JOURNAL OF combinatorial CHEMISTRY

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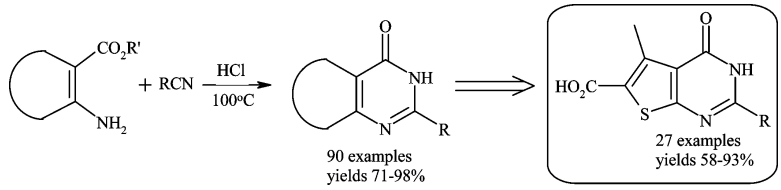
J. Comb. Chem., **2008**, 10 (6), 858-862• DOI: 10.1021/cc800074t • Publication Date (Web): 04 September 2008



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Dry HCl in Parallel Synthesis of Fused Pyrimidin-4-ones

Andrey V. Bogolubsky,[†] Sergey V. Ryabukhin,*[,†,‡] Andrey S. Plaskon,[†,‡] Svetlana V. Stetsenko,[†] Dmitriy M. Volochnyuk,[†,§] and Andrey A. Tolmachev[†,‡]

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Received May 2, 2008

The parallel solution-phase synthesis of substituted thieno[2,3-*d*]pyrimidin-6-carboxylic acids has been accomplished. This strategy relies on a cyclization of 2-aminothiophen-3,5-dicarboxylates with a set of nitriles, followed by hydrolysis to construct the library of corresponding acids. The convenient procedure for use and dosage of dry HCl for the reaction was elaborated and adapted for semiautomated solution-phase parallel synthesis. With the use of another (hetero)aromatic *ortho*-aminocarboxylate, mini-libraries of diverse fused pyrimidin-4-ones were synthesized. The scope and limitations of the approach are discussed.

Introduction

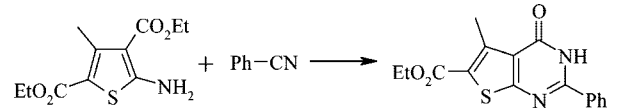
Thienopyrimidine derivatives have been the focus of great interest because of their remarkable biological properties.[1] The subject of our interest[2] was the synthesis of the library of thieno[2,3-*d*]pyrimidine-6-carboxylic acids **I** with diverse substituents at the C-2. Analogous compounds are reported as phosphodiesterase PDE9 inhibitors.[3] Retrosynthesis of compounds **I** showed that the sole commercially available starting compounds that are suitable for our purpose are the 2-aminothiophen-3,5-dicarboxylates **III**, which can cyclize with the nitriles **IV** (Scheme 1).[4] Earlier, the reaction was carried out via bubbling of dry HCl through a solution of starting materials at room temperature, followed by heating during 3−8 h.[4a−f] The reaction time decreased to 0.5−1 h in the case of MeCN as the reagent and solvent.[4d,e] However, utilization of this procedure in parallel synthesis needs elaboration and expensive equipment. At the same time, other starting compounds for the cyclization, derivatives of 2-aminothiophen-3,5-dicarboxylic acids, for example, aminoamides **V**, are not commercially available and not described in open literature.[5] Therefore, the problem of use and dosage of dry HCl is very critical for the successful performance of the thienopyrimidine synthesis. The solution to this problem would allow cyclization through path **B** by parallel synthesis to be performed. Herein, we report the results of using HCl solutions in organic solvents instead of gaseous HCl in such cyclizations. The scope and limitations of the approach are discussed.

Results and Discussions

On the basis of our recent experience in using TMSCl under high temperatures in sealed pressure tubes,[6] we expect that analogous techniques would allow us to use saturated solutions of dry HCl in organic solvents. Carrying out the reaction in sealed pressure tubes offers the advantage of heating the reaction mixture to the desired temperature without releasing the HCl from the reaction mixture. This keeps a sufficiently high concentration of HCl, not attainable in other protocols.

The reactions between 2-aminothiophen-3,5-dicarboxylates **1**(*1*) and benzonitrile **2**(*1*) was chosen for optimization (Table 1). To optimize the reaction conditions, we varied the solvent,

Table 1. Conversion of Starting Compound **1**(*1*) into **3**{*1*(*1*)−*2*(*1*)} Depending on Solvent, Temperature, and Time



1(1) **2(1)** **3{1(1)-2(1)}**

	solvent	HCl[a] (%)	C(HCl)[a] (M)	conditions	conversion[b] (%)
1	dioxane	20.5	7.63	20 °C, 24 h	100
2	THF	22.4	6.03	20 °C, 24 h	17[c]
3	Et_2O	23.5	5.05	20 °C, 24 h	18
4	MeOH	35.9	8.85	20 °C, 24 h	4
5	EtOH	29.9	8.05	20 °C, 24 h	3
6	dioxane	20.5	7.63	100 °C, 6 h	100
7	THF	22.4	6.03	70 °C, 12 h	36
8	MeOH	35.9	8.85	70 °C, 12 h	11
9	EtOH	29.9	8.05	70 °C, 12 h	6

[a] Titration of the solution was performed in the analytical laboratory at Enamine Ltd. at 20 °C. [b] According to HPLC APCI MS of the reaction mixture. [c] In saturated HCl solution in THF the cleavage of THF to $Cl(CH_2)_4OH$ observed.

Table 2. Conversion of Starting Compound **1**(*1*) into **3**{*1*(*1*)−*2*(*1*)} in Dioxane Solution Depending on Molar Concentration of Hydrogen Chloride

	C(HCl) (M)	conditions	conversion (%)
1	7.63	100 °C, 6 h	100
2	4	100 °C, 6 h	45
3	2	100 °C, 6 h	12
4	1	100 °C, 6 h	0
5	0.5	100 °C, 6 h	0

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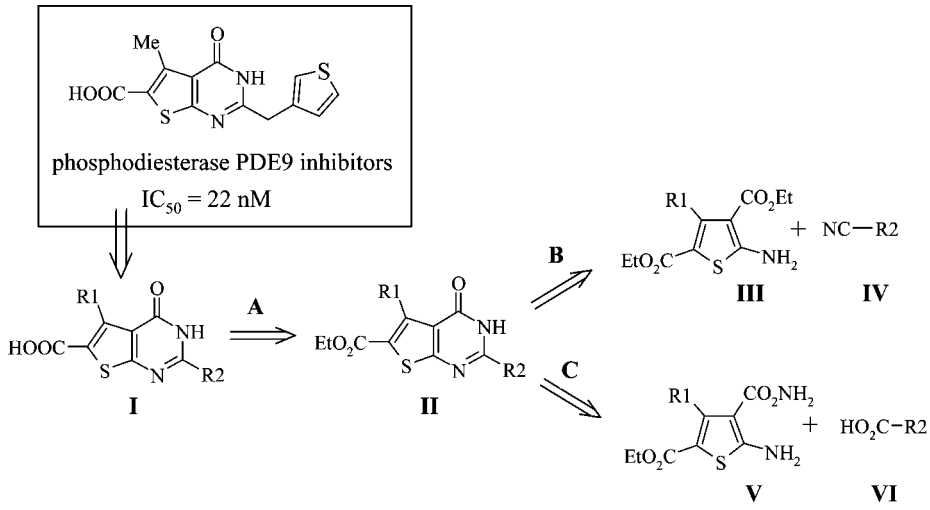
10.1021/cc800074t CCC: $40.75
Published on Web 09/04/2008

Scheme 1. Retrosynthesis of Thieno[2,3-*d*]pyrimidin-6-carboxylic Acids



the reaction time, and the temperature. One millimole of thiophene **1**(*1*) and 1 mmol of PhCN was dissolved in 2 mL of saturated solution of HCl in the corresponding solvent in a sealed pressure tube. The reaction mixture was maintained at different temperatures during different time. Then the samples were subjected to HPLC MS analysis. The results are summarized in Table 1. The influence of HCl concentration in dioxane on the reaction was also investigated, and the concentration appears critical to be for the transformation (Table 2).

The optimal reaction conditions involve heating of the reagents at 100 °C in saturated solution of HCl in dioxane for 6 h. Then, the reaction mixtures were diluted with 5 volumes of water, and the amorphous precipitate formed was triturated in an ultrasonic bath for several hours yielding the targeted product. The crude products **3**{*1*(*1*)−*2*(*1*)} isolated by simple filtration had >95% homogeneity determined by RP-HPLC.

This procedure was used in the parallel synthesis for preparation of an array of substances **3** using various substituted nitriles shown in the Figure 1. The hydrolysis of esters using KOH in dioxane−water led to target acids **4**{*1*(*1*)−*2*(*1*−*27*)} in 80−98% yields (Scheme 2).

The reaction proceeded in high yields with a wide range of nitriles. (Hetero)Aromatic, as well as aliphatic, nitriles can be used. Nevertheless, some limitations have been found, which are summarized in the Table 3.

The hydrochloric acid is also a good reagent for hydrolysis of *tert*-butyl carboxylates;[7] therefore, we tried to elaborate a one-pot procedure for synthesis of acid **4** starting from *t*-Bu ester **1**(*2*) instead ethyl ester **1**(*1*). However, the target acids **4** appeared unstable toward concentrated HCl, and as the result, decarboxylated thienopyrimidines **5** formed in the reaction. It should be noted that compounds **5** are not easily accessible[8] (Scheme 3).

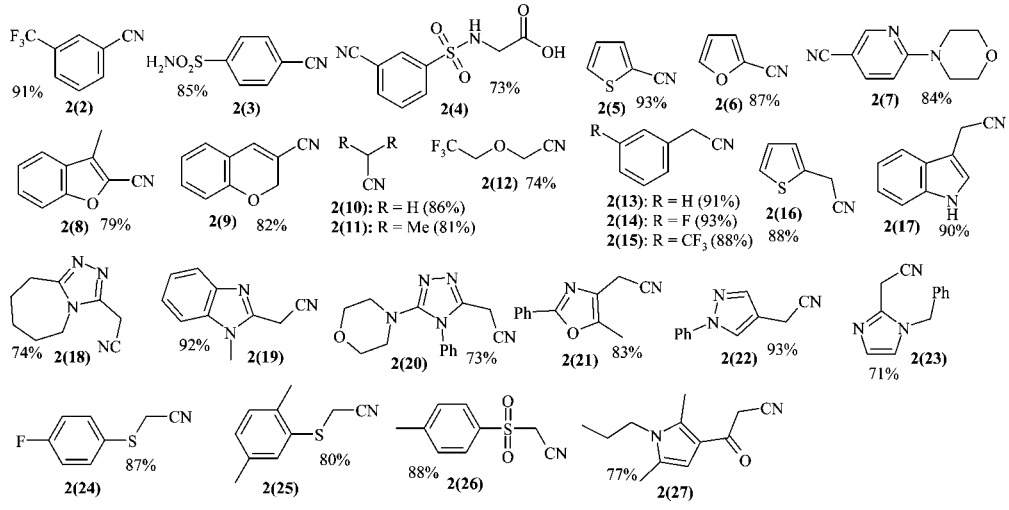


Figure 1. Nitriles **2** and yields of products **3**.

Scheme 2

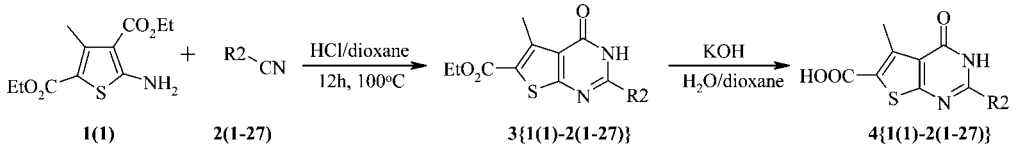
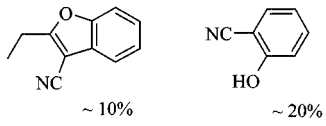
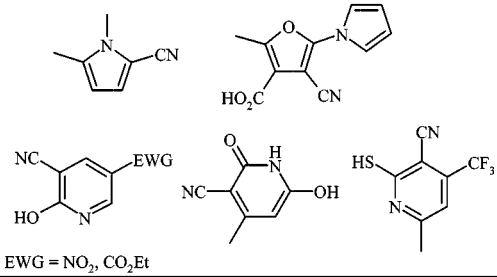
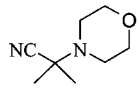
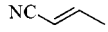
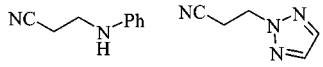
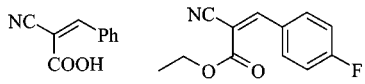
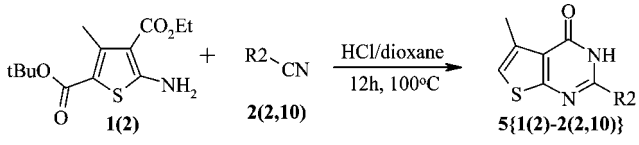


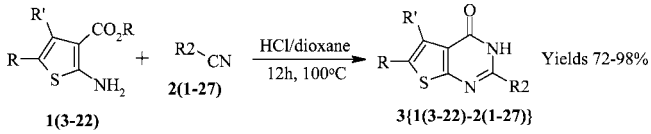
Table 3. Limitation of the Procedure of Using HCl/Dioxane Solution for Synthesis of Thieno[2,3-*d*]pyrimidines **3**

Entry	Nitrile	Results	Comments
1		No reaction	The nitrile is not sufficiently active due to steric hindrance.
2	 ~ 10% ~ 20%	The yields of targeted products using general procedure ~ 10-20%, the procedure of purification of crude products (impurity – the starting compounds) needs chromatographic separation.	The low conversion could be explained by the decreased activity of the nitrile group due to conjugation with OH-group or the electron-rich ring.
3	 EWG = NO_2, CO_2Et	No reaction	The nitrile is not sufficiently active due to conjugation with OH-group or electron-rich ring.
4		No reaction.	The nitrile function is not protonated due to the presence of other basic groups and steric hindrance.
5		The reaction proceeds non-selective. For purification of target compounds requires chromatographical separation	Side process – Michael addition occurs
6		The reaction proceeds non-selective. For purification of target compounds requires chromatographical separation	The side reaction – elimination of aniline or heterocycle
7		Complex reaction mixture	The side process – hydrolysis and decarboxylation occur

Scheme 3

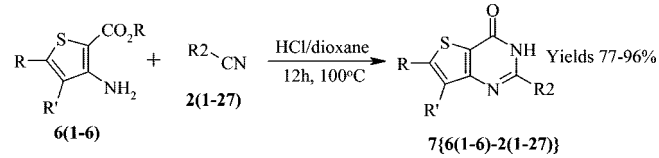


Scheme 4



The elaborated procedure appears general for such cyclization and works well with another type of 2-amino-3-carbethoxythiophenes **1**(*3*−*22*) (Scheme 4, Figure 2), as well as for other esters of *ortho*-aminoacids, such as 3-amino-2-carbethoxythiophene derivatives **6**(*1*−*6*) (Scheme 5, Figure 3) and derivatives of anthranilic acid **8**(*1*−*9*) (Scheme 6, Figure 4). The limitations on using of the nitriles are similar to the ones for thiophene **1**(*1*) (Table 3).

Scheme 5



In the course of the study, we found a set of inactive heterocyclic aminocarboxylates **10**−**18** (Figure 5). In this case, after using the typical procedure, the starting heterocyclic derivatives were recovered after the workup of the reaction mixture. It could be explained by low nucleophilicity of the amino group in the substrates in comparison with the corresponding benzene and thiophene derivatives.

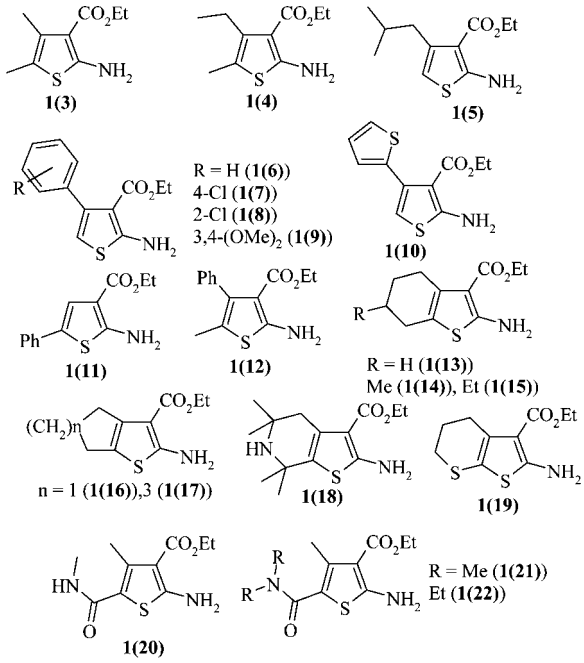


Figure 2

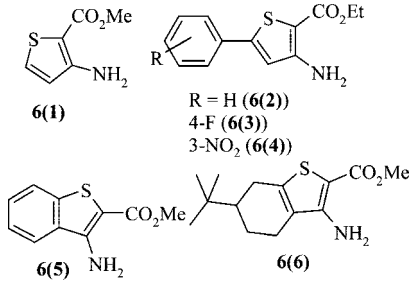


Figure 3

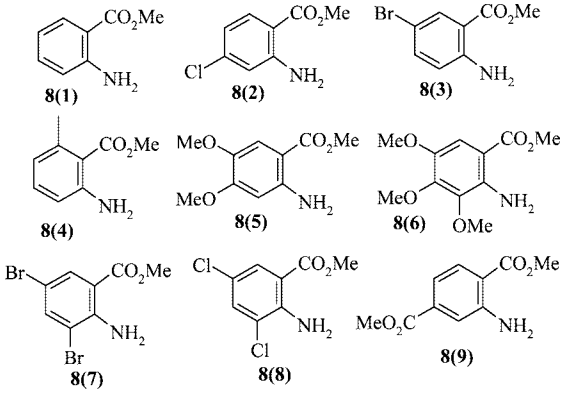
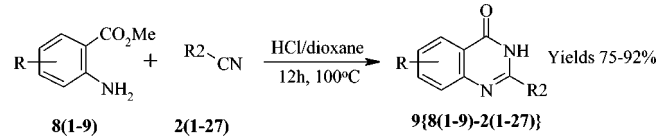


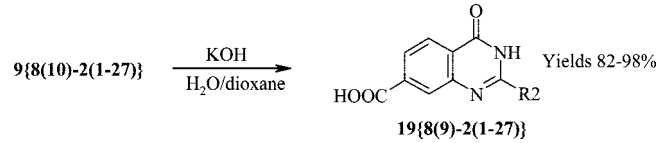
Figure 4

The two-step approach to thieno[2,3-*d*]pyrimidine-6-carboxylic acids was applied to synthesis of a library of 4-oxo-3,4-dihydroquinazoline-7-carboxylic acids **19** (Scheme 7). The derivatives of these acids attracted the attention in recent time because of the wide set of biological activities.[9]

Scheme 6



Scheme 7



Conclusion

In summary, a new method for using saturated solution of HCl in dioxane instead gaseous HCl was elaborated. The procedure was adapted to solution phase parallel synthesis. On the basis of this method, an efficient synthetic route to thieno[2,3-*d*]pyrimidin-6-carboxylic acids, benzopyrimidin-7-carboxylic acids, and other (hetero)aromatic annelated pyrimidine libraries in solution was developed. In most cases of the reaction investigated, the corresponding libraries were generated with low levels of impurities using a simple crystallization from the reaction mixtures. The yields of the products varied according to the reactant structure, but in most cases, the desired products were obtained in high yields.

Experimental Section

General Information. All chemicals were obtained from commercially available sources and used without further purification (Aldrich, Fluka, Enamine Ltd.). All solvents for the reactions (DMF, MeCN, DMSO, dioxane) were freshly distilled and dried by standard methods, monitoring of the water concentration in solvents (all solvents had <0.05%, usually 0.02% of water) was performed using Mettler Toledo DL31 KF titrator. All solvents for the crystallizations were used as aquired. Melting points were measured with a Buchi melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker Avance DRX 500 using DMSO-d_6 as a solvent and TMS as an internal standard. LC/MS spectra were recorded using chromatography/mass spectrometric system consisting of high-performance liquid chromatograph Agilent 1100 Series equipped with diode-matrix and mass-selective detector Agilent LC\MSD SL. The parameters of chromatography−mass analysis: Column,

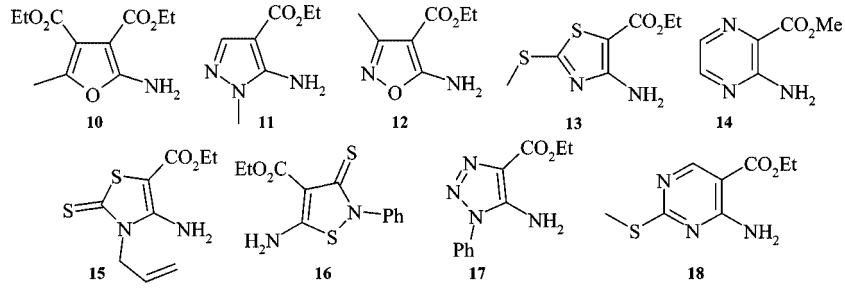


Figure 5

Zorbax SB-C18, 1.8 μm, 4.6 mm × 15 mm; Eluent, A MeCN−water with 0.1% of TFA (95:5), B water with 0.1% of TFA; Flow rate, 1.8 mL/min; Volume of the injected sample, 1 μL. The UV detectors were operate at 215, 254, and 265 nm. The ionization method was chemical ionization under atmospheric pressure (APCI), and the ionization mode was simultaneous scanning of positive and negative ions in the mass range of 80−1000 *m**z*. According to HPLC/MS and ^{1}H NMR data, all the synthesized compounds have purity over 95%.

Preparation of the Pirimidin-4-ones 3, 5, 7, and 9: General Procedure. The appropriate aminoester, **1**, **6**, or **8** (2 mmol), and the appropriate nitrile, **2** (2 mmol), were placed in 15 mL pressure tube, and saturated HCl solution in dioxane (4 mL) was added dropwise. The tube was carefully sealed and left at rt in ultrasonic bath for 4 h and than heated at 100 °C with stirring for 4−16 h. After it was cooled to rt, the tube was opened (**Caution!** *Excessive pressure inside*), and the reaction mixture was poured into water (25 mL). The precipitate formed was filtered and washed with a small amount of EtOH.

Preparation of the Acids 4 and 19: General Procedure. The appropriate ester, **3** or **9** (2 mmol), and KOH (224 mg, 4 mmol) were placed in 15 mL pressure tube, and dioxane (2 mL) with water (1 mL) was added by one portion. The tube was carefully sealed heated at 100 °C with stirring for 2−16 h. After it was cooled to rt, the tube was opened, and the reaction mixture was poured into water (5 mL); then the suspension was neutralized with 2% aq HCl. The precipitate formed was filtered and washed with a small amount of MeCN.

Acknowledgment. The authors acknowledge Mr. V. V. Polovinko (Enamine Ltd.) and Dr. S. A. Alekseev (Kyiv National Taras Shevchenko University) for spectral measurements.

Supporting Information Available. Details of the experimental procedures and spectroscopic data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) For our attempts to synthesize **V**, see Supporting Information.

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