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A facile synthesis of 2-(*N*-alkylamino)-pyrimidin-4-one derivatives

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Abstract

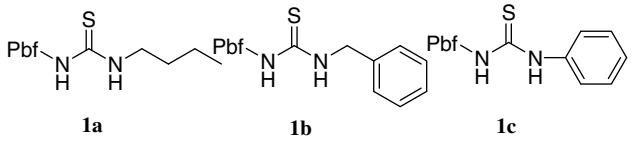
Substituted 2-(*N*-alkylamino)-pyrimidin-4-ones were synthesized from *N*-alkyl β-amino acid esters starting with guanidinylation using Pbf-activated thiourea. The six-membered pyrimidinones were obtained in good yields via intramolecular cyclization during TFA cleavage of the Pbf protecting group.

Keywords: 2-(*N*-Alkylamino)-pyrimidin-4-ones; Heterocycles

The biologically important guanidine moiety has been incorporated into many drugs or drug candidates covering a variety of therapeutic areas. Reported examples include guanidine-containing cardiovascular antihistaminic, anti-inflammatory, antidiabetic and antibacterial drugs.[1] For this widespread utility, we became interested in the synthesis of six-membered dihydropyrimidines containing guanidine skeletons.[2] Furthermore, this class of compounds has been demonstrated to have a selectivity for the sodium channel in the muscle membrane similar to that from tetrodotoxin or saxitoxin[3] and also are important intermediates in the catabolism and anabolism of pyrimidines.[4] Presently, there are few reports on the synthetic method of substituted 2-(*N*-alkylamino)-pyrimidin-4-ones. Among several reported methodologies,[5] the protocol reported by Kim's group involved the reactions of substituted guanidines with α,β-unsaturated ketones and methyl acrylate, respectively.[6] However, the requirement of strong base for deprotonation of the guanidine moiety may limit the application of this route. We present here an alternative synthetic methodology for the substituted 2-(*N*-alkylamino)-pyrimidin-4-ones from β-amino acid under mild conditions.

We have previously developed protocols for the synthesis of *N*,*N*′-substituted guanidines based on Pbf-activated thiourea (Pbf: 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl), and utilized this protocol for the synthesis of five-membered 1,5-substituted 2-(*N*-alkylamino)-imidazolidin-4-ones from α-amino acid.[7] A pivotal step in the synthesis of the imidazolidinone derivatives is the intramolecular cyclization while the Pbf group is cleaved by TFA. We sought to extend this intramolecular cyclization strategy for the synthesis of six-membered pyrimidinones. In our design, Pbf-activated thioureas bearing substitutions as shown in Figure 1 are reacted with N-alkylated β-amino acid esters as shown in Figure 2 to form the intermediate guanidines **3**. Subsequently, the guanidine intermediates **3** are deprotected with TFA to generate pyrimidin-4-ones as shown in Scheme 1.

Thioureas **1a**–**c** containing the Pbf group were prepared directly from Pbf-isothiocyanate with the corresponding



1a **1b** **1c**

Fig. 1. Pbf-activated thioureas.

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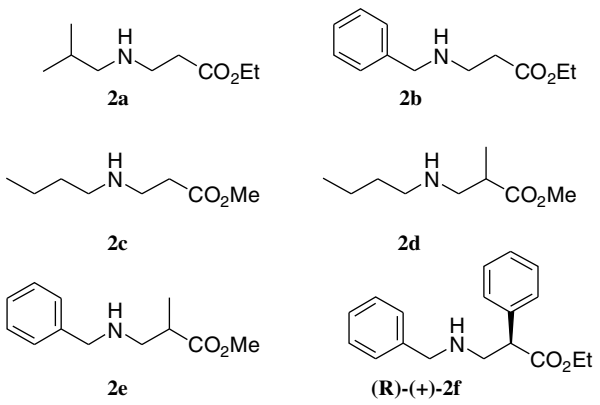
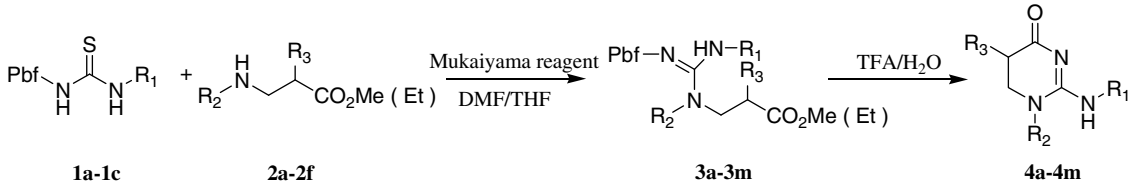


Fig. 2. N-Alkylated β-amino acid esters.

alkylamine and aniline when stirred in dichloromethane.[8] Methyl or ethyl esters of β-amino acid (3-aminopropanoic acid) and branched β-amino acid (2-methyl 3-aminopropanoic acid) that are commercially available were selected as starting materials. In order to assess the preservation of chirality during the reaction, we also prepared optically pure (*R*)-(+)-2-phenyl 3-aminopropanoic acid based on the literature report[9] in 75% ee. This non-racemic sample subsequently gave us the corresponding ethyl ester. These β-amino acid esters were reacted with benzaldehyde, isobutylaldehyde or *n*-butylaldehyde under $NaBH_3CN$ condition to produce N-alkylated β-amino acid esters **2a**–**f** through the classic N-alkylation reaction.[10] At room temperature, substituted thioureas **1a**–**c** were treated with N-alkylated β-amino acid esters **2a**–**f** in THF/DMF mixed solvent followed by the Mukaiyama reagent to produce the guanidine intermediates **3a**–**m**. All intermediates **3a**–**m** are white solids isolated through column chromatography eluted with ethyl acetate and petroleum ether. The sterically bulky *N*-alkyl group such as isobutyl seemed to give lower but still reasonable isolated yields (Table 1, entries 1 and 6) than the benzyl or *n*-butyl counter parts.

The target 1- or 1,5-alkyl 2-(*N*-alkylamino)-pyrimidin-4-ones **4** were easily obtained with high yields when compounds **3** were treated with 95% aqueous TFA solution at room temperature to remove Pbf and promote cyclization (Scheme 1).[11] The formation of the crude products **4** were monitored by TLC on silica gel eluting with ethanol and ethyl acetate. It was necessary to add Et_3N to the crude compound after the last reaction step and evaporated most part of solvent before purification. All compounds were obtained after chromatographic purification as white solid, and confirmed by ^1H NMR and electrospray MS. Yields of the purified products were high (72–94%, Table 1). The ester group of ethyl or methyl had little influence on reaction yield, and so did other substituted groups in this key intramolecular cyclization step. Moreover, no racemization occurred in the reactions of guanidinylation and intramolecular cyclization during TFA cleavage of the Pbf protecting group.[12]

In conclusion, we have demonstrated an efficient route to 1- or 1,5-alkyl-2-(*N*-alkylamino)-pyrimidin-4-ones via guanidine intermediates with high yields. Compared to other methods reported in the literature, our procedure allows for a mild guanidinylation and cyclization towards the products with the preservation of stereochemistry. Secondly, β-amino acid bearing various functional groups are easily obtained as starting materials from commercial



Scheme 1. Strategy for the synthesis of substituted 2-(*N*-alkylamino)-pyrimidin-4-ones.

Table 1
Summary of the reaction compounds and yields obtained in the synthesis of substituted 2-(*N*-alkylamino)-pyrimidin-4-ones referred to Scheme 1

Entry	R_1	R_2	R_3	Compound **3**	Isolated yield (%)	Product **4**	Isolated yield (%)
1	*n*-Bu	*i*-Bu	H	**3a**	64	**4a**	93
2	*n*-Bu	$PhCH_2$	H	**3b**	94	**4b**	86
3	*n*-Bu	*n*-Bu	H	**3c**	88	**4c**	92
4	*n*-Bu	*n*-Bu	CH_3	**3d**	95	**4d**	91
5	*n*-Bu	$PhCH_2$	CH_3	**3e**	71	**4e**	84
6	$PhCH_2$	*i*-Bu	H	**3f**	71	**4f**	94
7	$PhCH_2$	$PhCH_2$	H	**3g**	92	**4g**	72
8	$PhCH_2$	*n*-Bu	H	**3h**	89	**4h**	72
9	$PhCH_2$	*n*-Bu	CH_3	**3i**	80	**4i**	80
10	$PhCH_2$	$PhCH_2$	CH_3	**3j**	80	**4j**	85
11	Ph	$PhCH_2$	H	**3k**	82	**4k**	86
12	Ph	*n*-Bu	CH_3	**3l**	85	**4l**	88
13	Ph	$PhCH_2$	Ph	(***R***)-(+)-**3m**	80	(***R***)-(+)-**4m**	80

sources in comparison to α,β-unsaturated ketones or methyl acrylate. Furthermore, substituted group variations can be introduced directly to β-amino acid through N-alkylation reaction, and the existence of N-substituted group from reductive amination may enhance the intramolecular cyclization process. This synthetic methodology is in principle suitable for large scale synthesis.

Acknowledgements

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11. A representative procedure is given here. For compound **3b**, the corresponding N-alkylated β-amino acid ester **2b** (1.25 mmol) was added to thiourea **1a** (0.5 mmol) dissolved in a solution mixture of DMF/THF (1:4 2.5 mL) followed by the Mukaiyama reagent (1.25 mmol), and the reaction mixture was stirred for 2 h at room temperature. Solvent was removed under vacuum and then 10 mL water was added. The residue was extracted with DCM (20 mL × 2). Then the combined organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica (300–400 mesh, EtOAc/petroleum ether) to give white solid **3b** in 94% yield. ^{1}H NMR ($CDCl_3$, 300 MHz). δ (ppm): 7.29–7.27 (m, 3H), 7.18–7.16 (m, 2H), 6.80 (s, 1H), 4.47 (s, 2H), 4.09 (t, $J = 7.2$ Hz, 2H), 3.47 (t, $J = 6.9$, 2H), 3.17 (m, 2H), 2.95 (s, 2H), 2.57 (s, 3H), 2.54 (t, $J = 6.9$, 2H), 2.51 (s, 3H), 2.08 (s, 3H), 0.90 (t, $J = 7.35$, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz). δ (ppm): 171.81, 160.06, 158.65, 138.40, 136.57, 132.36, 128.73, 127.63, 127.35, 124.50, 117.40, 86.34, 60.76, 53.19, 45.99, 44.34, 43.19, 32.33, 28.54, 19.87, 19.25, 18.04, 14.12, 13.65, 12.38.
For compound **4b**, compound **3b** (0.35 mmol) was added into a mixture of TFA/H_2O (95:5 2 mL), and stirred for 24 h at room temperature, the solvent was removed under vacuum and then Et_3N was dropped into the residue until pH 8–9 checked by pH paper, and the crude product was purified by column chromatography on silica gel (300–400 mesh EtOAc/EtOH) to give white solid **4b** in 86% yield. ESI-MS (m/z) 260.2 ($[M+H]^+$). ^{1}H NMR ($CDCl_3$, 300 MHz). δ (ppm): 7.44–7.42 (m, 3H), 7.25–7.23 (m, 2H), 4.52 (s, 2H), 3.61 (t, $J = 6.9$ Hz, 2H), 3.41 (t, $J = 7.5$ Hz, 2H), 2.64 (t, $J = 6.9$ Hz, 2H), 1.42 (m, 2H), 1.19 (m, 2H), 0.85 (t, $J = 7.2$, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz). δ (ppm): 176.82, 158.87, 134.94, 129.35, 128.31, 126.24, 109.72, 53.68, 47.64, 41.47, 31.70, 31.58, 19.74, 13.66.
12. Following the literature reported route (Ref. 9a), *N*-Boc protected (*R*)-(+)-2-phenyl-3-aminopropanoic acid was obtained with $[\alpha]_D^{20}$ +66.4 (*c* 0.247, $CHCl_3$), which has 75% ee based on Ref. 9b ($[\alpha]_D^{20}$ +88 (*c* 1.25, $CHCl_3$)). Using this non-racemic sample, (*R*)-(+)-**2f** was subsequently obtained with $[\alpha]_D^{20}$ +60.2 (*c* 0.166, $CHCl_3$); (*R*)-(+)-**3m**: $[\alpha]_D^{20}$ +50.0 (*c* 0.204, $CHCl_3$); and (*R*)-(+)-**4m**: $[\alpha]_D^{20}$ +58.2 (*c* 0.175, $CHCl_3$). This clearly indicates that no significant racemization occurred during the transformation from **2f** to **4m**.