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Oxidative dimerization of azoles via copper(II)/silver(I)-catalyzed CH homocoupling

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ABSTRACT

When several azole derivatives such as imidazole, thiazole, and oxazole are treated with a catalyst system of copper(II)/silver(I) under oxygen atmosphere, oxidative dimerization at the CH bond of the 2-position takes place to afford the corresponding bisazoles up to 86% yield.

1. Introduction

We have recently shown that CH, NH coupling of azoles occurs with several amines and amides by the catalysis of copper(II) salt under an oxygen atomosphere.[1] The reaction was found to proceed with thiazole, oxazole, and imidazole derivatives leading to the 2-aminated azoles, which were found in a variety of biologically active compounds.[2] During the course of our studies on further understanding of the reaction details, we found that undesirable dimerization of an imidazole derivative occurred to give the corresponding imidazole dimer as a minor side product.[3] Since azole dimers are shown to serve as a supramolecular compound as well as bidentate ligand of transition metals,[4] development of an efficient synthetic protocol toward such molecules are of significant interest in organic synthesis. Nevertheless, catalytic dimerization of azoles that occurs at the electron-deficient CH bond, in a reasonable yield has not yet been shown to the best of our knowledge.[5–7] It is thus intriguing if such a catalytic CH, CH coupling is achieved in a facile manner. Herein, we report that a catalyst system with Cu(II)/Ag(I) is highly effective for the oxidative dimerization of azoles.

2. Results and discussion

When the oxidative amination of 1-methylbenzimidzole (**1a**) was carried out in the presence of 20 mol % of copper(II) acetate with *N*-methylaniline, homocoupled product **2a** was obtained in <10% along with the aminated product **3** (51%) as shown in Eq. 1.[1] It was found that such dimerization to give **2a** took place in the absence of the amine reagent to result in 11% yield when the reaction of **1a** was carried out in the presence of copper(II) acetate (10 mol %)/PPh_3 (20 mol %) and 1.1 equiv of sodium acetate under an oxygen atmosphere as shown in Eq. 2. These results suggest that the reaction conditions to give **3** are not effective for the homocoupling of **1a**. However, the yield of homocoupling was found to improve to 86% when the additive base was switched to silver(I) carbonate[8] in place of NaOAc. With such highly effective homocoupling in hand, the reaction conditions were examined as summarized in Table 1. Lower silver(I) carbonate loading (20 mol %) also afforded **2a** in 75% yield suggesting that the silver reagent did not serve as a base but as an oxidant. The yield was, indeed, decreased to 44–47% when the reaction was performed under a nitrogen atmosphere. The addition of PPh_3 as a ligand of copper was not crucial to undergo the C–H homocoupling. Thus, **2a** was afforded in 71% yield. The use of other copper catalysts, including Cu_2O, CuF_2, and Cu was found to promote the reaction although the yield was slightly inferior to that of $Cu(OAc)_2$.

Table 1
Oxidative dimerization of 1-methylbenzimidazole (**1a**) [a]

Cu (equiv)	Ag (equiv)	O_2 [b]	% Yield
$Cu(OAc)_2$–$2PPh_3$ (0.1)	Ag_2CO_3 (1.1)	+	86
$Cu(OAc)_2$–$2PPh_3$ (0.1)	Ag_2CO_3 (0.2)	+	75[c]
$Cu(OAc)_2$–$2PPh_3$ (0.1)	Ag_2CO_3 (1.1)	–	47[c]
$Cu(OAc)_2$–$2PPh_3$ (0.1)	Ag_2CO_3 (0.2)	–	44
$Cu(OAc)_2$ (0.1)	Ag_2CO_3 (0.2)	+	71
Cu_2O (0.1)	Ag_2CO_3 (0.2)	+	Trace
CuF_2 (0.1)	Ag_2CO_3 (0.2)	+	62
Cu (0.1)	Ag_2CO_3 (0.2)	+	69
$Cu(OAc)_2$ (0.1)	AgF (0.2)	+	69
$Cu(OAc)_2$ (0.1)	$AgNO_3$ (0.2)	+	24
$Cu(OAc)_2$ (0.1)	Ag_2O (0.2)	+	82
$Cu(OAc)_2$ (0.1)	–	+	13
–	Ag_2CO_3 (0.2)	+	0

[a] Unless noted, the reaction was performed with **1** (0.2 mmol) in 1 mL of xylene at 140 °C for 24 h under 1 atm of O_2.
[b] In the absence of O_2, the reaction was performed under a N_2 atmosphere.
[c] The reaction period: 20 h.

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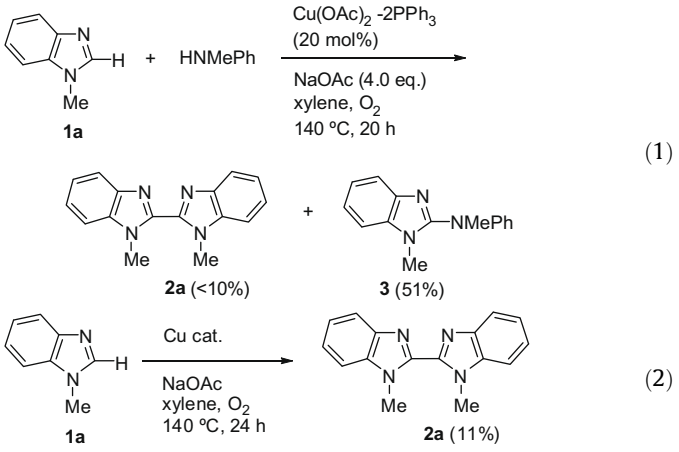


(1)

(2)

The use of silver(I) fluoride and oxide instead of carbonate similarly promoted the reaction to afford 69% and 82% of the dimerized product, respectively, while the yield was significantly decreased when silver(I) nitrate was employed. It appeared to be important to carry out the reaction with catalytic amounts of both copper and silver. The yield was decreased to 13% when the reaction was performed without silver, and no reaction took place without copper catalyst.

Table 2 summarizes the effect of the substituent on the nitrogen atom at the 1-position. Several benzimidazole derivatives (**1a–h**) with different substituents were subjected to the homocoupling reaction. The use of allyl (**1b**)-, and benzyl (**1c**)-substituted derivatives effected the reaction to afford the corresponding 2,2'-bis(benzimidazole). It was found that the *N*-arylated (4-methylphenyl) derivative **1d** also effected homocoupling in a moderate yield. The reaction with CH_2COOEt **1e**-substituted one resulted in a lower yield. By contrast, benzimidazoles bearing an electron-withdrawing substituent did not promote the reaction at all under similar conditions. The use of *t*-butoxycarbonyl (**1f**: Boc), benzoyl (**1g**: Bz), and 4-toluenesulfonyl (**1h**: Ts) derivatives resulted in completely no reaction.

In addition to benzimidazoles, CH homocoupling of several other azoles are examined as shown in Table 3. Benzoxazole (**4**) underwent the dimerization to give **5** in a poor yield (22%) and benzothiazole (**6**) resulted in no reaction, these results contrasted to that of imidazole derivatives. However, several methylated thiazole derivatives such as 4-methylthiazole (**8**) and 4,5-dimethylthiazole (**9**) were found to induce homocoupling to afford the corresponding dimerized product **10** and **11**, respectively, although the yield was slightly inferior (42% and 43%). The reaction of a mixture of 1-benzyl-4- and 5-methyl-imidazoles (**12**), which was obtained by the reaction of 4-methylimidazole with benzyl bromide to give ca. 1:2 of the mixture,[9] also effected homocoupling highly efficiently although the product **13** was a statistic amount of mixture. These results suggest that the order of the reactivity of oxidative dimerization (imidazole > thiazole ~ oxazole) is not consistent with the palladium-catalyzed CH functionalization reactions with organic halides, which we have shown previously.[10,11]

Scheme 1 shows a plausible reaction mechanism of the oxidative homocoupling reaction. Although further studies are necessary for the understanding of the mechanism, the reaction would be reductive coupling of the intermediate copper bisazole complex **I**, which is the resultant of CH substitution with copper. As discussed in the CH, NH coupling of azoles,[1] the reaction of $Cu(OAc)_2$ and azole in the presence of a base would form an organocopper species bearing a carbon–metal bond at the 2-position of azole. Since this process has shown to occur without a silver salt, the role of silver in the homocoupling reaction would be a kind of base to neutralize thus formed HX. Formation of the dimerized product accompanies Cu^0, which would be oxidized by O_2 to regenerate Cu^{II} species. This step would also occur mediated by silver(I) carbonate although the role of the silver salt has not been clear yet.

In conclusion, we have demonstrated the CH homocoupling of azoles in the presence of catalytic amounts of copper and silver species. The 1-substituted benzimidzole derivatives with an

Table 2
C–H homocoupling of N-substituted benzimidazoles **1**[a]

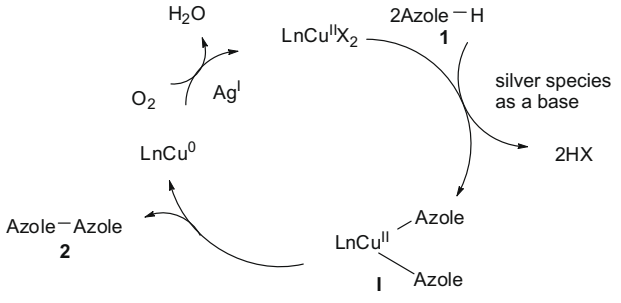
Substrate	Substituent	% Yield
1a	CH_3	81
1b	$CH_2CH{=}CH_2$	83
1c	$CH_2C_6H_5$	62
1d	C_6H_4-*p*-CH_3	52
1e	CH_2COOEt	11
1f	COO^tBu (Boc)	0
1g	COC_6H_5 (Bz)	0
1h	$SO_2C_6H_4$-*p*-CH_3 (Ts)	0

[a] The reaction was carried out with 1-substituted benzimidazole (0.2 mmol), $Cu(OAc)_2$ (10 mol %), and Ag_2CO_3 (20 mol %), under 1 atm of O_2, 1 mL of xylene, at 140 °C for 24 h.

Table 3
C–H homocoupling of azoles[a]

Entry	Azole–H	Product	Yield[b] (%)
1	**4**	**5**	22
2	**6**	**7**	0
3	**8**	**10**	43
4	**9**	**11**	42[c]
5	**12**	**13**	82

[a] Reaction conditions: Azole–H (0.2 mmol), $Cu(OAc)_2$ (10 mol %), and Ag_2CO_3 (20 mol %), under 1 atm of O_2, 1 mL of xylene, at 140 °C for 24 h.
[b] Isolated yield.
[c] Performed with 20 mol % Ag_2O.



Scheme 1.

electron-donating substituent afforded the homocoupled products in good yields. It is worthy of note that a simple mixed catalyst system undergoes oxidative dimerization at an acidic CH bond of azoles. The reaction would be a complimentary coupling protocol in addition to the palladium-catalyzed oxidative homocoupling of thiophene and thiazoles (5-position),[4] which occurs at the electron-enriched CH bond.[12]

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References and notes

1. (a) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607; See also (b) Fukuzawa, S.; Shimizu, E.; Atsumi, Y.; Haga, M.; Ogata, K. *Tetrahedron Lett.* **2009**, *50*, 2374.
2. (a) Yoshida, S.; Shiokawa, S.; Kawano, K.; Ito, T.; Murakami, H.; Suzuki, H.; Sato, Y. *J. Med. Chem.* **2005**, *48*, 7075; (b) Jimonet, P.; Audiau, F.; Barreau, M.; Blanchard, J.-C.; Boireau, A.; Bour, Y.; Coléno, M.-A.; Doble, A.; Doerflinger, G.; Huu, C. D.; Donat, M.-H.; Duchesne, J. M.; Ganil, P.; Guérémy, C.; Honoré, E.; Just, B.; Kerphirique, R.; Gontier, S.; Hubert, P.; Laduron, P. M.; Blevec, J. L.; Meunier, M.; Miquet, J.-M.; Nemecek, C.; Pasquet; Piot, M.; Pratt, J.; Rataud, J.; Reibaud, M.; Stutzmann, J.-M.; Mignani, S. *J. Med. Chem.* **1999**, *42*, 2828; (c) Stewart, G. W.; Baxter, C. A.; Cleator, E.; Sheen, F. J. *J. Org. Chem.* **2009**, *74*, 3229.
3. (a) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178; (b) Besselièvre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*. doi:10.1002/anie.200904776.
4. (a) Park, S. B.; Alper, H. *Org. Lett.* **2003**, *5*, 3209; (b) Mathieu, J.; Ghermani, N.; Bouhmaida, N.; Fenet, B.; Marsura, A. *Eur. J. Inorg. Chem.* **2004**, 3172.
5. (a) Catalytic dimerization of indoles: Tsuchimoto, T.; Nagase, Y. *Abstract, 89th Annual Meeting of the Chemical Society of Japan* 4F3-20.; See also (stoichiometric): (b) Keawin, T.; Rajviroongit, S.; Black, D. S. *Tetrahedron* **2005**, *61*, 853; (c) Keller, P. A.; Yepuri, N. R.; Kelso, M. J.; Mariani, M.; Skelton, B. W.; White, A. H. *Tetrahedron* **2008**, *64*, 7787.
6. Catalytic oxidative CH homocoupling at electron-enriched carbon of heteroaromatics: (a) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074; (b) Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. *J. Am. Chem. Soc.* **2006**, *128*, 10930; (c) Sugie, A.; Kobayashi, K.; Suzaki, Y.; Osakada, K. *Chem. Lett.* **2006**, *35*, 1100; (d) Mori, A.; Sugie, A.; Furukawa, H.; Suzaki, Y.; Osakada, K.; Akita, M. *Chem. Lett.* **2008**, *37*, 542; (e) Matsuda, S.; Takahashi, M.; Monguchi, D.; Mori, A. *Synlett* **2009**, 1941; (f) Dohi, T.; Morimoto, K.; Kiyono, Y.; Maruyama, A.; Tohma, H.; Kita, Y. *Chem. Commun.* **2005**, 2930; (g) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668.
7. For reviews: (a) Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548; Lautens, M. *Chem. Rev.* **2007**, *107*, 174; (b) Campeau, L. C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35; (c) Zificsak, C. A.; Hlasta, D. J. *Tetrahedron* **2004**, *60*, 8991; (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200; (e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. and references cited therein.
8. CH, NH coupling of azoles with stoichiometric Ag_2CO_3 was recently shown: Cho, S.-H.; Kim, J. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127.
9. The ratio of **13** was ca. 1:3:4.
10. (a) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700; (b) Arai, N.; Takahashi, M.; Mitani, M.; Mori, A. *Synlett* **2006**, 3170; (c) Kobayashi, K.; Mohamed Ahmed, M. S.; Mori, A. *Tetrahedron* **2006**, *62*, 9548; (d) Mori, A.; Shikuma, J.; Kinoshita, M.; Ikeda, T.; Misaki, M.; Ueda, Y.; Komura, M.; Asaoka, S.; Iyoda, T. *Chem. Lett.* **2008**, *37*, 272; (e) Miyaoku, T.; Mori, A. *Heterocycles* **2009**, *77*, 151; (f) Shikuma, J.; Mori, A.; Masui, K.; Matsuura, R.; Sekiguchi, A.; Ikegami, H.; Kawamoto, M.; Ikeda, T. *Chem. Asian J.* **2007**, *2*, 301.
11. See also: (a) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996; (b) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970; (c) Alagille, D.; Baldwin, R. M.; Tamagnan, G. D. *Tetrahedron Lett.* **2005**, *46*, 1349; (d) Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, *2*, 3111; (e) Gottumukkala, A. L.; Doucet, H. *Eur. J. Inorg. Chem.* **2007**, *23*, 3629; (f) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578; (g) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467; (h) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185.
12. *Typical procedure for the CH homocoupling*: A solution of $Cu(OAc)_2$ (9.1 mg, 0.05 mmol), 1-methylbenzimidazole **1** (66 mg, 0.5 mmol) and silver carbonate (27.6 mg, 0.1 mmol) in 2.5 mL of xylene under O_2 atmosphere was stirred at 140 °C for 24 h. After cooling to room temperature, the mixture was passed through a Celite® pad, which was washed with chloroform repeatedly. The filtrate was washed with water three times. The organic layer was concentrated under reduced pressure to leave a crude oil, which was purified by chromatography on silica gel to afford 47 mg of **2** (71%).
1,1′-Allyl-2,2′-bis(benzimidazole) (**2b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (d, J = 17.3 Hz, 2H), 5.14 (d, J = 10.2 Hz, 2H), 5.60 (d, J = 5.4 Hz, 4H), 6.02–6.08 (m, 2H), 7.34–7.39 (m, 4H), 7.48 (d, J = 6.9 Hz, 2H), 7.88 (d, J = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 47.8, 110.8, 117.2, 120.7, 123.0, 124.0, 133.2, 135.6, 142.84, 142.86; IR (neat) 914, 1184, 1331, 1398, 1405, 1643, 2919, 2989, 3062 cm^{-1}; HRMS found: m/z 314.1532. Calcd for 314.1531.
1,1′-Benzyl-2,2′-bis(benzimidazole) (**2c**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (s, 4H), 7.03 (d, J = 6.3 Hz, 4H), 7.14–7.18 (m, 6H), 7.31–7.33 (m, 4H), 7.38–7.40 (m, 2H), 7.86–7.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.9, 111.2, 120.7, 123.1, 124.3, 127.0, 127.6, 128.8, 137.1; IR (neat) 732, 966, 1176, 1358, 1360, 1455, 1496, 2922, 2929, 2997 cm^{-1}; HRMS found: m/z 414.1842. Calcd for 414.1844.
1,1′-p-Tolyl-2,2′-bis(benzimidazole) (**2d**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 6H), 6.87 (d, J = 8.2 Hz, 4H), 7.03 (d, J = 8.0 Hz, 4H), 7.24–7.30 (m, 4H), 7.35 (t, J = 7.2 Hz, 2H), 7.91 (d, J = 7.9 Hz, 2H); IR (neat) 742 822, 1271, 1452, 1513, 1715, 2849, 2919 cm^{-1}; HRMS found: m/z 414.1841. Calcd for 414.1844.
Compound **11**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.38 (s, 6H), 2.39 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8, 14.6, 129.6, 149.2, 156.5; IR (neat) 918, 1014, 1089, 1210, 1375, 1531, 2847, 2915, 3368 cm^{-1}; HRMS found: m/z 224.0440. Calcd for 224.0442.
Compound **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11 (s, 0.5H), 2.12 (s, 1.5H), 2.22 (s, 1.5H), 2.25 (s, 2.5H), 5.64 (s, 2.6H), 5.79 (s, 1.4H), 6.65 (s, 1H), 6.82-6.83 (m, 0.7H), 6.86–6.94 (m, 0.3H), 7.02–7.06 (m, 3H), 7.20–7.35 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.1, 13.9, 50.58, 50.67, 117.9, 126.4, 126.5, 127.2, 127.58, 127.61, 127.63, 128.0, 128.69, 128.72, 128.8, 137.68, 137.73, 137.9; IR (neat) 691, 695, 965, 1103, 1388, 1404, 1424, 1557, 2905, 3041 cm^{-1}; HRMS found: m/z 342.1849. Calcd for 342.1844.
Other coupling products **2a**,[4a] **5**,[13] and **10**[4b] are known compound.
13. Tauer, E.; Grellmann, K. H. *J. Org. Chem.* **1981**, *46*, 4252.