# Practical One-Pot Syntheses of Regioisomeric Furan-Fused Pyridinones (and Quinolinones) from Common Precursors

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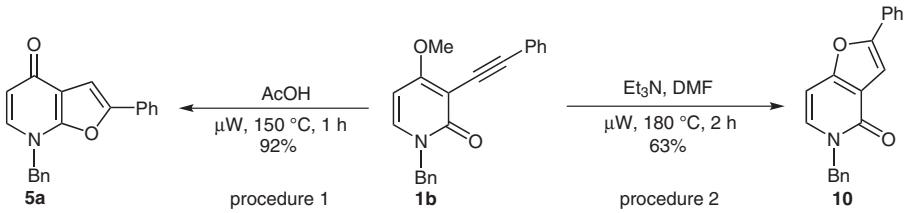
**Abstract:** 3-Alkynyl-4-methoxypyridin-2(1*H*)-ones undergo cyclization via divergent pathways when heated in acetic acid or triethylamine as reagent–solvent under microwave irradiation to furnish selectively furo[2,3-*b*]pyridin-4-ones or their regioisomeric furo[3,2-*c*]pyridin-4-ones, respectively. The same strategy applies to the synthesis of furoquinolinones.

**Key words:** annulation, furan, alkyne, cross-coupling reaction, microwave irradiation




**Scheme 1** Divergent access to regioisomeric furo[2,3-*b*]pyridin-4-ones and furo[3,2-*c*]pyridin-4-ones from 3-alkynyl-4-methoxypyridin-2-ones

## Introduction

The furopyridinone system is present in a wide range of biologically relevant synthetic targets as well as in naturally occurring furoquinolinone alkaloids.[1] In recent years, our group has demonstrated the synthetic value of diversely halogenated 4-alkoxypyridin-2-one scaffolds as precursors of differently fused furopyridinones via acetylide cross-coupling reactions followed by heteroannulations.[2–6] Herein, we wish to disclose practical, one-step procedures that allow selective access to regioisomeric furopyridinones of type **II** and **III** from common 3-alkynyl-4-methoxypyridin-2-one precursors **I** (Schemes 1 and 2). The procedures may also be applied to the synthesis of linearly or angularly fused furoquinolinones.

Our strategy takes advantage of the presence of two potential nucleophilic oxygen centers in the 4-oxypyridin-2-one system that can be amenable to addition onto the alkyne in a selective manner to form a furan ring. Hence, by varying the reagents and reaction conditions, two distinct mechanistic pathways may arise. On the one hand (path a), the presence of an electrophilic species such as acetic acid, capable of activating the triple bond, triggers attack of the alkyne by the carbonyl oxygen of the amide group to form a furopyridinium intermediate **A**. The latter undergoes cleavage of the *O*-methyl group by action of the associated counteranion resulting in the formation of a furo[2,3-*b*]pyridin-4-one **II**. On the other hand (path b), triethylamine-induced $S_N2$-type deprotection of the methoxy oxygen atom unmasks a delocalized β-ketoenolate **B** that undergoes regioselective anionic cycloisomerization to furnish, upon hydrolysis, the regioisomeric furo[3,2-*c*]pyridin-4-one **III**.

## Scope and Limitations

3-Alkynylpyridin-2-ones **1** and **2** and related quinolin-2-ones **3** (Figure 1) are easily prepared from the corresponding iodo precursors using classical Sonogashira cross-coupling procedures.[2–5] Efficient and reliable protocols are also available to iodinate C3 of 4-alkoxypyridin-2-ones and 4-alkoxyquinolin-2-ones on a large scale and in high yields using *N*-iodosuccinimide.[2,4] Introduction of an aryl moiety at C5 of the pyridin-2-one nucleus may be achieved by regioselective Suzuki cross-coupling reactions of 3,5-diiodopyridin-2-ones with arylboronic acids.[7]

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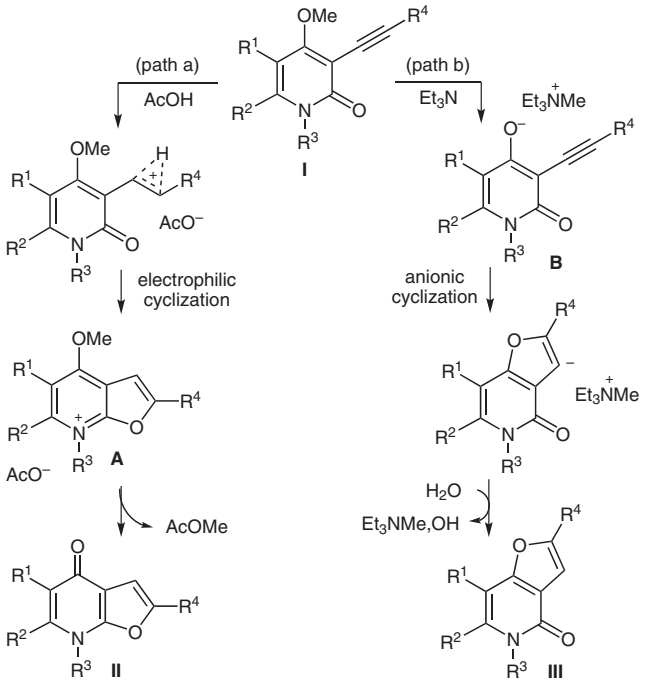



**Scheme 2** Two possible cyclization pathways leading to regioisomeric furan-fused pyridinones

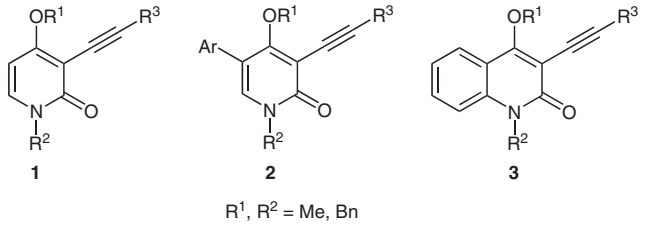
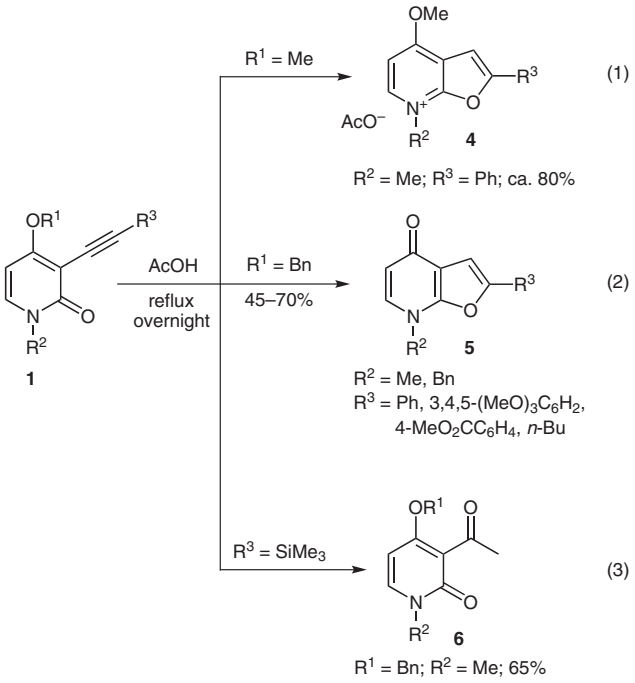



**Figure 1** Various alkyne substrates for heteroannulations

### *Procedure 1: Tandem electrophilic heteroannulation/ dealkylation*

4-Alkoxy-3-alkynylpyridin-2-ones **1** have been shown to undergo electrophilic heteroannulation in refluxing acetic acid under conventional heating.[4] When 4-methoxypyridin-2-ones were involved, the cyclization reaction led to the formation of relatively stable furopyridiniums **4** that did not undergo facile demethylation under the reaction conditions to deliver the desired furo[2,3-*b*]pyridin-4-ones [Scheme 3 (1)]. In contrast, 4-(benzyloxy)pyridin-2-ones were found to undergo clean cyclization/dealkylation due to the better acid lability of the benzyl protecting group with respect to methyl. Thus, a variety of 2-substituted furopyridinones **5** could be obtained under standard reaction conditions. Aryl- as well as alkyl-substituted acetylenes participated equally well in the cyclization process [Scheme 3 (2)]. However, trimethylsilyl acetylenic compounds showed different behavior, furnishing 3-acetylpyridin-2-ones **6** as the sole reaction products upon concomitant desilylation and regioselective hydration of the alkyne[8] [Scheme 3 (3)].

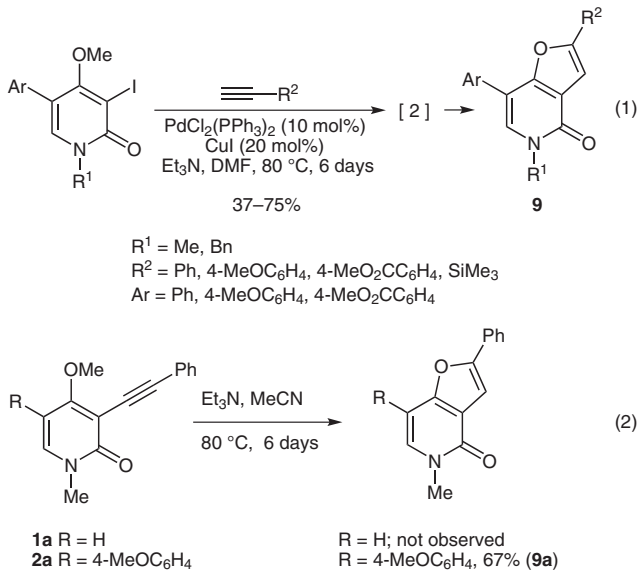
In an effort to widen the substrate scope of our tandem cyclization/dealkylation process to include 4-methoxypyridin-2-ones, we envisaged the possibility of accelerating demethylation of furopyridiniums **4** by performing the reactions under microwave irradiation. Hence, as illustrated with the syntheses of furopyridinones **5a** and **7a** (Table 1), simple microwave heating (150 °C, 1 h) of 3-alkynyl-4-methoxypyridin-2-ones in acetic acid allowed rapid production of the desired compounds in good yields (92% and 80%, respectively) after simple removal of the volatiles in vacuo and chromatographic purification. The same procedure applied nicely to the synthesis of the linearly fused furoquinolinone **8** in quantitative yield.[9]




**Scheme 3** Acetic acid promoted cyclization of alkynylpyridinones under conventional heating

### *Procedure 2: Tandem dealkylation/anionic heteroannulation*

3-Alkynyl-5-aryl-4-methoxypyridin-2-ones **2**, generated under classical Sonogashira cross-coupling conditions from the corresponding 3-iodopyridinones, have been shown to suffer in situ triethylamine-induced demethylation and subsequent anionic cyclization to furo[3,2-*c*]pyridin-4-ones **9** when reaction times longer than normally required were applied.[5] After optimization, the process was found to be effective for the synthesis of diversely substituted furopyridin-2-ones in moderate to good yields from both electron-rich and electron-poor arylpyridinones. Besides, in addition to arylacetylenes, (trimethylsilyl)acetylene took also part in the process [Scheme 4 (1)]. From a mechanistic point of view, it was demonstrated that triethylamine, used as co-solvent, was the sole reagent responsible for the demethylation/heteroannulation



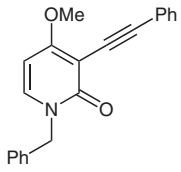
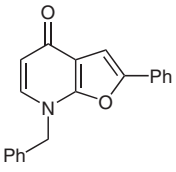
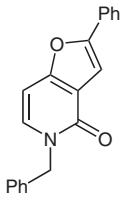
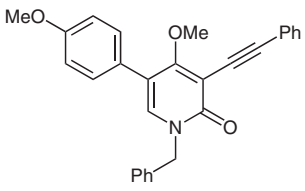
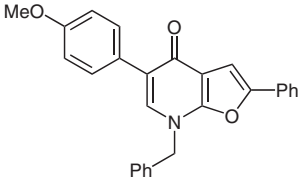
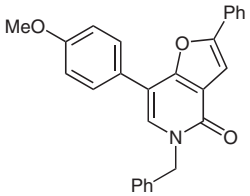
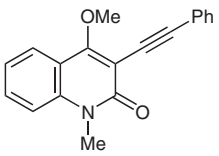
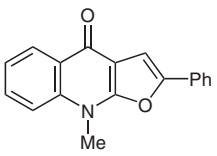
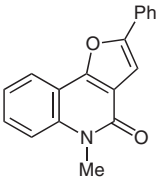

**Scheme 4** Triethylamine-promoted cyclization of alkynylpyridinones under conventional heating

of 3-alkynyl-4-methoxypyridin-2-ones **2**. For example, furopyridinone **9a** was isolated in 67% yield upon simple conventional heating (80 °C) of 3-alkynylpyridin-2-one **2a** in a mixture of triethylamine–acetonitrile (2:1) as solvent. Interestingly, the presence of an aryl group at the C5 position of the pyridinone nucleus was shown to have a beneficial effect on the demethylation step. Indeed, no reaction was observed when 3-alkynylpyridin-2-one **1a** lacking the 5-aryl group was subjected to the same reaction conditions [Scheme 4 (2)].[10]

We were concerned that the synthetic value of this chemical transformation was limited by the inconvenience of the long reaction times (5–6 days) needed to achieve acceptable yields of the desired compounds due to an exceedingly slow demethylation step. We therefore envisaged the possibility that microwave irradiation may again enhance this type of process significantly and possibly extend its substrate scope. Indeed, complete conversion of 5-arylpyridin-2-one **2b** into the corresponding furo[3,2-*c*]pyridin-4-one **9b** was achieved in 90 minutes reaction time in a mixture of triethylamine–acetonitrile (2:1) under microwave irradiation (150 °C). After removal of the volatiles in vacuo and chromatographic purification, **9b** was obtained in 62% isolated yield (Table 1). The same reaction conditions applied to the preparation of the linearly fused furoquinolinone **11**[9] in nearly quantitative yield. Interestingly, even 5-unsubstituted pyridin-2-one **1b** reacted by this procedure to give furopyridinone **10** (63% yield), albeit a higher temperature (DMF, 180 °C) and longer reaction time were required.

In summary, we have shown that microwave irradiation of 3-alkynyl-4-methoxypyridin-2-ones allows access to either furo[2,3-*b*]pyridin-4-ones or their regioisomeric furo[3,2-*c*]pyridin-4-ones depending on the solvent system used (AcOH or $Et_3N$/co-solvent, respectively), the same strategy was applied to the synthesis of linearly and angularly fused furoquinolinones. These metal-free procedures

**Table 1** Acetic Acid versus Triethylamine-Promoted Heteroannulations under Microwave Irradiation

| Entry | Substrate | AcOH-Promoted annulations | | | $Et_3N$-Promoted annulations | | |
|---|---|---|---|---|---|---|---|
| | | Conditions | Product | Yield[a] (%) | Conditions | Product | Yield[a] (%) |
| 1 |  **1b** | AcOH, μW, 150 °C, 1 h |  **5a** | 92 | $Et_3N$–DMF, μW, 180 °C, 2 h |  **10** | 63 |
| 2 |  **2b** | AcOH, μW, 150 °C, 1 h |  **7a** | 80 | $Et_3N$–MeCN, μW, 150 °C, 1.5 h |  **9b** | 62 |
| 3 |  **3a** | AcOH, μW, 150 °C, 1 h |  **8** | 99 | $Et_3N$–MeCN, μW, 150 °C, 1.5 h |  **11** | 96 |

[a] Isolated yields.

are simple and inexpensive, only requiring off-the-shelf reagent–solvents.

**Experimental Section**

Commercially available reagents and solvents were used as purchased. $^1$H and $^{13}$C NMR were recorded in $CDCl_3$ with the solvent resonance as the internal standard. Yields refer to spectroscopically ($^1$H and $^{13}$C NMR) homogeneous materials. Chromatography was performed using Acros silica gel, 35–70 μm, 60A. Melting points are uncorrected.

**7-Benzyl-2-phenylfuro[2,3-*b*]pyridin-4(7*H*)-one (5a); Typical Procedure**

A soln of **1b** (45 mg, 0.14 mmol) in glacial AcOH (1 mL) was added to an appropriate small microwave process vial containing a magnetic stir bar. The vial was sealed with a Teflon septum and placed into a Biotage Initiator™ microwave cavity. After irradiation at 150 °C for 60 min and subsequent cooling of the vessel to 37 °C by the unit, the mixture was concentrated in vacuo and the residue was purified by column chromatography (silica gel, EtOAc–EtOH, 95:5) to give **5a** (40 mg, 92%) as a solid; mp 127–132 °C. The synthesis of **5a** was also performed on a 1.5 mmol preparative scale (84% isolated yield).

FT-IR (neat): 1639 cm$^{-1}$ (C=O).

$^1$H NMR (300 MHz): δ = 5.31 (s, 2 H), 6.31 (d, *J* = 7.8 Hz, 1 H), 7.20–7.23 (m, 2 H), 7.30–7.35 (m, 3 H), 7.36–7.43 (m, 5 H), 7.64 (d, *J* = 7.3 Hz, 2 H).

$^{13}$C NMR (75 MHz): δ = 53.9, 101.8, 114.7, 115.4, 127.9, 128.6, 129.0, 129.1, 129.3, 129.4, 134.2, 134.6, 150.8, 153.5, 175.5.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{16}NO_2$: 302.1181; found: 302.1184.

**5-Benzyl-2-phenylfuro[3,2-*c*]pyridin-4(5*H*)-one (10); Typical Procedure**

A soln of **1b** (45 mg, 0.14 mmol) in a mixture of DMF (1 mL) and $Et_3N$ (2 mL) was added to an appropriate small microwave process vial containing a magnetic stir bar. The vial was sealed with a Teflon septum and placed into a Biotage Initiator™ microwave cavity. After irradiation at 180 °C for 120 min and subsequent cooling of the vessel to 37 °C by the unit, the mixture was concentrated in vacuo and the residue was purified by column chromatography (silica gel, EtOAc–cyclohexane, 20:80) to give **10** (27 mg, 63%) as a solid; mp 165–170 °C. The synthesis of **10** was also performed on a 1.5 mmol preparative scale (58% isolated yield).

FT-IR (neat): 1656 cm$^{-1}$ (C=O).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 5.19 (s, 2 H), 6.50 (d, *J* = 9.0 Hz, 1 H), 7.29–7.12 (m, 8 H), 7.38–7.34 (m, 2 H), 7.69 (d, *J* = 8.8 Hz, 2 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 51.5, 96.3, 102.2, 118.5, 124.6, 128.0, 128.1, 128.6, 129.0, 129.9, 133.7, 137.0, 155.2, 159.0.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{16}NO_2$: 302.1181; found: 302.1177.

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(10) It is likely that, due to steric congestion, the methoxy methyl group in **2a** is rotated out of the plane of the pyridinone ring resulting in decreased stability to nucleophilic attack with respect to **1a**. This effect has often been invoked to explain the high degree of selectivity observed in the cleavage of polymethoxyarenes and is also expected to affect the rate of demethylation of benzo-fused 4-methoxypyridin-2-ones (quinolin-2-ones) like **3a**. For leading references, see: (a) Ahmad, R.; Saá, J. M.; Cava, M. P. *J. Org. Chem.* **1977**, *42*, 1228. (b) Jardon, P. W.; Vickery, E. H.; Pahler, L. F.; Pourahmady, N.; Mains, G. J.; Eisenbraun, E. J. *J. Org. Chem.* **1984**, *49*, 2130. (c) Carvalho, C. F.; Sargent, M. V. *Chem. Commun.* **1984**, 227.