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Flexible Strategy for Differentially 3,5-Disubstituted 4-Oxypyridin-2(1*H*)-ones Based on Site-Selective Pd-Catalyzed Cross-Coupling Reactions†

David Conreaux,‡ Emmanuel Bossharth,‡ Nuno Monteiro,*,‡ Philippe Desbordes,§ Jean-Pierre Vors,*,§ and Geneviève Balme*,‡

Laboratoire de Synthèse Organométallique et Molécules Bioactives, CNRS UMR 5181, Université Claude Bernard- Lyon 1, ESCPE Lyon 43, Boulevard du 11 Novembre 1918, 69622 Villeurbanne, France, and Bayer CropScience, 14/20 rue Baizet, BP9163, 69623 Lyon Cedex 09, France

balme@univ-lyon1.fr; monteiro@univ-lyon1.fr; jean-pierre.vors@bayercropscience.com

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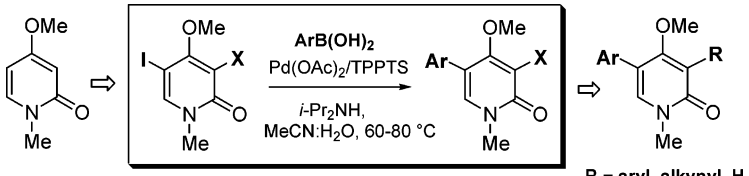
ABSTRACT



3,5-Dihalogeno-4-methoxy-*N*-methylpyridin-2(1*H*)-ones have been shown to undergo single Suzuki coupling reactions in a site-selective fashion. Monoarylations occur at the C-5 position preferentially, thus leaving the remaining C-3 halide free for further functionalization, to finally access differentially 3,5-disubstituted 2-pyridones. This two-step strategy has been applied to the elaboration of the 3-acyl-5-aryl-4-oxy-2-pyridone subunit that is prevalent in numerous bioactive natural products.

The 3,5-disubstituted 4-oxypyridin-2(1*H*)-one system is found in several structurally and biologically interesting alkaloids which include a small group of antibiotic fungal metabolites featuring a *p*-hydroxyphenyl (or phenyl) moiety at the C-5 position (Figure 1). These natural products have been shown to display a wide range of biological properties, including antifungal, antiinsecticidal, and antitumoral properties.[1] From a synthetic point of view, this class of compounds has aroused a significant amount of interest, and various strategies have already been developed to access the central 5-aryl-2-pyridone nucleus to be further elaborated to the natural products. The arylpyridone nucleus was generally built up via condensation of preassembled acyclic precursors already bearing the requisite aryl moiety.[2] Occasionally, Pd-catalyzed cross-coupling reactions have been used to install the aryl group on precyclized intermediates, although, to the best of our knowledge, the latter were in all cases hetero-aromatic precursors of the desired 4-oxy-2-pyridones.[3]

† Dedicated to the memory of Marcial Moreno-Mañas.
‡ Université Lyon 1.
§ Bayer CropScience.

(1) (a) Jayasinghe, L.; Abbas, H. K.; Jacob, M. R.; Herath, W. H. M. W.; Nanayakkara, N. P. D. *J. Nat. Prod* **2006**, *69*, 439. (b) Gutierrez-Cirlos, E. B.; Merbitz-Zahradnik, T.; Trumpower, B. L. *J. Biol. Chem.* **2004**, *279*, 8708. (c) Zhang, C.; Jin, L.; Mondie, B.; Mitchell, S. S.; Castelhano, A. L.; Cai, W.; Bergenhem, N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1433. (d) Schmidt, K.; Riese, U.; Li, Z.; Hamburger, M. *J. Nat. Prod.* **2003**, *66*, 378. (e) Sakemi, S.; Bordner, J.; DeCosta, D. L.; Dekker, K. A.; Hirai, H.; Inagaki, T.; Kim, Y.-J.; Kojima, N.; Sims, J. C.; Sugie, Y.; Sugiura, A.; Sutcliffe, J. A.; Tachikawa, K.; Truesdell, S. J.; Wong, J. W.; Yoshikawa, N.; Kojima, Y. *J. Antibiot.* **2002**, *55*, 6. (f) Hirano, N.; Kohno, J.; Tsunoda, S.; Nishio, M.; Kishi, N.; Okuda, T.; Kawano, K.; Komatsubara, S.; Nakanishi, N. *J. Antibiot.* **2001**, *54*, 421. (g) Takahashi, S.; Uchida, K.; Kakinuma, N.; Hashimoto, R.; Yanagisawa, T.; Nakagawa, A. *J. Antibiot.* **1998**, *51*, 1051.

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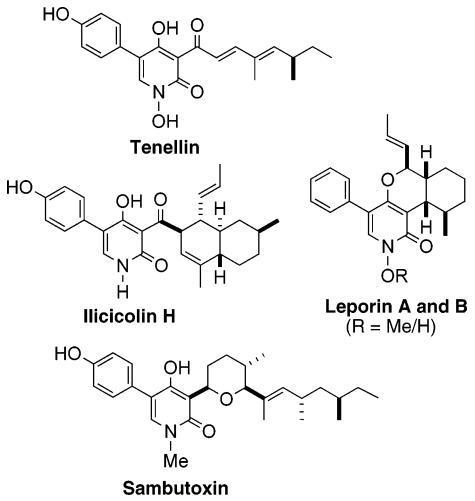
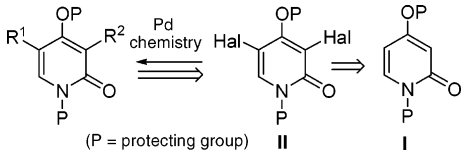


Figure 1. Some representative, naturally occurring 5-aryl-4-oxypyridin-2(1*H*)-ones.

In connection with our ongoing program devoted to the synthesis of structurally diversified pyridone derivatives in a search for new drug candidates,[4] we became interested in the synthetic utility of 3,5-dihalogenated 4-alkoxy-2-pyridones for the synthesis of differentially difunctionalized 2-pyridones by means of site-selective Pd-catalyzed C−C bond forming processes (Scheme 1).[5] Indeed, the probable

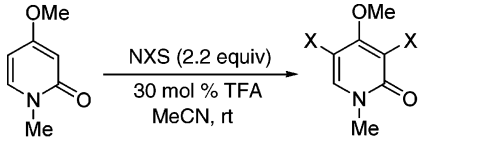
Scheme 1. Convergent Approach to Differentially 3,5-Disubstituted 4-Alkoxy-2-pyridones



difference in reactivity between the C-3 and C-5 positions was expected to allow the successive introduction of two different substituents to the pyridone ring in a highly convergent and flexible manner.[6] We envisioned this approach being particularly useful for the rapid generation of libraries of simplified analogues of bioactive natural 5-aryl-2-pyridone alkaloids. We report herein our preliminary results toward this goal.

As we began to assess our strategy, we required a method to effect the dihalogenation of *N*-alkyl-4-alkoxy-2-pyridones **I** at the C-3 and C-5 positions. Although scattered dibrominations of the related aromatic 2,4-dioxypyridines had been previously reported,[3c,7] no general method was available from the literature to achieve the dihalogenation of the corresponding N-substituted pyridones. With this backdrop, there was an opportunity for us to develop an effective, scalable method for the preparation of these potentially useful 3,5-dihalogeno-2-pyridones (**II**). Our initial efforts focused on the preparation of the diiodo derivatives, and the reactivity of *N*,*O*-dimethylpyridone **1**, as a model substrate, was first investigated toward a series of iodination reagents and reaction conditions. Although the expected iodination at the C-3 position[4a,8] was observed in the presence of various iodonium generating systems (i.e., NIS; ICl/AcOH; or bis(*sym*-collidine)iodine(I), PF_6[9]), further iodination at the C-5 position proved to be extremely troublesome. After considerable effort, we found that the desired transformation could be achieved by using superelectrophilic iodine(I) trifluoroacetate generated in situ from NIS and catalytic TFA.[10] On the basis of this, we devised a convenient, mild, and high-yielding procedure for the preparation of milligram to multigram quantities of diiodopyridone **2a**. Interestingly, the method was also effective for the preparation of the dibrominated pyridone **2b** by simply using NBS in lieu of NIS (Scheme 2).

Scheme 2. Dihalogenation of *N*-Alkyl-4-alkoxy-2-pyridone **1**



Having secured a reliable preparative method to the dihalogenopyridones, we next focused our attention on their

(2) For selected examples, see: (a) Williams, D. R.; Sit, S. Y. *J. Org. Chem.* **1982**, *47*, 2846. (b) Williams, D. R.; Bremmer, M. L.; Brown, D. L.; D'Antuono, J. *J. Org. Chem.* **1985**, *50*, 2807. (c) Rigby, J. H.; Burkhardt, F. J. *J. Org. Chem.* **1986**, *51*, 1374. (d) Rigby, J. H.; Qabar, M. *J. Org. Chem.* **1989**, *54*, 5852. (e) Buck, J.; Madeley, J. P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 67. (f) Snider, B. B.; Lu, Q. *J. Org. Chem.* **1996**, *61*, 2839. (g) Williams, D. R.; Turske, R. A. *Org. Lett.* **2000**, *2*, 3217. (h) Zhang, Q.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 5774. (i) Fürstner, A.; Feyen, F.; Prinz, H.; Waldmann, H. *Tetrahedron* **2004**, *60*, 9543. (j) Snider, B. B.; Che, Q. *Org. Lett.* **2004**, *6*, 2877.

(3) (a) Jones, R. C. F.; Bhalay, G.; Carter, P. A.; Duller, K. A. M.; Dunn, S. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 765. (b) Rao Irlapati, N.; Baldwin, J. E.; Adlington, R. M.; Pritchard, G. J.; Cowley, A. *Org. Lett.* **2003**, *5*, 2351. (c) Rao Irlapati, N.; Adlington, R. M.; Conte, A.; Pritchard, G. J.; Marquez, R.; Baldwin, J. E. *Tetrahedron* **2004**, *60*, 9307.

(4) For previous reports from this group, see: (a) Bossharth, E.; Desbordes, P.; Monteiro, N.; Balme, G. *Org. Lett.* **2003**, *5*, 2441. (b) Aillaud, I.; Bossharth, E.; Conreaux, D.; Desbordes, P.; Monteiro, N.; Balme, G. *Org. Lett.* **2006**, *8*, 1113.

(5) For an excellent review on site-selective cross-coupling reactions of multiple halogenated heterocycles, see: Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245.

(6) Previously, the simple 3,5-dibromo-2-pyridone (3,5-dibromo-2-hydroxypyridine) failed to undergo Suzuki bis-coupling with *p*-methoxyphenylboronic acid: Bracher, F.; Daab, J. *Eur. J. Org. Chem.* **2002**, 2288.

(7) (a) den Hertog, H. J. *Recl. Trav. Chim.* **1945**, *64*, 85. (b) Kolder, C. R.; den Hertog, H. J. *Recl. Trav. Chim.* **1953**, *72*, 853. (c) den Hertog, H. J.; Combe, W. P.; Kolder, C. R. *Recl. Trav. Chim.* **1954**, *73*, 704. (d) Wang, C.-S.; McGee, T. W. U.S. Patent (1972), US 3637722.

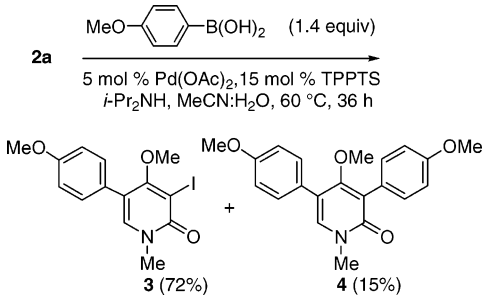
(8) Devadas, B.; Rogers, T. E.; Gray, S. H. *Synth. Commun.* **1995**, *25*, 3199.

(9) This reagent is known to effect the diiodination of pyridinols: Rousseau, G.; Robin, S. *Tetrahedron Lett.* **1997**, *38*, 2467.

(10) This reagent was introduced by Colobert and co-workers: Castanet, A.-S.; Colobert, F.; Broutin, P.-E. *Tetrahedron Lett.* **2002**, *43*, 5047. Note that the group of Olah had previously introduced iodine(I) trifluoromethanesulfonate as a powerful reagent for the iodination of deactivated aromatics: Olah, G. A.; Wang, Q.; Sandford, G.; Surya Prakash, G. K. *J. Org. Chem.* **1993**, *58*, 3194.

application in Pd-catalyzed cross-coupling reactions. At this point, predictions regarding the C-3/C-5 selectivity were not obvious. We could nevertheless hypothesize that steric factors may intervene in the relative rates of coupling and possibly favor cross-coupling at the less-hindered C-5 position.[11] We thus selected the reaction of **2a** with *p*-methoxyphenylboronic acid under Suzuki-type conditions as a model system. Pleasingly, early experiments conducted with various catalyst systems have established the coupling reaction to proceed essentially at C-5, giving the desired 5-aryl-2-pyridone **3** as the only monocoupled product.[12] After further exploration of the reaction parameters, we determined that the system Pd/TPPTS/*i*-Pr_2NH[13] in aqueous MeCN was the most effective to achieve the desired coupling reaction in reasonably good yield (72%) (Scheme 3). Small amounts (ca. 15%) of

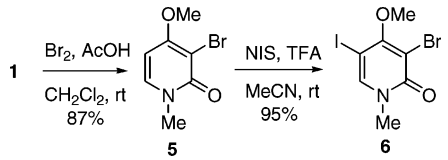
Scheme 3. Site-Selective Suzuki Coupling of **2a**



the bis-arylated 2-pyridone (**4**) were also formed as a slight excess of the boronic acid was needed to ensure complete conversion of the diiodo compound.[14]

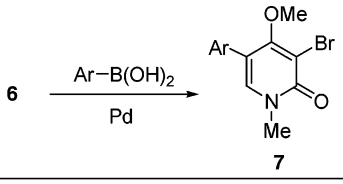
As an alternative, and a potentially enhanced site-selective approach to the 5-aryl-2-pyridones, we next examined the reactivity of 3-bromo-5-iodo-2-pyridone **6** with the hope that the lower capability of the C−Br bond to oxidative addition to palladium would avoid formation of the bis-arylated side product. Thus, **6** was prepared in two high-yielding steps from **1** as depicted in Scheme 4 and subjected to the previous

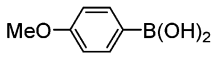
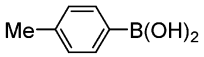
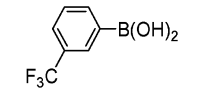
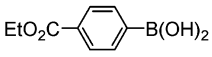
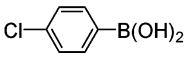
Scheme 4. Synthesis of 2-Pyridone **6** Bearing Two Distinguishable Halides



cross-coupling reaction. Gratifyingly, displacement of the iodine atom took place selectively, affording the desired monosubstituted product **7a**, exclusively, in 88% isolated yield. Accordingly, application of this strategy to a series of arylboronic acids furnished the corresponding 5-aryl-3-bromo-2-pyridones as single products in good to excellent yields (Table 1). Remarkably, both electron-rich and electron-poor boronic acids were found to be suitable partners in this process.

Table 1. Suzuki Monocoupling of 3-Bromo-5-iodo-2-pyridone **6** with Various Boronic Acids[a]



entry	boronic acid	product	yield[b] (%)
1		**7a**	88
2		**7b**	87
3		**7c**	94
4		**7d**	81
5		**7e**	60

[a] Conditions: 1.4 equiv of boronic acid, 5 mol % of $Pd(OAc)_2$, 15 mol % of TPPTS, *i*-Pr_2NH (2.5 equiv), $MeCN/H_2O$ (3:1), 80 °C, 16 h. [b] Isolated yields.

We then briefly explored the reactivity of the remaining halogen atom at C-3 with the aim of further diversifying the 5-aryl-2-pyridones (Scheme 5). For example, Pd-catalyzed reduction of 3-bromo-2-pyridone **7a** by sodium formate provided access to the corresponding monosubstituted alkoxypyridone **8**, a potential precursor of naturally occurring 4-oxy-2-pyridones.[2e] The bromine atom acts here as a removable blocking group that allows regioselective monosubstitution of the pyridone at C-5.[15] Pd-catalyzed C−C bond forming processes have also been investigated. As illustrated by the synthesis of 3-(*p*-chloro)-phenyl-2-pyridone **9** (81% isolated yield), Suzuki cross-coupling reactions of bromine derivative **7a** with arylboronic acids proved very successful

(11) In a study toward pyridovericin, Baldwin and co-workers have examined the Suzuki coupling of the isomeric 3,5-dibromo-2,4-dimethoxypyridine with *p*-methoxyphenylboronic acid, which afforded a 3:1 ratio of the C5−C3 isomers. See ref 3c.

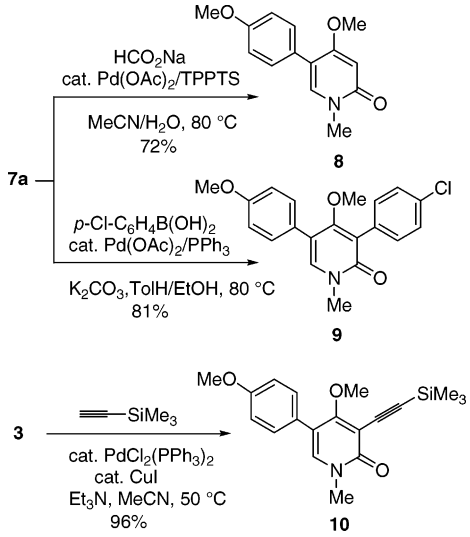
(12) The structure of **3** has been secured by X-ray analysis. See Supporting Information.

(13) TPPTS: tris(3-sulfonatophenyl)phosphane trisodium salt.

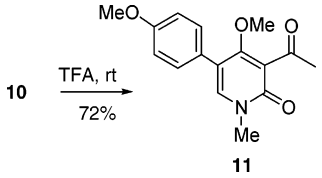
(14) It should be noted that reaction of 3,5-dibromo-2-pyridone **2b** under identical conditions proved rather sluggish and afforded inseparable mixtures of mono- and bis-arylated adducts.

(15) It is worth mentioning that the related C-5 (or C-3) monoarylated 4-methoxy-2-pyrones have previously been prepared by Suzuki coupling of the corresponding monohalogenated pyrones: (a) Cerezo, S.; Moreno-Mañas, M.; Pleixats, R. *Tetrahedron* **1998**, *54*, 7813. (b) Marrison, L. R.; Dickinson, J. M.; Fairlamb, I. J. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2667.

Scheme 5. Diversification of 5-Aryl-3-halo-2-pyridones



Scheme 6. TFA-Promoted Hydration of Alkynylpyridone **10**



with the system $Pd/PPh_3/K_2CO_3$ in toluene/EtOH, thereby opening access to unsymmetrically bis-arylated pyridones.[16] On the other hand, **7a** did not undergo facile cross-coupling reactions with terminal acetylenic compounds. For example, attempts to couple **7a** with trimethylsilylacetylene under classical Sonogashira conditions only afforded low yields (<15%) of the corresponding 3-alkynyl-2-pyridone **10**. However, the iodine derivative **3** could alternatively be successfully used in place of **7a** to furnish **10** in a satisfactory 96% isolated yield.

As an additional synthetic application of this work, it was found that trimethylsilylacetylenic compound **10** could be easily converted to the corresponding 3-acetyl-2-pyridone **11** upon concomitant desilylation and regioselective hydration of the alkyne in TFA (Scheme 6).[17,18] 3-Acetyl-5-aryl-4-oxy-2-pyridones have been the focus of considerable interest, notably as potential precursors of the more elaborate natural 3-acyl-2-pyridones.[19]

In conclusion, we have developed a new, convergent synthetic entry to 3,5-disubstituted 4-oxy-2-pyridones based on sequential, site-selective, Pd-catalyzed cross-coupling reactions on dihalogenated 2-pyridone scaffolds.

The chemistry described herein should find useful applications most probably in the production of simplified analogues of natural alkaloids or, potentially, in total synthesis. Further studies into the synthetic potential of 3,5-dihalogenated 2-pyridones are currently underway in our laboratories.

Acknowledgment. This research was assisted financially by a grant to E.B. and D.C. from Bayer CropScience and the Centre National de la Recherche Scientifique. We thank Dr. E. Jeanneau (Centre de Diffractométrie Henri Longchambon, Université Claude Bernard, Lyon 1) for the X-ray crystallographic analysis.

Supporting Information Available: Experimental procedures, characterization for all compounds, and CIF file for compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Symmetrically 3,5-diarylated 2-hydroxypyridines had been previously prepared from 3,5-dihalopyridines and then converted to the corresponding pyridones: Tagat, J. R.; McCombie, S. W.; Barton, B. E.; Jackson, J.; Shortall, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2143. See also ref 6.

(17) It is likely that the trimethylsilyl group is initially cleaved from the alkyne which then undergoes acidic hydrolysis to the corresponding 3-acetylpyridone. The acid-induced desilylation of silylacetylenes has been documented: Siehl, H.-U.; Kaufmann, F.-P.; Hori, K. *J. Am. Chem. Soc.* **1992**, *114*, 9343.

(18) Usually, acid-promoted hydrations of alkynes require metal catalysis, typically Hg(II) salts. For a review, see: Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. For metal-free methods, see: Olivi, N.; Thomas, E.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Synlett* **2004**, 2175 and references therein.

(19) 3-Acetyl-4-oxypyridones have been used as intermediates in the syntheses of tenellin and ilicicolin H. See refs 2a,b. For other approaches to 3-acetyl-5-aryl-4-oxypyridones, see refs 2c and 3a,b.