Concise Entries to 4-Halo- and 3-Bromo-4-halo-2-pyridones.

Aurélien Honraedt and Timothy Gallagher *

School of Chemistry, University of Bristol, Bristol BS8 1TS, UK
Fax: (+44) 117 929 8611
E-mail: t.gallagher@bristol.ac.uk

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Abstract: Methods for the synthesis of both simple 4-halo-2-pyridones and more functionalized 3,4-di- and (3,4,5-tri) halo-2-pyridones are described that are based on a combination of Sandmeyer and regioselective (Cu-mediated) halogenation, with a 2-chloro or a 2-benzyloxy moiety serving as a masked 2-pyridine.

Key words: pyridone, polyhalopyridine

2-Pyridones represent a structural motif present in a range of biologically and medicinally important molecules, including current pharmaceuticals and a wide variety of different natural products, such as the Lupin and Lycopodium alkaloids cytisine1 and lyconadin C2 respectively (Figure 1). The ability to modify and vary the substitution pattern of this heterocyclic unit is often dependent on the inherent reactivity of the pyridone nucleus and unlike 3- and 5-halogenated 2-heterocyclic unit is often dependent on the inherent reactivity of the pyridone nucleus and unlike 3- and 5-halogenated 2-pyridones, which are available directly by electrophilic halogenation, the corresponding 4-halo analogues 1a are less readily obtained.3,5

![Figure 1. Pyrid-2-one natural products and target halopyrid-2-ones](image)

Given our interest in the 4-substituted pyridones for the synthesis of cytisine analogs,6 issues around the accessibility of both simple and more complex 4-halo-2-pyridones became apparent. Here we describe general approaches to 4-halopyrid-2-ones (1 X=F, Cl, Br, I), all of which are based on available 2-chloropyridines, and the extension of this chemistry to more complex 3-bromo-4-halopyrido-2-ones 2 (X=F, Cl, Br, I, Figure 1).

4-Amino-2-chloropyridine 3 provided a suitable, commercially available and versatile starting material (Scheme 1) and use of the Sandmeyer reaction, employing t-BuONO (as opposed to protic acid conditions), in the presence of a copper halide, gave the corresponding 2-chloro-4-halopyridines 4 (X=Cl, Br, I). The volatile nature of 4b (X=Cl) made efficient isolation and purification difficult, but also (and in a general sense) unnecessary, and direct conversion of chlorides 4 to the pyridones 1a-c was achieved using sodium acetate in acetic acid.8 This simple two-step procedure was also carried out on a 50 mmol scale in the case of bromide 1c.

Clearly this sequence failed in the case of 4a (X=F) and also 1a but reversing the sequence and carrying out the diazotization/flourination step after the pyridone moiety had been unmasked provided an effective entry to 1a (Scheme 2).

![Scheme 1. Synthesis of 4-halo-2-pyridones 1b-d](image)

4-Amino-2-pyridone 5 has been reported (via hydrolysis of 3) but in our hands, use of the Yoneda and Fukuhara’s procedure9 (KOH in MeOH10) gave a 1:1 mixture of the target pyridone 5 with the corresponding 2-methoxypyridine (i.e. 5, X=OMe). However, use of KOH in toluene (170 °C, sealed tube, 3 d) gave 5 in 97% yield, and Balz-Schiemann fluorination provided 1a in 58% overall yield from 3.

![Scheme 2. 4-Fluoro-2-pyridone 1a](image)

In Schemes 1 and 2, the 2-chloro unit represents the latent pyridone. We have evaluated the use of a 2-benzyloxy moiety as an alternative that can be unmasked under different conditions. This is illustrated for the 4-bromo-2-pyridone 1c with initial halide displacement11 followed by Sandmeyer halogenation of 6 and acidic hydrolysis (of intermediate 7a) to release the 2-pyridone (Scheme 3).

![Scheme 3. Alternative approach to 1c](image)

The overall yield of 1c here is lower than in Scheme 1 (28 vs. 78%) but offers an alternative approach (i.e. via 3) that has
also enabled extension of the product scope as discussed below.

Diazotisation and bromination of 6, in addition to the 3-bromopyridine 7a (62%), also produced di- and tribrominated adducts 7b and 7c in 13 and 12% yields respectively (Scheme 4, and see below).13 These were all readily separated by chromatography and acidic hydrolysis of each provided the corresponding di- and tribrominated pyrid-2-ones 8 and 9 in good yields.

Under Balz-Schiemann conditions, 7d underwent both diazotisation and OBN cleavage (in the presence of HF/py) to give the desired 3-bromo-4-fluoro-2-pyridine 12 directly, and simple exposure of 7d to acidic methanol provided a new entry to the known17 4-amino-3-bromo-2-pyridone 13.

In summary, generally applicable methods for the synthesis of the range of 4-halo-2-pyridones (1a-d) and a series of di and trihalo-2-pyridones (8-12) have been developed.

Supporting information

Experimental procedures, full characterization of compounds, and copies of 1H and 13C NMR spectra are available as a pdf.

Acknowledgment

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References

(3) Scifinder indicates that simple 4-halopyridones are commercially available together with a variety of different methods for synthesis available primarily within the patent literature. Some of the results reported here draw on that patent literature, but our goal has been to define generally applicable methods, rather than different procedures for each specific case.
(5) (a) Leznoff, C. C.; Svisrakaya, P. I.; Yedidia, V.; Miller, J. M., J. Heterocycl. Chem. 1985, 22, 145. (b) We have described an alternative route to 1 (X=F, see ref. 6), because of issues encountered with the separation of 4-and 5-nitropyridines.5a This alternative employed 4-fluoro-2-methoxy pyridine, which is also prepared from 3. (c) 4-Bromo-2-pyridone has also been prepared by O-demethylation (using TMSI) of 4-bromo-2-methoxy pyridine (Litchfield, J.; Sharma, R.; Atkinson, K.; Filipski, K. J.; Wright, S. W.; Pfefferkorn, J. A.; Tan, B.; Kosa, R. E.; Steven, B.; Tu, M.; Kalgutkar, A. S. Bioorg. Med. Chem. Lett. 2010, 20, 6262).
(7) The 3,4-dibromopyridine 2 (X=Br) has commercial suppliers listed with Scifinder but there is no literature describing the synthesis of this derivative.
(9) Attempts to achieve Balz-Schiemann fluorination of 3 under various conditions (as well as in situ conversion to 1a) failed but this may also reflect the likely high volatility of 4a.


(11) Hydrolysis using NaOH in MeOH at 170°C has also been reported. Searls, T.; McLaughlin, W. Tetrahedron 1999, 55, 11985.

(12) This transformation has also been reported in the patent literature using BrOH, NaH in dioxane at 160 °C: Bahmanyar, S. et al. WO 2010/027500.

(13) A control experiment involving exposure of 7b to CuBr2 (MeCN, r.t., as in Scheme 5) failed to give a tribrominated derivative such as 7c. Both 7b and 7c can be prepared in higher yield starting from 7d.16


(15) When Cul was used in this reaction, we saw a less efficient transformation (24% yield based on 28% conversion, see Supporting Information) to give the 3-iodo analogue of 7d. With CuCl2, no reaction with 6 was observed.

(16) Reaction of 7d with CuBr2 under these conditions gave a mixture of 7b and 7c in 54% and 33% isolated yields respectively (see Supporting Information).

GRAPHICAL ABSTRACT REVISED

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\text{NH}_2 \quad \xrightarrow{\text{CuBr}_2; \text{t-BuONO/“halide”; HCl, MeOH}} \quad \begin{array}{c}
\text{X} \\
\text{Br}
\end{array} \\
\begin{array}{c}
\text{Br}
\end{array} \\
\begin{array}{c}
\text{Br}
\end{array}
\]

\[
\begin{array}{c}
\text{X=F, Cl, Br, I} \\
(36-62\% \text{ overall})
\end{array}
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