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ORIGINAL ARTICLE

Synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles using chlorosulfonic acid at room temperature

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Abstract Chlorosulfonic acid ($ClSO_3H$) used to be a catalyst for the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles which was efficiently simple and convenient. This method afforded short reaction time, easy workup, moderate to excellent isolated yields which make this protocol practical and economically attractive.

1. Introduction

Interest in benzimidazole containing structures stems from their widespread occurrence in molecules that exhibit significant activity against several virus such as HIV (Porcari et al., 1998), herpes (HSV-1) (Migawa et al., 1998), RNA and human cytomegalovirus (HCMV) (Tamm and Seghal, 1978). In addition, benzimidazole derivatives are also used as potential antitumour agents, smooth muscle cell proliferation inhibitors, antimicrobial agents, a treatment for interstitial cystitis, as factor Xa inhibitors and in diverse areas of chemistry (Stevenson et al., 1999; Zhao et al., 2000; Forseca et al., 2001). In light of the affinity they display toward a variety of enzymes and protein receptors medicinal chemists would certainly classify them as 'privileged sub-structures' for drug design (Mason et al., 1999). Therefore the preparation of benzimidazoles has gained considerable attention in recent years.

The traditional synthesis of benzimidazoles involves the reaction between an *o*-phenylenediamine and a carboxylic acid or its derivatives (nitriles, amidates orthoesters) under harsh dehydrating conditions (Preston et al., 1981; Chi and Sun, 2000; Huang and Scarborough, 1999). Benzimidazoles have also been prepared on solid phase to provide a combinatorial approach (Wu et al., 2000). The most popular strategies for their synthesis utilize *o*-nitroanilines as intermediates or resort to direct N-alkylation of an unsubstantiated benzimidazole (Kim et al., 2004; Itoh et al., 2004). A number of synthetic protocols that involve intermediate *o*-nitroanilines have evolved to include the synthesis of benzimidazoles on solid support (Tumelty et al., 2001, Kilburn et al., 2000). 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 (Pertry and Wilson, 1993; Esser et al., 1999; Brain and Brunton, 2002; Perumal et al.,

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Table 1 Optimization of reaction conditions and mol% of chlorosulfonic acid for the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles.

Entry	Solvent	Mol% of $ClSO_3H$	Time (h)	Yield (%)
1	DCM	0.10	3.3	80
2	Methanol	0.10	2.4	71
3	Acetonitrile	0.10	3.2	63
4	Ethanol	0.10	2.3	74
5	Chloroform	0.10	3.0	58
6	2-Propanol	0.10	1.8	93
7	2-Propanol	0.07	1.8	93
8	2-Propanol	0.05	1.8	93
9	2-Propanol	0.025	2.5	85
10	2-Propanol	0.001	3.0	78

Table 2 Synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazole.

Entry	R	Reaction time (h)	Yield (%)[a]	M.p. (°C)
3a	C_6H_5	1.8	93	132–134
3b	4-Cl–C_6H_4	2.2	84	237–239
3c	4-CH_3 C_6H_4	2	88	126–128
3d	2-Cl–C_6H_4	2.4	80	154–156
3e	4-NO_2–C_6H_4	3.2	91	192–194
3f	2-NO_2–C_6H_4	3.3	82	118–120
3g	4-$(CH_3)_2N$–C_6H_4	2.6	92	252–254
3h	4-OCH_3–C_6H_4	2.1	85	130–131
3i	C_4H_3O	2.3	88	96–98
3j	2-OCH_3–C_6H_4	2.1	87	151–153

Compounds **1** (10 mmol, 1.08 g), **2(a–j)** (20 mmol, 2.12 g) and chlorosulfonic acid (10 mol%, 0.11 g) in 2-propanol was stirred at room temperature.

[a] Isolated yields.

2004; Sapkal et al., 2009; Salehi et al., 2006; Varala et al., 2007). However many of these methods have several drawbacks such as low use of expensive reagents a special oxidation process or long reaction time, tedious work up procedures, co-occurrence of several side reaction and low yield. Therefore the search continues for a better catalyst for the synthesis of benzimidazoles in terms of operational simplicity and economical viability of chlorosulfonic acid that was discovered in 1854 and soon became a reagent of widespread use. It has found application in many diverse types of reactions, such as alkylation, halogenations, rearrangement, cyclization and polymerization, usually operating as a strong acid catalyst and efficient halogenations and dehydrating agent (Cremylan, 2002). It is also used in the synthesis of 14-aryl-14*H*-dibenzo[a,j]xanthenes derivatives under microwave irradiation (Shelke et al., 2007).

2. Experimental

2.1. Materials and methods

All aldehydes were obtained from a freshly opened container and used without further purification with the exception of benzaldehyde and 2-furaldehyde which were distilled prior to use. Melting point was determined in open capillary tubes and is uncorrected. IR spectra were recorded on Perkin Elmer FTIR spectrophotometer in KBr disc, ^{1}H NMR spectra were recorded on variant 300 MHz spectrophotometer in $CDCl_3$ using TMS as the internal standard. The chemical shifts have been expressed in δ-ppm scale, the melting points and other data were recorded in Table 2. General procedure for the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles.

2.2. General procedure

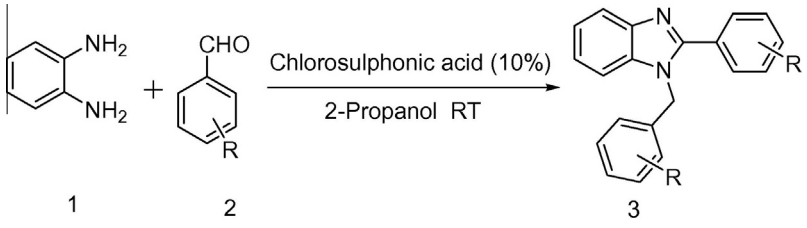
A mixture of *o*-phenylenediamine (10 mmol, 1.08 g), aromatic aldehyde (20 mmol, 2.12 g), and chlorosulfonic acid (0.10 mol%, 0.11 g) in 2-propanol was stirred at room temperature for appropriate time given in Table 2. After completion of the reaction as indicated by TLC, the solvent was evaporated on rota-vapor, the residue was poured on crushed ice and the solid that was obtained which was filtered. The solid was recrystallized from ethanol to expecting the pure product the results were summarized in Table 1. The structures of the products were confirmed by IR and ^{1}H NMR spectral data and were compared with authentic samples prepared according to the literature method (Scheme 1).

2.3. Spectral data of some compounds

Compound **3a**. M.p.: 132–134 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): 5.46 (s, 2H), 7.05 (d, 2H, J = 7.6 Hz), 7.25–7.28 (m, 5H), 7.53–7.58 (m, 4H), 7.75–7.80 (m, 3H).

Compound **3b**. M.p.: 137–139 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): 5.21 (s, 2H), 7.11 (d, 2H, J = 8.6 Hz), 7.21–7.25 (m, 2H), 7.35 (d, 2H, J = 8.4 Hz), 7.48 (d, 1H, J = 8.6 Hz), 7.79 (d, 2H, J = 8.6 Hz), 7.70 (d, 3H, J = 8.4 Hz).

Compound **3c**. M.p.: 126–128 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): 2.41 (s, 3H), 2.45 (s, 3H), 5.51 (s, 2H), 6.85 (d, 2H, J = 7.6 Hz), 7.10 (d, 2H, J = 7.6 Hz), 7.23–7.25 (m, 2H), 7.31 (d, 2H, J = 7.4 Hz), 7.45 (d, 1H, J = 7.4 Hz), 7.70 (d, 2H, J = 7.4 Hz), 7.76 (d, 1H, J = 7.4 Hz).



Scheme 1

Compound **3h**. M.p.: 130–131 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): 3.60 (s, 3H), 3.89 (s, 3H), 5.53 (s, 2H), 6.88 (d, 2H, J = 8.6 Hz), 6.99 (d, 2H, J = 8.5 Hz), 7.04 (d, 2H, J = 8.7 Hz), 7.21–7.26 (m, 2H), 7.55 (d, 1H, J = 8.1 Hz), 7.82 (d, 3H, J = 8.5 Hz).

3. Results and discussion

To evaluate the ability of chlorosulfonic acid in this reaction, we report a simple synthesis of 2-aryl-1-arylmethyl-1*H* -benzimidazole derivatives by the reaction of various aromatic aldehydes with *o*-phenyldiamine in 2-propanol in the presence of $ClSO_3H$ as a catalyst to establish the optimized condition, we carried out a set of experiments varying the reaction time. In 2-propanol the best condition to prepare 2-aryl-1-arylmethyl-1*H*-benzimidazoles was achieved when 0.10 mol% of $ClSO_3H$ equivalent of aldehyde, *o*-phenyldiamine were mixed and the reaction mixture was stressed at room temp for 2–3 h expecting the desired product in excellent yield. The ability of $ClSO_3H$ is to promote the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazole azoles in various solvents. Among these solvents and percentage (%) of yield and time required is given in Table 1.

To show the merit of the present work in comparison with reported results in the literature we compared results of chlorosulfonic acid with L-proline (Varala et al., 2007) and silica sulfuric acid (Salehi et al., 2006) also yields are excellent in the synthesis of some substituted 2-aryl-1-arylmethyl-1*H*-benzimidazoles previously in the literature and were characterized by the comparison of IR and NMR spectra with authentic samples.

4. Conclusion

In conclusion we have developed a new, efficient, and improved procedure for the synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazole catalyzed by $ClSO_3H$. Its advantages are, the catalyst is inexpensive, easily available, and excellent yields are obtained.

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