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A convenient synthesis of trisubstituted pyrido[2,3-*d*]pyrimidin-7-ones

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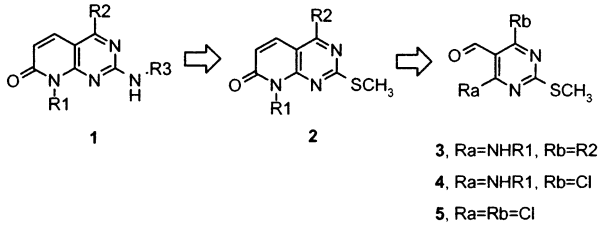
Abstract—A novel, highly efficient and scalable route for the synthesis of trisubstituted pyrido[2,3-*d*]pyrimidin-7-ones was developed. The target compounds were synthesized in five steps from readily available reagents in about 40% overall yield.

As part of our effort to design novel scaffolds for drug discovery programs, we investigated the synthesis of trisubstituted pyrido[2,3-*d*]pyrimidin-7-ones **1**. Unlike the less substituted pyridopyrimidinones previously described by other groups,[1–3] the present series of compounds has three derivatization sites, allowing for the convenient introduction of diversity around the central core. Interestingly, trisubstituted pyrido[2,3-*d*]-pyrimidin-7-ones constitute a novel structural compound class, with no published description or synthesis to the best of our knowledge.

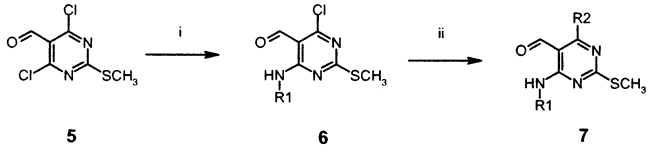
The present paper reports a novel synthetic route to trisubstituted pyrido[2,3-*d*]pyrimidin-7-ones, in which the readily available 4,6-dichloro-2-methylsulfanyl-pyrimidine-5-carboxyaldehyde **5**[4] is converted to the pyrido[2,3-*d*]pyrimidin-7-ones in five steps in about 40% overall yield. This route allows for the stepwise derivatization of the bicyclic core and can be easily scaled up (>10 g scale). Experimental conditions are presented and discussed below.

The retrosynthetic scheme for the trisubstituted pyrido[2,3-*d*]pyrimidin-7-one **1** is shown in Scheme 1. Sulfide **2** may be converted to **1** by oxidation to the corresponding sulfone and displacement with an amine nucleophile. The key step in our synthesis is the conversion of aldehyde **3** to bicyclic intermediate **2**. Such a transformation has been previously performed employing a Horner-Emmons procedure with Still's modification.[5,6] In this reaction, the aldehyde is converted to a *cis* α,β-unsaturated ester, which undergoes spontaneous intramolecular condensation with the *ortho* disubstituted amine under the reaction conditions. Intermediate **3** may be prepared from the commercially available **5** in a two-step procedure, involving a nucleophilic displacement to introduce R1 (**4**), followed by a Suzuki coupling to introduce R2 (**3**).

As shown in Scheme 2, 4,6-dichloro-2-methylsulfanyl-pyrimidine-5-carboxyaldehyde **5** was coupled to amines (1.2–5 equiv.) at room temperature (for alkyl-



Scheme 1.



Scheme 2. *Reaction conditions*: (i) alkylamine, $CHCl_3$, triethylamine, 15 min, 20°C, or arylamine, $CHCl_3$, triethylamine, reflux, 24 h; (ii) K_2CO_3, $Pd(Ph_3)_4$, arylboronic acid, dioxane, water, reflux, 16 h.

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amines) or reflux (for anilines).[1] In all cases studied, only monosubstitution was observed, presumably because the monochloro derivative **6** is not prone to subsequent nucleophilic displacement under the reaction conditions. Product **6** was easily isolated from the reaction mixture by evaporating the solvent and recrystallizing the residue. Under the reaction conditions cited, no imine formation was observed.[7]

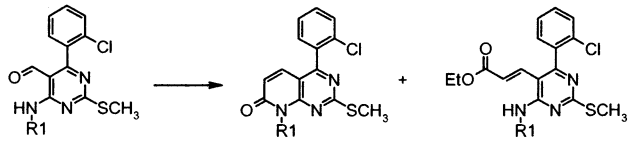
Chloride **6** was coupled to aromatic boronic acids under standard Suzuki conditions, using 1.2–1.5 equiv. of the appropriate boronic acid, 3 equiv. of potassium carbonate and catalytic amounts of tetrakis(triphenylphosphine) palladium (3 mole%) in a 3:1 dioxane/water mixture for 24 h. Product **7** was isolated by crystallization in very good yields (Table 1).

The conversion of aldehyde **7** to bicyclic compound **8** was investigated (Table 2). For the purposes of this discussion, the transformations where R1 is alkyl or aryl will be exemplified with 3-pentyl and 2-chlorophenyl groups, respectively, since they were found to be representative of their respective classes.

Table 1. Suzuki cross-coupling of **6** with various boronic acids

R1 group in **6**	R2 group, from boronic acid $R2B(OH)_2$	Isolated yield of **7** (%)
2-Propyl	2-Chlorophenyl	87
3-Pentyl	2-Chlorophenyl	82[8]
Methylcyclopropyl	2-Chlorophenyl	69
Phenyl	Phenyl	88
Phenyl	2-Chlorophenyl	93
2-Chlorophenyl	Phenyl	85
2-Chlorophenyl	2-Chlorophenyl	84[8]

Table 2. Studies of cyclization of aldehyde **7**



7a, R1=3-pentyl
7b, R1=2-chlorophenyl

8a, R1=3-pentyl
8b, R1=2-chlorophenyl

9a, R1=3-pentyl
9b, R1=2-chlorophenyl

Entry	Conditions	Reagent	Total yield (%)	Ratio **8**:**9**
I	[a]	**7a**	88	45:55
		7b	76	70:30
II	[b]	**7a**	78	85:15
		7b	94	5:95
III	[c]	**7a**	10	Only **8**
		7b	96	Only **8**

[a] Horner-Emmons/Still: $(CF_3CH_2O)_2POCH_2COOMe$, 18-crown-6, KHMDS, THF, −78°C, 6 h.
[b] Horner-Emmons: $(CH_3CH_2O)_2POCH_2COOMe$, NaH, THF, reflux, 2 h.
[c] Acetic anhydride, pyridine, reflux.

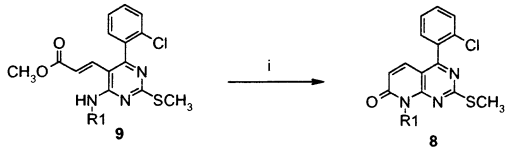
We originally envisioned performing this transformation using the Horner-Emmons reaction with Still's modification.[5] Surprisingly, the Horner-Emmons/Still reaction (entry I) afforded a mixture of desired pyridopyrimidinone **8**[9] and *trans* ester **9**. Formation of the *trans* isomer can be rationalized by the extreme steric crowding around the reactive center, which may disfavor formation of the *cis* product. The ratio between **8** and **9** was found to be highly substrate dependent, and all attempts to modify reaction conditions to afford pure **8** failed.

Besides affording a significant amount of undesired **9** along with **8**, the Horner-Emmons/Still reaction on **7** proved difficult to scale up because of the cost of the fluorinated phosphonate reagent and large excess of crown ether needed (5 equiv.). Other routes for the conversion of **7** to **8** were thus explored.

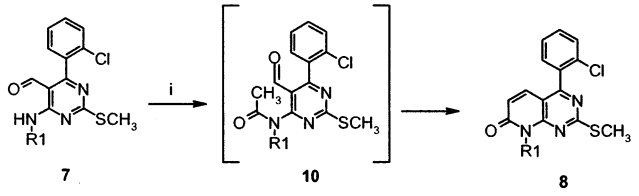
When **7** was submitted to a standard Horner-Emmons reaction (entry II), a mixture of **8** and **9** was formed in good yield. In the case of R1 = alkyl, to our pleasant surprise the desired **8a** was heavily favored. Apparently, under the reaction conditions, the initially formed *trans* ester isomerized to the *cis* ester and underwent intramolecular condensation. In the case of R1 = aryl, the major product was the *trans* ester **9b**.

Interestingly, **9** was quantitatively converted to **8** by heating in toluene to 200°C (Scheme 3).[10] Attempts to reduce the required reaction temperature using catalytic amounts of acids (TFA) or bases (DBU, NaH or DMAP) were not successful.

As an alternative to the Horner-Emmons procedure, we envisioned that acetylation of **7** would yield **10**, which could undergo an intramolecular aldol condensation to generate the desired **8** (Scheme 4). Indeed, when **7** was refluxed in a 1:1 mixture of acetic anhydride and pyridine for 48 h the desired pyridopyrimidinone **8** was observed (Table 1, entry III). Transient formation of the acylated intermediate **10** was observed by LC–MS. The reaction afforded good yields of **8** for R1 = 2-

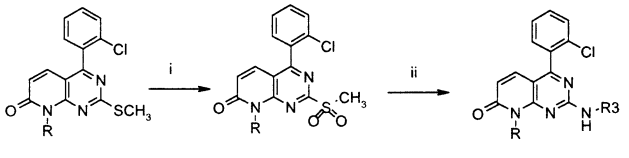


Scheme 3. *Reaction conditions*: (i) toluene, sealed tube, 200°C, quantitative.



Scheme 4. *Reaction conditions*: (i) acetic anhydride, pyridine, reflux, 24 h.

Table 3. Introduction of amine side chain



8a, R1=3-pentyl
8b, R1=2-chlorophenyl

11a, R1=3-pentyl, 75%
11b, R1=2-chlorophenyl, 89%

1

Sulfoxide used	R3 group, derived from amine $R3NH_2$	Isolated yield (%)
11a	$-CH_2CH_2OH$	**1a** (94)
11a	$-CH_2CH_2NH_2$	**1b** (78)
11b	$-CH_2CH_2OH$	**1c** (96)
11b	$-CH_2CH_2N(CH_2CH_3)_2$	**1d** (92)
11b	1-Methylpiperidin-4-yl	**1e** (85)
11b	$-CH_2CH_2NH_2$	**1f** (82)

chlorophenyl but not for R1 = 3-pentyl (only 10% yield after 48 h).

As shown above, the optimal method for the conversion of **7** to **8** is highly dependent on the nature of R1, i.e. whether R1 is alkyl or aryl. Our studies indicated that, when R1 = alkyl, **7** is cleanly converted to **8** in one step using the Horner-Emmons reaction (Table 1, entry II). When R1 = aryl, the conversion of **7** to **8** is most efficiently performed by reflux with acetic anhydride and pyridine (Table 1, entry III). These procedures have worked well for all examples of R1 used so far in this research.

As part of the final derivatization step in this synthesis, oxidation of sulfide **8** with *m*CPBA afforded sulfone **11**,[11] which was then reacted with a wide range of amine nucleophiles under mild conditions to afford the desired product **1**[12] (Table 3). The final trisubstituted pyrido[2,3-*d*]pyrimidin-7-ones were easily purified by a combination of aqueous work-up and column chromatography.

Conclusion

A novel, highly efficient and scalable route to trisubstituted pyrido[2,3-*d*]pyrimidin-7-ones was developed. Readily available starting material **5** was converted into the desired pyrimidinones **1** in five steps in about 40% overall yield.

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4. Aldehyde **5** is available from Maybridge but may also be easily prepared in one step from the more readily available 4,6-dihydroxy-2-methylsulfanylpyrimidine using the procedure described in: (a) Santilli, A. A.; Dong, H. K.; Wander, S. K. *J. Heterocyclic Chem.* **1971**, *8*, 445–453. For other examples of previously described pyrimidines which could be used to assemble a heavily derivatized bicyclic system, see: (b) Taylor, E. C.; Gillespie, P. *J. Org. Chem.* **1992**, *57*, 5757–5761; (c) Wormstadt, F.; Brinckman, U.; Gutschow, M.; Eger, K. *J. Heterocyclic Chem.* **2000**, *37*, 1187–1191.
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7. Under the reaction conditions, the weak base used (excess alkylamine or aniline added) plays a key role in ensuring that no imine is formed. When the reaction was run in DMSO using 1 equiv. of NaH, up to 50% yield of the corresponding imine was observed. 4-Chloro-6-(1-ethylpropylamino)-2-methylsulfanylpyrimidine-5-carboxaldehyde (**6a**): ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 6H, J=7.3 Hz), 1.50–1.74 (m, 4H), 2.52 (s, 3H), 4.22 (m, 1H), 9.21 (br s, 1H), 10.33 (s, 1H). LC MS (m/e) = 274 (MH+). 4-Chloro-6-(2-chlorophenylamino)-2-methylsulfanylpyrimidine-5-carboxaldehyde (**6b**): ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H), 7.17 (m, 1H), 7.29 (m, 2H), 7.44 (m, 1H), 10.37 (s, 1H), 11.49 (br s, 1H). LC MS (m/e) = 315 (MH+).
8. 4-(2-Chlorophenyl)-6-(1-ethylpropylamino)-2-methylsulfanylpyrimidine-5-carboxaldehyde (**7a**): ^{1}H NMR ($CDCl_3$): δ 0.91 (m, 6H), 1.42–1.60 (m, 4H), 2.45 (s, 3H), 4.21 (m, 1H), 7.32 (m, 4H), 8.96 (br s, 1H), 9.44 (s, 1H). LC MS (m/e) = 350.2 (MH+). 4-(2-Chlorophenyl)-6-(2-chlorophenylamino)-2-methylsulfanylpyrimidine-5-carboxaldehyde (**7b**): ^{1}H NMR ($CDCl_3$): δ 2.58 (s, 3H), 7.01–7.59 (m, 7H), 8.61 (d, 1H, J=4.7 Hz), 9.65 (s, 1H), 11.48 (br s, 1H). LC MS (m/e) = 390 (MH+).
9. 4-(2-Chlorophenyl)-8-(1-ethylpropyl)-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**8a**): ^{1}H NMR ($CDCl_3$): δ 0.85 (m, 6H), 2.01 (m, 2H), 2.26–2.44 (m, 2H), 2.63 (s, 3H), 5.39 (m, 0.5H), 5.75 (m, 0.5H), 6.62 (br d, 1H, J=9.6), 7.31–7.60 (m, 5H). LC MS (m/e) = 374.2 (MH+). 4-(2-Chlorophenyl)-8-(2-chlorophenyl)-2-methylsulfanyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**8b**): ^{1}H NMR ($CDCl_3$): δ 1.99 (s, 3H), 6.50 (d, 1H, J=9.7 Hz), 7.11–7.48 (m, 9H). LC MS (m/e) = 414 (MH+).

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11. 4-(2-Chlorophenyl)-8-(1-ethylpropyl)-2-methanesulfonyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**11a**): ^{1}H NMR ($CDCl_3$): δ 0.91 (m, 6H), 2.07 (m, 2H), 2.15 (s, 3H), 2.24–2.36 (m, 2H), 5.51 (m, 0.5H), 5.87 (m, 0.5H), 6.68 (br d, 1H, $J=9.6$), 7.22–7.59 (m, 5H). LC MS (m/e) = 406 (MH+). 4,8-Bis-(2-chlorophenyl)-2-methanesulfonyl-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**11b**): ^{1}H NMR ($CDCl_3$): δ 3.15 (s, 3H), 6.96 (d, 1H, $J=9.8$ Hz), 7.26 (m, 2H), 7.51–7.80 (m, 9H). LC MS (m/e) = 446 (MH+).
12. 4-(2-Chlorophenyl)-8-(1-ethylpropyl)-2-(2-hydroxyethylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**1a**): ^{1}H NMR ($CDCl_3$): δ 0.75 (m, 6H), 1.98 (m, 2H), 2.05 (m, 2H), 3.40 (m, 2H), 3.59 (m, 2H), 4.71 (m, 1H), 6.09 (m, 0.5H), 6.18 (m, 0.5H), 7.04 (m, 1H), 7.50 (m, 4H), 7.89 (m, 1H). LC MS (m/e) = 387 (MH+). 2-(2-Aminoethylamino)-4-(2-chlorophenyl)-8-(1-ethylpropyl)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**1b**): ^{1}H NMR ($CDCl_3$): δ 0.83 (m, 6H), 1.99 (m, 4H), 2.44 (m, 2H), 2.98 (m, 2H), 3.59 (m, 2H), 5.35 (m, 0.5H), 5.59 (m, 0.5H), 6.01 (br s, 1H), 6.28 (dd, 1H, $J=56$ Hz, $J'=9.5$ Hz), 7.13 (d, 1H, $J=9.5$ Hz), 7.42 (m, 3H), 7.54 (m, 1H). LC MS (m/e) = 386 (MH+). 4-(2-Chlorophenyl)-8-(2-chlorophenyl)-2-(2-hydroxyethylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**1c**): ^{1}H NMR ($CDCl_3$): δ 3.17 (m, 2H), 3.48 (m, 2H), 6.08 (br s, 1H), 6.45 (d, 1H, $J=9.6$ Hz), 7.26–7.67 (m, 9H). LC MS (m/e) = 427 (MH+). 4,8-Bis-(2-chlorophenyl)-2-(2-diethylaminoethylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**1d**): ^{1}H NMR ($CDCl_3$): δ 0.97 (m, 6H), 2.49 (s, 6H), 3.12 (m, 2H), 6.00 (br s, 1H), 7.18–7.63 (m, 9H). LC MS (m/e) = 482 (MH+). 4,8-Bis-(2-chlorophenyl)-2-(1-methylpiperidin-4-ylamino)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**1e**): ^{1}H NMR ($CDCl_3$): δ 1.42 (m, 2H), 1.79 (m, 4H), 2.25 (s, 3H), 2.75 (m, 2H), 3.15 (m, 1H), 5.33 (s, 1H), 6.39 (d, 1H, $J=9.8$ Hz), 7.24–7.59 (m, 9H). LC MS (m/e) = 480 (MH+). 2-(2-Aminoethylamino)-4,8-bis-(2-chlorophenyl)-8*H*-pyrido[2,3-*d*]pyrimidin-7-one (**1f**): ^{1}H NMR ($CDCl_3$): δ 2.59 (m, 2H), 3.11 (m, 2H), 5.91 (br s, 1H), 6.40 (d, 1H, $J=9.6$ Hz), 7.25–7.61 (m, 9H). LC MS (m/e) = 426 (MH+).