ChemComm

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Palladium catalyzed C3-arylation of 4-hydroxy-2-pyridones†

Cite this: *Chem. Commun.*, 2014, **50**, 6879

Received 24th March 2014,
Accepted 8th May 2014

DOI: 10.1039/c4cc02166e

www.rsc.org/chemcomm

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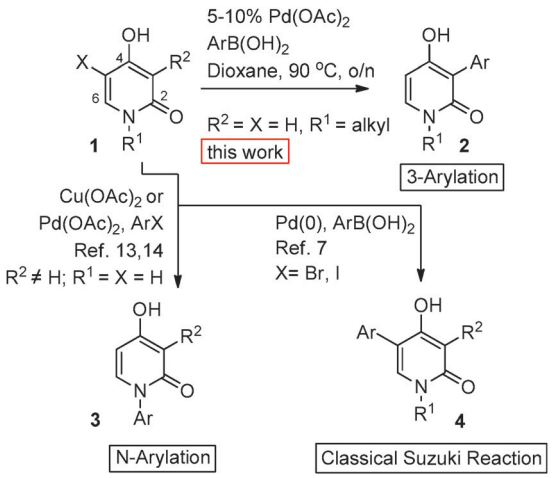
The direct arylation of *N*-substituted-4-hydroxy-2-pyridones with aryl boronic acids has been achieved under palladium catalysis. The mild reaction conditions applied in this method and the use of a conventional catalytic system offer an attractive protocol for the efficient synthesis of a variety of 3-arylated products.

The pyridone-2 heteroaromatic core is widely isolated from natural sources covering a wide range of biological space.[1] The subclass of 4-hydroxy-2-pyridones, which appears as a component of natural alkaloids, possesses usually diverse molecular decoration of the main core in 3,5 and 6-positions, contributing majorly to their biological activity.[2] Despite the increasing pharmaceutical interest in the 2-pyridone alkaloid family, many questions, concerning their true biological potential, still remain unanswered, hampered by the lack of efficient synthetic methodologies in order to build their molecular complexity.

Whereas significant progress has been made in protocols for constructing their ring systems with a diverse range of substitution patterns,[3] regioselective introduction of substituents into existing pyridone derivatives has not been well documented. Based on this drawback, various synthetic approaches to modified pyridones using palladium-catalyzed coupling reactions have been described recently, involving usually 3-, 5- or 6-alkyl or aryl functionalization of their cores either by the classical Suzuki[4] and Heck[5] reactions or through their CH-variants.[6] On the other hand, cross-coupling reactions of 4-hydroxy-2-pyridones have been developed to much less extent and their direct CH-variants are rather unexplored. In some scarce reported examples, the classical Suzuki arylation of the 3- or 5-position of the pyridone ring has been described (Scheme 1).[7] To the best of our knowledge, the only CH-alkyl functionalization of the 4-hydroxy-2-pyridone ring was reported by Fürstner, who managed to couple enantioselectively an unsaturated



Scheme 1 Current and existing arylation protocols for 4-hydroxy-2-pyridones.

ketone at the enolic 3-position of the pyridone ring in the presence of a chiral diphosphane and allylpalladium chloride.[8] In this regard, the development of a regioselective and direct functionalization of the 4-hydroxy-2-pyridone core would be a significantly valuable synthetic method allowing for the rapid access to substituted pyridone derivatives.

Recently, our group was engaged in the total synthesis of 4-hydroxy-2-pyridone alkaloids utilizing the context of a common synthetic scaffold.[9,10] During this endeavor, we were invoked in the direct 3-alkyl functionalization of the pyridone moiety based on the inherent dicarbonyl character of the heterocycle. Wishing to further expand our synthetic libraries with 3-aryl-4-hydroxy-2-pyridone derivatives **2**, we sought for the development of an efficient, direct method to achieve our goal. In general, although the α-functionalization of activated methylene compounds with aryl halides in the presence of copper metal or copper salts is a well known protocol for more than a century,[11] its initial scope was very narrow. Recently, significant improvements in the scope and reaction conditions of these Hurtley-type reactions

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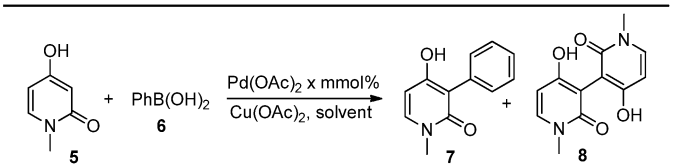
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc02166e

have been achieved using a combination of copper complexes with ancillary ligands[12] but still none of these reactions have been applied in the arylation of heteroaromatics.

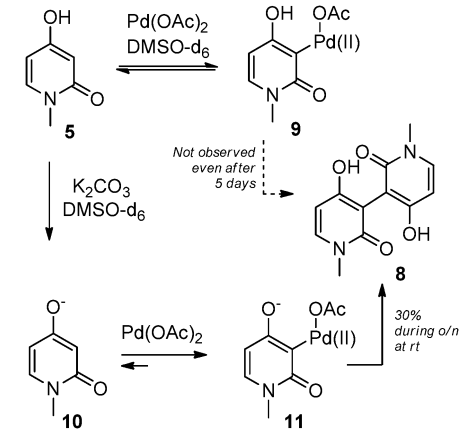
In this Communication, we wish to report the first direct arylation of 4-hydroxy-2-pyridones with the aid of aryl boronic acids under palladium acetate catalysis (Scheme 1). *N*-Methyl-4-hydroxy-2-pyridone (**5**) was chosen as the model compound for our survey, based on literature reports[13] and on our own laboratory experience[14] which witnessed the formation of *N*-aryl derivatives when unsubstituted nitrogen 4-hydroxy-2-pyridone compounds were used in the presence of either copper or palladium catalysts. Gratifyingly, in our first attempt, when *N*-methyl derivative **5** was allowed to react with phenyl boronic acid (**6**) in the presence of palladium acetate, and potassium carbonate in DMSO at 140 °C, a mixture of the desired 4-hydroxy-3-phenyl-2-pyridone (**7**), dipyridone **8** and diphenyl was obtained in a 1 : 1 : 0.4 ratio (Table 1). Optimization of reaction conditions revealed the direct dependence of solvent polarity on mixture composition. Polar solvents (entries 1 and 2) show a preference for the formation of dipyridone **8**, while non-polar solvents lead to the enhancement of diphenyl yields by the homocoupling of phenylboronic acid, diminishing the yields of product **7** (entry 6). On the other hand, the use of water hampers completely the formation of **7**, while anhydrous dioxane provided the best product to the dipyridone ratio which increased up to 1 : 0.2 (entries 5 and 3). Unfortunately, efforts to further diminish dipyridone formation failed under these conditions. Preliminary studies on the reaction mechanism revealed the essentiality of palladium acetate as a catalyst and the oxidative synergistic effect of copper acetate on the initiation and termination of the catalytic cycle (entries 8, 11 and 12). On the other hand, the absence of phenylboronic acid or utilization of other coupling partners instead (*e.g.* phenyl halides) led only to the production of the homocoupling product **8** in good yields (entry 7).

Table 1 Optimization of reaction conditions[a]



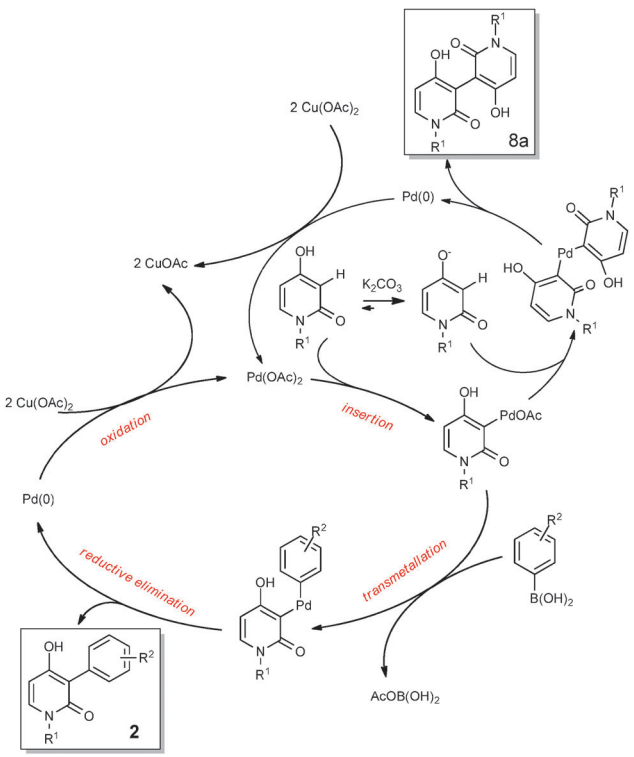
Entry	Oxidant (x equiv.)	Solvent/ temp. (°C)	$Pd(OAc)_2$ (x mmol%)	Base	Ratio[e] (7 : 8)	Yield of 7 (%)
1	$Cu(OAc)_2$ (3)	DMSO/120	10	K_2CO_3	1 : 1	30
2	$Cu(OAc)_2$ (3)	DMF/120	10	K_2CO_3	1 : 0.7	43
3	$Cu(OAc)_2$ (3)	Dioxane/120	10	K_2CO_3	1 : 0.2	72
4	$Cu(OAc)_2$ (3)	Acetonitrile/120	10	K_2CO_3	1 : 0.3	63
5	$Cu(OAc)_2$ (3)	H_2O/120	10	K_2CO_3	—	Traces
6	$Cu(OAc)_2$ (3)	Toluene/120	10	K_2CO_3	1 : 0.2	23
7[b]	$Cu(OAc)_2$ (3)	Dioxane/120	10	K_2CO_3	0 : 1	70[c]
8	$Cu(OAc)_2$ (3)	Dioxane/120	—	K_2CO_3	—	0
9	$Cu(OAc)_2$ (3)	Dioxane/120	10	—	1 : 0	88
10	$Cu(OAc)_2$ (3)	Dioxane/90	5	—	1 : 0	85
11	O_2	Dioxane/90	5	—	—	Traces
12	$AgNO_3$ (3)	Dioxane/90	5	—	—	0
13	$Cu(OAc)_2$ (2)	Dioxane/90	5	—	1 : 0	85
14[d]	$Cu(OAc)_2$ (2)	Dioxane/90	5	—	1 : 0.3	60
15	$Cu(OAc)_2$ (2)	Dioxane/90	2	—	1 : 0	85

[a] Reaction conditions: *N*-methyl-4-hydroxy-2-pyridone (0.24 mmol), phenylboronic acid (3 equiv.), $Pd(OAc)_2$ (x mmol%), base (3 equiv.), $Cu(OAc)_2$ (x equiv.), solvent (2 mL) at indicated temperature for 12 h. [b] Without phenylboronic acid. [c] Yield of compound **8**. [d] Equimolar amount of phenylboronic acid. [e] Ratio observed by H^1-NMR.



Scheme 2 NMR kinetic experiments.

While trying to rationalize these observations an array of kinetic experiments were set up with the aid of NMR in the presence or absence of basic reaction conditions (Scheme 2). Based on these, when 4-hydroxy-2-pyridone **5** was dissolved in DMSO-d_6 followed by the addition of 10 mol% of palladium acetate at room temperature, in the presence of 1 equiv. of potassium carbonate, the formation of 3-palladium-4-hydroxy-2-pyridone complex **11** was



Scheme 3 Postulated catalytic cycle of the reaction.

observed instantly in almost 20% which raised up to 38% after heating the sample to 50 °C for 3 min.

When the same sample was allowed to stand at room temperature for 16 hours the formation of new peaks was observed corresponding majorly to dipyridone compound **8**, along with the residual peaks of **10** and complex **11**.[15] When the same experiment was set up in the absence of potassium carbonate, the formation of complex **9** was diminished to 15–20% yield and remained unaltered even when the sample was heated to 70 °C for 20 min. In contrast to the previous experiment, when the sample remained at room temperature for several days no other products were observed. The latter indicated not only the reversibility of the complex formation in the absence of potassium carbonate but also the synergistic effect of a base in the formation of a dipyridone byproduct as presented in the postulated catalytic cycle of Scheme 3.

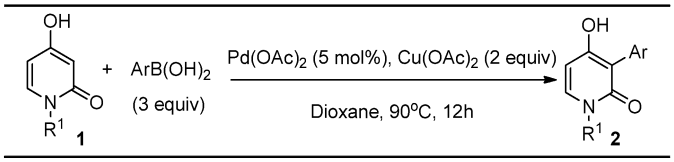
Based on these observations, the use of potassium carbonate has been precluded from the reaction mixture. The new runs in dioxane solvent and various temperatures and reaction times showed an enhanced production of compound **7**, which was ascribed to the elimination of dipyridone **8** from the reaction products (Table 1, entries 9–15). Further optimization showed that the reaction retains its performance at lower temperatures (90 °C), even when the catalyst loadings have been reduced to 2–5% without any evidenced decrease of product yields.

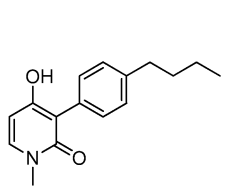
In order to explore the scope and limitation of this reaction *N*-substituted-4-hydroxy-2-pyridone was reacted with several aryl boronic acids under our optimal conditions (Table 2). In general, the reaction proceeds smoothly to afford the desired product at 90 °C. Reaction of pyridone substrates with arylboronic acids possessing electron-donating substituents provided moderate to good yields of coupling products. *ortho*-Substitution on the aryl partner does not affect the efficiency of the reaction, while highly conjugated arylboronic acids provided lower yields of products. On the other hand, electron-deficient aryl boronic acids (*m*-nitrophenyl boronic acid and 3,5-difluorophenyl boronic acid) failed to provide useful yields of the desired coupling products (5–10%) mainly due to the competitive formation of dipyridone compounds.

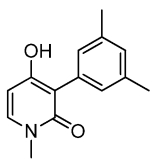
In summary, the first direct arylation of 4-hydroxy-2-pyridones through palladium acetate catalysis has been described. The method represents a powerful and efficient method for the rapid construction of 3-arylated heterocyclic products. Although none of the natural congeners of 4-hydroxy-2-pyridones, which are isolated until today, possess 3-aryl substitution, we believe that the ease and efficiency of the described methodology will enrich the library of synthetic 4-hydroxy-2-pyridones with novel privileged scaffolds.

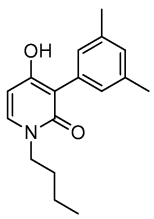
This work was supported by Pharmathen S.A.

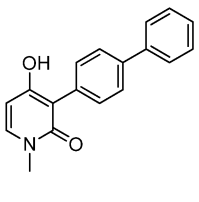
Table 2 Scope of the reaction

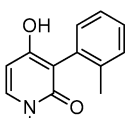


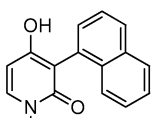

2a (89%)

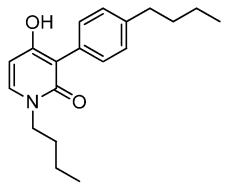

2b (71%)

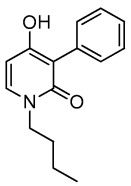

2c (80%)

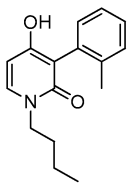

2d (33%)


2e (67%)


2f (54%)


2g (86%)


2h (82%)


2i (62%)

Notes and references

1 (*a*) W. Adam, J. Hartung, H. Okamoto, S. Marquardt, W. M. Nau, U. Pischel, C. R. Saha-Moller and K. Spehar, *J. Org. Chem.*, 2002, **67**, 6041; (*b*) F. Surup, O. Wagner, J. Frieling, M. Schleicher, S. Oess, P. Müller and S. Grond, *J. Org. Chem.*, 2007, **72**, 5085.
2 H. J. Jessen and K. Gademann, *Nat. Prod. Rep.*, 2010, **27**, 1168.
3 (*a*) M. Torres, S. Gil and M. Parra, *Curr. Org. Chem.*, 2005, **9**, 1757; (*b*) M. D. Hill and M. Movassaghi, *Chem. – Eur. J.*, 2008, **14**, 6836.
4 (*a*) L. A. Hasvold, W. Wang, S. L. Gwaltney, T. W. Rockway, L. T. G. Nelson, R. A. Mantei, S. A. Fakhoury, G. M. Sullivan, Q. Li, N.-H. Lin, L. Wang, H. Zhang, J. Cohen, W.-Z. Gu, K. Marsh, J. Bauch, S. Rosenberg and H. L. Sham, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 4001; (*b*) C. Bengtsson and F. Almqvist, *J. Org. Chem.*, 2010, **75**, 972.
5 T. Itahara and F. Ouseto, *Synthesis*, 1984, 488.
6 (*a*) Y. Nakao, H. Idei, K. S. Kanyiva and T. Hiyama, *J. Am. Chem. Soc.*, 2009, **131**, 15996; (*b*) R. Tamura, Y. Yamada, Y. Nakao and T. Hiyama, *Angew. Chem., Int. Ed.*, 2012, **51**, 5679; (*c*) H. Ge, M. J. Niphakis and G. I. Georg, *J. Am. Chem. Soc.*, 2008, **130**, 3708; (*d*) Y. Chen, F. Wang, A. Jia and X. Li, *Chem. Sci.*, 2012, **3**, 3231; (*e*) A. Nakatani, K. Hirano, T. Satoh and M. Miura, *Chem. – Eur. J.*, 2013, **19**, 7691; (*f*) A. Nakatami, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2014, **79**, 1377.
7 (*a*) N. R. Irlapati, J. E. Baldwin, R. M. Adlington and G. J. Pritchard, *Org. Lett.*, 2003, **5**, 2351; (*b*) N. R. Irlapati, J. E. Baldwin, R. M. Adlington, G. J. Pritchard and A. R. Cowley, *Tetrahedron*, 2006, **62**, 4603; (*c*) D. Conreaux, E. Bossharth, N. Monteiro, P. Desbordes, J.-P. Vors and G. Balme, *Org. Lett.*, 2007, **9**, 271; (*d*) D. Conreaux, T. Delaunay, P. Desbordes, N. Monteiro and G. Balme, *Tetrahedron Lett.*, 2009, **50**, 3299; (*e*) M. Lamblin, H. Bares, J. Dessolin, C. Marty, N. Bourgougnon and F.-X. Felpin, *Eur. J. Org. Chem.*, 2012, 5525.
8 A. Fürstner, F. Feyen, H. Prinz and H. Waldmann, *Angew. Chem., Int. Ed.*, 2003, **42**, 5361–5364.
9 E. E. Anagnostaki and A. L. Zografos, *Chem. Soc. Rev.*, 2012, **41**, 5613.
10 A. D. Fotiadou and A. L. Zografos, *Org. Lett.*, 2011, **13**, 4592.
11 (*a*) W. R. H. Hurtley, *J. Chem. Soc.*, 1929, 1870; (*b*) A. Bruggink, S. J. Ray and A. McKillop, *Org. Synth.*, 1978, **58**, 52.
12 For selected references regarding the arylation of dicarbonyl compounds please refer to: (*a*) K. Okuno, M. Furuune, M. Miura and

M. Nomura, *J. Org. Chem.*, 1993, **58**, 7606; (*b*) E. J. Hennessy and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 269; (*c*) H. J. Cristau, P. P. Cellier, J. F. Spindler and M. Taillefer, *Chem. – Eur. J.*, 2004, **10**, 5607; (*d*) X. A. Xie, Y. Chen and D. W. Ma, *J. Am. Chem. Soc.*, 2006, **128**, 16050; (*e*) S. F. Yip, H. Y. Cheung, Z. Zhou and F. Y. Kwong, *Org. Lett.*, 2007, **9**, 3469; (*f*) Z. Huang and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 1028.

13 For the *N*-arylation of 2-pyridones: (*a*) R. A. Altman and S. L. Buchwald, *Org. Lett.*, 2007, **9**, 643; (*b*) P.-S. Wang, C.-K. Liang and M.-K. Leung, *Tetrahedron*, 2005, **61**, 2931; (*c*) K. J. Filipski, J. T. Kohrt, A. Casimiro-Garcia, C. A. Van Huis, D. A. Dudley, W. L. Cody, C. F. Bigge, S. Desiraju, S. Sun, S. N. Maiti, M. R. Jaber and J. J. Edmunds, *Tetrahedron Lett.*, 2006, **47**, 7677.

14 Under our own conditions employing 4-hydroxy-pyridone derivatives (1 equiv.), phenylbromide (2 equiv.), $Pd(OAc)_2$ (5% mmol) in DMF at 120 °C we succeeded the *N*-arylation of pyridone moiety in up to 90% yield; V. Demertzidou, BSc thesis, Aristotle University of Thessaloniki, 2013.

15 Please refer to the ESI† for further details.

