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Cerium (IV) ammonium nitrate-mediated reactions: Simple route to benzimidazole derivatives

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Abstract The reaction of *o*-phenylenediamine with aromatic aldehydes in MeOH at room temperature catalyzed by cerium (IV) ammonium nitrate (CAN) afforded either 2-aryl-1-aryl-methyl-1*H*-benzimidazoles and/or 2-aryl-substituted benzimidazoles.

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1. Introduction

The benzimidazole moiety is found in various biologically active compounds having antiviral (Gabril et al., 2001), antiulcer (Kim et al., 1996), antihypertensive (Roth et al., 1997), anti-cancer (Moukhoodhyay et al., 2002), and antihistaminic properties (Junsens et al., 1985). In addition, benzimidazole derivatives have been used as topoisomerase inhibitors, selective Neuropeptide y1 receptor antagonists, smooth muscle cell

proliferation inhibitors, a treatment for interstitial cystitis, as factor Xa inhibitors (Zarrinmayeh et al., 1999; Kohara et al., 1996; Lopez et al., 1990; Fonseca et al., 2001; Zhao et al., 2000). They also display a great affinity towards a variety of enzymes and protein receptors (Pason et al., 1999). The most common synthesis of benzimidazoles involves the reaction between *o*-phenylenediamine and a carboxylic acid (or their synthetic equivalents) or aromatic aldehydes (Wang et al., 2006; Lin et al., 2006; Preston and “Chemistry of Heterocyclic Compounds, 1981; Chi and Sun, 2000; Dudd et al., 2003; Curini et al., 2004; Zheng et al., 2007) under harsh dehydrating conditions. Benzimidazoles have also been prepared on solid phase to provide a combinatorial approach (Mazurov, 2000). Recently, R. Kumar et al. Kumar and Joshi (2007) have reported a one-step synthesis of 2-aryl-1*H*-benzimidazoles from the reaction of *o*-phenylenediamine with various aldehydes in dichloromethane in the presence of CAN under reflux. Also, *o*-nitroaniline has evolved to include the synthesis of benzimidazoles *via* one step reduction and cyclisation (Kim et al., 2004; Wu et al., 2000). In all of these approaches, the sole isolable products were 2-aryl-1*H*-benzimidazoles. Recently,

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(Varala et al., 2007) a selective synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles from the reaction of *o*-phenylenediamine with aromatic aldehydes catalyzed by L-proline in which two molecules of aldehyde reacted with one molecule of *o*-phenylenediamine has been reported. Ceric ammonium nitrate (CAN) has emerged as a versatile reagent for a variety of synthetic transformations which have been well documented (Nair and Deepthi, 2007; Nair et al., 2004). In continuation to our interest in the synthesis of azoles and azines (Fawzia et al., 2008; Mekheimer et al., 2008a; Mekheimer et al., 2008b) *via* simple, efficient and environmentally friendly techniques we investigated the reaction of *o*-phenylenediamine with several aromatic aldehydes catalyzed by CAN in different solvents (CH₃OH, CH₃CN, C₆H₅CH₃) at room temperature, both the expected products were obtained which revealed the dependence of such condensation on the nature of the solvent and enabled achieving a direct simple route to benzimidazole derivatives.

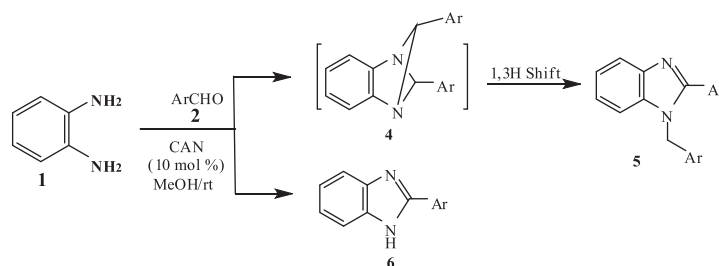
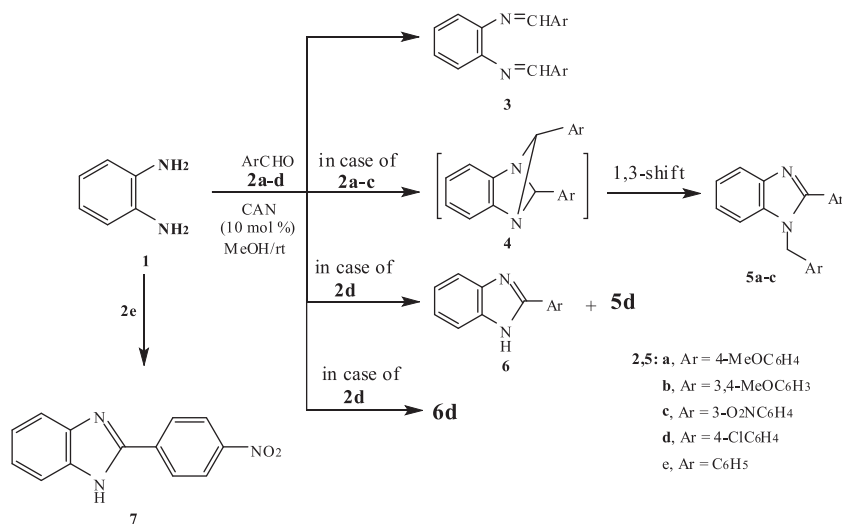
2. Results and discussion

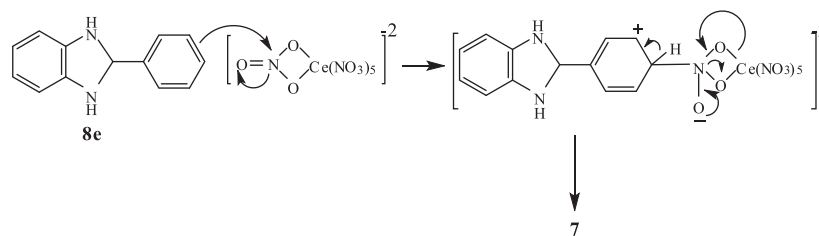
Thus, when *o*-phenylenediamine **1** was treated with 4-methoxybenzaldehyde **2a** in MeOH in the presence of CAN (10 mol%) at room temperature a compound of molecular formula C₂₂H₂₀N₂O₂ (MS = 344 m/e) was obtained in 90% yield. ¹³C NMR of the reaction product revealed a methylene carbon, at $\delta = 46.86$ in addition to two methoxy carbons at

$\delta = 54.97$ and 55.27 as well as aromatic carbons. ¹H NMR shows a band at $\delta = 5.49$ ppm integrated for two protons in addition to two methoxy and 12 aromatic protons. This excludes structure **3a** since it will reveal two azomethine protons at $\delta = 8.16$ ppm. Consequently, the 2-aryl-1-arylmethyl-1*H*-benzimidazole derivative **5a** was established for the reaction product. Similarly, 3,4-dimethoxybenzaldehyde **2b** reacts with **1** under the same reaction conditions to afford the corresponding 2-aryl-1-arylmethyl-1*H*-benzimidazole derivative **5b** (Scheme 1).

The formation of **5a** and **b** was assumed to proceed *via* the formation of the dihydro-2-arylbenzimidazole intermediate **8** which condenses with another molecule of the aldehyde under the effect of the catalyst to afford the 1,4-diazabicyclo (Kim et al., 1996; Gabril et al., 2001; Gabril et al., 2001) hexane intermediate **4**, which undergoes a thermally allowed 1,3-hydrogen shift to yield the final isolable product **5** (Scheme 2).

In contrast, the reaction of 3-nitrobenzaldehyde **2c** with **1** afforded a mixture of 2-(3-nitrophenyl)-benzimidazole **6c** and the 1-arylmethyl derivative **5c** in 2:1 ratio. The structure proposed for the reaction products was established based on analytical and spectral data (see Section 4). The reaction of **1** with 4-chlorobenzaldehyde **2d** afforded mainly the corresponding 2-(4-chlorophenyl)-benzimidazole derivative **6d**. The structure of **6d** was established based on ¹H NMR which revealed besides the aromatic protons an (NH) band at $\delta = 8.2$ ppm. The formation of **6d** was proposed to be formed *via* condensation of





Scheme 3

Table 1 Reaction of aromatic aldehydes with *o*-phenylenediamine.

Product	Ar	Yield (%)	m.p. (°C)	Published data m.p. (°C)
5a	4-MeOC ₆ H ₄	90	130–131	129–130
5b	3,4-MeOC ₆ H ₃	89	170–172	–
5c	3-NO ₂ C ₆ H ₄	15	162–164	–
6c	3-NO ₂ C ₆ H ₄	55	206–207	207–208
6d	4-ClC ₆ H ₄	70	293–294	292–293
7	4-O ₂ NC ₆ H ₄	82	323–325	327

one molecule of **2d** followed by oxidation of the formed adduct by the effect of (CAN). The oxidizing effects of (CAN) are well known and have been established. (Varala et al., 2007) Interestingly, the reaction of benzaldehyde **2e** with **1** afforded a product of molecular formula C₁₃H₉N₃O₂ (Ms = 239 m/e). The ¹H NMR spectrum of this product revealed a singlet at δ = 11.62 integrated for one (NH) proton besides aromatic protons. Moreover, its ¹³C NMR reveals absorption bands for aromatic carbons and 2-benzimidazolyl carbons. Accordingly, structure **7** was established for the reaction product. It is assumed to be formed *via* the formation of the corresponding condensation product **6e** followed by nitration of the phenyl group at position 2 of the benzimidazole by the action of (CAN). If nitration of benzaldehyde is prior to the condensation step it will afford **6c**. The nitration process was illustrated in Scheme 3 in which (CAN) acts as a carrier of nitronium species and is similar to that observed with metal nitrates (Goonbes and Russel, 1971) (Table 1).

In order to investigate the quantity effect of CAN on the reaction yield we studied the efficiency of the catalyst ratio (1, 2, 5, 10, 15 mol%) and we revealed that 10 mol% of the catalyst was the optimum ratio to carry out the forward reaction. For less than 10% the yield decreases to 65–70% while an increase in the quantity of CAN has no significant effect on the overall yield. In addition, methanol was the best solvent among others (CH₃CN, C₆H₅CH₃).

3. Conclusion

The results obtained in our investigation clearly revealed that the reaction of *o*-phenylenediamine with aromatic aldehydes proceeds mainly *via* two different routes. The first is a 1:1 condensation followed by oxidation to afford the 2-aryl-substituted benzimidazoles. Second is a 1:2 condensation to afford 2-aryl-1-arylmethyl-1*H*-benzimidazole. Both the expected products were obtained whose ratios depended on the nature of the solvent. It was previously reported that in methanol as

a solvent both **5** and **6** were obtained with **5** as a predominant one (Salehi et al., 2006).

4. Experimental section

Melting points were determined on a Gallenkamp apparatus and are uncorrected. The reactions were monitored by TLC (thin layer chromatography) and visualized with UV light. IR spectra (KBr) were recorded on Perkin–Elmer FTIR model 2000 spectrometer and the NMR spectra were measured on Bruker-DPX-400 (400 MHz) spectrometer using TMS as an internal standard. Mass spectra were carried out on a VG-Autospac-Q high performance tri-sector GC/MS/MS Spectrometer. Microanalyses were performed by the Microanalytical Data Unit at Kuwait University.

4.1. General procedure of the reaction 1 and 2a–d

A mixture of *o*-phenylenediamine **1** and aromatic aldehydes **2a–d** in MeOH (10 mL) was treated with Ceric ammonium nitrate (CAN) (10 mol%). The reaction mixture was stirred at room temperature overnight and then treated with brine solution. The solid formed was collected by filtration and crystallized from ethanol. In case of **2c** a fractional crystallized from EtOH and EtOH/H₂O mixture afforded **5c** and **6c**.

4.2. 2-(4-Methoxyphenyl)-1-(4-methoxyphenyl)methyl-1*H*-benzimidazole **5a**

Yield 90%; m.p. 130–131 °C (lit Salehi et al., 2006 m.p 129–130 °C); IR (KBr, cm⁻¹): ν_{max} = 3060, 3049 (arom. CH), 2986 (aliph. CH), 1609 (C=C); ¹H NMR δ, ppm = 7.70–6.84 (m, 12H, Ar-H), 5.49 (s, 2H, CH₂), 3.83 (s, 3H, OCH₃), 3.69 (s, 3H, OCH₃); ¹³C NMR δ, ppm = 160.31, 158.45, 153.11, 142.64, 138.72 135.80, 130.47, 128.78, 127.37, 122.31, 121.99, 118.94, 114.21, 114.11, 110.97, 55.27, 54.97, 46.86; MS: *m/z* (%) 344.15 (34%); Anal. Calcd for C₂₂H₂₀N₂O₂: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.66; H, 5.80; N, 8.11.

4.3. 2-(3,4-Dimethoxyphenyl)-1-(3,4-dimethoxyphenyl)methyl-1*H*-benzimidazole **5b**

Yield 89%; m.p. 170–172 °C; IR (KBr, cm⁻¹): ν_{max} = 3050 (arom. CH), 2999, 2963, 2838 (aliph. CH), 1611 (C=C); ¹H NMR δ, ppm = 7.71–6.43 (m, 10H, Ar-H), 5.50 (s, 2H, CH₂), 3.82, 3.71, 3.68, 3.64 (4 s, 4 OCH₃); ¹³C NMR δ, ppm = 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; MS: *m/z* (%) 404.17 (77%); Anal. Calcd for

$C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.32; H, 5.88; N, 6.92.

4.4. 2-(3-Nitrophenyl)-1-(3-nitrophenyl)-methyl-1H-benzimidazole 5c

Yield 15%; m.p. 162–164 °C; IR (KBr, cm^{-1}): ν_{max} = 3054 (arom. CH), 2960 (aliph. CH), 1619 (C=C); 1H NMR δ , ppm = 8.30–7.20 (m, 12H, Ar-H), 5.80 (s, 2H, CH₂); MS: m/z (%) 374.1 (100%); *Anal.* Calcd for $C_{20}H_{14}N_4O_4$: C, 64.17; H, 3.77; N, 14.97. Found: C, 64.15; H, 3.72; N, 14.86.

4.5. 2-(3-Nitrophenyl)-1H-benzimidazole (6c) and 2-(4-chlorophenyl)-1H-benzimidazole (6d)

The compounds were obtained in 55% and 70% yields and were found identical with authentic specimens Nagawade and Shinde, 2006 (m.ps., IR, NMR).

4.6. 2-(4-Nitrophenyl)-1H-benzimidazole 7

Yield 82%; m.p. 323–325 °C (lit (Deluca and Kerwin, 1997) m.p 327 °C); IR (KBr, cm^{-1}): ν_{max} = 3338 (NH), 3100 (arom. CH), 2830 (aliph. CH), 1655 (C=C); 1H NMR δ , ppm = 11.65 (S, 1H, NH), 7.91–7.74 (m, 8H, Ar-H); ^{13}C NMR δ , ppm = 115.2; 123.11; 124.42; 127.33; 135.12; 141.70; 147.82; 152.22. MS: m/z (%) 239.07 (100%); *Anal.* Calcd for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.33; H, 3.69; N, 17.55.

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