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Tosic Acid-on-Silica Gel: A Cheap and Eco-friendly Catalyst for a Convenient One-pot Synthesis of Substituted Benzimidazoles

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Summary. 2-Substituted and 1,2-disubstited benzimidazoles were prepared efficiently from *o*-phenylenediamines and aryl aldehydes using *p*-toluenesulphonic acid (5 mol%)-on-silica gel as a cheap and environmentally benign catalyst.

Keywords. Benzimidazoles; Synthesis; *o*-Phenylenediamines; Aryl aldehydes; Tosic acid-on-silica gel.

Introduction

1,3-Azoles are known to be useful pharmacophores. Of them, benzimidazoles are especially important because of their use as anthelmintics in veterinary medicine [1] and their potential as anticancer, antiviral, antiallergic, antiulcer, and anticoagulant compounds in human therapeutics [2]. The commonest route to substituted benzimidazoles is the condensation of *o*-phenylenediamines (*o-PD*s) with carboxylic acids, nitriles, amidates, or orthoesters [3], which usually require strongly acidic reagents under harsh conditions. In recent years, the preferred route has, therefore, been the oxidative cyclisation of *o-PD*s with aryl aldehydes employing a variety of catalysts [4]. But practically all the catalysts used for this purpose have their drawbacks. Accordingly, new catalysts continue to be developed [5, 6]. In view of this need for more suitable catalysts for the synthesis of substituted benzimidazoles by this route and in continuation of our interest in the newer applications of environmentally benign catalysts in the synthesis of useful heterocyclic molecules [7], we found that TLC-grade silica gel doped with a catalytic amount (5 mol%) of *p*-toluenesulphonic acid (*Ts*OH-SiO_2), can act as an efficient catalyst. Our findings, since important, are presented briefly in this paper.

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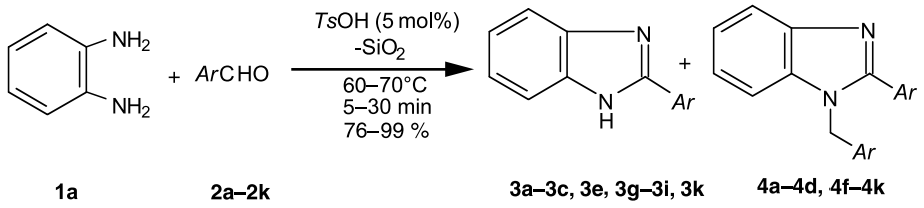
Results and Discussion

In order to ascertain a suitable condition, *o-PD* (**1a**) was treated with benzaldehyde (**2a**) (2 equivalents) by adsorbing them uniformly on *Ts*OH-SiO_2 (i) at room temperature, (ii) by heating at 60–70°C in an oven, (iii) in acetonitrile solution, both at room temperature and under reflux, and (iv) in methanol solution, also at room temperature as well as under reflux. These experiments furnished in each case the same mixture of two differently substituted benzimidazoles (see later) in respective overall yields of 93% (1.25 h), 91% (0.25 h), 84/77% (3.5/1.75 h), and 89/85% (2.0/0.75 h). These results demonstrated that heating at 60–70°C (condition ii) was the best of the conditions used in terms of both the reaction time and the overall yields of benzimidazoles. Accordingly, *o-PD* (**1a**) was treated separately with each of the aryl aldehydes (**2a**–**2h**, **2k**) and two heteroaryl aldehydes (**2i**, **2j**) on *Ts*OH-SiO_2 at 60–70°C (oven). Two products were formed (TLC) from each of the aldehydes (**2a**–**2c**, **2g**–**2i**, **2k**), whereas each of the other aldehydes furnished a single product. The products, identified by physical and spectroscopic

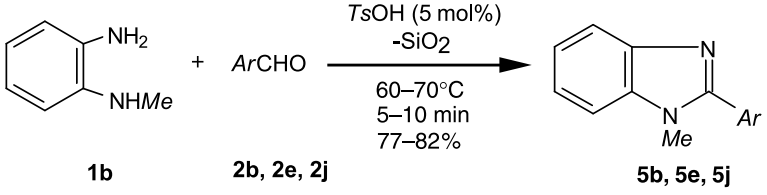


Scheme 1

Table 1. Formation of substituted benzimidazoles from *o-PD* (**1a**) and (hetero)aryl aldehydes **2a**–**2k**

Entry	Ar	Time/min	Yield/%			mp/°C found (reported)	
			3	**4**	Total	**3**	**4**
1	**2a** = C_6H_5	15	32	59	91	292–293 (292)[a]	132 (132)[b]
2	**2b** = 4-OCH_3-C_6H_4	30	22	75	97	227–228 (226)[a]	130–131 (131)[b]
3	**2c** = 4-BrC_6H_4	25	56	35	91	291–292 (291–294)[c]	159 (158)[d]
4	**2d** = 4-CNC_6H_4	10	–	84	84	–	218–219 (–)[e]
5	**2e** = 4-$NO_2C_6H_4$	5	87	–	87	311–312 (316)[a]	–
6	**2f** = 3-$NO_2C_6H_4$	10	–	78	78	–	167–168 (170)[f]
7	**2g** = 2-$NO_2C_6H_4$	5	42	46	88	262–263 (260)[g]	132–133 (120)[d]
8	**2h** = 1-Naphthyl	20	39	60	99	264–265 (266)[h]	158–159 (160)[d]
9	**2i** = 2-Thienyl	20	35	62	97	324–325 (326)[g]	145–146 (146–148)[g]
10	**2j** = 3-Indolyl	15	–	76	76	–	256–257 (–)[e]
11	**2k** = 3,4-$OCH_2OC_6H_3$	30	26	63	89	244–245 (246)[g]	170–171 (171–172)[g]

[a] Ref. [9]; [b] Ref. [8a]; [c] Ref. [10]; [d] Ref. [11]; [e] new compound; [f] Ref. [12]; [g] Ref. [7d]; [h] Ref. [13]



Scheme 2

means (*vide* Experimental), were either the 2-arylbenzimidazoles (**3**), the 1-arylmethyl-2-arylbenzimidazoles (**4**), or both. The reactions are shown in Scheme 1 and the results in Table 1.

Clearly, the aldehydes bearing electron-donating groups (**2a**–**2c**, **2k**), furnished both **3** and **4**, whereas the aldehydes bearing electron-withdrawing groups (**2d**–**2f**) behaved otherwise. Thus, **2d** and **2f** furnished only the respective 1,2-disubstituted benzimidazoles (**4d**, **4f**), whereas **2e** gave only the corresponding 2-arylbenzimidazole (**3e**).

As an extension, *N*-methyl-*o-PD* (**1b**) was separately treated with three aryl aldehydes (**2b**, **2e**, **2j**), which furnished, as expected, only the respective 1-methyl-2-arylbenzimidazoles (**5b**, **5e**, **5j**) efficiently and expeditiously. The reactions are shown in Scheme 2 and the results in Table 2.

Table 2. Formation of *N-Me*-2-arylbenzimidazoles from *N-Me-o-PD* **1b** and (hetero)aryl aldehydes

Entry	**2**	Time/min	Yield/% of **5**	mp/°C found (reported)
1	**2b**	10	82	118–119 (118.5–119.5)[a]
2	**2e**	5	77	210–211 (208–209)[b]
3	**2j**	10	81	302–303 (–)[c]

[a] Ref. [14]; [b] Ref. [15]; [c] new compound

For a comparative evaluation of the efficacy of *Ts*OH-SiO_2 with those of other catalysts reported recently for the preparation of substituted benzimidazoles *via* this route, two points require to be highlighted. Firstly, in all the cases, including those claimed to be a ''green'' procedure [6a], ''eco-friendly'' methods [5d–f], and ''solvent-free'' proto-

cols [8], the final products were invariably extracted with volatile organic solvents – ethyl acetate in most cases. Secondly, since the present catalyst contains *Ts*OH, the purification of the products necessitated the washing of the solvent extracts with dilute aqu. sodium bicarbonate, which does not pose any hazard to the environment and consequently does not affect the eco-friendliness of the catalyst. In view of the aforesaid, *Ts*OH-SiO_2 is definitely eco-friendly and undoubtedly cheap too. Additionally, the present method is indeed more expeditious than the rest of the methods except those mediated by iodobenzene diacetate [5a] and montmorillonite K-10 clay-microwave [8a]. Consequently, our method can certainly be considered as a convenient alternative to the other eco-friendly catalysts used for the one-pot synthesis of substituted benzimidazoles *via* this route.

Experimental

Melting points were recorded on a Toshniwal apparatus. The IR spectra were recorded on a Nicolet Impact 410 FT-IR spectrophotometer, the ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra, both 1D and 2D, including DEPT-135, HMQC and HMBC spectra, on a BRUKER DRX-500 NMR spectrometer and the LR EI-MS, the HR EI/FAB-MS, and the HR ESI-MS spectra on a JEOL JMS-AX505HA, JEOL JMS-700M Station, and a Q-TOF MICRO YA263 mass spectrometer. Individual ^{1}H and ^{13}C NMR spectral assignments of **4d** were ascertained additionally from its HMQC and HMBC spectra. The three new compounds (**4d**, **4j**, **5j**) were subjected to elemental analysis in a Perkin Elmer 2400 Series II C, H, N Analyser and the results were found to be in good agreement with the calculated values. The thin layer chromatographies (TLCs), both analytical and preparative, were carried out on silica gel G (Merck, India) plates. *p*-Toluenesulphonic acid (Pure) was procured from Riedel, Germany.

Preparation of the Catalyst (TsOH-SiO_2)

A solution of 5 mg *Ts*OH (5 mol% with respect to *o-PD*) in 0.5 cm^3 dry *Me*OH was uniformly adsorbed on 0.5 g silica gel G, the solvent was allowed to evaporate at rt inside a hood. Within few minutes, it led to a free-flowing solid to be used as the catalyst.

*Preparation of Benzimidazoles **3** and **4***

A solution of 54 mg *o-PD* (0.5 mmol) and 1 mmol aldehyde in 0.5 cm^3 of *ca.* 10% *Me*OH in *Et*OAc was adsorbed on 0.5 g freshly prepared *Ts*OH-SiO_2. After a few minutes at rt, when the reactants-on-SiO_2 did not smell of solvent, it was heated at 60–70°C in an oven. When the starting materials were consumed (TLC), silica gel was leached with *Et*OAc (3×10 cm^3), and the pooled extracts were freed from acid by washing with 2% aqu. $NaHCO_3$, washed free of alkali with water, dried (Na_2SO_4), and the solvent removed. The resulting residue was purified by preparative TLC (except for **4d**, **3e**, **4f**, and **4j**). The latter, each a single product, were purified by direct crystallisation to afford the pure benzimidazoles.

1-(4-Cyanophenyl)methyl-2-(4-cyanophenyl)benzimidazole (**4d**, $C_{22}H_{14}N_4$)

Off-white crystals, mp 218–219°C; IR (nujol): $\bar{\nu} = 2223$, 1606, 1288, 1162, 1023, 850, 744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.90$ (d, $J = 8$ Hz, H-4), 7.76–7.72 (m, H-2″, 6″, H-3″, 5″), 7.65 (d, $J = 8.5$ Hz, H-3′, 5′), 7.38 (dt, $J = 1$, 7.5 Hz, H-5), 7.32 (dt, $J = 1$, 7.5 Hz, H-6), 7.19 (d, $J = 8$ Hz, H-2′, 6′), 7.18 (d, $J = 8$ Hz, H-7), 5.51 (s, CH_2) ppm; ^{13}C NMR (125 MHz): $\delta = 152.1$ (C-2), 143.5 (C-3a), 141.4 (C-1′), 136.3 (C-7a), 134.5 (C-1″), 133.5 (CH-3′, 5′), 133.0, 130.0 (CH-2″, 6″, −3″, 5″), 126.9 (CH-2′, 6′), 124.7 (CH-6), 124.0 (CH-5), 121.1 (CH-4), 118.49, 118.40 (C-4′, C-4″-CN), 114.2 (C-4″), 112.8 (C-4′), 110.6 (CH-7), 48.5 (CH_2) ppm; LR EI-MS: m/z (%) = 334 (M^+, 100), 219 (38), 116 (90); HR ESI-MS TOF (+ve) calcd for $C_{22}H_{14}N_4Na$, 357.1116 $(M + Na)^+$, found 357.1113.

1-(Indol-3-yl)methyl-2-(indol-3-yl)benzimidazole (**4j**, $C_{24}H_{18}N_4$)

Pale yellow crystals, mp 256–257°C; IR (nujol): $\bar{\nu} = 3397$, 1619, 1573, 1242, 1122, 1016, 937, 746 cm^{-1}; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 11.69$ (s, 1H), 11.01 (s, 1H), 8.33 (d, $J = 8$ Hz, 1H), 7.86 (s, 1H), 7.68 (d, $J = 7.5$ Hz, 1H), 7.54 (d, $J = 7.5$ Hz, 1H), 7.49 (d, $J = 8$ Hz, 1H), 7.32 (d, $J = 8$ Hz, 1H), 7.26 (d, $J = 8$ Hz, 1H), 7.22 (t, $J = 7$ Hz, 1H), 7.18 (t, $J = 7.5$ Hz, 2H), 7.14 (t, $J = 7.5$ Hz, 1H), 7.03 (t, $J = 7.5$ Hz, 1H), 7.03 (s, 1H), 6.84 (t, $J = 7.5$ Hz, 1H), 5.82 (s, 2H) ppm; ^{13}C NMR (125 MHz): $\delta = 150.5$, 144.2, 137.2, 136.9, 136.5, 127.4, 126.4, 111.2, 106.0 (all C), 127.2, 124.3, 123.1, 122.27, 122.26, 122.25, 122.23, 121.1, 119.6, 119.2, 119.0, 112.6, 112.5, 111.3 (all CH), 41.5 (CH_2) ppm; LR EI-MS: m/z (%) = 362 (M^+, 11), 233 (100), 205 (24), 129 (51); HR FAB-MS (*m-NBA*) calcd for $C_{24}H_{19}N_4$, 363.1610 $(M + H)^+$, found 363.1614.

1-Methyl-2-(indol-3-yl)benzimidazole (**5j**, $C_{16}H_{13}N_3$)

Brown crystals, mp 302–303°C; IR (nujol): $\bar{\nu} = 3383$, 1558, 1281, 1239, 1145, 1008, 746 cm^{-1}; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 11.77$ (s, 1H), 8.36 (d, $J = 7.5$ Hz, 1H), 8.07 (d, $J = 2.5$ Hz, 1H), 7.65 (d, $J = 7$ Hz, 1H), 7.56 (d, $J = 7$ Hz, 1H), 7.50 (d, $J = 7.5$ Hz, 1H), 7.22 (t, $J = 7.5$ Hz, 1H), 7.20 (t, $J = 7.5$ Hz, 1H), 7.20–7.17 (m, 1H), 7.16 (t, $J = 7$ Hz, 1H), 3.96 (s, 3H) ppm; ^{13}C NMR (125 MHz): $\delta = 150.7$, 143.8, 136.9, 136.8, 127.2, 105.9 (all C), 127.7, 123.1, 122.3, 122.2 (×2), 121.0, 119.0, 112.6, 110.5 (all CH), 32.3 (N-CH_3) ppm; LR EI-MS: m/z (%) = 247 (M^+, 70), 246 (100); HR EI-MS calcd for $C_{16}H_{13}N_3$, 247.1110 $(M)^+$, found 247.1107.

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