Journal of the Korean Chemical Society
2011, *Vol. 55, No. 2*
Printed in the Republic of Korea
DOI 10.5012/jkcs.2011.55.2.304

단 신

회수 가능한 indion 190 resin 촉매를 이용한 2-aryl-1-arylmethyl-1*H*-benzo[*d*]imidazoles계 화합물의 선택적인 합성

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(접수 2010. 7. 19; 수정 2010. 9. 1; 게재확정 2010. 9. 7)

Chemoselective Synthesis of 2-Aryl-1-arylmethyl-1*H*-benzo[*d*]imidazoles Using Indion 190 Resin as a Heterogeneous Recyclable Catalyst

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(Received July 19, 2010; Revised September 1, 2010; Accepted September 7, 2010)

주제어: o-페닐렌디아민, 방향족 알데히드, Indion 190 레진, Heterogeneous회수 가능 촉매

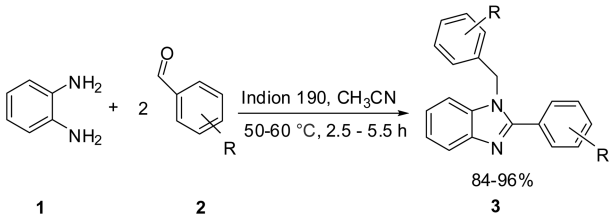
Keywords: o-Phenylenediamine, Aromatic aldehydes, Indion 190 resin, Heterogeneous Recyclable Catalyst

INTRODUCTION

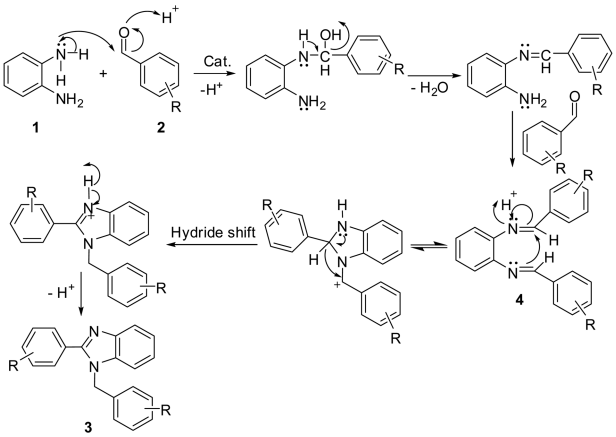
1,2-Disubstituted benzimidazoles show significant activity against several viruses such as HIV, herpes (HSV-1), RNA, influenza, and human cytomegalovirus (HCMV).[1-5] In addition, benzimidazoles are also used in various fields of chemistry as topoisomerase inhibitors, selective neuropeptide YY1 receptor antagonists, angiotensin II inhibitors, 5-HT_3 antagonists in isolated guinea pig ileum, potential antitumor agents, antimicrobial agents, smooth muscle cell proliferation inhibitors, factor Xa inhibitors and in the treatment of interstitial cystitis.[6-11] In light of the affinity, they display towards a variety of enzymes and protein receptors, medicinal chemists would certainly classify them as 'privileged sub-structures' for drug design.[12,13] In view of remarkable biological activities of the substituted benzimidazoles, their preparation has gained significant interest in recent years. A number of improved methods have been developed for the synthesis of benzimidazoles involves a reaction between an *o*-phenylendiamine and a carboxylic acid or its derivative (nitrile, amidate and orthoester) under harsh dehydrating condition.[14-17] The most popular strategies for the synthesis of 1,2-disubstitted benimidazoles include *N*-alkylation of 2-substituted benimidazole in the presence of strong base,[18,19] *N*-alkylation of *o*-nitroanilides followed by a reductive cyclization,[20,21] cyclocondensation of *N*-substituted *o*-aminoanilides,[22] and the condensation of *N*-substituted phenylenediamine with sodium salt of α-hydroxy benzylsulphonic acid.[23] In addtion, 1,2-disbstituted benzimidazoles are also be accessed by direct one-step condensation of *o*-phenylenediamines with aldehydes by involving the influence of different acid catalysts under various reaction conditions[24-33] or by using polymer-supported hypervalent iodine (PDIAS) as a reagent.[34] But one of the major margins of these methodologies is that they show poor selectivity in terms of *N*-substitution, which results in the formation of two compounds i.e, the formation of a 2-substituted benzimidazole along with 1,2-disubstituted benzimidazole as a mixture.[24-26,28,33-40]

Herein, we report the synthesis of 1,2-disubtituted benzimidazoles (**3**) by the reaction of an o-phenylenediamine (**1**) and various aromatic aldehydes (**2**) in the presence of Indion 190 resin (*Scheme* 1).

The plausible mechanism of conversion is shown in *Scheme* 2. The activation of the aldehydic carbonyl oxy-



***Scheme* 1.** Preparation of 2-aryl-1-arylmethyl-1*H*-benzo[*d*]imidazoles (**3**).



***Scheme* 2.** The formation of 2-aryl-1-arylmethyl-1*H*-benzo[*d*] imidazoles (**3**) from *o*-phenylenediamine (**1**) and aromatic aldehyde (**2**) through dibenzylidene-*o*-phenylenediamine (**4**).

gen by the acidic proton of Indion 190 resin and followed by condensation with o-phenylenediamine gives dibenzylidene-*o*-phenylenediamine (**4**), which is on further cyclization followed by hydride shift provides 1,2-disubtituted benzimidazoles.

RESULTS AND DISCUSSIONS

At the beginning, to evaluate the catalytic efficiency of Indion 190, the reaction of *o*-phenelenediamine (**1**) and benzaldehyde (**2a**) was carried out by employing 0.100 g of the catalyst in methanol at room tempetarure for 24 h. However, the resulting yield was not good (entry a, *Table* 1). Later optimization of the reaction conditions was studied next to increase the yield of the product. Towards this direction, reactions were performed in various solvents by loading different amounts of catalyst. The results were listed in *Table* 1. The conversion was significantly increased to 96% within shoter time by adding 0.100 g of the catalyst in acetonitrile (entry f, *Table* 1). Other solvents such as DMF, acetone, DCM, ethanol and methanol are provided unfavorable results for this reaction.

The efficiency of this method was proved by reacting

***Table* 1.** Effect of the solvent on time and isolated yield of the reaction of o-phenylenediamine (**1**) and benzaldehyde (**2a**) in presence of a catalytic amounts of Indion 190.

Entry	Solvent	Time (h)	Loading of resin Indion 190 (g)	Isolated yield (%)
a	Methanol	24	0.1	69
b	DMF	16	0.1	65
c	Acetone	12	0.1	72
d	Ethanol	20	0.1	73
e	DCM	13	0.1	81
f	Acetonitrile	04	0.1	96
g	Acetonitrile	04	0.2	96

various aromatic aldehydes (**2**) with *o*-phenylenediamine (**1**) using 0.100 g of Indion 190 resin in acetonitrile (*Scheme* 1, *Table* 2). However, an aldehyde with a strong electron withdrawing group afforded the product with high yield in less time compared to an aldehyde with a strong electron releasing group. As for an example the reaction of *p*-nitrobenzaldehyde (**2e**) reacted with o-phenylenediamine (**1**) takes 3.5 h to form its corresponding product (**3e**) with an yield of 93% (entry e, *Table* 2), while, p-methoxybenzaldehyde (**2c**) has taken 5.0 h to provide its corresponding product (**3c**) with an yield of 82% (entry c, *Table* 2).

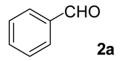
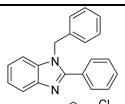
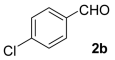
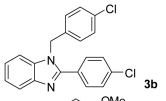
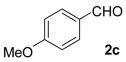
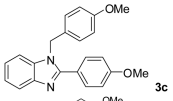
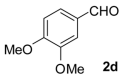
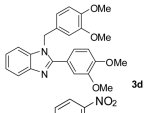
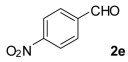
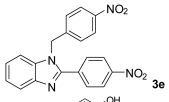
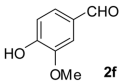
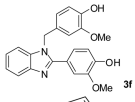
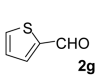
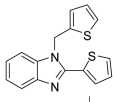
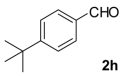
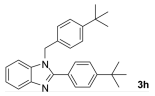
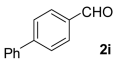
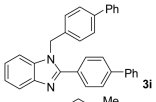
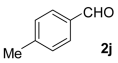
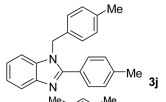
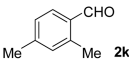
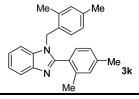
The catalyst, Indion 190 resin is a commercially available acidic reagent. It can be easily handled and removed by filtration from the reaction mixture. Thus the process is environmentally benign. The catalyst was recovered, activated and reused for consecutive times without loss of selectivity.

In conclusion, we have developed a novel and highly efficient method for the synthesis of 2-aryl-1-arylmethyl-1*H*-benzo[*d*]imidazoles (**3**) in high yields from an *o*-phenylenediamine (**1**) and a wide variety of aromatic aldehydes (**2**) in the presence of Indion 190 resin as a heterogeneous catalyst. The mildness of the conversion, simple experimental procedure, clear reaction profiles, high yields and chemoselectivity, short reaction times and reusability of the catalyst are the noteworthy advantages of the protocol. We feel the procedure can be utilized for large-scale eco-friendly preparation of 2-aryl-1-arylmethyl-1*H*-benzo [*d*]imidazoles (**3**).

General Experimental Procedure

In a 50 mL, round-bottom flask, *o*-phenylenediamine (**1**) (1 mmol) and an aromatic aldehyde (**2a**) (2 mmol) were stirred in the presence of Indion 190 in an acetonitrile (10 ml) at 50-60 °C temperature. The reaction progress was

***Table* 2.** Synthesis of 2-aryl-1-arylmethyl-1H-benzo[d]imidazoles (**3**) from diamine (**1**) and aldehyde (**2**) using Indion 190 resin.[a]

Entry	Aldehyde	Time (h)	Product	Isolated yield (%)
a	 **2a**	4.0	 **3a**	96
b	 **2b**	4.5	 **3b**	89
c	 **2c**	5.0	 **3c**	82
d	 **2d**	5.5	 **3d**	80
e	 **2e**	3.5	 **3e**	93
f	 **2f**	5.5	 **3f**	85
g	 **2g**	2.5	 **3g**	92
h	 **2h**	4.5	 **3h**	89
i	 **2i**	5.5	 **3i**	88
j	 **2j**	5.0	 **3j**	86
k	 **2k**	5.5	 **3k**	84

[a]Physical Properties of Indion 190 resin: Macroporous Strong Acidic Cationic resin, styrene DVB matrix, SO_3^- functional group, particle size range 0.42-1.2, Max. Operating temp. 150 °C, total exchange capacity 4.7 meq/g. and the structures of the products were determined from their spectroscopic (^{1}H NMR and MS) and elemental analysis data.

monitored by TLC. After completion of the reaction (as shown in *Table* 2), the reaction mixture and catalyst were separated by filtration. The filtrate was concentrated under reduced pressure to furnish the crude product, which was further purified by column chromatography [Silica gel, EtOAc/hexane (1:6)] to obtain the pure 2-aryl-1-arylmethyl-1*H*-benzo[*d*]imidazoles. The catalyst was washed with water, activated and reused for fresh reactions. All the compounds gave satisfactory spectroscopic data in accordance with their proposed structures. Compounds **3a-d, 3f** and **3j** are synthesized and reported in literature.[32] The spectral data of unknown compounds **3e, 3g-i** and **3k** were given below.

Compound 3e

mp: 131-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.58 (s, 2H), 7.52-7.20 (m, 4H), 7.78 (dd, J = 8.0 and 2.0 Hz, 1H), 7.83 (d, J = 9.2 Hz, 1H), 7.93 (d, J = 8.4 Hz, 2H), 8.24 (d, J = 8.8 Hz, 2H), 8.38-8.31 (m, 2H); ESI-MS (m/z): 375 (M^++1); Anal. Calcd for $C_{20}H_{14}N_4O_4$: C, 64.17; H, 3.77; N, 14.97. Found: C, 64.12; H, 3.74; N, 14.93.

Compound 3g

mp: 93-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72 (s, 2H), 6.87 (d, J = 6.2 Hz, 1H), 6.90 (dd, J = 8.0 and 2.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.31-7.24 (m, 3H), 7.39 (d, J = 8.8 Hz, 1H), 7.48 (dd, J = 8.0 and 2 Hz, 1H), 7.53 (dd, J = 8.0 and 2.0 Hz, 1H), 7.84 (d, J = 9.2 Hz, 1H); ESI-MS (m/z): 297 (M^++1); Anal. Calcd for $C_{16}H_{12}N_2S_2$: C, 64.83; H, 4.08; N, 9.45. Found: C, 64.75; H, 4.04; N, 9.42.

Compound 3h

mp: 122-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 18H), 5.45 (s, 2H), 7.06 (d, J = 8.0 Hz, 2H), 7.22 (dd, J = 8.2 and 2.8 Hz, 2H), 7.35-7.29 (m, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H); ESI-MS (m/z): 397 (M^++1); Anal. Calcd for $C_{28}H_{32}N_2$: C, 84.80; H, 8.13; N, 7.06. Found: C, 84.76; H, 8.10; N, 7.04.

Compound 3i

mp: 230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.56 (s, 2H), 6.91 (dd, J = 7.8 and 2.1 Hz, 1H), 6.99 (dd, J = 7.6 and 2.3 Hz, 1H), 7.64-7.35 (m, 15H), 7.7 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H); ESI-MS (m/z): 437 (M^++1); Anal. Calcd for: $C_{32}H_{24}N_2$: C, 88.04; H, 5.54; N, 6.42. Found: C, 88.00; H, 5.50; N, 6.38.

Compound 3k

mp: 119-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (s, 6H), 2.38 (s, 3H), 2.58 (s, 3H), 5.17 (s, 2H), 6.53 (d, J = 8.2 Hz, 1H), 6.83 (dd, J = 8.0 and 2.6 Hz, 1H), 7.00-6.95 (m, 2H), 7.31-7.15 (m, 4H), 7.86 (d, J = 8.0 Hz, 2H); ESI-MS (m/z): 341 (M^++1); Anal. Calcd for $C_{24}H_{24}N_2$: C, 84.67; H, 7.11; N, 8.23; Found: C, 84.65; H, 7.07; N, 8.21.

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