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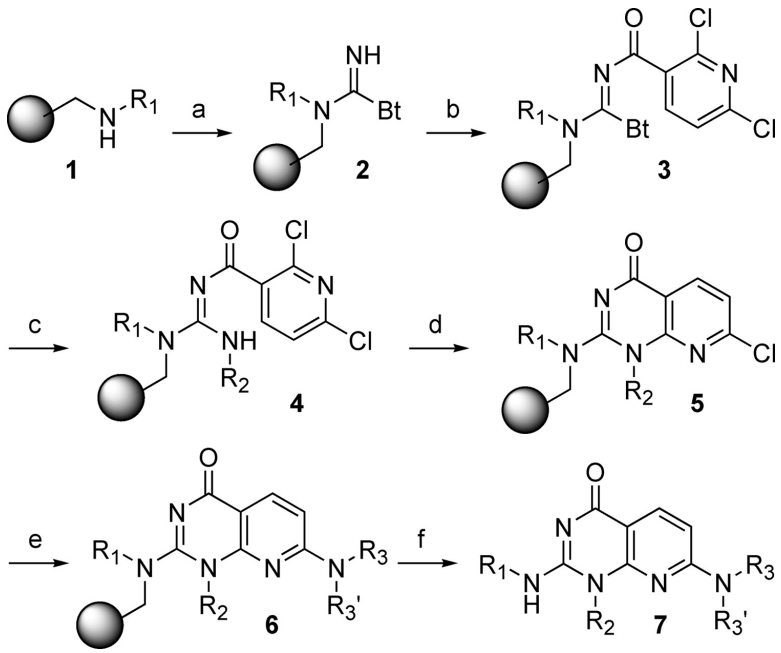

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Versatile Solid-Phase Synthesis of Trisubstituted 1*H*-Pyrido[2,3-*d*]pyrimidin-4-ones and Related Heterocycles

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A solid-phase synthesis of trisubstituted 1*H*-pyrido[2,3-*d*]pyrimidin-4-ones has been developed. The synthesis utilizes solid-phase bound *N*-2,6-dichloronicotinoyl-1*H*-benzotriazole-1-carboximidamides as key intermediates. Sequential substitution of benzotriazole and the two chlorines furnishes the title compounds with regioselectivity and high purity. Application of the method to various disubstituted analogues is also demonstrated.

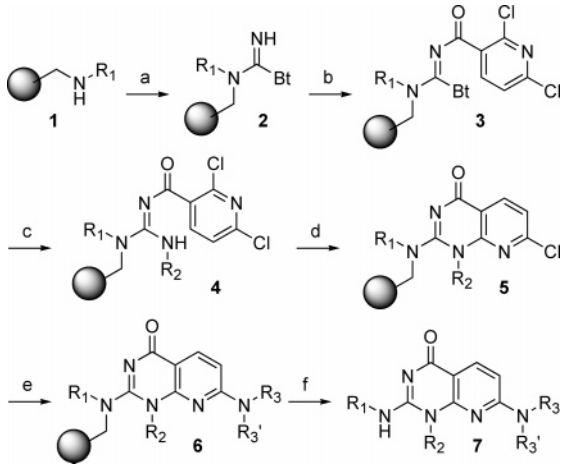
Introduction

Solid-phase organic synthesis is a well-established method for the synthesis of small organic molecules. Heterocycles are particularly interesting targets for new method development due to their structural diversity and importance in a broad range of therapeutic areas.[1,2] Herein we report an efficient synthesis of trisubstituted 1*H*-pyrido[2,3-*d*]pyrimidin-4-ones with three points of diversity. Only a few examples of syntheses of 1-alkyl-2-alkylamino-1*H*-pyrido-[2,3-*d*]pyrimidin-4-ones have been described before, with limited versatility and harsh reaction conditions.[3] 1-Alkyl-2-alkylamino-1*H*-pyrido[2,3-*d*]pyrimidin-4-ones have previously shown antihistaminic activity.[4] Syntheses to structurally related 2-aminoquinazolinones[5,6] have been reported, and they have shown promise in many therapeutic areas.[1,7]

The overall synthetic strategy for the synthesis of di- and trisubstituted 1*H*-pyrido[2,3-*d*]pyrimidin-4-ones is outlined in Scheme 1. Resin-bound secondary amines **1**, generated by the standard solid-phase reductive amination protocol ($NaBH(OAc)_3$/1% AcOH/DMF)[8] from commercially available FMP-resin, were reacted with a solution of di(benzotriazolyl)methanimine[9] in THF to give resin **2**. Resin **2** was acylated with 2,6-dichloronicotinoyl chloride using a variant of our previously described protocol[10,11] to obtain resin **3**.

After screening of several tertiary amine bases, 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (Barton's base) proved to be most efficient for the formation of resin **4**, in terms of both yield and selectivity for benzotriazole displacement. The reaction proceeds at room temperature and no chlorine displacement could be detected. Subsequent cyclization takes place at 95 °C, with DIEA in NMP, giving the best results for cyclized resin **5**. The displacement of the second chlorine by a primary or secondary amine was achieved with DIEA as base at the same temperature. Cleavage of resin **6** with TFA gave the desired trisubstituted 1*H*-pyrido[2,3-*d*]pyrimidin-4-ones (**7**) as TFA salts in good yields and with high purity.

Scheme 1



(a) 3.5 equiv of ($Bt^1C(=NH)Bt^1$ + $Bt^1C(=NH)Bt^2$) in THF, rt; (b) 3 equiv of 2,6-dichloronicotinoyl chloride/20 equiv of diisopropylethylamine (DIEA) in dichloromethane, rt; (c) 5 equiv of R_2NH_2/5 equiv of 2-*tert*-butyl-1,1,3,3-tetramethylguanidine in dimethylacetamide (DMA), rt; (d) 5 equiv of DIEA in *N*-methyl pyrrolidine (NMP), 95 °C; (e) 5 equiv of $R_3R_3'NH$/5 equiv of DIEA in NMP, 95 °C; (f) TFA/H_2O (95:5).

Table 1 summarizes our results using a diverse set of amines at all three sites. 1*H*-Pyrido[2,3-*d*]pyrimidin-4-ones (**7**) were characterized by ^1H NMR or LC/MS using an evaporative light-scattering detector (ELSD). A wide variety of amines at all three positions could be used to give rise to products of high purity. Anilines were also tried as R_2- and R_3-nucleophiles, but gave poor results (data not shown). Both primary and secondary amines were well-tolerated as R_3-amines. When amines were used as their corresponding salts, an additional equivalent of base was added to the reaction mixture (Table 1, entries **7e**, **7i**, and **7q**).

It should be noted that a monocyclic byproduct (**8a**) could also be identified in the LC/MS spectra. Compound **8a** can conceivably be the result of incomplete ring closure in step

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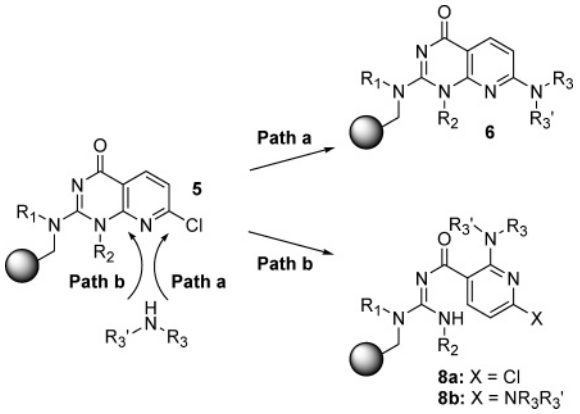
Table 1. Crude 1-Alkyl-2-alkylamino-7-alkylamino-1*H*-pyrido[2,3-*d*]pyrimidin-4-ones **7** and Related Bicyclic Heterocycles **9**−**13** Synthesized According to Scheme 1

	R_1	R_2	R_3R_3'−NH	purity[a], %	yield[b], %
7a	4-methylbenzyl	4-fluorobenzyl	morpholine	92	68
7b	2-(morpholino)ethyl	4-fluorobenzyl	morpholine	93	59[f]
7c	2-(methoxy)ethyl	4-fluorobenzyl	morpholine	95	42
7d	4-methylbenzyl	*n*-propyl	morpholine	92	55
7e	4-methylbenzyl	4-chloro-2-fluorobenzyl[d]	morpholine	95	62
7f	4-methylbenzyl	2-phenoxyethyl	morpholine	91	67
7g	4-methylbenzyl	2-(3-pyridyl)ethyl	morpholine	90	44[f]
7h	4-methylbenzyl	4-carboxybenzyl[e]	morpholine	90	48
7i	4-methylbenzyl	4-fluorobenzyl	dimethylamine[d]	95	67
7j	4-methylbenzyl	4-fluorobenzyl	1-methyl piperazine	95	59[f]
7k	4-methylbenzyl	4-fluorobenzyl	*N*,*N*,*N*′-trimethyl-1,2-ethanediamine	92	66[f]
7l	4-methylbenzyl	4-fluorobenzyl	2-(methoxy)ethylamine	95	71
7m	4-methylbenzyl	4-fluorobenzyl	*N*,*N*-diethylethylenediamine	95	70[f]
7n	4-methylbenzyl	4-fluorobenzyl	isobutylamine	92	54
7o	*n*-propyl	4-carboxybenzyl[e]	2-(methoxy)ethylamine	85	31
7p	4-methylbenzyl	2-(morpholino)ethyl	morpholine	75[c]	62[f]
7q	cyclohexyl	*n*-propyl	dimethylamine[d]	50[c]	59
9	4-methylbenzyl	2-(morpholino)ethyl	-	92	59[f]
10	4-methylbenzyl	2-(methoxy)ethyl	-	90	62
11	4-methylbenzyl	2-(4-hydroxyphenyl)ethyl	-	89	60
12	4-methylbenzyl	3-trifluoromethylbenzyl	-	95	54
13	4-methylbenzyl	4-fluorobenzyl	-	85	57

[a] By ELSD-HPLC of the desired ion. [b] Isolated yields of a 25-μmol reaction, resin loss due to handling not included; yields calculated on the basis of mono-TFA salt if not noted otherwise. [c] Side product as described in Scheme 2 is main impurity. [d] Amine was added as HCl salt to the reaction. [e] Amine added as *tert*-butyl ester of the carboxylate to the reaction. [f] Yield calculated on the basis of bis-TFA salt.

Scheme 2. Side Reaction during the Synthesis of Trisubstituted 1*H*-pyrido[2,3-*d*]pyrimidin-4-ones **6**



d (Scheme 1), followed by chloride displacement of resin **4** by R_3,R_3'-amine in step e. However, when resin **5** was cleaved with TFA, no substantial monocyclic intermediate could be seen in the LC/MS spectra (typically a small amount of the resin is cleaved for a quality check after every step). Thus, we hypothesize that **8a** is formed in the second displacement step. Instead of displacing the chlorine in resin **5** to give the desired resin **6**, ring opening may occur to form the monocyclic acyl guanidine resin **8a** (Scheme 2). This side product could be identified in most cases in only trace amounts by LC/MS, but in some cases, a considerable amount (up to 40%) was formed (Table 1, entries **7p** and **7q**). Interestingly, the monocyclic compound **8b** was not observed.

This methodology may be further extended through the use of alternative acid chlorides in place of 2,6-dichloronicotinoyl chloride. After acylation of resin **2** with these compounds, displacement of benzotriazole by a primary amine allows the subsequent cyclization to form other

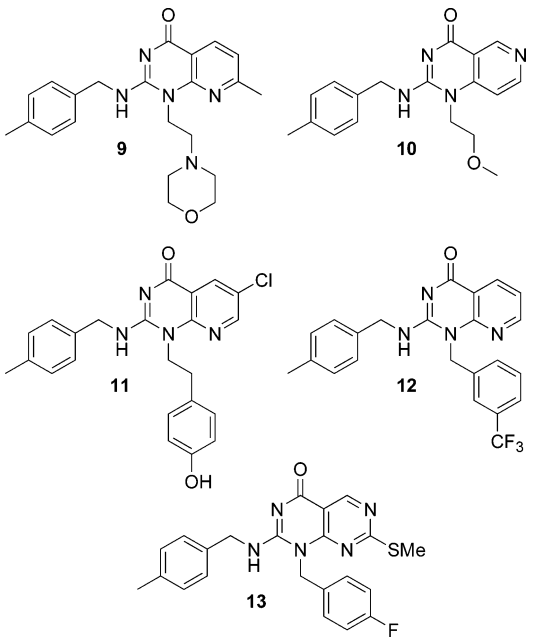


Figure 1. Structures of additional bicylic heterocycles synthesized.

bicyclic heterocycles. The reaction scheme is nearly identical to the one shown in Scheme 1, with the cyclization step being performed at a slightly higher reaction temperature of 120 °C for **9**−**12** and a slightly lower reaction temperature of 80 °C for **13**. The structures of these examples with two diversity points (**9**−**13**) are depicted in Figure 1, and the results are included in Table 1.

In conclusion, we demonstrated an effective method for the solid-phase synthesis of 1-alkyl-2-alkylamino-7-alkylamino-1*H*-pyrido[2,3-*d*]pyrimidin-4-ones as well as related pyridopyrimidin-4-ones. The title compounds were prepared with high purity and in good yields. The three variable groups, R_1−R_3, derive from easily available amines. The

procedure is quite general and is suitable for the preparation of combinatorial libraries.

Experimental Section

1-(4-Fluorobenzyl)-2-(4-methylbenzylamino)-7-morpholin-4-yl-1*H*-pyrido[2,3-*d*]pyrimidin-4-one (7a). Step 1: Reductive Amination (1a). StratoSpheres PL-FMP resin (100−200 mesh, loading 0.9 mmol/g; 28 mg, 25 μmol) was suspended in 1% AcOH/DMF (1 mL). 4-Methylbenzylamine (17 mg, 138 μmol) and $NaBH(OAc)_3$ (29 mg, 138 μmol) were added, and the resulting mixture was shaken on an orbital shaker for 2 days. MeOH (0.5 mL) was added, the mixture was filtered, and the resin was washed with DMF (3×), MeOH (3×), CH_2Cl_2 (3×), and ether (2×) and dried.

Step 2: Reaction with Di(benzotriazolyl)methanimine (2a). Resin **1a** (0.025 mmol) and $Bt^1C(=NH)Bt^1$ + $Bt^1C(=NH)Bt^2$ (23 mg, 0.088 mmol) in THF (1 mL) was flushed with argon and tumbled overnight at room temperature. The resin was filtered and washed with THF (5×), CH_2Cl_2 (5×), and ether (2×) and dried to give resin **2a**.

Step 3: Acylation (3a). To resin **2a** was added CH_2Cl_2 (1 mL), DIEA (87 μL, 0.5 mmol), and 2,6-dichloronicotinoyl chloride (16 mg, 0.075 mmol), and the resulting mixture was tumbled at room temperature for 3 h. The resin was filtered and washed with CH_2Cl_2 (3×), isopropyl alcohol (IPA) (3×), CH_2Cl_2 (3×), and ether (2×) and dried to give resin **3a**.

Step 4: Benzotriazol Displacement (4a). Resin **3a** was suspended in dimethylacetamide (DMA) (1 mL), then 4-fluorobenzylamine (14 μL, 0.125 mmol) and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (25 μL, 0.125 mmol) were added, and the resulting mixture was tumbled at room temperature for 16 h. The resin was filtered and washed with DMF (3×), water (1×), 1% AcOH/water (1×), water (1×), THF (3×), IPA (3×), CH_2Cl_2 (3×), and ether (2×) and dried to give resin **4a**.

Step 5: Cyclization (5a). Resin **4a** was suspended in a mixture of NMP (1 mL) and DIEA (22 μL, 0.125 mmol) and heated to 95 °C for 16 h. The resin was filtered and washed with DMF (3×), IPA (3×), CH_2Cl_2 (3×), and ether (2×) and dried to give resin **5a**.

Step 6: Chlorine Displacement (6a). Resin **5a** was suspended in NMP (1 mL). DIEA (22 μL, 0.125 mmol) and morpholine (11 μL, 0.125 mmol) were added, and the resulting mixture was heated to 95 °C for 16 h. The resin was filtered and washed with DMF (3×), IPA (3 ×), CH_2Cl_2 (3×), and ether (2×) to give resin **6a**.

Step 7: Cleavage from the Resin (7a). Resin **6a** was suspended in TFA/water, 95:5 (1 mL), and the resulting mixture was tumbled at room temperature for 90 min. The resin was filtered and washed with acetonitrile (1 mL). The combined filtrates were evaporated; dissolved in acetonitrile/water, 1:2; and lyophilized to give **7a**. ^{1}H NMR (DMSO-d_6) δ 8.72 (br. s, 1H), 7.99 (d, J = 9.1 Hz, 1H), 7.28−7.24 (m, 2H), 7.15−7.10 (m, 2H), 7.06−7.00 (m, 4H), 6.84 (d, J = 8.9 Hz, 1H), 5.57 (s, 2H), 4.61 (s, 2H), 3.59−3.57 (m, 8H), 2.24 (s, 3H). MS m/z [M^+ + H] 460.2.

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Supporting Information Available. Analytical and spectral characterization data for compounds **7a**−**o** and **9**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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