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One-pot synthesis of thieno [2,3-*d*] pyrimidin-4-ol derivatives mediated by polyphosphonic anhydride

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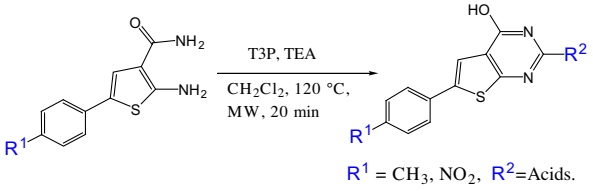
ABSTRACT

An efficient synthesis of thiopyrimidines with different substituents in position 2 is described. A rapid, mild and high yielding microwave-assisted one-pot cyclization of 5-substituted 2-amino thiophene-3-carboxamide derived from Gewald reaction[1] with T3P and different acids gives the corresponding thiopyrimidines. The significant feature of this method includes less reaction time, high purity and reduced toxicity of the reaction.

Over the past few years, the poly phosphonic acid cyclic anhydride has attracted significant interest as an efficient and mild coupling reagent and dehydrating agent. This is due to its efficient functional group tolerance, low toxicity[1] and low epimerization tendency and easy work-up procedures. Accordingly, a variety of new applications have been developed for this reagent, including the direct conversion of ketoximes to amides, and aldoximes to nitriles,[2] the synthesis of alkenes from alcohols,[3] peptide synthesis,[4] the formation of isonitriles from formamide,[5] oxidation of alcohols,[6] ester synthesis,[7] C–C coupling reactions,[8] the conversion of carboxylic acids into azides,[9] the Lossen[10] and preparation of substituted heterocycles (Scheme 1).

The thiopyrimidine core moiety is a versatile heterocyclic system, occurring in a variety of compounds with a broad spectrum of biological activities,[11] consequently, thiopyrimidines and its derivatives continue to capture the attention of organic and medicinal chemists and a variety of well established methods are now available for their production. Moreover, they are important intermediate organic synthesis providing access to other highly desirable structures (Scheme 2).

The synthesis of substituted thiopyrimidines from 5-substituted 2-amino thiophene-3-carboxamide[12] and carboxylic acids is the most widely used synthetic procedure. This reaction involves the base catalysed amidations followed by the elimination of water.



Scheme 1.

However, despite their common use, most reported methods to prepare these heterocyclics suffer from long reaction times and often require the use of strong acid media. Consequently, new mild and expedient protocols for this valuable and widely utilized reaction are of significant importance.

Polyphosphonic anhydride[13] is a mild water scavenger, but its synthetic utility has not been investigated in the synthesis of fused pyrimidine derivatives. Herein we report an efficient and operationally simple one-pot synthesis of fused pyrimidines.

The classical reactions between 5-substituted 2-amino thiophene-3-carboxamide (**1a**, 1 equiv) or 2-amino-5-(4-nitrophenyl) thiophene-3-carboxamide (**1b**, 1 equiv) and carboxylic acid (**4a**, 1.1 equiv) in the presence of T3P (50% solution in EtOAc, 2.5 equiv) were used.[14] The reaction mixture was heated at 120 °C under microwave irradiation for 20 min with 2.5 equiv of T3P (Table 1, entry 2). Further optimization showed that use of T3P (2.5 equiv) was appropriate for the full conversion of **1a** and **1b** and requires only 20 min of microwave irradiation at 120 °C. Increasing the equivalent of T3P and also reducing the reaction time lowered the cyclized products (Table 1, entry, 5).

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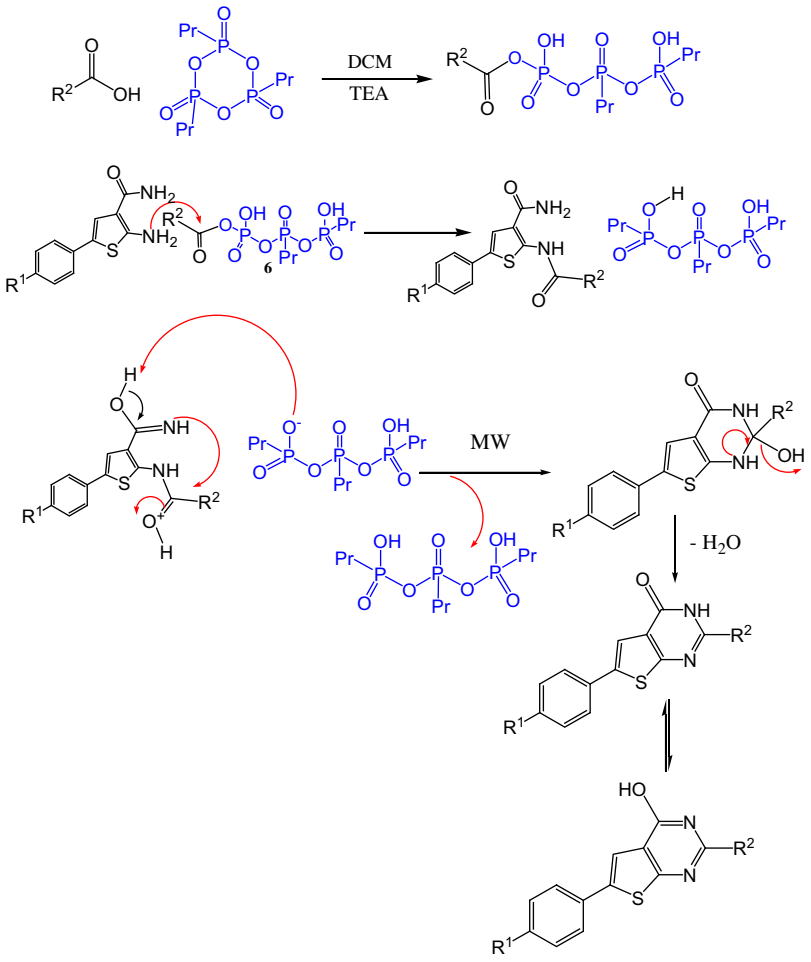


Scheme 2.

Table 1
Screening optimal conditions

Entry	T3P (equiv)	Time (min)	Temp (°C)	Yield (%)
1	1.5	30	120	55
2	2.5	20	120	98
3	1.0	20	130	50
4	3.0	20	120	67
5	5.0	10	120	30
6	0.5	30	120	20
7[a]	0.0	20	120	NR[b]

[a] Reaction was performed in the absence of T3P.
[b] No reaction.

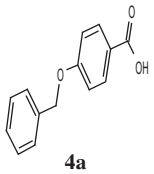
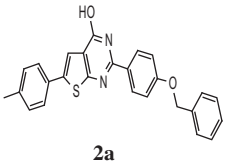
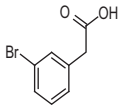
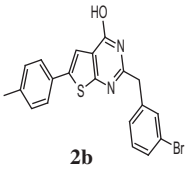
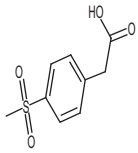
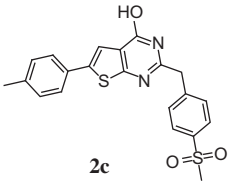
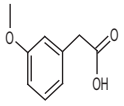
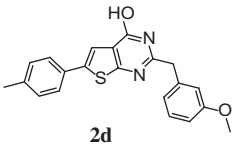
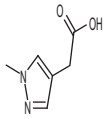
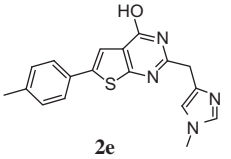
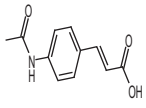
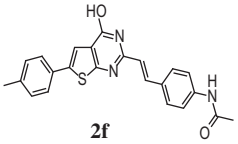
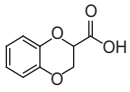
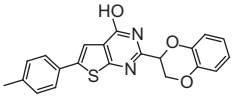
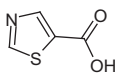
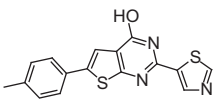
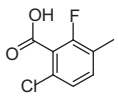
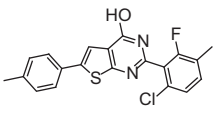
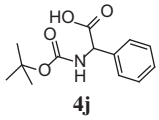
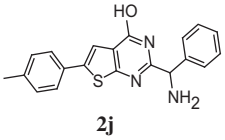
The intramolecular cyclization was mediated by T3P and not via a thermal process; a control experiment without the addition of T3P was performed. As expected, there were no cyclized products when the carboxamide was heated at 120 °C in chloroform in the absence of T3P. (LC/MS analysis). (Table 1, entry 7).

The transformation of carboxylic acids **4a**–**4w** into the corresponding substituted fused thiopyrimidines (see Table 2) however, occurred rapidly under microwave irradiation. Although the reaction proceeded well with 4-benzyloxy benzoic acid (**4a**) a longer reaction time was needed (20 min) to achieve full conversion. The use of aliphatic acid and heterocyclic acids also required slight adjustment of the conditions. In case of linear acids such as 4-actamido cinnamic acid (**4f)** and 3-[3-(trifluoromethyl) phenyl] propionic acid (**4m)** they gave the corresponding cyclic compounds in good yields (entries 6 and 14) after heating at 120 °C for extra 10 min compared to **4a**. 2,3-Dihydro 1,4-benzodixine -2-carboxylic acid (**4g**) and cyclopentanoic acid (**4p**) both performed well, affording 88% and 94% yields of the desired products (**2g)** and (**2p**) respectively. The reaction with substituted substrates such as 6-chloro-2-fluoro-3-methylbenzoic acid (**4i**) and 4-(trifluoromethyl)-1,3-thiazole-2-carboxylic acid (**4s**) was carried out in two steps. Firstly, the intermediate amide derivative was formed by heating at 60 °C for 10 min followed by cyclization at 120 °C for 20 min. This procedure furnished the desired products in an excellent yield (91% and 86% entries 9 and 19).

A set of substituted carboxylic acids were investigated. In general, carboxamide bearing electron- donating (entries 1–16) or electron withdrawing groups (entries 17–23) were well tolerated affording good to excellent yields of the corresponding products.

We have developed a convenient one pot method for the synthesis of thieno [2,3-*d*] pyrimidin-4-ol derivatives. We have also provided rapid, mild and high yielding protocol for the intramolecular cyclization with T3P under microwave irradiation. This method seems to be convenient for large scale preparation due to the ease of isolation of products in good purity by simple work-up. Moreover, these new protocols allow for an iterative analogue library synthesis approach for lead optimization to be employed for the rapid synthesis of library compounds.

Table 2
Synthesis of thiopyrimidines derivatives from 1**a** and 1**b** with various acids

Entry	Amide	Acid (R^2)	Product	Yield[a] (%)
1	**1a**	 **4a**	 **2a**	94
2	**1a**	 **4b**	 **2b**	97
3	**1a**	 **4c**	 **2c**	95
4	**1a**	 **4d**	 **2d**	98
5	**1a**	 **5e**	 **2e**	92
6	**1a**	 **4f**	 **2f**	98
7	**1a**	 **4g**	 **2g**	88
8	**1a**	 **4h**	 **2h**	87
9	**1a**	 **4i**	 **2i**	91
10	**1a**	 **4j**	 **2j**	87

(*continued on next page*)

Table 2 (*continued*)

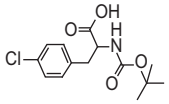
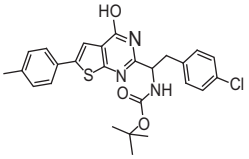
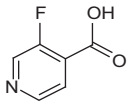
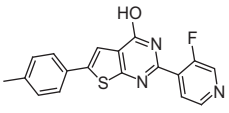
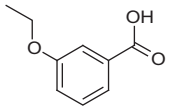
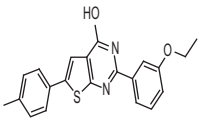
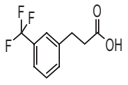
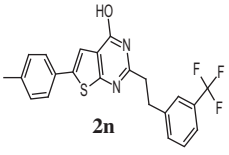
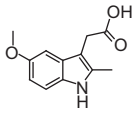
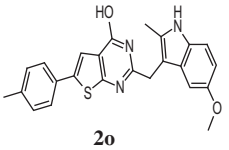
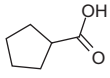
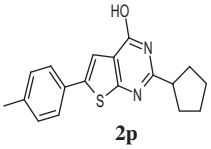
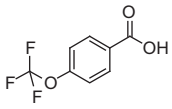
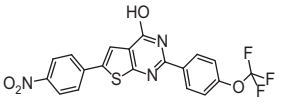
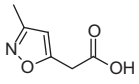
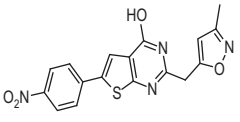
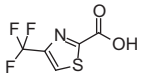
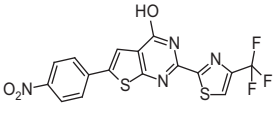
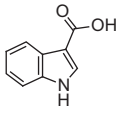
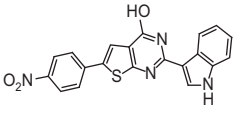
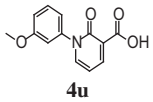
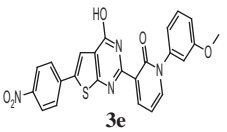
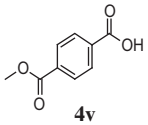
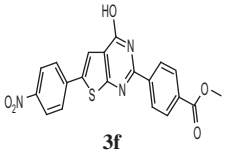
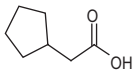
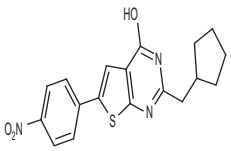
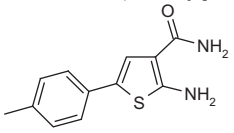
Entry	Amide	Acid (R^2)	Product	Yield[a] (%)
11	**1a**	 **4k**	 **2k**	92
12	**1a**	 **4l**	 **2l**	92
13	**1a**	 **4m**	 **2m**	99
14	**1a**	 **4n**	 **2n**	98
15	**1a**	 **4o**	 **2o**	84
16	**1a**	 **4p**	 **2p**	94
17	**1b**	 **4q**	 **3a**	96
18	**1b**	 **4r**	 **3b**	86
19	**1b**	 **4s**	 **3c**	93
20	**1b**	 **4t**	 **3d**	84
21	**1b**	 **4u**	 **3e**	89

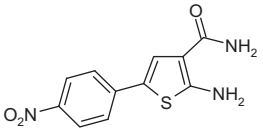
Table 2 (*continued*)

Entry	Amide	Acid (R^2)	Product	Yield[a] (%)
22	**1b**	 **4v**	 **3f**	84
23	**1b**	 **4w**	 **3g**	97

1a = 2-amino-5-(4-methylphenyl)thiophene-3-carboxamide.



1b = 2-amino-5-(4-nitrophenyl)thiophene-3-carboxamide.



[a] Isolated yield.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.017.

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13. For a brief review of the reagent, see: (a) Llanes García, L. *Synlett* **2007**, 1328; (b) Schwarz, M. *Synlett* **2000**, 1369.
14. To a mixture of 2-amino-5-(4-methylphenyl) thiophene-3-carboxamide **1a** (0.25 g, 0.107 mol) and 4-benzyloxy benzoic acid **4a** (0.319 g, 0.140 mol) in anhydrous chloroform (4 ml) was added triethylamine (0.32 g, 0.323 mol) and phosphonic acid cyclic anhydride (1.02 g, 0.323 mol). The reaction mixture was irradiated at 120 °C in a microwave initiator for a given period of time (Table 1, entry 1). Once the substrate was completely consumed as monitored by TLC, the brown reaction mixture was cooled and poured into ice-cold water (10 ml). The product was extracted with ethyl acetate (2 × 25 ml) and the combined organic phase was washed with water, brine solution and dried over anhydrous sodium sulfite. The solvent was removed under vacuum and the brown residue was passed through a small plug of silica gel using petroleum ether/ethyl acetate (9/1) to afford 429 mg (94%) of **2a** as a yellow solid.