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Confirmation and prevention of halogen exchange: practical and highly efficient one-pot synthesis of dibromo- and dichloropyridazinones

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Abstract—Commercially available anilines were converted by a two step, one-pot process to the corresponding pyridazinones in good to excellent yields. During the process research, a significant halogen exchange was confirmed and prevented which allowed the process to be scaled to multikilogram quantities.

Substituted pyridazinones are useful compounds with a broad array of biological activities.[1] They have been utilized as herbicides, such as Norflurazon and as insecticides, like Pyridaben for crop protection.[2] In drug discovery, pyridainones were identified as selective COX-2 inhibitors (ABT-963[3] and CK-126[4]) and as cardiotonic agents[5] and α_4 integrin receptor antagonists[6] (Fig. 1). Consequently, 4,5-dihalo-3(2H)pyridazinones **1** and **2** are valuable and versatile building blocks[7] for access to these targets and mono- or poly-cyclic pyridazinones because both Cl and Br atoms at the 4- and 5-positions can be easily substituted by a wide variety of N-, O- and C-nucleophiles, allowing introduction of different side chains regioselectively. In addition, **1** and **2** are electron deficient halogenated heterocycles, and they have been successfully applied in palladium catalyzed C–C coupling reactions, such as the Heck, Suzuki and Sonogashira cross-coupling reactions.[8] However, the synthesis of these versatile intermediates has not been previously reported from the commercially available and cheap mucohalic acid precursors, and substituted anilines in a one-pot version.[9] Herein, we report the first practical syntheses of **1** and **2** where the corresponding hydrazine is not commercially available.

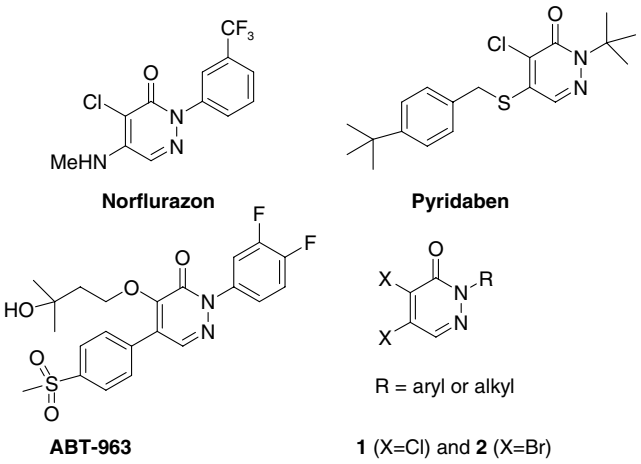

Figure 1. Some important substituted pyridazinone compounds.

During our process research on ABT-963, a selective COX-2 inhibitor, we required an efficient approach to prepare multikilogram quantities of dibromopyridazinone **6**. The early approach to **6** was via a two step process (Scheme 1). A suitably substituted aniline is diazotized with $NaNO_2$/HCl and reduced by excess $SnCl_2$ (3 equiv) to the corresponding hydrazine **4**, isolated and subsequently reacted with mucobromic acid in acetic acid to give **6** in 43% overall yield. This process has several issues: (a) Sn species were precipitated when sodium hydroxide solution was used to neutralize the excess HCl to liberate hydrazine **4**. (b) Serious emulsion

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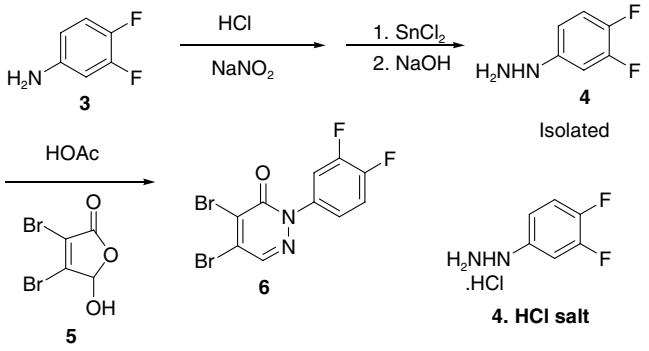


Scheme 1. The original approach to dibromopyridazinone **6**.

occurred when **4** was extracted with organic solvent. (c) The crude hydrazine **4** is brown in color and unstable to storage, making it difficult to determine the amount of mucobromic acid to use in the next step. Finally when a larger amount of $SnCl_2$ was used, it was not easy to stir well during the reaction. Accordingly, initial improvements were realized by reducing the amount of $SnCl_2$ from 3 equiv to 2 equiv, and, instead of isolation of **4**, the HCl salt of **4** was separated and used directly in the next step to make dibromopyridazinone **6**. Thus, the overall yield increased from 43% to 58%, and the product **6** was obtained as a light yellow solid with good purity (>90%). Although the extraction and emulsion were avoided and the yield was improved, it was found that the **4**·HCl salt is soluble in water, resulting in yield loss when **4**·HCl salt was isolated.

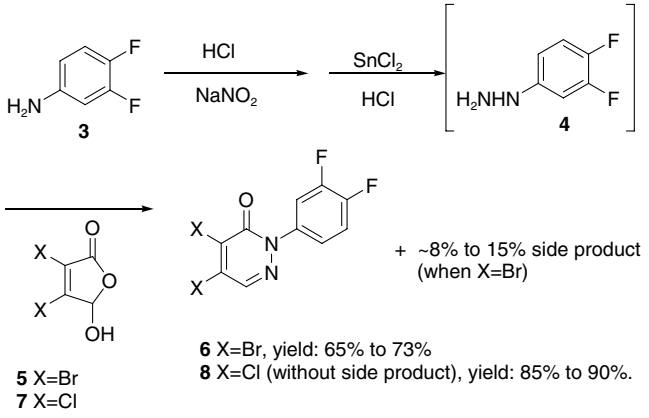
Mucobromic acid and mucochloric acid are soluble in hot HCl solution, while the final dibromopyridazinone **6** has poor solubility in water, therefore, we anticipated the separation of the final products **6** and **8** from excess starting material, mucohalic acid, would be very simple. Thus, we studied the possibility of using a telescoped one-pot process:[10] After **4**·HCl salt formation was completed, *without adding acetic acid as solvent*, 1 equiv of mucobromic acid was added directly, and the reaction was heated to 80–90 °C. The product **6** precipitated during the reaction. After 2 h of heating, the reaction mixture was cooled to room temperature, and the dibromide was isolated in moderate yield (between 65% and 73%), *unfortunately it also generated a new compound* (average 8–15% in HPLC area at 215 nm) which proved prohibitively difficult to remove by recrystallization. Surprisingly, under similar conditions, 4,5-dichloro-3(2H)pyridazinones **8** were produced in excellent yield (85% and 90%) and high purity (96% HPLC area), without the corresponding side product! (Scheme 2).

The analysis of crude product **6** via LC/MS gave an unexpected peak at $m/z = 321$ and 323. This indicated that the side product was from halogen exchange.[11] A further stepwise investigation suggested that the halogen exchange happens at higher temperature, or in the final step. To further prove this, a pure bromide **11** was treated with 6 N HCl for 2 h in HOAc (reflux), and indeed it gave a molecule at $m/z = 285$ and 287, corresponding to a single chlorine–bromine exchange and a purity reduction from 99% to 77% (Scheme 3).

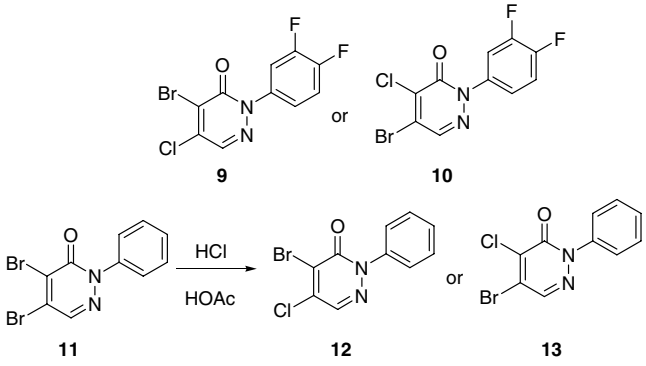
Finally, we decided to use $HBr/NaNO_2$ for diazotization, $SnCl_2$/HBr for the reduction step and water as the sole solvent for the whole process. After these changes, **6** was isolated in 82% with excellent chemical purity (96%). Without further purification, **6** was used directly for the next step. This one-pot process has been successfully scaled up to make 22.0 kg of bromide **6** and utilized in the ABT-963 multikilogram synthesis.

It became clear that to prepare bromide, HBr/water must be used as solvent and, to prepare the chloride, HCl/water must be used as solvent.[12] The generality of this one-pot approach was then tested (Table 1). Several dibromides and dichlorides were prepared in high yield with high purity (>95%). If the aromatic ring contained an electron donating group, the yield was lower (entries 4 and 9), mostly likely due to the lower stability of the diazonium salt and the side reaction (denitrogenation); if the aromatic ring contained electron-withdrawing groups, the yield was higher (entries 3 and 8).

In summary, we have developed a simple, highly efficient one-pot process for preparing 4,5-dihalo-3(2H)pyridazinones. Halogen exchange during the process was confirmed and was prevented by careful choice of reagents.

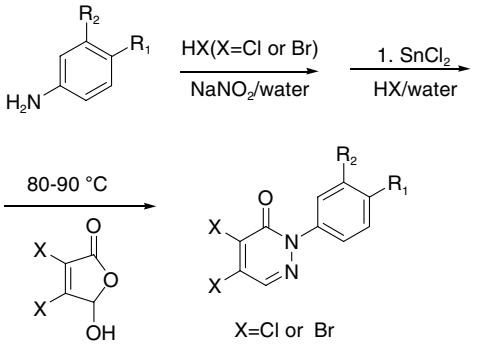


Scheme 2. One-pot process to dibromide and dichloride.



Scheme 3. Confirmation of halogen exchange.

Table 1. Results of one-pot process to dibromo- and dichloro-pyrodazinones



5 X=Br *Using HBr with mucobromic acid*
7 X=Cl *Using HCl if mucochloric acid was used*

Entry	R_1	R_2	X	Isolated yield (%)[a]
1	F	Cl	Cl	87
2	H	CF_3	Cl	74
3	F	F	Cl	90
4	OMe	H	Cl	35
5	H	H	Cl	88
6	F	F	Br	82
7	H	H	Br	78
8	H	CF_3	Br	85
9	OMe	H	Br	34
10	F	Cl	Br	86

[a] The reaction was carried out using 1 (1.0 equiv), $NaNO_2$ (1.05 equiv), $SnCl_2$ (2.0 equiv) and mucobromic acid or mucochloric acid (1.0 equiv). HX (X = Cl or Br)/water as solvent.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.009.

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9. 4,5-Dihalo-3(2H)pyridazinones were normally synthesized from hydrazine or arylhydrazines and mucohalic acid (X = Cl or Br) in acetic acid medium.
10. Several issues were considered in our early study: (1) the stability of diazonium salt and its safety profile; (2) how to control the ratio of several reagents and how to simplify the separation; (3) will the process work without removing excess $SnCl_2$? (4) Is water the best solvent for this one-pot process?
11. (a) Treating chloropyridazinones with KF in DMSO at 100 °C gave 32–82% fluoropyridazinones, see *Gaodeng Xuexiao Huaxue Xuebao*, **1988**, 9, 1083–1084; (b) Treatment of, 4,5-dichloro-3(2H)-pyridazinones with 47% HBr gave a mixture of 4,5-dibromo-3(H)-pyridazinone and 4-bromo-5-chloro-3(2H)-pyridazinone, see *Yakugaku Zasshi*, **1988**, 108, 911–915.
12. $SnCl_2$ was still used in the preparation of dibromide since (1) $SnCl_2$ is much cheaper than $SnBr_2$; (2) the solubility of $SnBr_2$ in water is much lower; (3) when HBr was used as solvent, [Br] ≫ [Cl], therefore it will inhibit the halogen exchange.