Copper-Mediated N-Arylation of Quinazolinediones

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Abstract: A mild, ligand-free method of arylating 2,4-quinazolinediones using arylboronates in the presence of copper salts is described. The reaction is tolerant of a variety of functional groups and works for arylboronic acid, arylboronic ester, and aryltrifluoroboronate donors. A catalytic variant is also described.

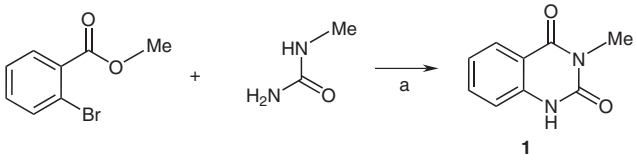
Key words: heterocycle, arylation, copper, cross-coupling, boronic

1-Aryl-2,4-quinazolinediones have long attracted the interest of the pharmaceutical industry because they demonstrate notable anti-inflammatory activity, which has led to their development as potential analgesic, antiasthmatic, and arthritis therapies.[1] Several methods for their preparation have been reported in the literature, including elaboration of uracils[2] and nucleophilic aromatic substitution,[3] but by far the most common approach is to condense a carbonyl equivalent such as phosgene or urea with an appropriately functionalised aniline (Scheme 1, disconnection a).[1a,4] All of these methods are afflicted by a lack of generality and/or poor yield, as well as two bugbears of pharmaceutical synthesis: route linearity and the use of potentially mutagenic aniline components. Linear routes not only lead to lower overall yields during scale up, but limit diversity-oriented synthesis, while aniline reagents are often toxic, can persist throughout multistep preparations, and must be rigorously removed from any potential drug before in vivo test, with an attendant impact on time and cost.[5]

An alternative preparation of 1-aryl-2,4-quinazolinediones involving arylation of a quinazolinedione core (Scheme 1, disconnection b) is therefore desirable. Such an approach does not demand anilinic reagents, is convergent, and is also amenable to library synthesis since molecular diversity is incorporated during the last step of the sequence.

N-Arylation technology has come far since the discovery of the Goldberg–Ullmann reaction in 1906.[6] Research driven by the groups of Stephen Buchwald and John Hartwig among others has delivered important metal-mediated methods for heteroatom–aryl bond formation, initially using palladium catalysts[7] and later more economically viable copper-based systems.[8] The aryl donor is generally an aryl halide which can react with a wide range of nitrogen nucleophiles including amines,[9] amides,[10] and nitrogen heterocyles.[11] It was envisaged given the wide range of substrate and catalyst combinations described in the literature that similar technology could be used to effect the N-arylation of quinazolinediones.

3-Methyl-2,4(1*H*,3*H*)-quinazolinedione (**1**) was chosen as a model substrate and synthesised in one step via Willis' elegant tandem palladium-catalysed urea arylation–cyclisation (Scheme 2).[12]



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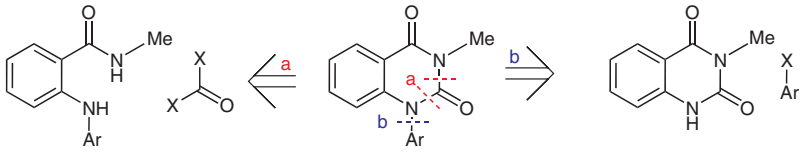
Scheme 2 Synthesis of a model quinazolinedione substrate. *Reagents and conditions*: a) Cs_2CO_3 (2 equiv), $Pd_2(dba)_3$ (5 mol%), XantPhos (10 mol%), dioxane, 100 °C, 24 h (61%).

In an attempt to develop a one-pot synthesis of N-arylated quinazolines based around this chemistry 4-iodotoluene was added into the reaction broth once the formation of **1** was complete, but unfortunately the palladium which moderated the original reaction failed to catalyse any subsequent N-arylation. A more comprehensive investigation was therefore undertaken, treating quinazolinedione **1** with many reported palladium and copper N-arylation



Scheme 1 Possible approaches to 1-aryl quinazolinediones

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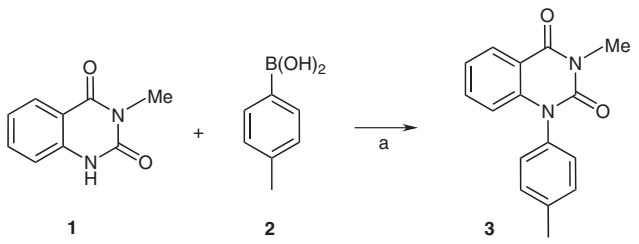
systems in the presence of 4-iodotoluene as an aryl donor, but in every case no trace of arylated product was evident.

It was clear that a mechanistically dissimilar arylation using an alternative aryl donor might give better results. Alternative aryl sources such as arylboronic acids,[13] arylsiloxanes,[14] arylbismuths,[15] and arylleads[16] have all been used to arylate nitrogen nucleophiles, with arylboronic compounds representing the most attractive alternative due to their wide availability and ease of preparation from aryl halides.[17] Further support for use of this donor as a possible arylation agent for quinazolinediones was found in a recent publication describing the arylation of the related heterocycle uracil with phenylboronic acid.[18]

Consultation of the literature revealed that most common N-arylation procedures using boronic acid donors are mediated by stoichiometric copper(II) salts under basic, aerobic conditions. Pleasingly, when model **1** was treated with 4-tolylboroxy acid in the presence of copper(II) acetate and triethylamine the desired arylquinazolinedione was obtained in moderate to good yield (Table 1).

Table 1 Copper-Mediated N-Arylation of Quinazolinedione **1**



1 **2** **3**

Entry	Base	Solvent	Conversion (%) [b]
1[c]	Et_3N	CH_2Cl_2	59
2[d]	Et_3N	CH_2Cl_2	29
3	Et_3N	CH_2Cl_2	80 (72)
4	pyridine	CH_2Cl_2	34
5	K_2CO_3	CH_2Cl_2	<5
6	Et_3N	MeCN	74
7	Et_3N	toluene	53
8	Et_3N	DMF	35
9[e]	Et_3N	CH_2Cl_2	50

[a] Unless otherwise stated reactions were performed using boronic acid (2 equiv), copper(II) acetate (2 equiv), base (2 equiv), and 4 Å MS at r.t. for 20 h.
[b] LC-MS conversion based on unreacted quinazolinedione **1**, isolated yield in parentheses.[19,]
[c] With 1 equiv $Cu(OAc)_2$.
[d] With 1 equiv $ArB(OH)_2$.
[e] Without molecular sieves.

Copper(II) acetate was found to be the best copper salt with an excess required for consistently high yields (Table 1, entries 1 and 3). Unfortunately, a surplus of boronic acid was also necessary for efficient reaction (entry 2), although using a greater than twofold excess gave no further yield improvement. Choice of base or solvent had a significant impact on conversion: using most common inorganic bases resulted in a poor reaction (e.g., entry 5), and of the organic bases investigated triethylamine proved superior to pyridine. Solvent was less crucial, with dichloromethane, acetonitrile, and toluene (entries 3, 6, and 7, respectively) giving reasonable conversions, though dimethylformamide was found to be a poor solvent. As in related reactions, 4 Å molecular sieves were used to remove traces of water in the reaction which might cause degradation of the arylboronic acid reagent and a concomitant drop in yield (entry 9).[20]

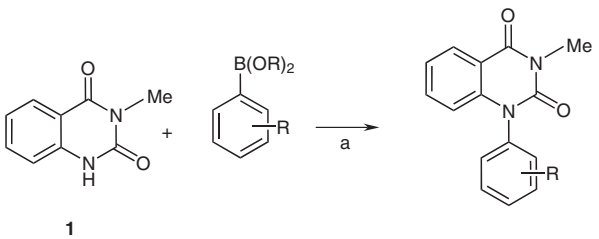
One useful feature of the procedure is that high conversions were obtained under very mild ambient conditions. Furthermore, no inert atmosphere was required, making the reaction operationally very convenient. The kinetics of the reaction are also worthy of comment. Similar arylation procedures commonly suffer from extremely long reaction times of up to three days,[13] whereas quinazolinediones were found to react more rapidly. For example, the reaction in Table 1 entry 3 reached 50% conversion after only two hours and a synthetically useful isolated yield of 72% after 20 hours.[21]

With optimised conditions in hand the focus of the investigation shifted to an exploration of reaction scope. Several commercial arylboronic derivatives possessing a range of steric, electronic, and chemical properties were reacted with quinazolinedione **1** under standard conditions, as shown in Table 2.

These results demonstrate a wide reaction scope, tolerant of functionality. Yields seemed unaffected by the electronic nature of the arylboronic substituent, with electron-rich (Table 1 entries 1–3) and electron-deficient aryl donors (entries 6–8) giving comparable conversions. The reaction is, however, sensitive to steric effects, as demonstrated by the very poor conversion observed when using *o*-tolyl arylboronic acid as a reactant (entry 5). Oxidatively labile groups (entry 2) participate well despite an oxidative mechanism mooted for similar reactions,[20] as do acids, bases, and hydrolytically sensitive groups (entries 3, 7, and 8). Using a phenolic arylboronic acid (entry 4) led to a messy reaction, an unsurprising observation given the nucleophilicity of phenolic hydroxy groups in similar arylations.[20] The nature of the boron group on the aryl donor was also investigated, with both aryltrifluoroborate (hitherto unreported as N-arylating amidic nitrogens) and arylboronate ester donors found to furnish product, significantly widening the range of commercially available coupling partners.

Lam and others have reported catalytic variants of N-arylation reactions using boronic acids.[22] In an attempt to discover whether arylation of quinazolinediones could also be rendered catalytic several literature-derived conditions were applied to model **1**. Gratifyingly arylation was found to occur readily, albeit more slowly than the stoichiometric version. The best conditions found used a catalytic

Table 2 Scope of the N-Arylation of Quinazolinedione **1**



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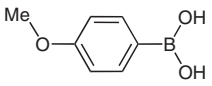
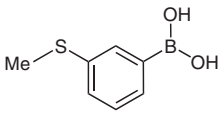
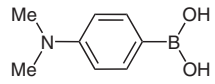
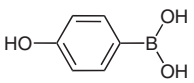
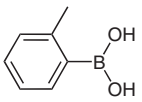
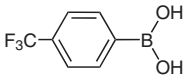
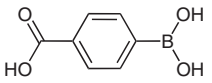
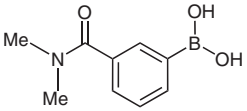
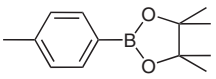
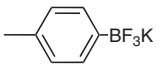
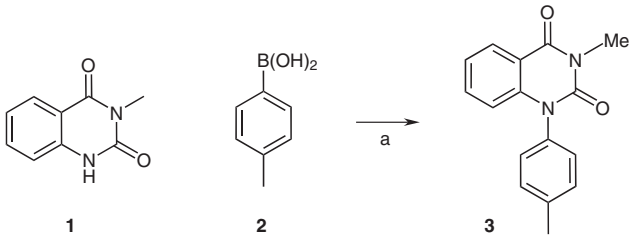
Entry	Arylboronate	Product	Yield (%)
1		**4**	72
2		**5**	74
3		**6**	78
4		**7**	0
5		**8**	<5
6		**9**	64
7		**10**	73
8		**11**	77
9		**3**	40
10		**3**	92[b]

[a] Reactions were performed using boronic acid (2 equiv), copper(II) acetate (2 equiv), base (2 equiv), and 4 Å MS at r.t. for 20 h.
[b] Reaction was performed in refluxing MeCN for 20 h.

amount of copper(II) acetate in the presence of TEMPO as co-oxidant (Scheme 3).



1 **2** **3**

Scheme 3 Catalytic arylation of quinazolinedione **1**. *Reagents and conditions*: a) $Cu(OAc)_2$ (10 mol%), TEMPO (1.1 equiv), Et_3N (2 equiv), 4 Å MS, r.t., 48 h (71%).

As a final demonstration of utility the new arylation technology was applied in the synthesis of known pharmaceutical H 27 (**13**), a known phosphodiesterase inhibitor (Scheme 4).[1a] Synthesis of this compound by cyclisation of methyl-2-bromobenzoate and ethyl urea followed by N-arylation using 3-trifluoromethyl phenylboronic acid gave **13** in 76% overall yield over two convergent steps, compared to the three-step linear literature synthesis.[1a]

A mild, ligand-free, and practically convenient method of synthesising 1-aryl-2,4-quinazolinediones has been developed. The reaction tolerates a range of functional groups and furnishes products in good yield even under aerobic, ambient conditions. Further investigations are under way to investigate potential chemo- and regioselectivity, and apply the reaction in the synthesis of novel compounds of biological interest.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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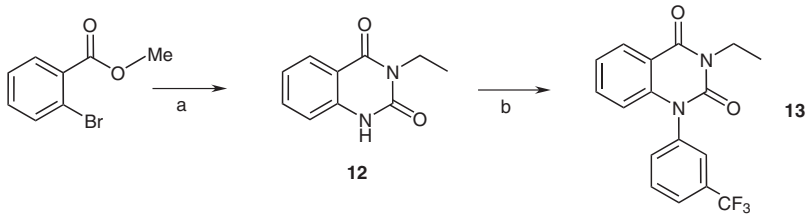

12 **13**

Scheme 4 H 27 via quinazolinedione arylation. *Reagents and conditions*: a) *N*-ethylurea (1 equiv), Cs_2CO_3 (2 equiv), $Pd_2(dba)_3$ (5 mol%), XantPhos (10 mol%), dioxane, 100 °C, 24 h (77%); b) 3-trifluoromethyl phenylboronic acid (2 equiv), $Cu(OAc)_2$ (2 equiv), Et_3N (2 equiv), 4 Å MS, r.t., 16 h (99%).

References and Notes

(1) (a) Noda, K.; Nakagawa, A.; Hachiya, T.; Ide, H. DE 2459090, **1975**; *Chem. Abstr.* **1975**, *83*, 114468. (b) Wilhelm, R.; Chin, R.; Lipp, R.; Devens, B.; Alvarez, R. WO 9319068, **1993**; *Chem. Abstr.* **1993**, *120*, 164213. (c) Crespo, M. I.; Gracia, J.; Puig, C.; Vega, A.; Bou, J.; Beleta, J.; Domenech, T.; Ryder, H.; Segarra, V.; Palacios, J. M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2661.

(2) Takahashi, M.; Nagaoka, H.; Inoue, K. *J. Heterocycl. Chem.* **2004**, *41*, 525.

(3) Tran, T.; Ellsworth, E.; Watson, B.; Sanchez, J.; Showalter, H.; Rubin, J.; Stier, M.; Yip, J.; Nguyen, D.; Bird, P.; Singh, R. *J. Heterocycl. Chem.* **2005**, *42*, 669.

(4) Baraka, M. *Boll. Chim. Farm.* **2001**, *140*, 90.

(5) Bhat, K.; Hayik, S.; Sztandera, L.; Bock, C. *QSAR Comb. Sci.* **2005**, *24*, 831.

(6) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691.

(7) (a) Muci, A. R.; Buchwald, S. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Wolfe, J.; Wagaw, S.; Marcoux, J.; Buchwald, S. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Hartwig, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2046.

(8) (a) Beletskaya, I.; Cheprakov, A. *Coord. Chem. Rev.* **2004**, *248*, 2337. (b) Thomas, A.; Ley, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.

(9) (a) Goodbrand, H.; Hu, N. *J. Org. Chem.* **1999**, *64*, 670. (b) Patil, N.; Kelkar, A.; Nabi, Z.; Chaudhari, R. *Chem. Commun.* **2003**, 2460.

(10) Klapars, A.; Antilla, J.; Huang, X.; Buchwald, S. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(11) (a) Kiyomori, A.; Marcoux, A.; Buchwald, S. *Tetrahedron Lett.* **1999**, *40*, 2657. (b) Antilla, J.; Klapars, A.; Buchwald, S. *J. Am. Chem. Soc.* **2002**, *124*, 11684.

(12) Willis, M.; Snell, R.; Fletcher, A.; Woodward, R. *Org. Lett.* **2006**, *8*, 5089.

(13) Chan, D.; Monaco, K.; Wang, R.-P.; Winters, M. *Tetrahedron Lett.* **1998**, *39*, 2933.

(14) Lam, P.; Deudon, K.; Averill, K.; Li, R.; He, M.; DeShong, P.; Clark, C. *J. Am. Chem. Soc.* **2000**, *122*, 7600.

(15) Chan, D. *Tetrahedron Lett.* **1996**, *37*, 9013.

(16) Kim, J.-J.; Park, Y.-D.; Cho, S.-D.; Kim, H.-K.; Chung, H.; Lee, S.-G.; Falck, J.; Yoon, Y.-J. *Tetrahedron Lett.* **2004**, *45*, 8781.

(17) Hall, D. In *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Hall, D., Ed.; John Wiley and Sons: New York, **2005**, 1.

(18) Jacobsen, M.; Knudsen, M.; Gothelf, K. *J. Org. Chem.* **2006**, *71*, 9183.

(19) A regiochemically controlled synthesis of quinazolinedione **3** was carried out using the route outlined in Scheme 1 (disconnection a). The material so obtained was spectroscopically identical to that generated by direct arylation of **1**, confirming that the regiochemistry of substitution was limited to the free nitrogen position and not either of the available carbonyl oxygens.

(20) Evans, D.; Katz, J.; West, T. *Tetrahedron Lett.* **1998**, *39*, 2937.

(21) **Typical Procedure**
3-Methylquinazoline-2,4 (1*H*,3*H*)-dione (200 mg, 1.14 mmol), 4-methoxyphenylboronic acid (345 mg, 2.27 mmol), $Cu(OAc)_2$ (412 mg, 2.27 mmol), and Et_3N (0.316 mL, 2.27 mmol) were suspended in CH_2Cl_2 (12 mL) along with 200 mg of activated 4 Å MS. The suspension was allowed to stir at r.t. for 20 h then partitioned between 1 M HCl (50 mL) and EtOAc (50 mL). The organic layer was isolated, dried ($MgSO_4$), and concentrated in vacuo, and the residue was purified by flash chromatography (15% EtOAc–*i*-hexane) to furnish 1-(4-methoxyphenyl)-3-methylquinazoline-2,4-(1*H*,3*H*)-dione (**4**) as a colourless solid (230 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.1–8.4 (m, 1 H), 7.4–7.6 (m, 1 H), 7.1–7.3 (m, 3 H), 7.0–7.2 (d, 2 H), 6.59 (d, 1 H), 3.89 (s, 3 H), 3.52 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 159.9, 151.2, 141.7, 134.5, 129.9, 129.0, 128.5, 123.0, 115.5, 115.3, 115.0, 55.5, 28.3; MS (ES^+): *m/z* = 281 $[M - H]^+$.

(22) (a) Lam, P.; Vincent, G.; Clark, C.; Deudon, S.; Jadhav, P. *Tetrahedron Lett.* **2001**, *42*, 3415. (b) Collman, J.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233.