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An efficient synthesis of Schiff bases containing benzimidazole moiety catalyzed by transition metal nitrates

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A simple and efficient method has been developed for the synthesis of some novel Schiff bases via the reaction of aromatic aldehydes with 2-aminobenzimidazole by using catalytic amount of $M(NO_3)_2.xH_2O$ in an organic solvent at room temperature. Some advantages of this protocol are its very good yields, use of available catalysts, simple workup procedure, and short reaction times.

Key Words: Aldehyde, 2-aminobenzimidazole, catalyst, Schiff bases.

Introduction

Compounds containing a benzimidazole moiety attached to a heterocyclic system are important chemical classes as a result of their significant biological activities against several viruses such as HIV, herpes (HSV-1), influenza, and Epstein-Barr.[1−3] Moreover, benzimidazole derivatives have been studied as anticancer and antiproliferative chemicals.[4,5]

Schiff bases derived from aromatic amines and aromatic aldehydes are also a very important class of organic compounds because of their applications in many fields including biological,[3,6−11] inorganic,[12−16] and analytical chemistry.[17−21]

The hybrid molecules composed of the combination of part of a heterocyclic ring, like benzimidazole, and part of the Schiff base may exert potential biological activities. Several synthetic methods have been reported for the synthesis of Schiff bases. However, most of them have limitations including long reaction times, need for a special catalyst, low yields, and extensive recrystallization.[22−25] Therefore, the pursuance of more convenient and practical synthetic methods for preparation of these compounds still remains an active research area. Recently, the use of several catalysts, like inorganic salts[26] and zeolites,[27,28] in organic synthesis

has attracted considerable attention. They have many advantages such as their handling, low cost, and being environmentally safe.

In view of this report and also due to our attention in the synthesis of Schiff bases[29] we studied a simple and efficient synthetic method for the preparation of Schiff bases containing benzimidazole moiety in the presence of inorganic salts as homogeneous catalysts.

Experimental

All chemicals used were purchased from Merck or Fluka. Melting points were determined using an electrothermal digital apparatus and are uncorrected. IR spectra were performed on a Galaxy series FTIR 5000 spectrometer using KBr discs. NMR spectra were recorded on a Bruker (300 MHz) spectrometer. Chemical shifts (ppm) were referenced to the internal standard tetramethylsilane (TMS). Reactions were monitored by thin layer chromatography (TLC).

General preparation of Schiff bases 3a-l

To a solution of 2-aminobenzimidazole (1 mmol) in methanol (5 mL) was added corresponding aromatic aldehyde (1 mmol). Then $Ni(NO_3)_2.6H_2O$ (5 mol%) was added and the reaction mixture stirred at room temperature for the desired time. After completion of the reaction, cold water (15-25 mL) was added to give the product. The solid product was filtered and washed with cold water and air dried.

N-benzylidene-1*H*-benzo[d]imidazol-2-amine (3a)

Green solid; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 12.72 (s, 1H, NH), 9.46 (s, 1H, CH) and 8.06-6.88 (m, 9H, $H_{Arom.}$) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 165.8, 156.1, 136.6, 135.5, 135.0, 133.2, 129.9, 129.5, 122.4, 119.2 and 111.7 ppm. FT-IR (KBr): 3375 (w), 3059 (m), 1621 (s), 1575 (s), 1450 (s), 1275 (m), 1213 (w), 740 (s) and 688 (m) cm^{-1}.

N-(2-chlorobenzylidene)-1*H*-benzo[d]imidazol-2-amine (3b)

Green solid; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 12.86 (s, 1H, NH), 9.78 (s, 1H, CH), 8.28 (d, J=7.7 Hz, 1H, $H_{Arom.}$), 7.65-7.48 (m, 5H, $H_{Arom.}$) and 7.21 (q, 2H, $H_{Arom.}$) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 161.0, 155.6, 136.6, 134.6, 132.2, 130.8, 128.8, 128.3, 122.7, 119.4 and 111.7 ppm. FT-IR (KBr): 3053 (m), 2986 (w), 1604 (s), 1520 (m), 1427 (s), 1273 (m), 1053 (m), 756 (s), 684 (w) and 451 (w) cm^{-1}.

N-(3-chlorobenzylidene)-1*H*-benzo[d]imidazol-2-amine (3c)

Green solid; ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 12.78 (s, 1H, NH), 9.46 (s, 1H, CH) and 8.10-7.20 (m, 8H, $H_{Arom.}$) ppm. ^{13}C-NMR (75 MHz, DMSO-d_6) δ: 164.3, 155.6, 137.6, 134.3, 132.7, 131.4, 129.1, 128.5, 122.6, 119.1 and 111.9 ppm. FT-IR (KBr): 3161 (w), 3067 (m), 2995 (w), 1606 (m), 1568 (m), 1423 (s), 1211 (w), 1076 (w), 840 (m), 740 (s) and 677 (m) cm^{-1}.

***N*-(4-chlorobenzylidene)-1*H*-benzo[d]imidazol-2-amine (3d)**

Green solid; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ: 12.86 (s, 1H, NH), 9.46 (s, 1H, CH) and 8.08-7.18 (m, 8H, H$_{Arom.}$) ppm. ^{13}C-NMR (75 MHz, DMSO-d$_6$) δ: 164.5, 155.8, 137.8, 134.4, 131.5, 129.7, 122.5, 118.6 and 112.5 ppm. FT-IR (KBr): 3375 (w), 3065 (m), 2993 (w), 1612 (m), 1570 (m), 1500 (m), 1429 (s), 1311 (w), 1234 (w), 1089 (m), 821 (m), 738 (s) and 505 (w) cm^{-1}.

***N*-(4-bromobenzylidene)-1*H*-benzo[d]imidazol-2-amine (3e)**

Green solid; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ: 12.75 (s, 1H, NH), 9.44 (s, 1H, CH) and 7.99-7.18 (m, 8H, H$_{Arom.}$) ppm. ^{13}C-NMR (75 MHz, DMSO-d$_6$) δ: 164.7, 155.6, 134.7, 132.6, 131.7, 126.9, 122.5, 119.3 and 111.8 ppm. FT-IR (KBr): 3422 (w), 3063 (m), 2991 (w), 1610 (m), 1489 (m), 1429 (s), 1070 (m), 819 (m) and 738 (s) cm^{-1}.

***N*-(3-nitrobenzylidene)-1*H*-benzo[d]imidazol-2-amine (3f)**

Green solid; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ: 12.86 (s, 1H, NH), 9.61 (s, 1H, CH) and 8.88-7.21 (m, 8H, H$_{Arom.}$) ppm. ^{13}C-NMR (75 MHz, DMSO-d$_6$) δ: 163.6, 155.4, 148.7, 137.1, 136.1, 131.1, 127.0, 123.4, 122.7, 119.7 and 111.4 ppm. FT-IR (KBr): 3346 (m), 3088 (m), 1608 (m), 1529 (s), 1431 (m), 1350 (s), 1278 (w), 1085 (w), 742 (s) and 665 (w) cm^{-1}.

***N*-(4-nitrobenzylidene)-1*H*-benzo[d]imidazol-2-amine (3g)**

Brown solid; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ: 12.89 (s, 1H, NH), 9.58 (s, 1H, CH), 8.37-8.16 (m, 4H, H$_{Arom}$) and 7.60-7.20 (m, 4H, H$_{Arom}$) ppm. ^{13}C-NMR (75 MHz, DMSO-d$_6$) δ: 163.6, 155.2, 149.8, 141.0, 130.8, 124.6, 122.8, 119.3 and 111.8 ppm. FT-IR (KBr): 3167(m), 3080 (m), 1614 (w), 1591 (m), 1514 (s), 1425 (m), 1342 (s), 1228 (w), 1109 (w), 833 (m) 763 (s), 680 (w) and 441 (w) cm^{-1}.

***N*-(4-methylbenzylidene)-1*H*-benzo[d]imidazol-2-amine (3h)**

Green solid; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ: 12.66 (s, 1H, NH), 9.41 (s, 1H, CH), 7.94-7.16 (m, 8H, H$_{Arom.}$) and 3.38 (s, 3H, Me) ppm. ^{13}C-NMR (75 MHz, DMSO-d$_6$) δ: 165.6, 156.3, 143.6, 133.0, 130.2, 130.0, 122.3, 119.0, 111.5 and 35 (CH$_3$) ppm. FT-IR (KBr): 3053 (m), 2862 (w), 1604 (s), 1525 (s), 1429 (s), 1280(s), 1174 (s), 1045 (m), 1001 (w), 815 (s), 742 (s), 503 (m) and 451 (w) cm^{-1}.

***N*-(4-Methoxybenzylidene)-1*H*-benzo[d]imidazol-2-amine (3i)**

Green solid; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ: 12.62 (s, 1H, NH), 9.38 (s, 1H, CH), 8.01-7.11 (m, 8H, H$_{Arom.}$) and 3.83 (s, 3H, OMe) ppm. ^{13}C-NMR (75 MHz, DMSO-d$_6$) δ: 165.0, 163.4, 156.6, 132.0, 128.4, 122.2, 118.7, 115.0, 111.4 and 55.99 (OMe) ppm. FT-IR (KBr): 3002 (w), 2931 (w), 1601 (s), 1568 (s), 1525 (s), 1425 (s), 1307 (w), 1255 (s), 1165 (s), 1022 (m), 837 (m) and 744 (m) cm^{-1}.

***N*-(2-hydroxybenzylidene)-1*H*-benzo[d]imidazol-2-amine (3j)**

Yellow solid; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ: 12.78 (s, 1H, NH), 12.11 (s, 1H, OH), 9.66 (s, 1H, CH), 7.88 (d, J=7.9 Hz, 1H, H$_{Arom.}$), 7.58-7.47 (m, 3H, H$_{Arom.}$), 7.21 (q, 2H, H$_{Arom.}$) and 7.04 (t, J=6.5 Hz, 2H, H$_{Arom.}$) ppm. ^{13}C-NMR (75 MHz, DMSO-d$_6$) δ: 165.9, 160.9, 154.3, 135.1, 132.7, 122.5, 120.1, 119.8, 119.0, 117.3 and 111.7 ppm. FT-IR (KBr): 3236 (w), 3047 (w), 1608 (s), 1570 (m), 1520 (w), 1431 (s), 1278 (s), 1192 (w), 1151 (w), 866 (w) and 746 (s) cm^{-1}.

***N,N'*-(1,3-phenylenebis(methan-1-yl-1-ylidene))bis(1*H*-benzo[d]imidazol-2-amine) (3k)**

Yellow solid; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ: 12.80 (br, 2H, NH), 9.56 (s, 2H, CH), 8.57 (s, 1H, H$_{Arom}$), 8.13-8.36 (m, 3H, H$_{Arom}$) and 6.99-7.78 (m, 8H, H$_{Arom}$) ppm. ^{13}C-NMR (75 MHz, DMSO-d$_6$) δ: 164.7, 155.8, 137.2, 136.4, 134.2, 133.5, 130.6, 122.6 and 111.7 ppm. FT-IR (KBr): 3367 (w), 3063 (w), 1616 (s), 1579 (s), 1516 (m), 1438 (s), 1275 (m), 1149 (m), 999 (w), 798 (w) 744 (s), 680 (m) and 432 (w) cm^{-1}.

***N,N'*-(1,4-phenylenebis(methan-1-yl-1-ylidene))bis(1*H*-benzo[d]imidazol-2-amine) (3l)**

Dark yellow solid; ^{1}H-NMR (300 MHz, DMSO-d$_6$) δ: 12.82 (br, 2H, NH), 9.55 (s, 2H, CH), 8.25 (s, 4H, H-phenylene), 7.54 (m, 4H, H$_{Arom}$) and 7.20 (m, 4H, H$_{Arom}$) ppm. ^{13}C-NMR (75 MHz, DMSO-d$_6$) δ: 164.7, 155.6, 140.4, 138.9, 130.4, 122.7 and 112.8 ppm. FT-IR (KBr): 3337 (m), 3051 (w), 1612 (s), 1568 (m), 1437 (s), 1309 (w), 1205 (s), 812 (m) and 746 (m) and 505 (m) cm^{-1}.

Results and discussion

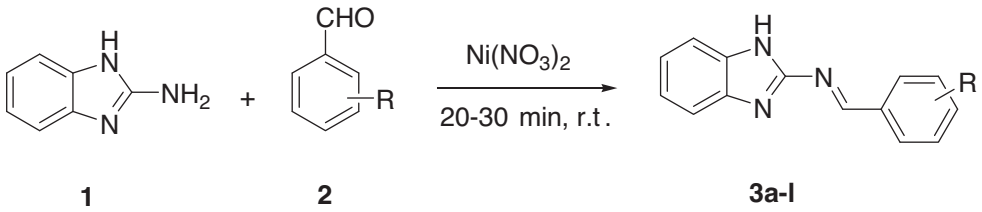
Initially we sought a mild and convenient method for the synthesis of benzimidazole Schiff bases at room temperature. For optimization of the amount of catalyst, the reaction of 2-aminobenzimidazole with 4-nitrobenzaldehyde at ambient temperature was carried out as a model reaction and different amounts of catalyst were tested under the same conditions. The use of 5 mol% of $Cu(NO_3)_2.6H_2O$ in ethanol for 20 min afforded the corresponding Schiff base in 77% yield (Table 1, entry 1). The optimization of the other reaction conditions was undertaken to increase the yield employing different catalyst loadings in several solvents. The results are summarized in Table 1. The yield of reaction in the presence of 5 mol% of $Ni(NO_3)_2.6H_2O$ and using methanol as a solvent was increased up to 89%.

To study the development of this method, the optimized procedure was extended for preparation of other Schiff bases. The reaction was carried out at room temperature by taking a 1:1 mol ratio mixture of 2-aminobenzimidazole **1** and the corresponding aromatic aldehyde **2** in the presence of 5 mol% of $Ni(NO_3)_2.6H_2O$ in methanol to give Schiff bases **3a-l** (Scheme). The results are summarized in Table 2.

Table 1. Schiff bases derived from the reaction of 2-aminobenzimidazole and 4-nitrobenzaldehyde using different catalysts and solvents for 20 min at room temperature.

Entry	Catalyst	Catalyst loading (mol%)	Solvent	Yield (%) [a]
1	$Cu(NO_3)_2.6H_2O$	5	EtOH	77
2	$Cu(NO_3)_2.6H_2O$	5	MeOH	83
3	$Ni(NO_3)_2.6H_2O$	5	MeOH	89
4	$Ni(NO_3)_2.6H_2O$	10	MeOH	77
5	$Ni(NO_3)_2.6H_2O$	15	MeOH	73
6	$Ni(NO_3)_2.6H_2O$	20	MeOH	67
7	$Mn(NO_3)_2.4H_2O$	5	MeOH	52
8	$Fe(No_3)_2.6H_2O$	5	MeOH	25
9	$Co(NO_3)_2.6H_2O$	5	MeOH	77
10	$Ni(NO_3)_2.6H_2O$	5	EtOH	80
11	$Ni(NO_3)_2.6H_2O$	5	DMF	60
12	$Ni(NO_3)_2.6H_2O$	5	CH_3CN	73

a) Isolated yields



1 **2** **3a-l**

Scheme. Preparation of Schiff bases **3a-l**.

The yields of reactions using this practical procedure for the preparation of various Schiff bases in comparison with the previously reported methods[30−34] are quite fair and the reaction times are very short.

Aliphatic aldehydes or ketones such as formaldehyde, acetaldehyde, and acetophenone were also examined under the same conditions, but the corresponding products were isolated in trace amounts.

The structure of products was characterized by the spectroscopic data. The ^{1}H- and ^{13}C-NMR spectra of all synthesized Schiff bases are consistent with their structures. The ^{1}H-NMR spectra of these compounds are simple and consist of the aromatic protons signals and 2 singlet signals related to the resonance of the C-H and N-H proton, which appeared at 9.38-9.78 and 12.62-12.89 ppm, respectively. The aromatic protons resonate as a multiple signal at 6.88-8.88 ppm depending on the Ar group.

Table 2. Schiff bases derived from reaction of 2-aminobenzimidazole with aromatic aldehydes in the presence of 5 mol% of $Ni(NO_3)_2.6H_2O$ in methanol.

Compound	R	Time (min)	Mp (°C)	Yield (%)[b]
3a	H	25	149-152 (152-154)[a]	81
3b	2-Cl	20	205-207 (212-217)	60
3c	3-Cl	22	212 (200-202)	78
3d	4-Cl	25	230-231 (179-181)	75
3e	4-Br	25	245-246 (256-257)	77
3f	3-NO_2	25	191-193	70
3g	4-NO_2	20	264 (266-268)	89
3h	4-Me	27	212-213 (226-228)	78
3i	4-OMe	30	222-223 (220-222)	79
3j	2-OH	20	225-227 (217-218)	84
3k	3-CHO	35	257-261	63
3l	4-CHO	22	> 300	88

a) Melting points of the **3a-j** reported in the literature[30−34]

b) Isolated yields

Conclusion

$Ni(NO_3)_2.6H_2O$ was employed as an efficient catalyst for the preparation of Schiff bases containing benzimidazole moiety by reaction of 2-aminobenzimidazole and aromatic aldehydes.

The attractive features of this procedure are its good conversions, easy workup, and short reaction times, making it a useful practical method for the synthesis of Schiff bases.

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