ORGANIC LETTERS

2003
Vol. 5, No. 14
2441−2444

Palladium-Mediated Three-Component Synthesis of Furo[2,3-*b*]pyridones by One-Pot Coupling of 3-Iodopyridones, Alkynes, and Organic Halides

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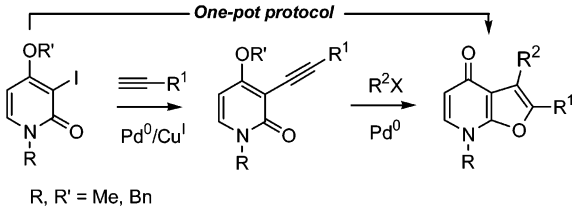
Received April 15, 2003

ABSTRACT



The one-pot assembly of 4-alkoxy-3-iodo-2-pyridones, terminal alkynes, and organic halides has been achieved by integration of two sequential palladium-mediated cross-coupling reactions–Sonogashira and Wacker-type heteroannulation processes–and subsequent deprotection of the alkoxy group to afford furo[2,3-*b*]pyridones.

Chemical processes that allow assembly of several flexible, readily available building blocks in a single operation are drawing increasing attention in the search for new efficient, diversity-oriented synthetic methodologies, and particularly those directed toward heterocycles. Such processes are highly desirable for the rapid generation of libraries of small drug-like molecules for high-throughput screaning.[1] The design of multicomponent syntheses often relies on the integration of multiple individual reactions to give a one-pot synthetic operation, a new concept that also addresses important economical and environmental issues.[2,3] As part of a program aimed at evaluating the synthetic potential of 4-alkoxy-2-pyridones (**1**) as precursors of new drug-like heterocycles, we envisioned that their halogenated analogues **2** could be particularly attractive substrates for the development of a Pd-mediated three-component synthesis of furo[2,3-*b*]pyridones **7**. The strategy would consist of assembling various iodopyridones, alkynes, and organic halides by means of two sequential cross-coupling reactions (Scheme 1).[4] Hence, the unprecedented cross-coupling of 3-alkynylpyridones **4**—obtained in situ from **2** by Sonogashira coupling reaction—with organic halides, if successful, should produce furopy-

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(1) For reviews, see: (a) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133−1144. (b) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321−3329. (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (d) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366−374. (e) Dax, S. L.; McNally, J. J.; Youngman, M. A. *Curr. Med. Chem.* **1999**, *6*, 255−270. (f) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123−131.

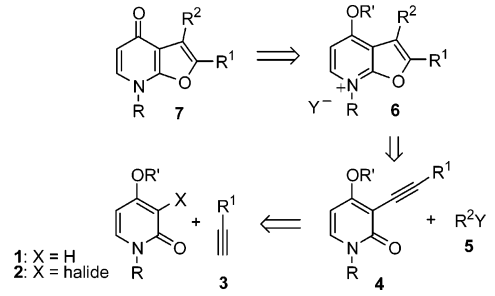
(2) The concept of integrated chemical processes has been recently introduced by Otera: Orita, A.; Yoshioka, N.; Struwe, P.; Braiser, A.; Beckmann, A.; Otera, J. *Chem. Eur. J.* **1999**, *5*, 1355−1363.

(3) For leading references on Pd-based multicomponent reactions relying on integrated chemical processes, see: (a) Grigg, R.; Liu, A.; Shaw, D.; Sunganthan, S.; Washington, M.; Woodall, D.; Yoganathan, G. *Tetrahedron Lett.* **2000**, *41*, 7129−7133. (b) Braun, R.; Zeitter, K.; Müller, T. *Org. Lett.* **2001**, *3*, 3297−3300. (c) Clique, B.; Vassiliou, S.; Monteiro, N.; Balme, G. *Eur. J. Org. Chem.* **2002**, 1493−1499.

(4) A similar strategy had been previously applied to *o*-iodophenols: Chaplin, J. H.; Flynn, B. L. *Chem. Commun.* **2001**, 1594−1595.

10.1021/ol034644y CCC: $25.00 © 2003 American Chemical Society
Published on Web 06/06/2003

Scheme 1. Retrosynthetic Analysis of Furo[2,3-*b*]pyridones

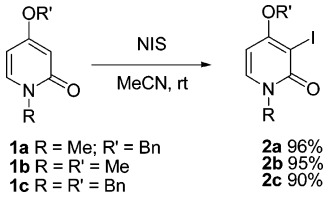


ridinium salts of type **6**. The latter would then collapse to the desired pyridones through subsequent cleavage of the oxygen protecting group. In contrast to their benzannulated homologues—the furo[2,3-*b*]*quinolines*—which are widespread in nature and have been the subject of numerous synthetic and biological studies,[5] the chemistry and biological properties of furo[2,3-*b*]*pyridones* have been much less documented.[6]

The cyclization of nucleophiles bearing a tethered alkyne with organopalladium reagents has been developed by us and other groups into a versatile and efficient method to access diversely substituted carbo- and heterocyclic systems[7,8] and has already contributed to the development of new multicomponent reactions.[9] *To date, however, N-substituted 2-pyridones, and N,N-disubstituted amides in general, have not been used as nucleophilic partners in this process which remains essentially based on the use of anionic nucleophiles*.

To test the feasibility of our concept, we first prepared a series of 4-alkoxy-3-iodo-2-pyridones **2a**−**c**. These were easily prepared in high yields through iodination of the corresponding alkoxypyridones using *N*-iodosuccinimide in MeCN at room temperature (Scheme 2).[10,11]

Scheme 2. Preparation of 4-Alkoxy-3-iodo-2-pyridones **2**



Preliminary studies of the integrated process focused on the separate optimization of each step under the same set of conditions and, preferably, using the same Pd catalyst.[12] Reactions were conducted using 4-benzyloxy-*N*-methyl-2-pyridone **2a**, (*p*-MeO_2C)phenyl acetylene **3a**, and (*p*-MeO_2C)-phenyl iodide **5a** as model substrates. Sonogashira coupling of **2a** with **3a** was found particularly effective when conducted under $PdCl_2(PPh_3)_2$/CuI catalysis in MeCN/Et_3N (9:1) at 60 °C, which afforded the desired 3-alkynylpyridone **4a** in 75% isolated yield. The participation of **4a** in the cyclization−coupling reaction was then probed using 4 mol % $PdCl_2(PPh_3)_2$ reduced by *n*-BuLi, as Pd^0 catalyst,[13] and MeCN as solvent under neutral conditions as no base should be needed in this process. Pleasingly, upon heating **4a** for 24 h under these conditions in the presence of 1.4 equiv of **5a** as coupling partner, the desired furopyridinium **6a** (27%)-was obtained together with the corresponding furopyridone **7a** (22%) and a substantial amount of unreacted **4a** (29%). Conversion of **4a** into the targeted pyridone as the sole bicyclic heterocycle was optimized by extending the reaction time to 48 h, which yielded **7a** in a satisfactory 67% isolated yield (78% based on recovered **4a**) (Scheme 3).

The facile debenzylation of pyridinium iodide **6a** under our reaction conditions was somewhat unexpected.[14] Interestingly, while **6a** proved stable when heated in MeCN for prolonged reaction times (up to 3 days), it was found that its complete conversion into **7a** could be achieved within 24 h by simply adding a catalytic amount of a Pd^{II} complex, for instance $PdCl_2(MeCN)_2$. We reasoned that palladium was probably not only acting as an organometallic reagent in the

(5) For recent reports, see: (a) Pirrung, M. C.; Blume, F. *J. Org. Chem.* **1999**, *64*, 3642−3649 and references therein. (b) Chang, G.-J.; Wu, M.-H.; Chen, W.-P.; Kuo, S.-C.; Su, M.-J. *Drug Dev. Res.* **2000**, *50*, 170−185. (c) Butenschön, I.; Möller, K.; Hänsel, W. *J. Med. Chem.* **2001**, *44*, 1249−1256. (d) Michael, J. P. *Nat. Prod. Rep.* **2001**, 543−559 and previous annual reports.

(6) (a) Snyder, H.; Ebetino, F. *J. Heterocycl. Chem.* **1966**, *3*, 202−205. (b) Prankerd, R.; Stella, V. *Int. J. Pharm.* **1989**, *52*, 71−78. (c) Bhupathy, M.; Conlon, D.; Wells, K.; Nelson, J.; Reider, P.; Rossen, K.; Sager, J.; Volante, P.; Dorsey, B. *J. Heterocycl. Chem.* **1995**, *32*, 1283−1287.

(7) For reactions involving carbonucleophiles, see: Balme, G.; Monteiro, N.; Bouyssi, D. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley & Sons: New York, 2002; pp 2245−2265. For oxygen nucleophiles, see: Cacchi, S.; Arcadi, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley & Sons: New York, 2002; pp 2193−2210. For nitrogen nucleophiles, see: Cacchi, S.; Marinelli, F. in *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley & Sons: New York, 2002; pp 2227−2244.

(8) The methodology has already been successfully applied to the synthesis of other fused furans. Benzo[*b*]furans: (a) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280−9288. (b) Cacchi, S.; Fabrizi, G.; Moro, L. *Synlett* **1998**, 741−745. (c) Monteiro, N.; Balme, G. *Synlett* **1998**, 746−747. (d) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101−5104. (e) Monteiro, N.; Arnold, A.; Balme, G. *Synlett* **1998**, 1111−1113. (f) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670−2673. (g) Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem.* **2002**, *67*, 2365−2368. Furo[2,3-*d*]-pyrimidin-2-ones: Carangio, A.; McGuigan, C.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *Antiviral Chem. Chemother.* **2001**, 187−197.

(9) (a) Inoue, Y.; Itoh, Y.; Yen, I. F.; Imaizumi, S. *J. Mol. Catal.* **1990**, *60*, L1−L3. (b) Wei, L.-M.; Lin, C.-F.; Wu, M.-J. *Tetrahedron Lett.* **2000**, *41*, 1215−1218. (c) Bottex, M.; Cavicchioli, M.; Hartmann, B.; Monteiro, N.; Balme, G. *J. Org. Chem.* **2001**, *66*, 175−179. (d) Garçon, S.; Cavicchioli, M.; Vassiliou, S.; Hartmann, B.; Monteiro, N.; Balme, G. *J. Org. Chem.* **2001**, *66*, 4069−4073. See also ref 8f.

(10) For the preparation of N-substituted 4-alkoxy-2-pyridones, see: (a) Katigiri, N.; Sato, M.; Yoneda, N.; Saikawa, S.; Sakamoto, T.; Muto, M.; Kaneko, C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1289−1296. (b) Buck, J.; Madeley, J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 67−73.

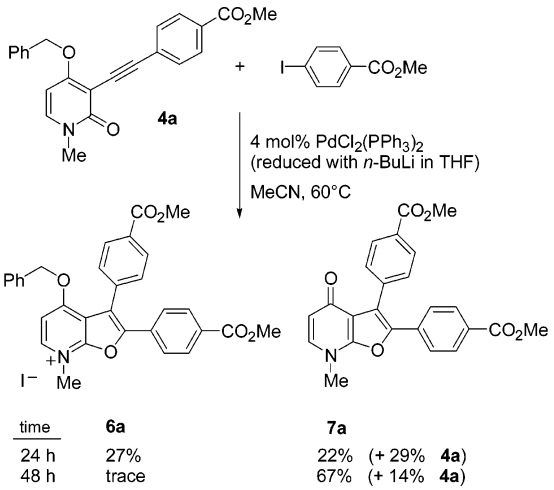
(11) For the iodination of analogous 4-alkoxy-2-pyridones, see: Devagas, B.; Rogers, T. E.; Gray, S. H. *Synth. Commun.* **1995**, *25*, 3199−3210.

(12) The one-pot realization of two consecutive, independent Pd-mediated reactions based on the use of a single Pd catalyst are rare. For recent examples related to multicomponent reactions, see: Grigg, R.; Mariani, E.; Sridharan, V. *Tetrahedron Lett.* **2001**, *42*, 8677−8680. Organ, M. G.; Arvanitis, E. A.; Dixon, C. E.; Cooper, J. T. *J. Am. Chem. Soc.* **2002**, *124*, 1288−1294. See also ref 8f.

(13) Negishi, E.; Takahashi, T.; Akiyoshi, K. *Chem. Commun.* **1986**, 1339. We have already reported the high efficiency of this Pd^0 source in similar reactions; see ref 9c.

(14) Based on literature precedents, we had anticipated that further treatment of the reaction mixture with a source of halide would have been necessary. Sekar, M.; Prasad, J. R. *J. Nat. Prod.* **1998**, 294−296.

Scheme 3



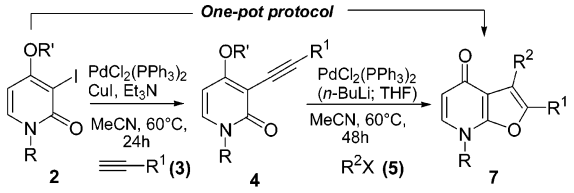
time	6a	7a
24 h	27%	22% (+ 29% **4a**)
48 h	trace	67% (+ 14% **4a**)

cyclization process but also as a Lewis acid[15] in making the benzyloxypyridinium intermediate more prone to cleavage of the benzyl ether through complexation to the alkoxy group.[16,17] Indeed, when **6a** was heated in MeCN in the presence of 4 mol % $Pd(PPh_3)_4$ as a source of Pd^0 and (*p*-MeO_2C)phenyl iodide (5 mol %) clean debenzylation was achieved within 48 h.

A sequential addition, one-pot protocol for the conversion of iodopyridone **2a** into furo[2,3-*b*]pyridone **7a** was then optimized as follows: **2a** (1.0 equiv) and (*p*-MeO_2C)phenyl acetylene (**3a**) (1.2 equiv) underwent the Sonogashira coupling reaction under the conditions previously used (4 mol % $PdCl_2(PPh_3)_2$, 4 mol % CuI, MeCN−Et_3N, 60 °C). After 24 h, (*p*-MeO_2C)phenyl iodide (**5a**) (1.4 equiv) was added and the reaction was left to stir for 48 h at 60 °C to afford **7a** in 83% isolated yield. As a comparison, the same compound was obtained in only 50% overall yield when the reactions were conducted independently. This probably reflects another advantage of the concept which follows from the simplification of experimental procedures: loss of material during the isolation and purification of intermediates is avoided.

The generality of the process was then explored with various iodopyridones, alkynes, and organic halides. Results have been compared with those obtained with the stepwise procedure (Table 1). *With only a few exceptions, an increase in overall yields was observed with the integrated protocol*. Moderate to good yields were generally obtained with arylic halides bearing electron-withdrawing groups. In contrast, as illustrated with the reaction of *p*-methoxyphenyl iodide (Table 1, entry 6), the presence of an electron-donating group

Table 1. One-Pot versus Two-Step Coupling of 4-Alkoxy-3-iodo-2-pyridones with Alkynes and Organic Halides



entry	pyridone (**2**)	alkyne (**3**) R^1 =	organic halide (**5**) R^2X =	*two-step sequence* (**2** → **4** → **7**) overall yield (%) [a,b]	*one-pot protocol* (**2** → **7**) yield (%) [a,c]
1	R=Me R'=Bn (**2a**)	*p*-Me O_2C-C_6H_5 (**3a**)	*p*- MeO_2C-C_6H_4I (**5a**)	**7a** 50 (67)	83
2	**2a**	**3a**	C_6H_5I (**5b**)	**7b** 40 (53)	63
3	**2a**	**3a**	*p*-I-C_6H_4I (**5c**)	**7c** 70 (93)	41
4	**2a**	**3a**	*m*-F_3C-C_6H_4I (**5d**)	**7d** 64 (86)	90
5	**2a**	**3a**	2-iodo thiophene (**5e**)	**7e** 43 (57)	52
6	**2a**	**3a**	*p*-MeO-C_6H_4I (**5f**)	**7f** 24 (32)	6
7	**2a**	**3a**	*p*-O_2N-C_6H_4Br (**5g**)	**7g** 22 (29)	46
8	**2a**	C_6H_5 (**3b**)	**5a**	**7h** 70 (74)	80
9	**2a**	**3b**	*p*-F-C_6H_4I (**5h**)	**7i** 67 (71)	35
10	**2a**	*n*-C_4H_9 (**3c**)	**5a**	**7j** 32 (45)	61
11	R,R'=Me (**2b**)	**3a**	**5a**	**7a** 70 (86)	84
12	R,R'=Bn (**2c**)	**3a**	**5a**	**7k** 38 (47)	58

[a] Isolated yields (single runs). There was essentially no material loss as unreacted alkynylpyridones **4** were generally recovered. [b] Numbers in parentheses refer to yields of the cyclization−coupling reaction (**4** → **7**). [c] See text for reaction conditions.

on the arylic coupling partner had a negative effect on the heteroannulation process,[18] the intermediate 3-alkynylpyridone being recovered as the main product of the reaction. It should be noted that, in this case, best results were achieved using the stepwise protocol. Remarkably, bis-iodobenzene **5c** did not produce any product of double cyclization−coupling reaction even when used in substoichiometric quantities (Table 1, entry 3).[19] It was also found that 4-methoxy- and

(15) Examples of Lewis acid catalysis using Pd^{II} complexes are quite rare; see: Strukul, G. *Top. Catal.* **2002**, *1*, 33−42. Deacetalizations may be induced by palladium catalysts: Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705−708.

(16) The possibility that an arylpalladium halide may serve as a Lewis acid has been suggested recently. Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 15168−15169.

(17) Another palladium-catalyzed process where Pd^{II} acts simultaneously as transition-metal catalyst and Lewis acid has been reported recently. Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764.

(18) A similar trend was recently reported by Larock in the cyclization of *o*-alkynyl benzaldimines: Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920−928.

4-benzyloxypyridones participate equally well in this process, affording the same reaction product after cleavage (Table 1, entries 1 and 11).

Although the NMR spectroscopic data support the formation of furopyridones **7**, the structure was unambiguously secured by an X-ray crystal structure analysis of compound **7i** (Figure 1).[20]

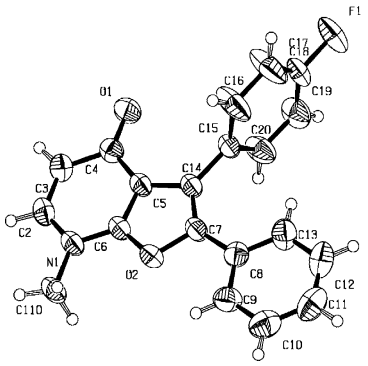
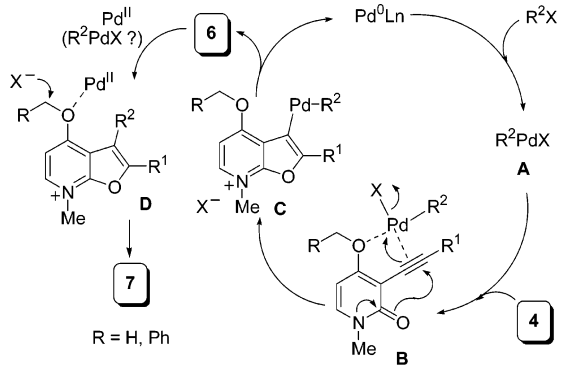


Figure 1. ORTEP representation of compound **7i**.

A plausible mechanism accounting for the cyclization−coupling−deprotection process is depicted in Scheme 4. Oxidative addition of the organic halide to the Pd^0 catalyst generates a σ-aryl$Pd^{II}X$ complex (**A**) which activates, through coordination, the alkyne triple bond of **4** toward nucleophilic attack of the amide. Complexation of the metal to the *o*-alkoxy group may contribute to stabilize intermediate **B** and facilitate the cyclization process to give the Pd-containing furopyridinium **C**. Reductive elimination liberates the cyclization product **6** and recycles the catalyst. Finally, attack of the alkoxy function, supposedly activated by a Pd^{II} species,

Scheme 4. Working Mechanism for the Cyclization−Coupling−Deprotection Process



by the halide counterion induces intermediate **D** to collapse to furopyridone **7**.

In conclusion, we have shown that hitherto unknown, diversely substituted furo[2,3-*b*]pyridones can be prepared in a single, practical operation through the sequential coupling of three readily available starting materials, 3-iodo-2-pyridones, terminal alkynes, and aryl iodides. *In this process, a single palladium catalyst intervenes in three different transformations acting alternatively as an organometallic reagent or as a Lewis acid*: Sonogashira coupling, cyclization, and fragmentation. The successful participation of N-substituted 3-alkynyl-2-pyridones in the Pd-catalyzed cyclization with organic halides prefigures future extensions of this chemistry to the synthesis of other bis-heterocyclic compounds of interest.

Acknowledgment. This research was assisted financially by a grant to E.B. from Bayer CropScience and the Centre National de la Recherche Scientifique. We thank Dr. C. Bavoux for the X-ray crystallographic analysis and Dr. J. P. Vors (Bayer CropScience, Lyon) for his interest in this work.

Supporting Information Available: Experimental procedures, characterization for all compounds, and X-ray data for compound **7i** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) For multicomponent syntheses of symmetrical compounds involving bis-iodobenzene, see: (a) de Meijere, A.; Nüske, H.; Es−Sayed, M.; Labahn, T.; Schroen, M.; Bräse, S. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3669−3672. (b) Azoulay, S.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **2002**, *43*, 9311−9314.

(20) See the Supporting Information for data of the X-ray single-crystal structure determination of compound **7i**.