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Iron-Catalyzed Intramolecular *O*-Arylation: Synthesis of 2-Aryl Benzoxazoles

Julien Bonnamour and Carsten Bolm*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, D-52056 Aachen, Germany

carsten.bolm@oc.rwth-aachen.de

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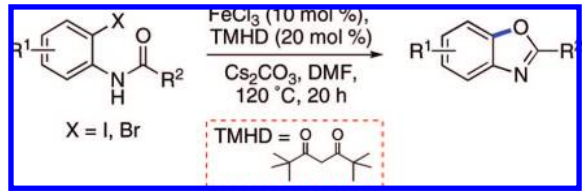
ABSTRACT



A practical iron-catalyzed intramolecular *O*-arylation reaction and its application in the synthesis of benzoxazole derivatives, starting from the readily available 2-haloanilines, is presented. The key cyclization step involves the use of a combination of the cheap and environmentally friendly $FeCl_3$ and 2,2,6,6-tetramethyl-3,5 heptanedione (TMHD) as the catalyst system.

Benzoxazoles are privileged organic compounds of medicinal significance due to their recognized biological and therapeutic activities.[1] As such, these heterocycles constitute key structural motifs in a wide range of natural products and are thus appealing targets in drug synthesis.[2] Commonly, the preparation of 2-substituted benzoxazoles starts from *ortho*-aminophenols, and often it implies the use of either highly toxic reagents or harsh reaction conditions such as those involving strong acids in combination with high temperatures.[3] Some of these drawbacks have recently been overcome by the development of novel and more sustainable processes, which allow the efficient assembly of the target heterocycles under comparatively milder reaction conditions.[4] Among those protocols, copper-catalyzed intramolecular *O*-arylations of *ortho*-haloanilides represent an elegant and straightforward means for the preparation of the benzoxazole ring system.[5]

(1) For examples in medicinal chemistry, see: (a) McKee, M. L.; Kerwin, S. M. *Bioorg. Med. Chem.* **2008**, *16*, 1775. (b) Oksuzoglu, E.; Tekiner-Gulbas, B.; Alper, S.; Temiz-Arpaci, O.; Ertan, T.; Yildiz, I.; Diril, N.; Sener-Aki, E.; Yalcin, I. *J. Enzyme Inhib. Med. Chem.* **2008**, *23*, 37. (c) Oksuzoglu, E.; Temiz-Arpaci, O.; Tekiner-Gulbas, B.; Eroglu, H.; Sen, G.; Alper, S.; Yildiz, I.; Diril, N.; Aki-Sener, E.; Yalcin, I. *Med. Chem. Res.* **2007**, *16*, 1. (d) Potashman, M. H.; Bready, J.; Coxon, A.; DeMelfi, T. M., Jr.; DiPietro, L.; Doerr, N.; Elbaum, D.; Estrada, J.; Gallant, P.; Germain, J.; Gu, Y.; Harmange, J.-C.; Kaufman, S. A.; Kendall, R.; Kim, J. L.; Kumar, G. N.; Long, A. M.; Neervannan, S.; Patel, V. F.; Polverino, A.; Rose, P.; Van der Plas, S.; Whittington, D.; Zanon, R.; Zhao, H. *J. Med. Chem.* **2007**, *50*, 4351. (e) Huang, S.-T.; Hsei, I-J.; Chen, C. *Bioorg. Med. Chem.* **2006**, *14*, 6106.

(2) For example: (a) Easmon, J.; Purstinger, G.; Thies, K.-S.; Heinisch, G.; Hofmann, J. *J. Med. Chem.* **2006**, *49*, 6343. (b) Sun, L.-Q.; Chen, J.; Cruce, M.; Deskus, J. A.; Epperson, J. R.; Takaki, K.; Johnson, G.; Iben, L.; Malhe, C. D.; Ryan, E.; Xu, C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3799. (c) Kumar, D.; Jacob, M. R.; Reynolds, M. B.; Kerwin, S. M. *Bioorg. Med. Chem.* **2002**, *10*, 3997.

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(4) Selected examples: (a) Sezen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607. (b) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35. (c) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589. (d) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (e) Downer-Riley, N. K.; Jackson, Y. A. *Tetrahedron* **2007**, *61*, 10276.

(5) (a) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal.* **2004**, *346*, 1661. (b) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802. (c) Barbero, N.; Carril, M.; SanMartin, R.; Domínguez, E. *Tetrahedron* **2007**, *63*, 10425. (d) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452.

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Despite the recent findings of various iron-catalyzed organic transformations,[6] the challenging field of carbon−heteroatom bond formations has remained largely undeveloped.[7] Along these lines, we have recently reported novel and practical C−N, C−O, and C−S cross-couplings of aryl halides with nitrogen,[8] oxygen,[9] and sulfur nucleophiles,[10] respectively, utilizing catalyst systems comprised of $FeCl_3$ in combination with appropriately chosen ligands. More specifically, *N*- and *S*-arylations efficiently proceeded in the presence of catalytic amounts of $FeCl_3$ and *N*,*N*′-dimethylethylendiamine (DMEDA), whereas *O*-arylations required the use of a combination of $FeCl_3$ and 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD). In connection with these encouraging results, we report herein an iron-catalyzed intramolecular *O*-arylation reaction, which yields synthetically valuable 2-substituted benzoxazoles.

N-(2-Bromophenyl)benzamide (**1a**), which can easily be synthesized by benzoylation of commercially available 2-bromoaniline, was selected as a model substrate for the optimization of the reaction conditions. Taking into account the observations made in the intermolecular *O*-arylations,[9] a reagent combination of $FeCl_3$, TMHD, Cs_2CO_3, and DMF was tested (Table 1, entry 1). To our delight, benzamide **1a** cyclized smoothly at 135 °C to give benzoxazole **2a** in 98% yield. Noteworthy was the fact that in this case the bromo derivative reacted so well, whereas the intermolecular coupling processes required the use of the more reactive iodoarenes. There, bromo derivatives reacted slowly, needing prolonged reaction times to ensure acceptable yields.[9] A reaction performed in the absence of $FeCl_3$/TMHD afforded **2a** in only 42% yield, suggesting that in the initial experiment both an iron-catalyzed cyclization as well as a nucleophilic substitution led to the high yield of **2a**. Consequently, the subsequent reactions were carried out at lower temperatures to minimize the annulation *via* aromatic substitution.[11] Thus, at 120 °C benzoxazole **2a** was obtained in 88% yield, and the blank experiment (without the iron catalyst) confirmed that those results corresponded predominantly to the iron-catalyzed arylation reaction (Table 1, entry 2). At lower temperatures, the yield of **2a** significantly dropped (entries 3−5).

Table 1. Iron-Catalyzed *O*-Arylations of Amide **1a**[a]

1a **2a**

entry	base	solvent	temp (°C)	**2a**[b] (%)
1	Cs_2CO_3	DMF	135	98 (42)
2	Cs_2CO_3	DMF	120	88 (traces)
3	Cs_2CO_3	DMF	110	66 (0)
4	Cs_2CO_3	DMF	80	22 (0)
5	Cs_2CO_3	DMF	60	0 (0)
6	K_3PO_4	DMF	120	56
7	K_2CO_3	DMF	120	54
8	NaO*t*-Bu	DMF	120	13
9	none	DMF	120	0
10	Cs_2CO_3	dioxane	120	72
11	Cs_2CO_3	DME	120	40
12	Cs_2CO_3	toluene	120	0
13	Cs_2CO_3	CH_3CN	120	65

[a] Reaction conditions: **1a** (1 equiv), $FeCl_3$ (0.1 equiv), TMHD (0.2 equiv), base (2.0 equiv), solvent (1 mL/mmol of **1a**), 20 h. [b] Yield of product after chromatography; in parentheses, results from experiments performed in the absence of $FeCl_3$/TMHD.

Another set of experiments revealed the crucial role of the base and the solvent. Thus, use of Cs_2CO_3 led to the best results, and other bases such as K_3PO_4, K_2CO_3 and NaO*t*-Bu (Table 1, entries 6−8) furnished the target benzoxazole **2a** in lower yields. In the absence of the base no product was obtained (entry 9). Also the use of solvents other than DMF resulted in lower yields of **2a** (entries 10−13).

Table 2. Influence of the Nature of the Catalyst in the Intramolecular Cyclization of **1a** to give Benzoxazole **2a**[a]

entry	iron source	ligand	**2a** (%)[b]
1	$FeCl_3$	TMHD	88
2	none	TMHD	0
3	$FeCl_3$	none	0
4	$FeCl_3$	DMEDA	25
5	$FeCl_3$	*N*,*N*′-dimethylglycine	77
6	Fe_2O_3	TMHD	75
7	$FeCl_3{\cdot}6H_2O$	TMHD	85
8	$FeBr_2$	TMHD	80
9	$Fe(OAc)_2$	TMHD	86
10	$Fe(ClO_4)_2$	TMHD	75

[a] Reaction conditions: **1a** (1 equiv), [Fe] (0.10 equiv), ligand (0.20 equiv), Cs_2CO_3 (2.0 equiv), DMF (1 mL/mmol of **1a**), 120 °C, 20 h. [b] Yield of isolated product after chromatography.

Next, the effect of the catalyst composition on the benzoxazole formation with Cs_2CO_3 in DMF at 120 °C was studied (Table 2). Reactions performed in the absence

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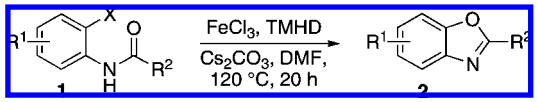
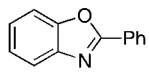
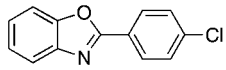
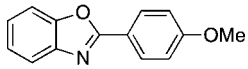
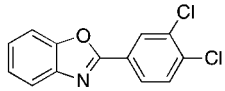
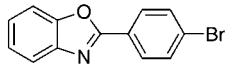
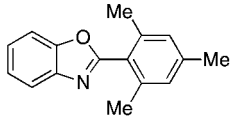
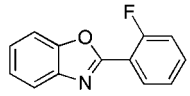
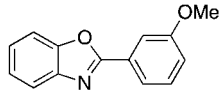
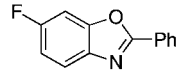
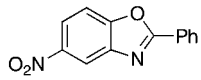
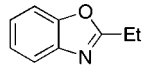
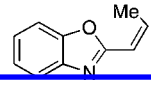
(11) For examples of benzoxazole formations that proceeded *via* either aryne intermediates or aromatic substitutions, see: (a) Hrutford, B. F.; Bunnett, J. F. *J. Am. Chem. Soc.* **1958**, *80*, 2021. (b) El-Sheikh, M. I.; Marks, A.; Biehl, E. R. *J. Org. Chem.* **1981**, *46*, 3256. (c) Reavill, D. R.; Richardson, S. K. *Synth. Commun.* **1990**, *20*, 1423. (d) Inukai, Y.; Sonoda, T.; Kobayashi, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2657.

Table 3. Iron-Catalyzed Synthesis of Benzoxazole Derivatives **2**[a]



entry	X of **1**	benzoxazole		yield (%)[b]
1	Br		**2a**	88
2	I			92
3	Cl			--
4	Br		**2b**	75
5	Br		**2c**	96
6	Br		**2d**	65
7	Br		**2e**	92
8	Br		**2f**	16[c]
9	Br		**2g**	48[c]
10	I			22
11	Br		**2h**	82
12	Br		**2i**	89
13	Br		**2j**	72
14	Br		**2k**	--
15	Br		**2l**	--
16	I			--

[a] **1** (1 equiv), $FeCl_3$ (0.10 equiv), TMHD (0.20 equiv), Cs_2CO_3 (2.0 equiv), DMF (1 mL/mmol of **1**), 20 h. [b] Yield of isolated product after chromatography. [c] Reaction time: 72 h.

of either $FeCl_3$ or the ligand confirmed that the presence of both was required for amide cyclization (entries 2 and 3). The combination of the iron salt with TMHD proved superior to those involving $FeCl_3$ together with DMEDA or *N,N′*-dimethylglycine (entries 1 vs 4, and 5). Furthermore, the process proved compatible with the use of other iron(III) sources such as Fe_2O_3 and $FeCl_3{\cdot}6H_2O$ (entries 6 and 7). Iron in the oxidation state +2 was also applicable as shown by the successful use of $FeBr_2$, $Fe(OAc)_2$ and $Fe(ClO_4)_2$ (entries 8−10). In all cases benzoxazole **2a** was obtained in good to high yields. Balancing all results it was concluded that the optimal conditions for the intramolecular *O*-arylation involved the use of $FeCl_3$, TMHD, and Cs_2CO_3 in DMF at 120 °C.

Finally, the scope of the iron-catalyzed intramolecular *O*-arylation was explored. As summarized in Table 3, several *ortho*-halobenzamides provided the corresponding 2-substituted benzoxazole derivatives in good to excellent yields. Also the iodo analogue of **1a** cyclized well affording benzoxazole **2a** in high yield (entry 2). Conversely, the chloro derivative proved unreactive under those conditions (entry 3). The nature of the substituent R^2 directly linked to the carbonyl moiety was of major importance. Thus, various substrates bearing differently substituted aromatic motifs at that position were converted to the desired benzoxazoles **2** in satisfactory to high yields (entries 1−13). In contrast, halobenzamides with aliphatic or vinylic substituents R^2 did not cyclize at all (entries 14−16). Steric hindrance hampered the reaction and hence benzoxazoles **2f** and **2g** were obtained in comparatively lower yields, despite performing the cyclization for longer reaction times or using the iodo-arene as electrophilic coupling partner. Aromatic amides bearing additional substituents (R^1) on the bromoarene portion of the molecule furnished the corresponding benzoxazoles in good yields (entry 12 and 13).

In summary, we have developed an efficient iron-catalyzed intramolecular *O*-arylation, which represents a practical and straightforward approach toward 2-aryl substituted benzoxazole derivatives. The key cyclization step involves the use of cheap, easy-to-handle and environmentally benign $FeCl_3$ in combination with TMHD. The use of a simple iron salt as catalyst renders the protocol suitable for large-scale synthesis, providing a valuable synthetic tool for industrial applications.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet http://pubs.acs.org.

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