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Antimony chloride immobilized on neutral alumina: an efficient catalyst for the solvent-free selective synthesis of 1,2-disubstituted benzimidazoles

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ABSTRACT

$SbCl_3$–Al_2O_3 is proposed as a highly efficient, cost effective and reusable Lewis acid catalyst for the selective synthesis of 1,2-disubstituted benzimidazoles from o-phenylenediamine and aromatic aldehydes in an excellent yield (86-95%) using microwave (MW) irradiation under solvent-free conditions. The present methodology shows some specific advantages such as mildness, short reaction times and enhanced selectivity under solvent-free conditions.

Keywords microwave assisted synthesis, Lewis acid, catalyst, selectivity, benzimidazoles, reusability.

INTRODUCTION

The benzimidazole and their derivatives exhibit wide range of biological activities such as antiprotozoal [1], antihistaminic [2], antiallergic [3] and anti-diabetic [4], making them attractive compounds for organic chemists. Several compounds from this class have been used as inhibitors of hepatitis C virus NS5B polymerase [5], thrombopoietin receptor agonists [6], selective inhibitors of 1KK-ε kinase [7] and non steroidal antiandrogen [8], currently predominantly used for the treatment of androgen dependent prostate cancer in mature rats.

A simple synthesis of this biologically important pharmacophore was first reported by Ladenberg in 1877 by the reaction of aldehydes and o-phenylenediamine. The major drawbacks of this protocol were low yields and formation of inseparable mixture of mono and disubstituted benzimidazoles. Therefore, this reaction continues to be the focus of the researchers striving to

find milder and more efficient procedures for the synthesis substituted benzimidazoles. This has led to the development of several synthetic methodologies synthesis of benzimidazole. These involves the condensation of *o*-phenylenediamine (OPDA) and aryl carboxylic acid or their derivatives such as amidates, orthoesters, nitriles in presence of strong acid such as polyphosphoric acid or mineral acid [8-112] and the thermal or acid promoted cyclization of N-(N-arylbenzimidoyl))-1,4-benzoquinone-imines [13]. Another protocol for the synthesis of these compounds involves the reaction of o-phenylenediamine and aldehyde in presence of acid catalysts under various reaction conditions [14-17]. However, despite their potential utility, there are still some limitations with the existing protocols such as drastic reaction conditions, tedious work-up procedures, poor selectivity, low yields and non recyclability of the catalyst. Recently, several reports [18-19] that have applied MW technology in solid-phase synthesis are now widely reported because of its faster chemistry and formation of cleaner products compared with conventional heating. In continuation of our recent efforts [20-23] into the applications of $SbCl_3$ adsorbed on inorganic support as a post transitional Lewis acid in organic synthesis, we wished to explore the usage of $SbCl_3/Al_2O_3$ for the selective synthesis of 1,2-disubstitued benzimidazoles by the application of MW technology. To the best of our knowledge, the $SbCl_3/Al_2O_3$ catalyst-system has not been used earlier for the synthesis of benzimidazoles.

EXPERIMENTAL SECTION

Melting points were measured by using the capillary tube method with an electrothermal method 9200 apparatus. The IR spectra were recorded on KBr pellets on a Shimadzu IR-470. ^{1}H NMR and ^{13}C spectra were recorded on a Brucker 300 DRX Avance instrument at 300 MHz spectrometer. The catalyst was prepared by the same procedure as described in the literature [21]. All products were known and characterized by comparison of their physical and spectroscopic data with those already reported [14-17].

General procedure for the synthesis of benzimidazoles **(2a-m)**

Freshly distilled aromatic aldehyde **1a** (20 mmol), *o*-phenylenediamine (10 mmol) and 3.1 g of catalyst (5 mol% with respect to $SbCl_3$) were mixed thoroughly in a 100 cm^3 beaker with glass rod and then irradiated in the MW oven for about 10 min at power level 800 W with 30 sec pause after every one min. Upon completion of the reaction (TLC), the reaction mixture was cooled at rt, ethyl acetate (100 cm^3) was added, and stirred well followed by filtration through celite under suction. The organic layer was washed with water (2 × 30 cm^3) and brine (30 cm^3). After drying over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure and the residue upon column chromatography affords the pure product. Under thermal condition the reaction mixture of same composition as mentioned above was heated in an oil bath at 100 ºC in solvent-free condition, till the completion of reaction. Work-up was done as mentioned above to yield desired product.

1-Benzyl-2-phenyl-1H-1,3-benzimidazole (2a)

Melting point 133 ºC. IR ν_{max}/cm^{-1} (KBr): 3056, 2960, 1597, 1493, 1469, 1400, 1391, 1361, 1331, 776, 696. ^{1}H NMR: (200 MHz, $CDCl_3$) δ: 7.80 (d, *J* = 8 Hz, 1H); 7.61 (dd, *J* = 8 and 2 Hz, 2H); 7.39-7.32 (m, 3H); 7.25-7.10 (m, 6H); 7.10 (dd, *J* = 8 and 2 Hz, 2H); 5.32 (s, 2H); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 153.5, 142.4, 136.2, 135.5, 129.5(3), 129.6(0), 128.8, 128.6, 128.4, 127.2, 125.5, 122.8, 122.3, 119.4, 110.4, 47.8. MS m/z: 286.26 (M^+ + 1).

RESULTS AND DISCUSSION

In our preliminary experimentation, OPDA and benzaldehyde in 1:2 molar ratio in presence of $SbCl_3/Al_2O_3$ (5 mol%) was irradiated under MW for 10 minutes afforded the selective formation of desired 2-phenyl-1-benzyl-1*H*-1,3-benzimidazole, **2a** in 92% yield which was confirmed by comparison of its spectral data with that of reported earlier [16].

Scheme 1 Selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles

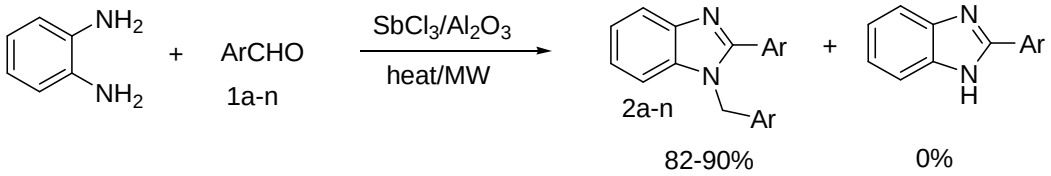


Table 1. $SbCl_3$-Al_2O_3 catalysed synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles

Entry	Ar	Products 2	Time MWI/min,	Thermal/h	Yield/%[a] MWI	Thermal
1	C_6H_5	a	10	4	92	90
2	*p*-MeC_6H_4	b	6	4	94	93
3	*p*-ClC_6H_4	c	7	5	95	95
4	*o*-ClC_6H_4	d	8	4	95	80
5	*p*-$MeOC_6H_4$	e	8	5	90	89
6	*o*-$MeOC_6H_4$	f	10	5	92	82
7	*p*-$NO_2C_6H_4$	g	10	4	89	90
8	*o*-$NO_2C_6H_4$	h	10	4	86	76
9	*p*-OHC_6H_4	i	10	4.5	87	86
10	2-Furyl	j	10	4	94	93
11	2-pyridyl	k	10	5	88	86
12	*p*-$N(Me)_2C_6H_4$	l	10	4.5	89	87
13	$(MeO)_3C_6H_2$	m	10	5	89	84
14	*p*-CNC_6H_4	n	10	5	87	84

[c]*Yield refer to pure and isolated products.*

In another set of experiments, 1:2 mixture of OPDA and benzaldehyde was irradiated in MW in the presence of (i) neat 5 mol% of $SbCl_3$ and (ii) neat Al_2O_3 (3g with respect to 10 mmol of reactants) respectively for 10 minutes. In the case of neat $SbCl_3$ only 40% of desired product along with bis anil was obtained while with neat Al_2O_3, less than 10% of desired product formation was noticed as against the 92% yield with $SbCl_3/Al_2O_3$ (entry 1). This reveals that $SbCl_3/Al_2O_3$ is presumably acting in a synergistic fashion to catalyze the reaction. Encouraged by these results and to establish the versatility of antimony (III) chloride impregnated on alumina, various substrate were subjected to the optimized reaction conditions and the results are depicted in the (Table I). The heterocyclization reaction worked well in the presence of electron donating as well as electron withdrawing substitution in *ortho*-, *meta*-, or *para*- position of the phenyl ring. Furthermore, the protocol is equally effective with heterocyclic aldehydes (entries

10-11). All the products **2a-2n** gave satisfactorily spectral data and in agreement with reported values [14-17].

In order to obtain the optimum concentration of catalyst, a set of experiments was performed employing different concentrations of $SbCl_3$ for a reaction between 20 mmol of benzaldehyde and 10 mmol of OPDA and it was observed as shown in the Table II that 5 mol% of catalyst was required to obtain the optimum yield of the product. In absence of the catalyst, reaction yields mixture of products such as bis anil, dihydrobenzimidazole, 2-arylbenzimidazole along with 1,2-disubstituted benzimidazole in agreement with as earlier reported in the literature [24].

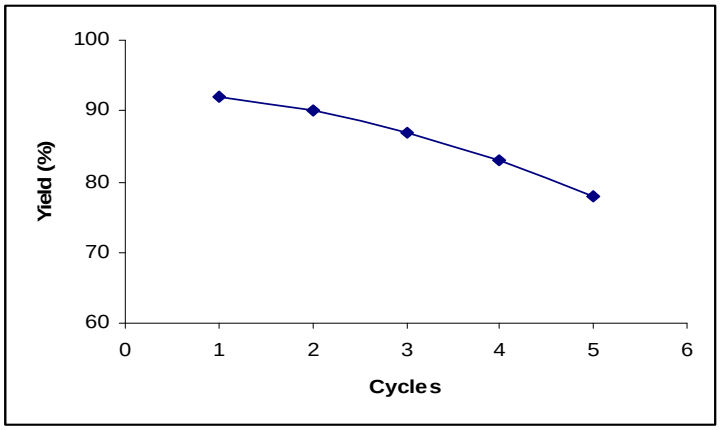
Table 2 Optimization of amount of $SbCl_3$ for synthesis of benzimidazole, 2a

Entry	mol%	Amount of Al_2O_3 (g)	Yield (%]
1	0	0	^
2	2	3	55
3	3	3	60
4	5	3	92
5	7	3	93
6	10	3	92

^ *mixture of product is obtained*

In order to investigate the recyclability, $SbCl_3/Al_2O_3$ was recovered, activated at 110 ºC in an oven and reused five times, successively, for the reaction of benzaldehyde and OPDA; no significant decrease in its activity was noticed (Fig. 1).

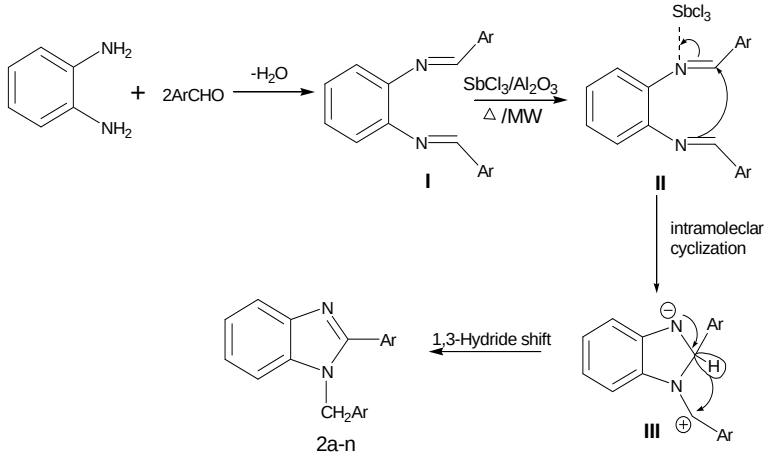
Figure 1 Catalyst reusability



Furthermore, in order to probe into the effect of conventional heating, 1:2 mixture of OPDA and benzaldehyde was heated in an oil bath at 100 ºC in presence of 5 mol% of $SbCl_3/Al_2O_3$ under solvent-free conditions, formation of products, akin to that of MW irradiation, was observed in 4-5 h, in comparison to MW heating which required 10 min for this transformation to go to completion.

The proposed mechanism is shown in scheme II, Antimony(III) chloride is believed to chelate with the imino-N and thereby facilitating the intramolecular cyclisation of II to III followed by 1,3-hydride shift to give 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles.

Scheme 2 A plausible mechanism of the reaction



CONCLUSION

In conclusion, $SbCl_3/Al_2O_3$ is highly efficient and reusable catalyst for the selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles. The present methodology is very simple, cheap and shows some specific advantages such as mildness, short reaction times and enhanced selectivity under solvent-free conditions. This reaction worked smoothly for wide range of aldehydes.

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