Tetrahedron 64 (2008) 7283–7288

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Copper-catalyzed intramolecular N-arylation of ureas in water: a novel entry to benzoimidazolones

Nekane Barbero, Mónica Carril, Raul SanMartin *, Esther Domínguez *

Kimika Organikoa II Saila, Zientzia eta Teknologia Fakultatea, Euskal Herriko Unibertsitatea, PO Box 644, 48080 Bilbao, Spain

ARTICLE INFO

Article history:
Received 4 April 2008
Received in revised form 9 May 2008
Accepted 15 May 2008
Available online 21 May 2008

Keywords:
Urea
Copper-catalyzed
Water
Benzoimidazolones

ABSTRACT

The copper-catalyzed intramolecular N-arylation of 2-bromoarylureas performed in water leading to the benzo[*d*]imidazolone framework is reported. The scope of the methodology presented herein proved to be broad and afforded a significant number of benzoimidazolones in good to excellent yields. The reported protocol is based on the use of CuI and TMEDA acting both as the ligand and as the base in a water solution, which allows for the easy separation of the catalyst containing aqueous phase from the products by simple extraction. Additionally, the N- versus O-arylation competitive processes are also discussed.

© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

Transition metal-catalyzed carbon–heteroatom bond formation reactions have undoubtedly proved to be a tool of paramount utility and a significant contribution to organic chemistry. Among the few metals that are able to perform such transformations, copper stands out as a convenient alternative to palladium catalysts, since copper salts are often inexpensive and air and moisture stable. While the copper-catalyzed N-arylation of amides and amines has attracted most of the attention in this field,[1] the arylation of other appealing nitrogen nucleophiles such as urea derivatives remains comparatively unexplored, despite this moiety being present in a number of biologically active molecules.[2] In this context, a few examples of copper-catalyzed N-arylation of ureas have been reported thus far but they are mostly limited to the use of aryl iodides as electrophilic counterpart as well as very simple urea compounds as starting material.[3]

Considering our experience in the synthesis of heterocyclic systems by means of copper-catalyzed arylation processes in aqueous medium,[4] we envisaged the application of such methodology to access the benzoimidazolone core through an intramolecular N-arylation of 2-haloarylureas, as a logical extension of our recently reported intramolecular O-arylation leading to benzoxazole derivatives.[5] Moreover, benzoimidazolones constitute the core of a number of biologically relevant structures, including non-nucleoside reverse transcriptase inhibitors of potent antiretroviral activity against HIV strains,[6] potassium channel regulators[7] and orally bio-available inhibitors of respiratory syncytial virus fusion,[8] inter alia.[9]

A search in the literature revealed that most of the methods for the formation of the imidazolone core in benzoimidazolones involved the use of hazardous chemicals such as phosgene, toxic chlorinated solvents or harsh reaction conditions (pressures $\geq$20 atm).[7,9,10] In this context, a few palladium-catalyzed synthesis of the benzoimidazolone core have been reported and have contributed to overcome some of the aforementioned drawbacks. In these examples, the imidazolone ring closure was achieved either by means of an intramolecular N-arylation of 2-haloarylureas[11] or through an amination followed by a condensative cyclization.[12] However, the pursuit of inexpensive and more benign reaction conditions for this transformation, such as the use of copper catalysts in water as the solvent, remains a challenge and an appealing goal. Hence, we present herein a copper-catalyzed intramolecular N-arylation of urea derivatives leading to the benzo[*d*]imidazolone framework, using water as the only solvent.

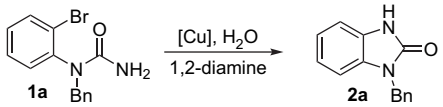
2. Results and discussion

Thus, 1-benzyl-1-(2-bromophenyl)urea **1a**, readily prepared from commercial 2-bromoaniline by benzylation followed by reaction with chlorosulfonyl isocyanate, was chosen as the model substrate to optimize the conditions for the target cyclization leading to benzoimidazolone **2a**. As shown in Table 1, a survey of commercially available copper salts and nitrogen ligands was

* Corresponding authors. Tel.: +34 94 601 54 35; fax: +34 94 601 27 48.
E-mail address: raul.sanmartin@ehu.es (R. SanMartin).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.05.072

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



Entry	Copper source[a]	Base/ligand[b]	**2a** (%)[c]
1	CuCl	CHDA	0
2	CuI	DABCO	0
3	CuI	BHEP	28
4[d]	CuI	BHEP/KO^{t}Bu	17
5	CuI	THEED	tr.
6	CuI	2AP	0
7	CuI	PMDTA	66
8	CuI	TMEDA	87
9	CuCl	TMEDA	71
9	CuBr	TMEDA	67
11	$Cu(OAc)_2 \cdot H_2O$	TMEDA	83
12	$Cu(OTf)_2$	TMEDA	73
13	$Cu(ClO_4)_2 \cdot 6H_2O$	TMEDA	76
14	CuO	TMEDA	14

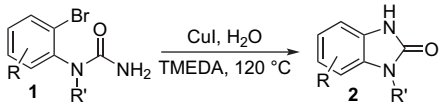
[a] Cu(I) salt (8.5 mol %) or 12 mol % of the Cu(II) salt, and 3.5 equiv of ligand. All reactions were run in water (12 mL/mmol) at 120 °C for 15 h.
[b] CHDA: *trans*-1,2-diaminocyclohexane; DABCO: 1,4-diaza-bicyclo[2.2.2]octane; BHEP: 1,4-bis(2-hydroxyethyl)piperazine; THEED: *N*,*N*,*N*′,*N*′-tetrakis(2-hydroxyethyl)ethylenediamine; 2AP: 2-aminopyridine; PMDTA: *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylene-triamine; TMEDA: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.
[c] Isolated yields.
[d] BHEP (30 mol %) and 2.0 equiv of base were used.

combined along with substrate **1a** and its efficacy to effect the desired intramolecular N-arylation was evaluated. Interestingly, the use of CHDA or DABCO, two standard bidentate ligands in copper catalysis,[3a,4b,13] and aromatic amine ligand 2AP provided negligible results (Table 1, entries 1, 2 and 6). Slightly better yields were obtained on using two ligands incorporating hydroxy units (BHEP and THEED) but those were not improved, even when combined with additional bases (entries 3–5). However, moderate to good yields were achieved when the remaining aliphatic diamine and triamine (TMEDA and PMDTA) were employed (entries 7 and 8). Finally, after comparison of the effect of different Cu(I) and Cu(II) salts, and noticing some interesting similarities (entries 8–13), which suggest common catalytic species,[14] it was decided that the best conditions were those which involved stirring substrate **1a** in the presence of 8.5 mol % of CuI and 3.5 equiv of TMEDA, acting both as the ligand and as the base, in water at 120 °C for 15 h (Table 1, entry 8). In accordance with our previous reports on copper-catalyzed arylations in aqueous media, the proportion of the diamine resulted crucial for the reaction outcome. The use of smaller amounts of TMEDA (1.1 or 2 equiv) provided negligible results, even when combined with other inorganic bases (KOH, Na_2CO_3, K_3PO_4, etc.) probably due to its double role, which has been discussed in the synthesis of benzofuranes.[4a]

Accordingly, a range of *N*1-functionalized 2-bromoarylureas **1b**–**t** were prepared from commercially available 2-bromoanilines by a starting alkylation/arylation step followed by carbamoylation with inexpensive chlorosulfonyl isocyanate. These intermediates **1** were subjected to the above optimized cyclization conditions, affording the corresponding benzoimidazolones **2** in good to excellent yields, as displayed in Table 2. In addition to constituting the first example of a metal-catalyzed N-arylation of ureas in water, it should be pointed out the tolerability of the process to a number of functionalities present in **1**, not only in the bromoarene moiety, but also attached to the N1 position. However, some considerations could be offered to explain the effect of the nature of the substituents on the reaction outcome.

With regard to *N*1-substituent, substrates **1** bearing alkyl groups generally provided better yields than *N*-arylated ones (e.g., Table 2,

Table 2
Copper-catalyzed cyclization to benzoimidazolones **2**[a]



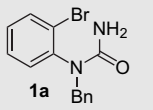
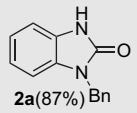
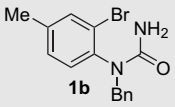
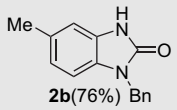
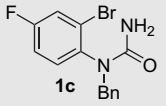
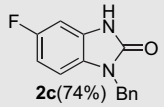
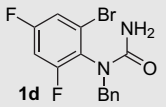
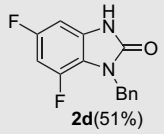
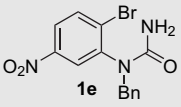
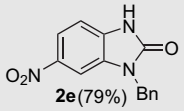
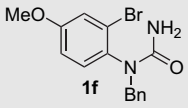
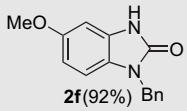
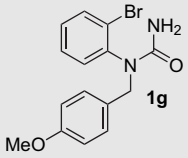
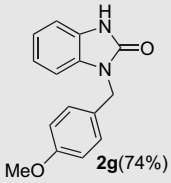
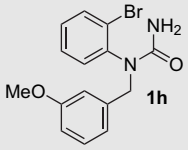
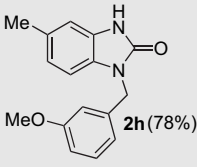
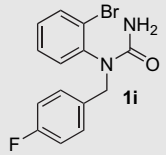
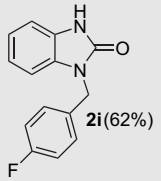
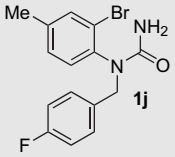
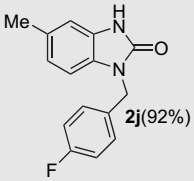
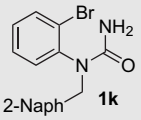
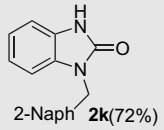
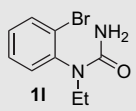
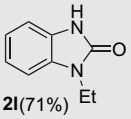
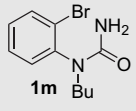
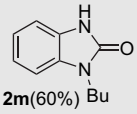
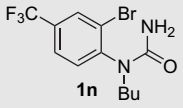
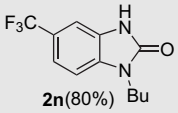
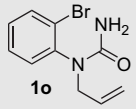
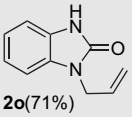
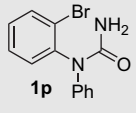
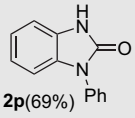
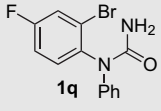
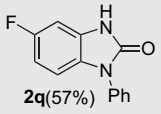
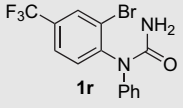
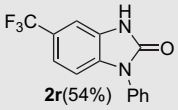
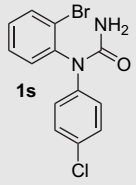
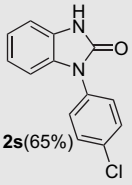
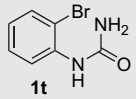
Entry	**1**	**2**[b]
1	 **1a**	 **2a**(87%)
2	 **1b**	 **2b**(76%)
3	 **1c**	 **2c**(74%)
4	 **1d**	 **2d**(51%)
5	 **1e**	 **2e**(79%)
6	 **1f**	 **2f**(92%)
7[c]	 **1g**	 **2g**(74%)
8	 **1h**	 **2h**(78%)
9	 **1i**	 **2i**(62%)
10	 **1j**	 **2j**(92%)
11	 **1k**	 **2k**(72%)

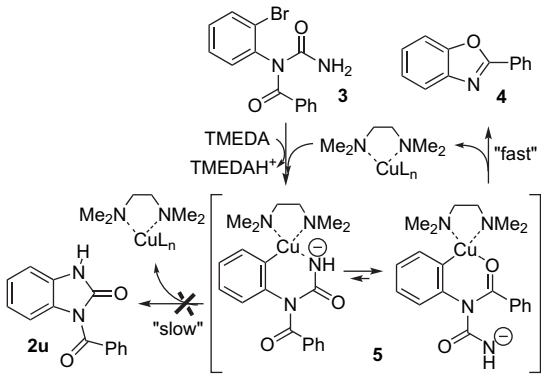
Table 2 (*continued*)

Entry	1	2[b]
12	 **1l**	 **2l**(71%)
13	 **1m**	 **2m**(60%)
14	 **1n**	 **2n**(80%)
15	 **1o**	 **2o**(71%)
16	 **1p**	 **2p**(69%)
17[c]	 **1q**	 **2q**(57%)
18	 **1r**	 **2r**(54%)
19	 **1s**	 **2s**(65%)
20	 **1t**	—

[a] CuI (8.5 mol %), 3.5 equiv of TMEDA, H_2O (12 mL/mmol), 120 °C, 15 h.
[b] Yield of isolated product.
[c] $Cu(OAc)_2 \cdot H_2O$ (12 mol %) was used instead of CuI.

entry 1 vs entry 16, entry 14 vs entry 18). Surprisingly, with the exception of the 4-methoxy group (Table 2, entry 6), no clear trend towards activation by electron-donating or electron-withdrawing groups on the bromoarene moiety was observed. For example, depending on the *N*1-substituent, the presence of 4-methyl group increases or decreases the yields in comparison with non-substituted substrates (Table 2, entries 2 and 10 vs entries 1 and 9, respectively). In order to test the need of substitution at N1, 2-bromophenylurea **1t** was subjected to the optimized reaction conditions affording unreacted material (Table 2, entry 20). This result suggests that only by using *N*1-substituted (alkylated or arylated) ureas the reaction can proceed, a behaviour already glimpsed in the previous report by McLaughlin et al.[11a] on palladium-catalyzed amidations of *N*-alkylated ureas, and probably caused by a competition between two amide-type nucleophiles in the transmetallation or halide displacement step of the catalytic cycle. In spite of the latter limitation, a number of interesting features of the presented procedure should be pointed out such as its reproducibility, its scalability to multigram quantities and the ready separation of the reaction products from the catalyst containing aqueous mixture, effected by simple extraction with dichloromethane or diethyl ether.

Finally, an additional experiment was conducted in order to provide some light on N- and O-arylation as competitive processes in this system. Thus, *N*-benzoylated 2-bromoarylurea **3** was subjected to the same reaction conditions, and instead of the corresponding benzoimidazolone **2u**, which could not be detected, 2-phenylbenzo[*d*]oxazole **4** was isolated as the main product (46%). Thus, it could be concluded that when the intramolecular O- and N-arylation reactions are both potentially feasible, the former takes place preferentially over N-arylation, although a common intermediate **5** could be involved and the reaction outcome determined by a marked difference in reductive elimination rates, as depicted in the mechanistic proposal shown in Scheme 1.



Scheme 1. Competitive formation of benzo[*d*]oxazole **4** and benzo[*d*]imidazolone **2u**.

3. Conclusion

In summary, a highly efficient, general methodology for the synthesis of benzo[*d*]imidazol-2-ones is presented, featuring as the key step a copper-catalyzed intramolecular N-arylation of *N*1-substituted 2-bromoarylureas. In addition to the simplicity of the procedure, broad scope and the low cost of the starting materials, reagents and catalysts employed, it must be outlined that this reaction is conducted for the first time in such a benign, safe and inexpensive solvent as water. Furthermore, considering that although CuI provides the best results in this novel protocol, other copper salts (CuCl, CuBr, $Cu(OAc)_2 \cdot H_2O$, $Cu(OTf)_2$ and $Cu(ClO_4)_2 \cdot 6H_2O$) can be used with similar efficiency, this method could be easily transferred to industrial applications.

4. Experimental section

4.1. 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 work-up of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a Büchi rotatory evaporator. HRMS were measured using a Waters GCT Mass Spectrometer.

4.1.1. 1-Benzyl-1,3-dihydrobenzoimidazol-2-one (**2a**): typical procedure

A screw-capped tube was charged with 1-benzyl-1-(2-bromophenyl)urea **1a** (108.2 mg, 0.329 mmol), CuI (5.2 mg, 0.028 mmol), TMEDA (0.17 mL, 1.15 mmol) and water (3.9 mL) at room temperature. After closing, the tube was heated to 120 °C for 15 h, allowed to cool to room temperature and the resulting mixture was extracted with CH_2Cl_2. The organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo to give an oily residue, which was purified by flash chromatography (20% hexane/EtOAc), providing benzoimidazolone **2a** (69.7 mg, 87%) as a white powder. Mp: 185–186 °C (hexane), lit.[12] 187–189 °C. HRMS (EI): calculated for $C_{14}H_{12}N_2O$, 224.0950; found, 224.0939.

4.1.2. 1-Benzyl-5-methyl-1,3-dihydrobenzoimidazol-2-one (**2b**)

The same procedure was applied to 1-benzyl-1-(2-bromo-4-methylphenyl)urea **1b** (68.0 mg, 0.21 mmol) and CuI (3.8 mg, 0.020 mmol) to provide **2b** (40.9 mg, 80%) as a white powder.[11a] Mp: 170–172 °C (hexane); IR (KBr) (ν, cm^{-1}) 3026 (NH), 1702 (CO); MS (EI) *m*/*z*: 239 (M+1, 4), 238 (M, 98), 91 (100).

4.1.3. 1-Benzyl-5-fluoro-1,3-dihydrobenzoimidazol-2-one (**2c**)

The same procedure was applied to 1-benzyl-1-(2-bromo-4-fluorophenyl)urea **1c** (104.9 mg, 0.43 mmol) and CuI (5.3 mg, 0.028 mmol) to provide **2c** (58.1 mg, 74%) as a white powder.[11a] Mp: 151–152 °C (hexane); IR (KBr) (ν, cm^{-1}) 3120 (NH), 1710 (CO); MS (EI) *m*/*z*: 243 (M+1, 3), 242 (M, 70), 91 (100).

4.1.4. 1-Benzyl-5,7-difluoro-1,3-dihydrobenzoimidazol-2-one (**2d**)

The same procedure was applied to 1-benzyl-1-(2-bromo-4,6-difluorophenyl)urea **1d** (94.6 mg, 0.28 mmol) and CuI (4.7 mg, 0.024 mmol) to provide **2d** (37.2 mg, 51%) as a white powder. Mp: 160–161 °C (hexane); IR (KBr) (ν, cm^{-1}) 3132 (NH), 1710 (CO); ^{1}H NMR (300 MHz, DMSO-d_6) (δ, ppm): 5.01 (s, 2H, CH_2), 6.76 (dd, *J*=8.4, 1.6 Hz, 1H, H_{arom}), 6.81–6.89 (m, 1H, H_{arom}), 7.19–7.24 (m, 3H, H_{arom}), 7.26–7.33 (m, 2H, H_{arom}), 11.46 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 44.9 (CH_2), 93.9 (dd, *J*=27.8, 3.7 Hz), 96.5 (dd, *J*=28.2, 23.1 Hz), 126.8, 127.6, 128.7 (CH), 113.7 (dd, *J*=12.9, 2.2 Hz), 131.1 (dd, *J*=14.9, 9.6 Hz), 137.7, 143.9 (dd, *J*=245, 14.5 Hz), 154.5, 158.7 (dd, *J*=251, 11.6 Hz, C); MS (EI) *m*/*z*: 261 (M+1, 5), 260 (M, 42), 91 (100). HRMS (EI): calculated for $C_{14}H_{10}F_2N_2O$, 260.0761; found, 260.0762.

4.1.5. 1-Benzyl-6-nitro-1,3-dihydrobenzoimidazol-2-one (**2e**)

The same procedure was applied to 1-benzyl-1-(2-bromo-5-nitrophenyl)urea **1e** (80.6 mg, 0.23 mmol) and CuI (4.0 mg, 0.021 mmol) to provide **2e** (49.4 mg, 79%) as a white powder. Mp: 228–229 °C (hexane); IR (KBr) (ν, cm^{-1}) 3084 (NH), 1526 and 1338 (NO_2), 1702 (CO); ^{1}H NMR (300 MHz, DMSO-d_6) (δ, ppm): 5.12 (s, 2H, CH_2), 7.17 (d, *J*=8.5 Hz, 1H, H_{arom}), 7.21–7.52 (m, 5H, H_{arom}), 7.93–7.97 (m, 2H, H_{arom}), 11.77 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 43.5 (CH_2), 103.6, 108.6, 118.3, 127.4, 127.6, 128.8 (CH), 130.2, 134.4, 136.6, 141.6, 154.8 (C); MS (EI) *m*/*z*: 269 (M, 3), 239 (100), 148 (99), 91 (33). HRMS (EI): calculated for $C_{14}H_{11}N_3O_3$, 269.0800; found, 269.0806.

4.1.6. 1-Benzyl-5-methoxy-1,3-dihydrobenzoimidazol-2-one (**2f**)

The same procedure was applied to 1-benzyl-1-(2-bromo-4-methoxyphenyl)urea **1f** (109.9 mg, 0.33 mmol) and CuI (5.1 mg, 0.026 mmol) to provide **2f** (76.6 mg, 92%) as a white powder.[12] Mp: 159–160 °C (hexane); IR (KBr) (ν, cm^{-1}) 3096 (NH), 1696 (CO); MS (EI) *m*/*z*: 255 (M+1, 12), 254 (M, 100), 163 (64), 136 (18), 111 (13), 97 (22), 96 (12), 95 (15), 81 (22), 69 (38).

4.1.7. 1-(4-Methoxybenzyl)-1,3-dihydrobenzoimidazol-2-one (**2g**)

The same procedure was applied to 1-(2-bromophenyl)-1-(4-methoxybenzyl)urea **1g** (104.3 mg, 0.31 mmol) and CuI (4.8 mg, 0.025 mmol) to provide **2g** (58.8 mg, 74%) as a white powder.[11a] Mp: 174–176 °C (hexane); IR (KBr) (ν, cm^{-1}) 3143 (NH), 1696 (CO); MS (EI) *m*/*z*: 255 (M+1, 5), 254 (M, 29), 121 (100), 78 (12).

4.1.8. 5-Methyl-1-(3-methoxybenzyl)-1,3-dihydrobenzoimidazol-2-one (**2h**)

The same procedure was applied to 1-(2-bromo-4-methylphenyl)-1-(3-methoxybenzyl)urea **1h** (246.6 mg, 0.71 mmol) and $Cu(OAc)_2$ (18.8 mg, 0.094 mmol) to afford **2h** (147.9 mg, 78%) as a white powder. Mp: 145–146 °C (hexane); IR (KBr) (ν, cm^{-1}) 3108 (NH), 1696 (CO); ^{1}H NMR (300 MHz, DMSO-d_6) (δ, ppm): 2.34 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 5.06 (s, 2H, CH_2), 6.73–6.81 (m, 3H, H_{arom}), 6.87–6.96 (m, 3H, H_{arom}), 7.15–7.29 (m, 1H, H_{arom}), 10.55 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 21.3 (CH_3), 44.4 (CH_2), 55.1 (OCH_3), 108.1, 110.4, 112.9, 113.0, 119.5, 121.8, 129.7 (CH), 127.9, 128.2, 131.5, 137.9, 156.1, 159.9 (C); MS (EI) *m*/*z*: 268 (M, 2), 121 (17), 95 (17), 81 (72), 69 (100). HRMS (EI): calculated for $C_{16}H_{16}N_2O_2$, 268.1212; found, 268.1208.

4.1.9. 1-(4-Fluorobenzyl)-1,3-dihydrobenzoimidazol-2-one (**2i**)

The same procedure was applied to 1-(2-bromophenyl)-1-(4-fluorobenzyl)urea **1i** (114.0 mg, 0.35 mmol) and CuI (6.6 mg, 0.034 mmol) to afford **2i** (53.5 mg, 62%) as a white powder. Mp: 170–172 °C (hexane); IR (film) (ν, cm^{-1}) 3190 (NH), 1690 (CO); ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 5.07 (s, 2H, CH_2), 6.87 (d, *J*=7.36 Hz, 1H, H_{arom}), 6.93–7.11 (m, 4H, H_{arom}), 7.14 (dd, *J*=6.8, 1.7 Hz, 1H, H_{arom}), 7.29–7.34 (m, 2H, H_{arom}), 10.44 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 43.8 (CH_2), 109.1 (d, *J*=11.9 Hz), 115.5, 115.8, 121.6 (d, *J*=34.7 Hz), 120.0, 129.1 (CH), 128.0, 129.9, 131.9 (d, *J*=3.2 Hz), 155.8, 162.3 (d, *J*=246.2 Hz, C); MS (EI) *m*/*z*: 243 (M+1, 4), 242 (M, 46), 109 (100), 83 (7). HRMS (EI): calculated for $C_{14}H_{11}FN_2O$, 242.0855; found, 242.0858.

4.1.10. 1-(4-Fluorobenzyl)-4-methyl-1,3-dihydrobenzoimidazol-2-one (**2j**)

The same procedure was applied to 1-(2-bromo-4-methylphenyl)-1-(4-fluorobenzyl)urea **1j** (100.2 mg, 0.28 mmol) and CuI (4.8 mg, 0.025 mmol) to afford **2j** (70.6 mg, 92%) as a white powder. Mp: 182–183 °C (hexane); IR (film) (ν, cm^{-1}) 3143 (NH), 1696 (CO); ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 2.35 (s, 3H, CH_3), 5.05 (s, 2H, CH_2), 6.71–6.83 (m, 2H), 6.96–7.02 (m, 3H), 7.26–7.32 (m, 2H), 10.15 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 21.3 (CH_3), 43.8 (CH_2), 109.2 (d, *J*=18. 7 Hz), 115.5, 115.8, 121.9, 127.9 (d, *J*=29.0 Hz, CH), 129.0 (d, *J*=8.2 Hz), 131.6, 132.0, 132.1, 155.8, 162.2 (d, *J*=246.1 Hz, C′); MS (EI) *m*/*z*: 257 (M+1, 3), 256 (M, 35), 137 (12), 121 (12), 109 (88), 95 (18), 83 (12), 81 (54), 69 (100). HRMS (EI): calculated for $C_{15}H_{13}FN_2O$, 256.1012; found, 256.1003.

4.1.11. 1-(2-Naphthylmethyl)-1,3-dihydrobenzoimidazol-2-one (**2k**)

The same procedure was applied to 1-(2-bromophenyl)-1-(2-naphthylmethyl)urea **1k** (104.7 mg, 0.29 mmol) and CuI (5.2 mg, 0.027 mmol) to afford **2k** (58.2 mg, 72%) as a white powder. Mp: 192–193 °C (hexane); IR (KBr) (ν, cm^{-1}) 3155 (NH), 1690 (CO); ^{1}H NMR (300 MHz, DMSO-d_6) (δ, ppm): 5.17 (s, 2H, CH_2), 6.89–7.05 (m, 4H, H_{arom}), 7.44–7.49 (m, 3H, H_{arom}), 7.82–7.91 (m, 4H, H_{arom}), 11.02 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 43.6 (CH_2), 108.2, 109.0, 120.7, 121.1, 125.6, 125.9, 126.1, 126.5, 127.6, 127.7, 128.5 (CH), 128.5, 130.1, 132.4, 132.9, 134.8, 154.5 (C); MS (EI) *m*/*z*: 275 (M+1, 1), 274 (M, 16), 141 (100); HRMS (EI): calculated for $C_{18}H_{14}N_2O$, 274.1106; found, 274.1101.

4.1.12. 1-(Ethyl)-1,3-dihydrobenzoimidazol-2-one (**2l**)

The same procedure was applied to 1-(2-bromophenyl)-1-(ethyl)urea **1l** (54.4 mg, 0.22 mmol) and CuI (4.0 mg, 0.021 mmol) to afford **2l** (25.8 mg, 71%) as a white powder. Mp: 111–112 °C (hexane), lit.[15] 117–118 °C (EtOH); IR (film) (ν, cm^{-1}) 3190 (NH),

1684 (CO); ^{1}H NMR (300 MHz, DMSO-d_6) (δ, ppm): 1.18 (t, J=7.1 Hz, 3H, CH_3), 3.81 (q, J=7.0 Hz, 2H, CH_2), 6.88–7.05 (m, 3H, H_{arom}), 7.11 (d, J=5.7 Hz, 1H, H_{arom}), 10.81 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 13.6 (CH_3), 34.7 (CH_2), 107.7, 108.8, 120.6, 120.8 (CH), 128.4, 129.9, 154.0 (C); MS (EI) m/z: 163 (M+1, 1), 162 (16), 147 (15), 119 (14), 84 (10); HRMS (EI): calculated for $C_9H_{10}N_2O$, 162.0793; found, 162.0793.

*4.1.13. 1-(Butyl)-1,3-dihydrobenzoimidazol-2-one (**2m**)*

The same procedure was applied to 1-(2-bromophenyl)-1-(ethyl)urea **1m** (138.9 mg, 0.51 mmol) and CuI (8.5 mg, 0.044 mmol) to afford **2m** (58.8 mg, 60%) as a white powder. Mp: 132–134 °C (hexane); IR (film) (ν, cm^{-1}) 3178 (NH), 1696 (CO); ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 0.97 (t, J=7.3 Hz, 3H, CH_3), 1.36–1.48 (m, 2H, CH_2), 1.71–1.81 (m, 2H, CH_2), 3.91 (t, J=7.3 Hz, 2H, CH_2), 7.00 (dd, J=5.8, 3.2 Hz, 1H, H_{arom}), 7.04–7.09 (m, 2H, H_{arom}), 7.13–7.19 (m, 1H, H_{arom}), 10.93 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 13.7 (CH_3), 20.0, 30.4, 40.5 (CH_2), 107.7, 109.7, 120.9, 121.2 (CH), 128.2, 130.0, 156.0 (C); MS (EI) m/z: 191 (M+1, 2), 190 (M, 62), 173 (19), 148 (34), 134 (100), 119 (58), 106 (13). HRMS (EI): calculated for $C_{11}H_{14}N_2O$, 190.1106; found, 190.1098.

*4.1.14. 1-(Butyl)-4-(trifluoromethyl)-1,3-dihydrobenzoimidazol-2-one (**2n**)*

The same procedure was applied to 1-(2-bromo-4-trifluoromethylphenyl)-1-(butyl)urea **1n** (133.4 mg, 0.39 mmol) and CuI (7.1 mg, 0.037 mmol) to afford **2n** (81.0 mg, 80%) as a white powder. Mp: 115–116 °C (hexane); IR (film) (ν, cm^{-1}) 3155 (NH), 1708 (CO); ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 00.97 (t, J=7.4 Hz, 3H, CH_3), 1.29–1.53 (m, 2H, CH_2), 1.55–1.97 (m, 2H, CH_2), 3.92 (t, J=7.3 Hz, 2H, CH_2), 7.05 (d, J=8.2 Hz, 1H, H_{arom}), 7.36 (d, J=8.2 Hz, H_{arom}), 7.40 (s, 1H, H_{arom}), 11.13 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 13.6 (CH_3), 20.0, 30.4, 40.9 (CH_2), 107.0 (q, J=3.7 Hz), 107.6, 118.6 (q, J=3.8 Hz), 123.7 (q, J=238.9 Hz, CF_3), 125.6, 128.1, 132.8, 156.2 (C); MS (EI) m/z: 259 (M+1, 1), 258 (M, 26), 241 (17), 216 (33), 215 (40), 202 (100), 187 (47). HRMS (EI): calculated for $C_{12}H_{13}F_3N_2O$, 258.0980; found, 258.0984.

*4.1.15. 1-(Allyl)-1,3-dihydrobenzoimidazol-2-one (**2o**)*

The same procedure was applied to 1-allyl-1-(2-bromophenyl)-urea **1o** (100.0 mg, 0.39 mmol) and CuI (7.2 mg, 0.037 mmol) to afford **2o** (48.3 mg, 71%) as a white powder.[12] Mp: 79–80 °C (hexane); IR (film) (ν, cm^{-1}) 3143 (NH), 1696 (CO); MS (EI) m/z: 175 (M+1, 4), 174 (M, 100), 133 (25), 131 (13), 119 (18), 106 (22).

*4.1.16. 1-(Phenyl)-1,3-dihydrobenzoimidazol-2-one (**2p**)*

The same procedure was applied to 1-(2-bromophenyl)-1-(phenyl)urea **1p** (98.8 mg, 0.34 mmol) and $Cu(OAc)_2$ (9.2 mg, 0.046 mmol) to afford **2p** (49.2 mg, 69%) as a white powder. Mp: 187–188 °C (hexane), lit.[16] 200–202 °C (benzene); IR (film) (ν, cm^{-1}) 3143 (NH), 1702 (CO); ^{1}H NMR (300 MHz, DMSO-d_6) (δ, ppm): 6.85–7.17 (m, 2H, H_{arom}), 7.34–7.45 (m, 2H, H_{arom}), 7.43–7.69 (m, 5H, H_{arom}), 11.16 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 108.2, 109.2, 121.0, 121.9, 126.0, 127.4, 129.5 (CH), 128.5, 130.1, 134.6, 153.3 (C); MS (EI) m/z: 211 (M+1, 5), 210 (m, 100), 181 (37), 168 (11), 84 (10), 66 (11). HRMS (EI): calculated for $C_{13}H_{10}N_2O$, 210.0793; found, 210.0792.

*4.1.17. 1-Phenyl-5-fluoro-1,3-dihydrobenzoimidazol-2-one (**2q**)*

The same procedure was applied to 1-(2-bromo-4-fluorophenyl)-1-(phenyl)urea **1q** (80.7 mg, 0.22 mmol) and $Cu(OAc)_2 \cdot H_2O$(7.0 mg, 0.036 mmol) to afford **2q** (34.0 mg, 57%) as a white powder. Mp: 211–212 °C (hexane); IR (KBr) (ν, cm^{-1}) 3414 (NH), 1655 (CO); ^{1}H NMR (300 MHz, DMSO-d_6) (δ, ppm): 6.73–6.80 (m, 1H, H_{arom}), 6.89 (d, J=2.37 Hz, 1H, H_{arom}), 6.90–7.01 (m, 1H, H_{arom}), 7.33–7.50 (m, 1H, H_{arom}), 7.51–7.62 (m, 4H, H_{arom}), 10.57 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 98.2 (d, J=28.5 Hz), 108.1 (d, J=24.2 Hz), 109.2 (d, J=9.3 Hz), 126.1, 128.0, 129.7 (CH), 126.4, 129.1 (d, J=21.6 Hz), 134.3, 153.4 (C), 158.1 (d, J=235.3 Hz, C); MS (EI) m/z: 229 (M+1, 2), 228 (M, 26), 199 (13), 137 (12), 121 (11), 95 (18), 83 (11), 81 (56), 69 (100). HRMS (EI): calculated for $C_{13}H_9FN_2O$, 228.0699; found, 228.0701.

*4.1.18. 1-Phenyl-5-(trifluoromethyl)-1,3-dihydrobenzoimidazol-2-one (**2r**)*

The same procedure was applied to 1-(2-bromo-4-trifluoromethylphenyl)-1-(phenyl)urea **1r** (104.0 mg, 0.29 mmol) and CuI (4.6 mg, 0.024 mmol) to afford **2r** (43.9 mg, 44%) as a white powder. Mp: 215–216 °C (hexane); IR (film) (ν, cm^{-1}) 3132 (NH), 1708 (CO); ^{1}H NMR (300 MHz, DMSO-d_6) (δ, ppm): 7.11 (d, J=7.8 Hz, 1H, H_{arom}), 7.26 (s, 1H), 7.35 (dd, J=16.4, 9.0 Hz, 1H, H_{arom}), 7.45–7.67 (m, 5H, H_{arom}), 10.09 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 106.1 (q, J=3.65 Hz), 108.7, 118.8 (q, J=4.1 Hz), 126.6, 128.4, 130.0 (CH), 122.7 (q, J=31.9 Hz), 125.1 (q, J=271.3 Hz, CF_3), 129.2, 133.6, 134.3, 153.8 (C); MS (EI) m/z: 279 (M+1, 3), 278 (M, 100), 249 (25). HRMS (EI): calculated for $C_{14}H_9F_3N_2O$, 278.0667; found, 278.0674.

*4.1.19. 1-(4-Chlorophenyl)-1,3-dihydrobenzoimidazol-2-one (**2s**)*

The same procedure was applied to 1-(2-bromophenyl)-1-(4-chlorophenyl)urea **1s** (96.7 mg, 0.30 mmol) and CuI (4.9 mg, 0.025 mmol) to afford **2s** (47.1 mg, 57%) as a white powder. Mp: 206–208 °C (hexane); IR (KBr) (ν, cm^{-1}) 3131 (NH), 1702 (CO); ^{1}H NMR (300 MHz, DMSO-d_6) (δ, ppm): 6.97–7.05 (m, 2H, H_{arom}), 7.04–7.11 (m, 2H, H_{arom}), 7.48–7.73 (m, 4H, H_{arom}), 11.21 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) (δ, ppm): 108.3, 109.4, 121.1, 122.1, 127.7, 129.5 (CH), 128.5, 129.7, 131.6, 133.6, 153.2 (C); MS (EI) m/z: 246 (M+2, 17), 245 (M+1, 6), 244 (M, 100), 181 (30), 167 (12). HRMS (EI): calculated for $C_{13}H_9Cl^{35}N_2O$, 244.0403; found, 244.0401.

The same procedure was applied to 1-benzyl-1-(2-bromophenyl)urea **1a** (20.00 g, 60.81 mmol), CuI (0.96 g, 5.17 mmol), TMEDA (31.42 mL, 216.6 mmol) and water (720.9 mL) to provide the corresponding benzoimidazolone **2a** (12.83 g, 85%) as a white powder.

Acknowledgements

This research was supported by Regional Government of Biscay/Basque Government/University of the Basque Country (Projects DIPE 06/10, UNESCO07/08 and GIC07/IT-349-07) and the Spanish Ministry of Education and Science (MEC CTQ2007-64501). N.B. thanks the Ministry of Education and Science (MEC) for a predoctoral scholarship. The authors also thank S. A. Petronor for generous donation of hexane.

Supplementary data

Experimental procedures, characterization data of all new starting urea derivatives **1** and intermediates as well as ^{1}H and ^{13}C for all new compounds. This material is available free of charge via Internet. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.05.072.

References and notes

1. (a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428; (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400; (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.
2. Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609.
3. (a) Nandakumar, M. V. *Tetrahedron Lett.* **2004**, *45*, 1989; (b) Buchwald, S. L.; Klapars, A.; Antilla, J.; Job, G. E.; Wolter, M.; Kwong, F. Y.; Nordmann, G.; Hennessy, E. J. International Patent WO02085838, 2002; *Chem. Abstr.* **2002**, *137*, 352492; (c) Hosseinzadeh, R.; Sarrafi, Y.; Mohadjerani, M.; Mohammadpourmir, F. *Tetrahedron Lett.* **2008**, *49*, 840.

4. (a) Carril, M.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2006**, *8*, 1467; (b) Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Chem.—Eur. J.* **2007**, *13*, 5100; (c) Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Green Chem.* **2007**, *9*, 219.
5. Barbero, N.; Carril, M.; SanMartin, R.; Domínguez, E. *Tetrahedron* **2007**, *63*, 10425.
6. Barreca, M. L.; Rao, A.; De Luca, L.; Iraci, N.; Monforte, A.-M.; Maga, G.; De Clercq, E.; Pannecouque, C.; Balzarini, J.; Chimirri, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1956.
7. (a) Calderone, V.; Coi, A.; Fiamingo, F. L.; Giorgi, I.; Leonardo, M.; Livi, O.; Martelli, A.; Martinotti, E. *Eur. J. Med. Chem.* **2006**, *41*, 1421; (b) Gessner, G.; Heller, R.; Hoshi, T.; Heinemann, S. H. *Eur. J. Pharmacol.* **2007**, *555*, 185.
8. Yu, K. L.; Sin, N.; Civiello, R. L.; Wang, X. A.; Combrink, K. D.; Gulgeze, H. B.; Venables, B. L.; Wright, J. J. K.; Dalterio, R. A.; Zadjura, L.; Marino, A.; Dando, S.; D'Arienzo, C.; Kadow, K. F.; Cianci, C. W.; Li, Z.; Clarke, J.; Genovesi, E. V.; Medina, I.; Lamb, L.; Colonno, R. J.; Yang, Z.; Krystal, M.; Meanwell, N. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 895.
9. Benzoimidazolones have found application in the treatment of wide range of diseases such as urinary incontinence, migraine, sexual desire disorders, female contraception and hyperglycemia. See, for example: (a) Terefenko, E. A.; Kern, J.; Fensome, A.; Wrobel, J.; Zhu, Y.; Cohen, J.; Winneker, R.; Zhang, Z.; Zhang, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3600; (b) Hammach, A.; Barbosa, A.; Gaenzler, F. C.; Fadra, T.; Goldberg, D.; Hao, M.-H.; Kroe, R. R.; Liu, P.; Qian, K. C.; Ralph, M.; Sarko, C.; Soleymanzadeh, F.; Moss, N. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6316; (c) Olesen, I. J.; Olesen, J. International Patent WO2007009462, 2007; *Chem. Abstr.* **2007**, *146*, 198708; (d) Ceci, A. International Patent WO2007048801, 2007; *Chem. Abstr.* **2007**, *146*, 448502; (e) Liu, W.; Wood, H. B.; Lau-Phua, F. W.-Y. International Patent WO2006022954, 2006; *Chem. Abstr.* **2006**, *144*, 274270.
10. See, for example: (a) Jha, A. *Arkivoc* **2006**, 13; (b) Li, Q.; Li, T.; Woods, K. W.; Gu, W.-Z.; Cohen, J.; Stoll, V. S.; Galicia, T.; Hutchins, C.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2918; (c) Xiaofang, W.; Gang, L.; Yang, X.; Shiwei, L. *Eur. J. Org. Chem.* **2005**, *8*, 1675; Yasushi, T.; Ryo, T.; Yoshihisa, W. *J. Organomet. Chem.* **1985**, *290*, 249; (d) Kawamoto, H.; Nakashima, H.; Kato, T.; Arai, S.; Kamata, K.; Iwasawa, Y. *Tetrahedron* **2001**, *57*, 981; (e) Nefzi, A.; Ostresh, J. M.; Meyer, J.-P.; Houghten, R. A. *Tetrahedron Lett.* **1997**, *38*, 931. For methods based on nucleophilic cyclisation of 2-aminoarylcarbamates, which imply the use of phosgene, see: (f) Ermann, M. *J. Comb. Chem.* **2002**, *4*, 352; (g) Wang, C.-C.; Li, W.-R. *J. Comb. Chem.* **2004**, *6*, 899. For methods using high pressure, see: (h) Wang, X.; Ling, G.; Xue, Y.; Lu, S. *Eur. J. Org. Chem.* **2005**, 1675 and references cited therein. Other methods are described in: (i) Romero, A. G.; Darlington, W. H.; Jacobsen, E. J.; Mickelson, J. W. *Tetrahedron Lett.* **1996**, *37*, 2361.
11. (a) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3311; (b) Xu, X.-J.; Zong, Y.-X. *Tetrahedron Lett.* **2007**, *48*, 129; (c) Benedí, C.; Bravo, F.; Uriz, P.; Fernández, E.; Claver, C.; Castillón, S. *Tetrahedron Lett.* **2003**, *44*, 6073.
12. Zou, B.; Yuan, Q.; Ma, D. *Org. Lett.* **2007**, *9*, 4291.
13. (a) Li, J.-H.; Wang, D. P.; Xie, Y.-X. *Tetrahedron Lett.* **2005**, *46*, 4941; (b) Jiang, N.; Ragauskas, A. J. *J. Org. Chem.* **2006**, *71*, 7087; (c) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, 695.
14. In contrast with palladium, where several steps of the catalytic cycle are well defined, the mechanism of copper-catalyzed N-arylations is still a subject of discussion regarding oxidation states and step-order issues. See Ref. 1 for more details.
15. Eckstein, Z.; Jadach, T.; Lipczynska-Kochany, E. *J. Chem. Eng. Data* **1983**, *28*, 279.
16. Bianchi, M.; Butti, A.; Rossi, S.; Barzagui, F.; Marcaria, V. *Eur. J. Med. Chem.* **1981**, *16*, 321.