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Electrophilic Cyclization of *o*-Acetoxy- and *o*-Benzyloxyalkynylpyridines: An Easy Entry into 2,3-Disubstituted Furopyridines

Antonio Arcadi,*,† Sandro Cacchi,*,‡ Sabrina Di Giuseppe,† Giancarlo Fabrizi,‡ and Fabio Marinelli†

Dipartimento di Chimica Ingegneria Chimica e Materiali della Facoltà di Scienze, Università di L'Aquila, Via Vetoio, Coppito Due, I-67100 L'Aquila, Italy, and Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi "La Sapienza", P.le A. Moro 5, 00185 Rome, Italy

sandro.cacchi@uniroma1.it

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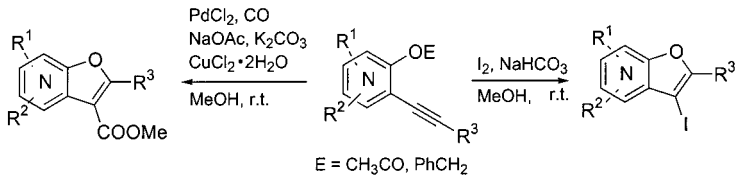
ABSTRACT



2,3-Disubstituted furo[3,2-*b*]pyridines, 2,3-disubstituted furo[2,3-*b*]pyridines, and 2,3-disubstituted furo[2,3-*c*]pyridines are readily prepared under mild conditions via the palladium-catalyzed cross-coupling of 1-alkynes with *o*-iodoacetoxy- or *o*-iodobenzyloxypyridines, followed by electrophilic cyclization by I_2 or by $PdCl_2$ under a balloon of carbon monoxide.

The furopyridine nucleus represents a useful pharmacophore in a variety of therapeutic areas.[1] Recently, this structural unit has been incorporated into HIV protease inhibitor candidates.[2] Despite its importance, however, synthetic methodologies for its construction remain limited, and the provision of sufficient amounts of these substances may represent the bottleneck for further studies and development in medicinal chemistry.[3] Our palladium-catalyzed coupling-cyclization of *o*-iodopyridinols with terminal alkynes[4,5] and of *o*-alkynylpyridinols with aryl and vinyl halides or triflates[6] are among the most general and versatile synthetic methodologies for the preparation of a variety of 2-substituted furopyridines. The synthesis of 3-substituted furopyridines is carried out by the palladium-catalyzed cyclization of iodopyridinyl allyl ethers.[7] However, the preparation of 2,3-disubstituted furopyridines still remains a synthetic challenge.

* Email for A.A.: arcadi@univaq.it.
† Università di L'Aquila.
‡ Università degli Studi "La Sapienza".

(1) (a) Rapoport, H.; Van Sickle, A. P. *J. Org. Chem.* **1990**, *55*, 895. (b) Hoffman, J. M., Jr. U.S. Patent 4,808,595, 1989; *Chem. Abstr.* **1989**, *111*, 115159m.

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(5) For some applications of our palladium-catalyzed coupling-cyclization of *o*-iodopyridinols with terminal alkynes, see: (2-substituted furo[2,3-*b*]-pyridines) ref 2b and 2c, (2-substituted furo[2,3-*c*]pyridines) Wishka, D. G.; Graber, D. R.; Seest, E. P.; Dolak, L. A.; Han, F.; Watt, W.; Morris, J. *J. Org. Chem.* **1998**, *63*, 7851. Reference 2a.

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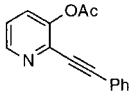
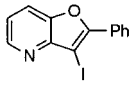
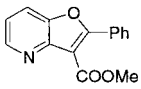
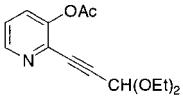
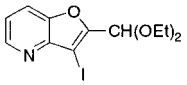
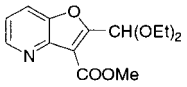
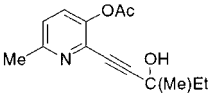
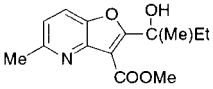
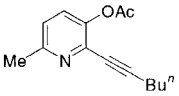
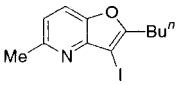
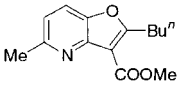
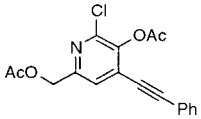
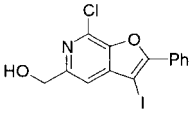
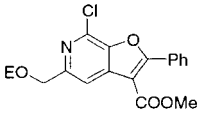
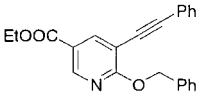
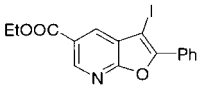
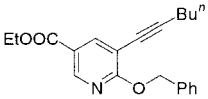
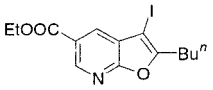
There are only a few reports concerning the synthesis of this class of compounds,[8] and the development of new, more versatile procedures appears desirable. Our success in preparing 2,3-disubstituted benzo[*b*]furans via iodocyclization of *o*-alkynylphenols[9,10] followed by palladium-catalyzed reactions of the resultant 2-substituted 3-iodobenzo[*b*]furans encouraged us to employ related chemistry for the preparation of 2,3-disubstituted furopyridines. We were also stimulated by our involvement in a program devoted to the development of more potent Aβ aggregation inhibitors, based on the synthesis of isosteres of related benzofurans. Recently, a number of benzofurans have been identified as efficient Aβ aggregation inhibitors.[11] The formation of fibrillar protein aggregates is an important pathological feature of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and the prion diseases.[12]

In analogy to our previous work,[9] *o*-akynylpyridinols were initially selected as the starting alkynes. However, under the conditions used by us for the preparation of *o*-alkynylphenols from *o*-alkynylphenylacetates,[13] *o*-acetoxyalkynylpyridines produced *o*-akynylpyridinols in low yield, 2-substituted furopyridines being the main reaction products. For example, removal of the protective acetyl group from **1a** (acetone/2 N HCl, 4 h, 60 °C) gave 2-phenyl-furo[3,2-*b*]pyridine in 68% yield. The desired 2-phenylethynyl-pyridin-3-ol was isolated only in 25% yield and showed a strong tendency to cyclize on storage.

After some experimentation, we were very pleased to find that *o*-acetoxyalkynylpyridines **1** could be directly employed in the preparation of 2-substituted 3-iodofuropyridines via iodocyclization, with the advantage of replacing a stepwise synthesis with a domino process.[14] Compounds **1a**−**e**, bearing electron-donating and moderately electron-withdrawing substituents in the pyridine fragment, were prepared by using a procedure based on the palladium-catalyzed reaction of 1-alkynes with *o*-acetoxyhalopyridines in THF at room temperature in the presence of a catalytic amount of CuI[15] (see Table 1).

Table 1. Preparation of 2-Substituted 3-Iodofuropyridines **2** and 2,3-Disubstituted Furopyridines **7**

entry	compounds **1** and **3** (% yield)	procedure[a]	products (% yield)[b]
1	 **1a** (80)	A	 **2a** (76)
2	**1a**	B	 **7a** (62)
3	 **1b** (74)	A	 **2b** (60)
4	**1b**	B	 **7b** (50)
5	 **1c** (84)	B	 **7c** (70)
6	 **1d** (75)	A	 **2c** (62)
7	**1d**	B	 **7d** (67)
8	 **1e** (72)	A	 **2d** (72)
9	**1e**	B	 E = H, **7e** (31) E = Ac, **7e'** (50)
10	 **3a** (91)	C	 **2e** (72)
11	 **3b** (93)	C	 **2f** (57)

[a] Procedure A. **1**/I_2/$NaHCO_3$ = 1:3:3 in MeOH at rt (0.51−3.38 mmol scale). Procedure B. **1**/K_2CO_3/NaOAc/$CuCl_2 \cdot 2H_2O$/$PdCl_2$ = 1:2:2:3:0.05 in MeOH at rt, under a balloon of carbon monoxide (0.47−2.72 mmol scale). Procedure C. **3**/I_2/$NaHCO_3$ = 1:3:3 in EtOH at rt (0.62−1.23 mmol scale). [b] Yields refer to single runs and are given for isolated products.

Iodocyclization of *o*-acetoxyalkynylpyridines **1a**−**e** generates, under the conditions shown in Scheme 1, the corresponding 2-substituted 3-iodo-furo[3,2-*b*]pyridines and 2-sub-

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(9) Arcadi, A.; Cacchi, S.; Fabrizi, G., Marinelli, F.; Moro, L. *Synlett* **2000**, 1432.

(10) For other examples of iodine-promoted cyclization of alkynes to give heterocycles, see: (a) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 622. (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973. (c) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651. (d) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron Lett.* **2001**, *42*, 2859. (e) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857. (f) Djuardi, E.; McNelis, E. *Tetrahedron Lett.* **1999**, *40*, 7193. (g) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **1999**, *64*, 3798. (h) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc. Chem. Commun.* **1998**, 2207. (i) Redfern, A. L.; Gilmore, J. *Synlett* **1998**, 731. (j) Ren, X.-F., Konaklieva, M. I.; Shi, H.; Dicy, H.; Lim, D. V.; Gonzales, J.; Turos, E. *J. Org. Chem.* **1998**, *63*, 8898. (k) Bew, S. P.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1996**, 1007.

(11) (a) Allsop, D.; Howlett, D.; Christie, G., Karran, E. *Biochem. Soc. Trans.* **1998**, *26*, 459. (b) Howlett, D.; Allsop, D.; Karran, E. *Neurobiology of Alzheimer's Disease*; Dawbarn, D., Allen, S. J., Eds.; Bios Scientific Publishers: Oxford, 1999; pp 9−49.

(12) Kakizuka, A. *Trends Genet.* **1998**, *14*, 396.

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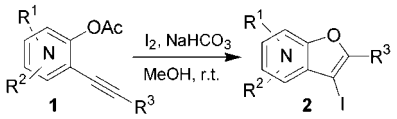
(14) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

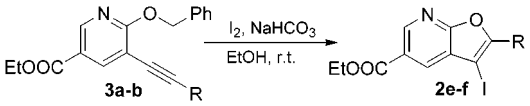
Scheme 1



stituted 3-iodo-furo[2,3-*c*]pyridines **2** in good yields (Table 1, entries 1, 3, 6, 8).

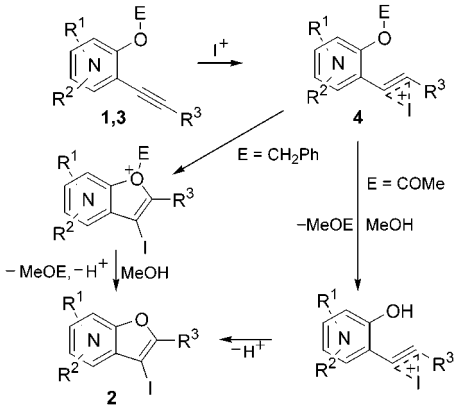
The preparation, according to the above procedure,[15] of *o*-acetoxyalkynylpyridines containing strongly electron-withdrawing substituents in the pyridine ring was prevented by the instability of the corresponding *o*-acetoxyhalopyridines. The latter, in fact, whose preparation was attempted via acetylation of *o*-halopyridinols, were found to undergo a deacetylation reaction under workup conditions, thus making them unsuitable as partners in the coupling step. The use of other protecting groups was explored, and the benzyl group proved to give satisfactory results. The benzyl derivatives **3a,b**, prepared in high yield through the palladium-catalyzed coupling of the corresponding *o*-iodobenzyloxy derivative and phenylacetylene, afforded the furo[2,3-*b*]pyridines **2e,f** in good yield (Scheme 2) (Table 1, entries 10 and 11).

Scheme 2



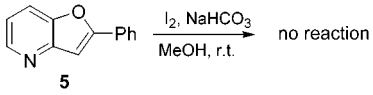
As for the reaction mechanism of *o*-acetoxyalkynylpyridines (Scheme 3), a tentative rationale considers the following steps: (1) initial formation of the bridged-ion intermediate **4**, (2) nucleophilic attack of methanol to the carbonyl group to free the pyridinolic oxygen, and (3) intramolecular nucleophilic attack of the oxygen across the activated carbon−carbon triple bond to give the target furopyridine product.

Scheme 3



Though removal of the acetyl group before formation of **4** cannot be excluded, a deacetylation step following the formation of **4** appears more likely. Premature removal would be expected to generate 2-substituted furopyridines in significant yield, whereas the formation of 2-substituted furopyridines has been observed only in trace amounts under iodocyclization conditions. Isolation of 2-phenylfuro[3,2-*b*]-pyridine **5** in 45% yield together with 2-(phenylethynyl)-pyridin-3-ol (52% yield) after subjecting **1a** to our standard conditions for 4 h, omitting I_2, gives support to this hypothesis. The possibility that the formation of **2** may proceed through (1) deacetylation, (2) cyclization, and (3) iodination of the resultant 2-substituted furopyridines is ruled out by the following experiment: 2-phenyl-furo[3,2-*b*]pyridine **5** was recovered essentially unchanged (90%) after treatment with I_2 and $NaHCO_3$ in CH_3OH at room temperature for 24 h (Scheme 4).

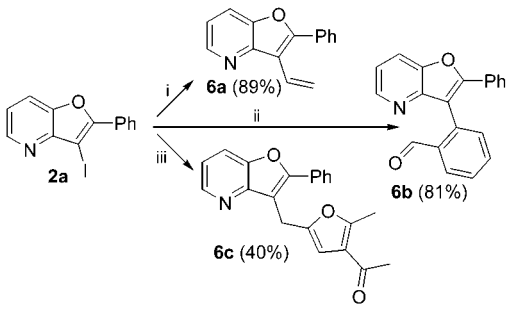
Scheme 4



With benzyl derivatives, the reaction may proceed through an alternative reaction pathway involving the nucleophilic attack of the oxygen to the activated carbon−carbon triple bond before the cleavage of the O−C_{benzyl} bond. Accordingly, the benzyl derivative **3a** was recovered unchanged after treatment under reaction conditions omitting I_2.

The potential of 2-substituted 3-iodofuropyridines **2** as precursors for increasing molecular complexity via palladium-catalyzed reactions[16] has been briefly investigated using **2a** as the model compound. Some examples are shown in Scheme 5.

Scheme 5



i: $H_2C{=}CH{\cdot}SnBu_3$, LiCl, $Pd(PPh_3)_4$, *tert*-butylcatechol, 90°C, 12h
ii: *o*-$C_6H_4(CHO)B(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, $PhCH_3$, 85°C, 2h
iii: $CH_3COCHCOCH_3$, K_2CO_3, $Pd(PPh_3)_4$, DMF, 60°C, 3h
$CH_2C{\equiv}CH$

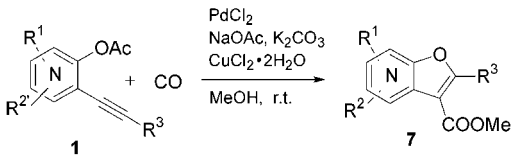
Compound **2a**, however, failed to give the corresponding 2-phenyl-3-carboxymethylfuropyridine **7a** in satisfactory yield under alkoxycarbonylation conditions. For example,

treatment of **2a** (0.79 mmol) with methanol (5 mL) under a balloon of CO in the presence of triethylamine (15.8 mmol) and $Pd(PPh_3)_4$ (0.04 mmol) at 60 °C for 24 h led to the formation of **7a** in only 13% yield.

A nice solution to this came up when we discovered that electrophilic activation by $PdCl_2$ can allow the direct formation of 2-substituted 3-carboxymethylfuro[3,2-*b*]pyridines and 2-substituted 3-carboxymethylfuro[2,3-*c*]pyridines **7** from *o*-acetoxyalkynylpyridines **1**. Reactions were carried out by subjecting **1** to $PdCl_2$ in methanol, under a balloon of carbon monoxide, in the presence of NaOAc and K_2CO_3 as the bases and $CuCl_2$ as the oxidative agent (Scheme 6). Our preparative results are summarized in Table 1 (entries 2, 4, 5, 7, 9).

In summary, we have shown that employment of *o*-acetoxy- and *o*-benzyloxyalkynylpyridines in sequential *O*-deprotection/electrophilic cyclization reactions can provide an easy entry into 2,3-disubstituted furopyridines at room temperature. Further work is in progress to extend the synthetic ease of the present methodology to the preparation of more complex molecular structures.

Scheme 6



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Supporting Information Available: A complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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