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A Synthetic Entry to Furo[2,3-*b*]pyridin-4(1*H*)-ones and Related Furoquinolinones via Iodocyclization

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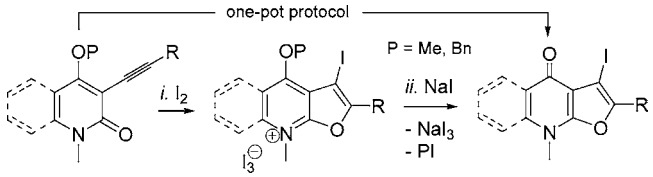
ABSTRACT



***N*-Methyl-4-alkoxy-3-alkynylpyridin-2(1*H*)-ones readily undergo iodine-promoted 5-*endo*-heteroannulation under mild conditions to 3-iodofuropyridinium triiodide salts in moderate to good yields. The latter may be dealkylated in situ upon exposure to an iodide anion to provide the corresponding 3-iodofuro[2,3-*b*]pyridin-4(1*H*)-ones. The same strategy applies to the formation of furo[2,3-*b*]quinolin-4(9*H*)-ones.**

Heteroannulation processes involving acetylenic compounds bearing a tethered nucleophilic substituent are among the most versatile and efficient synthetic methods toward ring-fused heterocycles, of which many rely on transition-metal catalysis.[1] For instance, organopalladium complexes have been extensively used as electrophilic partners which allow the selective formation of functionalized heterocyclic compounds via cyclo-palladation−reductive elimination sequences.[2] On the other hand, iodonium-promoted heteroannulations are also highly attractive since they offer an alternative tactic to similar structures upon subsequent transformation of the iodide functional group into other substituents that are not always accessible by the aforementioned organometallic methods. This has been particularly well illustrated in recent syntheses of benzo[*b*]furans,[3] furopyridines,[4] furo-pyrimidines,[5] benzo[*b*]thiophenes,[6] indoles,[7] isoquinolines and naphthyridines,[8] isoindolinones,[9] isochromenes,[10] isocoumarins,[11]phosphaisocoumarins,[12] and coumestans.[13,14]

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[‡] Bayer CropScience.

(1) For representative illustrations, see the following reviews: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev* **2004**, *104*, 2127. (b) Zeni, G.; Larock, R. C. *Chem. Rev* **2004**, *104*, 2285. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev* **2004**, *104*, 3079. (d) Vizer, S. A.; Yerzhanov, K. B.; Al Aziz Al Quntar, A.; Dembitsky V. M. *Tetrahedron* **2004**, *60*, 5499.

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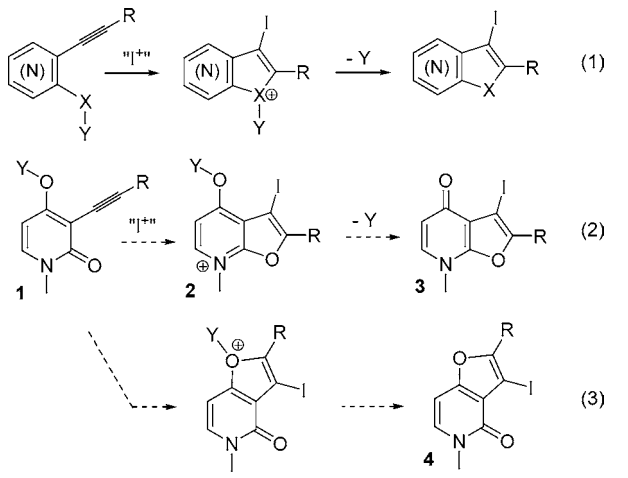
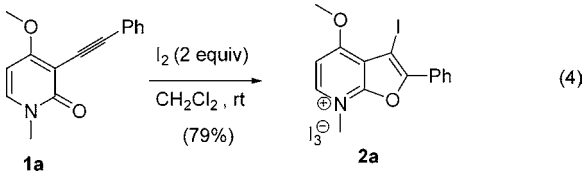
In conjunction with a recent drug development program, we became interested in the furopyridinone ring system, a key structural subunit prevalent in numerous natural products and structural analogues associated with interesting biological activities.[15] Pursuant to our longstanding interest in Pd-catalyzed cyclization processes, we have recently reported the construction of 2,3-disubstituted furo[2,3-*b*]pyridin-4(1*H*)-ones from 3-alkynylpyridin-2(1*H*)-ones (3-alkynyl-2-pyridones) and aryl halides.[16] As a complement to this chemistry, we have now investigated the reactivity of the alkynylpyridones toward iodonium reagents.

Iodonium-promoted cyclizations often require a removable functional group on the nucleophile, which implies a stepwise electrophilic addition/dealkylation sequence involving cationic intermediates (Scheme 1, eq 1). Recent methods have been mainly focused on the cyclization of readily available ortho-functionalized aryl (or heteroaryl) acetylenes. Notably, *o*-benzyloxyalkynylpyridines have been shown to yield 3-iodofuro[2,3-*b*]pyridines upon exposure to iodine in basic medium.[4] In contrast, and in analogy to our previous work, we anticipated that 4-alkoxy-1-methyl-2-pyridones (**1**) would generate pyridinium salts **2** as intermediates and that, hopefully, the counterion would subsequently displace the alkyl group from the remote alkyl ether on the 2-pyridone nucleus to afford the desired 3-iodofuro[2,3-*b*]pyridin-4(1*H*)-ones **3** (Scheme 1, eq 2). The alternative heteroannulative pathway that would lead to the regioisomeric furo[3,2-*c*]-pyridin-2(1*H*)-ones (**4**) via preferential attack of the triple bond by the alkoxy group[17] could also be expected (Scheme 1, eq 3). The iodocyclization precursors **1** were prepared from the corresponding 3-iodo-2-pyridones via Pd-catalyzed cross-coupling reaction with terminal alkynes. Gratifyingly, preliminary experiments conducted with 2-pyridone **1a** as a model substrate have shown that iodine could indeed promote the expected iodocyclization, whereas other iodonium sources (ICl, NIS) proved rather inefficient. The reaction proceeded cleanly at room temperature in CH_2Cl_2 in the presence of 2 equiv of I_2 to afford within 5 h the corresponding pyridinium triiodide salt **2a** exclusively, in 79% isolated yield (eq 4).

Scheme 1. Heteroannulative Strategies toward Fused Heterocycles





The generality of the cyclization process was then explored with other *N*,*O*-dialkylated pyridones. The results summarized in Table 1 demonstrate that I_2 was efficient in most cases and a variety of annulated 3-iodofurans were obtained under the standard conditions. Best results have been achieved with aryl-substituted alkynes **1a**−**e** (Table 1, entries 1−5), which provided the corresponding 2-aryl-3-iodofurans in good yields. Alkyl-substituted alkyne **1f** participated less efficiently in the cyclization process (Table 1, entry 6), whereas acetylene **1g** bearing a $SiMe_3$ group led to a complex mixture of products (Table 1, entry 7). Finally, to explore the scope and generality of the reaction, we further examined the cyclization of the benzo-homologated substrate **1h**. If successful, this would open access to analogous derivatives of the linearly fused furoquinoline alkaloids, of which some important members are substituted at the nitrogen atom, either in the form of 4-methoxyquinolinium methosalts or *N*-alkylated quinolin-4-ones.[18] To our satisfaction, **1h** afforded the desired furoquinolinium triiodide **2h** under identical reaction conditions, albeit in a moderate 56% isolated yield (Table 1, entry 8).

Having examined the scope of the iodocyclization process, we sought an effective method to convert the pyridinium and quinolinium triiodide salts into the corresponding pyridinones and quinolinone, respectively.[19] Various methods have been reported to effect the *O*-dealkylation of 4-alkoxy-

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(15) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627 and previous annual reports.

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(17) An example of such an outcome, albeit not involving activation by iodonium species, has been reported: Gaston, J. L.; Greer, R. J.; Grundon, M. F. *J. Chem. Res., Miniprint* **1985**, 1873.

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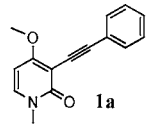
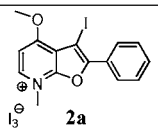
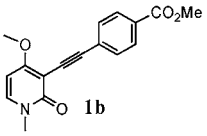
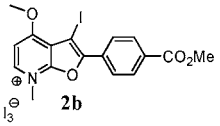
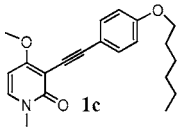
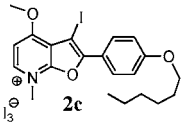
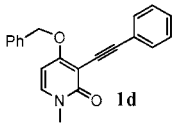
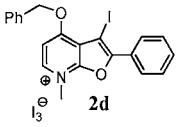
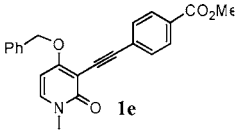
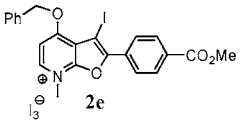
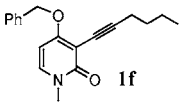
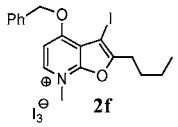
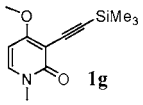
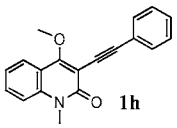
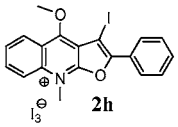
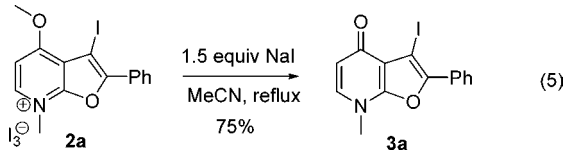
Table 1. Iodocyclization of 4-Alkoxy-3-alkynyl-2-pyridones[a]

entry	pyridone	product(s)	yield (%)[b]
1	 **1a**	 **2a**	79
2	 **1b**	 **2b**	73
3	 **1c**	 **2c**	67
4	 **1d**	 **2d**	72
5	 **1e**	 **2e**	65
6	 **1f**	 **2f**	38
7	 **1g**	complex mixture	-
8	 **1h**	 **2h**	56

[a] All reactions were run on 0.2 mmol of the acetylenic compounds using 2 equiv of I_2 in 2 mL of CH_2Cl_2. [b] Isolated yields (single runs).

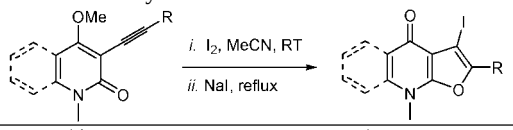
pyridinium (and quinolinium) salts, which include treatment with a halide salt,[20] methanolic sodium hydroxide,[21] or Pd(II) complexes[16] or upon heating in pyridine.[22] After some experimentation, the desired transformation was successively achieved upon simple exposure of the triiodide salts to an external source of iodide. For instance, treatment of **2a** with 1.5 equiv of NaI in refluxing MeCN gave **3a** in 75% isolated yield (eq 5).

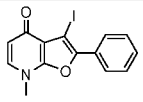
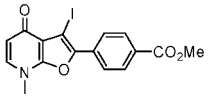
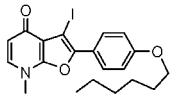
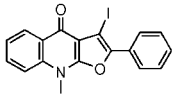


(5)

We next considered the possibility of conducting the heteroannulation and dealkylation steps sequentially in the same reaction vessel without isolation of the triiodide salts. A test experiment was conducted on pyridone **1a** using MeCN as solvent for both steps,[23] which allowed access to **3a** in 79% isolated yield. Accordingly, a range of 3-iodofurans **3b**−**d** were obtained in good to excellent yields from the corresponding *O*-methylated acetylenic precursors (Table 2).

Table 2. One-Pot Synthesis of 3-Iodofurans[a]

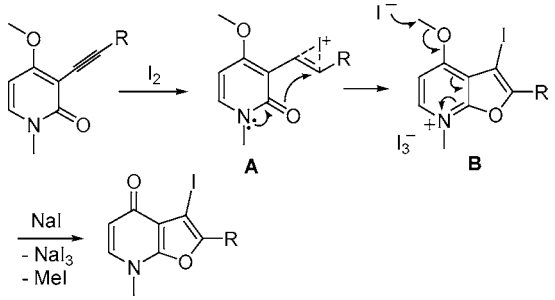


entry	pyridone	product	yield [b]
1	**1a**	 **3a**	79%
2	**1b**	 **3b**	92%
3	**1c**	 **3c**	80%
4	**1h**	 **3d**	85%

[a] All reactions were run on 0.2 mmol of the acetylenic compounds using 2 equiv of I_2 in 2 mL of MeCN at 20 °C (5 h), followed by addition of 1.5 equiv of NaI and refluxing overnight. [b] Isolated yields (single runs).

A plausible mechanism for the formation of the furopyridinones is shown in Scheme 2. Cyclizations are believed

Scheme 2. Mechanism for the Cyclization−Dealkylation Process



to proceed via activation of the carbon−carbon triple bond by coordination to I^+ and subsequent intramolecular attack of the carbonyl oxygen (**A**) to give the pyridinium-fused

(19) The triiodide salts proved remarkably stable, withstanding treatment with aqueous $Na_2S_2O_3$.

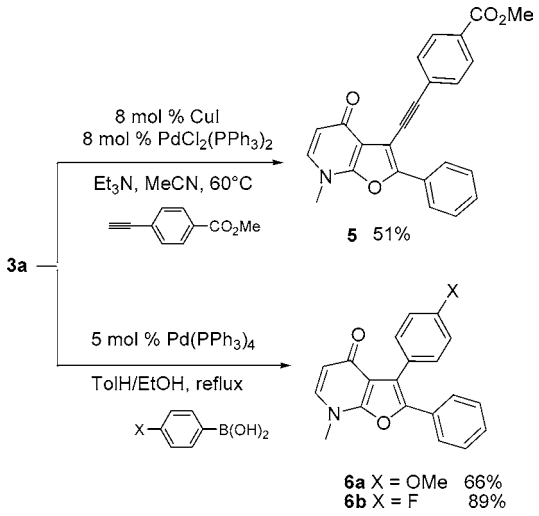
(20) Sekar, M.; Rajendra Prasad, K. J. *J. Nat. Prod.* **1998**, *61*, 294.

(21) Gaston, J. L.; Grundon, M. F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 905.

furan. Upon exposure to iodide, the latter undergoes removal of the protective methyl group via S_N2 displacement (**B**) to liberate the desired pyridinone. Importantly, these reactions only produced volatile (MeI) and water-soluble (NaI_3) byproducts, thus rendering purification of the products very simple.[24]

As mentioned in the Introduction, the presence of the iodide functional group on the furan ring provides an opportunity for further functionalization (Scheme 3). For example, **3a** underwent Sonogashira coupling with 4-methoxycarbonylphenylacetylene to give the corresponding 3-alkynylfuropyridinone **5** in 51% yield. In addition, Suzuki coupling of **3a** with 4-methoxyphenyl boronic acid afforded the bisarylic furan **6a** in 66% isolated yield. This result is particularly interesting in view of the fact that direct cyclofunctionalization of 3-alkynyl-2-pyridones via our cyclopalladation/reductive elimination sequence[16] proved rather difficult using electron-rich aryl halides. On the other hand, the coupling reaction of **3a** with 4-fluorophenylboronic acid furnished, under identical conditions, the previously reported[16] compound **6b** (89% yield), which gave us a chemical confirmation of the furo[2,3-*b*]pyridinone structure (X-ray).

Scheme 3



In summary, the scope of our furo[2,3-*b*]pyridin-4(1*H*)-one synthesis via electrophilic heteroannulation of *N*-alkylated-3-alkynyl-2-pyridones has been expanded to include iodine as electrophile. The presence of the halogen functionality on the heterocyclic products further makes them useful substrates for derivatization, most probably via metal-catalyzed C−C bond formation. Interestingly, the intermediate iminium salts are stable compounds that can be easily isolated. This is of particular importance in the furoquinolinium series due to the occurrence of this subunit in natural products. Further studies into the scope and limitations of this chemistry are currently underway in our laboratories. Future investigations will also focus on the development of other electrophilic cyclizations of alkynyl-2-pyridones and their benzo-fused homologues.

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 M. Trosset for preliminary experiments.

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

OL053048W

(22) Neville, C. F.; Grundon, M. F.; Ramachandran, V. N.; Reisch, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 259.

(23) MeCN was found as effective as CH_2Cl_2 in the cyclization process.

(24) See the Supporting Information. It should be noted that the 4-benzyloxypyridinium salts undergo debenzylation in the same manner. However, purification of the products required chromatography.