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Ligand-Free Copper-Catalyzed Synthesis of Substituted Benzimidazoles, 2-Aminobenzimidazoles, 2-Aminobenzothiazoles, and Benzoxazoles

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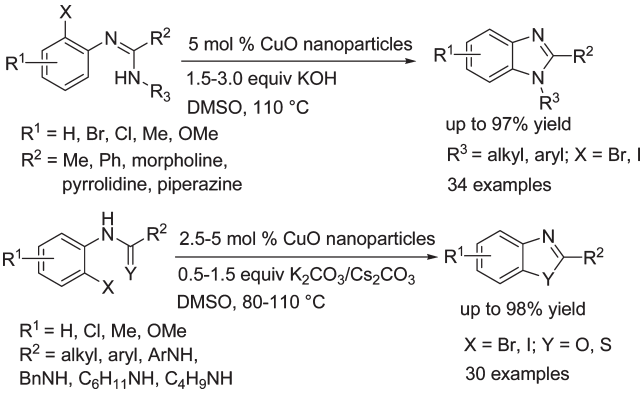

The synthesis of substituted benzimidazoles, 2-aminobenzimidazoles, 2-aminobenzothiazoles, and benzoxazoles is described via intramolecular cyclization of *o*-bromoaryl derivatives using copper(II) oxide nanoparticles in DMSO under air. The procedure is experimentally simple, general, efficient, and free from addition of external chelating ligands. It is a heterogeneous process and the copper(II) oxide nanoparticles can be recovered and recycled without loss of activity.

Introduction

Benzimidazoles,[1] 2-aminobenzimidazoles,[2] 2-aminobenzothiazoles,[3] and benzoxazoles[4] are privileged organic compounds due to their recognition in biological and therapeutic activities (Figure 1). Recent medicinal chemistry applications of these heterocyclic compounds include 5-lipoxygenase inhibitor,[5a] poly(ADP-ribose)polymerase (PARP) inhibitor,[5b] factor Xa(FXa) inhibitor,[5c] histamine H_1-receptor,[5d−f] 5-HT_3-receptor agonist 2,[5d] HIV reverse

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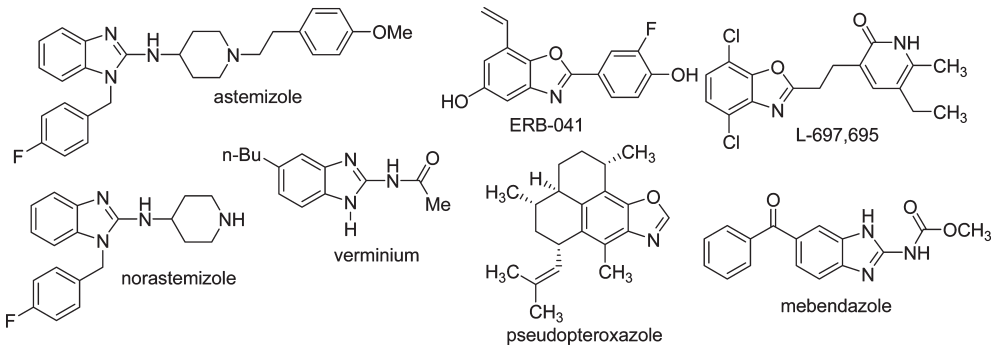

FIGURE 1. Examples of some biologically active compounds.

transcriptase inhibitor L-697,695,[5g] anticancer agent NSC-693638,[4a] and orexin-1 receptor antagonist SB-334867.[5h] Other applications of these compounds include their use as anti-inflammatory,[6a] antibacterial,[2l] antimicrobial,[6b] and antiviral[2k,4c] agents. Development of general methods for the synthesis of these compounds is thus highly relevant for drug discovery.

The classical methods used for the preparation of these compounds framework starts from either *o*-aminoaniline,[7] *o*-aminothiophenol,[8] or *o*-aminophenol,[9] and often they imply the use of either toxic reagents or harsh reaction conditions such as those involving strong acids in combination with high temperature. Some of these drawbacks are recently overcome by the development of more sustainable cross-coupling reactions, which allow the efficient assembly of the target heterocycles under comparatively milder reaction conditions.[10,11] The cyclization of *o*-haloarylamidines to benzimidazoles is accomplished via intramolecular cross-coupling reaction with palladium(0) under thermal[12a] and microwave[12b] conditions. Copper(I)/(II) complexes are studied for benzimidazole synthesis via intramolecular[13a] and intermolecular followed by intramolecular cross-coupling reactions.[13b] Copper(I) complexes are reported as effective catalysts compared to palladium(0) complexes for the

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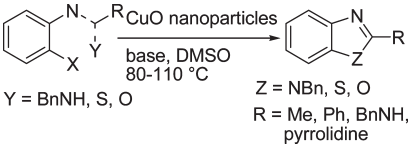
formation of 2-aminobenzimidazoles[14] and 2-aminobenzothiazoles[15] via inter- as well as intramolecular cross-coupling reactions. The synthesis of benzoxazoles is reported using copper(I)/(II) complexes via intramolecular or interfollowed by intramolecular cross-coupling reactions.[16] More recently, iron(III) complex has been employed for the cyclization of *o*-bromoanilides to afford 2-arylbenzoxazoles.[17] Most of these reactions function under homogeneous conditions and the ligands chelated with the metals play a crucial role in the catalysis. Among these studies, the cyclizations via intramolecular cross-coupling reactions provide a straightforward route with wide substrate scope for the synthesis of these target heterocycles in high yield.

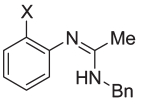
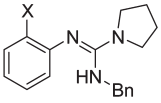
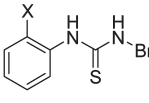
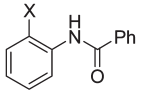
Recently, we and others reported the intermolecular cross-coupling reactions of aryl iodides with nitrogen, oxygen, and sulfur nucleophiles using copper(II) oxide nanoparticles[18] under ligand-free conditions.[11w−z] Since the copper(II) oxide nanoparticles are readily accessible, air stable, recyclable, and free from addition of external chelating ligands, we became further interested to investigate them for the synthesis of important organic compounds. In this contribution, we wish to describe a general method for the synthesis of substituted benzimidazoles, 2-aminobenzimidazoles, 2-aminobenzothiazoles, and benzoxazoles by intramolecular cyclization in the presence of the copper(II) oxide nanoparticles under air. The procedure is experimentally simple and efficient to afford the heterocyclic compounds in high yield. The reaction involves a heterogeneous process and the copper(II) oxide nanoparticles can be recovered and recycled without loss of activity. From an industrial standpoint, these studies are attractive since the cost and environmental impact of the process (E-factor) can be further lowered.[19]

Results and Discussion

The optimized reaction conditions for the formation of benzimidazoles **2a**−**p**, 2-aminobenzimidazoles **4a**−***l***, 2-aminobenzothiazoles **6a**−**j**, and benzoxazoles **8a**−**n** via intramolecular cross-coupling reactions are presented in Table 1. Both *o*-iodoaryl and *o*-bromoaryl derivatives readily underwent cyclization to afford the heterocyclic compounds in high yield. In contrast, *o*-chloroaryl derivatives were less reactive providing the target molecules in <28% yield.

TABLE 1. Optimization of the Reaction Conditions



entry	substrate	X	time(h)	conversion(%)[e]
1[a]		H	24	nr
		Cl	24	nr
		Br	6	>99
		I	3	>99
2[b]		H	24	nr
		Cl	24	nr
		Br	24	78
		I	7	98
3[c]		H	24	nr
		Cl	24	28
		Br	10	>99
		I	3	>99
4[d]		H	24	nr
		Cl	24	nr
		Br	16	>99
		I	7	>99

[a]Substrate (0.5 mmol), CuO nanoparticles (5 mol %), and KOH (1 mmol) were stirred at 110 °C in DMSO (1 mL) under air. [b]Substarte (0.5 mmol), CuO nanoparticles (5 mol %), and KOH (0.75 mmol) were stirred at 110 °C in DMSO (1 mL) under air. [c]Substrate (0.5 mmol), CuO nanoparticles (2.5 mol %), and K_2CO_3 (0.25 mmol) were stirred at 80 °C in DMSO (1 mL) under air. [d]Substrate (0.5 mmol), CuO nanoparticles (5 mol %), and K_2CO_3 (0.75 mmol) were stirred at 110 °C in DMSO (1 mL) under air. [e]Determined by ^{1}H NMR.

Under these conditions, the cyclization via C−H activation did not occur. The cyclization of *o*-haloarylamidines and -guanidines provided the best results in the presence of KOH, while the formation of benzothiazoles and benzoxazoles could be accomplished with K_2CO_3 or Cs_2CO_3. The cyclizations occurred at 80−110 °C in DMSO under air. Solvents such as DMF (15−85%), toluene (5−10%), and dioxane (10−66%) were less effective. Control experiments of these reactions without copper(II) oxide nanoparticles showed no reaction.

Synthesis of Benzimidazoles. *o*-Bromoarylamidines **1a**−**p** were prepared from the readily accessible *o*-bromoanilines and amides in the presence of $POCl_3$ in high yield.[12a] The amidines **1a**−**p** were then investigated for the cyclization reaction under the optimized conditions, using 5 mol % copper(II) oxide nanoparticles at 110 °C in the presence of KOH in DMSO under air (Table 2). The reactions occurred in an intramolecular manner to provide the corresponding substituted benzimidazoles **2a**−**p** in 80−97% yield. The substrates with R^3 = aryl groups **1j**−**p** exhibited enhanced reactivity compared to that having R^3 = alkyl substituents **1a**−**i**. These results clearly suggest that this protocol could be used for the synthesis of the substituted 2-alkyl and 2-aryl benzimidazoles in high yield.

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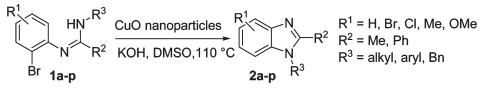
TABLE 2. CuO Nanoparticles-Catalyzed Synthesis of Substituted Benzimidazoles



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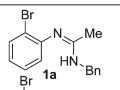
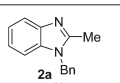
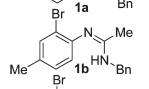
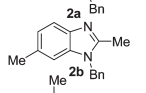
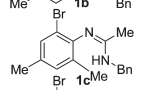
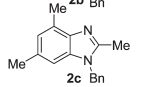
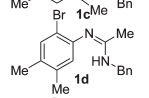
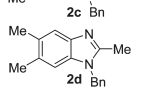
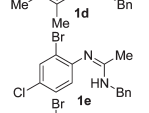
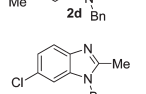
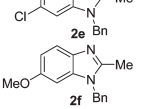
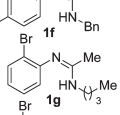
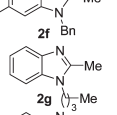
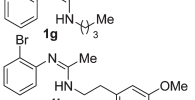
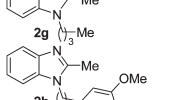
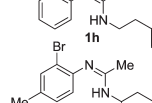
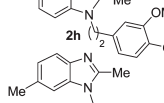
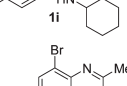
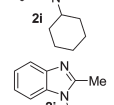
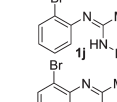
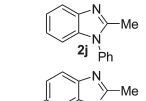
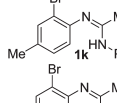
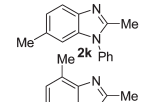
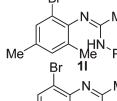
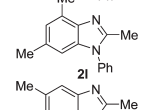
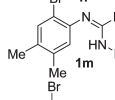
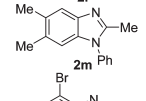
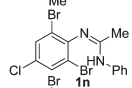
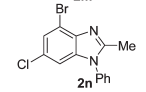
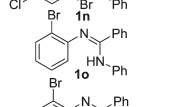
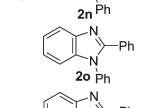
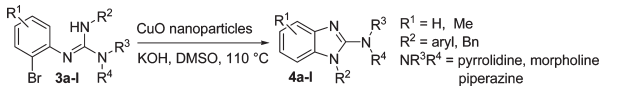
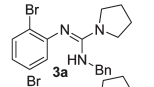
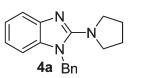
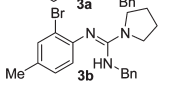
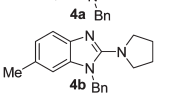
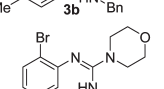
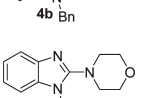
1	 1a	6	 2a	95
2	 1b	8	 2b	93
3	 1c	15	 2c	88[b]
4	 1d	13	 2d	92[b]
5	 1e	4	 2e	92
6	 1f	3	 2f	87
7	 1g	5	 2g	83
8	 1h	6	 2h	82
9	 1i	16	 2i	91[b]
10	 1j	4	 2j	94
11	 1k	5	 2k	95
12	 1l	4	 2l	90
13	 1m	4	 2m	93
14	 1n	4	 2n	80
15	 1o	3	 2o	97
16	 1p	3	 2p	96

[a] *o*-Bromoarylamidine (0.5 mmol), CuO nanoparticles (5 mol %), and KOH (1 mmol) were stirred at 110 °C in DMSO (1 mL) under air. [b] 3 equiv of KOH was used.

TABLE 3. CuO Nanoparticles-Catalyzed Synthesis of Substituted 2-Aminobenzimidazoles



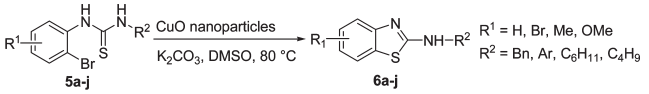
entry	substrate	time(h)	product	yield (%)[a]
1	 3a	24	 4a	73
2	 3b	14	 4b	89
3	 3c	18	 4c	88
4	3d	12	4d	90
5	3e	5	4e	95
6	3f	5	4f	78
7	3g	4	4g	93
8	3h	5	4h	88
9	3i	5	4i	83
10	3j	5	4j	80
11	3k	4	4k	95
12	3l	4	4l	90

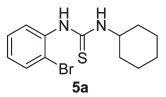
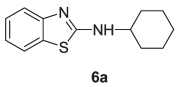
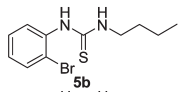
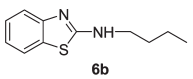
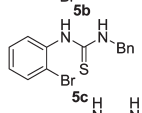
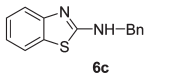
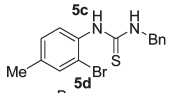
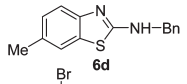
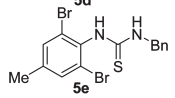
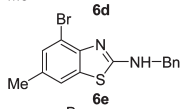
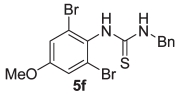
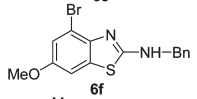
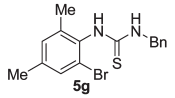
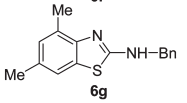
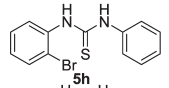
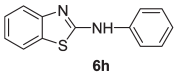
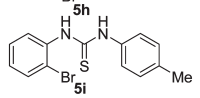
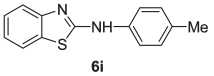
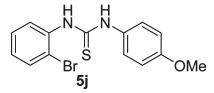
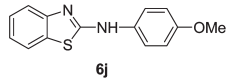
[a] *o*-Bromoarylguanidine (0.5 mmol), CuO nanoparticles (5 mol %), and KOH (0.75 mmol) were stirred at 110 °C in DMSO (1 mL) under air.

Synthesis of 2-Aminobenzimidazoles. Reaction of *o*-haloanilines with isothiocyanate gave thioureas which were treated with amines in the presence of $HgCl_2$ to provide *o*-haloarylguanidines **3a**−***l*** in high yield.[14b] Using the above reaction conditions described for benzimidazole formation, the intramolecular cross-coupling reaction of *o*-bromoarylguanidines **3a**−***l*** was studied (Table 3). The cyclization reactions proceeded efficiently to afford the substituted 2-aminobenzimidazoles **4a**−***l*** in 73−95% yield. Both the substrates having alkyl and aryl substituents were compatible affording the cyclized compounds with 100% selectivity. The substrates **3a**−***l*** with R^2 = aryl substituents exhibited greater reactivity (4−5 h) compared to those containing R^2 = alkyl groups (12−24 h). This could be due to lower pK_a of N*H*-aryl substituents in comparison to N*H*-alkyl moieties.

Synthesis of 2-Aminobenzothiazoles. The preparation of the cyclization precursors, *o*-bromoaryl thioureas **5a**−**j**, was

TABLE 4. CuO Nanoparticles-Catalyzed Synthesis of 2-Aminobenzothiazoles



entry	substrate	time (h)	product	yield (%)[a]
1	 5a	10	 6a	90
2	 5b	10	 6b	97
3	 5c	10	 6c	98
4	 5d	10	 6d	98
5	 5e	14	 6e	85
6	 5f	14	 6f	80
7	 5g	10	 6g	82
8	 5h	8	 6h	37
9	 5i	8	 6i	34
10	 5j	8	 6j	27

[a] *o*-Bromoarylthiourea (0.5 mmol), CuO nanoparticles (2.5 mol %), and K_2CO_3 (0.25 mmol) were stirred at 80 °C in DMSO (1 mL) under air.

accomplished from *o*-bromoaniline and isothiocynate in high yield. The intramolecular cyclization reactions of the substituted *o*-bromoaryl thioureas **5a**−**j** were pursued at 80 °C in the presence of K_2CO_3 in DMSO under air (Table 4). The cross-coupling reactions occurred readily to afford the corresponding substituted 2-aminobenzothiazoles. The substrates **5a**−**g** having R^2 = alkyl groups proceeded well to give the cyclized products **6a**−**g** selectively in 82−98% yield. In contrast, the substrates **5h**−**j** containing R^2 = aryl groups were not selective affording the desired cyclized products **6h**−**j** in 27−37% yield.[20] These reaction conditions were further examined for the cyclization of *o*-bromophenyl benzothioamide (Scheme 1). However, both

SCHEME 1. Cyclization Reaction of *N*-(2-Bromophenyl)benzothioamide

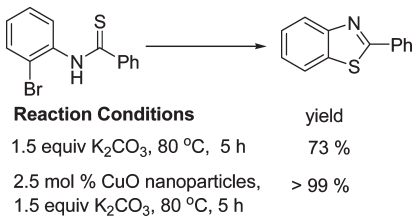
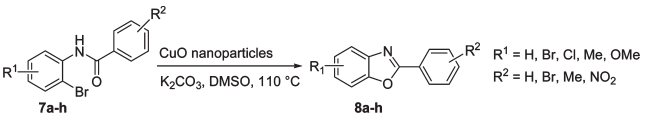


TABLE 5. CuO Nanoparticles-Catalyzed Synthesis of 2-Arylbenzoxazoles



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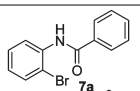
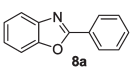
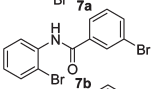
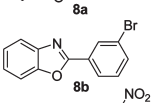
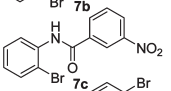
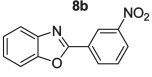
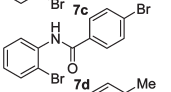
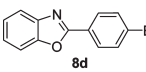
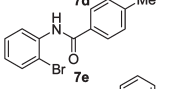
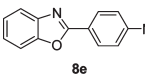
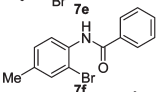
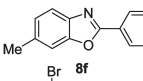
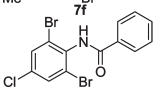
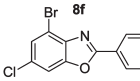
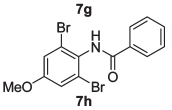
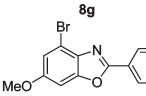
1	 7a	16	 8a	95
2	 7b	24	 8b	79
3	 7c	26	 8c	60
4	 7d	27	 8d	71
5	 7e	16	 8e	92
6	 7f	30	 8f	61
7	 7g	12	 8g	91
8	 7h	16	 8h	89

[a] *o*-Bromoanilide (1 mmol), CuO nanoparticles (5 mol %), and K_2CO_3 (1.5 mmol) were stirred at 110 °C in DMSO (1 mL) under air.

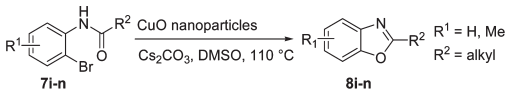
the blank reaction as well as the reaction with copper(II) oxide exhibited the cyclization to afford the 2-phenylbenzothiazole in 73% and >99% yield, respectively.[21]

Synthesis of Benzoxazoles. The substituted *o*-haloanilides **7a**−**o** were prepared from the readily available *o*-haloanilines and acid chlorides. The cyclization reactions of *o*-haloanilides **7a**−**o** were studied at 110 °C in the presence of either K_2CO_3 or Cs_2CO_3 in DMSO under air (Tables 5 and 6). The reactions proceeded efficiently to afford the substituted benzoxazoles in high yield. *N*-(*o*-Bromophenyl)benzamides **7a**−**e** having 3-Br, 3-NO_2, 4-Br, and 4-Me substituents underwent reactions with 60−92% yield. Under these conditions, *o*-bromoanilides **7f**−**h** substituted with Br, Cl, OMe,

(20) The substrates undergo decomposition to give 2-bromoaniline as a byproduct.

(21) (a) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. *Org. Lett.* **2008**, *10*, 5147. (b) Gurupadaiah, B. M.; Jayachandran, E.; Kumar, B. S.; Nagappa, A. N.; Nargund, L. V. G. *Indian J. Heterocycl. Chem.* **1998**, *7*, 213. (c) Kashiyama, E.; Hutchinson, I.; Chua, M. S.; Stinson, S. F.; Phillips, L. R.; Kaur, G.; Sausville, E. A.; Bradshaw, T. D.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **1999**, *42*, 4172. (d) Boger, D. L. *J. Org. Chem.* **1978**, *43*, 2296. (e) Ben-Alloum, A.; Bakkas, S.; Soufiaoui, M. *Tetrahedron Lett.* **1997**, *38*, 6395. (f) Bowman, W. R.; Heaney, H.; Smith, P. H. G. *Tetrahedron Lett.* **1982**, *23*, 5093. (g) Ma, H. C.; Jiang, X. Z. *Synlett* **2008**, 1335.

TABLE 6. CuO Nanoparticles-Catalyzed Synthesis of 2-Alkylbenzoxazoles



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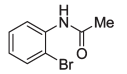
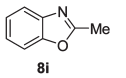
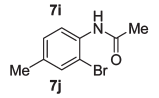
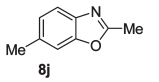
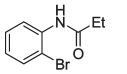
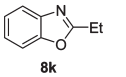
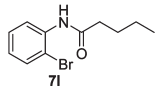
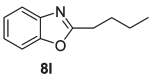
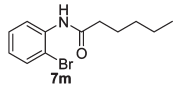
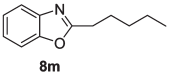
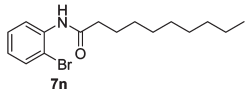
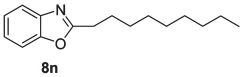
1	 7i	15	 8i	79
2	 7j	21	 8j	67
3	 7k	15	 8k	82
4	 7l	16	 8l	81
5	 7m	16	 8m	80
6	 7n	16	 8n	84

[a] *o*-Bromoanilide (1 mmol), CuO nanoparticles (5 mol %), and Cs_2CO_3 (1.5 mmol) were stirred at 110 °C in DMSO (1 mL) under air.

and Me groups cyclized with 61−91% yield. Similarly, *N*-(*o*-bromophenyl)alkylamides **7i**−**n** underwent cyclization to afford the corresponding benzoxazoles in 67−84% yield. These results clearly reveal that the present method is general and can be used for the synthesis of substituted 2-aryl- and 2-alkylbenzoxazoles in high yield.

Mechanism. To reveal the leaching of the catalyst, the copper(II) oxide nanoparticles were stirred at the reaction temperature (110 °C) for 10 h in the presence of K_2CO_3 in DMSO. The solution was then cooled to room temperature and subjected to centrifugation. The particles were recovered and the clear solution was investigated for the cyclization of *o*-bromophenylbenzamide **7a** in the presence of fresh K_2CO_3. No reaction was, however, obtained and the starting *o*-bromophenylbenzamide **7a** was recovered intact. Furthermore, atomic absorption spectroscopy (AAS) showed the amount of copper species present in the clear solution was below the detection limit (<0.25%). These studies suggest that the reaction involves a heterogeneous process and the leaching of the copper(II) oxide nanoparticles has not occurred under these conditions. Thus, the DMSO stabilized copper(II) oxide nanoparticles **a** may undergo reaction with the substrate on their surface to generate intermediate **b** and the positive charge developed could be shared among the copper oxide nanoparticles present on the surface of the cluster (Scheme 2). The intermediate **b** can then transform to intermediate **c** in the presence of base that can complete the catalytic cycle by the reductive elimination of the cross-coupled product.

Recyclability Experiment. The copper(II) oxide nanoparticles can be recovered and recycled (Table 7). After the cyclization of the *o*-bromophenylbenzamide **7a**, the reaction mixture was treated with ethyl acetate and water. The copper(II) oxide nanoparticles were collected by centrifugation and washed successively with water and acetone. After drying under vacuum, the catalyst was reused for the cyclization of fresh *o*-bromophenylbenzamide **7a**. This process was repeated for five runs and the reactions took place efficiently to afford the cross-coupled product **8a** with 97% conversion and >98% catalyst recoverability. The TEM images and powder X-ray diffraction peaks of the fresh and recovered copper(II) oxide nanoparticles were found to be similar, which suggests that the nanoparticles do not undergo significant changes during the recycling process (see the Supporting Information).[22,23]

SCHEME 2. Proposed Catalytic Cycle for Intramolecular Cyclization Reactions

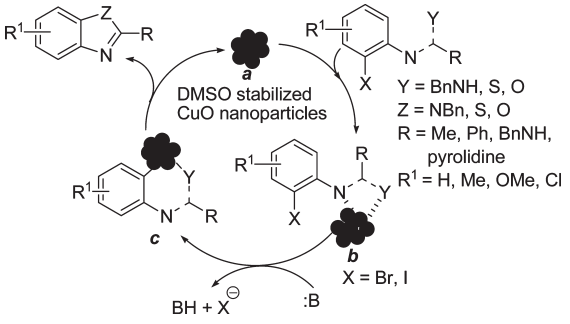
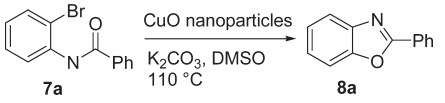


TABLE 7. Recyclability of CuO Nanoparticles



run	catalyst recoverability (%)	product conversion(%)[a,b]
1	>99	100
2[c]	>99	100
3[c]	99	>99
4[c]	98	99
5[c]	98	97

[a] Substrate **7a** (2.5 mmol), CuO nanoparticles (5 mol %), and K_2CO_3 (3.75 mmol) were stirred at 110 °C in DMSO (2.5 mL) under air. [b] Determined by ^1H NMR. [c] Recovered used.

Conclusions

The synthesis of substituted benzimidazoles, 2-aminobenzimidazoles, 2-aminobenzothiazoles, and benzoxazoles is described using copper(II) oxide nanoparticles under ligand-free conditions. The reactions are simple, general, and efficient and the catalyst can be recovered and recycled without loss of activity and selectivity. It is a clean technological process and a wide range of substrates can undergo reactions in high yield.

Experimental Section

General Procedure for the Synthesis of 2-Aryl- and Alkylbenzimidazoles. *o*-Bromoarylamidine (0.5 mmol), CuO nanoparticles (5 mol %, 2 mg), and KOH (1 mmol, 56 mg) were stirred at

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110 °C in DMSO (1 mL) for the appropriate time (Table 2). The progress of the reaction was monitored by TLC, using ethyl acetate and hexane as eluent. The reaction mixtures were then cooled to room temperature and diluted with ethyl acetate (20 mL). The organic layer was washed successively with brine (1 × 5 mL) and water (3 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography, using ethyl acetate and hexane as eluent.

1-Benzyl-2-methyl-1*H*-benzo[*d*]imidazole (2a):[23a]**.** analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f 0.28; yellow solid; yield 95%; mp 67 °C (lit.[23b] mp 68−69 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 1H), 7.32−7.19 (m, 6H), 7.05 (d, J = 8.0 Hz, 2H), 5.31 (s, 2H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 142.8, 136.0, 135.6, 129.1, 128.0, 126.4, 122.4, 122.1, 119.2, 109.5, 47.2, 14.1; FT-IR (KBr) 3060, 2929, 1655, 1618, 1518, 1454, 1404, 1355, 1330, 1286, 1251, 1143, 1029 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.14; H, 6.31; N, 12.55.

General Procedure for the Synthesis of 2-Aminobenzimidazoles. *o*-Bromoarylguanidine (0.5 mmol), CuO nanoparticles (5 mol %, 2 mg), and KOH (0.75 mmol, 42 mg) were stirred at 110 °C in DMSO (1 mL) for the appropriate time (Table 3). The progress of the reaction was monitored by TLC, using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and treated with ethyl acetate (25 mL). The organic layer was washed successively with brine (1 × 5 mL) and water (3 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography, using ethyl acetate and hexane as eluent.

1-(Phenylmethyl)-2-(1-pyrrolidinyl)-1*H*-benzo[*d*]imidazole (4a):. analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f 0.42; yellow solid; yield 73%; mp 133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 1H), 7.32−7.27 (m, 3H), 7.16−7.12 (m, 2H), 7.02−6.95 (m, 3H), 5.27 (s, 2H), 3.54 (s, 4H), 1.91 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 142.5, 137.1, 136.3, 129.0, 127.6, 125.9, 121.9, 120.1, 116.7, 108.4, 50.6, 47.9, 25.8; FT-IR (neat) 3027, 2958, 2924, 2868, 1606, 1594, 1552, 1484, 1455, 1406, 1361, 1349, 1285, 1008 cm^{-1}. Anal. Calcd for $C_{18}H_{19}N_3$: C, 77.95; H, 6.90; N, 15.15. Found: C, 78.13, H, 6.87; N, 15.00.

General Procedure for the Synthesis of 2-Aminobenzothiazole. *N*-(2-Bromoaryl)thiourea (0.5 mmol), CuO nanoparticles (2.5 mol %, 1 mg), and K_2CO_3 (0.25 mmol, 34.5 mg) were stirred at 80 °C in DMSO (1 mL) for the appropriate time (Table 4). The progress of the reaction was monitored by TLC, using ethyl acetate and hexane as eluent. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). The organic layer was successively washed with brine (1 × 5 mL) and water (3 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography, using ethyl acetate and hexane as eluent.

***N*-Cyclohexylbenzo[*d*]thiazol-2-amine (6a):**[15d]**.** analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f 0.43; yellow liquid; yield 90%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.55 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.25 (dt, J = 1.2 Hz, 7.2 Hz, 1H), 7.04 (dt, J = 1.2 Hz, 7.6 Hz, 1H), 5.39 (s, 1H), 3.54 (s, 1H), 2.11 (d, J = 3.2 Hz, 2H), 1.80−1.61 (m, 4H), 1.45−1.13 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 152.5, 130.3, 126.0, 121.3, 120.9, 118.6, 54.8, 33.4, 25.6, 24.9; FT-IR (neat) 2927, 2851, 1596, 1544, 1440, 1251, 1033 cm^{-1}. Anal. Calcd for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06; S, 13.80. Found: C, 67.30; H, 6.91; N, 12.09; S, 13.70.

General Procedure for the Synthesis of Benzoxazoles. *o*-Haloanilide (1 mmol), CuO nanoparticles (5 mol %, 4 mg), and K_2CO_3 (1.5 mmol, 207 mg) were stirred at 110 °C in DMSO (1 mL) for the appropriate time (Tables 5 and 6). The progress of the reaction was monitored by TLC, using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (20 mL). The organic layer was washed successively with brine (1 × 5 mL) and water (2 × 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography, using ethyl acetate and hexane as eluent.

2-Phenylbenzoxazole (8a):[16c]**.** analytical TLC on silica gel, 1:20 ethyl acetate/hexane R_f 0.47; white solid; yield 95%; mp 101 °C (lit.[16c] mp 101−102 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26−8.24 (m, 2H), 7.77−7.75 (m, 1H), 7.58−7.56 (m, 1H), 7.53−7.49 (m, 3H), 7.35−7.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.2, 150.9, 142.2, 131.7, 129.1, 127.8, 127.3, 125.3, 124.7, 120.2, 110.8; FT-IR (KBr) 3060, 2961, 1616, 1552, 1472, 1447, 1344, 1318, 1241, 1196, 1052, 1022 cm^{-1}. Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 80.12; H, 4.59; N, 7.08.

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Supporting Information Available: X-ray diffraction analysis and TEM micrographs of fresh and recovered CuO nanoparticles, characterization data of **2b**−**p**, **4p**−***l***, **6b**−**j**, and **8b**−**n**, and NMR spectra (^{1}H and ^{13}C) of **2a**−**p**, **4a**−***l***, **6a**−**j**, and **8a**−**n**. This material is available free of charge via the Internet at http://pubs.acs.org.