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COMMUNICATION

Solvent- and catalyst-free synthesis of 2,3-dihydro-1*H*-benzo[*d*]imidazoles†

Da-Peng Li,[a] Guang-Liang Zhang,[a] Li-Tao An,[a] Jian-Ping Zou*[a] and Wei Zhang*[b]

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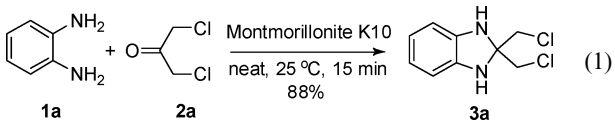
Reactions of acyclic ketones and *o*-phenylenediamines under solvent- and catalyst-free conditions have been developed for the preparation of dihydrobenzimidazoles. This method can also be used for the synthesis of other heterocyclic compounds such as dihydrobenzothiazoles and perimidines.

Benzimidazole and its analogue dihydrobenzimidazole are privileged heterocycles that can be found in commercial medicines such as Liarozole,[1] Omeprazole,[2] Thiabendazole[3] and Domperidone.[4] Their derivatives have broad medicinal,[5] biological,[6] and photochemical[7] utilities. It is well-documented that acid-catalyzed reactions of *o*-phenylenediamines with appropriate carbonyl compounds afford benzimidazoles,[8] dihydrobenzimidazoles,[9] benzo[1,5]diazepines,[10] and quinoxalines.[11] However, only cyclic ketones were reported for the synthesis of dihydrobenzimidazoles under the catalyst-free conditions.[12] Trichloromethylketone is the only acyclic substrate that was used for the synthesis of bisbenzimidazoles,[13] but not for dihydrobenzimidazoles. Reported here are new reactions of acyclic ketones and *o*-phenylenediamines under catalyst- and solvent-free conditions for the synthesis of 2,3-dihydro-1*H*-benzo[*d*]imidazoles.[14] These condensed products have dichloro, dihydroxy, and dimethoxy functional groups that are useful for further derivatizations.

As a part of our continuous efforts toward the development of new synthetic methods for heterocyclic compounds, we have reported $Ga(OTf)_3$-catalyzed reactions of *o*-phenylenediamines to form benzo[1,5]diazepines[15a] and quinoxalines.[15b] Recently, when carried out a Montmorillonite K10-catalyzed reaction of *o*-phenylenediamine **1a** and 1,3-dichloroacetone **2a** under the solvent-free conditions, we were surprised to find that the product was neither the 7-membered benzo[1,5]diazepine nor the 6-membered quinoxaline, but the 5-membered 2,2-dichloromethyl 2,3-dihydro-1*H*-benzo[*d*]imidazole **3a** (eqn (1)). This result encouraged us to explore the scope of this unusual solvent-free reaction.



1a **2a** **3a** (1)

We found that in the absent of a catalyst, reactions of unsubstituted acyclic ketones with **1a** gave benzimidazoles **3** in low yield. However, the reaction of **2a** could afford **3a** in good yield under solvent- and catalyst-free conditions. An optimized reaction carried out using 1 : 2 of **1a** : **2a** at room temperature for 15 min gave **3a** in 90% yield. Interestingly, solvents such as CH_3CN and $CHCl_3$ were found to slow down the reaction, presumably due to unfavorable solvation effects.[16]

To evaluate the generality of this reaction, **2a** was used to react with several substituted *o*-phenylenediamines **1** and the results are summarized in Table 1. Diamines **1** bearing a methyl group increased the reaction speed (Table 1, entry 2), whereas those bearing an electron-withdrawing group decreased the reaction speed and required heating to reach completion (Table 1, entries 3, 5, 7, 9, 10). The reaction of 5-bromo-2,3-diaminopyridine **1f** offered product **3f** in 82% yield (Table 1, entry 6). Stericly hindered diamine **1h** gave product **3h** in 90% yield (Table 1, entry 8). The structures of compounds **3c** and **3g** were confirmed by single crystal X-ray anaylsis (see Supporting Information†). It was found that products containing an electron-withdrawing group are more stable than those with an electron-donating group. For example, **3a** was only stable for 2 days in the refrigerator, whereas **3c** was stable at room temperature for more than 3 months.

After exploring the reaction scope of 1,3-dichloroacetone **2a**, reactions of 1,3-dihydroxyacetone **2b** with diamines were performed and the results are listed in Table 2. Reactions of **2b** with **1**, except with **1c** and **1j**, could proceed at room temperature. Reactions of **2b** with diamines gave slightly lower yields than those of **2a**, but products **4** are more stable than **3**. Extension of the reaction scope using 1,3-dimethoxyacetone **2c** to react with diamines were performed at room temperature and under solvent- and catalyst-free conditions (Table 3). The product yields are in the range comparable to the reactions of **2b**. Products **5** were found to be stable at room temperature.

[a]*Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou, Jiangsu 215123, China. E-mail: jpzou@suda.edu.cn*
[b]*Department of Chemistry, University of Massachusetts Boston, 100 Morrissey Boulevard, Boston, MA, 02125, USA. E-mail: wei2.zhang@umb.edu*

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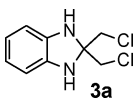
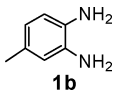
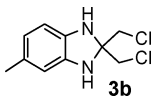
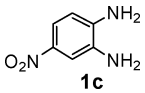
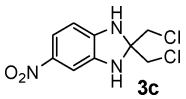
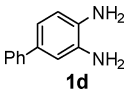
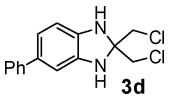
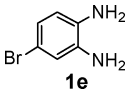
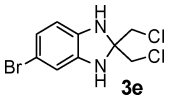
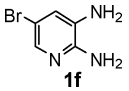
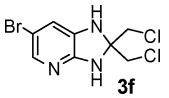
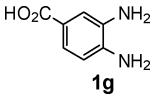
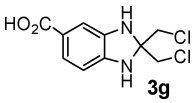
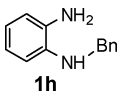
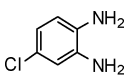
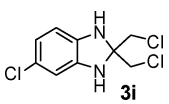
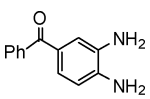
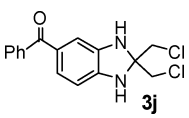
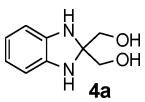
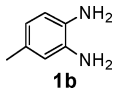
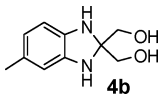
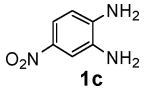
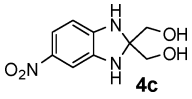
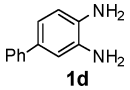
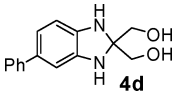
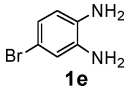
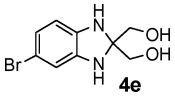
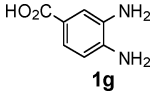
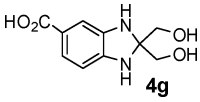
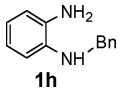
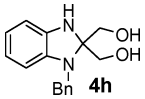
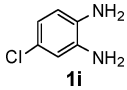
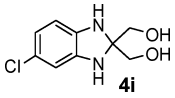
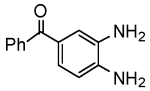
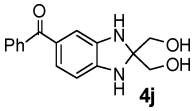
Table 1 Reactions of 1,3-dichloroacetone **2a** with diamines **1**[a]

Entry	Diamine **1**	Time (min)	Product	Yield[b](%)
1	 **1a**	15	 **3a**	90[c]
2	 **1b**	15	 **3b**	89
3	 **1c**	5	 **3c**	92(84)[d,e]
4	 **1d**	25	 **3d**	93[e]
5	 **1e**	20	 **3e**	90[e]
6	 **1f**	10	 **3f**	82[e]
7	 **1g**	45	 **3g**	92[e]
8	 **1h**	45	 **3h**	90
9	 **1i**	125	 **3i**	91[e]
10	 **1j**	15	 **3j**	96[e]

[a] Reaction conditions: 1 mmol of **1** and 2 mmol of **2a** were ground at 20 °C unless mentioned otherwise. [b] Isolated yield. [c] Stable for 2 days in the refrigerator. [d] At 30 mmol scale, 84% yield was obtained. [e] At 60 °C in an oil bath.

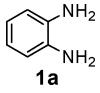
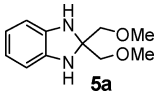
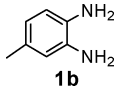
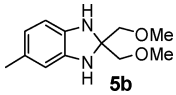
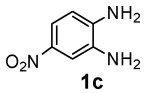
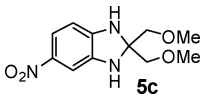
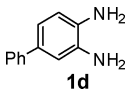
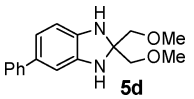
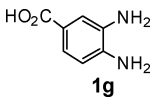
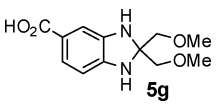
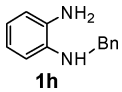
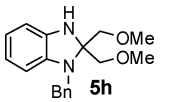
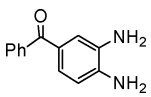
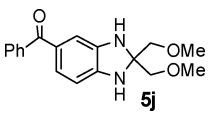
Table 2 Reactions of 1,3-dihydroxyacetone **2b** with diamines **1**[a]

Entry	Diamine **1**	Time (h)	Product	Yield[b](%)
1	 **1a**	2	 **4a**	78
2	 **1b**	1.5	 **4b**	82
3	 **1c**	0.5	 **4c**	93[c]
4	 **1d**	6	 **4d**	70
5	 **1e**	5	 **4e**	85
6	 **1g**	7	 **4g**	86
7	 **1h**	1	 **4h**	62
8	 **1i**	1.6	 **4i**	84
9	 **1j**	0.3	 **4j**	81[d]

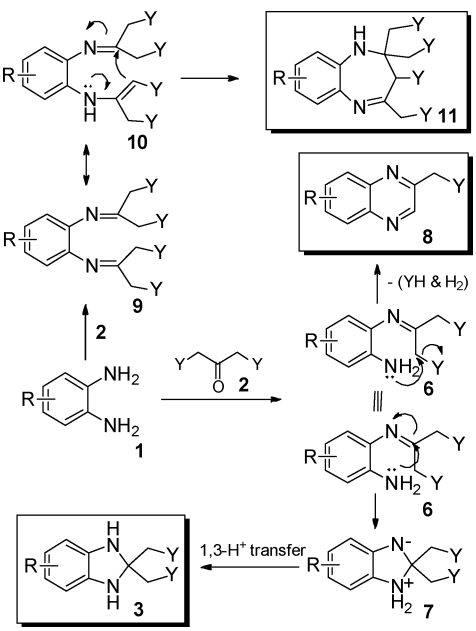
[a] Reaction conditions: 1 mmol of **1** and 2 mmol of **2b** were ground at 20 °C unless mentioned otherwise. [b] Isolated yield. [c] 50 °C in an oil bath. [d] 60 °C in an oil bath.

Reactions of 1,3-dibromoacetone and 1,3-diiodoacetone with **1a** were also conducted. However, both reactions gave complicated mixtures containing benzimidazole, benzo[1,5]diazepine, and quinoxaline. This result is related to our recent work on the reactions of *o*-phenylenediamine to form benzo[1,5]diazepines and quinoxalines.[15] 1,3-Disubstituted ketones with less electron-withdrawing groups such as bromine and iodine may have competitive pathways to form by-products. A mechanism to explain the possible transformations is proposed in Scheme 1. The first pathway is the reaction of diamine **1** with ketone **2** to form imine **6**, followed by nucleophilic addition of the amino group to the C=N bond to yield **7**. Electron-withdrawing group Y facilitates the cyclization process. Intramolecular 1,3-proton transfer of **7** gives benzimidazole **3**. Reactions of *o*-phenylenediamines with **2a**, **2b** and **2c** go through this route. Intermediate **6** may undergo an alternative pathway to form quinoxaline **8**. The reactions of ketones **2a**, **2b** and **2c** do not follow this pathway because the Y groups (Cl, OH, OMe) are not good leaving groups. However, Br and I are better leaving groups so reactions of 1,3-dibromoacetone and 1,3-diiodoacetone could form quinoxaline **8**. The third pathway generates benzo[1,5]diazepine **11** through the formation of diimine **9** and then the cyclization of its tautomer **10**. This does not seem to be a favored path for catalyst-free reactions with 1,3-disubstituted ketones. To prove that imine **6** and **9** are the key intermediates for the proposed mechanism, the reactions of N^1,N^2-(1,2-phenylene)diacetamide and N^1,N^2-dibenzylbenzene-1,2-diamine were tested, and

Table 3 Reactions of **2c** with diamines **1**[a]

Entry	Diamine **1**	Time (min)	Product	Yield[b] (%)
1	 **1a**	20	 **5a**	79
2	 **1b**	60	 **5b**	74
3	 **1c**	20	 **5c**	63
4	 **1d**	30	 **5d**	70
5	 **1g**	240	 **5g**	72
6	 **1h**	30	 **5h**	85
7	 **1j**	50	 **5j**	69

[a] Reaction conditions: 1 mmol of **1** and 2 mmol of **2c** were ground at 20 °C. [b] Isolated yield.

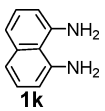
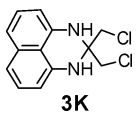
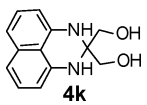
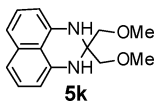
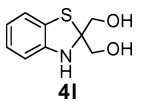
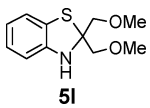


Scheme 1 Proposed mechanism for the competitive pathways.

neither of them reacted with **1a** because they could not form the mono- or diimine intermediates. However, we observed that *N*-benzylbenzene-1,2-diamine **1h** gave the desired benzimidazole **3h** through the formation of a monoimine (Table 1, entry 8).

This method has been extended for the synthesis of perimidines and dihydrobenzothiazoles by the reaction of 1,3-disubstituted ketones **2** with 1,8-diaminonaphthalene **1k** and 2-aminothiophene **1l**, respectively (Table 4). These reactions proceeded at room temperature and gave excellent yields of products.

Table 4 Synthesis of perimidines and dihydrobenzothiazoles[a]

Entry	Amine **1**	Ketone **2**	Time (min)	Product	Yield[b] (%)
1	 **1k**	**2a**	3	 **3K**	93
2	**1k**	**2b**	3	 **4k**	92
3	**1k**	**2c**	10	 **5k**	92
4	 **1l**	**2b**	6	 **4l**	75
5	**1l**	**2c**	20	 **5l**	94

[a] Reaction conditions: 1 mmol of **1** and 2 mmol of **2** were ground at 20 °C. [b] Isolated yield.

In conclusion, a new and green method has been developed for the synthesis of unique 2,2-disubstituted 2,3-dihydro-1*H*-benzo[*d*]imidazoles by the reaction of *o*-phenylenediamines and acyclic acetones under solvent- and catalyst-free conditions. This method is also suitable for the synthesis of perimidines, benzothiazoles and potentially other heterocycles. The dichloro, dihydroxy, and dimethoxy functional groups on the condensed products are useful for further derivatizations.

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