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Copper-catalysed intramolecular O-arylation of aryl chlorides and bromides: a straightforward approach to benzo[*d*]oxazoles in water

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Dedicated to Professor Vicente Gotor on the occasion of his 60th birthday

Abstract—A general, efficient and more sustainable protocol for the copper-catalysed intramolecular O-arylation of *o*′-haloanilides leading to the benzo[*d*]oxazole core is reported. Remarkably, the optimised conditions allowed for the use of inexpensive and easily available aryl chlorides as arylating agents. Moreover, all reactions were carried out employing exclusively water as the solvent, rendering the methodology presented herein highly valuable from both environmental and economic points of view.

1. Introduction

Since the first reports by Ullmann on copper-catalysed arylation reactions, the scope and impact of such useful methodology have notably increased over the last century. However, despite its well-known utility for the construction of carbon–heteroatom linkages, the copper-catalysed arylation of diverse nucleophiles is largely restricted to the use of aryl iodides or bromides as the electrophilic counterparts, and its extension to the corresponding aryl chlorides remains a limitation.[1] Nowadays, the use of aryl chlorides to effect such transformations is considered highly attractive due to their greater availability and lower cost, but it is also regarded as a challenge given their poorer tendency to undergo oxidative addition to transition metal complexes. Hence, only a few examples of copper-catalysed N- and O-arylation processes employing aryl chlorides have been reported thus far,[2,3] for which this field remains largely unexplored. It must be pointed out that, given the important applications of copper-catalysed arylation reactions as a tool for the synthesis of biologically active heterocycles,[4,5] the design of a methodology allowing for the use of aryl chlorides as starting materials would be of great interest for industry.

Benzo[*d*]oxazole derivatives are among those heterocycles of particular interest for their recognised utility in the treatment of stroke, depression, immune diseases[6] and cerebral ischaemia,[6,7] as well as for their known activity as antibacterial, antiviral,[8] antimicrobial,[9] oestrogenic modulator[10] and anticancer agents.[11] The classical preparation of benzo[*d*]oxazole compounds involved reacting 2-aminophenols with either aldehydes[9,12] or carboxylic acid derivatives[13,14] under oxidative conditions. Additionally, straightforward cyclisation of 2′-haloanilides by means of intramolecular O-arylation processes to furnish the corresponding benzo[*d*]oxazole has also been reported.[15] Nevertheless, the aforementioned procedures implied the use of toxic and hazardous organic solvents[15] and, in some cases, rather harsh reaction conditions.[9,12–15b] Given the importance of such heterocycles for their therapeutic properties, the design of an environmentally and economically more advantageous methodology for their preparation is imperative, which would be of high practical value for their application in the pharmaceutical industry.

In this context and in connection with the ongoing research developed in our group dealing with copper-catalysed carbon–heteroatom bond formation in the presence of water,[16] we envisaged the application of this sustainable methodology to the synthesis of the benzo[*d*]oxazole framework. As shown in Scheme 1, we propose the synthesis of benzo[*d*]oxazoles **2** through an intramolecular O-arylation reaction, starting from the corresponding 2′-bromoanilide **1b** and using the copper-catalysed aqueous protocol developed in our research group, which consists of the use of catalytic amounts of a copper salt and a 1,2-diamine derivative, acting both as the ligand and as the base, in such a benign solvent as water.[16] Furthermore, we present herein a general methodology, which allows for the use of inexpensive and easily

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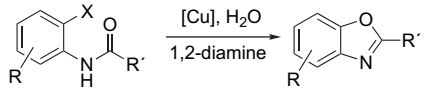
available aryl chloride derivatives as starting materials to effect the projected copper-catalysed O-arylation reaction.



1 X= Cl, Br **2**

Scheme 1. Proposed approach to the synthesis of 2-arylbenzo[*d*]oxazoles **2**.

2. Results and discussion

Thus, in order to optimise the reaction conditions for the target intramolecular O-arylation reaction, 2′-chloro and 2′-bromoanilides **1a** and **b**, respectively, were chosen as model substrates, readily synthesised in one step from the corresponding 2-haloanilines, following known procedures in the literature.[17] Then, based on the excellent results obtained by our research group in previous works,[16a,b] those anilides **1a** and **b** were treated with an aqueous solution of CuI and TMEDA at 120 °C. However, given the moderate conversion observed for both substrates **1a** and **b**, we decided to test the efficiency of several commercially available ligands (Fig. 1) in combination with different copper(I) or copper(II) salts. The main results of such optimisation process are shown in Table 1.

Of the different ligands assayed, shown in Figure 1, the more basic TMEDA provided the best results for the synthesis of target benzo[*d*]oxazole **2a**, starting from both 2′-chloro and 2′-bromoanilides **1a** and **b** (Table 1, entries 1–9). Interestingly, when combined with TMEDA, a good number of copper salts furnished target benzo[*d*]oxazole **2a** in fairly similar yields, regardless of the oxidation state of copper in those salts (Table 1, entries 1, 2 and 6–12), but CuCl proved generally superior starting from both **1a** and **b** (Table 1, entries 8 and 9), as well as CuBr when **1a** was the starting material (Table 1, entry 7). The combination of some of those diamine ligands shown in Figure 1 or ethylene glycol[18] in catalytic amounts together with a water-soluble inorganic base was additionally tested with negative results (<30% yield), even when TMEDA was used as the ligand (Table 1, entries 14–18). Finally, in order to enhance the homogeneity of the process, aqueous/organic biphasic systems were tested delivering target **2a** in moderate yields, lower than

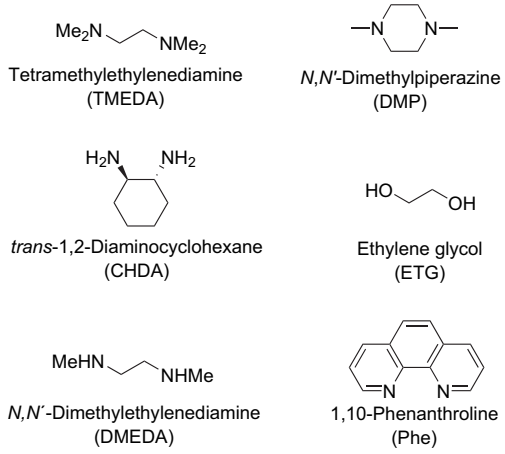
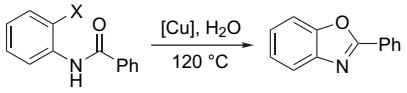


Figure 1. Selected ligands for the optimisation of the reaction conditions.

Table 1. Selected O-arylation assays for the synthesis of **2a**



1a X=Cl
1b X=Br

2a

Entry	X	Cu salt, ligand, base[a]	**2a** (%)[b]
1	Br	CuI, TMEDA	48
2	Cl	CuI, TMEDA	63
3	Br	CuI, DMEDA	9
4	Br	CuI, CHDA	Traces
5	Br	CuCl, DMP	14
6	Br	CuBr, TMEDA	56
7	Cl	CuBr, TMEDA	72
8	Br	CuCl, TMEDA	67
9	Cl	CuCl, TMEDA	73
10	Br	$Cu(OTf)_2$, TMEDA	59
11	Br	$Cu(ClO_4)_2 \cdot 6H_2O$, TMEDA	59
12	Br	$Cu(OAC)_2$, TMEDA	62
13	Cl	$Cu(OAC)_2$, TMEDA	15
14[c]	Br	CuI, Phe, Cs_2CO_3	30
15[d]	Br	CuI, ETG, Cs_2CO_3	4
16[d]	Br	CuI, TMEDA, K_3PO_4	9
17[e]	Br	CuCl, TMEDA, NaO^{t}Bu	18
18[e]	Br	CuCl, TMEDA, NaOH	24
19[f]	Br	CuCl, TMEDA	45
20[g]	Br	CuCl, TMEDA	39

[a] Cu(I) salt (8.5 mol %), 12 mol % of Cu(II) salt and 3.5 equiv of ligand when no additional base was used. All reactions were run in water (12 mL/mmol **1**) at 120 °C, unless otherwise stated.
[b] Isolated yields.
[c] Ligand (10 mol %), 1.5 equiv of base.
[d] Ligand (20 mol %), 2.0 equiv of base.
[e] Ligand (20 mol %), 1.5 equiv of base.
[f] A mixture of H_2O/EtOH (v/v=9/1) was used as the solvent.
[g] A mixture of H_2O/DMF (v/v=9/1) was used as the solvent.

those obtained when the same reaction was performed in neat water, for which it could be suggested that homogeneity is not a requirement for the success of the reaction (Table 1, entries 19 and 20).

Once CuCl and TMEDA were chosen as the optimal copper source and amine derivative, respectively, other aspects of the reaction conditions were explored. Hence, the number of equivalents of TMEDA, initially set to 3.5 based on previous research in our group,[16] was subsequently varied from 1.5 to 4.5 equiv, but poorer yields compared to those obtained when using 3.5 equiv were observed in all cases. Moreover, the outcome of the reaction appeared to be clearly affected by temperature. Indeed, when the O-arylation reaction of 2′-bromoanilide **1b** was run at 100 °C instead of 120 °C, a substantial decrease in the yield from 67% (Table 1, entry 8) to 50% was observed.

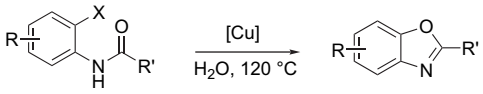
The effect of dilution was also examined by performing the reaction under both solvent-free and diluted conditions. The solvent-free assays mostly led to dehalogenation along with traces of target benzo[*d*]oxazole **2a**. On the contrary, the use of an increased amount of water (18 mL/mmol **1**) over the optimal value of 12 mL/mmol resulted in a lower yield of **2a**, 43% versus 67% (Table 1, entry 8). Interestingly, despite the increasing number of publications dealing with organic chemistry in aqueous solution, the role of water in these processes remains largely unknown. On one hand,

some authors suggest that hydrophobic effects might be responsible for the improved results observed for the reactions carried out in the presence of water because water-insoluble molecules in an aqueous environment are brought closer and react more efficiently.[19] However, the negative results obtained in our particular case under solvent-free conditions may imply that the increase in the relative concentration of organic compounds is not the only reason for the better results observed in the presence of water. On the other hand, the reaction might take place in the organic–aqueous interface, hypothetically through small portions of dissolved solutes.[19] Since in the system presented herein, the copper catalyst is dissolved in the aqueous phase and the substrate in the organic phase, this second hypothesis seems to be more adequate for the present case.

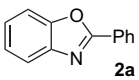
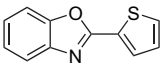
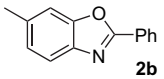
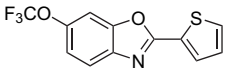
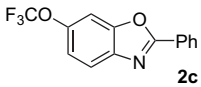
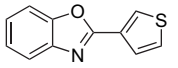
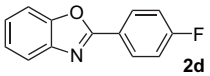
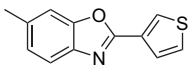
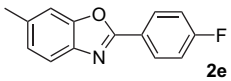
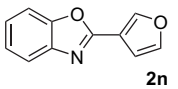
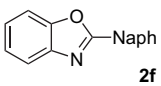
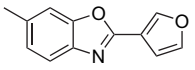
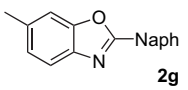
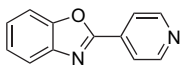
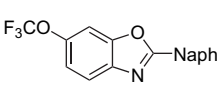
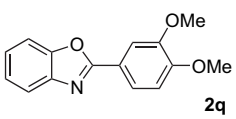
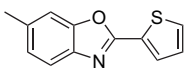
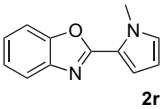
Considering the above issues, it was concluded that the optimal conditions for the preparation of target benzo[*d*]oxazole **2a** involved stirring the corresponding 2′-haloanilide in an aqueous solution of 8.5 mol % of CuCl and 3.5 equiv of TMEDA, starting from either 2′-bromoanilide **1b** or its a priori more challenging 2′-chloro analogue **1a**.

To explore the scope of the optimised reaction conditions, we decided to apply such protocol and slight modifications of it to the O-arylation of a series of 2′-haloanilide

Table 2. Copper-catalysed synthesis of benzo[*d*]oxazole derivatives **2**



1 R' = Ar, HetAr **2**

Entry	X	Method[a]	Product	2 (%)[b]	Entry	X	Method[a]	Product	**2** (%)[b]
1	Cl	A	 **2a**	73	18	Cl	A	 **2j**	52
2	Br	A		67	19	Br	A		52
3	I	B		24	20	I	A		30
4[c]	Cl	B	 **2b**	59	21	Br	A, B	 **2k**	30
5	Br	B		73					
6	Br	A, B	 **2c**	49	22	Cl	B	 **2l**	40
					23	Br	B		59
7[d]	Cl	A	 **2d**	75	24	Cl	A	 **2m**	73
8	Br	B		59	25	Br	A		57
9[d]	Cl	A	 **2e**	53	26	Cl	B	 **2n**	45
10	Br	B		61	27	Br	A		43
11	Cl	B	 **2f**	67	28	Cl	B	 **2o**	60
12	Br	A		72	29	Br	A		47
13	Cl	A	 **2g**	64	30	Cl	B	 **2p**	38
14	Br	B		65					
15	Br	B	 **2h**	57	31[d]	Cl	A	 **2q**	Traces
					32	Br	A		Traces
16	Cl	A	 **2i**	59	33	Br	A, B[c]	 **2r**	0
17	Br	B[c]		54					

[a] Method A: 8.5 mol % CuCl, 3.5 equiv TMEDA, H_2O (12 mL/mmol **1**), 120 °C overnight; Method B: 12 mol % $Cu(OTf)_2$, 3.5 equiv TMEDA, H_2O (12 mL/mmol **1**), 120 °C overnight.
[b] Isolated yields.
[c] $Cu(OAc)_2$ was used instead of $Cu(OTf)_2$.
[d] CuBr was used instead of CuCl.

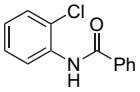
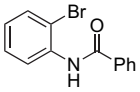
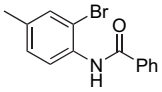
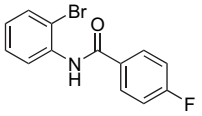
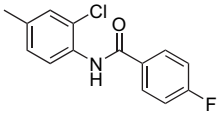
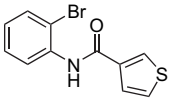
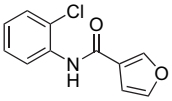
derivatives, readily accessible in one step from commercially available substrates.[17] The so-obtained results are summarised in Table 2.

As shown in Table 2, the presented methodology proved to be efficient for the synthesis of a number of benzo[*d*]oxazoles **2** in moderate to good yields. Regarding the aryl halide moiety, it must be pointed out that the results obtained starting from 2′-chloroanilides were of particular interest, given the lack of a general methodology for the copper-catalysed coupling of aryl chloride derivatives. Indeed, the yields for the O-arylation of 2′-chloroanilide derivatives were comparable, and in some cases clearly higher than those observed when using the corresponding bromo analogues (Table 2, entries 1 and 2; 7 and 8; 24 and 25; 28 and 29). Furthermore, it is remarkable that both 2′-chloro and 2′-bromoanilides afforded surprisingly superior results compared to their iodo analogues (Table 2, entries 1–3 and 18–20), which are known to be the most active coupling partners for copper-catalysed arylation reactions.

Moreover, the electronic nature of the aromatic substituent directly linked to the carbonyl moiety affected the reaction outcome in very different ways. For instance, whereas electron rich aromatic and heteroaromatic rings led in general to lower yields of the corresponding benzo[*d*]oxazole (Table 2, entries 11–32), the presence of a relatively electron withdrawing *p*-fluorophenyl substituent did not affect much and led to similar results to the non-substituted phenyl analogue (Table 2, entries 1–5 and 7–10). Furthermore, despite the tendency of heteroatoms to coordinate with copper and potentially inhibit the reaction, it is remarkable that a broad number of heteroaromatic amides successfully afforded the corresponding benzo[*d*]oxazoles **2** in moderate to good yields (Table 2, entries 16–30), except for the pyrrol derivative, which appeared to be unstable under the optimised reaction conditions leading to decomposition of the substrate (Table 2, entry 33). On the contrary, the presence of substituents, such as methyl or trifluoromethoxy groups, in the aryl halide coupling partner of the substrates had hardly any influence on the arylation process.

The results shown thus far in Table 2 refer to those yields of benzo[*d*]oxazoles **2** obtained under the most effective reaction conditions. Nevertheless, it must be pointed out that during the study of the scope of those conditions, the methodology exhibited a remarkable insensitivity to the choice of the copper salt, which was considered of high practical value and hence, explored. As shown in Table 3, for several substrates, both copper(I) and copper(II) salts proved interchangeable and CuBr or CuCl was replaced by $Cu(OTf)_2$ or $Cu(OAc)_2$ without significant loss in the yields (Table 3, entries 3–17). In this context, the 'equivalence' observed between CuCl and CuBr with $Cu(OTf)_2$ was especially remarkable. Indeed, those copper salts apparently led to similarly active catalysts in combination with TMEDA and water, as it can be inferred from the almost equal yields obtained in some examples using those catalysts (Table 3, entries 3–5 and 12–17). Such freedom to choose the most convenient copper source without significant variations in the final result renders the presented methodology extremely valuable and highly appealing for industry from an economical point of view.

Table 3. Selected O-arylation assays employing different copper sources

Entry	Substrate	Copper[a]	**2** (%)[b]
1		CuCl	**2a** (73)
2		CuBr	**2a** (72)
3		CuCl	**2a** (65)
4		CuBr	**2a** (56)
5		$Cu(OTf)_2$	**2a** (59)
6		$Cu(OAc)_2$	**2a** (62)
7		$Cu(ClO_4)_2$	**2a** (59)
8		CuCl	**2b** (69)
9		$Cu(OTf)_2$	**2b** (73)
10		CuBr	**2d** (57)
11		$Cu(OTf)_2$	**2d** (59)
12		CuBr	**2e** (53)
13		$Cu(OTf)_2$	**2e** (48)
14		CuCl	**2l** (56)
15		$Cu(OTf)_2$	**2l** (59)
16		CuCl	**2n** (40)
17		$Cu(OTf)_2$	**2n** (45)

[a] Cu(I) salt of 8.5 mol % or 12 mol % Cu(II) salt was used, 3.5 equiv of TMEDA, H_2O (12 mL/mmol) at 120 °C overnight.
[b] Isolated yields.

To sum up, we have developed a general, more sustainable methodology for the copper-catalysed intramolecular O-arylation of conveniently substituted 2′-haloanilides to deliver benzo[*d*]oxazoles, a valuable framework with interesting therapeutic properties. In addition, the presented work features a simple and efficient protocol for the copper-catalysed arylation of aryl chlorides, field that remains under-explored in the context of copper catalysis despite the lower cost and greater availability of chlorophenyl derivatives relative to their bromo and iodo analogues. Furthermore, the value of such methodology, which allows for the free choice of the copper salt in combination with a simple diamine derivative, and the use of such a benign and accessible solvent as water render the protocol described herein economically and environmentally advantageous and of remarkable practical value for its industrial application.

3. Experimental section

3.1. General remarks

All reagents and solvents were purchased and used without further purification. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in a Bruker AC-250, AC-300 and AC-500. Chemical shifts are reported in parts per million downfield

(δ) from Me_4Si. IR spectra were recorded on a Perkin–Elmer 1600 FT infrared spectrophotometer and only noteworthy absorptions are listed. Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230–400 mesh ASTM). Drying of organic extracts after the workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a Büchi rotatory evaporator. HRMS were recorded using a Waters GCT Mass spectrometer.

3.2. Typical procedure for the synthesis of 2-arylbenzo[*d*]oxazoles

3.2.1. 2-Phenylbenzo[*d*]oxazole (2a) (Table 2, entries 1–3). A flask (approximate volume: 18 mL) was charged with 2′-chloroanilide **1a** (81.2 mg, 0.35 mmol), CuCl (3.1 mg, 0.031 mmol), TMEDA (0.18 mL, 0.31 mmol) and water (4.1 mL). The flask was sealed with a screw cap and the resulting solution was heated overnight at 120 °C. The product was extracted from the aqueous layer with dichloromethane, dried and concentrated in vacuo. The crude mixture was then purified by flash chromatography (EtOAc/hexane 10/90) to give benzo[*d*]oxazole **2a** (50.3 mg, 73%) as a white solid.

The typical procedure was followed starting from the corresponding 2′-bromoanilide (61.1 mg, 0.22 mmol) and CuCl (2.1 mg, 0.020 mmol) to afford benzo[*d*]oxazole **2a** (28.8 mg, 67%).

The typical procedure was followed starting from the corresponding 2′-iodoanilide (103.3 mg, 0.32 mmol) and $Cu(OTf)_2$ (13.3 mg, 0.037 mmol) to afford benzo[*d*]oxazole **2a** (14.9 mg, 24%). Mp 94–96 °C (AcOEt/hexane) (lit.[15a] 101–102 °C).

3.2.2. 6-Methyl-2-phenylbenzo[*d*]oxazole (2b) (Table 2, entries 4 and 5). The typical procedure was followed starting from the corresponding 2′-chloroanilide (99.2 mg, 0.41 mmol) and $Cu(OAc)_2$ (9.6 mg, 0.048 mmol) to afford benzo[*d*]oxazole **2b** (50.2 mg, 59%) as a white solid.

The typical procedure was followed starting from the corresponding 2′-bromoanilide (98.1 mg, 0.34 mmol) and $Cu(OTf)_2$ (14.8 mg, 0.041 mmol) to afford benzo[*d*]oxazole **2b** (51.9 mg, 73%) as a white solid. Mp 73–76 °C (hexane) (lit.[15a] 93 °C). MS (EI) *m*/*z*: 210 (92, M+1), 209 (100, M), 208 (98), 180 (90), 106 (73), 105 (77), 103 (71), 78 (90), 77 (81). HRMS (EI): calculated for $C_{14}H_{11}NO$, 209.0841; found, 209.0832.

3.2.3. 2-Phenyl-6-(trifluoromethoxy)benzo[*d*]oxazole (2c) (Table 2, entry 6). The typical procedure was followed starting from the corresponding 2′-bromoanilide (98.8 mg, 0.28 mmol) and CuCl (2.4 mg, 0.024 mmol) to afford benzo[*d*]oxazole **2c** (39.9 mg, 49%) as a white solid. Mp 55–58 °C (hexane); IR (film): ν (cm^{-1}) 3061, 1620, 1549, 1479, 1244, 1161; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (d, J=8.9 Hz, 1H), 7.49–7.55 (m, 4H), 7.75 (d, J=8.7 Hz, 1H), 8.23 (dd, J=7.5, 1.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 104.6, 118.3, 120.3, 127.7, 129.0, 131.9 (CH), 120.5 (q, J=257.5 Hz), 126.6, 140.8, 146.4, 150.5, 164.5 (C). MS (EI) *m*/*z*: 280 (M+1, 76), 279 (M, 88), 219 (75), 211 (73), 210 (100), 182 (86), 154 (45) 105 (56), 77 (48). HRMS (EI): calculated for $C_{14}H_8NO_2F_3$, 279.0507; found, 279.0432.

3.2.4. 2-(4-Fluorophenyl)benzo[*d*]oxazole (2d) (Table 2, entries 7 and 8). The typical procedure was followed starting from the corresponding 2′-chloroanilide (100.4 mg, 0.40 mmol) and CuBr (5.1 mg, 0.035 mmol) to afford benzo[*d*]oxazole **2d** (64.8 mg, 75%) as a white solid.

The typical procedure was followed starting from the corresponding 2′-bromoanilide (98.7 mg, 0.34 mmol) and $Cu(OTf)_2$ (14.2 mg, 0.039 mmol) to afford benzo[*d*]oxazole **2d** (42.1 mg, 59%) as a white solid. Mp 92–95 °C (hexane); IR (film): ν 3061, 1608, 1490, 1232, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.14–7.30 (m, 2H), 7.36 (dd, J=6.0, 3.2 Hz, 2H), 7.58 (dd, J=5.7, 3.4 Hz, 1H), 7.77 (dd, J=6.1, 2.8 Hz, 1H), 8.23–8.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 110.6, 116.2 (d, J=22.3 Hz), 120.0, 124.7, 125.1, 129.8 (d, J=8.8 Hz) (CH), 123.5 (d, J=3.0 Hz), 142.1, 150.8, 164.8 (d, J=252.8 Hz), 162.1 (C). MS (EI) *m*/*z*: 214 (M+1, 53), 213 (M, 83), 185 (92), 184 (76), 121 (75), 95 (80), 92 (72), 75 (62), 64 (98), 63 (100). HRMS (EI): calculated for $C_{13}H_8NOF$, 213.0590; found, 213.0591.

3.2.5. 2-(4-Fluorophenyl)-6-methylbenzo[*d*]oxazole (2e) (Table 2, entries 9 and 10). The typical procedure was followed starting from the corresponding 2′-chloroanilide (99.2 mg, 0.38 mmol) and CuBr (4.8 mg, 0.033 mmol) to afford benzo[*d*]oxazole **2e** (45.4 mg, 53%) as a white solid.

The typical procedure was followed starting from the corresponding 2′-bromoanilide (81.9 mg, 0.27 mmol) and $Cu(OTf)_2$ (12.4 mg, 0.034 mmol) to afford benzo[*d*]oxazole **2e** (36.7 mg, 61%) as a white solid. Mp 113–116 °C (hexane); IR (film): ν (cm^{-1}) 1596, 1490, 1215, 1150, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.49 (s, 3H), 7.14–7.21 (m, 3H), 7.35 (s, 1H), 7.62 (d, J=8.1 Hz, 1H), 8.21 (dd, J=8.8, 5.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.8 (CH_3), 110.7, 116.1 (d, J=22.1 Hz), 119.3, 125.9, 129.6 (d, J=8.8 Hz) (CH), 123.6 (d, J=3.2 Hz), 135.5, 139.8, 151.0, 161.6, 164.6 (d, J=252.2 Hz) (C). MS (EI) *m*/*z*: 228 (M+1, 10), 227 (M, 100), 198 (12), 78 (18). HRMS (EI): calculated for $C_{14}H_{10}FNO$, 227.0746; found, 227.0749.

3.2.6. 2-(2-Naphthyl)benzo[*d*]oxazole (2f) (Table 2, entries 11 and 12). The typical procedure was followed starting from the corresponding 2′-chloroanilide (59.8 mg, 0.21 mmol) and $Cu(OTf)_2$ (8.9 mg, 0.024 mmol) to afford benzo[*d*]oxazole **2f** (35.1 mg, 67%) as a white solid.

The typical procedure was followed starting from the corresponding 2′-bromoanilide (100.2 mg, 0.31 mmol) and CuCl (2.7 mg, 0.027 mmol) to afford benzo[*d*]oxazole **2f** (54.6 mg, 72%) as a white solid. Mp 105–108 °C (hexane); IR (film): ν (cm^{-}1) 3049, 1608, 1543, 1443, 1355, 1238, 1179, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.37 (dd, J=5.4, 3.6 Hz, 2H), 7.52–7.58 (m, 2H), 7.61 (dd,

J=6.2, 2.9 Hz, 1H), 7.82 (dd, J=6.4, 2.6 Hz, 1H), 7.84–7.91 (m, 1H), 7.96 (dd, J=8.6, 5.0 Hz, 2H), 8.31 (d, J=8.6 Hz, 1H), 8.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 110.5, 120.0, 123.9, 124.6, 125.1, 126.8, 127.7, 127.8, 128.1, 128.7, 128.9 (CH), 124.3, 132.9, 134.7, 142.2, 150.8, 163.1 (C). MS (EI) *m/z*: 246 (M+1, 8), 245 (M, 100), 244 (11), 69 (11). HRMS (EI): calculated for $C_{17}H_{11}NO$, 245.0841; found, 245.0840.

3.2.7. 6-Methyl-2-(2-naphthyl)benzo[*d*]oxazole (2g) (Table 2, entries 13 and 14). The typical procedure was followed starting from the corresponding 2′-chloroanilide (101.8 mg, 0.34 mmol) and CuCl (3.1 mg, 0.031 mmol) to afford benzo[*d*]oxazole **2g** (57.6 mg, 64%) as a white solid.

The typical procedure was followed starting from the corresponding 2′-bromoanilide (102.0 mg, 0.30 mmol) and $Cu(OTf)_2$ (12.5 mg, 0.034 mmol) to afford benzo[*d*]oxazole **2g** (50.3 mg, 65%) as a white solid. Mp 130–132 °C (hexane); IR (KBr): ν (cm^{-1}) 3249, 3049, 2920, 1649, 1502, 1302, 1043; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.52 (s, 3H), 7.18 (d, J=8.1 Hz, 1H), 7.40 (s, 1H), 7.50–7.61 (m, 2H), 7.67 (d, J=8.1 Hz, 1H), 7.83–7.91 (m, 1H), 7.96 (dd, J=8.9, 5.6 Hz, 2H), 8.29 (dd, J=8.6, 1.6 Hz, 1H), 8.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.8 (CH_3), 110.7, 119.3, 123.8, 125.8, 126.8, 127.6, 127.8, 127.9, 128.7, 128.8 (CH), 124.5, 132.9, 134.6, 135.6, 140.0, 151.1, 162.6 (C). MS (EI) *m/z*: 260 (M+1, 76), 259 (M, 100), 258 (90), 230 (64), 219 (69), 153 (81), 127 (54), 78 (48). HRMS (EI): calculated for $C_{18}H_{13}NO$, 259.0997; found, 259.0994.

3.2.8. 2-(2-Naphthyl)-6-(trifluoromethoxy)benzo[*d*]oxazole (2h) (Table 2, entry 15). The typical procedure was followed starting from the corresponding 2′-bromoanilide (101.3 mg, 0.25 mmol) and $Cu(OTf)_2$ (10.5 mg, 0.029 mmol) to afford benzo[*d*]oxazole **2h** (45.9 mg, 57%) as a white solid. Mp 86–89 °C (hexane); IR (film): ν (cm^{-1}) 1614, 1543, 1361, 1244, 1114, 1038; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25 (d, J=6.5 Hz, 1H), 7.50 (s, 1H), 7.52–7.62 (m, 2H), 7.75 (d, J=8.7 Hz, 1H), 7.80–7.91 (m, 1H), 7.95 (dd, J=8.7, 4.1 Hz, 2H), 8.24 (dd, J=8.6, 1.3 Hz, 1H), 8.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 104.5, 118.3, 120.2, 123.7, 126.9, 127.9, 128.0, 128.3, 128.8, 128.9 (CH), 132.8, 134.8, 140.8, 146.3, 146.4, 150.52, 164.6 (C). MS (EI) *m/z*: 330 (M+1, 8), 329 (M, 100), 260 (33), 127 (4). HRMS (EI): calculated for $C_{18}H_{10}F_3NO_2$, 329.0664; found, 329.0670.

3.2.9. 6-Methyl-2-(2-thienyl)benzo[*d*]oxazole (2i) (Table 2, entries 16 and 17). The typical procedure was followed starting from the corresponding 2′-chloroanilide (100.9 mg, 0.40 mmol) and CuCl (3.4 mg, 0.035 mmol) to afford benzo[*d*]oxazole **2i** (50.6 mg, 59%) as a white solid.

The typical procedure was followed starting from the corresponding 2′-bromoanilide (100.4 mg, 0.34 mmol) and $Cu(OAc)_2$ (8.5 mg, 0.042 mmol) to afford benzo[*d*]oxazole **2i** (39.2 mg, 54%) as a white solid. Mp 66–69 °C (hexane); IR (film): ν (cm^{-1}) 3096, 2920, 1608, 1557, 1485, 1420, 1250, 1050; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.49 (s, 3H), 7.16 (t, J=5.2 Hz, 2H), 7.33 (s, 1H), 7.52 (dd, J=4.9, 1.0 Hz, 1H), 7.59 (d, J=8.1 Hz, 1H), 7.87 (dd, J=3.6, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.75 (CH_3), 110.5, 119.1, 125.9, 128.1, 129.5, 129.8 (CH), 135.5, 139.7, 150.6, 158.5 (C). MS (EI) *m/z*: 216 (M+1, 99), 215 (M, 100), 214 (99), 213 (81), 186 (99), 185 (79), 111 (99), 108 (85), 95 (99), 78 (99), 77 (99), 69 (97), 63 (99), 52 (99), 51 (98). HRMS (EI): calculated for $C_{12}H_9NOS$, 215.0405; found, 215.0409.

3.2.10. 2-(2-Thienyl)benzo[*d*]oxazole (2j) (Table 2, entries 18–20). The typical procedure was followed starting from the corresponding 2′-chloroanilide (99.0 mg, 0.42 mmol) and CuCl (3.7 mg, 0.037 mmol) to afford benzo[*d*]oxazole **2j** (43.5 mg, 52%) as a white solid.

The typical procedure was followed starting from the corresponding 2′-bromoanilide (99.6 mg, 0.35 mmol) and CuCl (3.3 mg, 0.033 mmol) to afford benzo[*d*]oxazole **2j** (36.8 mg, 52%) as a white solid.

The typical procedure was followed starting from the corresponding *o*-iodobenzenamide (103.3 mg, 0.32 mmol) and $Cu(OTf)_2$ (13.3 mg, 0.037 mmol) to afford benzo[*d*]oxazole **2j** (17.9 mg, 30%) as a white solid. Mp 97–99 °C (hexane) (lit.[15a] 81–82 °C).

3.2.11. 2-(2-Thienyl)-6-(trifluoromethoxy)benzo[*d*]oxazole (2k) (Table 2, entry 21). The typical procedure was followed starting from the corresponding 2′-bromoanilide (100.4 mg, 0.27 mmol) and $Cu(OTf)_2$ (11.8 mg, 0.032 mmol) to afford benzo[*d*]oxazole **2k** (23.3 mg, 30%) as a white solid. Mp 73–78 °C (hexane); IR (KBr): ν (cm^{-1}) 3096, 2908, 1614, 1573, 1473, 1255, 1155; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.22 (dd, J=12.7, 8.7 Hz, 2H), 7.46 (s, 1H), 7.59 (d, J=4.9 Hz, 1H), 7.71 (d, J=8.7 Hz, 1H), 7.91 (d, J=8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 104.5, 118.4, 120.0, 128.4, 130.4, 130.8 (CH), 120.5 (q, J=257.5 Hz), 129.0, 140.7, 146.3 (q, J=2.1 Hz), 150.2, 160.4 (C). MS (EI) *m/z*: 286 (M+1, 19), 285 (100), 284 (53), 207 (11), 191 (13). HRMS (EI): calculated for $C_{12}H_6F_3NO_2S$, 285.0071; found, 285.0083.

3.2.12. 2-(3-Thienyl)benzo[*d*]oxazole (2l) (Table 2, entries 22 and 23). The typical procedure was followed starting from the corresponding 2′-chloroanilide (57.6 mg, 0.24 mmol) and $Cu(OTf)_2$ (10.5 mg, 0.029 mmol) to afford benzo[*d*]oxazole **2l** (19.6 mg, 40%) as a white solid.

The typical procedure was followed starting from the corresponding 2′-bromoanilide (99.3 mg, 0.35 mmol) and $Cu(OTf)_2$ (14.6 mg, 0.040 mmol) to afford benzo[*d*]oxazole **2l** (41.9 mg, 59%) as a white solid. Mp 136–139 °C (hexane); IR (film): ν (cm^{-1}) 3084, 2920, 1614, 1572, 1449, 1402, 1243, 1056; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.29–7.40 (m, 2H), 7.44 (dd, J=4.8, 3.0 Hz, 1H), 7.49–7.60 (m, 1H), 7.72–7.77 (m, 1H), 7.79 (dd, J=5.1, 0.6 Hz, 1H), 8.19 (d, J=2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 110.4, 119.8, 124.5, 125.0, 126.6, 127.0, 128.0 (CH), 129.2, 141.9, 150.3, 159.7 (C). MS (EI) *m/z*: 201 (M, 22), 64 (25), 63 (100). HRMS (EI): calculated for $C_{11}H_7NOS$, 201.0248; found, 201.0243.

3.2.13. 6-Methyl-2-(3-thienyl)benzo[*d*]oxazole (2m) (Table 2, entries 24 and 25). The typical procedure was followed starting from the corresponding 2′-chloroanilide

(80.6 mg, 0.32 mmol) and CuCl (2.9 mg, 0.029 mmol) to afford benzo[*d*]oxazole **2m** (50.5 mg, 73%) as a white solid.

The typical procedure was followed starting from the corresponding 2′-bromoanilide (83.5 mg, 0.28 mmol) and CuCl (2.4 mg, 0.024 mmol) to afford benzo[*d*]oxazole **2m** (34.4 mg, 57%) as a white solid. Mp 68–71 °C (hexane); IR (film): ν (cm^{-1}) 3108, 2920, 1614, 1485, 1244; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.48 (s, 3H), 7.14 (d, J=8.1 Hz, 1H), 7.33 (s, 1H), 7.42 (dd, J=4.6, 3.1 Hz, 1H), 7.61 (d, J=8.1 Hz, 1H), 7.77 (d, J=5.0 Hz, 1H), 8.14 (d, J=2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.7 (CH_3), 110.6, 119.1, 125.7, 126.5, 126.8, 127.5 (CH), 129.3, 135.4, 139.6, 150.6, 159.2 (C). MS (EI) *m*/*z*: 216 (M+1, 6), 215 (M, 100), 214 (28), 78 (10). HRMS (EI): calculated for $C_{12}H_9NOS$, 215.0405; found, 215.0411.

3.2.14. 2-(3-Furyl)benzo[*d*]oxazole (2n) (Table 2, entries 26 and 27). The typical procedure was followed starting from the corresponding 2′-chloroanilide (105.7 mg, 0.48 mmol) and $Cu(OTf)_2$ (19.9 mg, 0.055 mmol) to afford benzo[*d*]oxazole **2n** (40.3 mg, 45%) as a white solid.

The typical procedure was followed starting from the corresponding 2′-bromoanilide (106.8 mg, 0.40 mmol) and CuCl (3.6 mg, 0.036 mmol) to afford benzo[*d*]oxazole **2n** (32.3 mg, 43%) as a white solid. Mp 104–107 °C (hexane); IR (film): ν (cm^{-1}) 3108, 1643, 1525, 1449, 1390, 1308, 1238, 1155; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.02 (s, 1H), 7.26–7.34 (m, 2H), 7.51–7.54 (m, 2H), 7.72 (dd, J=5.9, 3.1 Hz, 1H), 8.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 108.9, 110.3, 119.6, 124.5, 124.9, 144.2, 144.3 (CH), 115.3, 141.7, 150.1, 158.2 (C). MS (EI) *m*/*z*: 186 (M+1, 10), 185 (M, 100), 157 (22), 149 (76). HRMS (EI): calculated for $C_{11}H_7NO_2$, 185.0477; found, 185.0466.

3.2.15. 2-(3-Furyl)-6-methylbenzo[*d*]oxazole (2o) (Table 2, entries 28 and 29). The typical procedure was followed starting from the corresponding 2′-chloroanilide (102.5 mg, 0.44 mmol) and $Cu(OTf)_2$ (18.4 mg, 0.051 mmol) to afford benzo[*d*]oxazole **2o** (52.0 mg, 60%) as a white solid.

The typical procedure was followed starting from the corresponding 2′-bromoanilide (98.1 mg, 0.35 mmol) and CuCl (3.2 mg, 0.032 mmol) to afford benzo[*d*]oxazole **2o** (32.7 mg, 47%) as a white solid. Mp 72–75 °C (hexane); IR (film): ν (cm^{-1}) 3108, 1637, 1478, 1249, 1155; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.47 (s, 3H), 8.18 (s, 1H), 7.00 (s, 1H), 7.13 (d, J=8.0 Hz, 1H), 7.31 (s, 1H), 7.53 (s, 1H), 7.58 (d, J=8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.6 (CH_3), 108.8, 110.4, 118.8, 125.6, 143.9, 144.1 (CH), 115.4, 135.2, 139.4, 150.3, 157.7 (C). MS (EI) *m*/*z*: 200 (M+1, 1), 199 (M, 100), 123 (30), 95 (29), 78 (71). HRMS (EI): calculated for $C_{12}H_9NO_2$, 199.0633; found, 199.0631.

3.2.16. 2-(4-Pyridyl)benzo[*d*]oxazole (2p) (Table 2, entry 30). The typical procedure was followed starting from the corresponding 2′-chloroanilide (101.4 mg, 0.44 mmol) and $Cu(OTf)_2$ (17.8 mg, 0.049 mmol). The crude mixture was then purified by flash chromatography (EtOAc/hexane 30/70) to afford benzo[*d*]oxazole **2p** (32.6 mg, 38%) as a white solid. Mp 116–119 °C (hexane); IR (film): ν (cm^{-1}) 1584, 1473, 1408, 1343, 1290; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38–7.44 (m, 2H), 7.61 (dd, J=6.1, 2.1 Hz, 1H), 7.81 (dd, J=5.9, 2.9 Hz, 1H), 8.08 (d, J=4.6 Hz, 2H), 8.82 (d, J=4.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 111.0, 120.8, 121.1, 125.2, 126.4, 150.8 (CH), 125.1, 134.3, 141.7, 160.5 (C). MS (EI) *m*/*z*: 197 (M+1, 61), 196 (M, 100), 195 (60), 169 (34), 168 (54). HRMS (EI): calculated for $C_{12}H_8N_2O$, 196.0637; found, 196.0604.

3.2.17. 2-(3,4-Dimethoxyphenyl)benzo[*d*]oxazole (2q) (Table 2, entries 31 and 32). The typical procedure was followed starting from the corresponding 2′-chloroanilide (197.9 mg, 0.68 mmol) and CuBr (8.8 mg, 0.061 mmol) to afford benzo[*d*]oxazole **2q** (5.7 mg, 3%) as a white solid.

The typical procedure was followed starting from the corresponding 2′-bromoanilide (197.0 mg, 0.59 mmol) and CuCl (5.4 mg, 0.053 mmol) to afford benzo[*d*]oxazole **2q** (9.6 mg, 6%) as a white solid. Mp 105–108 °C (hexane); IR (film): ν (cm^{-1}) 2920, 1602, 1502, 1449, 1249, 1138; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.98 (s, 3H), 4.03 (s, 3H), 7.00 (d, J=8.7 Hz, 1H), 7.34 (dd, J=6.1, 3.1 Hz, 2H), 7.57 (dd, J=6.0, 2.3 Hz, 1H), 7.70–7.81 (m, 2H), 7.87 (dd, J=8.3, 1.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 56.1, 56.2 (OCH_3), 110.1, 110.4, 111.1, 119.6, 121.2, 124.5, 124.7 (CH), 119.8, 142.3, 149.3, 150.7, 152.0, 163.2 (C). MS (EI) *m*/*z*: 256 (M+1, 36), 255 (M, 100), 240 (78), 212 (92), 169 (62). HRMS (EI): calculated for $C_{15}H_{13}NO_3$, 255.0895; found, 255.0884.

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Supplementary data

Typical experimental procedures, including spectroscopic and analytical data for all the new intermediates along with NMR spectra of the new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.08.013.

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