Selective Synthesis of 2-Aryl-1-benzylated-1*H*-benzimidazoles

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An efficient and simple procedure was developed for the green synthesis of various 2-aryl-1-benzylated-1*H*-benzimidazoles in high yields by condensation of *o*-phenylenediamine with aldehydes with P_2O_5/SiO_2 as catalyst under solvent-free and ambient conditions.

Keywords synthetic methods, aldehydes, one-pot, benzimidazoles, heterogeneous catalyst, solvent-free

Introduction

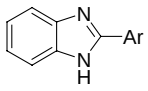
The benzimidazole nucleus is of significant importance in medicinal chemistry and many benzimidazole-containing compounds exhibit important biological activities such as selective neuropeptide YY1 receptor ntagonists,[1] angiotensin II inhibitors,[2] 5-HT_3 antagonists in isolated guinea pigileum,[3] potential antitumor agents,[4] antimicrobial agents,[5] smooth muscle cell proliferation inhibitors,[6] a treatment for interstitial cystitis,[7] as factor Xa inhibitors,[8] and in diverse areas of chemistry.[9] In addition, benzimidazoles are very important intermediates in organic reactions.[10]

Therefore, the preparation of benzimidazoles has gained considerable attention in recent years.[11-13] The common synthesis of benzimidazoles includes the reaction between an *o*-phenylendiamine and a carboxylic acid or its derivatives (nitriles, amidates and orthoesters) under harsh dehydrating conditions.[14] Another method for the synthesis of these compounds is the reaction of *o*-phenylenediamine with aldehydes in the presence of acidic catalysts under various reaction conditions.[15a,15b]

Phosphorus pentoxide is a white, flammable, dangerous, corrosive to metal and extremely deliquescent compound.[16] It reacts vigorously with water and water-containing substances, liberates much heat and may even cause fire.[16] There are many reports using phosphorus pentoxide as a reagent in organic reactions.[16a]

Phosphorus pentoxide-methanesulfonic acid was used for the first time as a convenient alternative to polyphosphoric acid by Eaton *et al*. to escape the difficulties encountered with polyphosphoric acid (PPA).[17a] P_2O_5 is difficult to handle due to its moisture sensitivity. However, the preparation of P_2O_5 on silica (P_2O_5/SiO_2) is straight forward to escape from disadvantages of P_2O_5.[17b,17c]

P_2O_5/SiO_2 as a heterogeneous catalyst shows several advantages such as the easiness of handling, clean reaction and simple work-up accompanied by removing it from the reaction mixture by simple filtration.[17] In continuation of our research on application of heterogeneous catalysts in organic reactions,[18] we have employed P_2O_5 supported on silica in preparation of benzimidazoles. In our work, the reaction of *o*-phynelenediamine (1 equiv.) and benzaldehyde (1 equiv.) produced 2-aryl-1-benzylated-1*H*-benzimidazoles instead of 2-aryl-1*H*-benzimidazoles (**1**) and almost 50% of *o*-phynelenediamine was intact. Thus, we used 2 equiv. of benzaldehyde to complete the reaction.



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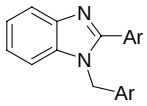

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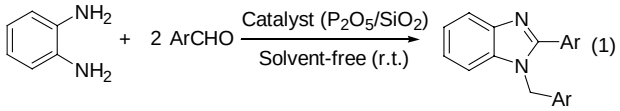
We found that the catalyst acted selectively for preparation of 2-aryl-1-benzylated-1*H*-benzimidazoles with molar ratio 2.0∶1.0 of aldehyde and *o*-phynylenediamine (Eq. 1).



Literature survey showed that 2-aryl-1*H*-benzimidazoles (**1**) and their derivatives are prepared from the reaction of *o*-phynelenediamine and aldehydes in the presence of catalysts such as (SiO_2-$FeCl_3$),[19a] nanoporous aluminosilicate,[19b] Dess-Martin-periodinane reagent (DMP),[19c] ammonium metavanadate,[19d] tungstophosphoric acid impregnated zirconium phosphate,[19e] cobalt(II) chloride hexahydrate.[19f] Whereas, 2-aryl-1-benzylated-1*H*-benzimidazoles (**2**) are synthesized in the presence of catalysts such as montmorillonite K-10,[15a] acetic acid,[15b] *L*-proline.[15c]

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Received April 29, 2011; revised June 13, 2011; accepted July 15, 2011.

Experimental

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. P_2O_5/SiO_2 (7% *w*/*w*) was prepared according to the reported procedure.[20] All yields refer to isolated products after purification. Products were characterized by comparison of physical data with authentic samples and spectroscopic data (IR and NMR). The NMR spectra were recorded on a Bruker Avance DPX 300 MHz instrument. The spectra were measured in DMSO relative to TMS. IR spectra were recorded on a JASCO FT-IR 460 plus spectrophotometer. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on Silica-gel polygram SILG/UV 254 plates.

General procedure for the selective synthesis of 2-aryl-1-benzylated-1*H*-benzimidazoles derivatives

A stirred mixture of arylaldehydes (20 mmol), *o*-phenylenediamine derivatives (10 mmol) and P_2O_5/SiO_2 (0.5 g, 7% *w*/*w*)[20] was added and the reaction mixture was stirred for the indicated time (Table 2) at room temperatures. After the completion of reaction (monitored by TLC), the reaction mixture was cooled, then 5 mL of ethanol was added to it and the total liquid was filtered to remove P_2O_5/SiO_2. The catalyst was washed four times with ethylacetate (5 mL×4), and then that recovered catalyst was dried in oven at 100 ℃ for 3 h. Finally the crude product was recrystallized from ethanol.

The desired pure product(s) was characterized by comparison of their physical data with those of known compounds.[15, 21-27]

2-(3,4-Dimethoxyphenyl)-1-(3,4-dimethoxyphenyl)methyl-1*H*-benzimidazole (Table 2, Entry 13) m.p. 170—172 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.71—6.43 (m, 10H, Ar-H), 5.50 (s, 2H, CH_2), 3.82, 3.71, 3.68, 3.64 (4s, 4OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 153.17, 149.98, 148.73, 148.58, 147.96, 142.55, 135.99, 129.31, 122.38, 122.35, 122.02, 121.55, 118.93, 117.91, 112.27, 111.74, 111.58, 110.92, 110.03, 55.52, 55.35, 55.31, 55.25, 47.19; IR (KBr) *v*: 3050, 2999, 2963, 2838, 1611 cm^{-1};

2-(2-Chlorophenyl)-1(2'-chlorophenylmethyl)-4-methyl-1*H*-benzimidazole (Table 2, Entry 6) m.p. 152—154 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.52—7.39 (m, 3H), 7.33 (d, J=7.9 Hz, 1H), 7.27 (d, J=7.7 Hz, 1H), 7.20—7.12 (m, 3H), 7.05 (t, J=7.5 Hz, 2H), 6.63 (d, J=7.5 Hz, 1H), 5.33 (s, 2H), 2.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 150.6, 142.3, 134.5, 134.4, 133.4, 132.3, 131.3, 130.0, 129.8, 129.5, 128.9, 127.8, 127.0, 126.9, 123.3, 123.1, 107.9, 45.7, 16.8; IR (KBr) *v*: 3436, 3055, 2922, 2373, 1604, 1441, 1382, 1046, 755.

Results and discussion

In our initial experiments, we found that the condensation of arylaldehyde, *o*-phenylenediamine (molar ratio 2.0∶1.0) was performed in the presence of P_2O_5/SiO_2 (0.5 g 7% *w*/*w*) as catalyst at room temperatures under solvent-free conditions.

Next, to optimize the amount of the catalyst in the mentioned reaction, we have carried out the reaction of *o*-phenylenediamine, benzaldehyde (molar ratio 1.0∶2.0) as model of our study with different amount of P_2O_5/SiO_2 as catalyst under solvent-free conditions at room temperatures (Table 1). It was found that 0.05 g of the catalyst showed maximum yield (95%) in minimum reaction time (6 min).

Table 1 Optimization the amount of P_2O_5/SiO_2 as the catalyst in the reaction of *o*-phenylenediamine and benzaldehyde under solvent-free conditions

Entry	Catalyst/mg	Time/min	Yield[a]/%
1	30	18	80
2	40	10	88
3	50	6	95
4	60	5	93

[a] Yields refer to isolated pure product.

Using these optimized reaction conditions (0.05 g of P_2O_5/SiO_2 (7% *w*/*w*) at room temperatures and molar ratio 2.0∶1.0 of aldehyde and *o*-phenylenediamine under solvent-free conditions), the scope and efficiency of the reaction were explored for the synthesis of a wide variety of substituted 2-aryl-1-benzylated-1*H*-benzimidazoles. The results are summarized in Table 2.

Table 2 Synthesis of 2-aryl-1-benzylated-1*H*-benzimidazole derivatives through direct condensation of aldehyde and *o*-phenylenediamine (molar ratio: 2.0/1.0) catalyzed by P_2O_5/SiO_2 (0.05 g) under solvent free conditions at room temperature

Entry	R	Time/min	Yield[a]/%	Found m.p./℃ [lit. m.p.][Ref]
1	C_6H_5	6	95	133—135 [134][21]
2	4-$MeOC_6H_4$	10	90	131—132 [131][15]
3	4-MeC_6H_4	8	92	129—130 [127—128][22]
4	4-ClC_6H_4	6	88	140—141 [137][15]
5	2-$MeOC_6H_4$	6	90	152—154 [151][15]
6	2-ClC_6H_4	8	91	158—159 [159][22]
7	4-$O_2NC_6H_4$	5	89	190—192 [192][15]
8	4-NCC_6H_4	7	80	216—218 [216—219][27]

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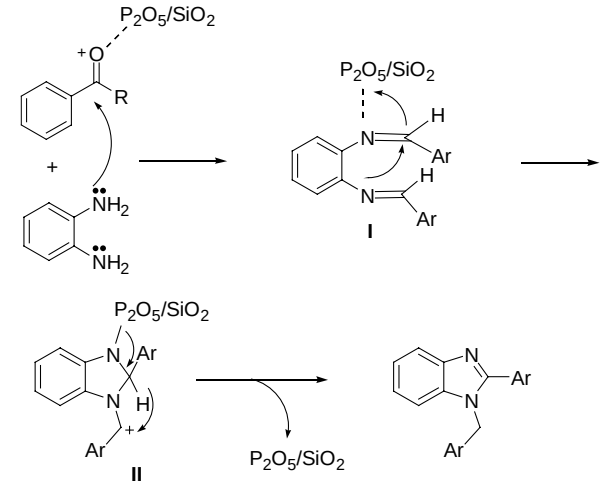
Entry	R	Time/min	Yield[a]/%	Found m.p./℃ [lit. m.p.][Ref]
9	2-$O_2NC_6H_4$	10	85	120—121 [120][22]
10	4-$(CH_3)_2NC_6H_4$	8	86	255—257 [255][22]
11	4-BrC_6H_4	8	87	158—160 [157—158][24]
12	4-FC_6H_4	5	85	113—115 [110—112][25]
13	3,4-$(MeO)_2C_6H_3$	10	80	173—175 [170—172][24]
14	3-(MeO)-4-$(HO)C_6H_3$	12	83	190—192 [184—186][24]
15	4(MeO)-3-$(HO)C_6H_3$	10	87	231—233 [229—231][24]
16	4-HOC_6H_4	8	80	224—226 [222][23]
17	3-HOC_6H_4	10	78	255—257 [253][24]
18	2-Furyl	8	75	97 [94—96][24] [94][26]
19	4-isoPropyl C_6H_4	6	78	176—178 [176][26]
20	2-Pyridyl	12	80	128—130 [130][26]

[a] Yields refer to the isolated pure products. The desired pure products were characterized by comparison of their physical data (melting points, IR, ^{1}H and ^{13}C NMR) with those of known compounds.[15,21-27]

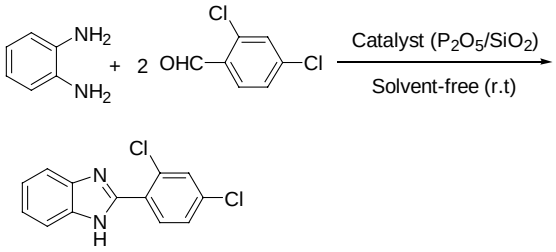
As shown in Table 2, aromatic aldehydes react without any significant difference in rate to give the corresponding 2-aryl-1-benzylated-1*H*-benzimidazoles in good yields. The method has the ability to tolerate other functional groups such as methyl, methoxy, nitro and halo groups. Consequently several aromatic aldehydes with different substituents on the aromatic ring were subjected to the condensation reaction. We examined these reactions using aliphatic aldehydes, but no appreciable amount of product was formed in the same conditions.

As reported in literature,[28] the proposed mechanism for synthesis of 2-aryl-1-benzylated-1*H*-benzimidazoles is shown in Scheme 1. P_2O_5/SiO_2 activated the carbonyl group of aldehydes for imine condensation to form the dibenzylidene-*o*-phenylenediamine (**I**) and then ring closure led to intermediate **II**. Finally, 1,3-hydride transfer afforded 2-aryl-1-benzylated-1*H*-benzimidazoles.

Scheme 1



Almost all substrates could give their corresponding 2-aryl-1-benzylated-1*H*-benzimidazoles exclusively as a single product (without the formation of 2-aryl-1*H*-benzimidazoles). The results are documented in Table 2. It is noteworthy that 2,4-dichlorobenzaldehyde represents as a single exceptional example by furnishing 2-aryl-1*H*-benzimidazole exclusively instead of 2-aryl-1-benzylated-1*H*-benzimidazole (Eq. 2). The formation of 2-aryl-1*H*-benzimidazole from 2,4-dichlorobenzaldehyde also reported by other catalyst such as Amberlite IR-120.[24]



(2)

In order to show the accessibility of the present work in comparison with the reported results in the literature such as LiCl or silica sulfuric acid,[26] Dowex 50W (acid form),[27] *L*-proline,[15c] acetic acid[15b] and Amberlite IR-120,[24] we summarized some of the results for the preparation of 2-aryl-1-benzylated-1*H*-benzimidazoles in Table 3, which shows that P_2O_5/SiO_2 (7% *w*/*w*) is the most efficient catalyst with respect to the reaction time and temperature and exhibits broad applicability in terms of yield (Table 3).

We also investigated the recycling of the catalyst under solvent-free conditions using a model reaction of benzaldehyde, *o*-phenylenediamine (Table 2, Entry 1). In this procedure, after completion of the reaction, the

Table 3 Comparison results of P_2O_5/SiO_2 with LiCl or silica sulfuric acid, Dowex 50 W (acid form), *L*-proline, acetic acid and Amberlite IR-120 in the synthesis of 2-aryl-1-benzylated-1*H*-benzimidazoles[a]

Entry	Catalyst	Amount of catalyst	Condition	Time	Yield/%
1	LiCl	0.02 g	In water (r.t.)	2 h	71
	Silica sulfuric acid	0.11 g	In ethanol (r.t.)	1.5 h	75
2	Dowex 50W (acid form)	10 mol%	In water (70 ℃)	8 h	83
3	*L*-Proline	10 mol%	In $CHCl_3$ (r.t.)	5 h	95
4	Acetic acid	10 mL	MW (50 ℃) (heating in air)	25 min	97
5	Amberlite IR-120	0.1 g	EtOH/H_2O (2∶1) (r.t.)	1.45 h	95
6	P_2O_5/SiO_2 (7% *w*/*w*)	0.05 g	Solvent-free (r.t.)	6 min	95

[a] Based on the reaction of *o*-phenylenediamine, benzaldehyde.

mixture was cooled to room temperature, and the crude solid product was dissolved in ethylacetate. The mixture was filtered for separation of the catalyst. The catalyst was washed four times with ethylacetate (5 mL×4), and then recovered catalyst was dried in oven at 100 ℃ for 3 h. The recovered catalyst was used for the subsequent catalytic runs. It was observed that on five successive runs with P_2O_5/SiO_2 as the catalyst, the reactivity in all runs remained almost unchanged (Figure 1).

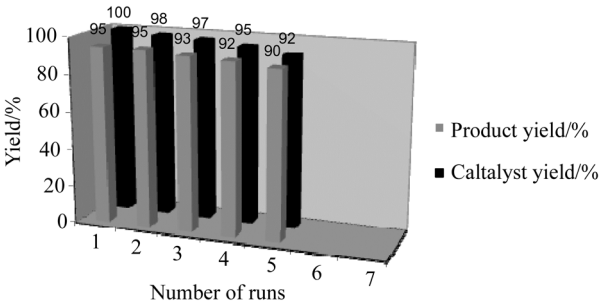


Figure 1 Reusability of the catalyst.

Conclusions

We have developed a green and straightforward protocol for the selective synthesis of 2-aryl-1-benzylated-1*H*-benzimidazoles in the presence of P_2O_5/SiO_2 as reusable and heterogeneous catalyst under solvent-free conditions at ambient conditions. This procedure provides several advantages such as cleaner reactions, easier workup, reduced reaction times, reusable catalyst, and eco-friendly promising strategy.

Acknowledgments

We are thankful to the University of Sistan and Baluchestan Research Council for the partial support of this research.

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(E1101138 Zhao, X.)

