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Application of the intramolecular aza-Wittig reaction to the synthesis of pyrido[2,3-*d*]pyrimidines

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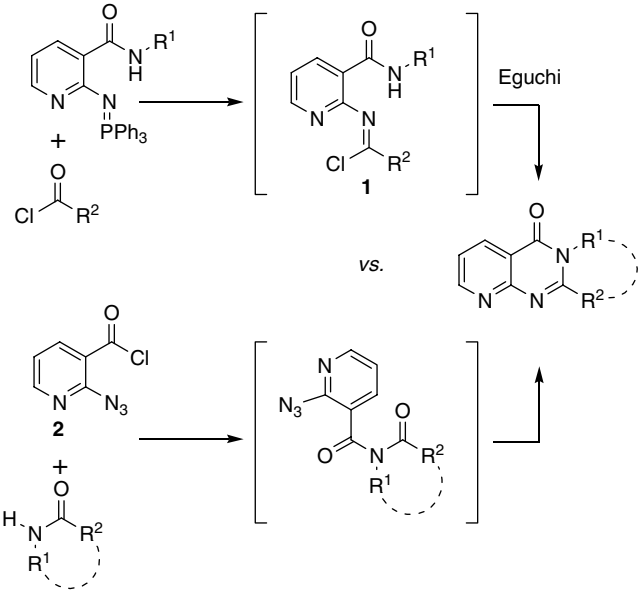
Abstract—Pyrido[2,3-*d*]pyrimidines are synthesized in a two-step procedure from amides and tetrazolo[1,5-*a*]pyridine-8-carbonyl chloride. Reaction of the crude imides with triphenylphosphine effects an intramolecular aza-Wittig reaction to afford a variety of substituted pyrido[2,3-*d*]pyrimidines in good to moderate yields (30–76%).

The beginnings of the aza-Wittig reaction are rooted in the work of Staudinger who synthesized the first iminophosphorane by reaction of tertiary phosphines and organic azides in the early 1900s.[1] The reaction of iminophosphoranes with carbonyl compounds, particularly in an intramolecular sense, provides an effective approach to C=N bond formation. Consequently, the use of iminophosphoranes as a synthetic intermediate toward a variety of nitrogen containing heterocycles has become commonplace.[2]

In the course of our investigations in the area of autoimmune diseases,[3] we required an alternative route to synthesize compounds that contained a pyrido[2,3-*d*]-pyrimidine core. Eguchi had previously reported that iminophosphoranes derived from 2-aminonicotinic-amides react with a variety of acid chlorides to furnish pyrido[2,3-*d*]pyrimidines in excellent yields.[4] The reaction was believed to proceed through an intermolecular aza-Wittig reaction followed by cyclization of the resultant imidoyl chloride **1** (Scheme 1). However, this method requires 200 mol % acyl chloride, and is limited to situations where the acyl chloride is stable or simple to prepare. Furthermore, this method is not applicable to substrates in which R^1 and R^2 are tethered. An alternative method that could overcome these drawbacks would be to perform the coupling between pyridine acyl chloride **2** and various amides, thus allowing access to



Scheme 1. Synthesis of pyrido[2,3-*d*]pyrimidines.

cyclic pyridopyrimidines.[5] To this end, we were pleased to find that the intramolecular aza-Wittig reaction indeed furnished the desired compounds in good to moderate yields. Herein, we report the participation of tetrazolo[1,5-*a*]pyridine-8-carbonyl chloride (**4**) in the synthesis of pyrido[2,3-*d*]pyrimidines by way of an intramolecular aza-Wittig reaction.

The synthesis of tetrazolo[1,5-*a*]pyridine-8-carbonyl chloride (**4**) is summarized in Scheme 2. Beginning with

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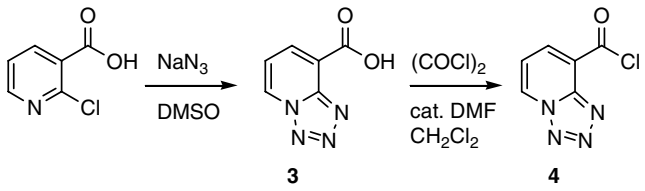
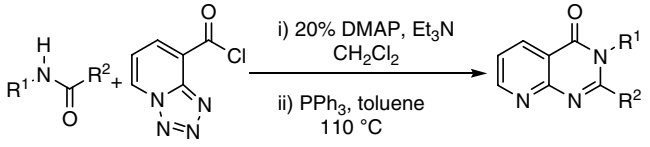


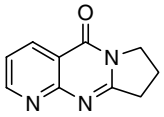
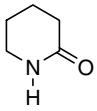
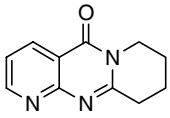
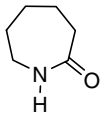
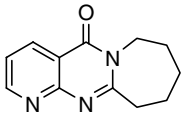
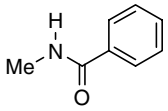
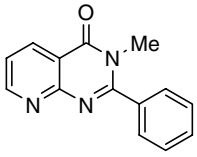
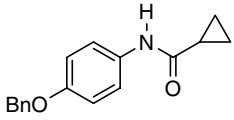
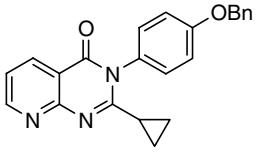
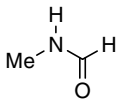
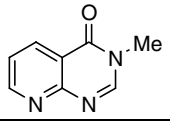
Scheme 2. Synthesis of tetrazolo[1,5-*a*]pyridine-8-carbonyl chloride.

2-chloronicotinic acid, treatment with sodium azide afforded tetrazole **3** in 65% yield. Notably, the equilibrium in water between tetrazole **3** and its isomeric 2-azidopyridine lies exclusively at the tetrazole, consistent with the earlier characterization data reported for this compound.[6] Reaction of **3** with oxalyl chloride afforded tetrazolo[1,5-*a*]pyridine-8-carbonyl chloride (**4**) in 95% isolated yield as a fine powder that is stable when stored at −20 °C under argon (Scheme 2).[7]

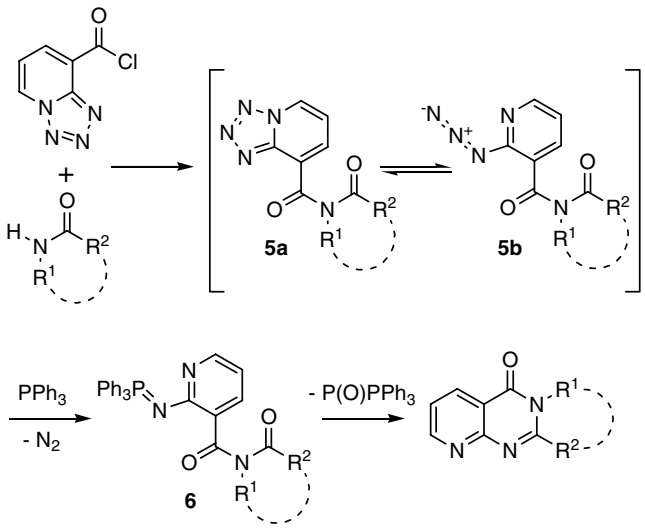
In a two-step process, amides were coupled with tetrazolo[1,5-*a*]pyridine-8-carbonyl chloride (**4**) and cyclized to generate pyrido[2,3-*d*]pyrimidines in good to moderate yields (Table 1).[8] *N*-acylation of the amide was achieved through the use of Et_3N/DMAP which afforded the desired imides (Scheme 3). Interestingly, the treatment of amides with NaH/THF or NaH/DMF followed by the addition of tetrazolo[1,5-*a*]pyridine-8-carbonyl chloride (**4**) gave a mixture of *N*- and *O*-coupled products. The crude imide was used directly in the cyclization to generate the desired products (Table 1). Entries 1, 2, and 3 illustrate the potential of this method to synthesize *cyclic pyridopyrimidines*, a class of compounds that are particularly challenging to access using existing technologies.[9] Electron-rich aromatic groups were well tolerated at R^1; however, coupling of amides possessing electron-deficient aromatic groups at R^1 (*p*-iodophenyl, *p*-cyanophenyl) suffered from poor conversion primarily due to imide hydrolysis.[10] Alkyl groups larger than methyl suffered from poor conversion. With respect to R^2, aromatic, aliphatic groups and hydrogen were suitable substrates (entries 4, 5, and 6).

Table 1. Two-step approach to the synthesis of pyrido[2,3-*d*]pyrimidines



Entry	Amide	Product	Yield (%)
1			53
2			71
3			76
4[a]			72
5[b]			53
6			30

[a] Difficulty purifying from $P(O)Ph_3$ in hexanes:ethyl acetate chromatography.
[b] Reaction conducted in THF at 60 °C.



Scheme 3. Proposed mechanism to pyrido[2,3-*d*]pyrimidine formation.

Although no mechanistic studies have been conducted, one reasonable proposal for this sequence begins with the standard coupling to form imide **5a/5b**. Treatment of **5a/5b** with triphenylphosphine could trap-out the desired iminophosphorane **6** from the equilibrium mixture.[11] Cyclization of iminophosphorane **6** would then lead to the desired product.

In summary, a new approach to the synthesis of pyridopyrimidines has been developed. Utilizing tetrazolo[1,5-*a*]pyridine-8-carbonyl chloride (**4**), imides were conveniently synthesized and transformed via an aza-Wittig reaction to furnish pyrido[2,3-*d*]pyrimidines in good to moderate yields. This two-step procedure offers an attractive alternative to conventional methods, and is particularly useful for the generation of cyclic pyridopyrimidines.

Acknowledgements

We would like to thank Randy Jensen for NMR assistance.

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7. Representative procedure: To a solution of 2-chloronicotinic acid (40.0 g, 254 mmol) in DMSO (150 mL) was added sodium azide (16.5 g, 254 mmol) and the resulting mixture heated to 90 °C for 3 h. The precipitated product was poured into 500 mL of acetone and filtered. The white filter cake was washed with an additional 1.5 L of acetone, and dried in a vacuum oven (room temperature) to obtain **3** (27.3 g, 65%) as a white solid. Synthesis of acyl chloride: To a slurry of the acid **3** (17.8 g, 108 mmol) in dichloromethane (150 mL) was added DMF (0.1 mL) followed by oxalyl chloride (18.9 mL, 217 mmol) *slowly*. The reaction mixture was stirred for 3 h, concentrated in vacuo, and washed 2× with hexane (50–75 mL). The slurry was concentrated in vacuo to afford **4** (19.6 g, 98%) as a fine gray powder. *Compounds **3** and **4** have not been tested for their propensity as explosives.
8. Synthesis of pyridopyrimidine representative procedure (entry 3): To a solution of azepan-2-one (226 mg, 2 mmol) in dichloromethane (5 mL) was added triethylamine (0.84 mL, 6 mmol), tetrazolo[1,5-*a*]pyridine-8-carbonyl chloride (**4**) (746 mg, 4 mmol), and DMAP (45 mg, 0.2 mmol) and stirred for 16 h. The reaction mixture was diluted with dichloromethane (125 mL) and washed with 1 M HCl (75 mL) and 2× water (75 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to afford crude imide. The crude imide was transferred to a 15 mL sealed tube and taken up in toluene (5 mL). Triphenylphosphine (640 mg, 1.2 mmol) was added and the reaction mixture heated to 110 °C for 16 h. The solution was concentrated in vacuo and purified by silica gel chromatography (4:1 ethylacetate:hexanes → 100% ethyl acetate) to afford the desired pyridopyrimidine (330 mg, 76%).
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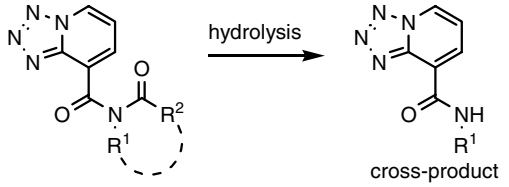

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