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The selective synthesis of *N*-arylbenzene-1,2-diamines or 1-arylbenzimidazoles by irradiating 4-methoxy-4′-substituted-azobenzenes in different solvents†

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The solvent-controllable photoreaction of 4-methoxyazobenzenes to afford 1-aryl-1*H*-benzimidazoles or *N*-arylbenzene-1,2-diamines has been studied. The irradiation of 4-methoxyazobenzenes in DMF containing 0.5 M hydrochloric acid provided N^2-aryl-4-methoxybenzene-1,2-diamines as the major product, while irradiation in acetal containing 0.16 M hydrochloric acid led to 1-aryl-6-methoxy-2-methyl-1*H*-benzimidazoles as the major product. A possible reaction mechanism explaining the selectivity was also discussed.

Compounds with 1-phenyl-1*H*-benzimidazole skeleton[1] have gained attention for a long time and been studied for the applications of platelet-derived growth factor receptor (PDGFR),[2] cyclooxygenase (COX),[3] and phosphodiesterase 10A[4] inhibitors, as well as for many optoelectronic materials.[5] *N*-Aryl-1,2-phenylenediamines are also important for synthesizing various benzimidazole derivatives, and 1,3,5-tris(*N*-phenylbenzimidazol-2-yl)benzene (TBPI) is an important electronic material for OLED applications that is still widely used nowadays.[6]

The synthesis of 1-aryl-1*H*-benzimidazoles can be achieved *via* many synthetic strategies, including single and multiple molecular reactions. Single-molecule synthetic methods include the intramolecular cyclization of arylamino and oxime groups,[7] the coupling of amidine and halogen (or hydrogen) groups,[8] and the condensation of amide and amino groups.[9] Methods involving bimolecular reactions include intermolecular coupling reactions of benzimidazoles,[10] the cyclocondensation of *o*-diaminoarenes and aldehydes obtained from the oxidation of alcohols,[11] and the catalytic cyclization of aryl halides/amidines[12] or anilines/oxime acetates.[13] Methods involving trimolecular reactions include one-pot reactions of arenediazonium salts, anilines, and nitriles,[14] and the catalytic cascade cyclization of aryl halides, anilines, and amides.[15] These synthetic methods provide solutions for the preparation of 1-phenyl-1*H*-benzimidazoles but they still present some difficulties, such as the use of transition metal catalysts and unsymmetrical starting materials.

Using azobenzenes as reactants to afford 1-phenyl-1*H*-benzimidazoles[16] and *N*-phenylbenzene-1,2-diamines[17] was reported three decades ago. Compared to the above-mentioned synthetic methods, synthesis from azobenzenes showed the benefits of a simple preparation procedure and the good stability of symmetrical azobenzenes as starting materials (Scheme 1). The synthesis of a 1-phenyl-1*H*-benzimidazole[16] from an azobenzene started from α-metallation with ruthenium trichloride, triggering the *o*-semidine rearrangement to produce the intermediate; this was then further transformed to a 1-phenyl-1*H*-benzimidazole upon reacting with an aldehyde that was produced *via* oxidizing an alcohol with ruthenium trichloride. However, the reaction needs high temperature, high pressure, transition-metal catalysts, and dangerous carbon monoxide, making it risky and environmentally unfriendly. Moreover, *N*-phenylbenzene-1,2-diamines[17] could be obtained *via* the *o*-semidine rearrangement of hydrazobenzenes, which are the reductive products of azobenzenes. However, tributyltin hydride, which is used for the reduction of azobenzenes, is toxic, and the hydrazobenzenes were unstable in the presence of air because they were easily oxidized back to azobenzenes. Considering the previously discovered reactions involving azobenzenes and hydrazobenzenes, it would be worth developing a modified synthetic method that could be used to synthesize *N*-phenylbenzene-1,2-diamines and 1-phenyl-1*H*-benzimidazoles from azobenzenes more safely and easily.

Inspired by research reporting the photoreduction of imine-containing compounds to amines in the presence of alcohols,[18] a possible idea was suggested: the photoreduction of azobenzenes to hydrazobenzenes with ethanol followed by the

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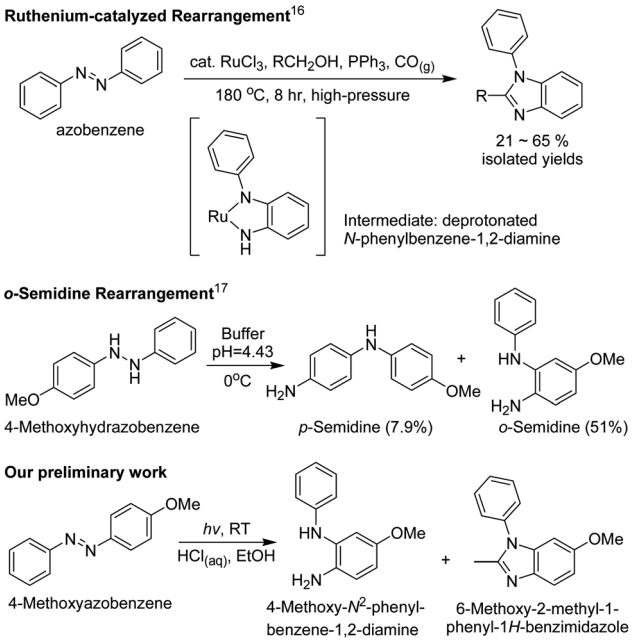
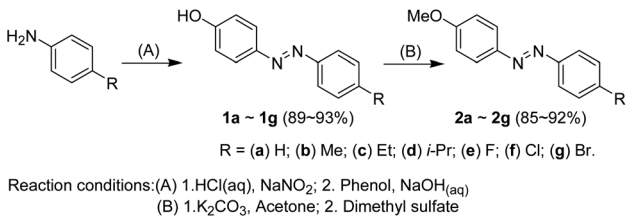
‡ This paper is dedicated to the memory of the late Prof. Tong-Ing Ho.



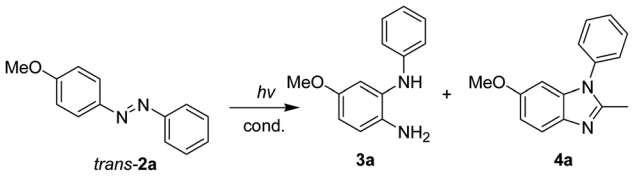
Scheme 1 The synthesis of 1-phenyl-1*H*-benzimidazoles and *N*-phenylbenzene-1,2-diamines from azobenzenes and hydrazobenzenes.

instant transformation of hydrazobenzenes to *N*-phenylbenzene-1,2-diamines in acidic media. To investigate this synthetic idea, the irradiation of 4-methoxyazobenzene in ethanol containing 0.5 M hydrochloric acid with UV light at 365 nm was performed (Scheme 1). Surprisingly, this irradiation afforded both 4-methoxy-N^2-phenylbenzene-1,2-diamine and 6-methoxy-2-methyl-1-phenyl-1*H*-benzimidazole as the two major products. This synthetic method seemed to have many advantages, including the use of stable and symmetrical azobenzenes as starting materials, the transition-metal-free synthesis, and the obtaining of two products in a one-pot synthesis process. Therefore, we report the study of the irradiation of 4-methoxy-4′-substitutedazobenzenes (**2a–2g**) to afford 4-methoxy-N^2-(substitutedphenyl)benzene-1,2-diamines (**3a–3g**) and 6-methoxy-2-methyl-1-(4-substitutedphenyl)-1*H*-benzimidazoles (**4a–4g**).

A series of 4-methoxy-4′-substituted azobenzenes (**2a–2g**) was synthesized *via* a two-step synthesis process (Scheme 2). The first step[19] was an azo coupling reaction between phenol and the corresponding aryl diazonizum salt, which was prepared *via* a diazotization reaction between 4′-substituted aniline and sodium nitrite, to afford the 4-hydroxy-4′-substituted



Scheme 2 The synthesis of the 4-methoxy-4′-substituted azobenzenes 2a–2g.



Scheme 3 The irradiation of 4-methoxyazobenzene (2a).

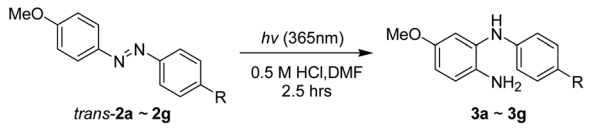
azobenzene (**1a–1g**) with a yield of 89–93%. The second step[20] was the methylation of the hydroxyl group of **1a–1g** using potassium carbonate and dimethyl sulfate, with yields of 94–99%. The total yields from these two steps are *ca.* 85–92%.

In order to investigate suitable reaction conditions for the formation of *N*-arylbenzene-1,2-diamines and 1-aryl-1*H*-benzimidazoles, a series of test reactions involving 4-methoxyazobenzene (**2a**) under different reaction conditions was performed (Scheme 3). The detailed experimental procedure for entry 10 in Table 1 is described as follows. A solution containing 20 mg of compound **2a**, 0.45 mL of concentrated HCl aqueous solution (12 M) and 10.55 mL of DMF was sealed in a quartz tube with a septum. The prepared solution was bubbled with nitrogen gas for 15 min and irradiated with a 365 nm UV lamp. After 2.5 h, the reaction solution was neutralized and extracted using water and ethyl acetate several times. The organic layers were collected, and the crude sample was obtained after removing the organic solvent under vacuum. The ^{1}H-NMR spectrum of the crude sample was obtained and the *trans*/*cis*-**2a : 3a : 4a** ratio was calculated based on the integration of the feature peaks of the compound (Table 1).

Table 1 The reaction conditions and results for the irradiation of 4-methoxyazobenzene (2a)

En.	WL (nm)	Solvent	Acid (conc.)	*t* (h)	Ratio: *t*/*c*-**2a : 3a : 4a**
1	365	CH_3CN	HCO_2H (1.26 M)	5	1 : 0 : 0
2	365	CH_3CN	AcOH (1.59 M)	3	1 : 0 : 0
3	365	DMF	None	1	1 : 0 : 0
4	365	DMF	HCl (0.05 M)	1	1 : 0 : 0
5	365	DMF	HCl (0.1 M)	1	49 : 1 : 0
6	365	DMF	HCl (0.3 M)	1	16 : 1 : 0
7	365	DMF	HCl (0.5 M)	1	0.33 : 1 : 0
8	365	DMF	HCl (0.7 M)	1	0.38 : 1 : 0
9	365	DMF	HCl (0.9 M)	1	0.47 : 1 : 0
10	365	DMF	HCl (0.5 M)	2.5	0.25 : 1 : 0
11	365	CH_3CN	HCl (0.5 M)	3	0.49 : 1 : 0.02
12	365	EtOH	HCl (0.5 M)	4	0.26 : 1 : 1.23[a]
13	419	EtOH	HCl (0.47 M)	0.33	2.6 : 1 : 0.35[a]
14	419	EtOH	HCl (0.77 M)	0.33	0.76 : 1 : 2.71[a]
15	419	EtOH	HCl (0.91 M)	0.33	0.74 : 1 : 1.96[a]
16	419	Acetal	HCl (0.77 M)	2	0 : 0 : 1[a]
17	419	Acetal	HCl (0.48 M)	2	0 : 0:1[b]
18	419	Acetal	HCl (0.16 M)	2	0 : 0 : 1[b]
19	419	Acetal	HCl (0.16 M)	0.66	0.08 : 0 : 1[c]
20	419	Acetal	HCl (0.16 M)	0.33	0.98 : 0 : 1[c]

[a] Aniline is observed in an amount of 20–30%. [b] Aniline is present in an amount of *ca.* 10%. [c] Aniline is present within an amount of 2%.



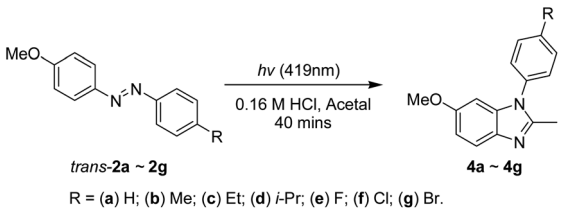
Scheme 4 The synthesis of **3a–3g** *via* the irradiation of **2a–2g**.

Based on the experimental results (Table 1), this photoreaction could not progress effectively without strong acid (entries 1–3) or at a low concentration of hydrochloric acid (entries 4–6). When the reaction solution was DMF containing hydrochloric acid with a strength of at least 0.5 M, the photoreaction effectively afforded 4-methoxy-N^2-phenyl-benzene-1,2-diamine (**3a**) as the major product (entries 7–10), and the best conditions led to a *trans*/*cis*-**2a** : **3a** ratio of 0.25 : 1, as shown in entry 10, Table 1. Subsequently, using acetonitrile and ethanol as the reaction solution could produce a mixed product containing **3a**, **4a**, and anilines (decomposed side products) (entries 11–15), and conditions for obtaining a higher amount of 6-methoxy-2-methyl-1-phenyl-1*H*-benzimidazole (**4a**) involved the use of ethanol as the solvent with 0.77 M hydrochloric acid under 419 nm irradiation (entry 14). Finally, using acetal as the solvent could produce **4a** as the major product with some aniline as an impurity (entries 16–20). It could be observed that the amount of impurities (anilines) increased as the concentration of hydrochloric acid increased; therefore, the best conditions for the formation of **4a** in acetal solution involved 0.16 M HCl under 419 nm irradiation for 40 min.

The selective synthesis of the 4-methoxy-N^2-arylbenzene-1,2-diamines **3a–3g** could be achieved through the 365 nm irradiation of the 4-methoxyazobenzenes **2a–2g** in DMF containing 0.5 M hydrochloric acid under ambient nitrogen conditions in a quartz tube for 2.5 h (Scheme 4 and Table 2). To avoid the dramatic loss of amine products due to silica gel column chromatography, conversions and yields were determined based on the weights of crude samples and the molar ratios of compounds (*trans*-**2**:*cis*-**2**:**3**) from ^{1}H-NMR spectrum integration. The reaction conversions of irradiated **2a–2g** were 61–82%, and the yields of **3a–3g** were 58–79%. No substitution effects were observed during this photoreaction. Considering the overall synthesis from the starting materials of phenol and substituted anilines, the total yields of **3a–3g** *via* this 3-step synthesis were 51–72%.

Table 2 The results of synthesizing **3a–3g** *via* the irradiation of **2a–2g** in HCl/DMF at 365 nm

En.	Starting	Conv. (%)	Yield (%) based on conversion	Yield of **3** (%)	3-Step yield (%)
1	**2a**: H	82	97	79.54	72.47
2	**2b**: Me	61	95	57.95	51.15
3	**2c**: Et	65	98	63.7	54.99
4	**2d**: *i*-Pr	74	98	72.52	62.72
5	**2e**: F	72	98	70.56	60.29
6	**2f**: Cl	76	97	73.72	65.74
7	**2g**: Br	77	96	73.92	68.06



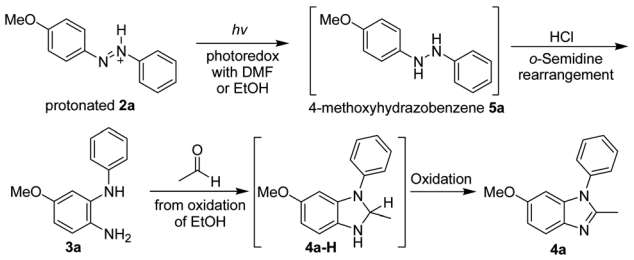
Scheme 5 The synthesis of **4a–4g** *via* the irradiation of **2a–2g**.

Table 3 Results of the synthesis of **4a–4g** *via* the irradiation of **2a–2g** in HCl/acetal at 419 nm

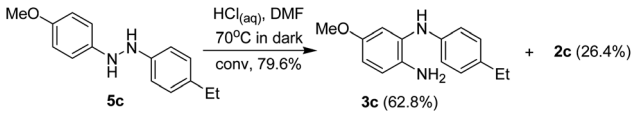
En.	Starting	Conv. (%)	Yield (%) based on conversion	Yield of **4** (%)	3-Step yield (%)
1	**2a**: H	93	96	89.28	81.37
2	**2b**: Me	76	86	65.36	57.69
3	**2c**: Et	75	86	64.50	55.68
4	**2d**: *i*-Pr	72	73	52.56	45.45
5	**2e**: F	67	91	60.97	52.09
6	**2f**: Cl	66	91	60.06	53.56
7	**2g**: Br	77	90	69.30	63.80

The selective synthesis of the 1-aryl-2-methyl-6-methoxy-1*H*-benzimidazoles **4a–4g** could be achieved *via* the 419 nm irradiation of the 4-methoxyazobenzenes **2a–2g** in acetal containing 0.16 M hydrochloric acid under ambient nitrogen conditions in a quartz tube for 40 min (Scheme 5). The reaction results are listed in Table 3, and the conversions and yields are determined based on the weights of crude samples and the molar ratios of compounds (*trans*-**2**:*cis*-**2**:**4**) from ^{1}H-NMR spectrum integration. The irradiation of **2a–2g** to afford **4a–4g** had conversions of 66–93% and yields of 60–89%. No substitution effects were observed in this photoreaction either. The 3-step reaction yields for the synthesis of **4a–4g** (including the preparation of compounds **1** and **2**) were 45–81%.

The proposed mechanism includes three main steps: (1) a photoredox reaction between a protonated azobenzene and the solvent to produce the hydrazobenzene; (2) an *o*-semidine rearrangement of the hydrazobenzene to afford the N^2-arylbenzene-1,2-diamine; and (3) a condensation reaction between the N^2-arylbenzene-1,2-diamine and acetaldehyde to produce the 1-arylbenzimidazole *via* oxidative aromatization



Scheme 6 The proposed mechanism for the transformation of **2a** to **3a** and **4a**.

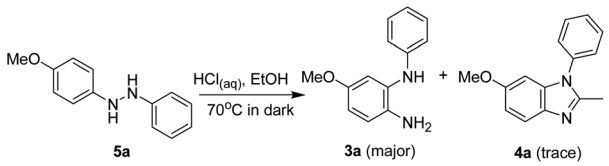


Scheme 7 The *o*-semidine rearrangement of **5c** in acidic DMF without irradiation.

(Scheme 6), and these are described below. 4-Methoxyazobenzene (**2a**) is protonated by hydrochloric acid in acidic media, and then protonated **2a** is irradiated and undergoes a photoredox reaction with DMF or EtOH to produce 4-methoxyhydrazobenzene (**5a**) as the photoreduction product. Afterwards, an *o*-semidine rearrangement[17,21] immediately takes place to transform **5a** into 4-methoxy-N^2-phenylbenzene-1,2-diamine (**3a**), which is the major product when using DMF as the reaction solvent. However, when EtOH is the reaction solvent, acetaldehyde may be produced during the photoredox reaction; this can consequently react with the di-amino groups of **3a** to afford the intermediate **4a-H**, and then 6-methoxy-2-methyl-1-phenyl-1*H*-benzimidazole (**4a**) can be quickly formed *via* aromatization with an appropriate oxidative reagent.[22] In addition, when irradiation occurs in acidic acetal, the hydrolysis of acetal[23] results in the production of a large amount of acetaldehyde in the reaction system, which leads to the formation of **4a** in high yields.

In order to confirm the possibility of the existence of 4-methoxyhydrazobenzene, the derivative **2c** was reduced to hydrazobenzene (**5c**)[24] with tributyltin hydride. When **5c** reacted with hydrochloric acid in DMF without irradiation, the product **3c** could be obtained as the major product (62.8%) with the oxidative product **2c** (26.4%) as the side product (Scheme 7). The formation of **3c** is consistent with the results from the irradiation of **2c** in DMF containing hydrochloric acid, which may explain the existence of hydrazobenzenes.

To understand the possible source of acetaldehyde, the *o*-semidine rearrangement (without irradiation) of 4-methoxyhydrazobenzene (**5a**) was performed in acidic EtOH, and compound **3a** was formed as the major product with a trace amount of **4a** (Scheme 8). However, when **2a** was irradiated in acidic EtOH, both **3a** and **4a** could be obtained as major products (entries 13–15, Table 1). The difference between the reactions with and without irradiation could be used to deduce the fact that acetaldehyde, which reacted with **3a** to afford **4a**, may come from the photoredox reaction between 4-methoxyazobenzene (**2a**) and ethanol. This is also the reason why benzimidazoles are barely obtained when irradiation occurred with DMF and acetonitrile as the reaction solvent (entries 7–11, Table 1); it is because DMF and acetonitrile were barely oxidized to aldehyde.



Scheme 8 The *o*-semidine rearrangement of **5a** in acidic EtOH without irradiation.

In summary, we have successfully developed a solvent-controllable photoreaction involving 4-methoxyazobenzenes that could be used to synthesize 1-aryl-1*H*-benzimidazoles or *N*-arylbenzene-1,2-diamines in moderate to good yields.

Conflicts of interest

We have no conflicts of interest to declare.

Acknowledgements

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