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Note

$TiCl_4$ Promoted synthesis of benzimidazole derivatives

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Differently substituted benzimidazoles have been synthesised in very good yields in solvent-free conditions from *o*-phenylenediamine and aldehydes in the presence of $TiCl_4$ as a catalyst. The method is applicable to aromatic, unsaturated and aliphatic aldehydes and to substituted *o*-phenylenediamines without significant differences.

Keywords: $TiCl_4$, aldehydes, benzimidazoles, solvent-free reactions, drugs

IPC Code: **Int Cl.[8] C07D**

Benzimidazole structures are classified under several classes of drugs[1], based on the possible substitution at different positions of the benzimidazole nucleus. Introduction of a small substituent into the 2-and 5-position is characteristic for benzimidazole anti-helmentics; alternatively, bulky 2-substituents characterize drugs used in the treatment of peptic ulcer and are sometimes referred as proton pump inhibitors; bulky 1-and 2-substituents are found in H1-anti-histaminics. All these compounds contain the benzimidazole skeleton and hence it has been assumed that this skeleton is necessary for the therapeutic effect.

Methods of benzimidazole synthesis include the condensation of *o*-aryldiamines and aldehyde in refluxing nitrobenzene[2,3], the condensation of *o*-aryldiamines with carboxylic acids or their derivatives in the presence of strong acids such as polyphosphoric acid[4] or mineral acids[5] and the thermal or acid promoted cyclization of *N*-(*N*-aryl-benzimidoyl)-1,4-benzoquinoneimines[6]. Direct condensation of *o*-aryl di-amines and aldehydes is not a good synthetic reaction, as it is well known to yield a complex mixture, being 1,2-disubstituted benzimidazoles, the bis anil and dihydrobenzimidazoles as the main side products[7]. In this case, however, the addition of transition metal, namely copper (II) acetate[8], mercury oxide[9] or lead tetracetate[10] allow a partial selective synthesis of benzimidazoles. Unfortunately, many of these process suffer some limitations, such as drastic reaction conditions, low yields, tedious work up procedures and co-occurrence of several side reactions.

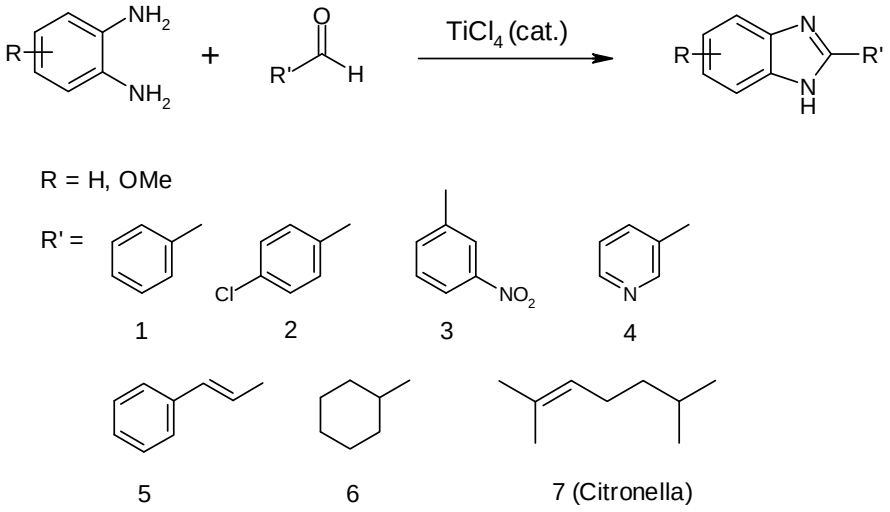
Titanium(IV) chloride is moderately strong Lewis acid with extreme wide applications such as in conversion of ketones to *N*-alkylimines, in Aldol condensation of aryl ketones with aryl aldehyde, in Michael addition of silyl enol ethers to α,β-enones, conjugate allylation of α,β-enones etc. However, there are no examples of the use of titanium(IV) chloride as a catalyst for the preparation of benzimidazoles.

Herein, we wish to disclose a novel protocol for the rapid synthesis of a variety of biologically significant benzimidazoles using a catalytic amount of $TiCl_4$ under extremely mild solvent-free conditions **(Scheme I)**. The reaction was carried out in neat at room temperature for 30 min, using *o*-phenylene-diamine (1 mmole) and aldehyde (1.1 mmole) in the presence of $TiCl_4$ (0.1 mmole). The results are summarized in **Table I**.

As shown in **Table I**, aromatic, aliphatic and α,β-unsaturated aldehydes and substituted *o*-phenylene-diamine react without any significant difference to give the corresponding benzimidazoles in good yields. Best results were obtained using 0.1 equivalents of $TiCl_4$, lower loading resulted in lower yields, while higher loading did not increase product yields significantly. The scope and generality of this procedure is illustrated with respect to various *o*-phenylenediamines and a wide range of aldehydes and the results are presented in **Table I**. This method offers several advantages such as high conversions, shorter reaction times, cleaner reaction profiles, solvent-free conditions and simple experimental and work-up procedures.

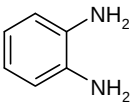
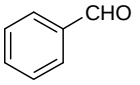
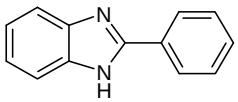
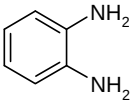
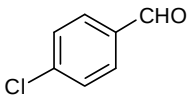
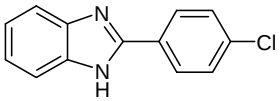
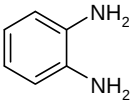
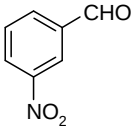
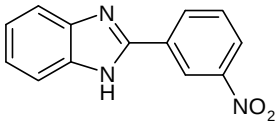
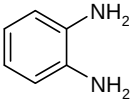
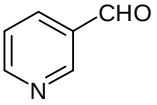
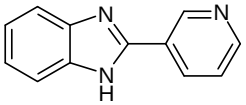
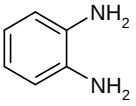
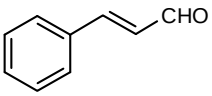
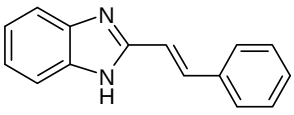
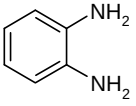
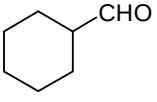
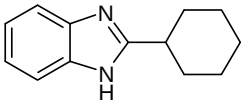
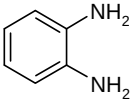
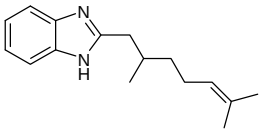
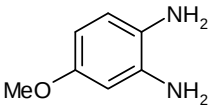
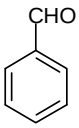
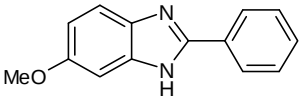
Experimental Section

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer. Chemical shifts are reported in δ units (ppm) relative to TMS as internal standard. Electron spray ionization mass spectra (ES-MS) were



Scheme I

Table I—Characterization data of compounds

Diamine	Aldehyde	Product	Yield (%)	m.p. (°C) Reported	m.p. (°C) Found
			90	291[11]	289-91
			89	294[11]	291-93
			87	308[11]	309-10
			93	248[12]	245-48
			91	201[13]	199-01
			93	282[13]	282-83
	Citronella		82	94[14]	92-94
			88	219[13]	220-21

recorded on a Water-Micromass Quattro-II spectrometer. IR spectra were recorded on a Varian spectrometer. All the reagents used were of AR grade and were used without further purification. Column chromatography employed silica gel of 60-120 mesh.

General Procedure. A mixture of *o*-phenylenediamine (1 mmole) and aldehyde (1.1 mmole) was well stirred with $TiCl_4$ (0.1 mmole) at room temperature for 30 min. To this reaction mixture, CH_2Cl_2 (25 mL) was added and washed with water and then with brine. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to get the crude compound. The crude compound was purified by silica gel column chromatography using CH_2Cl_2 – MeOH (99:1) as eluent.

2-Phenyl-1*H*-benzimidazole 1: mp 289-91ºC; IR (KBr) : 3046, 1444, 1410, 1275, 970, 745 cm^{-1}; Mass spectrum (ES/MS) : m/z 193 (M-H, 100 %); ^{1}H NMR spectrum (200 MHz, DMSO-d_6): δ 12.7 s (1H, NH), 7.95 m (2H), 7.25-7.35 m (5H), 7.05 m (2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 111.1, 118.6, 121.9, 126.2, 128.6, 129.5, 130.0, 134.8, 143.5, 151.0.

2-(4-Chlorophenyl)-1*H*-benzimidazole 2: m.p. 291-93ºC; IR (KBr) : 3041, 1450, 1402, 1280, 965, 750 cm^{-1}; Mass spectrum (ES/MS) : m/z 227 (M-H, 100 %); ^{1}H NMR spectrum (200 MHz, DMSO-d_6): δ 12.5 s (1H, NH), 8.20 d (2H), 7.6 d (2H), 7.30 m (2H), 7.10 m (2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 115.4, 123.2, 128.6, 128.9, 129.4, 134.3, 138.9, 152.9.

2-(3-Nitrophenyl)-1*H*-benzimidazole 3: m.p. 309-310ºC; IR (KBr) : 3063, 1523, 1444, 1357, 973, 746 cm^{-1}; Mass spectrum (ES/MS) : m/z 238 (M-H, 100 %); ^{1}H NMR spectrum (200 MHz, DMSO-d_6): δ 12.9 s (1H, NH), 8.90 s (1H), 8.50 d (1H), 8.10 d (1H), 7.70 t (1H), 7.50 m (2H), 7.2 m (2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 114.3, 121.2, 122.1, 123.2, 130.1, 131.6, 133.6, 138.9, 148.9, 152.7.

2-Pyridin-3-yl-1*H*-benzimidazole 4: m.p. 245-48ºC; IR (KBr) : 3068, 1449, 1402, 1280, 746 cm^{-1}; Mass spectrum (ES/MS) : m/z 194 (M-H, 100 %); ^{1}H NMR spectrum (200 MHz, CD_3OD): δ 13.05 s (1H, NH), 9.35 d (1H), 8.75 dd (1H), 8.60 m (1H), 7.70 m (3H), 7.40 m (2H); ^{13}C NMR (50 MHz, CD_3OD): δ 112.1, 119.2, 121.3, 121.7, 123.1, 124.5, 134.9, 137.3, 143.8, 148.5, 149.2, 150.7.

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References

1 Velik J, Baliharova V, Fink-Gremmels J, Bull S, Lamka J & Skalova L, *Res Vet Sci*, 76, **2004**, 95.
2 Yadagiri B & Lown J W, *Synth Commun*, 20, **1990**, 955.
3 Sun Q & Yan B, *Bioorg Med Chem Lett*, 8, **1998**, 361.
4 Preston P N, *Benzimidazoles and Congeneric Tricyclic Compounds, In The Chemistry of Heterocyclic Compounds*, Part 1, Vol. 40; edited by Weissberger & Taylor (Wiley: New York), **1981**, p. 6-60.
5 Grimmett M R, *Imidazoles and their Benzo Derivatives, In Comprehensive Heterocyclic Chemistry*, Vol. 5; edited by Katritzky & Rees, (Pergamon: Oxford), **1984**, p. 457-487.
6 Benincori T & Sannicolo F, *J Heterocycl Chem*, 25, **1988**, 1029.
7 Smith J G & Ho I, *Tetrahedron Lett*, 38, **1971**, 3541.
8 Weidenhagen R, *Ber*, 69, **1936**, 2263.
9 Jakobson P, Jannicke M & Meyer F, *Ber*, 29, **1896**, 2682.
10 Stevens F F & Bower J D, *J Chem Soc*, **1949**, 2971.
11 Abdou O A, Cyril P, Khaledur S M & Winston O L, *J Heterocycl Chem*, 25, **1988**, 403.
12 Myung H J, Jung M P, Ihl-Young C L & Miya A, *J Heterocycl Chem*, 40, **2003**, 37.
13 Cui Y, Tang X B, Shao C X, Li J T & Sun W H, *Chi J Chem*, 23, **2005**, 589.
14 Massimo C, Francesco E, Francesca M, Ornelio R & Sara T, *Synlett*, **2004**, 1832.