IRANIAN JOURNAL OF CATALYSIS

Trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane/HOAc/KI system as a new and mild catalyst for efficient synthesis of 1*H*-benzimidazoles and 1*H*-benzothiazoles in water

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Received 03 November 2013; received in revised form 23 December 2013; accepted 29 December 2013

ABSTRACT

An efficient method has been developed for the catalysis of condensation of 1,2-phenylenediamines and 2-aminothiophenoles with different aldehydes into their corresponding 2-aryl-1H-benzimidazoles and 2-aryl-1H-benzothiazoles under mild condition. In this method, trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane (DHPDMDO)/HOAc/KI system was used as a novel and effective oxidant in water at room temperature with excellent results.

Keywords*: 2-Aryl-1-arylmethyl-1H-benzimidazoles, 2-Aryl-1H-benzothiazoles, Condensation, Trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane (DHPDMDO), KI, Aldehydes.*

1. Introduction

Benzimidazoles and benzothiazoles rings have been extensively employed in pharmaceutical industries [1-4]. Benzimidazole derivatives exhibit significant activity against several viruses such as HIV [5], herpes (HSV-1) [6], RNA [7], influenza [8] and human cytomegalovirus (HCMV) [5]. Also, Bis-benzimidazoles are being interested as DNA minor groove binding agents with antitumor activity [9] and also, can be used as ligands for modeling biological system [10]. Benzothiazoles derivatives are widely found in bioorganic and medicinal chemistry with applications in drug discovery and developments. They have been applied for treatment of autoimmune and inflammatory diseases [11], in prevention of solid organ transplant rejection, epilepsy [12-14], amyotrophic lateral sclerosis [15], analgesim [16], tuberculosis [17], viral infection [18] and cancer [19, 20]. In addition, they have been applied in industry as antioxidants [21], vulcanization accelerators [22] and as a Dopant in a light emitting organic electroluminescent device [23]. Therefore, several attempts for synthesis of benzimidazoles and benzothiazoles have been reported. One of reported methods for preparation of benzimidazoles is the condensation of 1,2-phenylenediamines with carboxylic acids or their derivatives in the presence of strong acids such as poly phosphoric acid [24], or other mineral acids [24], PS-PPH_3/CCl_3CN [25], and the thermal or acid promoted cyclization of N-(N-arylbenzimidoyl)-1,4-benzoquinones [26].

In the other reported methods, benzimidazoles have been synthesized by condensation of 1,2-phenylendiamines with deferent aldehydes under oxidative conditions including using of lewis acids such as $Sc(OTf)_3$ [27], $Yb(OTf)_3$ [28], $In(OTf)_3$ [29], oxalic acid [30], proline [31], H_2O_2/HCl system [32], p-toluene sulfonic acid-silica gel [33] and Caro's acid silica gel (CA-SiO_2) [34]. For preparation of benzothiazoles many reports are available. Among these reports, the most popular approach generally involves condensation dehydrogenation of 2-aminothiophenols with carboxylic acids [35], or condensation with aldehydes under oxidative conditions [36]. Unfortunately, most of these procedures have many defects and limitations such as harsh reaction conditions, high reaction temperature, prolonged reaction times, requirement of excess of reagents, tedious work up procedures, low yields, using of costly, toxic or air sensitive catalysts, etc. Consequently, still, there is an important need to develop simple, mild, rapid and inexpensive procedures and/or further work on technical important.

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Recently, *gem*-dihydroperoxides have received attention as new, effective and strong oxygen transfer oxidants [37]. Therefore, we have synthesized the trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane (DHPDMDO) as a new and powerful oxidant and has used in many organic syntheses [38]. Thus, along with our interest in application of DHPDMDO, we used of DHPDMDO for in situ generation of I^+ from KI for catalysis of synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles and 2-aryl-1*H*-benzothiazoles in mild condition.

2. Experimental

2.1. Preparation of DHPDMDO

To a stirred solution of acetyl acetone (1 mmol) in CH_3CN (4 mL) was added silica sulfuric acid (SSA) (100 mg) and stirring of the reaction mixture was continued for 5 min at room temperature. Then, aqueous 30 % H_2O_2 (5 mmol) was added to the reaction mixture and stirred for 30 min at room temperature. After completion of the reaction as monitored by TLC, the resulting mixture was filtered and washed with EtOAc (2×5 mL) to separate the solid catalyst. The combined filtrates were diluted with water (5 mL) and extracted with EtOAc (3×5 mL). The organic layer was separated, dried over anhydrous Mg_2SO_4 and evaporated under reduced pressure to give almost pure white crystalline product 1 (Scheme 1).

2.2. General procedure for synthesis of 2-aryl-1-arylmethyl-1H-benzimidazoles

To a mixture of 1,2-phenylenediamines (1 mmol, 0.1081 g), HOAc (0.2 mmol, 0.012 mL) and aldehyde (2.2 mmol) in water (5 mL), DHPDMDO (1 mmol, 0.166 g) was added. Then KI (2 mmol, 0.332 g) was added to it and stirred for proper time at room temperature. The progress of reaction was followed by TLC. After completion of reaction, excess of peroxides and I^+ have been quenched with 1 mL of Na_2SO_3 solution (3 M) and stirred for 15 minutes. Then 15 mL of water was added. The solids was filtrated and dried for obtain corresponding 2-aryl-1-arylmethyl-1*H*-benzimidazoles. For more purification, the products were recrystallized in ethanol %96.

2.3. General procedure for synthesis of 2-aryl-1H-benzothiazoles

To mixture of 2-aminothiophenol (1 mmol, 0.1251 g) and HOAc (0.2 mmol, 0.012 mL) in water (5 mL) was added aldehydes (1 mmol). Then DHPDMDO (0.5 mmol, 0.083 g) and KI (1.3 mmol, 0.216 g) was added and stirred for proper time. The progress of reaction was followed by TLC. After completion of reaction, solution was quenched with 1 mL of Na_2SO_3 and then stirred for 15 minutes. Then 15 mL of water was added and processed solids were filtrated as the products. For more purification, the products were recrystallized in ethanol %96.

Selected spectral data:

DHPDMDO:

White crystall, m.p.: 98-100 °C; IR (KBr): $\bar{\nu}$ =: 3389 (w), 1433, 1380, 1333, 1173, 848, 790, 470. ^{1}HNMR (90 MHz, $CDCl_3$): δ= 1.59 (s, 6H, CH_3), 2.67 (s, 2H, CH_2), 8.43 (bs, 2H, OOH). ^{13}CNMR (22.5 MHz, D_2O): δ= 16.5 (CH_3), 50.7 (CH_2), 112.7 (C-3, C-5); Elemental analalysis: Calcd for $C_5H_{10}O_6$: C 36.14; H 6.02; Found: C 36.08; H 5.87 %.

*2-(4-Bipheny)benzothiazole (**3p**):*

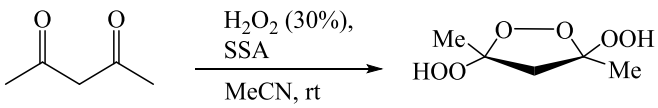
m.p.: 193-196 °C; IR (KBr): $\bar{\nu}$ = 3058, 3045, 1602, 1556, 1519, 1482, 1434, 1226, 965, 839; ^{1}HNMR (200 MHz, DMSO-d_6): δ= 7.25-7.48 (m, 5H),7.64-7.74 (m, 4H), 8.07-8.18 (m, 4H); ^{13}CNMR (50 MHz, DMSO-d_6): δ= 122.1, 123.6, 125.6, 126.8, 127.5, 128.1, 128.4, 129.4, 132.9, 135.5, 140.5, 144.1, 154.6, 168.1; Elemental analalysis: Calcd for $C_{19}H_{13}NS$: C 79.41; H 4.56; N 4.87; S 11.16. Found: C 79.42; H 4.72; N 4.79; S 10.90.

*2-Ethylbenzothiazole (**3q**):*

Colourless liquid, IR (KBr): $\bar{\nu}$ = 3056, 3025, 2924, 2920, 2850, 1597, 1561, 1497, 1309, 1293, 1093, 1061, 830; ^{1}HNMR (DMSO-d_6, 200 MHz) δ= 1.43 (t, 3H), 3.10 (q, 2H), 7.28 (t, 1H,), 7.40 (t, 1H,), 7.78 (d, 1H), 7.96 (d, 1H); ^{13}CNMR (50 MHz, DMSO-d_6): δ= 12.8, 26.6, 123.1, 123.5, 125.3, 126.1, 135.8, 154.5, 169.3; Elemental analalysis: Calcd for C_9H_9NS: C 66.22; H 5.56; N 8.58; S 19.64. Found: C 66.46; H 5.67; N 8.90; S 18.60.

3. Results and Discussion

In line with our work in synthesis and application of gem-dihydroperoxides [38,39], we have synthesized DHPDMO and used it as a new, solid and powerful oxidant in organic synthesis [38,39]. DHPDMO is prepared easily from acetyl acetone and aqueous hydrogen peroxide in the presence of Silica sulfuric acid (SSA) [39] (Scheme 1) and characterized by ^{1}H and ^{13}CNMR, IR spectroscopy and CHN analysis. Also, the amount of peroxides can be determined by iodometric or permanganometric titrations.

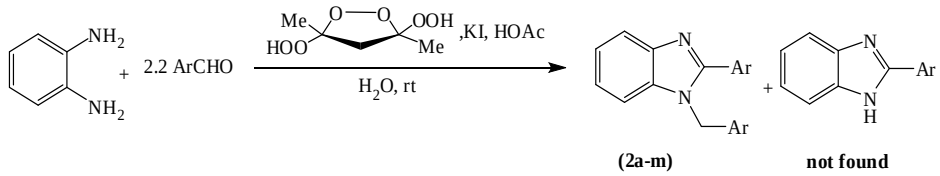


Scheme 1. The synthesis of trans-3,5-dihydroperoxy-3,5-dimethyl-1,2-dioxolane (DHPDMDO).

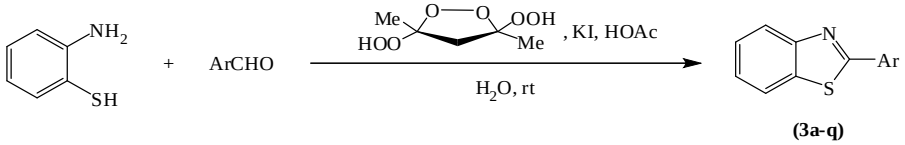
In this work, we wish to report the use of DHPDMO/HOAc/KI system to catalyze one-pot oxidative cyclocondensation of 1,2-phenylenediamines and 2-aminothiophenols with different aldehydes in excellent yields for the first time in water as a solvent at room temperature (Schemes 2 and 3). In condensation of 1,2-phenylendiamines with aldehydes, however, two compounds potentially could be achieved, (Scheme 2) but 2-aryl-1-arylmethyl-1*H*-benzimidazoles is obtained as the only product in the optimized condition (solvent, amount of oxidant, amount of HOAc, Table 1).

Also, we have used propanal as the aliphatic aldehyde for synthesis of benzothiazoles. It has been observed that the yields for aliphatic aldehydes are less than aromatic aldehydes (Table 2, entry 3q).

It is notable that addition of catalytic amount of HOAc clearly decreases the times of reactions and as shown in Scheme 4, this is deduced from formation of IOAc that is more active than IOH. The produced IOAc acts as a Lewis acid which activates the carbonyl group of aldehyde for nucleophilic attack of nitrogen atom. Finally, after cyclization, the I^+ coordinates to nitrogen atom and makes the hydrogen of α-carbon more acidic,



Scheme 2. Synthesis of 2-aryl-1-arylmetyl-1*H*-benzimidazoles.



Scheme 3. Synthesis of 2-aryl-1*H*-benzothiazoles.

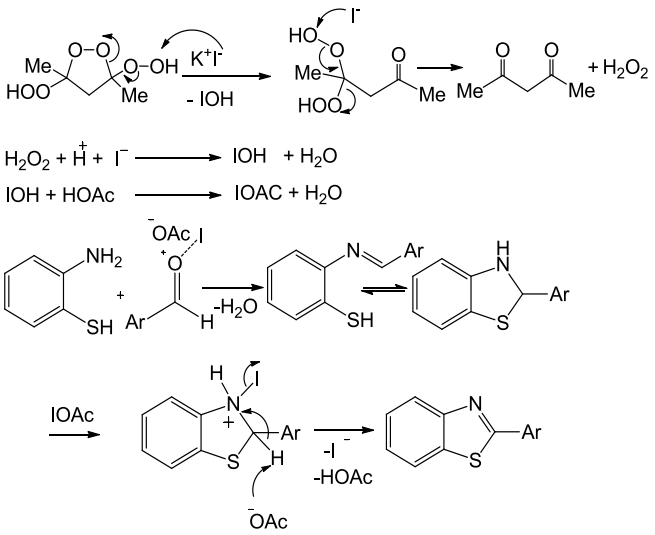
Table 1. Screening the reaction in synthesis of 2-phenylbenzo[*d*]thiazole.[a]

Entry	Amount of DHPDMDO (mmol)	Amount of HOAc (mmol)	Solvent	Time (min)	Yield (%)[b]
1	1	-	MeCN	25	92
2	1	-	EtOH	24	82
3	1	-	H_2O	40	91
4	1	-	THF	25	90
5	1	-	CH_2Cl_2	120	70
6	-	-	H_2O	120	-
7	0.3	-	H_2O	45	56
8	0.5	-	H_2O	30	87
9	1.3	-	H_2O	21	85
10	1.5	-	H_2O	25	74
11	1	0.1	H_2O	30	90
12	1	0.2	H_2O	22	91
13	1	0.3	H_2O	22	90

[a] Conditions:2-aminothiophenol (1 mmol), solvent (5 ml), benzaldehyde (1mmol), KI (1.3 mmol).
[b] Isolated yield.

therefore, this acidic hydrogen is removed by $^{-}$OAc as a base, and the I^{-} acts as a good living group and eventually the product is aromatized. The mechanism for synthesis of 2-aryl-1-arylmetrhyl-1*H*-benzimidazoles is similar. In addition, Aldehydes with both electron-withdrawing and electron-releasing groups reacted and corresponding 2-aryl-1-arylmethyl-1*H*-benzimidazoles and 2-aryl-1*H*-benzothiazoles were achieved in excellent yields and good purity (Table 1 and 3). As in synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles 2.2 mmol aldehydes and 1 mmol DHPDMDO have been used.

Finally, this method has been compared with some other methods (Table 4). The advantages of this method over the reported ones are: the products were obtained in high yield and purity, work-up of products was carried out in water (aqueous work-up) which is very attractive in green chemistry, acetylacetone and



Scheme 4. Mechanism for synthesis of 2-aryl-1-*H*-benzothiazoles

Table 2. Synthesis of different 2-aryl-1*H*-benziothiazoles in optimized conditions.

Product[a]	Ar	Time (min)	Yield (%)[b]	m.p. (°C)	
				Found	Reported [40b]
3a	C_6H_5	22	91	111-113	110-112
3b	4-MeC_6H_5	21	86	86-88	85-87
3c	2-MeC_6H_5	23	87	53-55	52-54
3d	2- MeOC_6H_5	30	83	102-104	99-102
3e	4- MeOC_6H_5	25	85	122-124	119-121
3f	2-ClC_6H_5	30	83	83-85	81-83
3g	4-ClC_6H_5	23	85	115-117	116-117
3h	2-OHC_6H_5	26	82	126-128	122-124
3i	4-OHC_6H_5	30	81	230-232	227-228
3j	2-$NO_2C_6H_5$	23	82	130-132	133-135
3k	3-$NO_2C_6H_5$	22	84	181-183	182-184
3l	4-BrC_6H_5	22	87	132-134	129-131
3m	4-FC_6H_5	24	85	95-97	98-100
3n	4-CNC_6H_5	25	86	162-164	165-166
3o	2-Furyl	40	77	101-103	100-103
3p	4-phenylC_6H_4	50	70	194-196	-
3q	Ethyl	20	67	oil	-

[a] All the isolated products were characterized on the basis of their physical properties and IR, ^{1}H NMR and ^{13}C NMR spectral analysis and by direct comparison with authentic materials.
[b] Isolated yield

Table 3. Synthesis of different 2-aryl-1-arylmethyl-1*H*-benzimidazoles in optimized conditions.

Product[a]	Ar	Time (min)	Yield (%)[b]	m.p. (°C)	
				Found	Reported [40a]
2a	C_6H_5	29	92	131-133	132-134
2b	4-MeC_6H_5	45	88	126-128	126-128
2c	4-$MeOC_6H_5$	38	83	131-133	130-131
2d	2- $MeOC_6H_5$	40	80	152-154	154-155
2e	2-ClC_6H_5	42	80	154-156	158-159
2f	4-ClC_6H_5	36	84	141-143	138-140
2g	2-OHC_6H_5	52	75	204-206	205-208
2h	4-OHC_6H_5	47	78	246-248	250-253
2i	2-$NO_2C_6H_5$	43	80	172-174	169-170
2j	4-$NO_2C_6H_5$	44	83	121-123	119-120
2k	4-CNC_6H_5	40	83	191-193	190-191
2l	4-$N(Me)_2C_6H_5$	35	90	251-253	254-256
2m	2-furyl	50	76	96-98	96-98

[a]All the isolated products were characterized on the basis of their physical properties and IR, ^{1}H NMR and ^{13}C NMR spectral analysis and by direct comparison with authentic materials.
[b] Isolated yield

KI are soluble in water and were separated from products easily and no toxic organic solvent was used, toxic metals and other toxic materials such as molecular iodine were eliminated in this procedure and no by-product was observed.

4. Conclusion

A mild an convenient method has been developed for the condensation of 1,2-phenylenediamines and 2-aminothiophenoles with different aldehydes into their corresponding 2-aryl-1H-benzimidazoles and 2-aryl-1H-benzothiazoles. This procedure is effective, rapid, inexpensive and nearly clean and the products were obtained in high yield and purity after an easy work-up.

Acknowledgment

We are grateful to Arak University Research Councils for supporting this work.

Table 4. Comparison of some reported methods for synthesis of 2-phenylbenzo[d]thiazole with current work.

Method	Conditions	Time(h)	Yield (%)	Ref.
This work	r.t.	0.36	91	This work
[pmIm]Br	Conventional heating	6	90	[41a]
I_2	DMF/100 °C	0.42	88	[41b]
$Cu_{3/2}PMo_{12}O_{40}/SiO_2$	1,4-dioxan/Reflux	0.25	85	[41c]
p-TsOH	MW	0.033	65	[41d]
Shirasagi KL	Xylene/50 °C	3	79	[41e]

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