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ORIGINAL ARTICLE

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*-benz-imidazoles and/or 2-aryl-substituted benzimidazoles.

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), anticancer (Moukhoopadhyay et al., 2002), and antihistaminic properties (Junsens et al., 1985). In addition, benzimidazole derivatives have been used as topisomerase inhibitors, selective Neuropeptide yy1 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-1H-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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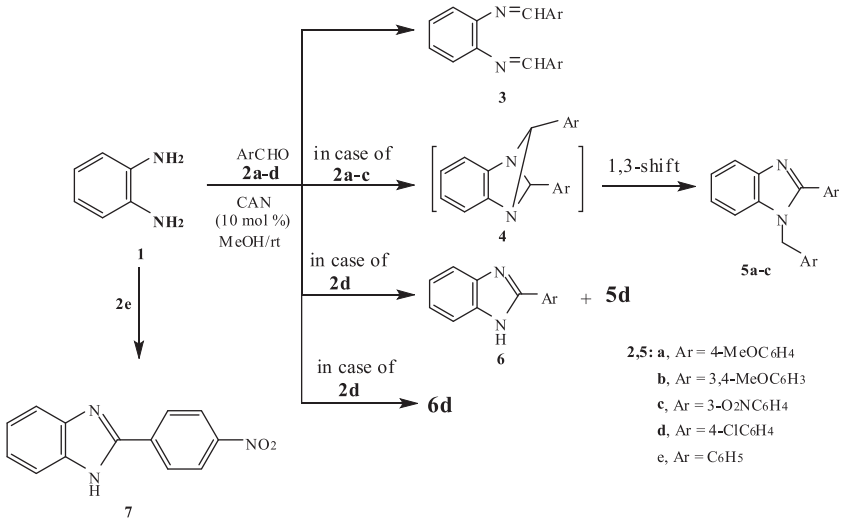
(Varala et al., 2007) a selective synthesis of 2-aryl-1-arylmethyl-1*H*-benzimidazoles from the reaction of *o*-phenylenediamine with aromatic aldehydes catalyzed by L-proline in which two molecules of aldehyde reacted with one molecule of *o*-phenylenediamine has been reported. Ceric ammonium nitrate (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 (CH_3OH, CH_3CN, $C_6H_5CH_3$) 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

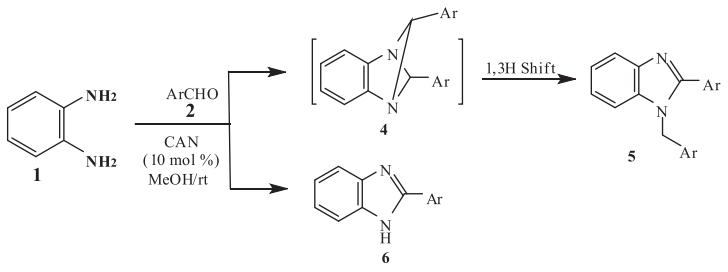
Thus, when *o*-phenylenediamine **1** was treated with 4-methoxybenzaldehyde **2a** in MeOH in the presence of CAN (10 mol%) at room temperature a compound of molecular formula $C_{22}H_{20}N_2O_2$ (MS = 344 m/e) was obtained in 90% yield. ^{13}C NMR of the reaction product revealed a methylene carbon. at δ = 46.86 in addition to two methoxy carbons at δ = 54.97 and 55.27 as well as aromatic carbons. ^1H NMR shows a band at δ = 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 δ = 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-diazbicyclo (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 δ = 8.2 ppm. The formation of **6d** was proposed to be formed *via* condensation of



Scheme 1



Scheme 2