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SYNTHESIS OF A TETRACYCLIC AMINOBENZIMIDAZOLE DERIVATIVE VIA TANDEM CYCLIZATION OF TRIPHENYLGUANIDINE

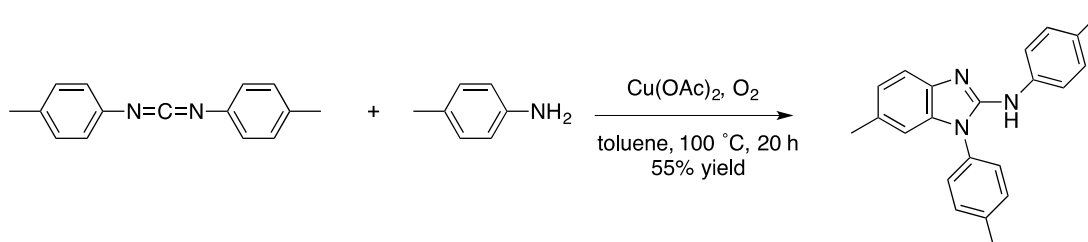
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Dedicated to Professor Dr. Tohru Fukuyama on the occasion of his 70th birthday

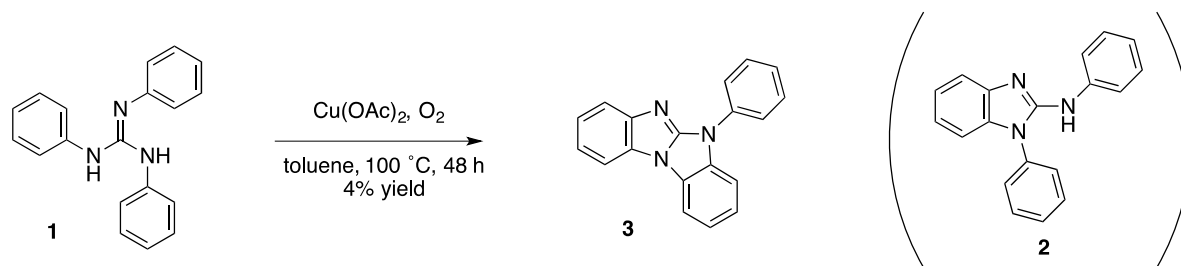
Abstract – We developed a new reaction for the one-pot synthesis of a fused cyclic compound from triphenylguanidine, which was thought to be tandem cyclization, with a moderate yield. In this reaction, conditions such as the metal reagent, oxidant, solvent, and ligand affected whether single or tandem cyclization was preferred.

Heteroaromatic compounds are valuable scaffolds and are present in many bioactive compounds and pharmaceuticals, and they often play important roles in some biological and pharmaceutical activities.¹ Therefore, the development of efficient and useful synthetic methods for heteroaromatic compounds is still a significant subject. During the course of our synthesis projects on heteroaromatic compounds, we became interested in the structure of 2-aminobenzimidazole, which contains three vicinal nitrogen atoms.² For the synthesis of 2-aminobenzimidazole, an aromatic compound containing a guanidino group should be a proper substrate, and with this substrate, a cyclization reaction to form a C-N bond between a nitrogen atom of the guanidino group and a phenyl moiety should be the key reaction.



Scheme 1. Synthesis of aminobenzimidazole derivative⁴

After a careful search for such a cyclization reaction, we found a precedent using guanidine derivatives and hypervalent iodine(III).³ Another precedent was found, involving a copper-catalyzed reaction (Scheme 1).⁴ This reaction proceeds through a cascade process; *p*-toluidine adds to bis(*p*-methylphenyl)carbodiimide and the resultant guanidine cyclizes to form the 2-aminobenzimidazole derivative via Cu(OAc)₂-catalyzed C-H activation/functionalization. On the basis of this reaction, we attempted a catalytic cyclization reaction using a simple substrate, triphenylguanidine (**1**),⁵ and we were unable to obtain expected compound **2**,⁶ but unexpected compound **3** was obtained in 4% yield⁷ and was thought to be generated by a tandem cyclization reaction (Scheme 2). The syntheses of compound **3**, benzo[4,5]imidazo[1,2-*a*]imidazole, and its derivatives have already been reported.⁸ However, both the tetracyclic heteroaromatic compound **3** and this tandem reaction based on C-H activation/amination were intriguing to us, and thus, we embarked on the development of this tandem cyclization reaction.



Scheme 2. Cyclization reaction using triphenylguanidine (**1**)

First, we examined the use of an oxidant to help the catalytic cycle proceed smoothly under similar reaction conditions (0.2 equivalent of Cu(OAc)₂, toluene, 100 °C). As shown in Table 1, some oxidants led to single-cyclization compound **2** along with compound **3** (entries 2–4).

Table 1. Optimization of oxidant^a

| Entry | oxidant | yield (%) of 2 | yield (%) of 3 |
|----------------|--|-----------------------|-----------------------|
| 1 ^b | O ₂ | 0 | 4 |
| 2 | K ₂ S ₂ O ₈ | trace | trace |
| 3 | PhI(OAc) ₂ | 12 | 2 |
| 4 | AgOAc | 15 | 5 |
| 5 | Ag ₂ O | 0 | 1 |
| 6 | Ag ₂ CO ₃ | 0 | 7 |
| 7 | benzoquinone | 0 | 0 |
| 8 | FeCl ₃ | 0 | 0 |
| 9 | TBHP ^c | 0 | 0 |

^a Reaction conditions: **1** (0.25 mmol), Cu(OAc)₂ (0.2 equiv.), and oxidant (2.0 equiv.) were stirred in toluene at 100 °C for 48 h under Ar (except entry 1). ^b The reaction was conducted under O₂. ^c TBHP: *tert*-butyl hydroperoxide.

AgOAc afforded the highest total yield of **2** and **3** (entry 4), and Ag₂CO₃ gave a slightly better result than did O₂, which both led to only compound **3** (entries 1 and 6). The other oxidants did not afford positive results, neither did the prolonged reaction time and higher reaction temperature. In this reaction, the starting material **1** was recovered, and only a few products, except the compounds **2** and **3**, were obtained. Therefore, we used AgOAc as the oxidant in solvent screening for efficient conversion of the starting material.

As shown in Table 2, we tested ten solvents using the same reaction conditions, and dimethylformamide (DMF) afforded the best result; the total yield of compounds **2** and **3** was 28% (entry 10). With respect to the reagents, we recognized Cu(OAc)₂ as the best after examining several other metal compounds (CuBr₂, Cu(OTf)₂, CuO, and Pd(OAc)₂). According to the results in Tables 1 and 2, especially for the tandem cyclization reaction for compound **3**, O₂ or Ag₂CO₃ should be used as the oxidant in DMF.

Table 2. Optimization of solvent^a

| Entry | solvent | yield (%) of 2 | yield (%) of 3 |
|-------|--------------------|-----------------------|-----------------------|
| 1 | toluene | 15 | 5 |
| 2 | <i>p</i> -xylene | 19 | 5 |
| 3 | TFE ^b | 10 | 1 |
| 4 | <i>t</i> -butanol | 11 | 11 |
| 5 | 2-methyl-2-butanol | 13 | 7 |
| 6 | 1,4-dioxane | 11 | 1 |
| 7 | MeCN | 16 | 8 |
| 8 | DMSO | 15 | 5 |
| 9 | DMA | 12 | 2 |
| 10 | DMF | 22 | 6 |

^a Reaction conditions: **1** (0.25 mmol), Cu(OAc)₂ (0.2 equiv.), and AgOAc (2.0 equiv.) were stirred in solvent at 100 °C for 48 h under Ar. ^b TFE: 2,2,2-trifluoroethanol.

Next, we inspected the effects of ligands in this reaction; unfortunately, when Ag₂CO₃ was used as the oxidant, some ligands gave negative effects. Therefore, we used O₂ with 1 equivalent of Cu(OAc)₂ in DMF for the examination of ligands (Table 3). In the initial screening of ligands, we found that glycine gave an interesting effect (entries 2–5); however, compound **2** was the sole product with glycine (entry 5). Then, *N*-protected glycines were studied carefully (entries 6–10), and we found that Boc-Gly-OH afforded a better result than that obtained without a ligand (entry 1), giving compound **3** in 37% yield (entry 7). Using Boc-Gly-OMe reduced the yield, implying that the carboxylic acid moiety plays some important role (entry 11). Then, various other Boc-protected amino acids were investigated (entries 12–22), and by using Boc-Asn-OH, compound **3** was obtained in 52% yield (entry 22).⁹ Some amino acid derivatives led to more of compound **2** than compound **3** (entries 5, 14, and 15), and we do not have a reasonable explanation for those results. Wang et al. synthesized compound **3** in 81% yield from

2-(1*H*-benzo[*d*]imidazol-1-yl)-*N*-phenylaniline;^{8(b)} however, the preparation of the starting material, 2-(1*H*-benzo[*d*]imidazol-1-yl)-*N*-phenylaniline, may be difficult, giving only low yields. Therefore, this tandem cyclization system has some advantages for the synthesis of compound **3**, although the yield is moderate.

Table 3. Optimization of ligand^a

| Entry | ligand | yield (%) of 2 | yield (%) of 3 |
|-------|---|-----------------------|-----------------------|
| 1 | - | 0 | 28 |
| 2 | PPh ₃ | 0 | 15 |
| 3 | 1,10-phenanthroline H ₂ O | 0 | 0 |
| 4 | TMEDA ^b | 4 | 0 |
| 5 | glycine | 19 | 0 |
| 6 | Ac-Gly-OH | 0 | 33 |
| 7 | Boc-Gly-OH | 0 | 37 |
| 8 | Z-Gly-OH | 0 | 0 |
| 9 | Fmoc-Gly-OH | 0 | 21 |
| 10 | Bz-Gly-OH | 0 | 36 |
| 11 | Boc-Gly-OMe | 0 | 11 |
| 12 | Boc-Gln-OH | 0 | 17 |
| 13 | Boc-Ser-OH | 0 | 20 |
| 14 | Boc-Asp-OH | 15 | 7 |
| 15 | Boc-His-OH | 26 | 0 |
| 16 | Boc-Phe-OH | 0 | 26 |
| 17 | Boc-Ala-OH | 0 | 31 |
| 18 | Boc-Val-OH | 0 | 39 |
| 19 | Boc-Leu-OH | 0 | 43 |
| 20 | Boc-Glu-OH | 0 | 46 |
| 21 | Boc-Pro-OH | 0 | 50 |
| 22 | Boc-Asn-OH | 0 | 52 |

^a Reaction conditions: **1** (0.25 mmol), Cu(OAc)₂ (1.0 equiv.), and ligand (2.0 equiv.) were stirred in DMF at 100 °C for 48 h under O₂. ^b TMEDA: *N,N,N',N'*-tetramethylethylenediamine.

In summary, we have developed a new reaction for the one-pot synthesis of fused cyclic compound **3** from triphenylguanidine, which was thought to be tandem cyclization, with a moderate yield. In this reaction, the metal reagent, oxidant, solvent, and ligand affected whether single or tandem cyclization was preferred, and the details of these mechanisms were not disclosed. Moreover, the single-cyclization compound was reported as the sole product of the reaction we followed (Scheme 1),⁴ and we presumed that guanidine would be a good starting material for the tandem cyclization. The reaction mechanism for this tandem system was thought to involve the repetition of the single cyclization step described in the precedent, that is i.e. Cu(OAc)₂-catalyzed C-H activation/amination.⁴ Using this potentially useful reaction, the syntheses of various aminobenzimidazole derivatives and functional molecules are now ongoing.

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- Typical procedure (entry 22 in Table 3): a solution of triphenylguanidine (**1**) (72 mg, 0.25 mmol), Cu(OAc)₂ (45 mg, 0.25 mmol), and Boc-Asn-OH (116 mg, 0.50 mmol) in DMF (2.0 mL) was sealed in a Schlenk tube and stirred under O₂ at 100 °C for 48 h. The reaction mixture was cooled to room temperature and then filtered through Celite, and the filtrate was evaporated to give the crude product, which was purified by flash column chromatography (hexane/EtOAc 20:1) to yield compound **3** as a yellow solid (52% yield).