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HETEROCYCLIZATIONS TOWARDS 2-ARYLBENZ-IMIDAZOLES *VIA* INTERMOLECULAR COUPLING OF 2-NITROANILINES AND ARYL ALDEHYDES

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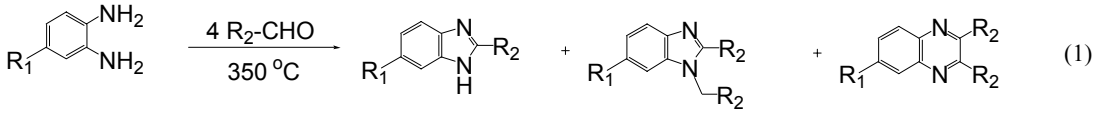
Abstract - The reductive intermolecular coupling/heterocyclization reaction between 2-nitroaniline and aromatic aldehydes towards 2-substituted and 1,2-disubstituted benzimidazoles was accomplished in the presence of 2-bromo-2-nitropropane/Zn in a MeOH/CH_2Cl_2 solution at room temperature.

Benzimidazole and its derivatives present interesting biological activities such as bacteriostats, bactericides, insecticides, fungicides, sedatives, anticarcinogens, and phycopharmacological agents.[1] Although there are several ways leading to benzimidazoles, traditional methods of 2-arylbenzimidazole preparation involve the condensation and cyclization of benzoic acid derivatives with *o*-diamino aromatic compounds in the presence of a mineral acid with high temperature.[2] Metal catalyzed reaction of *o*-phenylenediamines with haloaromatics or aromatic aldehydes is another candidate for 2-arylbenzimidazole preparation.[3]

During the course of our investigation of heterocyclic compound formation *via* reductive cyclization reaction of nitroarenes, [4, 5] we have found that the nitro group can be reduced by 2-bromo-2-nitropropane (BNP)/Zn and it can initiate the heterocyclization when it has a proper functional group at the *ortho* position. Thus *o*-nitro substituted aromatic carbonyl, imino, or azo compounds are successfully transformed into heterocyclic compounds such as 2,1-benzisoxazoles, benzotriazoles, and quinolines. All of those reactions are accomplished from a reductive reaction of the *ortho* nitro functional group and the following cyclization. Since 2-nitroaniline and aromatic aldehydes can couple with each other to

form 2-NO_2-Ph-N=CH-Ar *in situ*, the imine intermediate should undergo a cyclization to form benzimidazoles in the presence of BNP/Zn similar to our previous heterocyclization reactions. This realization prompted us to attempt the reductive intermolecular hetero ring formation reaction. Herein we wish to report the reductive intermolecular coupling/cyclization reaction of 2-nitroaniline and aromatic aldehydes toward benzimidazoles in presence of BNP/Zn dust in MeOH/CH_2Cl_2 solution at room temperature.

Ochoa *et al*. reported high temperature thermal cyclocondensation of *o*-phenylenediamines with aromatic aldehydes primarily producing three cyclized products (benzimidazoles and quinoxaline) with a variable product ratio depending on the substrate and a combined yield of less than 60% (eq. 1).[2d] It is well known that aryl aldehydes couple with anilines easily to form Ph-N=CH-Ar. If we use 2-nitroaniline in place of *o*-phenylenediamines and use a proper reducing system, we may have more chance to improve the cyclocondensation reaction.

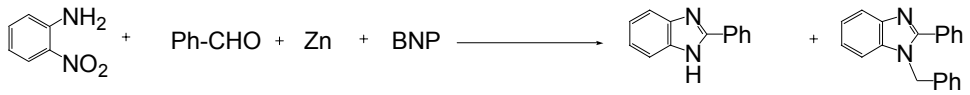


(1)

As control experiments, various reaction conditions were attempted to facilitate the reductive intermolecular coupling reaction of 2-nitroaniline with benzaldehyde and the results are summarized in Table 1. Reactions of 2-nitroaniline (**1**) with benzaldehyde (**2a**) in the presence of Zn produced a low yield of the desired 2-arylbenzimidazole (**3a**) (Table 1, entry 1). However, addition of BNP to the reaction mixture led to a more efficient reductive intermolecular coupling reaction. The overall yield toward 2-substituted and 1,2-disubstituted benzimidazoles was improved considerably accompanied by only a trace amount of quinoxaline. Furthermore, while the reactions in methanol produced relatively low yields of **3a** and **4b** (Table 1, entries 3, 4), the reactions using co-solvent MeOH/CH_2Cl_2 dramatically increased the overall yield of cyclized products at room temperature. In addition, as shown in Table 1, the reaction carried out in a 1 : 1 mixture (v/v) of MeOH/CH_2Cl_2 completed most successfully compared to other mixtures. The optimum conditions were obtained with 2-nitroaniline/aldehyde (2 equiv.)/BNP (2 equiv.)/Zn (2 equiv.) in MeOH/CH_2Cl_2 (v/v = 1 : 1) at room temperature (Table 1, entry 8, 90% of combined yield).

When we applied the acidic Zn reduction conditions [**1** (1 equiv.)/**2a** (2 equiv.)/Zn (5 equiv.)/ aq. HCl (5 equiv.) in MeOH at room temperature], the reaction was completed within an hour, however, overall yield was decreased to 51% [**3a** (22%) and **4b** (29%)] without any starting materials left. It reveals that reduction by BNP/Zn is more efficient than the traditional acidic Zn condition for the reductive

Table 1. Selected control experiments for reductive intermolecular coupling/heterocyclization reaction



1 **2a** **3a** **4a**

entry	**1** (mmol)	**2a** (mmol)	Zn (mmol)	BNP (mmol)	solvent MeOH (mL) : CH_2Cl_2 (mL)		temp. (¡É)	time (h)	isolated yield (%) **3a**	**4a**
1[a]	0.3	0.6	3.0	-	0.5	0.5	rt	24	19	trace
2	0.3	0.3	3.6	0.36	4.0	2.0	rt	9	41	36
3[b]	0.3	0.3	3.6	0.36	3.0	-	rt	30	19	16
4	0.3	0.3	3.6	0.36	3.0	-	50	44	26	28
5	0.3	0.3	3.6	0.36	1.0	5.0	rt	25	38	33
6	0.3	0.3	3.6	0.36	1.5	1.5	rt	4	42	19
7	0.3	0.6	3.6	0.36	0.5	0.5	rt	24	24	39
8	0.3	0.6	3.0	0.6	0.5	0.5	rt	12	57	33
9	0.3	0.3	1.5	0.6	0.5	0.5	rt	30	52	13

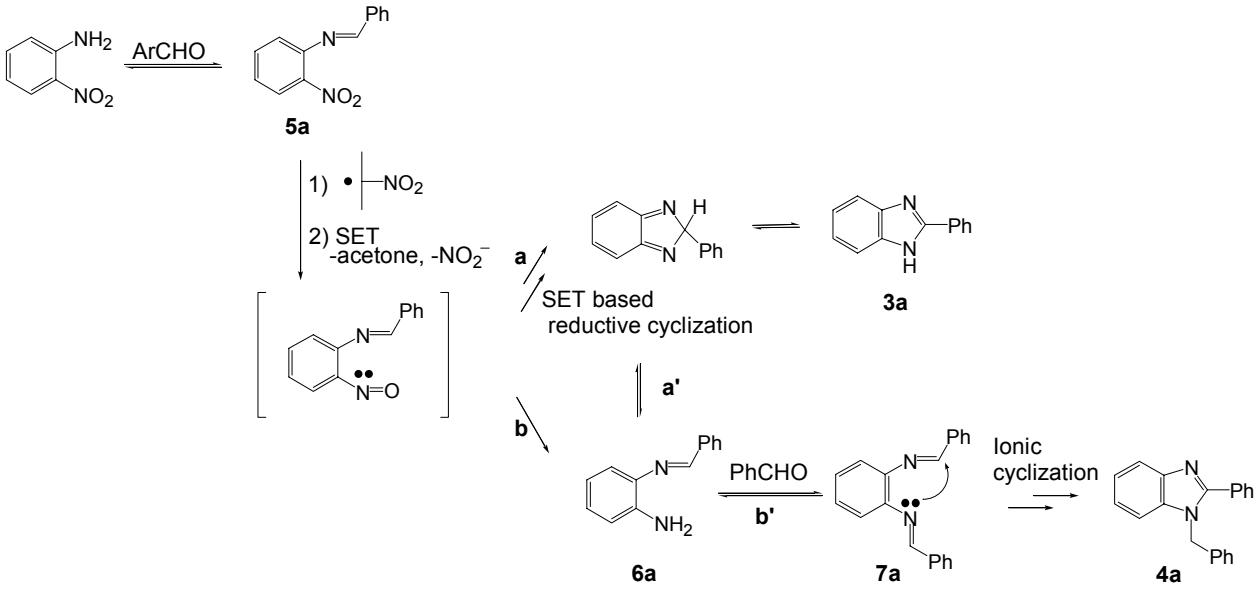
[a]80% of **1** was recovered. [b]**1** (49%) and **2** (5%) were recovered.

heterocyclization. The role of BNP is believed to be an electron acceptor due to its low-lying antibonding π-orbital and the utility of BNP has been described by Russell *et al*.[6] and by us.[5]

To disclose the reaction path and/or the intermediates of the reaction, various control experiments were examined. Our diverse efforts to detect the probable 2-NO_2-Ph-N=CH-Ph intermediate (**5a**) failed probably because of fast reduction by BNP/Zn as well as fast follow-up cyclization toward 2-arylbenzimidazoles. On the other hand, for the reaction in the absence of BNP (Table 1, entry 1), *i.e.* the nitro reduction is slowed down, **5a** (~1%) was detected on GCMS as a possible intermediate. To elucidate amino intermediacy of the reaction, the reaction of 4-NO_2-Ph-CH=N-Ph (1 equiv.) in the presence of BNP (2 equiv.)/Zn (10 equiv.) in MeOH/CH_2Cl_2 (v/v = 1 : 1) at room temperature was tried. After 30 min, the formation of 4-NH_2-Ph-N=CH-Ph (~6%) was observed on GCMS analysis and most of organic materials were consumed within 3 h possibly polymerizing by coupling reaction between amino and imino groups. Smith *et al*. reported coupling reaction of **1** with **2a** in refluxing toluene to afford **5a**.[7] In addition, the reduction potential of Ph-CH=N-Ph was -1.60 V, while that of nitrobenzene was -1.13 V (0.1 M TBAP/MeOH, working electrode; glassy carbon, scan rate; 60 mV/sec) which strongly supported our observation, *i.e.* nitro group is reduced selectively over the imino group. We also tried to analyze the reaction mixture prior to the reaction [**1** (1 equiv.)/**2a** (2 equiv.)/ BNP (2 equiv.)/Zn (10 equiv.) in MeOH/CH_2Cl_2 (v/v = 1/1) at room temperature for 2 h] was completed. In addition to the products **3a** and **4a**, 2-(Ph-CH=N)-Ph-N=CH-Ph (**7a**, ~6%) were detected on GCMS analysis which is another possible

intermediate for the cyclization reaction. Thus, the pathway 1) coupling of **1** with **2a** to form **5a**, 2) nitro group reduction, 3) reductive cyclization seems quite convincing. It seems intramolecular path **a** (or **a**') and intermolecular path **b** (or **b**') are competing with each other. When 1,2-diaminobenzene and benzaldehyde (2 equiv.) were reacted in MeOH/CH_2Cl_2 (v/v = 1/1), **3a** and **4a** were obtained in 41 and 47% yields respectively within an hour *via* the competition reaction between path **a**' and **b**' that is quite remarkable also compared to Ochoa's claim. Based on our and other's results, a plausible reaction path is shown in Scheme 1.

Scheme 1



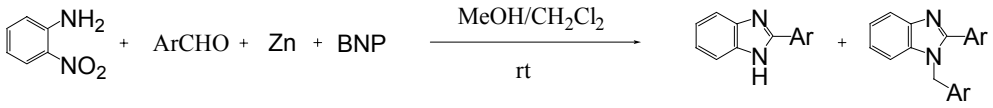
In order to test the possibility of BNP/Zn condition utilization, we examined the reductive intermolecular coupling reaction of 2-nitroaniline with aromatic aldehydes under the optimized conditions. Results are summarized in Table 2. In most cases, good to excellent yields of 2-substituted and 1,2-disubstituted benzimidazoles were obtained easily.

Typical procedure for the reductive intermolecular coupling reaction is as follows. To a stirred solution of 2-nitroaniline (41.4 mg, 0.3 mmol), aldehyde (0.6 mmol) and zinc dust (196 mg, 3.0 mmol) in MeOH (0.5 mL)/CH_2Cl_2 (0.5 mL) was added 2-bromo-2-nitropropane (0.064 mL, 0.6 mmol) at room temperature. The reaction mixture was stirred for a fixed time, and poured into a solution of aqueous 10% NH_4Cl. The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with ethyl acetate/hexane (v/v = 5/95 - 10/90) through the silica gel column to give **3** and **4**. All of synthesized new compounds are fully characterized.[8]

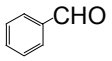
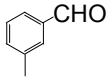
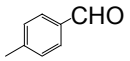
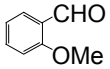
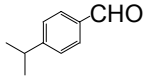
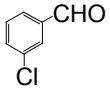
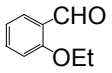
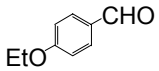
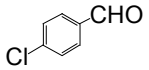
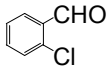
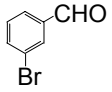
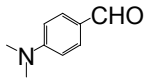
In conclusion, we have established a one-step reaction route for benzimidazole derivative

formation from 2-nitroaniline/aldehydes by using 2-bromo-2-nitropropane and Zn dust under mild conditions.

Table 2. The reactions of 2-nitroaniline/aldehyde (2 equiv.) with BNP (2 equiv.)/Zn (10 equiv.) in MeOH/CH_2Cl_2 (v/v = 1/1) at room temperature[a]



1 **2** **3** **4**

entry	ArCHO	time (h)	isolated yield (%)		entry	ArCHO	time (h)	isolated yield (%)	
			3	**4**				**3**	**4**
1		10	57 (**3a**)	33 (**4a**)	7		24	26 (**3g**)	55 (**4g**)
2		23	19 (**3b**)	53 (**4b**)	8		6	35 (**3h**)	43(**4h**)
3		12	40 (**3c**)	59 (**4c**)	9		40	42 (**3i**)	19 (**4i**)
4		24	34 (**3d**)	57 (**4d**)*	10		18	36 (**3j**)	43 (**4j**)
5		25	40 (**3e**)	45 (**4e**)	11		24	44 (**3k**)	29 (**4k**)
6		21	41 (**3f**)	56 (**4f**)	12		43	-	14 (**4l**)[b]

[a]All reactions were carried out with 0.3 mmol of 2-nitroaniline. [b]2-Nitroaniline was recovered (75%).

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8. **Spectral data for the selected new compounds : 4g**; white solid, mp 96.5-98.4 ^{o}C (haxane), ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.30 (s, 3H), 5.35 (s, 2H), 6.80-6.88 (m, 2H), 7.04 (d, 1H, *J* = 7.3 Hz), 7.12-7.27 (m, 6H), 7.32-7.37 (m, 1H), 7.52 (s, 1H), 7.78-7.83 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 154.4, 143.1, 138.8, 138.6, 136.5, 136.2, 130.7, 130.2, 129.9, 128.9, 128.5, 128.5, 126.6, 126.0, 123.1, 122.9, 122.6, 119.9, 110.5, 48.4, 21.5, 21.4; IR (KBr) 3064, 2909, 1608, 1449, 1386, 1250 cm^{-1} ; GC-MS m/z (rel. intensity) 312 (100, M^{+}), 297 (5), 221 (5), 207 (5), 192 (4), 180 (2), 116 (2), 105 (80), 90 (6), 77 (11); HRMS (EI) calcd for $C_{22}H_{20}N_2$ 312.1626, found 312.1622. Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.45; H, 6.50; N, 9.04. **4i**; white solid, mp 114.3-115.5 ^{o}C (acetone), ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.23 (s, 2H), 6.88 (d, 1H, *J* = 6.8 Hz), 7.06 (s, 2H), 7.14-7.35 (m, 6H), 7.38-7.44 (m, 1H), 7.65 (d, 1H, *J* = 1.5 Hz), 7.82 (d, 1H, *J* = 8.1 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 152.5, 143.0, 138.1, 135.9, 135.2, 134.9, 131.6, 130.5, 130.1, 130.0, 129.5, 128.2, 127.0, 126.2, 124.0, 123.6, 123.1, 120.3, 110.4, 47.8; IR (KBr) 3064, 2917, 1596, 1568, 1437, 1363, 1080 cm^{-1} ; GC-MS m/z (rel. intensity) 352 (91, M^{+}), 317 (8), 281 (3), 241 (6), 227 (6), 214 (3), 192 (5), 177 (2), 152 (4), 125 (100), 90 (19), 77 (5); HRMS (EI) calcd for $C_{20}H_{14}N_2Cl_2$ 352.0534, found 352.0532. Anal. Calcd for $C_{20}H_{14}N_2Cl_2$: C, 68.00; H, 3.99; N, 7.93. Found: C, 68.05; H, 3.98; N, 7.99.