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An improved and highly convergent synthesis of 4-substituted-pyrido[2,3-*d*]pyrimidin-7-ones

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Abstract—A novel and efficient route to 4-substituted-pyrido[2,3-*d*]pyrimidin-7-ones is described resulting in arrays of compounds with biological interest.

The strategy to design organic synthetic routes in such a way that is amenable to prepare a variety of analogues through an array approach has been widely employed by medicinal chemists in the pharmaceutical industry to carry out structure activity relationship (SAR) studies.[1] A recent demonstration can be found in the synthesis of 2,4,8-trisubstituted pyrido[2,3-*d*]pyrimidin-7-ones with general structure **III** (Fig. 1).[2] The key features of the synthesis include (a) conversion of aldehyde **I** to a *cis* α,β-unsaturated ester followed by a spontaneous intramolecular condensation to construct a bi-cyclic ring system **II**, and (b) displacement of methylsulfone with nucleophiles (e.g., amines) in the last step to afford compounds **III**. This sequence provided an excellent route to optimize substituents at carbon 2 (C2) of the central scaffold. In order to further exploit this template and to develop SAR, we sought to efficiently optimize substituents at carbon 4 (C4). Introduction of the C4 substituent as a final step would serve to increase the efficiency of the endeavour. In this paper, we report a novel synthetic route that meets these criteria and its subsequent utilization to prepare arrays of small molecules **III**.

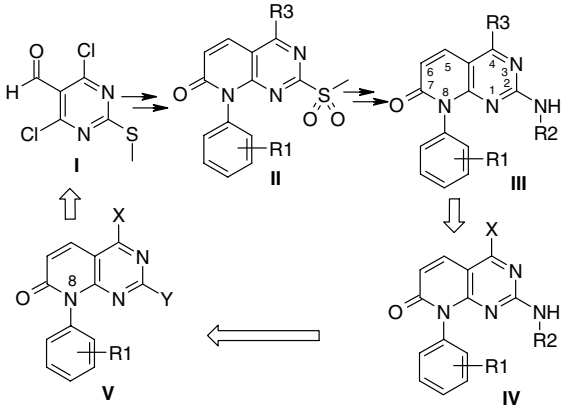

Figure 1. Retrosynthetic analysis.

From the perspective of retrosynthetic analysis (Fig. 1), the compounds related to **IV** wherein X is a leaving group (e.g., Cl) are envisioned as key intermediates of analogues **III**. Intermediates **IV** can be derived from **V** through the selective displacement of Y with various nucleophiles (e.g., amines). Pyridopyrimidinones with optimal substituents at N8 (**V**) can be constructed from **I**, a starting material used in previous syntheses.[2] Construction of the bi-cyclic ring system and selection of the two leaving groups (X and Y) with different reactivity are considered critical challenges to a successful route.

The synthesis commenced with investigating the formation of the pyridopyrimidinone ring system (Scheme 1). Starting from aldehyde **I**, displacement with aniline **2a** (1 equiv) under similar reaction conditions as reported previously[2] afforded a mixture of **4a** and **5a** (1:1, 90% combined yield). The formation of **4a** suggested that the aldehyde group was quite accessible and this could be utilized to our advantage to furnish the desired pyridopyrimidinone ring in a one pot sequence: in situ gen-

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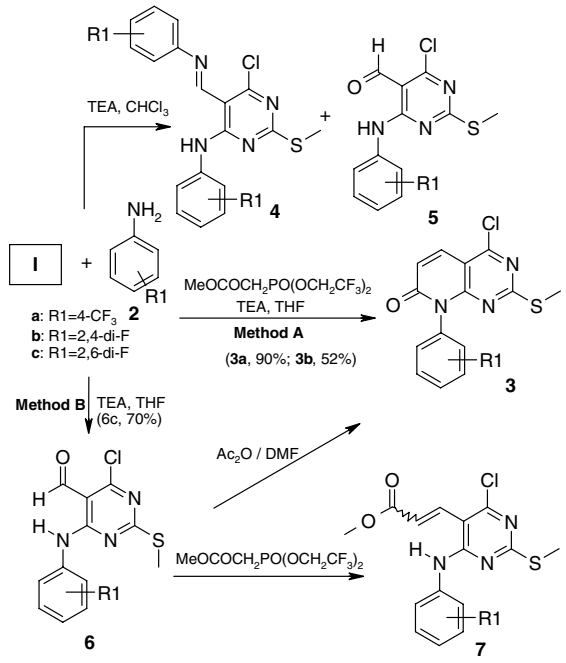


Scheme 1.

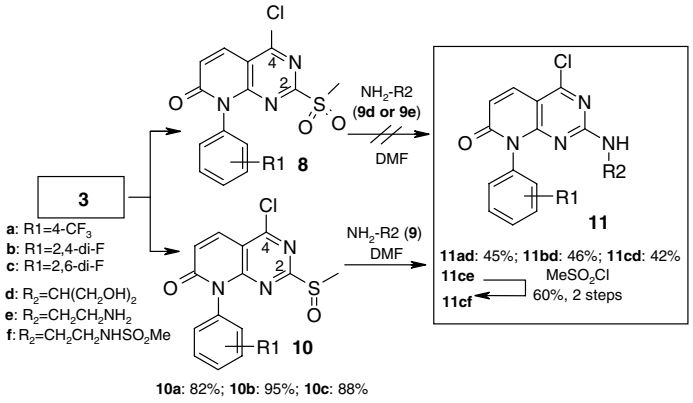
eration of a *cis* α,β-unsaturated ester via the Horner–Emmons protocol and spontaneous intramolecular condensation and ring closure. To this end, MeOCOCH$_2$PO(OCH$_2$CF$_3$)$_2$, a well-established reagent for Horner–Emmons olefination was added to the condensation of aldehyde **1** with aniline **2a** (**Method A**, Scheme 1), and remarkably furnished **3a** in one step with a 90% yield. Pyridopyrimidinone **3b** was prepared in the same way, although in a modest yield (52%) presumably due to an increased steric hinderance of **2b**. This process failed to shed any success on **2c**, an even more hindered substrate. Instead, **3c** was prepared in two steps (**Method B**). Displacement with 2,6-difluoroaniline **2c** to form anilinopyrimidine **6c** proved quite straightforward, however, ring formation to produce **3c** was problematic. Horner–Emmons reaction under Still's protocol[3] gave rise to an isomeric mixture (about 1:3) of **7c** (Table 1, entries 1 and 2). Intramolecular cyclization of the resultant mixture under various reaction conditions provided only trace amounts of **3c**.[4] Difficulties encountered in the spontaneous ring closure via amide formation might be related to the steric hinderance of 2,6-difluorophenyl unit in the substrates. This might be avoided by amide formation followed by spontaneous ring closure via intramolecular aldol condensation. Acetyl chloride was tested for the purpose (entry 3), and to our pleasure, the desired **3c** was isolated. The reaction was latter optimized providing **3c** in good overall yields (entries 4 and 5).

After securing the construction of pyrido[2,3-*d*]pyrimidin-7-ones, attention was directed towards the introduction of substituents at C2 (Scheme 2). Methylsulfone was chosen initially as the leaving group due to its success in previous syntheses.[2] Starting from sulfide **3a**, oxidation with Oxone® (5 equiv, Table 2) afforded sulfone **8a** (45%). Treatment of **8a** with serinol **9d** (1 equiv) in DMF did not result in the selective displacement of methylsulfone at C2. A similar result was obtained in the reaction of **8a** with amine **9e**. In light of a report that methanesulfinyl [MeS(O)–] displayed selectivity over chlorine in the nucleophilic displacements of 2-chloro-6-methanesulfinyl-pyridine,[5] MeS(O)– was studied as an alternative leaving group at C2.[6] To this end, the oxidation of **3a** with *m*-cPBA (1.5 equiv, 10 min) provided sulfoxide **10a** in an 82% yield. Treatment of **10a** with **9d**, to our pleasure furnished exclusive displacement at C2 producing **11ad**. This strategy was employed to pre-

Table 1. Formation of pyridopyrimidinone **3c** from **6c**

Entry	Reaction condition	Product	Yield (%)
1	MeOCOCH$_2$PO(OCH$_2$CF$_3$)$_2$, LiCl, DIPEA, MeCN	**7c**	60[a]
2	MeOCOCH$_2$PO(OCH$_2$CF$_3$)$_2$18-c-6, KHMDS, THF	**7c**	60
3	AcCl, 18-c-6, K_2CO_3, CH_2Cl_2	**3c**	13
4	Ac_2O, microwave, 15 min, 200 °C	**3c**	40
5	Ac_2O/DMF (1:2), microwave, 160 °C, 30 min	**3c**	50

[a] Mixture of *cis*- and *trans*-isomers with a ratio of 1:3 based on LC–MS and ^{1}H NMR of crude samples presumably favouring the *trans*-isomer.



Scheme 2.

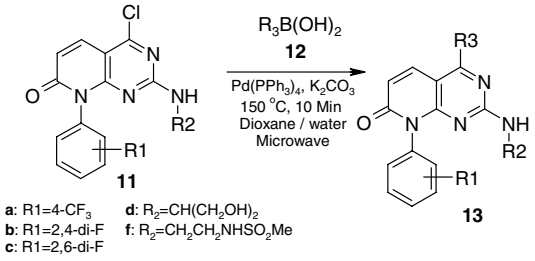
Table 2. Oxidation of sulfides **3**

Substrate	Reaction condition	Product	Yield (%)
3a	Oxone (5 equiv), acetone–water	**8a**	45
3a	Oxone (1.1 equiv), THF–water	**8a** + **10a**	37
3a	Oxone (1.1 equiv), acetone–water	**10a**	40
3a	*m*-cPBA (1.5 equiv), CH_2Cl_2, 10 min	**10a**	82
3b	*m*-cPBA (1.5 equiv), CH_2Cl_2, 10 min	**10b**	95
3c	*m*-cPBA (1.5 equiv), CH_2Cl_2, 10 min	**10c**	88

pare three additional compounds (**11bd**, **11cd** and **11cf**) in moderate yields.

With the intermediate 4-chloro-pyridopyrimidinone **11** finally in hand, the introduction of substituents at C4 via a microwave-assisted Suzuki cross-coupling[7] with boronic acids **12**(**g**–**t**)[8] was explored (Scheme 3) and the results are shown in Table 3. Group R3 includes a variety of phenyl and heterocyclic rings affording final products **13** in good yields.[9]

In summary, an improved synthesis that is amenable to the facile preparation of 4-substituted-pyrido[2,3-*d*]pyrimidin-7-ones was developed. The synthesis includes the efficient construction of the pyridopyrimidinone template and discovery of two differentially reactive groups [Cl vs MeS(O)–] allowing for selective substitution at C2 and C4. Fascile access to a number of analogues via an array approach was demonstrated. Noteworthily, the synthetic route provides an alternative method to prepare analogues with readily oxidizable



Scheme 3.

Table 3. Yield of Suzuki cross-coupling of **11** with **12**

R3	**11ad** (%)	**11bd** (%)	**11cd** (%)	**11cf** (%)
12g (2-SMe–Ph)	85	71	88	80
12h (3-SMe–Ph)	73	90	71	—[a]
12i (4-SMe–Ph)	56	56	67	—
12j (2-OMe–Ph)	76	95	91	53
12k (3-OMe–Ph)	65	89	78	—
12l (4-OMe–Ph)	60	75	70	—
12m (3,4-di-F–Ph)	65	77	96	—
12n (Thiophen-2-yl)	—	—	82	82
12o (Thiophen-3-yl)	—	—	90	93
12p (Furan-2-yl)	—	—	23	—
12q (Benzofuran-2-yl)	—	—	56	62
12r (Pyridine-3-yl)	—	—	75	85
12s (Pyridine-4-yl)	—	—	51	60
12t (Benzothiophen-2-yl)	—	—	74	75

[a] The coupling reaction was not tested.

substituents (e.g., compounds **13** with R3 = 2-SMe–Ph, 3-SMe–Ph or 4-SMe–Ph) that pose a pronounced challenge in the previous syntheses.[10] Biological evaluation of these compounds will be reported in due course.[11]

Acknowledgements

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References and notes

1. For reviews, see: (a) Coe, D. M.; Storer, R. *Annu. Rep. Comb. Chem. Mol. Div.* **1999**, *2*, 1; (b) Flynn, D. L. *Med. Res. Rev.* **1999**, *19*, 408; For an example of array approach with three points of diversity, see: (c) Wan, Z.; Boehm, J. C.; Bower, M. J.; Kassis, S.; Lee, J. C.; Zhao, B.; Adams, J. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1191.
2. Kasparec, J.; Adams, J. L.; Sisko, J.; Silva, D. J. *Tetrahedron Lett.* **2003**, *44*, 4567.
3. (a) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405; (b) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinez, L. E. *Tetrahedron* **1994**, *50*, 4323.
4. Less than 5% of **3c** was identified via LC–MS when treated under the condition of Ref. 2 (toluene, 200 °C, sealed tube). This is most likely due to the steric hinderance in the substrate.
5. Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *Tetrahedron Lett.* **1983**, *24*, 3243.
6. This template is apparently more closely related to 4-chloro-2-methanesulfinyl-pyrimidine wherein chlorine exhibited selectivity over methanesulfinyl, see: Hurst, D. T.; Johnson, M. *Heterocycles* **1985**, *23*, 611.
7. For a review of microwave-assisted organic synthesis see: Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
8. All boronic acids were purchased from commercial sources except **12h**. For the preparation of **12h**, see: Dack, K. N.; Whitlock, G. A. WO 99/29667, 1999.
9. To the solution of **11** in dioxane/water (3:1) were added **12** (1.5 equiv) and K_2CO_3 (3 equiv). The resultant mixture was bubbled with argon for 5 min before $Pd(PPh_3)_4$ (0.02 equiv) was added. The reaction tube was sealed and irradiated with a microwave reactor at 150 °C for 15 min. The mixture was concentrated under vacuo. Flash chromatography (EtOAc/hexane) then provided compound **13**.
10. As shown in Ref. 2, an oxidation reaction was carried out after the Suzuki cross-coupling and the group of –SMe would be likely oxidized in the reaction.
11. For Representative experimental procedures and compound characterization, see: Callahan, J. F.; Boehm, J.; Wan, Z.; Yan, H. WO 06/104917, 2006.