Synthesis of benzoxazoles via an iron-catalyzed \( \text{C–N/C–O cross-coupling} \) reaction†

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An eco-friendly and efficient method has been developed for the synthesis of 2-arylbenzoxazoles via a domino iron-catalyzed \( \text{C–N/C–O cross-coupling} \) reaction. Some of the issues typically encountered during the synthesis of 2-arylbenzazoles in the presence of palladium and copper catalysts, including poor substrate scope and long reaction times have been addressed using this newly developed iron-catalyzed method.

2-Arylbenzoxazoles are an important class of structures in natural products, and pharmaceuticals and has shown a wide range of biological activities, such as antitumor, antiviral, and antimicrobial activities. In particular, they show a marvellous efficacy in the treatment of Duchenne muscular dystrophy (DMD) which is one of the most common of the muscular dystrophies that is caused by a mutation in the gene \( \text{DMD} \) located on humans on the \( \text{X} \) chromosome (Xp21).

Numerous methods have been reported to synthesise this motif, one of the common methods is transition-metal-catalyzed (like \( \text{Pd, Ni, Cu, Mn} \) etc.) cross-coupling from pre-existing benzoxazoles with aryl halide or arylboronic acid. And another method is the classic one employing a cyclocondensation approach between an aminophenol and either a carboxylic acid or benzaldehyde (Scheme 1, path a). In 2004, Frank Glorius’ group reported a domino copper-catalyzed \( \text{C–N and C–O cross-coupling} \) for the conversion of primary amides into benzoxazoles (Scheme 1, path b) which is a new reaction type for the synthesis of benzoxazoles. Bunch et al. apply this domino reaction in the synthesis of planar heterocycles in 2014. In addition the cyclization of \( \sigma \)-halobenzenamides to benzoxazoles has been reported several times. Nevertheless, some limitations in the reported methods need to be overcome, such as the use of palladium complexes and narrow substrate range.

In the last few years, there has been a significant increase in the number of reports pertaining to the development of iron-catalyzed reactions in organic synthesis, where iron has shown several significant advantages over other metals, such as being more abundant, commercially inexpensive, environmentally friendly and drug safety. Compared with palladium and copper, the use of iron is particularly suitable for reactions involving the preparation of therapeutic agents for human consumption. With this in mind, it was envisaged that an new method should be developed for the synthesis of benzoxazoles via an iron-catalyzed domino \( \text{C–N/C–O cross-coupling} \) reaction.

The reaction of benzamide (1a) with 1-bromo-2-iodobenzene was used as model transformation to identify the optimum reaction conditions by screening a variety of different iron salts, bases, ligands and solvents (Table 1). Several iron salts were screened in this reaction, including \( \text{FeCl}_3, \text{FeCl}_2 \cdot 4\text{H}_2\text{O}, \text{FeSO}_4 \cdot 7\text{H}_2\text{O}, \text{Fe(acac)}_3, \text{Fe}_2\text{O}_3, \text{Fe}_3\text{O}_4, \text{Fe}_3\text{O}_4(\text{nano}), \text{Fe}_2\text{O}_3(\text{nano}), \text{Fe}_2(\text{SO}_4)_3 \) and \( \text{Fe(NO}_3)_3 \cdot 9\text{H}_2\text{O}, \text{Fe}_3\text{O}_4 \). Fe_3O_4 was found to give the best results with the desired product 3a being formed in a yield of 15% while most of the iron salt have no effect on the reaction (Table 1, entries 1–10). Then, several other bases, including \( \text{LiO}_2\text{Bu}, \text{Na}_2\text{CO}_3, \text{NaOAc}, \text{KOH} \) and \( \text{K}_2\text{CO}_3 \) were also evaluated under the same conditions using \( \text{Fe}_3\text{O}_4 \), but all of them failed to provided the desired product 3a except \( \text{K}_2\text{CO}_3 \) with a yield of 37% (Table 1, entries 11–15). When the reaction was stirred for 24 h at 110 °C in the presence of 20% mol of \( \text{Fe}_3\text{O}_4 \), 20% mol \( \text{N}_2\text{N}_2\text{dimethylethanediamine} \) (DMEDA) and 1 equiv. of \( \text{K}_2\text{CO}_3 \) in PhMe under nitrogen, \( \text{N}(\text{2-bromophenyl)benzamide} \) was obtained as an intermediate which could be converted to the final product with a yield of 87% if extend the reaction time from 24 h to 48 h (Table 1, entries 15, 16). Several ligands were also screened in the model reaction, and the results revealed that the

![Scheme 1](image-url)
nature of the ligand has a dramatic impact on the yield of the reaction. For example, the use of DMEDA gave 2-phenylbenz[d]oxazole in 85% yield, whereas 1,10-phenanthroline, dipyridyl and L-proline provided no product (Table 1, entries 16–19). The reaction was conducted in DMSO, DMF and PhMe2 respectively and none of them provided a much higher yield of the desired product than toluene (Table 1, entries 20–22). Control experiments was taken in the absence of Fe2O3, no product was obtained (Table 1, entry 23). In view of the fact that the trace metals in catalytic, as is well-known, sometime could play an important role in the reaction, high-purity Fe2O3 (99.999%) and K2CO3 (99.999%) were applied in the reaction (Table 1, entry 24). The product was formed in a yield of 86% which was similar with the one of the entry 16.

Table 1  Optimization of reaction conditions

| Entry | Iron salt | Ligand | Base | Solvent | Yield (%) |
|-------|-----------|--------|------|---------|-----------|
| 1     | FeCl3     | DMEDA  | KO’Bu| PhMe    | Trace     |
| 2     | FeCl2·4H2O| DMEDA  | KO’Bu| PhMe    | Trace     |
| 3     | FeSO4·7H2O| DMEDA  | KO’Bu| PhMe    | 0         |
| 4     | Fe(acac)3 | DMEDA  | KO’Bu| PhMe    | 0         |
| 5     | Fe3O4     | DMEDA  | KO’Bu| PhMe    | 0         |
| 6     | Fe3O4(nano)| DMEDA | KO’Bu| PhMe    | 0         |
| 7     | Fe2O3     | DMEDA  | KO’Bu| PhMe    | 0         |
| 8     | Fe2O3(nano)| DMEDA | KO’Bu| PhMe    | 0         |
| 9     | Fe2(SO4)3 | DMEDA  | KO’Bu| PhMe    | 0         |
| 10    | Fe(NO3)3·9H2O| DMEDA | KO’Bu| PhMe    | 0         |
| 11    | Fe3O4     | DMEDA  | LidO’Bu| PhMe    | 0         |
| 12    | Fe3O4     | DMEDA  | Na2CO3| PhMe    | 0         |
| 13    | Fe3O4     | DMEDA  | NaOAc | PhMe    | 0         |
| 14    | Fe3O4     | DMEDA  | KOH   | PhMe    | 0         |
| 15    | Fe3O4     | DMEDA  | K2CO3 | PhMe    | 37        |
| 16    | Fe3O4     | DMEDA  | K2CO3 | (48 h)  | PhMe 87   |
| 17    | Fe3O4     | Phen   | K2CO3| PhMe    | Trace     |
| 18    | Fe3O4     | L-Proline| K2CO3| PhMe    | 0         |
| 19    | Fe3O4     | Dpy    | K2CO3| PhMe    | 0         |
| 20    | Fe3O4     | DMEDA  | K2CO3| DMSO    | 0         |
| 21    | Fe3O4     | DMEDA  | K2CO3| DMF     | 0         |
| 22    | Fe3O4     | DMEDA  | K2CO3| PhMe2   | 0         |
| 23    | —         | DMEDA  | K2CO3| PhMe    | 0         |
| 24    | Fe3O4     | DMEDA  | K2CO3| PhMe    | 86        |
| 25    | Fe3O4     | DMEDA  | K2CO3| PhMe    | 58        |

a Reaction conditions: benzamides (0.5 mmol), 1-bromo-2-iodobenzene (1.5 eq.), iron salt (20% mol), base (1 eq.), ligand (20%) were added to a solvent (2 mL) and react at 110 °C for 48 h under N2. Isolated yield based on 1a after silica gel chromatography. b Fe2O3 and K2CO3 were applied in purity of 99.999% from alfa. d with Fe2O3 in a dosage of 10 mmol%.

nature of the ligand has a dramatic impact on the yield of the reaction. For example, the use of DMEDA gave 2-phenylbenz[d]oxazole in 85% yield, whereas 1,10-phenanthroline, dipyridyl and L-proline provided no product (Table 1, entries 16–19). The reaction was conducted in DMSO, DMF and PhMe2 respectively and none of them provided a much higher yield of the desired product than toluene (Table 1, entries 20–22). Control experiments was taken in the absence of Fe2O3, no product was obtained (Table 1, entry 23). In view of the fact that the trace metals in catalytic, as is well-known, sometime could play an important role in the reaction, high-purity Fe2O3 (99.999%) and K2CO3 (99.999%) were applied in the reaction (Table 1, entry 24). The product was formed in a yield of 86% which was similar with the one of the entry 16.

Table 2  Reagent scope of reaction

| Reaction conditions: 1a (0.5 mmol), o-dihalo substrate (1.5 eq.), Fe2O3 (20% mol), K2CO3 (1 eq.), DMEDA (20%) were added to PhMe (2 mL) and react at 110 °C for 48 h under N2. | Yield (%) |
|------------------------------------------------|-----------|
| 3a | X=Br, R1=H, R2=H | Y=87% |
| 3b | X=Br, R1=H, R2=Cl | Y=75% |
| 3c | X=Br, R1=Cl, R2=Me | Y=62% |
| 3d | X=Br, R1=H, R2=Cl | Y=56% |
| 3e | X=Br, R1=H, R2=Me | Y=80% |
| 3f | X=Br, R1=H, R2=Cl | Y=85% |
| 3g | X=Br, R1=H, R2=Me, R3=H | Y=70% |
| 3h | X=Br, R1=Me, R2=Me, R3=Cl | Y=65% |
| 3i | X=Br, R1=Me, R2=Me, R3=Cl | Y=65% |
| 3j | X=Br, R1=Me, R2=Me, R3=Cl | Y=50% |
| 3k | X=Br, R1=H, R2=Cl, R3=Cl | Y=50% |
| 3l | X=Br, R1=H, R2=Cl, R3=Cl | Y=35% |
| 3m | X=Br, R1=Me, R2=Cl, R3=Cl | Y=50% |
| 3n | X=Br, R1=Me, R2=Cl, R3=Cl | Y=54% |
| 3o | X=Br, R1=Cl, R2=Me, R3=Cl | Y=35% |
| 3p | X=Br, R1=Cl, R2=Me, R3=Cl | Y=15% |
| 3q | X=Br, R1=Cl, R2=Me, R3=Cl | Y=0% |
At last, the dosage of Fe₂O₃ was reduced to 10 mmol%, but only 58% yield was obtained (Table 1, entry 26). Taken together, the results of these screening experiments revealed that the optimal conditions for the reaction were Fe₂O₃ (20 mol%), DMEDA (20 mol%) and K₂CO₃ [1 eq.] in toluene at 110 °C for 48 h.

It is noteworthy that the intermediate product 4a was formed under the optimized conditions via the C–N cross coupling reaction of benzamide (1a) with 1-bromo-2-iodobenzene (2). So a possible pathway of the reaction was proposed as shown in Scheme 2.

With the optimized reaction conditions in hand, we proceeded to investigate the substrate scope of the reaction using a variety of different 1,2-dihalobenzene substrates and aryl formamide (Table 2). Benzamide containing electron poor (3d–f, 3l), electron-neutral (3a–c, 3k), and electron-rich (3g–j, 3m–n) substituents were all obtained in moderate to excellent yields. But some functional groups are intolerated in the reaction, like amino (3p) and nitro (3q).

Based on the results observed in the current study and Goldberg reaction, we have proposed a reaction mechanism for this transformation, which is shown in Scheme 3. The initial transmetalation of benzamide with Fe₂O₃L in the presence of K₂CO₃ would give rise to the iron(m) species A. Complex A would then undergo an oxidative addition reaction with 1-bromo-2-iodobenzene to give the iron(v) species B, which would undergo a reductive elimination reaction to give iron(m) species C with the concomitant formation of a C–N bond. Followed the tautomerism of intermediate C to D, the intermediate iron(m) species E was formed in the presence of K₂CO₃, which would undergo another oxidative addition reaction to afford iron(v) species F. Compound 3a would then be obtained via a reductive elimination reaction from iron(v) species F.

In summary, we have demonstrated that the cheap and environmental friendly catalyst system composed of Fe₂O₃ and ligand DMEDA is highly effective for the synthesis of 2-arylbenzoxazoles. The new catalyzed system can be effective for both C–N coupling and C–O coupling.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (a) S. Tzanopoulou, M. Sagnou, M. Paravatou-Petsotas, E. Gourni, G. Loudos, S. Xanthopoulos, D. Lafka, H. Kiaris, A. Varvarigou, I. C. Pirmellas, M. Papadopoulos and M. Pelecanou, *J. Med. Chem.*, 2010, 53, 4633–4641; (b) M. C. V. Zandt, M. L. Jones, D. E. Gunn, L. S. Geraci, J. H. Jones, D. R. Sawicki, J. Sredy, J. L. Jacot, A. T. DiCiocco, T. Petrove, A. Mitschler and A. D. Podjarny, *J. Med. Chem.*, 2005, 48, 3141–3152; (c) L. Katsu, *J. Am. Chem. Soc.*, 1953, 75, 712–714; (d) D. K. Dalvie, A. S. Kalgutkar, S. C. Khosasteh-Bakht, R. S. Obach and J. P. O'Donnell, *Chem. Res. Toxicol.*, 2002, 15, 269; (e) H. Z. Boeini and K. H. Najafabadi, *Eur. J. Org. Chem.*, 2009, 4926–4929.

2 D. R. Chancellor, K. E. Davies, O. D. Moor, C. R. Dorgan, P. D. Johnson, A. G. Lambert, D. Lawrence, C. Lecci, C. Maillol, P. J. Middleton, G. Nugent, S. D. Poignant, A. C. Potter, P. D. Price, R. J. Pye, R. Storer, J. M. Tinsley, R. V. Well, R. Vickers, J. Vile, F. J. Wilkes, F. X. Wilson, S. P. Wren and G. M. Wynne, *J. Med. Chem.*, 2011, 54, 3241–3250.

3 (a) M. R. Kumar, K. Park and S. Lee, *Adv. Synth. Catal.*, 2010, 352, 3255–3266; (b) A. M. Hamdy, N. Eleya, H. H. Mohammed, T. Patonay, A. Spannenberg and P. Langer, *Tetrahedron*, 2013, 69, 2081–2086; (c) F. Shibahara, E. Yamaguchi and T. Murai, *Chem. Commun.*, 2010, 46, 2471–2473; (d) J. Huang, J. Chan, Y. Chen, C. J. Borths, K. D. Baucom, R. D. Larsen and M. M. Faul, *J. Am. Chem. Soc.*, 2010, 132, 3674–3675; (e) R. S. Sánchez and F. A. Zhuravlev, *J. Am. Chem. Soc.*, 2007, 129, 5824–5825; (f) S. Ranjit and X.-G. Liu, *Chem.–Eur. J.*, 2011, 17, 1105–1108.

4 (a) T. Yamamoto, K. Muto, M. Komiyama, J. Canivet, J. Yamaguchi and K. Itami, *Chem.–Eur. J.*, 2011, 17, 10113–10122; (b) J. Canivet, J. Yamaguchi, I. Ban and K. Itami, *Org. Lett.*, 2009, 11, 1733–1736; (c) H. Hachiya, K. Hirano, T. Satoh and M. Miura, *ChemCatChem*, 2010, 2, 140–1406.

5 (a) H.-Q. Do and O. Daugulis, *J. Am. Chem. Soc.*, 2007, 129, 12404–12405; (b) W. Zhang, Q.-L. Zeng, X.-M. Zhang, Y.-J. Tian, Y. Yue, Y.-J. Guo and Z.-H. Wang, *J. Org. Chem.*, 2011, 76, 4741–4745; (c) W.-Y. Hu, P.-P. Wang and S.-L. Zhang, *Synthesis*, 2015, 47, 42–48; (d) F.-Z. Yang, Z.-Q. Xu, Z. Wang, Z.-K. Yu and R. Wang, *Chem.–Eur. J.*, 2011, 17, 6321–6325.

6 S. K. Guchhait, M. Kashyap and S. Saraf, *Synthesis*, 2010, 1166–1170.

7 (a) Y. Wang, K. Sarris, D. R. Sauer and S. W. Djuric, *Tetrahedron Lett.*, 2006, 47, 4827–4826; (b) C. O. Kangani,
D. E. Kelley and B. W. Day, Tetrahedron Lett., 2006, 47, 6497–6499.

8 (a) Y. Riadi, R. Mamouni, R. Azzalou, M. E. Haddad, S. Routier and G. Guillaumet, Tetrahedron Lett., 2011, 52, 3492–3495; (b) S. Banerjee, S. Payra, A. Saha and G. Sereda, Tetrahedron Lett., 2014, 55, 5515–5520; (c) Y.-X. Chen, L.-F. Qian, W. Zhang and B. Han, Angew. Chem., Int. Ed., 2008, 47, 9330–9333; (d) L. Tang, X.-F. Guo, Y. Yang, Z.-G. Zha and Z.-Y. Wang, Chem. Commun., 2014, 50, 6145–6148; (e) A. K. Nezhad and F. Panahi, ACS Catal., 2014, 4, 1686–1692; (f) K. Osowska and O. S. Miljanic, J. Am. Chem. Soc., 2011, 133, 724–727.

9 G. Altenhoff and F. Glorius, Adv. Synth. Catal., 2004, 346, 1661–1664.

10 C. S. Demmer, J. C. Hansen, J. Kehler and L. Bunch, Adv. Synth. Catal., 2014, 356, 1047–1055.

11 (a) D. Xue and Y.-Q. Long, J. Org. Chem., 2014, 79, 4727–4734; (b) Q.-C. Xu, Z.-N. Li and H.-Y. Chen, Chin. J. Chem., 2011, 29, 925–932.

12 (a) J.-Y. Lu, X.-Y. Gong, H.-J. Yang and H. Fu, Chem. Commun., 2010, 46, 4172–4174; (b) P. Saha, M. Ashif Ali, P. Ghosh and T. Punniyamurthy, Org. Biomol. Chem., 2010, 8, 5692–5699; (c) N. Khatun, S. Guin, S. K. Rout and B. K. Patel, RSC Adv., 2014, 4, 10770–10778; (d) R. J. Perry and B. D. Wilson, J. Org. Chem., 1992, 57, 6351–6354; (e) G. Evindar and R. A. Batey, J. Org. Chem., 2006, 71, 1802–1808; (f) P. Saha, T. Ramana, N. Purkait, M. A. Ali, R. Paul and T. Punniyamurthy, J. Org. Chem., 2009, 74, 8719–8725; (g) Y.-T. Park, C. H. Jung and K.-W. Kim, J. Org. Chem., 1999, 64, 8546–8556; (h) J. Bonnamour and C. Bolm, Org. Lett., 2008, 10, 2665–2667.

13 (a) C. Bolm, J. Legros, J. L. Paih and L. Zani, Chem. Rev., 2004, 104, 6217–6254; (b) D. Damodara, R. Arundhathi and P. R. Likhar, Catal. Sci. Technol., 2013, 3, 797–802; (c) O. Bistri, A. Correa and C. Bolm, Angew. Chem., 2008, 120, 596–598; (d) C. L. Sun, B. J. Li and Z. J. Shi, Chem. Rev., 2011, 111, 1293–1314; (e) H. B. Wang, L. Wang, J. S. Shang, X. Li, H. Y. Wang, J. Gui and A. W. Lei, Chem. Commun., 2012, 48, 76–78; (f) K. Gopalaiah, Chem. Rev., 2013, 113, 3248–3296; (g) I. Bauer and H.-J. Knolker, Chem. Rev., 2015, 115, 3170–3387.

14 (a) S. L. Buchwald and C. Bolm, Angew. Chem., Int. Ed., 2009, 48, 5586; (b) Z. Gonda, G. L. Tornai and Z. Novak, Chem. –Eur. J., 2010, 16, 11822.

15 (a) A. Klapars, X.-H. Huang and S. L. Buchwald, J. Am. Chem. Soc., 2002, 124, 7421–7428; (b) E. R. Strieter, D. G. Blackmond and S. L. Buchwald, J. Am. Chem. Soc., 2005, 127, 4120–4121.