **2b** **3d** (95%)

Table 1 Synthesis of benzoxazoles, benzimidazoles, and oxazolo[4,5-*b*]pyridines

Entry	1	2	3[a]	X	Y	R	R′	DBDMH (mol%)	Time (min)	Yield (%)[b]	M.P. (°C) [Ref]
1	**1a**	**2a**	**3a**	C	O	H	Et	2	2	98	Oil [17]
2	**1b**	**2a**	**3b**	C	O	Cl	Et	1	2	90	58–60 [26]
3	**1c**	**2a**	**3c**	C	O	Me	Et	1.5	6	98	29–31 [26]
4	**1a**	**2b**	**3d**	C	O	H	Me	2	2	95	Oil [17]
5	**1b**	**2b**	**3e**	C	O	Cl	Me	1	2	85	52–54 [26]
6	**1c**	**2b**	**3f**	C	O	Me	Me	2	8	98	Oil [26]
7[c]	**1a**	**2c**	**3g**	C	O	H	H	2	8	95	Oil [17]
8[c]	**1b**	**2c**	**3h**	C	O	Cl	H	1.5	5	85	34–36 [30]
9[c]	**1c**	**2c**	**3i**	C	O	Me	H	1	12	95	43–45 [31, 32]
10[c]	**1a**	**2d**	**3g**	C	O	H	H	2	10	90	Oil [17]
11[c]	**1b**	**2d**	**3h**	C	O	Cl	H	1.5	10	92	34–36 [30]
12[c]	**1c**	**2d**	**3i**	C	O	Me	H	3	20	95	43–45 [31, 32]
13[c]	**1d**	**2a**	**3j**	C	NH	H	Et	1	5	95	163–165 [33]
14[c]	**1e**	**2a**	**3k**	C	NH	Me	Et	2	5	95	159–161 [34]
15[c]	**1f**	**2a**	**3l**	C	NH	NO_2	Et	3	8	88	150–152 [35]
16[c]	**1d**	**2b**	**3m**	C	NH	H	Me	2	5	97	172–174 [36]
17[c]	**1e**	**2b**	**3n**	C	NH	Me	Me	2	6	93	197–199 [34]
18[c]	**1f**	**2b**	**3o**	C	NH	NO_2	Me	3	8	88	188–190 [35]
19[c]	**1d**	**2c**	**3p**	C	NH	H	H	2	7	92	170–172 [15]
20[c]	**1e**	**2c**	**3q**	C	NH	Me	H	2	8	90	113–115 [37]
21[c]	**1f**	**2c**	**3r**	C	NH	NO_2	H	4	12	80	184–186 [35]
22[c]	**1d**	**2d**	**3p**	C	NH	H	H	2	7	90	170–172 [15]
23[c]	**1e**	**2d**	**3q**	C	NH	Me	H	2	9	88	113–115 [37]
24[c]	**1g**	**2a**	**3s**	N	O	H	Et	1	10	98	50–52 [16]
25[c]	**1g**	**2b**	**3t**	N	O	H	Me	1	7	97	71–73 [38]
26[c]	**1g**	**2c**	**3u**	N	O	H	H	3	20	98	70–72 [16]
27[c]	**1g**	**2d**	**3u**	N	O	H	H	5	20	80	70–72 [16]

[a] Products were identified by comparison of their physical and spectral data with those of authentic samples

[b] Yields refer to pure products after isolation

[c] Reaction performed at 85 °C

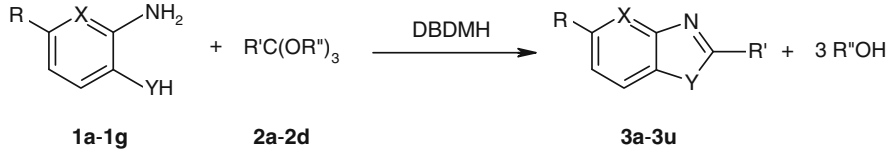
temperature under solvent-free conditions, 2-methylbenzoxazole being obtained in 95% yield after 2 min (Table 1, entry 4).

To show the catalytic effect of DBDMH, triethyl orthoacetate (1.2 mmol) was reacted with *o*-aminophenol (1 mmol) in the absence of catalyst at the same reaction conditions. Analysis of the reaction mixture after 20 min illustrated that only 5% 2-methylbenzoxazole had been formed. This result confirms the high catalytic activity of DBDMH in the current synthesis.

The applicability of this method was investigated by the reaction of a series of orthoesters **2a**–**2d** with *o*-aminophenols **1a**–**1c**, *o*-phenylenediamines **1d**–**1f**, or 2-amino-3-hydroxypyridine (**1g**) under optimized reaction conditions (Scheme 2). Results showed that all corresponding heterocycles **3a**–**3u** were successfully generated in high to excellent yields in very short time (Table 1).

As shown in Table 1, 2-ethyl- and 2-methylbenzoxazoles were produced at room temperature by reaction of 2-aminophenols with trialkyl orthoacetate or trialkyl orthopropionate (Table 1, entries 1–6). Trialkyl orthoformates did not react with *o*-aminophenols at room temperature, but the corresponding benzoxazoles were obtained at 85 °C in high yields (Table 1, entries 7–12). Reactions of

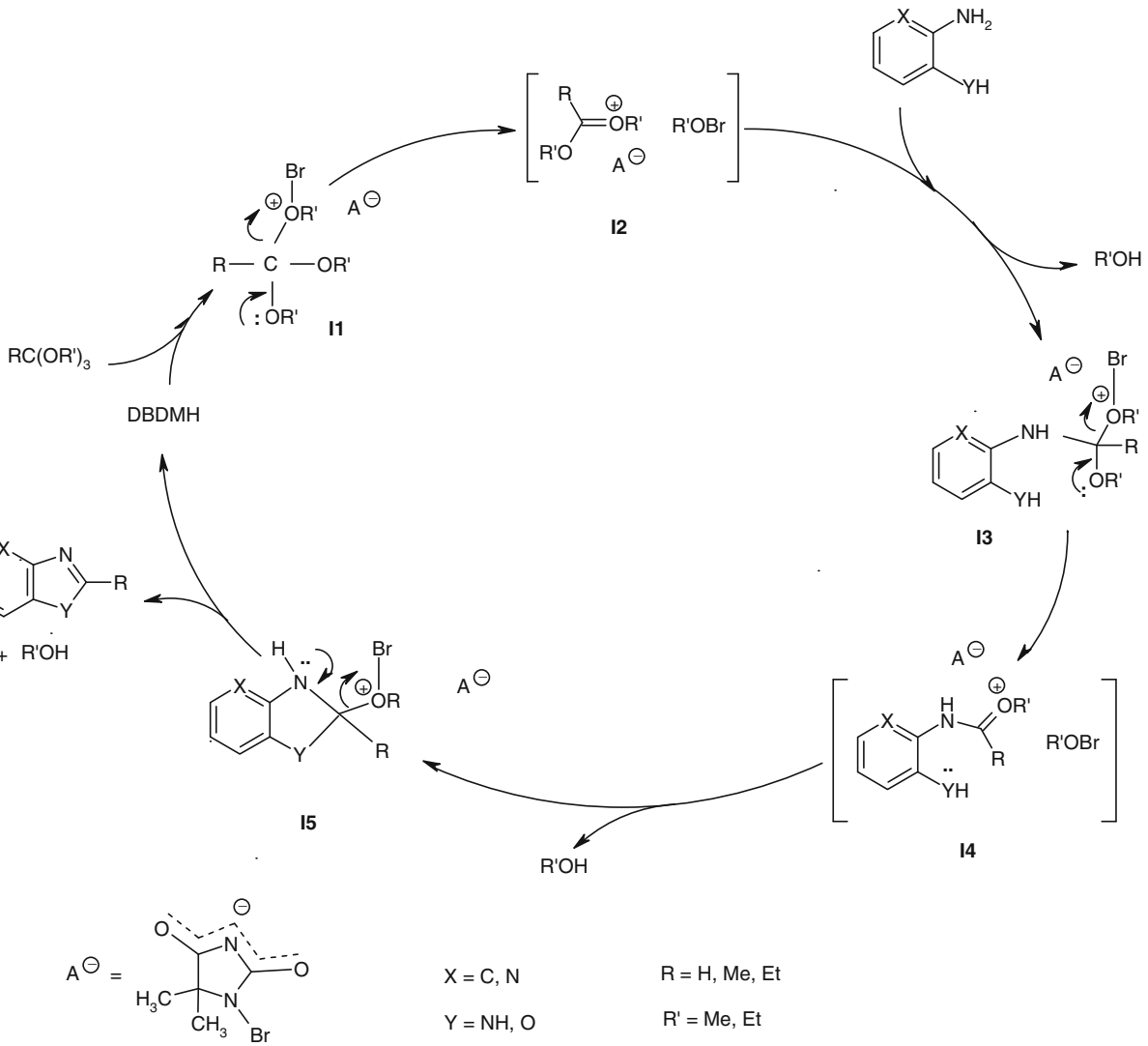
Scheme 2



1a-1g **2a-2d** **3a-3u**

1	X	Y	R
a	C	O	H
b	C	O	Cl
c	C	O	Me
d	C	NH	H
e	C	NH	Me
f	C	NH	NO_2
g	N	O	H

2	R'	R"
a	Et	Et
b	Me	Et
c	H	Et
d	H	Me



Scheme 3

Table 2 Comparison of some other procedures with the present method for synthesis of 2-methylbenzoxazole (**3d**) from triethyl orthoacetate

Entry	Catalyst	Solvent	Reaction conditions	Time	Yield (%) [Ref]
1	DBDMH (2 mol%)	–	r.t.	2 min	95
2	$ZrOCl_2{\cdot}8H_2O$ (1 mol%)	–	r.t.	5 min	93 [28]
3	KSF (180% w/w)	Toluene	Reflux under N_2	12 h	75 [15]
4	KSF (180% w/w)	–	MW under N_2	5 min	76 [15]
5	H_2SO_4 (4 mol%)	–	175–185 °C	2 h	75 [17]

o-phenylenediamines or 2-amino-3-hydroxypyridine with orthoesters were performed at 85 °C under optimized conditions to afford benzimidazoles and oxazolo[4,5-*b*]pyridines, respectively (Table 1, entries 13–27).

Although the actual mechanism of reaction is unclear, a reasonable explanation with respect to the high catalytic activity of DBDMH and mechanistic operation of DBDMH in similar reactions is shown in Scheme 3. First, DBDMH releases a bromium ion, which activates the orthoester to give **I1** and then **I2**. Nucleophilic attack of aniline or 2-amino-3-hydroxypyridine to the electrophilic center of **I2** yields **I3**. Compound **I3** is activated by a bromium ion and gives **I4**. Next, an intramolecular nucleophilic attack generates **I5**. Finally, elimination of methanol or ethanol from compound **I5** produces the corresponding heterocycle, and in this step, the bromium ion is released for the next catalytic cycle (Scheme 3).

To show the superiority of the present method over previous ones, we compared our results with some other results reported in the literature (Table 2).

In conclusion, we have introduced DBDMH as a highly efficient homogeneous catalyst for synthesis of benzoxazoles, benzimidazoles, and oxazolo[4,5-*b*]pyridines from orthoesters. This catalyst is commercially available, inexpensive, stable to air and moisture, and relatively nontoxic. Furthermore, very short reaction times, high yields of products, mild reaction conditions, absence of solvent, and easy work-up are other considerable advantages of this procedure.

Experimental

All materials were of commercial reagent grade and were purchased from Merck Company. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVANCE 500 MHz spectrometer. Melting points were taken on a Bamstead Electrothermal apparatus.

General procedure for synthesis of benzoxazoles, benzimidazoles, and oxazolo[4,5-b]pyridines

To a mixture of orthoester (1.2 mmol) and *o*-aminophenol, *o*-phenylenediamine, or 2-amino-3-hydroxypyridine (1 mmol) was added a catalytic amount of DBDMH (1–5 mol%) according to Table 1. The mixture was stirred at room temperature or at 85 °C for the appropriate time according to Table 1. Progress of the reaction was monitored by tin-layer chromatography (TLC, eluent: *n*-hexane/ethyl acetate 2:1). After completion of the reaction, the reaction mixture was concentrated to afford crude product. Then 10–15 cm^3 *n*-hexane was added, and the mixture was stirred at room temperature for 5–10 min and then filtered. The solvent of the filtrate was evaporated to give the corresponding heterocycle in high to excellent yield (Table 1). All products were identified by comparing their physical and spectral data with those reported in the literature.

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References

1. Chen C, Chen Y-J (2004) Tetrahedron Lett 45:113
2. Denny WA, Rewcastle GW, Baguley B (1990) J Med Chem 33:814
3. Kondo J, Suzuki N, Imaoka T, Kawasaki T, Nakanishi A, Kawahara Y (1994) Anal Sci 10:17
4. Lin S, Yang L (2005) Tetrahedron Lett 46:4315
5. Mortimer CG, Wells G, Crochard JP, Stone EL, Bradshaw TD, Stevens MFG, Westwell AD (2006) J Med Chem 49:179
6. Frachy G, Salidino R, Micione E (1994) Heterocycles 38:2621
7. Song X, Vig BS, Lorenzi PL, Drach JC, Townsend LB, Amidon GL (2005) J Med Chem 48:1274
8. Yildiz-Oren I, Yalcin I, Aki-Sener E, Ucarturk N (2004) Eur J Med Chem 39:291
9. Yamato M (1992) J Pharm Soc Jpn 112:81
10. Benazzouz A, Boraud T, Dubedat P, Boireau A, Stutzmann JM, Gross C (1995) Eur J Pharmacol 284:299
11. Kumar D, Jacob MR, Reynolds MB, Kerwin SM (2002) Bioorg Med Chem 10:3997
12. Evans DA, Sacks CE, Kleschick WA, Taber TR (1979) J Am Chem Soc 101:6789
13. Figge A, Altenbach HJ, Brauer DJ, Tielmann P (2002) Tetrahedron Asymmetr 13:137
14. So YH, Heeschen JP (1997) J Org Chem 62:3552
15. Villemin D, Hammadi M, Martin B (1996) Synth Commun 26:2895
16. Doise M, Dennin F, Blondeau D, Sliwa H (1990) Tetrahedron Lett 31:1155
17. Jenkins GL, Knevel AM, Davis CS (1961) J Org Chem 26:274
18. Zhang ZH, Li JJ, Gao YZ (2007) J Heterocycl Chem 44:1509
19. Reddy CS, Nagaraj A (2008) Indian J Chem 47B:1154

20. Zhang ZH, Li TS, Li JJ (2007) Monatsh Chem 138:89
21. Nadaf RN, Siddiqui SA, Daniel T, Lahoti RJ, Srinivasan KV (2004) J Mol Catal A Chem 214:155
22. Hein DW, Alheim RJ, Leavitt JJ (1957) J Am Chem Soc 79:427
23. Terashima M, Ishii M (1982) Synthesis 484
24. Salehi P, Dabiri M, Zolfigol MA, Otokesh S, Baghbanzadeh M (2006) Tetrahedron Lett 47:2557
25. Chakraborti AK, Rudrawar S, Kaur G, Sharma L (2004) Synlett 1533
26. Bhawal BM, Mayabhate SP, Likhite AP, Deshmukh ARAS (1995) Synth Commun 25:3315
27. Chen Y, Zeng DX (2004) J Org Chem 69:5037
28. Mohammadpoor-Baltork I, Khosropour AR, Hojati SF (2007) Catal Commun 8:200
29. Mohammadpoor-Baltork I, Khosropour AR, Hojati SF (2007) Monatsh Chem 138:663
30. Sam J, Plampin JN (1964) J Pharm Sci 53:538
31. Roussos M, Lecomte J (1962) German Patent 1:124–499
32. Roussos M, Lecomte J (1963) Chem Abstr 57:9858 g
33. Raban M, Chang H, Craine L, Hortelano E (1985) J Org Chem 50:2205
34. Wang H, Partch RE, Li Y (1997) J Org Chem 62:5222
35. Zhang Z-H, Yin L, Wang Y-M (2007) Catal Commun 8:1126
36. Mohammadpoor-Baltork I, Khosropour AR, Hojati SF (2007) Catal Commun 8:1865
37. Kato H, Shiba T, Kitajima E, Kiyosawa T (1976) J Chem Soc Perkin Trans I 863
38. Takahashi T, Yoneda F (1957) Pharm Bull 5:350