Solid-phase synthesis of *N*-(pyrimidin-2-yl)amino acid amides

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Dedicated in honor of Prof. Nikolai Zefirov on his 70th Anniversary

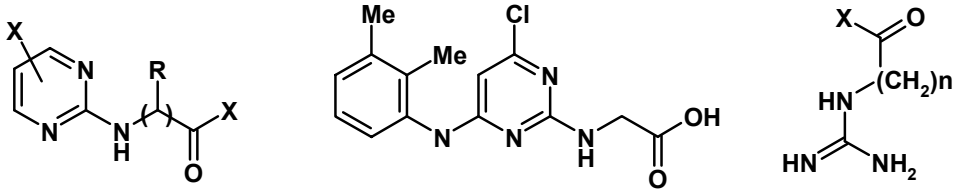
Abstract

A series of new primary amides of *N*-(pyrimidin-2-yl)amino acids were prepared using solid-phase chemistry techniques. Various protected amino acids were immobilized onto Rink resins and deprotected. Reaction with 2-fluoropyrimidines followed by cleavage from the resin afforded the target compounds in good yields. A general method for the synthesis of amino acid derivatives N-aminosubstituted with a heterocyclic core has been found, and the advantage of the solid-phase approach is also discussed.

Keywords: Solid-phase synthesis, *N*-(pyrimidin-2-yl)amino acid amides, 2-fluoropyrimidine, nucleophilic aromatic substitution

Introduction

2-Aminopyrimidine is an interesting structural element present in several marketed drugs, and its derivatives possess diverse biological activities, e.g. antipsychotic,[1a] cardioprotective,[1b] and antimalarial.[1c] An attractive and poorly investigated class of 2-aminopyrimidines are N-substituted amino acid derivatives I and II linked to the α-position of the pyrimidine ring via the ω-aminogroup. An example of a known drug which belongs to this class I is the atherosclerotic aronixil III (Figure 1).



I: X=OH
II: X=NH_2

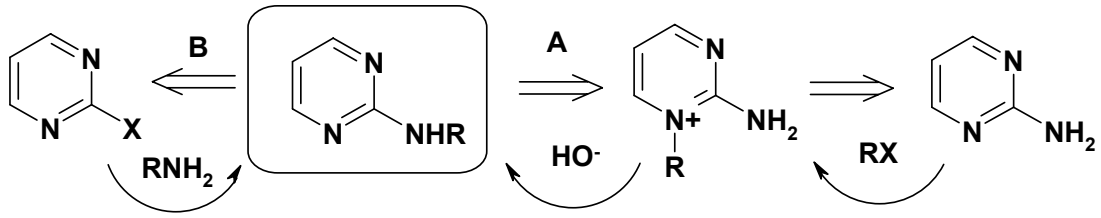
III

IV: X=OH, n=1
V: X=NH_2, n=2

Figure 1

A change from guanidine to aminopyrimidine[2] performed recently as a structural modification of an antidiabetic lead compound IV preserved the desired biological activity. Furhter, the chain elongation and change of the terminal acid group to an amide give the structure of the known antidiabetic thiformin V. These observations caught our interest, leading to the preparation of a library of N-(pyrimidin-2-yl)amino acid amides II. Although several series of N-(pyrimidin-2-yl)glycine amides are known,[3a-c] we have surprisingly not found any general route for the synthesis of primary amides of other (natural and unnatural) acids of the structural type II in the literature.

At least two main strategies for the synthesis of 2-alkylaminopyrimidines could be explored in order to achieve our goals (Scheme 1). Strategy A is based on the Dimroth rearrangement of 1-alkyl-2-aminopyrimidinium salts, and strategy B is the nucleophilic substitution of the pyrimidine ring. Although both strategies are widely used in the pyrimidine chemistry, our preliminary attempt to utilize both routes to prepare simple N-(pyrimidyl-2)-glycine derivatives by common solution-phase methods failed due to the predominance of side chain reactions.[4a]

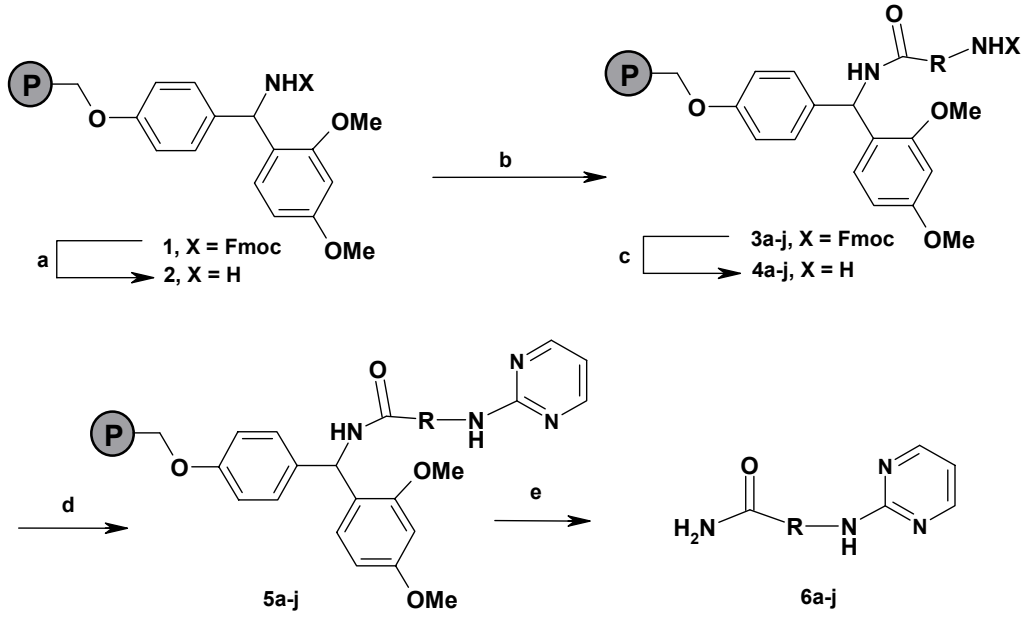


Scheme 1. Conventional solution-phase synthesis of *N*-substituted *N*-pyrimidin-2-ylamines.

We report here our successful attempt to prepare these compounds, involving the reaction of pyrimidines bearing a suitable leaving group at position 2, with polymer supported amino acids according to strategy B. Nucleophilic aromatic substitution in electron deficient 2-halopyrimidines is usually rapid and results in high yields. However, reactions of common 2-chloro- or 2-bromopyrimidine with amines require prolonged heating for hours or days, and harsh reaction conditions (>80°C) restrict the use of these two pyrimidines for solid-phase synthesis. By contrast, 2-fluoropyrimidine seems to be the reagent of choice. In a kinetic study, this compound exhibited a ~100-fold higher reaction rate in reaction with piperidine than its chloro- or bromo-analogs[4b]. To our knowledge, the only application of 2-fluoropyrimidine in solid-phase chemistry reported in literature[5] was the conversion of resin-bound aliphatic amines and anilines into the corresponding *N*-substituted *N*-pyrimidin-2-ylamines using a large excess of 2-fluoropyrimidine.

Results and Discussion

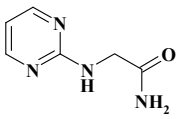
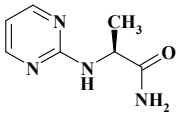
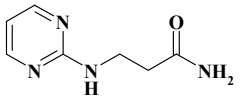
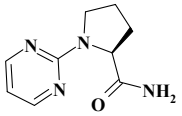
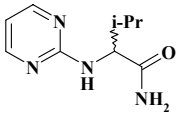
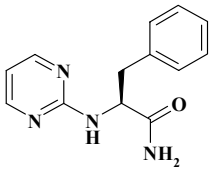
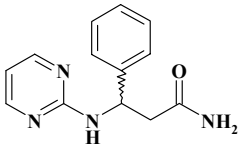
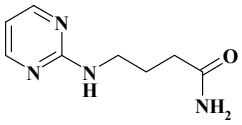
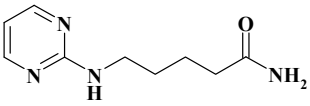
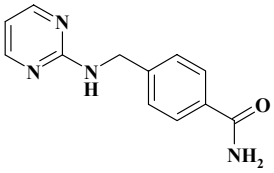
The optimized sequence involved five steps (see Scheme 2 and Table 1). The Rink resin **1** was deprotected to give free amine **2** with 20% piperidine in DMF. Standard peptide coupling conditions[6] were used to introduce Fmoc-protected amino acids[7] leading to resins **3a-j**.



Scheme 2. *Reagents and conditions*: (a) 20% piperidine/DMF 40 min, rt; (b) Fmoc-aminoacids (4 eq), BOP (4 eq), HOBt (4 eq) DIEA (8 eq), DMF/DCM, 3-3.5 hrs, rt; (c) 20% piperidine/DMF 45 min, rt; (d) 2-fluoropyrimidine (10 eq), DIEA (10 eq), DMF, 50ºC, 5 hrs; (e) 20% TFA/DCM, 1 hrs, rt.

After Fmoc group removal the polymer supported amino acids **4a-j** were treated with 2-fluoropyrimidine in the presence of DIEA at moderate temperature leading to products **5a-j**. 2-Fluropyrimidine was synthesized according to the modified procedure of Brown[8] with an improved yield of 40%. It should be noted that the reaction time of the resin-bound amino acids with 2-fluoropyrimidine varied from 1-2 hours to 1 day for sterically hindered amino acids. The conversion of the resin at this step **d** (as well as at the steps **a** and **c**) was monitored using the Kaiser color test for amines.[9] All steps were monitored by cleavage of resin aliquots, followed by ^{1}H NMR and mass spectrometry of the products. Cleavage of resin **5a-j** with trifluoroacetic acid gave the desired N-(pyrimidin-2-yl)amino acid amides **6a-j** in good yields and purities as judged by ^{1}H NMR (Table 1).

Table 1 Yields and MS of N-(pyrimidin-2-yl)amino acid amides **6a-j**

Fmoc-amino acids	Products	Yield, %	MS (M^+)
Fmoc-glycine		96	152
Fmoc-L-alanine		88	166
Fmoc-β-alanine		98	166
Fmoc-L-proline		72	192
Fmoc-DL-valine		35	194
Fmoc-L-phenylalanine		49	242
Fmoc-β-DL-phenylalanine		23	242
Fmoc-4-aminobutyric acid		87	180
Fmoc-5-aminovaleric acid		65	192
Fmoc-4-aminomethylbenzoic acid		83	228

Experimental Section

General Procedures. The 1-H NMR spectra were recorded on a Bruker AC 400 instrument.The mass spectra were obtained on an MS5988 instrument.

N-(pyrimidin-2-yl)-substituted amino acids amides **6a-j** (general procedure): Fmoc-protected Rink amide resin **1** (10 g, 0.65 mmol/g) was treated with 100 ml of 20% piperidine in DMF for 45 min. The obtained resin **2** was washed with DMF, DCM and dried under vacuum. Deprotected Rink resin **2** (400 mg, 0.26 mmol) was placed in a 30 ml flask capped with a Teflon® septum. Then 2 ml of a solution of 1-hydroxy-1*H*-1,2,3-benzotriazole (0.16 g, 1.04 mmol, 4 eq) in 50 % DMF/DCM was added and the resin was allowed to swell for about 10 min. The resin was treated with 8 ml of 50% DMF in DCM solution, containing BOP reagent (0.46 g, 1.04 mmol, 4 eq), 1.04 mmol of Fmoc-amino acid, and DIEA (0.27 g, 2.1 mmol, 8 eq). The flask was capped and shaken on an orbital shaker for 3-3.5 hours. The resulting resin **3** was washed with DMF (3×10 ml), DCM (2×10 ml), MeOH (2×10 ml) and dried in vacuum. The resin-bound Fmoc-amino acids **3** were deprotected by stirring in 10 ml of 20% piperidine/DMF solution for 40-45 min and then washed with DCM (4 times) and dried. To the resin-bound amino acid **4** with free amino groups was added a solution of 2-fluoropyrimidine (0.26 g, 2.6 mmol, 10 eq) and DIEA (0.34 g, 2.6 mmol, 10 eq) in 5 ml DMF. The mixture was heated at 50-55°C under constant shaking for 5 hours. The obtained resin **5** was washed consecutively with DMF (15 ml), 50% DMF/DCM (15 ml), DCM (2×25 ml), MeOH (2×15 ml) and dried in vacuum. The cleavage step for resin **5** was carried out in 15 ml of 20% TFA in DCM for 1 hour. The resin was separated, washed with MeOH (15 ml), DCM (10 ml) and MeOH (10 ml). Filtrates were combined and evaporated. The oily residue was purified by column chromatography (MeOH-$CHCl_3$, 4:1) leading to products **6a-j**.

***N*-(Pyrimidin-2-yl)glycine amide (6a).** White solid (38 mg, 96%), mp 137-140 °C; ^{1}H NMR (360 MHz, DMSO-d_6): δ 8.23 (d, J = 5.3 Hz, 2H), 7.09 (s, 1H), 6.81 (s, 2H), 6.54 (t, J = 5.6 Hz, 1H), 3.83 (d, J = 5.7 Hz, 2H); Anal. calcd for $C_6H_8N_4O$: C, 47.32; H, 5.26; N, 36.84; Found C, 46.88; H, 5.74; N, 36.57.

***N*-(Pyrimidin-2-yl)-L-alanine amide (6b).** White needles (38 mg, 88%), mp 82-85 °C; ^{1}H NMR (360 MHz, DMSO-d_6): δ 8.33 (d, J = 4.6 Hz, 2H), 7.25 (s, 1H), 6.78 (s, 2H), 6.54 (t, J = 4.8 Hz, 1H), 4.32 (m, 1H), 1.33 (d, J = 7.2 Hz, 3H). Anal. calcd for $C_7H_{10}N_4O$: C, 50.59; H, 6.07; N, 33.71; Found C, 50.39; H, 6.01; N, 33.82.

***N*-(pyrimidin-2-yl)-β-alanine amide (6c).** Yellow solid (42 mg, 98%), mp 125-126 °C; ^{1}H NMR (360 MHz, DMSO-d_6): δ 8.31 (d, J = 5.0 Hz, 2H), 7.31 (s, 1H), 6.80 (s, 2H), 6.63 (t, J = 4.9 Hz, 1H), 3.47 (t, J = 7.2 Hz, 2H), 2.35 (t, J = 7.1 Hz, 2H); Anal. calcd for $C_7H_{10}N_4O$: C, 50.54; H, 6.02; N, 33.69; Found C, 49.48; H, 6.73; N, 32.60.

***N*-(Pyrimidin-2-yl)-L-proline amide (6d).** Yellow needles (36 mg, 72%), mp 66-69 °C; ^{1}H NMR (360 MHz, DMSO-d_6): δ 8.27 (d, J = 4.1 Hz, 2H), 7.15 (s, 2H), 6.57 (t, J = 4.6 Hz,

1H), 3.59-3.71 (m, 3H), 1.96-2.08 (m, 4H). Anal. calcd for $C_9H_{12}N_4O$: C, 56.24; H, 6.29; N, 29.15; Found C, 56.00; H, 6.19; N, 29.26.

***N*-(Pyrimidin-2-yl)-DL-valine amide (6e).** White solid (18 mg, 35%), mp 78-80 °C; ^{1}H NMR (360 MHz, DMSO-d_6): δ 8.25 (d, J = 4.8 Hz, 2H), 6.81 (s, 1H), 6.68 (s, 2H), 6.57 (t, J = 5.0 Hz, 1H), 4.38 (d, J = 5.7 Hz), 2.21 (m, 1H), 1.00 (m, 6H). Anal. calcd for $C_9H_{14}N_4O$: C, 55.65; H, 7.27; N, 28.84; Found C, 55.75; H, 7.29; N, 28.63.

***N*-(Pyrimidin-2-yl)-L-phenylalanine amide (6f).** Brown solid (31 mg, 49%), mp 124-127 °C; ^{1}H NMR (360 MHz, DMSO-d_6): δ 8.20 (d, J = 4.7 Hz, 2H), 7.45 (s, 1H), 7.31 (s, 2H), 7.18 (m, 5H), 6.53 (t, J = 4.9 Hz, 1H), 3.74 (m, 1H), 2.47 (d, J = 7.1 Hz, 2H). Anal. calcd for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.12; Found C, 64.15; H, 5.80; N, 23.22.

***N*-(Pyrimidin-2-yl)-DL-β-phenylalanine amide (6g).** Brown solid (15 mg, 23%), mp 112-114 °C; ^{1}H NMR (360 MHz, DMSO-d_6): δ 8.19 (d, J = 5.7 Hz, 2H), 7.1-7.4 (m, 7H), 7.58 (s, 1H), 6.48 (t, J = 5.1 Hz, 1H), 5.34 (m, 1H), 2.67 (m, 2H). Anal. calcd for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.12; Found C, 64.37; H, 5.66; N, 23.10.

4-[*N*-(Pyrimidin-2-yl)]aminobutyric acid amide (6h). White solid (41 mg, 87%), mp. 67-68 °C; ^{1}H NMR (360 MHz, DMSO-d_6): δ 8.36 (d, J = 4.8Hz, 2H), 7.23 (s, 2H), 6.75 (t, J = 5.0 Hz, 1H), 6.64 (s, 1H), 3.38 (t, J = 7.5 Hz, 2H), 2.15 (t, J = 7.1 Hz, 2H), 1.78 (m, 2H); Anal. calcd for $C_8H_{12}N_4O$: C, 53.27; H, 6.59; N, 31.07; Found C, 52.51; H, 6.38; N, 30.95.

5-[*N*-(Pyrimidin-2-yl)]aminovaleric acid amide (6i). Yellow solid (32 mg, 65%), mp 53-56 °C; ^{1}H NMR (360 MHz, DMSO-d_6): δ 8.28 (d, J = 4.9 Hz, 2H), 7.14 (s, 2H), 6.56 (t, J = 5.0 Hz, 1H), 6.47 (s, 1H), 3.31 (t, J = 5.7 Hz, 2H), 2.08 (t, J = 7.2 Hz, 2H), 1.48-1.52 (m, 4H); Anal. calcd for $C_9H_{14}N_4O$: C, 55.61; H, 7.20; N, 29.86; Found C, 53.75; H, 6.89; N, 29.32.

4-[*N*-(Pyrimidin-2-yl)]-aminobenzoic acid amide (6j). White solid (50 mg, 83%), mp 73-75 °C; ^{1}H NMR (360 MHz, DMSO-d_6): δ 8.18 (d, J = 5.3 Hz, 2H), 7.07 (s, 1H), 7.81 (d, J = 7.9 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.01 (s, 2H), 6.59 (t, J = 5.1 Hz, 1H), 4.66 (s, 2H). Anal. calcd for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30; N, 24.55; Found C, 63.24; H, 5.20; N, 24.70.

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