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SHORT COMMUNICATIONS

Zirconyl(IV) Chloride-Promoted Synthesis of Benzimidazole Derivatives*

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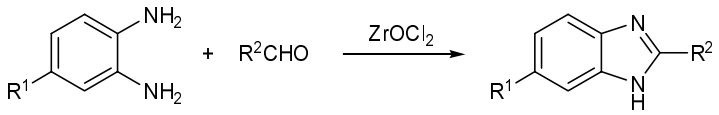
Benzimidazole structures are classified under several classes of drugs [1], depending on the substitution pattern in the benzimidazole nucleus. Introduction of a small substituent into the 2- or 5-position is characteristic of benzimidazole antihelminthics; alternatively, bulky 2-substituents are typical of drugs used in the treatment of peptic ulcer and of those sometimes referred to as proton pump inhibitors. Bulky substituents on the N^1 and C^2 atoms are found in H1-antihistaminics. All these compounds contain benzimidazole skeleton; therefore, the latter is believed to be necessary for the therapeutic effect.

Methods of synthesis of benzimidazole derivatives include condensation of aromatic *ortho*-diamines with aldehydes in boiling nitrobenzene [2, 3], condensation of aromatic *ortho*-diamines with carboxylic acids and their derivatives in the presence of strong acids, such as polyphosphoric acid [4] or other mineral acids [5], and thermal or acid-catalyzed cyclization of *N*-(*N*-arylbenzimidoyl)-1,4-benzoquinone imines [6]. Direct condensation of aromatic *ortho*-diamines with aldehydes is not a good synthetic method, for it leads to formation of complex mixtures of products containing 1,2-disubstituted benzimidazoles, the corresponding bis-anils, and dihydrobenzimidazoles as main by-products [7]. In some cases, addition of transition metal compounds, e.g., copper(II) acetate [8], mercury oxide [9], or lead tetraacetate [10] improves the reaction selectivity. Unfortunately, many of the above processes suffer from some limitations, such as drastic conditions, low yields, tedious workup procedures, and occurrence of side reactions.

In the recent years, zirconium(IV) salts have attracted much attention due to their accessibility and low toxicity. Zirconyl(IV) chloride $ZrOCl_2$ is stable to moisture, readily available, and inexpensive. However, this compound has not received so far wide application in synthetic organic chemistry as mild and versatile Lewis acid catalyst. As compared to conventional Lewis acids, zirconyl(IV) chloride is advantageous due to its high specific catalytic activity, resistance to moisture, and the possibility for recycling. No examples of using $ZrOCl_2$ as catalyst in the synthesis of benzimidazoles have been reported.

The present communication describes a fast procedure for the synthesis of various biologically important benzimidazole derivatives in the presence of a catalytic amount of zirconyl(IV) chloride under very mild solvent-free conditions (Scheme 1). The reactions were carried out at room temperature over a period of 30 min using 1 mmol of *o*-phenylenediamine, 1.1 mmol of the corresponding aldehyde, and 0.1 mmol of

Scheme 1.



R^1 = H, MeO, R^2 = Ar, Alk, Het (see table).

* The text was submitted by the authors in English.

Synthesis of benzimidazoles in the presence of zirconyl chloride

R	R'	Yield, %	mp, °C	Published data: mp, °C
H	Ph	91	291	288–290
H	4-ClC_6H_4	88	294	292–293
H	3-$O_2NC_6H_4$	85	308	310–311
H	3-Pyridyl	95	248	246–248
H	PhCH=CH	93	201	198–200
H	*cyclo*-C_6H_{11}	95	282	282–283
H	Me_2C=$CHCH_2CH_2CH(CH_3)CH_2$	80	94	91–93
MeO	Ph	88	219	220–221

$ZrOCl_2$. The results are summarized in table. It is seen that aromatic, aliphatic, and α,β-unsaturated aldehydes react with *o*-phenylenediamine and 4-methoxybenzene-1,2-diamine in the presence of $ZrOCl_2$ with equal efficiency to give the corresponding substituted benzimidazoles in good yields (80–95%). The best results were obtained with the use of 0.1 equiv of $ZrOCl_2$. When the amount of the catalyst was lower, the yield of the products decreased, whereas raising the catalyst concentration did not lead to an appreciable increase of the yield. The catalyst can readily be removed from the reaction mixture by filtration, at it can be used repeatedly for several times without appreciable loss in activity. The scope and general character of the proposed procedure is illustrated by the wide range of aldehydes and *o*-phenylenediamines involved in the reaction (see table). The method is advantageous due to high conversion, short reaction time, clean reaction profile, solvent-free conditions, and simple experimental and workup procedures.

General procedure for the synthesis of substituted benzimidazoles by condensation of *o*-phenylenediamines with aldehydes in the presence of zirconyl(IV) chloride. A mixture of 1 mmol of *o*-phenylenediamine, 1.1 mmol of the corresponding aldehyde, and 0.1 mmol of $ZrOCl_2$ was stirred for 30 min at room temperature. Methylene chloride, 5 ml, was then added, the catalyst was filtered off, the filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel using methylene chloride–methanol (99:1) as eluent.

2-(Pyridin-3-yl)-1*H*-benzimidazole. mp 246–248°C. ^{1}H NMR spectrum (200 MHz, CD_3OD), δ, ppm: 9.35 d (1H), 8.75 d.d (1H), 8.60 m (1H), 7.70 m (3H), 7.40 m (2H). Mass spectrum, *m*/*z* (I_{rel}, %): 196 $[M + H]^+$ (100). Found, %: C 73.46; H 4.70; N 21.62. $C_{12}H_9N_3$. Calculated, %: C 73.83; H 4.65; N 21.52.

The reaction of *o*-phenylenediamine with benzaldehyde was repeated 3 times using the same portion of the catalyst. After each run, the catalyst was filtered off, washed with methylene chloride, and dried for 2 h at 50°C. The yields of benzimidazole were 91, 88, and 88%.

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