Tetrahedron Letters 50 (2009) 614–616

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of furo[2,3-*b*]pyridin-4(7*H*)-ones and related quinolinone via Brønsted acid-promoted cyclisation of alkynes

Emmanuel Bossharth [a], Philippe Desbordes [b], Nuno Monteiro [a,*], Geneviève Balme [a,*]

[a] *ICBMS, Institut de Chimie et de Biochimie Moléculaire et Supramoléculaire (UMR 5246 du CNRS), Université Lyon 1, ESCPE Lyon, 43 Bd du 11 novembre 1918, 69622 Villeurbanne, France*
[b] *Bayer CropScience, 14/20 rue Baizet, BP9163, 69623 Lyon Cedex 09, France*

ARTICLE INFO

Article history:
Received 30 October 2008
Revised 14 November 2008
Accepted 18 November 2008
Available online 24 November 2008

Keywords:
Electrophilic annulation
3-Alkynyl-2-pyridones
Brønsted acids
Furopyridinium salts
Furo[2,3-*b*]pyridin-4-ones

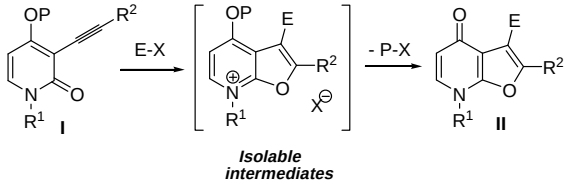
ABSTRACT

N-Alkyl-4-alkoxy-3-alkynylpyridin-2(1*H*)-ones readily undergo acid-promoted 5-*endo*-heteroannulation to furopyridinium intermediates that are dealkylated in situ to provide the corresponding furo[2,3-*b*]-pyridin-4(7*H*)-ones. The same strategy applies to the formation of furo[2,3-*b*]quinolin-4(9*H*)-ones. In the case of Me_3Si-substituted alkynes, hydration of the triple bond was observed.

As part of a drug development programme, we recently started exploring the reactivity of 4-alkoxy-3-alkynyl-2-pyridones (**I**) as potential precursors of the furo[2,3-*b*]pyridin-4-one ring system (**II**), a key-structural subunit prevalent in a number of natural products and structural analogues associated with interesting biological activities.[1] We have already successfully developed organopalladium- as well as iodonium-promoted heteroannulation processes as two complementary synthetic entries to 3-substituted furopyridones.[2] These one-pot transformations have been demonstrated to proceed via cationic cyclisation with subsequent in situ cleavage of the pyridonyl alkyl ether via nucleophilic displacement by a halide anion (Scheme 1).

In an effort to broaden the scope of this class of reactions, we set out to develop an alternative cyclisation process that may provide access to the analogous 3-unsubstituted furan derivatives (**II** with E = H), and have therefore turned our attention to the possible use of Brønsted acids as possible promoters of the electrophilic cyclisation/dealkylation reactions.[3]

Preliminary experiments conducted with 2-pyridone **1a** as model substrate indicated that acetic acid would effectively promote the desired transformation when used as solvent at refluxing temperature. It was also confirmed that the cyclisation process would generate 4-alkoxypyridinium salts as cationic intermediates and that benzyl, as the 4-oxy-2-pyridone protecting group, would



P = Me, Bn
E-X = I_2, organopalladium halide

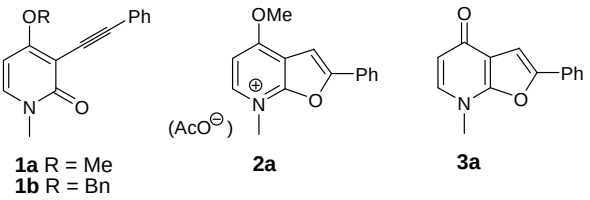
Scheme 1.

show better acid lability compared to methyl, and would therefore ensure efficient collapse of the pyridiniums to the desired pyridones. Indeed, when stirred in refluxing AcOH for 5 h, 4-methoxy-2-pyridone **1a** was totally converted to a cyclisation product leaving the methoxy group untouched, the structure of which was tentatively assigned to furopyridinium **2a** (Scheme 2).[4] Pleasingly, demethylation of **2a** could be observed when heating was prolonged. However, the process proved sluggish providing the desired furopyridone **3a** in only 35% isolated yield (50% conversion from **2a**) after 36 h reaction time.[5] In contrast, 4-benzyloxypyridone **1b** was found to undergo much faster cyclisation–dealkylation compared to **1a** as only 3 h was needed to achieve 70% yield of **3a**.

Although the spectroscopic data supported the formation of furo[2,3-*b*]pyridin-4(7*H*)-one **3a**, the structure was unambiguously secured by an X-ray crystal structure analysis (Fig. 1).[6]

* Corresponding authors. Tel.: +33 0472431416; fax: +33 0472431214 (G.B.).
E-mail addresses: monteiro@univ-lyon1.fr (N. Monteiro), balme@univ-lyon1.fr (G. Balme).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.11.073



Scheme 2.

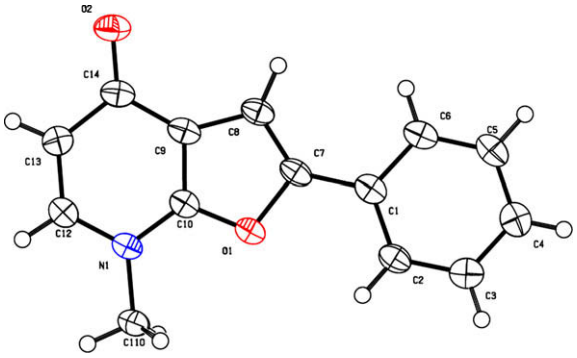


Figure 1. ORTEP representation of **3a**.

Table 1
Reaction of 3-alkynyl-2-pyridones in AcOH[a]

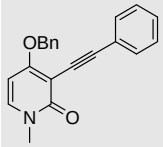
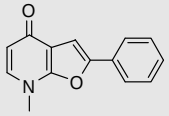
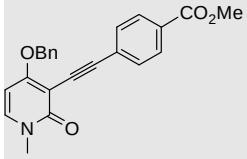
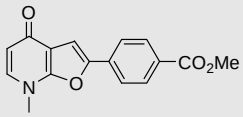
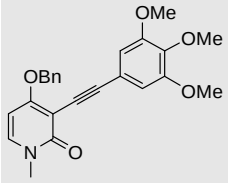
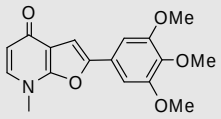
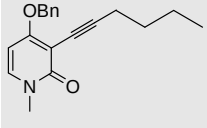
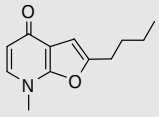
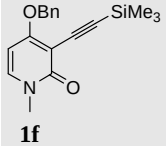
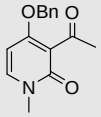
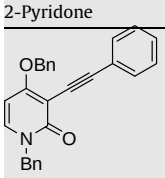
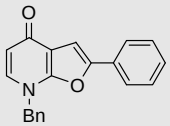
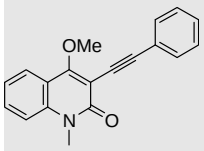
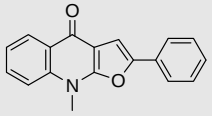
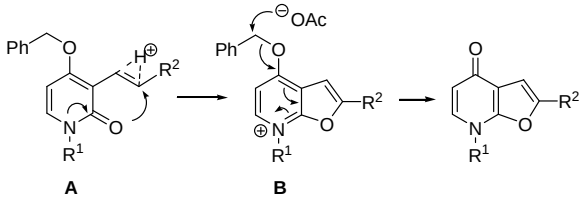
2-Pyridone	Product	Yield[b] (%)
 **1b**	 **3a**	70[c]
 **1c**	 **3b**	45
 **1d**	 **3c**	56
 **1e**	 **3d**	63
 **1f**	 **4**	65

Table 1 (*continued*)

2-Pyridone	Product	Yield[b] (%)
 **1g**	 **3e**	52
 **1h**	 **3f**	77

[a] Reactions performed overnight in refluxing AcOH ensuring complete conversion.
[b] Isolated yields (single runs).
[c] Yield determined after 3 h reaction time (see text).



Scheme 3.

The generality of the cyclisation process was then explored with other N,O-dialkylated pyridones (Table 1). The results summarized in Table 1 demonstrate that AcOH was efficient in most cases, and a variety of 2-substituted furopyridones were obtained under the standard reaction conditions.[7] Interestingly, aryl- as well as alkyl-substituted acetylenes participated equally well in the cyclisation process. However, trimethylsilyl acetylenic compound **1f** showed a different behaviour, furnishing 3-acetyl-2-pyridone **4**[8] as the only reaction product (65% isolated yield) upon concomitant desilylation and regioselective hydration of the alkyne. It is likely that the trimethylsilyl group was initially cleaved from the alkyne, which then underwent acidic hydrolysis to the corresponding 3-acetylpyridone.[9,10] We also examined the cyclisation of the benzo-homologated substrate **1h**[11] that might open access to analogous derivatives of the linearly fused furoquinoline alkaloids.[12] To our satisfaction, **1h** afforded the desired furoquinolinone **3f**[12c] under identical reaction conditions in a good 77% isolated yield.

A plausible mechanism for the cyclisation–debenzylation process is depicted in Scheme 3. The alkynylpyridone is activated by AcOH (intermediate **A**) and undergoes intramolecular nucleophilic attack by the carbonyl oxygen of the amide group to form the furopyridinium intermediate **B**. The latter would undergo cleavage of the *O*-benzyl group by action of the counteranion resulting in the formation of the neutral furopyridone.

In conclusion, we have enlarged the scope of our electrophilic heteroannulation processes of N-alkylated-3-alkynyl-2-pyridones to include access to 3-unsubstituted furo[2,3-*b*]pyridin-4(7*H*)-ones. The procedure is very simple only requiring heating of the 2-pyridones in acetic acid in the absence of any catalyst.

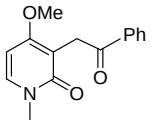
Acknowledgements

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. E. Jeanneau (Centre de Diffractométrie Henri Longchambon, Université Lyon 1) for the X-ray crystallographic analysis, and Dr. D. Bouchu for mass spectroscopic analysis.

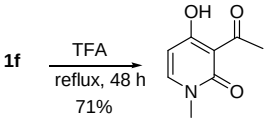
References and notes

1. Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627. and previous reports cited therein.
2. (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.
3. For recent reports dealing with cyclisation/dealkylations of acetylenic compounds in acidic media see: (a) Hellal, M.; Bourguignon, J.-J.; Bihel, F. J.-J. *Tetrahedron Lett.* **2008**, *49*, 62; (b) Ermolat'ev, D. S.; Mehta, V. P.; Van der Eycken, E. V. *Synlett* **2007**, 3117; (c) LeBras, G.; Provot, O.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron Lett.* **2006**, *47*, 5497; For previous acid-promoted syntheses of furopyridines, see: (d) VanSickle, A. P.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 895.
4. Diagnostic data obtained on analytical sample of furopyridinium **2a** collected by column chromatography (neutral alumina, 5–50% ethanol–acetone): solid, mp 165 °C (dec.). The NMR spectra did not exhibit signals ascribable to the counteranion: ^{1}H NMR (300 MHz, CD_3OD): 4.33 (s, 3H), 4.40 (s, 3H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.50–7.60 (m, 3H), 7.68 (s, 1H), 7.95–8.05 (m, 2H), 8.56 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD): 40.7, 59.8, 100.7, 106.7, 116.5 126.9, 129.1, 130.8, 132.2, 142.6, 157.0, 159.5, 167.8. HRMS (ESI): M^+, 240.1023; calcd for $C_{15}H_{14}NO_2^+$: 240.1025.
5. It is worthy of note that the use of TFA in lieu of AcOH allowed the cyclisation process to take place at room temperature. However, selective cleavage of the 4-methoxy group proved problematic as decomposition of the resulting furopyridinium salt occurred at higher temperatures. Isolation of 2-pyridone **5** as the major side product indicated that competitive cleavage of the furan ring was taking place. For an application of this type of process to the synthesis of quinolin-2-one alkaloids, see: Gaston, J. L.; Grundon, M. F. *J. Chem. Soc., Perkin Trans. 1* **1989**, 905.



5

6. Crystallographic data for compound **3a** have been deposited with the Cambridge Crystallographic Data Centre, No CCDC 684693. Copies of the data can be obtained, free of charge, on application to CCDC (e-mail: deposit@ccdc.cam.ac.uk).
7. Representative procedure for AcOH-promoted cyclisation–debenzylation reactions: A solution of acetylenic pyridone **1b** (225 mg, 0.68 mmol) in glacial acetic acid (4 mL) was refluxed for 3 h. The solvent was then removed in vacuo, and the residue was subjected to column chromatography (SiO_2, acetone) to afford 107 mg (70% yield) of 7-methyl-2-phenylfuro[2,3-*b*]pyridin-4(*7H*)-one (**3a**) as a solid: mp 170 °C (dec.). ^{1}H NMR (300 MHz, CD_3OD): 3.84 (s, 3H), 6.21 (d, *J* = 7.3 Hz, 1H), 7.09 (s, 1H), 7.25–7.35 (m, 3H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.60–7.65 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD): 36.6, 100.5, 113.1, 114.2, 124.1, 128.8, 129.0, 137.5, 151.9, 154.4, 175.7. HRMS (ESI): MH^+, 226.0867; calcd for $C_{14}H_{11}NO_2$: 226.0868.
8. *Selected data for* **4**: ^{1}H NMR (300 MHz, $CDCl_3$): 2.52 (s, 3H), 3.49 (s, 3H), 5.15 (s, 2H), 6.06 (d, *J* = 7.7 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.31–7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 31.7, 37.2, 70.7, 95.5, 115.9, 126.9, 128.4, 128.8, 135.4, 164.4, 200.0 (C4 not observed). HRMS (CI): MH^+, 258.1128; calcd for $C_{15}H_{16}NO_3$: 258.1130.
9. The acid-induced desilylation of silylacetylenes has been documented: Siehl, H.-U.; Kaufmann, F.-P.; Hori, K. *J. Am. Chem. Soc.* **1992**, *114*, 9343; For reviews dealing with acid-promoted hydrations of alkynes, see: Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368; Olivi, N.; Thomas, E.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Synlett* **2004**, 2175. and references cited therein.
10. The peculiar reactivity of TMS-substituted alkynylpyridones in acidic media was previously observed in our laboratories, see for instance: Conreaux, D.; Bossharth, E.; Monteiro, N.; Desbordes, P.; Vors, J.-P.; Balme, G. *Org. Lett.* **2007**, *9*, 271. It is interesting to note that when heated in boiling TFA, **1f** underwent concomitant O-debenzylation to afford the corresponding 3-acetyl-4-hydroxy-2-pyridone **6** in 71% isolated yield. Selected data: mp: 82 °C; ^{1}H NMR (300 MHz, CD_3COCD_3): 2.64 (s, 3H), 3.46 (s, 3H), 5.93 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (75 MHz, CD_3COCD_3): 31.9, 37.8, 100.1, 108.1, 147.3, 162.3, 177.9, 206.9. HRMS (CI): MH^+, 168.0662; calcd for $C_8H_{10}NO_3$: 168.0661.



6

11. Compound **1h** was prepared from 4-methoxy-1-methylquinolin-2-one via iodination (NIS/TFA:1/1, MeCN, rt, 90%), and subsequent Sonogashira coupling of the resulting 3-iodo-4-methoxy-1-methylquinolin-2-one with phenylacetylene (see Ref. 2b).
12. (a) Pirrung, M. C.; Blume, F. *J. Org. Chem.* **1999**, *64*, 3642. and references cited therein; (b) Boyd, D. R.; Sharma, N. D.; Barr, S. A.; Carroll, J. G.; Mackerracher, D.; Malone, J. F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3397; (c) Bar, G.; Parsons, A. F.; Thomas, C. B. *Tetrahedron* **2001**, *57*, 4719.