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Mild, convenient and versatile Cu-mediated synthesis of *N*-aryl-2-imidazolidinones

Paolo Stabile [a,*], Alessandro Lamonica [a], Arianna Ribecai [a], Damiano Castoldi [a], Giuseppe Guercio [a], Ornella Curcuruto [b]

[a] Chemical Development Department, GlaxoSmithKline Medicines Research Centre, Via Fleming 4, I37135 Verona, Italy
[b] Analytical Chemistry Department, GlaxoSmithKline Medicines Research Centre, Via Fleming 4, I37135 Verona, Italy

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ABSTRACT

A mild, general, convenient and practical methodology for the selective copper-mediated mono N-arylation of unprotected 2-imidazolidinone was developed. Strong electron-donating groups and free hydroxy and amino groups on the aryl iodide substrates were well tolerated. The use of *n*-butanol as the solvent for the copper-catalysed mono-arylation of 2-imidazolidinone is unprecedented.

The 2-imidazolidinone moiety is a structural motif common to a large number of biologically active compounds, as exemplified by dozens of patent applications and articles.[1] Conventional syntheses of ureas usually involve amines and anilines as starting materials,[2] along with hazardous and toxic reagents such as phosgene or its equivalents,[3] isocyanates[4] and carbon monoxide.[5] In alternative, transition metal-catalysed C–N bond-forming reactions have also been developed. In particular, starting from 1996, Buchwald reported on the intramolecular[6a,b] and intermolecular[6c,d] palladium-catalysed amidation of aryl halides. Interestingly, both five- and six-membered cyclic ureas efficiently reacted with 3-bromoanisole under Pd/Xantphos catalysis, leading to the doubly arylated products.[6d] In addition, in 2001 Beletskaya reported that urea and *N*-phenylurea could be efficiently coupled with activated *p*-substituted aryl bromides under Pd/Xantphos catalysis, leading, respectively, to symmetrical and unsymmetrical *N*,*N*′-diarylureas.[7a] Though unactivated aryl bromides reacted smoothly with urea and *N*-phenylurea when the electron-poor ligand 3,5-$(CF_3)_2$Xantphos was employed, this methodology still did not prove to be general, as the reaction of electron-rich *p*-methoxy- and *o*-dimethylamino-substituted aryl bromides with urea failed.[7b] Noteworthy, 2-imidazolidinone was efficiently coupled with benzo-fused bromine-containing heterocycles employing both Pd/Xantphos- and Pd/3,5-$(CF_3)_2$Xantphos-based catalytic systems.[7c] Despite the fact that the above-mentioned methodologies apply to the ureidation of a wide range of aryl halides, some limitations remain: (1) expensive and toxic palladium catalysts are employed; (2) high catalyst loadings and/or long reaction times are required in certain instances and finally (3) variable amounts of by-products arising from aryl–aryl exchange are often formed.[6,7] Moreover, general methodologies to obtain mono-substituted acyclic or cyclic *N*-arylureas are not described in those reports.[6–8] However, high yielding syntheses of mono-arylated *N*,*N*′-dimethyl-*N*-(pyridin-2-yl)urea and of the six-membered cyclic urea 1-(3-chloropyridin-2-yl)-tetrahydropyrimidin-2(1*H*)-one were recently reported.[9] Nonetheless, to the best of our knowledge, an advantageous and general method for the selective palladium-catalysed mono-arylation of 2-imidazolidinone has not been established to date.

A cheaper and phosphine-free approach to perform C–N bond-forming reactions utilises Cu-based catalytic systems. The copper-mediated amidation of aryl halides (Goldberg reaction)[10] has been studied for a long time by organic chemists.[11] However, only a few years ago Buchwald and co-workers developed an enhanced version of the Goldberg reaction,[12] giving the start to a large number of methodological studies[13] and practical applications.[14] In particular, the use of versatile ligand systems, such as ethyl 2-oxocyclohexanecarboxylate[15] and 1,1,1-tris(hydroxymethyl)ethane,[16] has allowed to perform copper-catalysed C–N, C–O and C–S bond-forming reactions. Copper-catalysis was also applied to the arylation of ureas, affording both symmetrical and unsymmetrical cyclic and acyclic diarylureas.[17] As to the copper-catalysed mono-arylation of 2-imidazolidinone, a few examples have been reported

* Corresponding author. Tel.: +39 0458219648; fax: +39 0458218117.
E-mail addresses: paolo.2.stabile@gsk.com, paostabile@googlemail.com (P. Stabile).

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so far.[17d,e,18] Furthermore, harsh conditions such as high temperatures and large amount of copper catalyst,[18a] use of MW irradiation,[17d,18c] large excesses of urea[17d] and use of toxic aprotic polar solvents (e.g., DMF)[17d] were usually required to often achieve only modest yields in the desired *N*-aryl-2-imidazolidinones. A few examples of copper-catalysed arylation of N-protected ureas were also reported, but involved tedious protection–deprotection steps.[17e,19]

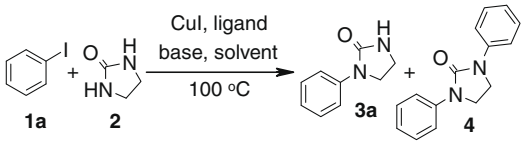
With all these considerations in mind, we decided to investigate in more detail the copper-catalysed mono N-arylation of 2-imidazolidinone, aiming at establishing a mild, simple, convenient and general methodology. As a first instance, we compared the effect of different solvents under reaction conditions similar to those previously described by Buchwald and co-workers for the amidation of aryl halides.[12] Accordingly, iodobenzene (our model substrate, **1a**) was let to react with 5 equiv of 2-imidazolidinone, **2**, in a suitable solvent at 100 °C in the presence of CuI (10 mol %), *N*,*N*′-dimethylethylenediamine (DMEDA, 30 mol %) and potassium carbonate (3 equiv). DMF, 1,4-dioxane and toluene were chosen for the initial screening, since they are amongst the most frequently used solvents in copper-catalysed N-arylation of ureas. DMSO was also included, being high boiling, non-flammable and non-toxic. However, in all these preliminary experiments the mono-arylated compound **3a** was formed with low yield and selectivity (Table 1, entries 1–4). Because of these discouraging results, we turned our attention to solvents with completely different characteristics. Therefore, we extended the screening to high boiling solvents that are not typical in copper-catalysed C–N bond-forming reactions, such as 4-methyl-2-pentanone (117–118 °C) and *n*-butanol (116–118 °C). To our delight, in the polar protic and weakly coordinating *n*-butanol, compound **1a** was completely consumed after 3 h at 100 °C and the desired product **3a** was isolated in a satisfactory 70% yield after chromatographic purification (Table 1, entry 5). Notably, in the polar protic medium the **3a**/**4** *ratio* was significantly higher than in the other solvents tested (Table 1, compare entries 1–4 with entry 5). On the contrary, the presence of water as the sole solvent or in a 1:1 mixture with *n*-butanol was deleterious, affording **3a** in only 4% and 29% yield, respectively. Interestingly, in both aqueous media the formation of *N*,*N*′-dimethyl-*N*-phenyl-1,2-ethanediamine was detected by LC–MS and ^{1}H NMR. The latter was likely formed through copper-catalysed amination of **1a** by DMEDA and was not formed to a noticeable extent when organic solvents were employed. The origin of this particular behaviour in the presence of water is currently under investigation. Having selected *n*-butanol as the solvent, we focused on the optimisation of the other reaction parameters, that is, the type of base and ligand and the equivalents of **2**. Whilst K_3PO_4 (Table 1, entry 6) proved slightly superior to K_2CO_3, a much slower reaction occurred with Cs_2CO_3 (Table 1, entry 7) affording **3a** in only 36% yield. With regard to the ligand, despite the fact that *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine (DMCHDA) is often described as a more efficient ligand in Cu-catalysed amidation of aryl halides,[12b] in our hands it gave less satisfactory results (Table 1, entry 8). Finally, we found that increasing the equivalents of **2** from 5 to 8 did not significantly improve the yield of **3a** (Table 1, entry 9). However, we proved that quite a large excess of **2** is required, since **3a** was recovered in only 51% yield with 2 equiv of 2-imidazolidinone (Table 1, entry 10).

With this piece of information in our hands, we selected a suitable set of reaction conditions to explore the reactivity of various aryl iodides **1** with **2**. K_2CO_3 was preferred to the more hygroscopic K_3PO_4. Furthermore, since we showed that only a little increase in yield was achieved with 8 equiv of **2**, we decided to use 5 equiv of 2-imidazolidinone, thus generating a lower amount of waste and simplifying the purification of the crude. Consequently, the aryl iodides **1** were reacted with **2** (5 equiv) in the presence of CuI (10 mol %), DMEDA (30 mol %) and K_2CO_3 (3 equiv) in *n*-BuOH at 100 °C for 5–30 h.

Electron-rich and electron-poor *p*-substituted aryl iodides **1b**–**k** reacted smoothly with **2**, affording the corresponding N-arylated 2-imidazolidinones **3b**–**k** in moderate to fairly good yields (Table 2). 4-Amino- and 4-hydroxy-substituted aryl iodides, respectively, **1d** and **1e**, afforded the corresponding *N*-aryl-2-imidazolidinones **3d** and **3e** in 54% and 61% yield (Table 2, entries 3 and 4).

Whilst fluoro- and chloro-containing substrates reacted selectively at the C–I bond (Table 2, entries 5 and 6), in the case of **1h** small amounts of several by-products deriving from ureidation of both C–Br and C–I bonds were formed (Table 2, entry 7). Finally, labile acetyl and cyano functionalities were well tolerated under our reaction conditions (Table 2, entries 8 and 9). Bis-arylated imidazolidinones were also isolated in some representative cases.

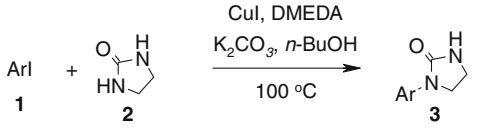
Table 1
Optimisation of the reaction conditions[a]

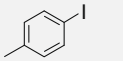
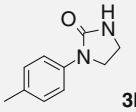
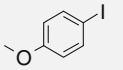
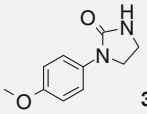
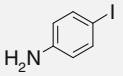
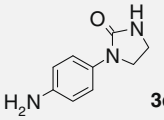
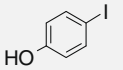
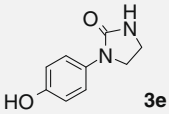
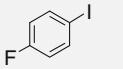
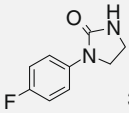
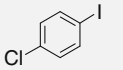
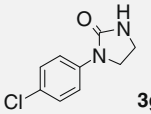
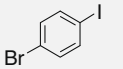
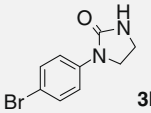
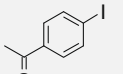
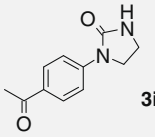
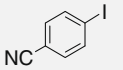
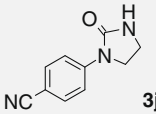
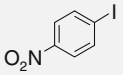
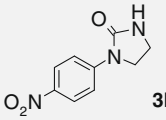


Entry	Ligand	Base	Solvent	Conversion of **1a**[b] (%)	**3a**/**4** *ratio*[c]	**3a**[d] (%)
1	DMEDA	K_2CO_3	DMF	87	55:45	43
2	DMEDA	K_2CO_3	DMSO	>99	57:43	46
3	DMEDA	K_2CO_3	1,4-Dioxane	57	68:32	46
4	DMEDA	K_2CO_3	Toluene	89	50:50	36
5	DMEDA	K_2CO_3	*n*-BuOH	>99	77:23	70
6	DMEDA	K_3PO_4	*n*-BuOH	>99	78:22	72
7	DMEDA	Cs_2CO_3	*n*-BuOH	29	87:13	36
8	DMCHDA	K_2CO_3	*n*-BuOH	82	80:20	65
9	DMEDA	K_2CO_3	*n*-BuOH	>99	81:19	74[e]
10	DMEDA	K_2CO_3	*n*-BuOH	>99	58:42	51[f]

[a] A mixture of **1a** (10 mmol), **2** (5 equiv unless differently stated), CuI (10 mol %), ligand (30 mol%) and base (3 equiv) in the appropriate solvent (40 ml) was stirred for 3 h at 100 °C.
[b] Reactions were monitored by HPLC and LC–MS.
[c] Determined by HPLC in the crude reaction mixture.
[d] Isolated yield.
[e] 8 equiv of **2** were used.
[f] 2 equiv of **2** were used.

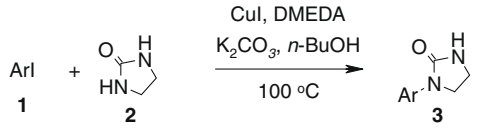
Table 2
Copper-catalysed arylation of 2-imidazolidinone with *p*-substituted aryl iodides[a]

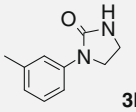
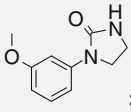
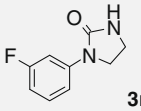
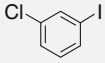
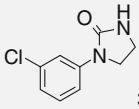
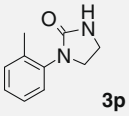
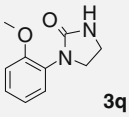
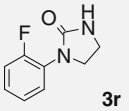
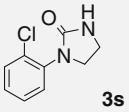
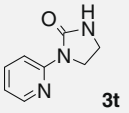


Entry	Aryl iodide	Product	Yield[b] (%)
1	 **1b**	 **3b**	61
2	 **1c**	 **3c**	54
3	 **1d**	 **3d**	54
4	 **1e**	 **3e**	61
5	 **1f**	 **3f**	67
6	 **1g**	 **3g**	65
7	 **1h**	 **3h**	48
8	 **1i**	 **3i**	45
9	 **1j**	 **3j**	46
10	 **1k**	 **3k**	52

[a] Reactions were run in Easy Max 102 equipment: a mixture of **1** (10 mmol), **2** (5 equiv), CuI (10 mol %), DMEDA (0.3 equiv) and K_2CO_3 (3 equiv) in *n*-butanol (40 ml) was stirred for 5 h at 100 °C.
[b] Isolated yields.

Table 3
Copper-catalysed arylation of 2-imidazolidinone with *m*-substituted[a] and *o*-substituted[b] aryl iodides and iodopyridines[a]



Entry	Aryl iodide	Product	Yield[c] (%)
1	 **1l**	 **3l**	65
2	 **1m**	 **3m**	71
3	 **1n**	 **3n**	67
4	 **1o**	 **3o**	53
5	 **1p**	 **3p**	55
6	 **1q**	 **3q**	70
7	 **1r**	 **3r**	60
8	 **1s**	 **3s**	49
9	 **1t**	 **3t**	45
10	**1u**	**3u**	46

[a] Reactions were run in Easy Max 102 equipment: a mixture of **1** (10 mmol), **2** (5 equiv), CuI (10 mol %), DMEDA (30 mol %) and K_2CO_3 (3 equiv) in *n*-butanol (40 ml) was stirred for 5 h at 100 °C.
[b] Reactions were run in Easy Max 102 equipment: a mixture of **1** (10 mmol), **2** (5 equiv), CuI (10 mol %), DMEDA (30 mol %) and K_2CO_3 (3 equiv) in *n*-butanol (40 ml) was stirred for 30 h at 100 °C.
[c] Isolated yield.

Compounds **1b**, **1d**, **1f** and **1j** afforded the corresponding *N*,*N*′-diarylimidazolidinones in molar yields ranging from 10% to 20%.

The scope of the N-arylation reaction of **2** was consequently extended to *m*- and *o*-substituted aryl iodides **1l–s** (Table 3). In particular, steric effects were investigated by comparing the behaviour of *m*- and *o*-iodo-substituted regioisomers. Whilst *m*-substituted aryl iodides **1l–o** reacted as fast as *p*-substituted aryl iodides **1b–k**, reactions of *o*-substituted aryl iodides **1p–s** were sluggish and were completed only after 30 h. Moreover, *o*-substituted aryl iodides **1p–s** afforded lower yields than corresponding *m*-substituted aryl iodides **1l–o** (Table 3, compare entries 5–8 with entries 1–4). The reactivity of heteroaryl iodides was also investigated. 2-Iodo- and 3-iodopyridine, respectively, **1t** and **1u**, coupled

with **2** affording the corresponding 1-(2-pyridinyl)- and 1-(3-pyridinyl)-2-imidazolidinones, respectively, **3t** and **3u**, in 45% and 46% yield (Table 3, entries 9 and 10).

A limitation of our method is that it does not work with aryl bromides. For example, 4-bromotoluene was proved to be a poor substrate under our reaction conditions. In fact, less than 15% of 1-(4-methylphenyl)-2-imidazolidinone was detected by HPLC in the crude reaction mixture after 30 h at 100 °C. However, further investigation is currently on going in our laboratories to set up suitable reaction conditions for the mono N-arylation of 2-imidazolidinone with aryl bromides.

In summary, we have developed a mild, practical, convenient and general methodology for the mono N-arylation of unprotected 2-imidazolidinone. A variety of aryl- and heteroaryl-2-imidazolidinones were prepared in moderate to fairly good yields. Strong electron-donating and free O–H and N–H groups on the aryl iodide substrates were well tolerated. More importantly, *n*-butanol promoted fast and clean reactions. Notably, its use in the copper-mediated synthesis of N-arylated 2-imidazolidinones is unprecedented.

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Supplementary data

Supplementary data (experimental procedures and characterisation data for all substrates **3a**–**u**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.064.

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