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

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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-pyridone.

Key words: pyridone, polyhalopyridone

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 cytisine[1] and lyconadin C[2] 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-pyridones, which are available directly by electrophilic halogenation, the corresponding 4-halo analogues **1**[3] are less readily obtained.[4,5]

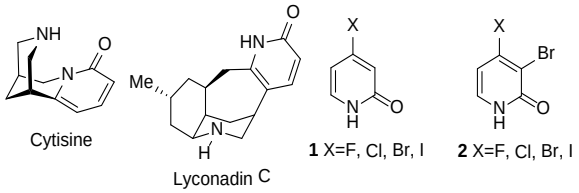
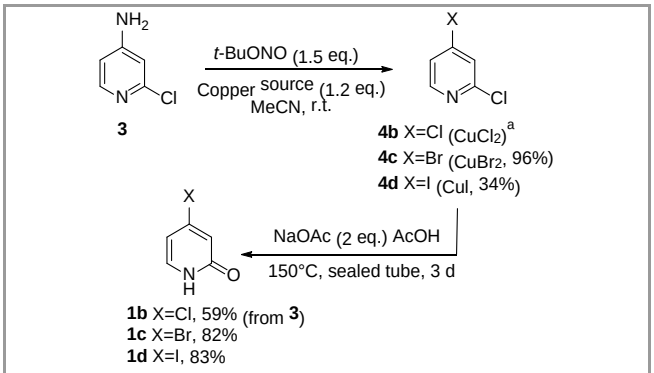


Figure 1. Pyrid-2-one natural products and target halopyrid-2-ones

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,[7] 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**.

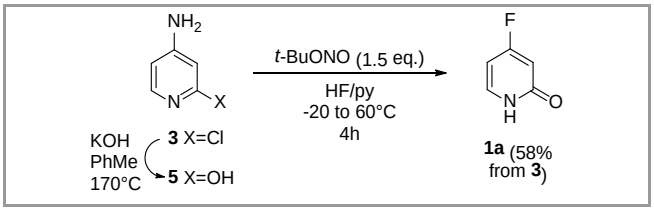
Clearly this sequence failed in the case of **4a** (X=F)[9] (and also **1a**) but reversing the sequence and carrying out the diazotization/fluorination step after the pyridone moiety had been unmasked provided an effective entry to **1a** (Scheme 2).



[a]The volatility of **4b** precluded isolation of solvent-free product, and the crude material was used directly to prepare **1b**.

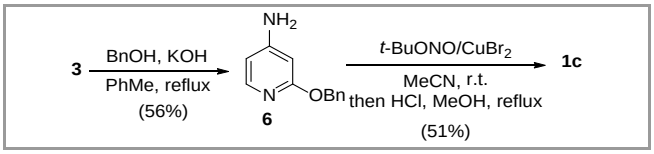
Scheme 1. Synthesis of 4-halo-2-pyridones 1b-d

4-Amino-2-pyridone **5** has been reported (via hydrolysis of **3**) but in our hands, use of the Yoneda and Fukuhara's procedure[10] (KOH in MeOH[11]) 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**

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 displacement[12] followed by Sandmeyer halogenation of **6** and acidic hydrolysis (of intermediate **7a**) to release the 2-pyridone (Scheme 3).

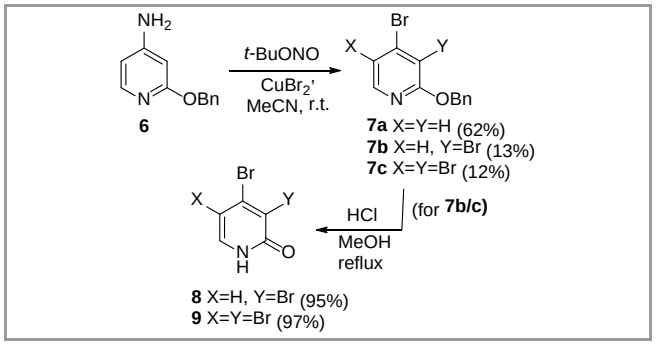


Scheme 3. Alternative approach to **1c**.

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

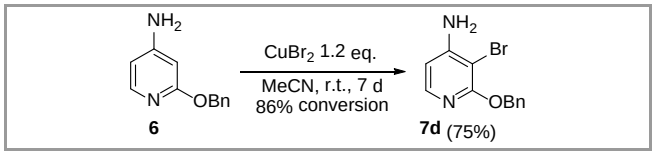
also enabled extension of the product scope as discussed below.

Diazotization and bromination of **6**, in addition to the 3-bromopyridine **7a** (62%), also produced di- and tri-brominated 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.



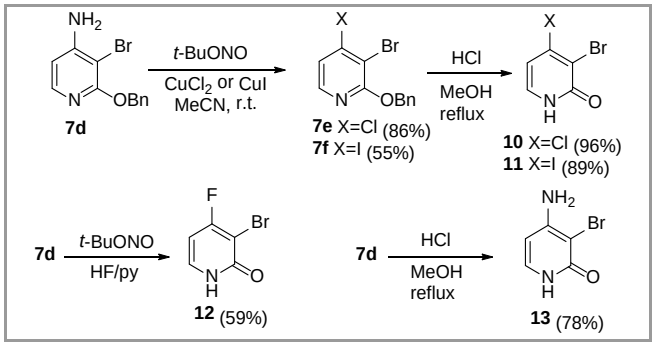
Scheme 4. Di- and Tribromo-2-pyridones **8** and **9**.

The reactivity of 4-aminopyridines towards selective 3-bromination,[14] offered an opportunity to extend this methodology to encompass a wider range of more highly functionalized pyridones as illustrated in Schemes 5 and 6. Using $CuBr_2$ as the preferred halide source, reaction of **6** gave the 4-amino-3-bromopyridine **7d** (Scheme 5).[15] This reaction was best carried out over an extended period at room temperature, however, and importantly, under these mild conditions, we did not observe any dibrominated products (cf. Scheme 4).



Scheme 5. Selective 3-bromination of **6**.

Sandmeyer halogenation of **7d** with the appropriate copper halide ($CuCl_2$ or CuI) gave the 4-chloro and 4-iodopyridines **7e** and **7f** in 86 and 55% yields respectively which underwent O-benzyl cleavage to provide the dihalogenated 2-pyridones **10** and **11**.[16]



Scheme 6. 4-Substituted-3-bromo-2-pyridones.

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-pyridone **12** directly, and simple exposure of **7d** to acidic methanol provided a new entry to the known[17] 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 ^{13}C NMR spectra are available as a pdf.

Acknowledgment

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References

(1) For a recent review on (-)-cytisine synthesis and applications see: Rouden, J.; Lasne, M.-C.; Blanchet, J.; Baudoux, J. *Chem. Rev.* **2014**, 114, 712.

(2) Ishiuchi, K.; Kubota, T.; Ishiyama, H.; Hayashi, S.; Shibata, T.; Kobayashi, J. *Tetrahedron Lett.* **2011**, *52*, 289.

(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.

(4) Key references to 2,4-dihalopyridines and 4-halo-2-pyridones: (a) 2,4-dichloropyridine: (from 2-chloro-4-iodopyridine) Marzi, E.; Bigi, A.; Schlosser, M. *Eur. J. Org. Chem*. **2001**, 1371 and references therein. 4-Chloro-2-pyridone: Graf, R.; Lederek-Ponzer, E.; Freiberg, L. *Ber*. 1931, 64B, 21. (b) 4-Bromo and 4-iodo-2-pyridones: Hadida, R. *et al* WO 2008/141119. Claremon, D. A. *et al* WO 2009/134400. Renz, M.; Schuehle, M.; Xu, Z. US Pat 2010/0331320; Roth, G. J.; Fleck, M.; Neubauer, H.; Nosse, B. US Pat 2012/0214782.

(5) (a) Leznoff, C. C.; Svirskaya, 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-methoxypyridine, which is also prepared from **3**. (c) 4-Bromo-2-pyridone has also been prepared by *O*-demethylation (using TMSI) of 4-bromo-2-methyoxypyridine (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).

(6) Durkin, P.; Magrone, P.; Matthews, S.; Dallanoce, C.; Gallagher, T. *Synlett*, **2010**, 2789.

(7) The 3,4-dibromopyridone **2** (X=Br) has commercial suppliers listed with Scifinder but there is no literature describing the synthesis of this derivative.

(8) This procedure had previously been applied to a 2-chloroquinoline: Ohashi, T.; Oguro, Y.; Tanaka, T.; Shiokawa, Z.; Shibata, S.; Sata, Y.; Yamakawa, H.; Hattori, H.; Yamamoto, Y.; Kondo, S.; Miyamoto, M.; Tojo, H, Baba, A.; Sasaki, S. *Bioorg. Med. Chem*. **2012**, *20*, 5496. See also Roth, G. J.; Fleck, M.; Heine, N.; Kley, J.; Lehmann-Lintz, T.; Neubauer, H.; Nosse, B. US Pat 2012/0214785 (as applied to 4-iodo-2-pyridone).

(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**.

See Scott, D.; Kuduk, S. D.; DiPardo, R. M.; Bock, M. G. *Org. Lett.* **2005**, *7*, 577.

(10) Yoneda, N.; Fukuhara, T. *Tetrahedron*, **1996**, 52, 23.

(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 BnOH, NaH in dioxane at 160 °C: Bahmanyar, S. *et al* WO 2010/027500.

(13) A control experiment involving exposure of **7b** to $CuBr_2$ (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]

(14) For studies associated with copper-mediated halogenation, see Menini, L.; da Cruz Santos, J. C.; Gusevskaya, E. V. *Adv. Synth. Catal.*, **2008**, 350, 2052. N-Bromosuccinimide will also achieve this transformation: Morgentin, R.; Pasquet, G.; Boutron, P.; Jung, F.; Lamorlette, M.; Maudet, M.; Plé, P. *Tetrahedron*, **2000**, *64*, 2772.

(15) When CuI 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 $CuCl_2$, no reaction with **6** was observed.

(16) Reaction of **7d** with $CuBr_2$ under these conditions gave a mixture of **7b** and **7c** in 54% and 33% isolated yields respectively (see Supporting Information).

(17) McNamara, D. J.; Cook, P. D.; Allen, L. B.; Kehoe, M. J.; Holland, C. S.; Teepe, A. G. *J. Med. Chem*. **1990**, *33*, 2006.

GRAPHICAL ABSTRACT **REVISED**