Synthesis of Mono- and Diaza-'Pyridones' via Stille Coupling of Alkoxystannanes

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Abstract: Various alkoxy-substituted heterocyclic stannanes provide access to the corresponding substituted 'pyridone' moieties via Stille cross-coupling. Both pyridyl and a series of diazinyl stannanes are prepared, and options for unmasking (via demethylation or debenzylation) of the pyridone unit are evaluated.

Key words: pyridine, heterocyclic stannane, Stille coupling

2-Pyridones and the related diazines (e.g., pyrazinone and pyrimidinone) are important motifs (Figure 1) found in biologically active compounds, such as pyridovericin (**1**) (kinase inhibitor),[1] dragmacidin D (**2**) (indication: Parkinson's and Alzheimer's disease),[2] raltegravir (**3**) (antiretroviral),[3] and lamivudine (**4**) (antiretroviral).[4] Consequently, and due to a number of physiochemical attributes, including polarity, low molecular weight (high heteroatom index), and in particular the condensed array of hydrogen bond donor/acceptor functionality, the ability to incorporate an intact mono and diaza 'pyridone' into a more complex scaffold is of interest, alongside methods for elaborating these core heterocyclic units.[5]

Our interest in substituted 2-pyridones stems from recent synthetic studies linked to cytisine (an α4β2 nicotinic partial agonist)[6] and, more pertinently, the development of core-modified variants in which alkoxystannanes **5a** and **6a** served as effective precursors to substituted (via Stille-based couplings) pyridones and pyrazinones, respectively (Figure 2).[7,8]

While Suzuki couplings with electron-deficient heteroaryl boronates are often difficult and 2-pyridyl organoboronates readily undergo protodeboronation,[9] the corresponding stannanes **5a** and **6a** are both readily accessible and exhibit a higher degree of stability (when stored at 5 °C), and provide a new and versatile set of 'pyridone' (both mono and diaza) building blocks.

In this communication, we describe the synthesis of a series of stannanes **5**–**8**, together with the application of these reagents to: (i) Stille cross-coupling, and (ii) subsequent dealkylation (via demethylation or debenzylation) to generate 6-arylated variants of 2-pyridones, 2-pyrazinones and 2-pyrimidinones, and 2-aryl 4-pyrimidinones. We report on the accessibility of the stannane reagents and, using a selected group of substrates, explore the scope and limitations of this chemistry.

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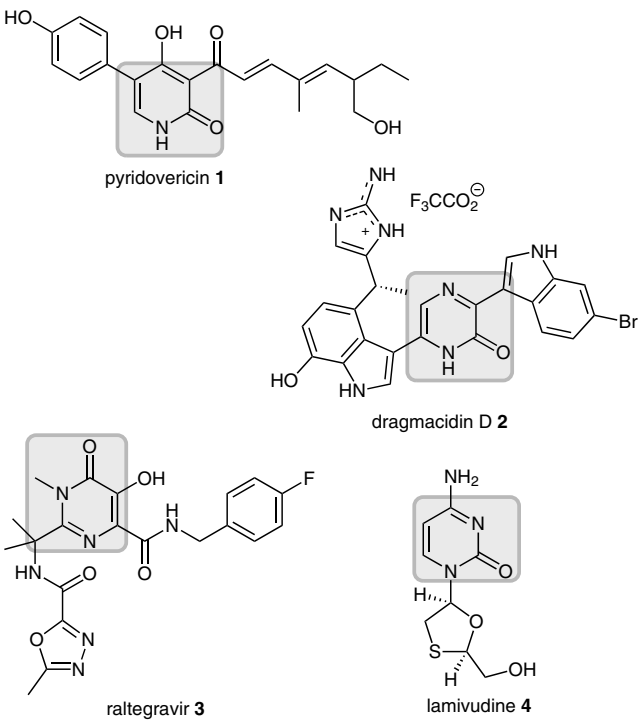


Figure 1 Biologically active mono and diaza 'pyridones'

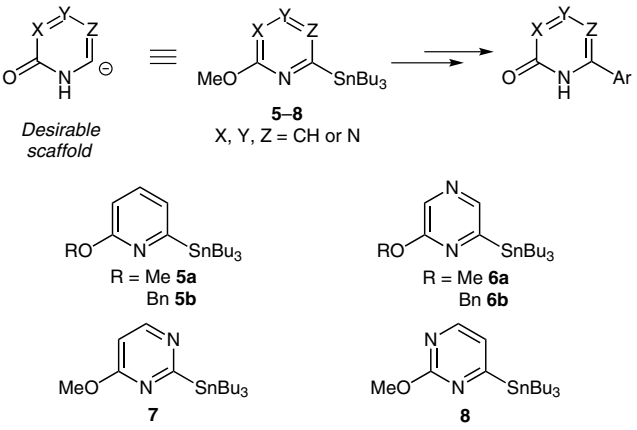
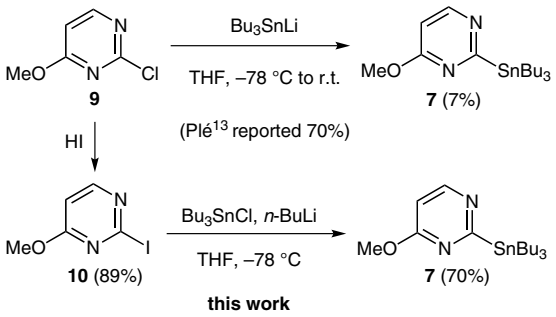


Figure 2 Heterocyclic stannanes as 'pyridone' precursors

In general, access to heteroaryl stannanes is achieved either by lithiation and subsequent (or in situ) quenching with R_3SnCl,[8] nucleophilic aromatic substitution using R_3SnLi, or transition-metal-catalyzed stannylation using R_6Sn_2.[10] Procedures for the synthesis of 6-methoxy stannanes **5a** and **6a** have been reported.[7,8,11] Furthermore, pyrimidine variant **7** has been described by Plé, via nu-

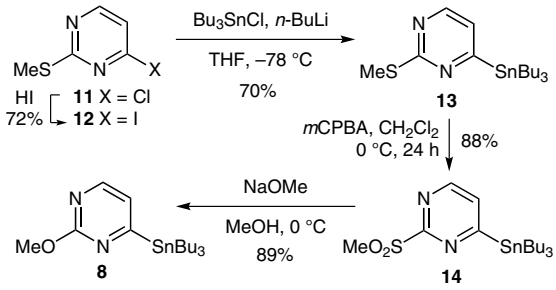
cleophilic aromatic substitution of chloride **9** with (tributylstannyl)lithium (Bu_3SnLi) (Scheme 1).

We were unable to reproduce the 70% yield reported by Plé, and at best we isolated pyrimidine **7** in 7% yield. Consequently, a more robust protocol has been developed and iodination of **9** to give **10** (89%) followed by slow addition of *n*-butyllithium (*n*-BuLi) to a mixture of **10** and tributyltin chloride (Bu_3SnCl) in tetrahydrofuran at –78 °C provided stannane **7**, reliably, in 70% isolated yield after flash chromatography. It should be noted that, although commercially available, **7** was (in our hands) the least stable reagent of those discussed here; even under nitrogen at 5 °C, stannane **7** degraded after 14 days.



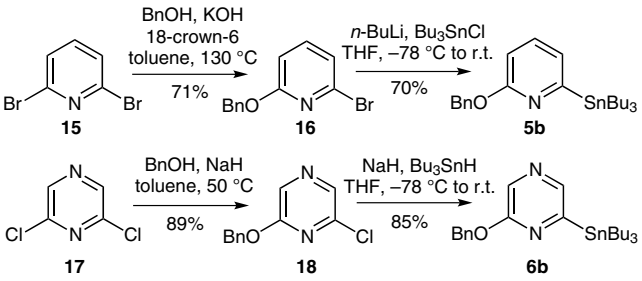
Scheme 1 Synthesis of pyrimidinyl stannane **7**

The 2-methoxypyrimidinyl stannane **8** was prepared from commercially available pyrimidine **11** via iodide **12**,[12] lithiation of which followed by an in situ quench gave stannane **13**. Oxidation of **13** gave sulfone **14**,[12] which underwent subsequent displacement with sodium methoxide to give **8** in 39% overall yield on a 3 g scale (Scheme 2).



Scheme 2 Synthesis of 2-methoxy-4-(tributylstannyl)pyrimidine (**8**)

The benzyloxy variants **5b** and **6b** were synthesized as shown in Scheme 3. Halides **15** and **17** were transformed into **16**[13] and **18**, respectively. Lithiation of **16** followed by in situ quenching with Bu_3SnCl gave stannane **5b**, and **6b** was obtained via chloride displacement in **18** with (tributylstannyl)sodium (Bu_3SnNa). Stannanes **5b** and **6b** were both stable over extended periods of time when stored at 5 °C.



Scheme 3 Synthesis of stannanes **5b** and **6b**

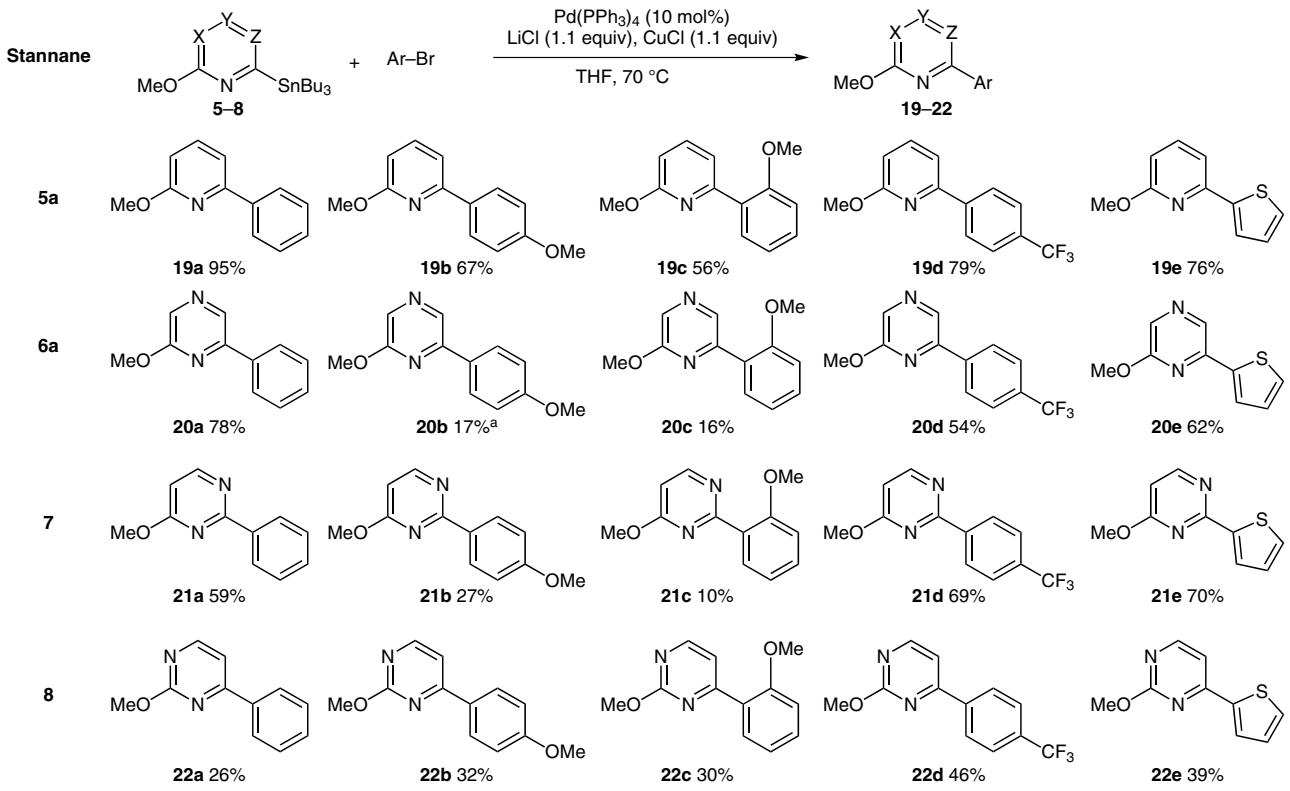
Stille coupling reactions of stannanes **5**–**8** with a range of aryl bromides led to adducts **19**–**24**, which are summarized in Schemes 4 and 5. Cross-couplings were conducted under well-established Stille conditions by heating stannanes **5**–**8** with an appropriate aryl bromide, tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] (10 mol%), lithium chloride (LiCl) (1.1 equiv) and copper(I) chloride (CuCl) (1.1 equiv) in tetrahydrofuran for 18 hours.[8] Generally, reactions proceeded in good yield, although electron-rich aryl halides were less efficient, and purification by flash chromatography was sufficient to give the coupled product with minimal tin contamination.

In both series, couplings to 4-bromoanisole gave significantly lower yields (see Schemes 4 and 5) and phenyl-containing by-products derived from ligand transfer from triphenylphosphine (Ph_3P) were isolated.[14] 3-Bromopyridine also highlighted a significant reactivity difference: reaction with pyridyl stannane **5b** was efficient, but attempts to couple to the pyrazine variant **6b** failed.

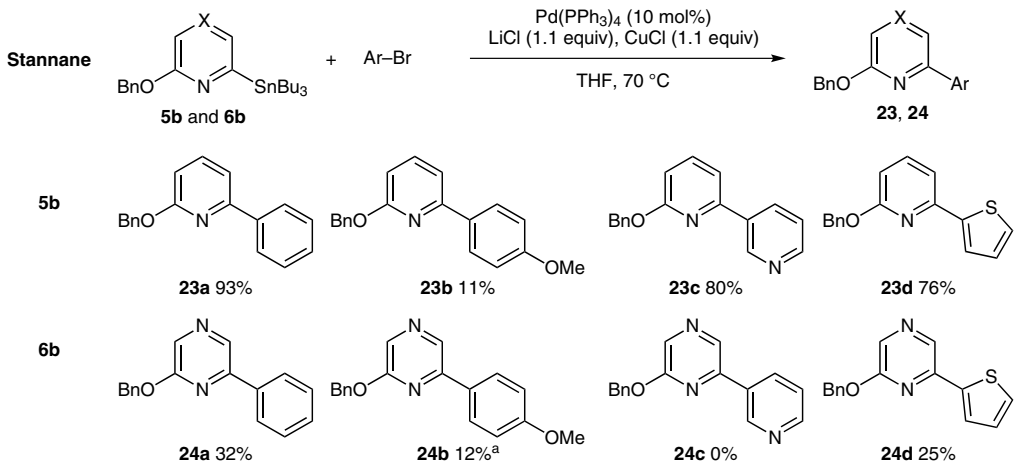
Releasing the masked pyridone by acidic hydrolysis (using HCl) was not successful. Representative substrates (pyridine **19a** and pyrimidine **22a**) were used and both failed to react. Consequently, several alternative procedures for demethylation and debenzylation (Tables 1 and 2) were examined, but in practice we could not identify a single, generally applicable dealkylation method.

Using pyridine **19a**, chlorotrimethylsilane (TMSCl) and sodium iodide (NaI)[15] gave pyridone **25** in 85% yield, but application of these conditions to **19b** and **20a** failed to give the desired products; we observed recovered **19b** and decomposition of **20a**. Similarly, lithium iodide (LiI) and *sym*-collidine[16] gave mixed results: demethylation of **19a**,**d**,**e** proceeded in moderate yields, however **19c**, **20a** and **22a** were unreactive. Sodium ethanethiolate (NaSEt)[17] successfully converted pyridine **19a**, pyrazine **20a** and pyrimidine **21a**, however, this reagent failed with the isomeric pyrimidine **22a**.

Generally, debenzylation via hydrogenolysis was easier to affect. Pyridyl substrates **23a**,**b**,**d** provided the corresponding pyridones in moderate to good yields. The 3-pyridyl variant **23c** was, however, unreactive and is pre-



Scheme 4 Stille couplings of stannanes **5**–**8** with representative aryl bromides. [a] Reaction of **6a** and 4-bromoanisole to give **20b** also gave **20a** in 40% yield reflecting competitive aryl ligand exchange from Ph_3P. All yields shown are those for isolated products following purification by chromatography

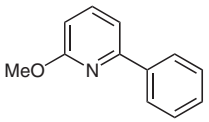
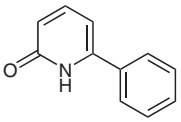
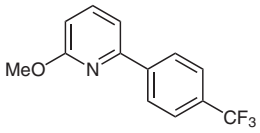
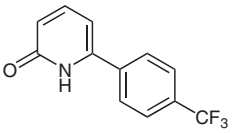
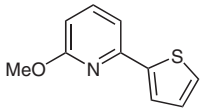
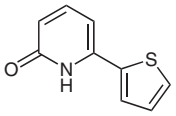
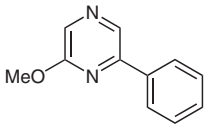
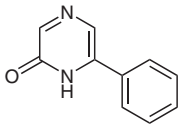
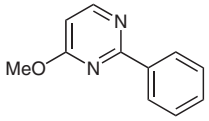
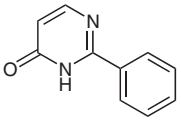


Scheme 5 Stille couplings of stannanes **5b** and **6b** with representative aryl bromides. [a] Reaction of **6b** and 4-bromoanisole to give **24b** also gave **24a** in 10% yield reflecting competitive aryl ligand exchange from Ph_3P. All yields shown are those for isolated products following purification by chromatography

sumed to have poisoned the catalyst. Pyrazines **24a** and **24d** were also (and surprisingly) unreactive. Debenzylation using boron tribromide (BBr_3) was also a viable option and converted both **23c** and **24a** into the desired products in good yields.

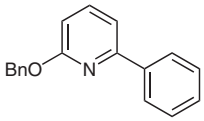
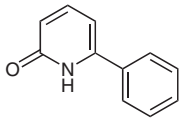
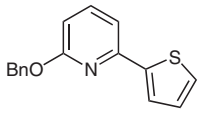
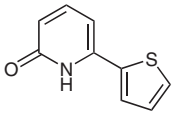
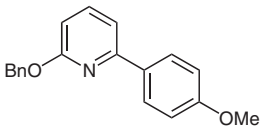
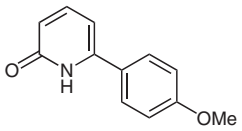
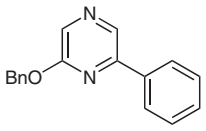
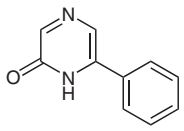
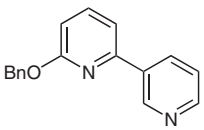
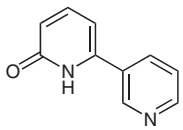
In conclusion, 2-methoxy- and 2-benzyloxy-6-stannylated pyridines, as well as the corresponding pyrazine and pyrimidine congeners, are suitable substrates for (generally) efficient Stille cross-coupling reactions. These reagents serve as vehicles for the introduction of pyridone, pyrazinone and pyrimidinone units where the carbonyl moiety is released via demethylation or debenzylation, albeit under substrate-dependent conditions.[18]

Table 1 Demethylation Conditions Evaluated and the 'Pyridone' Products

Substrate	Conditions	Yield[a]	2-Pyridone
	TMSCl (10 equiv), NaI (3 equiv), MeCN, 80 °C, 1.5 h	85%	
	LiI (2 equiv), *sym*-collidine, reflux, 6 h	51% (28%)	
	NaSEt (1.2 equiv), DMF, 140 °C, 48 h	63%	
19a			**25**
	LiI (2 equiv), *sym*-collidine, reflux, 6 h	38% (42%)	
19d			**26**
	LiI (2 equiv), *sym*-collidine, reflux, 6 h	28% (50%)	
19e			**27**
	TMSCl (10 equiv), NaI (3 equiv), MeCN, 80 °C, 48 h	no reaction	
	LiI (2 equiv), *sym*-collidine, reflux, 48 h	no reaction	
	NaSEt (1.2 equiv), DMF, 140 °C, 4 h	66%	
20a			**28**
	TMSCl (10 equiv), NaI (3 equiv), MeCN, 80 °C, 48 h	no reaction	
	LiI (2 equiv), *sym*-collidine, reflux, 48 h	no reaction	
	NaSEt (1.2 equiv), DMF, 140 °C, 4 h	75%	
21a			**29**

[a] Yields shown in parentheses refer to those of recovered starting material.

Table 2 Debenzylation Conditions and Debenzylation Products

Substrate	2-Pyridone[a]	Substrate	2-Pyridone[a]
			
23a	**25** 90%	**23d**	**27** 80%
			
23b	**30** 36%	**24a**	**28** 95%
		–	–
23c	**31** 52%		

[a] Conditions used for **23a**, **23b** and **23d**: H_2 (1 atm), Pd/C (5 mol%), MeOH–EtOAc (0.08 M), r.t., 4–24 h. Conditions used for **23c** and **24a**: BBr_3 (1 equiv), CH_2Cl_2 (0.02 M), r.t., 2–16 h.

Acknowledgment

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(17) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970**, 1327.
(18) **Representative ^{1}H NMR Data**
2-Methoxy-6-(2-methoxyphenyl)pyridine (19c)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (dd, *J* = 7.5, 2.0 Hz, 1 H), 7.61 (t, *J* = 7.5 Hz, 1 H), 7.55 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.37 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.09 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.01 (dd, *J* = 8.5, 1.0 Hz, 1 H), 6.68 (dd, *J* = 7.5, 1.0 Hz, 1 H), 4.01 (s, 3 H), 3.89 (s, 3 H).
4-Methoxy-2-(4-methoxyphenyl)pyrimidine (21b)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 5.5 Hz, 1 H), 8.40 (d, *J* = 9.0 Hz, 2 H), 6.98 (d, *J* = 9.0 Hz, 2 H), 6.56 (d, *J* = 5.5 Hz, 1 H), 4.07 (s, 3 H), 3.88 (s, 3 H).
2-(Benzyloxy)-6-(thien-2-yl)pyrazine (24d)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (br s, 1 H), 8.13 (br s, 1 H), 7.66 (dd, *J* = 4.0, 1.0 Hz, 1 H), 7.53 (d, *J* = 7.5 Hz, 2 H), 7.46 (dd, *J* = 5.0, 1.0 Hz, 1 H), 7.31–7.42 (m, 3 H), 7.14 (dd, *J* = 5.0, 4.0 Hz, 1 H), 5.48 (s, 2 H).
6-(Thien-2-yl)pyridin-2(1*H*)-one (27)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.82 (br s, 1 H), 7.98 (d, *J* = 3.5 Hz, 1 H), 7.43 (t, *J* = 8.5 Hz, 1 H), 7.38 (d, *J* = 5.0 Hz, 1 H), 7.16 (dd, *J* = 5.0, 3.5 Hz, 1 H), 6.52 (d, *J* = 8.5 Hz, 2 H).
2-Phenylpyrimidin-4(3*H*)-one (29)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (dd, *J* = 8.0, 1.5 Hz, 2 H), 8.15 (d, *J* = 6.5 Hz, 1 H), 7.52–7.61 (m, 3 H), 6.46 (d, *J* = 6.5 Hz, 1 H).

