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An Unexpected Reaction in the Copper/silver-catalyzed Oxidative Dimerization of Imidazole Derivatives

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An unexpected side reaction takes place in the oxidative dimerization of an imidazole derivative catalyzed by $CuCl_2$ (10 mol%) and Ag_2CO_3 (20 mol%). Unidentified product, whose estimated molecular weight is 278, is obtained along with the dimerized product at the CH bond at the 2-position (MW = 262). Measurements of NMR and mass spectra and several transformation reactions suggest a possible structure.

1. Introduction

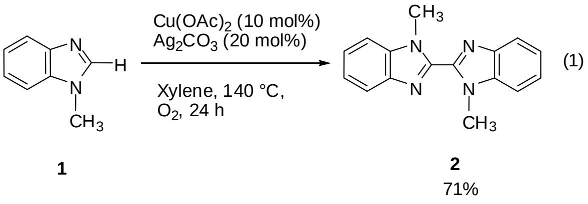
Transition metal-catalyzed coupling reaction attracts much attention in organic synthesis. Extensive works are performed recently and a variety of coupling reaction are shown to proceed by the catalysis of transition metals such as nickel, palladium, copper, iron, etc.[1] One of the widely studied in this field is the cross coupling, which is a bond formation of an main group organometallic compound with an organic electrophile, to construct various organic frameworks and thereby employed for the synthesis of biologically important molecules and advanced organic materials. Particularly remarkable, in addition, is the coupling reaction at a carbon-hydrogen (CH) bond, whose advantage is better atom efficiency in synthesis.[2] We have been studying CH coupling reactions of heteroaromatic compounds and revealed that several coupling reactions take place with a five-membered heteroaromatics such as thiazole, thiophene, imidazole, and furan, with organic halides and the related compounds.[3] It is also our recent concern that coupling reactions of azoles with nitrogen-containing organic molecules to undergo CH-NH coupling, which we have shown to proceed in the presence of a copper catalyst.[4]

On the other hand, dimerization at the CH bond of heteroaromatic compound also is of considerable interest. The reaction offers a facile synthetic pathway to bi(hetero)aryls, which leads to a wide range of functions such as chelating ligands of metallic compounds and π-conjugated organic materials showing light emission as well as (semi)conductive characteristics.[5] A homocoupling reaction of thiophene was shown to proceed with a palladium catalyst in the presence of a silver salt leading to bithiophene.[6] Very recently, we have found that homocoupling at the CH bond of azoles also proceeds when a mixed system of copper(II) and silver(I) is employed as a catalyst under oxidative conditions.[7]

During the course to study the above reaction, it was found that an unexpected reaction occurred to afford an unidentified compound. It is therefore our concern to clarify the structure of thus obtained molecule. We herein report the characterization of the unknown molecule with NMR, IR, and mass spectroscopic studies.

2. Results and Discussion

Upon studying oxidative coupling of imidazole derivatives, the reaction of *N*-methyl-benzimidazole (**1**) was revealed to proceed leading to the dimerized product when **1** was treated with 10 mol% of $Cu(OAc)_2$, 20 mol% of Ag_2CO_3 in xylene at 140 ºC under an oxygen atmosphere. After stirring the above mixture for 24 h, 71% of the corresponding dimer **2** was obtained as shown in eq 1.[7]



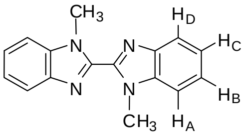
On the other hand, it was found that an unidentified side product **X** was obtained accompanied by desired **2** when $Cu(OAc)_2$ was switched to $CuCl_2$. TLC analysis shows that a slightly less polar by product was observed at R_f = 0.3 (hexanes:ethyl acetate = 1:1), while the homocoupled product **2** was found at R_f = 0.7. The reaction was carried out under several conditions by varying the amount and the ratio of Cu/Ag, reaction time, and temperature. The results are summarized in Table 1. When the reaction was carried out with 10 mol% of $CuCl_2$ and 20 mol% of $AgCO_3$, 65% of **1** was converted to afford 0.30:0.35 of **X** and **2**, respectively. Increasing amount of $CuCl_2$ to 50 mol% resulted in much lower conversion to obtain neither **X** nor **2**. Use of 50 mol% of $AgCO_3$ with 10 mol% of $CuCl_2$ resulted in lower conversion. It was also shown to give the similar product **X** with 10 mol% of CuI.

Table 1. Attempted dimerization of **1** with Cu/Ag system under O_2.[a]

Cu (mol%)	Ag_2CO_3, mol%	conv.[b]	ratio[b] X	2
$CuCl_2$ (10)	20	0.65	0.46	0.54
$CuCl_2$ (50)	20	trace		
$CuCl_2$ (10)	50	0.38	0.47	0.53
CuI (10)	20	0.53	0.72	0.28
$CuCl_2$ (10)[c]	20	0.47	0.81	0.19

[a] The reaction was carried out with **1** (0.5 mmol) in 2.5 mL of xylene at 140 ºC for 24 h. [b] The conversion of **1** and the ratio of **X**/**2** was estimated by the integration value from the ^1H NMR analysis of the crude product. [c] The reaction was carried out under N_2.

Measurement of ^1H NMR spectrum of **X** shows a more complecated signals in the aromatic region than that of **2** and two different methyl signals corresponding to N-methyl groups suggesting that **X** was transformed to an unsymmetrical structure. It was also found that an aromatic signal, which corresponds to H_A, reduced its integral value to a half of that of **2**. This suggests that the corresponding benzimidzole has lost its aromaticity or the proton is substituted.



2

We then measured the mass spectrum of unknown **X** to shown m/z of 278. The result proposes the molecular weight of **X** suggesting (M of **2**)+16, which indicates that one oxygen atom is incorporated into the structure of **2** if the peak is the parent ion's one. Candidates for the structure would be $\mathbf{X_1}$-$\mathbf{X_4}$ listed in Chart 1.

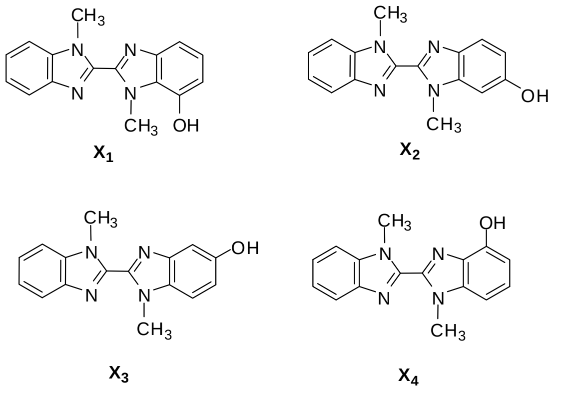
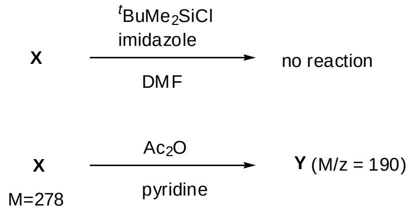
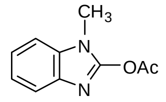


Chart 1. Possible structure of unidentifeid side product **X**.

If the structure of **X** is as shown in the Chart 1, incorpration of oxygen functionality takes place in the presence of a copper catalyst. The reaction would be recognized as a new class of CH functionalization on the aromatic ring. For the purpose to confirm the structure of **X**, further transformation reaction of a hydroxy group was attempted. The reaction of *t*-$BuMe_2SiCl$ to form the silyl ether was found to be unsuccessful to result in no reaction at all. On the other hand, treatment of **X** with acetic anhydride brought about complete convertion to afford another unidentified product **Y**. Figure 1 shows the ^1H NMR spectrum of **Y**. The spectrum shows that the ratio of the methyl group of acetate (3 H), the methyl group on nitrogen (3 H), and the protons in aromatic region (4n H) is ca. 3:3:4 suggesting that **Y** is not a dimeric structure and it is quite reasonable for **3**. Thus, the compound **3** was subjected to the measurement of mass spectrum. The peak of parent ion (M^+) also suggested the formation of **3** and fragment peaks 147, 119, and 92 would correspond to the dissociation of CH_3CO (-43), CH_3COOC (-71), and CH_3COOCH+NC (-98), respectively.





3 (**Y**)

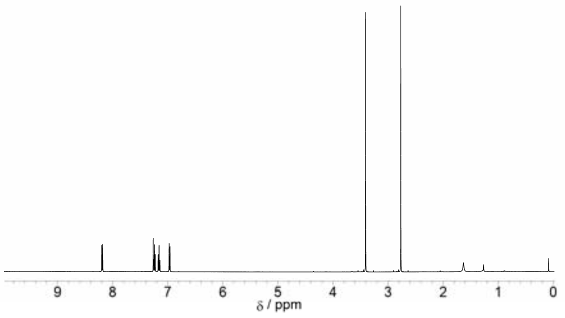
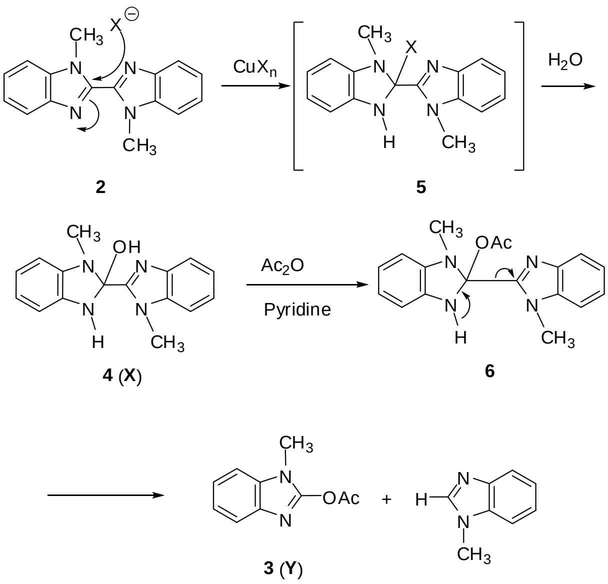


Fig. 1.^1H NMR spectrum of **Y**.

Consequently, the unidentified side product in the catalytic oxidative dimerization would be **4**, whose molecular weight is 280. The observed peak of the mass spectrum would be [M-2H]. The plausible mechanism of the unexpected reaction is as shown in Scheme 1. Copper catalyzed reaction of N-methyl-benzimidazole undergoes oxidative dimerization as we have reported to afford **2**. Attack of halogen ion to **2** to form probably unstable intermediate **5**, which would be hydrolyzed by water formed in a catalytic oxidative dimerization or a trace amount of water containing in a reagent or the solvent, to afford **4**. Under the conditions of acetylation, the OH group is transformed to $OCOCH_3$ to give **6**, which immediately decomposed to **3**.



Scheme 1. A plausible reaction pathway to afford **4** from **2**.

3. Conclusion

In conclusion, the structure of unidentified product in the catalytic oxidative dimerization of *N*-methyl-benzoimidazole was found to be **4**, which is the adduct of water to the imidazole dimer **2**, clarified by measurements of NMR and mass spectra and chemical transformation studies. Although it was not a synthetically interesting CH functionalization, a new class of reactivity was found in the reaction of imidazole dimer when a copper(I or II) halide is employed.

4. Experimental section

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured on a Bruker Avance 500 spectrometer. Unless specified, data of ^{1}H NMR and ^{13}C NMR as a $CDCl_3$ solution. The chemical shifts were expressed in ppm with $CHCl_3$ (7.26 ppm for ^{1}H) or $CDCl_3$ (77.2 ppm for ^{13}C) as internal standards. IR (ATR) spectra were measured with Bruker Optics Alpha with Ge. Mass spectra were meaured with JEOL MStation of Nara Institute of Science and Technology.

Dimerization of *N*-methyl-benzimidazole with $CuCl_2$: a solution of $CuCl_2$ (67 mg, 0.5 mmol), 1-methylbenzimidazole **1** (660 mg, 5.0 mmol) and silver carbonate (27.6 mg, 1.0 mmol) in 25 mL of xylene under O_2 atmosphere was stirred at 140 ºC 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 231 mg of **2** (35%) and 177 mg of **4** (25%) .
4: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.50 (s, 3H), 3.83 (s, 3H), 7.07 (d, J = 7.8 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 7.23 (t, J = 7.0 Hz, 1H), 7.32-7.41 (m, 3H), 7.45 (d, J = 7.6 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H); IR (neat) 734, 1084, 1251, 1487, 1526, 1714 cm^{-1}; MS *m/z* (rel intensity) 278 (35, M-2H), 277 (52), 236 (12), 144 (17), 119 (62), 77(100), 51 (47).

Attempted silylation of unidentified product 4 with *t*-$BuMe_2SiCl$: a solution of **4** (32 mg, 0.12 mmol), *t*-$BuMe_2SiCl$ (18 mg, 0.12 mmol) and imidazole (8.8 mg, 0.13 mmol) in 1 mL of DMF was stirred at room temperature. After 4 h the reaction mixture was no reaction.

Attempted acetylation of 4: a solution of **4** (21 mg, 0.08 mmol) and acetic anhydride (0.5 mL) in 0.5 mL of pyridine was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure to leave a crude oil, which was purified by chromatography on silica gel to afford 10 mg of **6** (66%).
6: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.76 (s, 3H), 3.40 (s, 3H), 6.96 (d, J = 7.8 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H), 7.24 (t, J = 7.9 Hz, 1H), 8.19 (d, J = 7.9 Hz, 1H); IR (neat) 762, 1211, 1492 cm^{-1}; MS *m/z* (rel intensity) 190 (M$^+$, 15), 148 (100), 147 (37), 119 (72), 92 (35), 83 (22), 65 (17), 51 (14); HRMS found: m/z 190.0742. Calcd for 190.0742.

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