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Synthesis of 4-trifluoromethylpyrido[1,2-*a*]pyrimidin-2-ones utilizing activated alkynoates

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Abstract—The synthesis of the biologically relevant, 4-trifluoromethylpyrido[1,2-*a*]pyrimidin-2-one **7**, is reported. Addition of substituted 2-aminopyridines **5** to activated alkynoates leads to the facile formation of a series of metabolically stable trifluoromethyl substituted pyrido[1,2-*a*]pyrimidines under mild conditions.

The pyrido[1,2-*a*]pyrimidine core has been a successful motif for the development of biologically interesting molecules, including the tranquilizer pirenperone,[1a] the antiallergic agent barmastine,[1b] an antiulcerative agent,[1c] and the antiasthmatic agent pemirolast (Fig. 1).[1d]

Due to their diverse biological activity, researchers have been interested in the synthesis of derivatives of this structural type. Several groups have described the synthesis of substituted pyrido[1,2-*a*]pyrimidin-4-ones **3**.[2a–g] In comparison, there have been few reports on the synthesis of the regioisomeric pyrido[1,2-*a*]pyrimidin-2-ones **4** (Fig. 2).

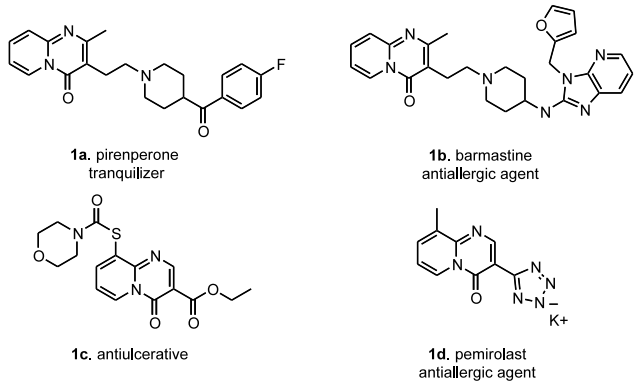

Figure 1. Known biologically active compounds that contain a pyrido[1,2-*a*]pyrimidinone core.

In our research program, we were interested in synthesizing pyridopyrimidin-2-ones that contain a trifluoromethyl group at the 4 position, as a replacement for a methyl group. The design and synthesis of fluorine containing compounds is important as fluorination often imparts metabolic stability to a drug molecule without compromising its biological activity. We herein report on the synthesis of trifluoromethyl substituted pyrido[1,2-*a*]pyrimidin-2-ones **4**, as an important contribution toward the synthesis of substituted pyridopyrimidines.

We found known literature conditions for the preparation of pyrido[1,2-*a*]pyrimidin-2-ones to be insufficient for our needs. Reported methods for the preparation of pyrido[1,2-*a*]pyrimidin-2-ones rely on the cyclization of 2-aminopyridine with ethyl cyanoacetate at high temperature and pressure,[3] or cyclization of 2-aminopyridine with a Vilsmeier–Haack reagent prepared in situ from *N*,*N*-dialkylethoxycarbonylacetamide and phosphorus oxychloride (Fig. 3).[4] In the latter case, a mixture of pyrido[1,2-*a*]pyrimidin-2-ones and pyrido[1,2-*a*]pyrimidin-4-ones was obtained from the reaction. The need to use high temperatures and pressure or the lack of regiocontrol in the reaction conditions further emphasizes the drawbacks of these methods.

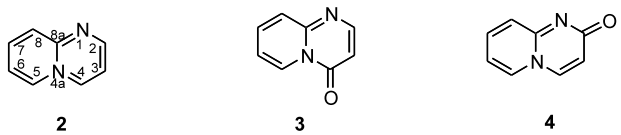

Figure 2. Pyrido[1,2-*a*]pyrimidine **2**, pyrido[1,2-*a*]pyrimidin-4-one **3**, and pyrido[1,2-*a*]pyrimidin-2-one **4**.

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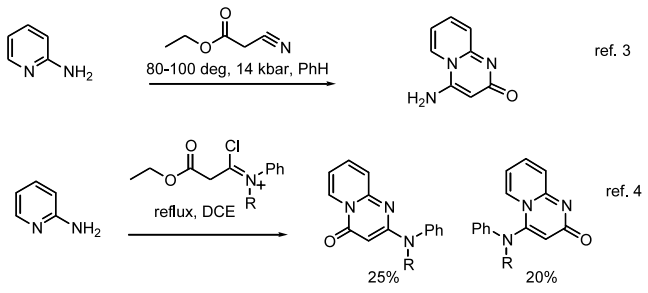


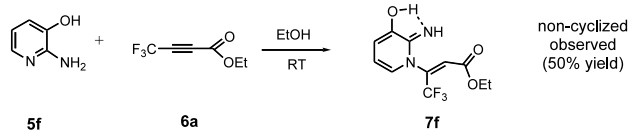
Figure 3. Synthesis of pyrido[1,2-*a*]pyrimidin-2-ones.

In an effort to devise a milder and more general method of synthesizing pyrido[1,2-*a*]pyrimidin-2-ones, we considered that substituted alkynoates could function as a 3-carbon synthon in a cyclization reaction with 2-aminopyridine. A search of the literature revealed a few examples of this type of reaction. Wilson[7] and Adams[8] described their efforts to use 2-bromoacrylic ester and propynoate ester for the cyclization reaction with 2-aminopyridine. In their reports, low yields of the desired pyrido[1,2-*a*]pyrimidin-2-ones were obtained and was accompanied by resinification of starting materials and/or formation of significant amounts of undesired sideproducts. Doad and Acherson independently described the condensation of 2-aminopyridine with an ene–ynoate and an allenic ester, that were both prepared via multistep synthesis.[5,6] In the previously reported cyclization conditions, the scope and generality of the reaction was never examined, and 2-aminopyridine was usually the sole substrate employed for the reaction.

With the goal of devising a milder and more general method of synthesizing pyrido[1,2-*a*]pyrimidin-2-ones, we set forth to examine scope of the cyclization reaction of various substituted 2-aminopyridines with activated alkynoates. Herein, we describe the synthesis of a series of pyrido[1,2-*a*]pyrimidin-2-ones utilizing commercially available activated alkynoates and substituted 2-aminopyridines under mild reaction conditions (Table 1).

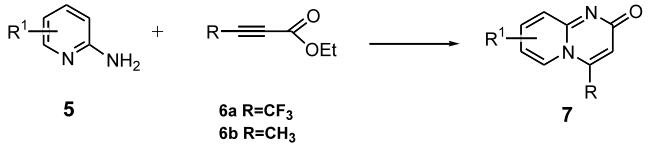
Reactions utilizing electron-rich aminopyridines (**5a**–**c**) and the highly electrophilic ethyl β-trifluoromethylalkynoate **6a** proceeded smoothly at room temperature in ethanol to afford the desired pyrido[1,2-*a*]-pyrimidines **7a**–**c**, in good yields (reaction is typically complete in 0.5 h). Electron-deficient aminopyridines **5d** and **5e** and alkynoate **6a** reacted more slowly to afford the desired pyrido[1,2-*a*]pyrimidin-2-ones **7d** and **7e** in fair yield, 74 and 37% respectively. Interestingly, while the reaction between 3-benzyloxy-2-aminopyridine **5b** proceeded smoothly, the reaction of aminopyridine **5f** with alkynoate **6a** resulted in the isolation of the intermediate Michael adduct **7f**, which is presumably stabilized via an intramolecular hydrogen bond between the 3-hydroxy group and the 2-imino group (Scheme 1).

The desired pyrido[1,2-*a*]pyrimidin-2-one products **7h** and **7i** could not be isolated following the reaction between 2-amino-4,6-dimethylpyridine **5h** or 2-amino-6-methylpyridine **5i** with alkynoate **6a**. Instead, decomposition of the starting materials were observed after extended reaction times (>24 h). As the reaction of the isomeric 5-methylaminopyridine **5g** provides the expected pyrido[1,2-*a*]pyrimidin-2-one good yield, it is



Scheme 1.

Table 1. Reaction of alkynoates **6** with 2-aminopyridines **5**



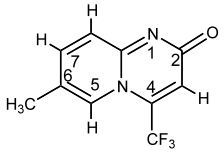
2-Aminopyridine	R_1	Alkynoate	R	Product (yield)
5a	H	**6a**	CF_3	**7a** (98%)
5b	3-OCH_2Ph	**6a**	CF_3	**7b** (95%)
5c	3-Br, 5-CH_3	**6a**	CF_3	**7c** (82%)
5d	5-Br	**6a**	CF_3	**7d** (74%)
5e	5-NO_2	**6a**	CF_3	**7e** (37%)
5f	3-OH	**6a**	CF_3	**7f** (50% noncyclized product)
5g	5-CH_3	**6a**	CF_3	**7g** (66%)
5h	6-CH_3	**6a**	CF_3	**7h** (decomposition)
5i	4,6-diCH_3	**6a**	CF_3	**7i** (decomposition)
5a	H	**6b**	CH_3	**7j** (0%)
5a	H	**6c**	Ph	**7k** (<5%)
5a	H	**6d**	CO_2Et	**7l** (5% noncyclized product)

likely that in these substrates, the pyridine nitrogen is too sterically hindered to react with alkynoate **6a**.

In these reactions, it is assumed that the Michael addition occurs at the pyridine nitrogen and this is then followed by lactam formation involving the 2-amino group to provide the pyrido[1,2-*a*]pyrimidinone as the regioisomer shown for **7**. The assignment of the structure of products **7** is supported by literature precedent.[10] NMR experiments performed on 6-methyl-2-trifluoromethylpyrido[1,2-*a*]pyrimidinone **7g** further confirmed the regiochemistry of the product (Table 2). Proton and carbon chemical shifts of **7g** were assigned based on HMQC and HMBC experiments. Initially, it was attempted to determine the regiochemistry of **7g** using 2D NMR experiments. We looked for long range $^{3}J_{CH}$ correlation between the H_5 with C_4. For either regioisomer, the C_4 carbon would have a distinctive resonance in the ^{13}C NMR spectrum (C_4 is the carbonyl carbon in isomer **4** and is the vinylic carbon in the alternate isomer **3**, see Figure 1). Unfortunately, correlation between H_5 to C_4 was not seen in the HMBC experiments. Instead, the structure of **7g** was assigned based on carbon–fluorine coupling observed in the ^{13}C NMR spectrum. Long range J_{CF} coupling, which has a large through space coupling component, can be observed in trifluoromethylvinyl compounds.[11] A 4.5 Hz C–F coupling was observed between the CF_3 group and C-5 at 125.7 ppm. This observation is consistent with structure **7g**[12,13] where attachment of the CF_3 group to C-4, results in the observed 4.5 Hz ^{4}J(C–F) ^{19}F coupling to C-5.

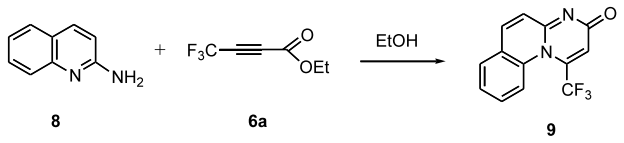
As expected, variations in the electrophilicity of the alkynoate dramatically effected the outcome of the reaction. The reaction of unsubstituted 2-aminopyridine **5a** with different β-substituted alkynoates (**6a–d**) was examined. The reaction between **5a** and β-CF_3 substituted alkynoate **6a** provided **7a** in 98% yield. However,

Table 2. NMR data for 6-methyl-4-trifluoromethylpyrido[1,2-*a*]pyrimidinone **7g**



7g

C	ppm	H (ppm)	J_{CF} (Hz)
C-2	166.3	–	–
C-3	116.8	7.01	4.7
C-4	135.2	–	35.1
C-5	125.7	7.66	4.5
C-6	124.0	–	–
C-7	139.4	7.47	–
C-8	125.5	7.35	–
CF_3	119.6	–	274.5
CH_3	18.2	2.34	–



8 **6a** **9**

Scheme 2.

under similar conditions, β-CO_2Et substituted alkynoate **6d** gave only a 5% yield of the uncyclized Michael adduct. Performing the reaction in refluxing ethanol did not improve the yield. Similarly in refluxing ethanol, the reaction between **5a** and β-methyl substituted alkynoate **6b** or β-phenyl substituted alkynoate **6c** proceeded sluggishly (**6c**) or not at all (**6b**). In both of these cases starting material was recovered.

Finally, it is worth noting that 2-aminoquinoline **8** reacted smoothly with **6a** utilized in this chemistry to afford the tricyclic benzopyrido[1,2-*a*]pyrimidine **9** in 78% yield (Scheme 2).

In summary, we have examined the scope and generality of the cyclization reaction between a diverse set of substituted 2-aminopyridines and activated alkynoates. The activated alkynoate, 3-trifluoromethyl propynoate **6a**, is an excellent partner in this cyclization reaction, providing novel 4-trifluoromethylpyrido[1,2-*a*]pyrimidin-2-ones **7** in good yields.

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10. X-Ray crystallographic analysis of the pyrido[1,2-*a*]pyrimidin-2-one product from the related cyclization of 2-aminopyridine with penta-2,3-dienedioic acid dimethyl ester has been obtained.[5] Similarly the regiochemistry of the pyrido[1,2-*a*]pyrimidin-2-one product can be identified by the absence of a strongly deshielded aromatic proton which is expected in the 6-position of the alternative pyrido[1,2-*a*]pyrimidin-4-one structure.[9]
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12. *General procedure*: To a solution of 5-methyl-2-aminopyridine **5g** (108 mg, 1 mmol) in ethanol (10 mL), was added the activated alkynoate **6** (166 mg, 1 mmol). The reaction was monitored by TLC and was complete in 30 minutes. Ethanol was removed in vacuo to provide the crude pyridino[1,2-*a*]pyrimidin-2-one **7g**. Purification by recrystallization from ethyl acetate/hexanes provided the desired product **7g** (150 mg, 66% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.44 ($J=9.3$, 1.7 Hz, 1H), 7.31 ($J=9.4$, 1H), 6.97 (s, 1H), 2.29 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.3, 151.9, 139.4, 135.2 (q, $J_{CF}=35.1$ Hz), 125.7 (q, $J_{CF}=4$ Hz), 125.5, 124.0, 119.6 (q, $J_{CF}=274.5$ Hz), 116.8 (q, $J_{CF}=4.7$ Hz), 18.2.
13. All compounds were characterized by NMR (Bruker AC 250 or 300 MHz instrument), LC/MS (Micromass platform LCZ with electrospray ionization and diode array LC detection at 200–400 nm), and CHN combustion analysis.