Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 1433–1443
Tetrahedron

A simple approach for the regioselective synthesis of imidazo[1,2-*a*]pyrimidiones and pyrimido[1,2-*a*]pyrimidinones

David Font,[a] Anthony Linden,[b] Montserrat Heras[a,*] and José M. Villalgordo[a,*,†]

[a]*Department of Chemistry, Faculty of Sciences, University of Girona, Campus de Montilivi, 17071 Girona, Spain*
[b]*Institute of Organic Chemistry, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland*

Received 25 October 2005; revised 9 November 2005; accepted 10 November 2005

Available online 2 December 2005

Abstract—Several imidazo and pyrimido[1,2-*a*]pyrimidinones of type **1** and **2** were synthesized through intramolecular cyclization of pyrimidines **9** or pyrimidinones **10** bearing a variety of β and γ-aminoalcohols at the 2-position. Ring closure of the pyrimidinones of type **10** under Mitsunobu conditions lead to mixtures of both bicyclic regioisomers **1** and **2**. Treatment of pyrimidines of type **9** with H_2SO_4 provided an efficient and operationally simple one-pot hydrolysis–cyclization procedure for obtaining imidazo and pyrimido[1,2-*a*]pyrimidinones **1** in good yields as the sole regioisomeric bicyclic product.

1. Introduction

The imidazo[1,2-*a*]pyrimidinones **1** ($n=1$) and **2** ($n=1$) and the pyrimido[1,2-*a*]pyrimidinones **1** ($n=2$) and **2** ($n=2$) (Fig. 1) constitute an important class of natural and non-natural products, many of which exhibit useful biological activities. The imidazo[1,2-*a*]pyrimidinone structure **1** ($n=1$) has been found in the Y base of yeast as a component of phenylalanine transfer ribonucleic acid,[1] and new acyclovir analogs possessing this ring system have exhibited antiherpetic activity on HIV-1,2.[2] Other members of this family of compounds also have pharmacological interest for their hypnotic,[3] anesthetic[4] and antiallergic[5] properties. Imidazo[1,2-*a*]pyrimidinone derivatives type **2** ($n=1$) are of considerable interest because of their activities as phosphodiesterase (PDE) inhibitors,[6] and antihypertensives.[7] Furthermore, some derivatives of pyrimido[1,2-*a*]pyrimidinones **1** ($n=2$) and **2** ($n=2$) have some utility for preventive and/or therapeutic treatment of a neurodegenerative disease caused by abnormal activity of GSK3β, such as Alzheimer's disease.[8]

The imidazo and pyrimido[1,2-*a*]pyrimidinones **1** and **2** incorporate both the guanidine and pyrimidinone functionalities (Fig. 1). It is well known that pyrimidin-4(3*H*)-ones are valuable scaffolds in different areas of research. For example, this class of compounds displays potent and selective activity as non-nucleoside HIV-1 reverse transcriptase inhibitors.[9] Other members of this family of compounds have found utility as herbicides,[10] antidepressants[11] and leishmanicides.[12] In addition, when pyrimidin-4(3*H*)-ones are substituted at the

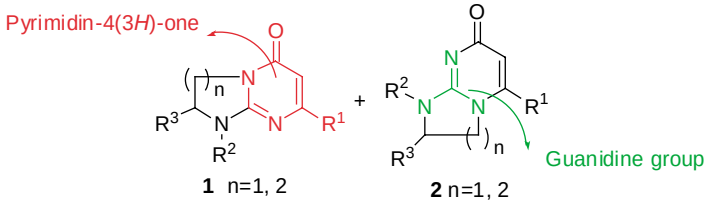


Figure 1. Imidazo and pyrimido[1,2-*a*]pyrimidinones **1** and **2**.

Keywords: Imidazo[1,2-*a*]pyrimidinone; Pyrimido[1,2-*b*]pyrimidinone; Mitsunobu reaction; *ipso*-Substitution; Acidic hydrolysis.
* Corresponding authors. Tel.: +34 972418247; fax: +34 972418150 (M.H.); Tel.: +34 968809089; fax: +34 968890024 (J.M.V.); e-mail addresses: montserrat.heras@udg.es; info@villapharma.com
† Present address: Villapharma Research, Polígono Industrial Oeste, c/Paraguay. Parcela 7/5-A, Módulo A, 30169 Murcia, Spain.

0040–4020/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tet.2005.11.014

2-position by an amino group, it can be considered to be a cyclic guanidine. Due to the hydrogen-bonding acceptor and donor abilities of the guanidine group,[13] 2-aminopyrimidin-4(3*H*)-ones have also served as suitable models for studies conducted on self-association[14] and the subsequent application of those studies to supramolecular chemistry.[15]

Numerous methods for the synthesis of the imidazo and pyrimido[1,2-*a*]pyrimidinones involve approaches based on either (i) cyclocondensation between 2-substituted pyrimidinone ring systems with appropriate 1,2 or 1,3-difunctionalized synthons, such as α or β-halocarbonyl compounds,[2,16] 1,2-dihaloalkanes,[17] acrolein,[18] glyoxal,[19] glycidaldehyde,[20] and α or β-aminoalcohols,[6,7,21] or (ii) cyclocondensation between 2-substituted imidazole or pyrimidine ring systems with appropriate 1,3-difunctionalized synthons, such as β-aminoesters[22] and α-acetylenic esters.[23] However, both routes can give mixtures of regioisomers. Other useful routes to these type of heterocycles involve the fusion of two heterocycles in one single step[24] or the ring contraction of other heterocyclic systems.[25]

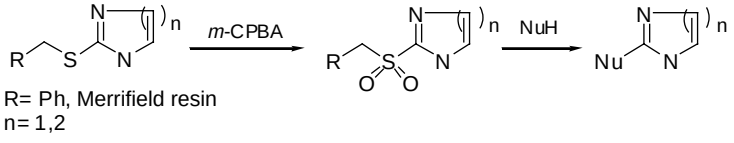
During the last few years, we have been engaged in a research program focused on the development of efficient methodologies that could be adapted readily for combinatorial and/or parallel synthesis of relevant core structures with potential therapeutic interest. We have described the synthesis of novel 2,3-dihydroimidazo[2,1-*b*][1,3]oxazoles[26] and multiple substituted pyrimidines.[27] The method has a nucleophilic *ipso*-substitution of the corresponding activated sulfones as one of the key steps, not only for introducing molecular diversity but also as cleavage reaction on solid phase synthesis (Scheme 1). In this way, several purines,[28] aminopyridazines[29] and pteridines[30] have also been prepared using an activatable sulfur linkage. Within this context, we recently reported on the synthesis of novel 2,6-disubstituted 3,4-dihydropyrimidin-4(3*H*)-ones[31] **7** starting from 2-alkylsulfanylpyrimidinones **3**. The methodology is based on a selective *O*-alkylation reaction with *i*-PrOH under Mitsunobu conditions, followed by a nucleophilic displacement of the corresponding activated sulfones with a wide variety of nucleophiles (phenoxides, Grignard reagents, and primary and secondary amines). Finally, the acidic hydrolysis of the 4-isopropoxy group under standard conditions afforded pyrimidinones **7** in good yields (Scheme 2).

As an extension of this work, an investigation was undertaken to expand the scope of this methodology and its potential application in the synthesis of more elaborate heterocyclic scaffolds based on the pyrimidin-4(3*H*)-one nucleus. Specifically, we focused our attention on imidazo[1,2-*a*]pyrimidinones and pyrimido[1,2-*a*]pyrimidinones **1** and **2**. The results of this investigation are disclosed herein.

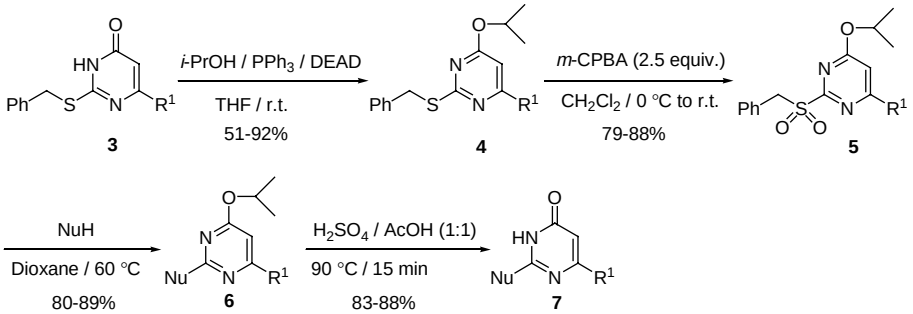
2. Results and discussion

Consistent with the goal of synthesizing more elaborate heterocyclic scaffolds based on the pyrimidin-4(3*H*)-one nucleus, and in complete analogy with the above-mentioned results, we reasoned that nucleophilic *ipso*-substitution of the sulfones **5** with a wide variety of β and γ-aminoalcohols[32] **8**, followed by subsequent acidic hydrolysis and a final cyclization step under Mitsunobu conditions would lead to the formation of a collection of imidazo and pyrimido[1,2-*a*]pyrimidin-5-ones **1** and imidazo and pyrimido[1,2-*a*]pyrimidin-7-ones **2** (Scheme 3). From these intermediates **10** the cyclization could, in principle, take place onto *N*(1) or *N*(3) to afford the regioisomers **2** and **1**, respectively.

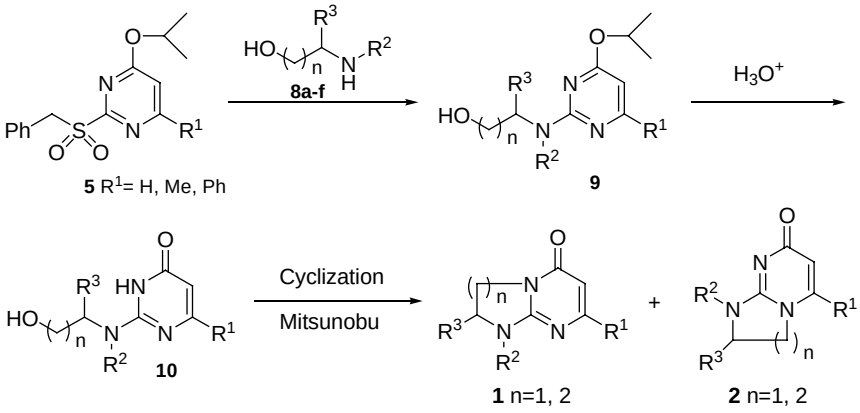
Thus, when pyrimidinyl sulfone derivatives **5** were allowed to react in 1,4-dioxane at reflux with several β and γ-aminoalcohols **8a–f** (Fig. 2), which are readily available from commercial sources and/or from the reduction of the corresponding amino acids,[33] the corresponding pyrimidines **9a–j** were obtained generally in good yields (Scheme 3, Table 1).



Scheme 1. Nucleophilic *ipso*-substitution of activated sulfones.



Scheme 2. Synthesis of 2,6-disubstituted 3,4-dihydropyrimidin-4(3*H*)-ones **7**.



Scheme 3. Preparation of imidazo and pyrimido[1,2-*a*]pyrimidinones.

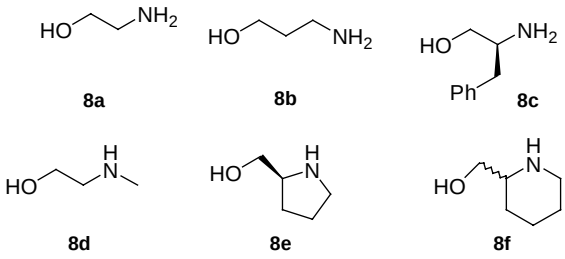


Figure 2. The employed β and γ-aminoalcohols **8**.

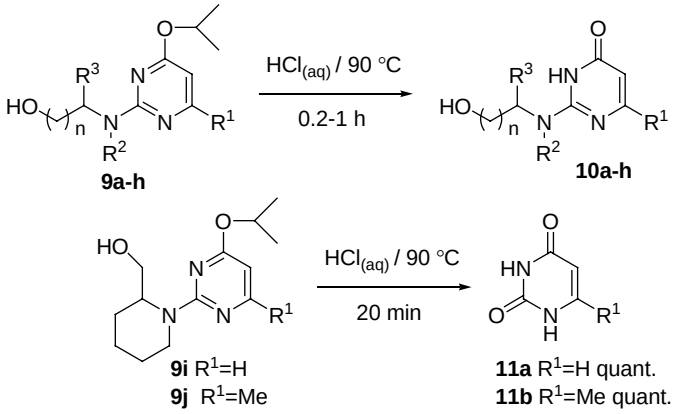
Table 1. Yields of compounds **9a–j**

Entry	Compound	R^1	Aminoalcohol	Yield (%)[a]
1	**9a**	H	**8a**	79
2	**9b**	Me	**8a**	76
3	**9c**	H	**8b**	65
4	**9d**	Me	**8b**	94
5	**9e**	Me	**8c**	79
6	**9f**	Ph	**8d**	85
7	**9g**	Me	**8d**	80
8	**9h**	Me	**8e**	95
9	**9i**	H	**8f**	79
10	**9j**	Me	**8f**	90

[a] Yields of isolated pure products.

Acidic hydrolysis of the pyrimidines **9** with concd HCl at 90 °C, followed by simple chromatographic filtration, yielded the corresponding target pyrimidinones **10** also in good yields (71–97%), except with the pyrimidines **9i** and **9j**, which led to the formation of the uracils **11** in quantitative yields (Scheme 4, Table 2). These results clearly indicate that the piperidinyl group in the 2-position of the pyrimidine ring is labile under these acidic conditions. We then focused our attention on the search for other acidic hydrolysis conditions that could selectively cleave the 4-alkoxy group in these two compounds, **9i** and **9j**.

When derivatives **9i** and **9j** were allowed to react with H_2SO_4 at 90 °C, compounds **1i** and **1j** were isolated in near quantitative yields (Scheme 5). The formation of products **1** could be rationalized in terms of a one-pot procedure simply by hydrolysis of the 4-isopropoxy group, followed by complete regioselective cyclization onto *N*(3) of the pyrimidinone ring to afford the corresponding imidazopyrimidinones **1**. In good agreement with this procedure, when pyrimidine **9f** was treated with H_2SO_4 at room temperature for 24 h, a mixture of pyrimidinone **10f** and imidazopyrimidinone **1f** was observed. After heating to 90 °C, the ring closure was completed in only 20 min and compound **1f** was isolated in good yield (Scheme 5). This one-pot hydrolysis–cyclization reaction was successfully extended to other pyrimidines to afford the corresponding

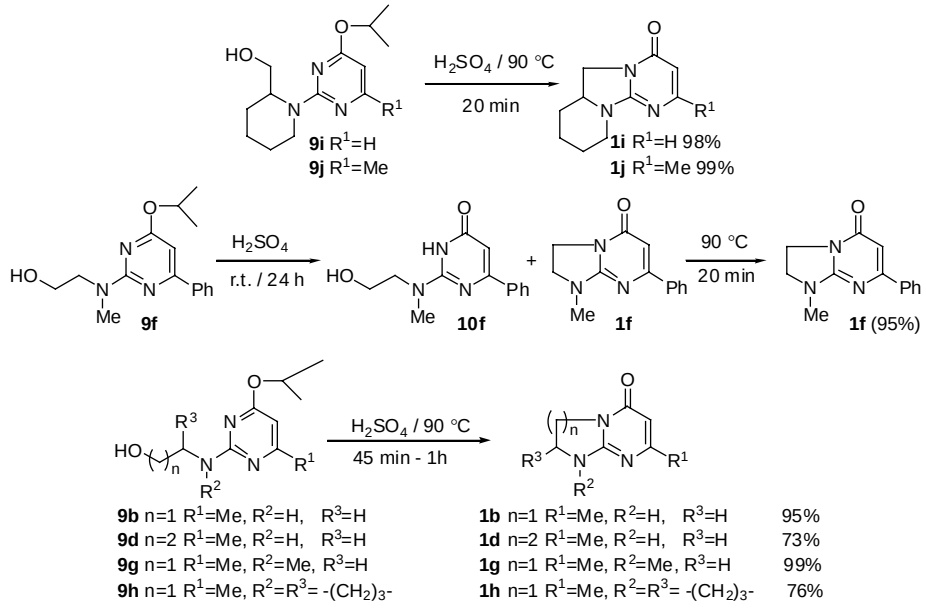


Scheme 4. Acidic hydrolysis of pyrimidines **9**.

Table 2. Yields of compounds **10a–j**

Entry	Compound	R^1	R^2	R^3	*n*	Yield (%)[a]
1	**10a**	H	H	H	1	86
2	**10b**	Me	H	H	1	97
3	**10c**	H	H	H	2	97
4	**10d**	Me	H	H	2	87
5	**10e**	H	H	Bn	1	71
6	**10f**	Ph	Me	H	1	95
7	**10g**	Me	Me	H	1	85
8	**10h**	Me	$-(CH_2)_3-$		1	94
9	**10i**	H	$-(CH_2)_4-$		1	—
10	**10j**	Me	$-(CH_2)_4-$		1	—

[a] Yields of isolated pure products.

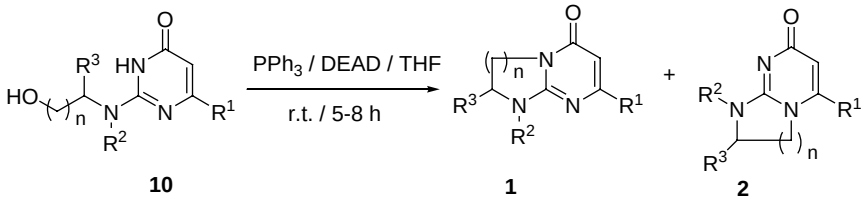


Scheme 5. Regioselective synthesis of imidazo and pyrimido[1,2-*a*]pyrimidinones **1**.

imidazopyrimidinones **1** ($n=1$) and pyrimidopyrimidinone **1** ($n=2$) with an absolute regioselectivity and in good yields (Scheme 5).

Following our initial plans we decided to investigate the feasibility of an intramolecular cyclization of the 4(3*H*)-pyrimidinones **10**, under Mitsunobu conditions. Thus, when pyrimidinones **10** were treated with PPh_3 and DEAD in anhydrous THF at room temperature for 5–8 h, a separable mixture of the regioisomeric bicyclic compounds **1** and **2** were isolated by flash chromatography in good yields (Scheme 6, Table 3). The cyclization reaction took place predominantly onto *N*(1) affording compounds of type **2** as the major regioisomer (Table 3, entries 1–4). However, when the *N*-atom at the 2-position on the pyrimidinone ring had an alkyl substituent ($R^2=Me$), the Mitsunobu reaction proceeded in high yield and with a high degree of selectivity. Only the isomer **1g** from cyclization onto *N*(3) of the pyrimidinone ring was obtained (Table 3, entry 5).

Generally, the intramolecular cyclization reaction of 2-substituted pyrimidinone ring systems takes place onto *N*(3), except when *N*(3) has an alkyl substituent,[5b,c] which blocks this nitrogen, and cyclization is only possible onto *N*(1) or when the 2-position on the pyrimidinone ring has a substituent prone to tautomerize, such as an amino[16b–c] group, with the cyclization then taking place onto both *N*(1) and *N*(3) to afford mixtures of the regioisomers **1** and **2**. This last case can explain the results in the Mitsunobu reaction. Thus, when the reaction was carried out by employing pyrimidinones **10** with a secondary amine in the 2-position ($R^2=H$), both regioisomers **1** and **2** were obtained (Table 3,



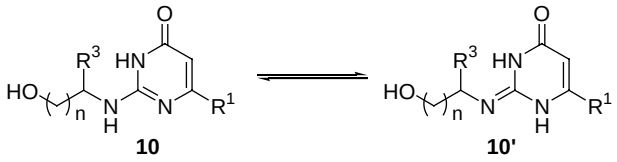
Scheme 6. Intramolecular cyclization of pyrimidinones **10** under Mitsunobu conditions.

Table 3. Yields of compounds **1** and **2**

Entry	R^1	R^2	R^3	*n*	Regioisomer **1**	Regioisomer **2**	**1**:**2**[a]	Yield (%)[b]
1	H	H	H	1	**1a**	**2a**	12:88	91
2	H	H	H	2	**1c**	**2c**	23:77	95
3	Me	H	H	2	**1d**	**2d**	27:73	91
4	Me	H	Bn	1	**1e**	**2e**	42:58	78
5	Me	Me	H	2	**1g**	—	100:0	96

[a] Ratios were calculated by yields of isolated compounds.
[b] Yields of isolated pure products.

entries 1–4). The cyclization reaction onto *N*(1) probably proceeded via its tautomeric form **10′** (Scheme 7). However, when pyrimidinone **10e** with a tertiary amine in the 2-position (R^2=Me) was employed, the tautomeric form **10′** was not possible and the cyclization reaction was completely regioselective in favor of the isomer **1** (Table 3, entry 5).



Scheme 7. Tautomerism of compounds **10**.

On the other hand, the absolute regioselectivity obtained during the synthesis of compounds **1**, regardless of the R^2 group (H, Me), when intramolecular cyclization was carried out with H_2SO_4, are in good agreement with the literature. To the best of our knowledge, intramolecular cyclization of 2-subtituted pyrimidin-4(3*H*)-ones always took place exclusively onto *N*(3) under acid reaction conditions.[34]

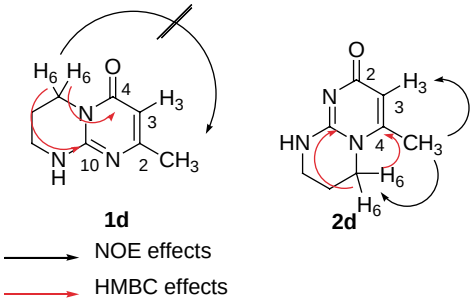


Figure 3. HMBC and NOE experiments of compounds **1d** and **2d**.

All products and intermediates were characterized by the usual spectroscopic methods, such as ^{1}H and ^{13}C spectroscopy, mass spectrometry, IR, and elemental analysis. The ^{1}H and ^{13}C NMR spectra for **1** and **2** were assigned by means of DEPT and HMQC experiments and the regiochemistry of both of these isomers **1** and **2** was established unequivocally by NOE and heteronuclear multiple bond correlation (HMBC) experiments. A NOE effect was observed between methyl protons and proton H_3, as well as between methyl protons and protons H_6 in isomers **1d**, while in isomers **2d**, a NOE effect was not observed between protons H_6 and methyl protons (Fig. 3). In addition, the HMBC experiments gave supplementary information: for isomer **1**, long range ^{1}H–^{13}C correlations are observed between protons H_6 and both carbons 4 (C=O) and 10 (C=N) (Fig. 3), while isomer **2** presented correlations between protons H_6 and carbon 2 (C=O) and carbon 4 (Fig. 3). Moreover, the structures of compounds **2e** and **1h** were established unambiguously by X-ray crystallography (Fig. 4).

3. Conclusion

In summary, we have shown that 2-substituted pyrimidinones **10** with a variety of β and γ-aminoalcohols, which are easily available from pyrimidinyl sulfone derivatives **5**, are good synthetic precursors for the preparation of imidazo and pyrimido[1,2-*a*]pyrimidinones **1** and **2** via an intramolecular ring closure. When cyclization was carried out under Mitsunobu conditions by employing pyrimidinones **10** with a secondary amine

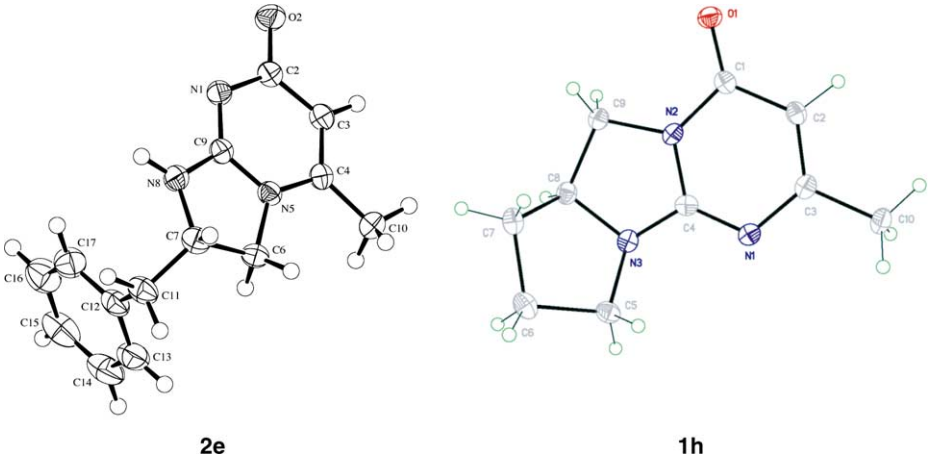


Figure 4. The molecular structures of **2e** and **1h** (Ortep-plot with ellipsoids at the 50% probability levels).

in the 2-position (R^2=H), both regioisomers **1** and **2** were obtained. In contrast, when the *N* atom in the 2-position on the pyrimidinone ring has an alkyl substituent (R^2=Me), the Mitsunobu reaction yielded the regioisomer **1** as the only product. On the other hand, treatment of the pyrimidines **9** with H_2SO_4 afforded, with an absolute regioselectivity, the imidazo and pyrimido[1,2-*a*]pyrimidinones **1** through a one-pot hydrolysis–cyclization procedure. Considering the easily available starting materials, generality of the reaction, simplicity of the procedure and good yields, this provides a straightforward method to construct a diverse array of imidazo and pyrimido[1,2-*a*]pyrimidinones **1** and **2**. However, we are aware that the orientation of the cyclization reaction could change when pyrimidinone ring would be substituted with strong electron-withdrawing or electron-donating groups. In this way, further investigation on regioselective cyclization of the pyrimidinones substituted at 6-position with nitro, amino, alkylamino or alkoxy groups are currently in progress in our laboratories.

4. Experimental

4.1. General remarks

4-Isopropoxy-2-phenylmethanesulfonyl-pyrimidine **5a**, 4-isopropoxy-6-methyl-2-phenylmethanesulfonyl-pyrimidine **5b** and 4-isopropoxy-6-phenyl-2-phenylmethanesulfonyl-pyrimidine **5c**, were prepared as previously reported by us.[28] All commercially available chemicals were used as purchased without further purification. DMF and dioxane were dried over activated molecular sieves (4 Å). THF was dried over Na/benzophenone prior use. Melting points (capillary tube) were measured with an Electrothermal digital melting point apparatus IA 91000 and are uncorrected. IR spectra were recorded on a Mattson-Galaxy Satellite FT-IR using a single reflection ATR system as a sampling accessory. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Brucker DPX200 Advance instrument. Spectra recorded in $CDCl_3$ were referenced to residual $CHCl_3$ at 7.26 ppm for ^{1}H or 77.0 ppm for ^{13}C. Spectra recorded in DMSO-d_6 were referenced to residual DMSO at 2.49 ppm for ^{1}H or 39.5 ppm for ^{13}C. Coupling constants (*J*) are given in Hertz (Hz). The terms s, d, t, q, sept, m, dd, refer to singlet, doublet, triplet, quartet, septet, multiplet; double doublet, br implies the signal is broad. Mass spectra were recorded by electron impact (EI, 70 eV) on a Thermo Quest 2000 series apparatus or by fast-atom bombardment (FAB) on a VG Quattro instrument or by electrospray ionitzation (ESI) using a quadrupole mass spectrometer equipped with an electrospray ion source. Elemental analyses were performed on an apparatus from Thermo Instruments, model EA1110-CHNS. Analytical thin-layer chromatography (TLC) was performed on glass plates precoated with silica gel 60 F_{254} (Merck). Visualitzation was accomplished by UV light (254 nm) and potassium permanganate. Flash-chromatography (FC) purifications were performed on silica gel 60 (230–400 mesh, Merck).

4.2. General procedure for the *ipso*-substitution reaction of pyrimidinyl sulfone derivatives 5 with amino alcohols 8. Synthesis of pyrimidines 9

Under a nitrogen atmosphere, to a solution of pyrimidinyl sulfones **5a–c** (1 equiv) in dry dioxane (3 mL/mmol), the corresponding amino alcohol **8a–f** (1.5–2 equiv) was added. The resulting mixture was refluxed for 5–24 h until the reaction was completed (TLC monitoring). The solvent was removed under reduced pressure and the resulting residue was purified by flash-chromatography (*n*-hexane/ethyl acetate 4:1 gradually increasing to pure ethyl acetate) to afford pyrimidines **9**.

4.2.1. 2-(4-Isopropoxy-pyrimidin-2-ylamino)-ethanol (9a). From 1.61 g (5.51 mmol) of sulfone **5a** and 0.50 mL (8.1 mmol) of 2-amino-ethanol **8a**, 857 mg (79%) of compound **9a** was obtained as a colorless solid. Mp: 100–101 °C. R_f 0.23 (dichloromethane/methanol 10:1). IR (neat): 3298, 3259, 1574 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (d, 6H, J=6.2 Hz), 3.56 (t, 2H, J=4.4 Hz), 3.81 (t, 2H, J=4.4 Hz), 4.55 (br, 1H), 5.28 (sept, 1H, J=6.2 Hz), 5.75 (br, 1H), 5.95 (d, 1H, J=5.6 Hz), 7.94 (d, 1H, J=5.6 Hz); ^{13}C NMR ($CDCl_3$): δ 21.8 (q, 2 CH_3), 44.4, 62.6 (2t, 2 CH_2), 68.5 (d, *C*H), 98.1, 157.3 (2d, 2 CH_{pyrim}), 169.4, 162.7 (2s, 2 C_{pyrim}); MS (EI) *m*/*z*: 197 ([M]$^{\cdot+}$, 13). Anal. Calcd for $C_9H_{15}N_3O_2$: C, 54.81; H, 7.67; N, 21.30. Found: C, 54.60; H, 7.78; N, 21.11.

4.2.2. 2-(4-Isopropoxy-6-methyl-pyrimidin-2-ylamino)-ethanol (9b). From 1.00 g (3.27 mmol) of sulfone **5b** and 0.30 mL (4.85 mmol) of 2-amino-ethanol **8a**, 524 mg (76%) of compound **9b** was obtained as a colorless solid. Mp: 109–110 °C. R_f 0.79 (dichloromethane/methanol 3:1). IR (neat): 3265, 3190, 1568 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (d, 6H, J=6.2 Hz), 2.25 (s, 3H), 3.56 (t, 2H, J=4.4 Hz), 3.83 (t, 2H, J=4.4 Hz), 4.65 (br, 1H), 5.25 (sept, 1H, J=6.2 Hz), 5.45 (br, 1H), 5.86 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.9, 23.4 (2q, 3 CH_3), 44.7, 63.5 (2t, 2 CH_2), 68.4 (d, *C*H), 96.9 (d, CH_{pyrim}), 162.7, 167.4, 170.0 (3s, 3 C_{pyrim}); MS (EI) *m*/*z*: 211 ([M]$^{\cdot+}$, 14). Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.96; H, 8.29; N, 19.70.

4.2.3. 3-(4-Isopropoxy-pyrimidin-2-ylamino)-propan-1-ol (9c). From 1.03 g (3.5 mmol) of sulfone **5a** and 0.4 mL (5.42 mmol) of 3-amino-propan-1-ol **8b**, 487 mg (65%) of compound **9c** was obtained as a colorless solid. Mp: 82–83 °C. R_f 0.33 (dichloromethane/methanol 10:1). IR (neat): 3280, 3219, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (d, 6H, J=6.2 Hz), 1.77 (m, 2H), 3.57 (q, 2H, J=6.0 Hz), 3.67 (t, 2H, J=5.7 Hz), 4.15 (br, 1H), 5.26 (sept, 1H, J=6.2 Hz), 5.30 (br, 1H), 5.96 (d, 1H, J=5.8 Hz), 7.96 (d, 1H, J=5.8 Hz); ^{13}C NMR ($CDCl_3$): δ 22.5 (q, 2 CH_3), 33.8, 38.4, 59.4 (3t, 3 CH_2), 69.2 (d, *C*H), 98.8, 158.1 (2d, CH_{pyrim}), 163.6, 170.1 (2s, 2 C_{pyrim}); MS (EI) *m*/*z*: 211 ([M]$^{\cdot+}$, 9). Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.74; H, 8.32; N, 19.86.

4.2.4. 3-(4-Isopropoxy-6-methyl-pyrimidin-2-ylamino)-propan-1-ol (9d). From 1.23 g (4.02 mmol) of sulfone **5b** 0.46 mL (6.24 mmol) of and 3-amino-propan-1-ol **8b**, 847 mg (94%) of compound **9d** was obtained as a colorless oil. R_f 0.12 (*n*-hexane/ethyl acetate 1:1). IR (neat): 3305,

3106, 1578 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 (d, 6H, J= 6.2 Hz), 1.81 (q, 2H, J=5.8 Hz), 2.33 (s, 3H), 3.56 (q, 2H, J=6.0 Hz), 3.70 (t, 2H, J=5.6 Hz), 5.30 (sept, 1H, J= 6.2 Hz), 5.55 (br, 2H), 5.83 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.8, 22.6 (2q, 3 CH_3), 32.5, 38.7, 59.9 (3t, 3 CH_2), 71.4 (d, CH), 98.4 (d, CH_{pyrim}), 158.3, 167.0, 171.3 (3s, 3 C_{pyrim}); MS (EI) m/z: 225 ($[M]^{\cdot+}$, 64). Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64; H, 8.50; N, 18.65. Found: C, 58.87; H, 8.62; N, 18.84.

4.2.5. 2-(4-Isopropoxy-6-methyl-pyrimidin-2-ylamino)-3-phenyl-propan-1-ol (9e). From 785 mg (2.56 mmol) of sulfone **5b** and 774 mg (5.13 mmol) of phenylalaninol **8c**, 612 mg (79%) of compound **9e** was obtained as a colorless oil. R_f 0.12 (chloroform/methanol 6:1). IR (neat): 3400, 3028, 1577 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.34 (d, 6H, J= 6.2 Hz), 2.97 (d, 2H, J=7.4 Hz), 3.67 (dd, 1H, J=10.8 Hz, J'=5.6 Hz), 3.82 (dd, 1H, J=10.8 Hz, J'=2.8 Hz), 4.20 (m, 1H), 4.30 (br, 1H), 5.27 (sept, 1H, J=6.2 Hz), 5.40 (br, 1H), 5.86 (s, 1H), 7.20–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 22.6, 23.8 (2q, 3 CH_3), 38.4 (t, CH_2), 55.6 (d, CH), 65.4 (t, CH_2), 69.3 (d, CH), 97.5 (d, CH_{pyrim}), 127.1, 129.2, 129.9 (3d, 5 CH_{arom}), 139.0 (s, C_{arom}), 162.2, 167.3, 170.8 (3s, 3 C_{pyrim}); MS (EI) m/z: 301 ($[M]^{\cdot+}$, 4). Anal. Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.56; H, 7.52; N, 14.12.

4.2.6. 2-[(4-Isopropoxy-6-phenyl-pyrimidin-2-yl)-methyl-amino]-ethanol (9f). From 1.00 g (2.72 mmol) of sulfone **5c** and 0.38 mL (5.4 mmol) of 2-methylamino-ethanol **8d**, 667 mg (85%) of compound **9f** was obtained as a colorless oil. R_f 0.23 (*n*-hexane/ethyl acetate 1:1). IR (neat): 3400–3200, 1534 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.42 (d, 6H, J=6.2 Hz), 3.30 (s, 3H), 3.85–4.00 (m, 4H), 5.40 (sept, 1H, J=6.2 Hz), 6.40 (s, 1H), 7.40, 7.50 (m, 3H), 7.95–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 22.6, 37.3 (2q, 3 CH_3), 53.5, 63.7 (2t, 2 CH_2), 69.3 (d, CH), 93.7 (d, CH_{pyrim}), 127.5, 129.2, 130.8 (3d, 5 CH_{arom}), 138.4 (s, C_{arom}), 163.6, 165.7, 170.9 (3s, 3 C_{pyrim}); MS (EI) m/z: 287 ($[M]^{\cdot+}$, 11). Anal. Calcd for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 67.15; H, 7.45; N, 14.35.

4.2.7. 2-[(4-Isopropoxy-6-methyl-pyrimidin-2-yl)-methyl-amino]-ethanol (9g). From 1.23 g (4.02 mmol) of sulfone **5b** and 0.48 mL (6.83 mmol) of 2-methylamino-ethanol **8d**, 721 mg (80%) of compound **9g** was obtained as a colorless oil. R_f 0.38 (*n*-hexane/ethyl acetate 1:1). IR (neat): 3450–3250, 1576 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.34 (d, 6H, J=6.2 Hz), 2.24 (s, 3H), 3.20 (s, 3H), 3.74 (t, 2H, J=4.0 Hz), 3.89 (t, 2H, J=4.0 Hz), 5.30 (sept, 1H, J= 6.2 Hz), 5.81 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.9, 23.5, 36.6 (3q, 4 CH_3), 53.2, 63.3 (2t, 2 CH_2), 68.2 (d, CH), 95.7 (d, CH_{pyrim}), 162.6, 167.0, 169.6 (3s, 3 C_{pyrim}); MS (EI) m/z: 225 ($[M]^{\cdot+}$, 29). Anal. Calcd for $C_{11}H_{19}N_3O_2$: C, 58.64; H, 8.50; N, 18.65. Found: C, 58.66; H, 8.62; N, 18.56.

4.2.8. [1-(4-Isopropoxy-6-methyl-pyrimidin-2-yl)-pyrrolidin-2-yl]-methanol (9h). From 1.00 g (3.27 mmol) of sulfone **5b** and 0.58 mL (5.6 mmol) of prolinol **8e**, 825 mg (95%) of compound **9h** was obtained as a colorless oil. R_f 0.34 (*n*-hexane/ethyl acetate 1:1). IR (neat): 3400–3300, 1574 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.33 (d, 6H, J=6.2 Hz), 1.70–2.20 (m, 4H), 2.23 (s, 3H), 3.50–3.80 (m, 4H), 4.25 (m, 1H), 5.30 (sept, 1H, J=6.2 Hz), 5.81 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 21.9, 23.3 (2q, 3 CH_3), 23.9, 29.9, 48.2 (3t, 3 CH_2), 61.1 (d, CH), 68.3 (t, CH_2), 68.8 (d, CH), 95.7 (d, CH_{pyrim}), 161.1, 166.5, 169.6 (3s, 3 C_{pyrim}); MS (EI) m/z: 251 ($[M]^{\cdot+}$, 3). Anal. Calcd for $C_{13}H_{21}N_3O_2$: C, 62.13; H, 8.42; N, 16.72. Found: C, 62.19; H, 8.64; N, 16.44.

4.2.9. [1-(4-Isopropoxypyrimidin-2-yl)piperidin-2-yl]-methanol (9i). From 875 mg (3.0 mmol) of sulfone **5a** and 618 mg (5.37 mmol) of piperidin-2-yl-methanol **8f**, 596 mg (79%) of compound **9i** was obtanied as a colorless oil. R_f 0.40 (*n*-hexane/ethyl acetate 1:1). IR (neat): 3405, 1587 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.37 (d, 6H, J=6.2 Hz), 1.65–1.80 (m, 6H), 3.05 (m, 1H), 3.40 (br, 1H), 3.73 (dd, 1H, J=10.7 Hz, J'=5, 5 Hz), 3.96 (dd, 1H, J=10.7 Hz, J'=8.8 Hz, CH_2N), 4.60 (m, 1H), 4.90 (m, 1H), 5.28 (sept, 1H, J=6.2 Hz), 5.90 (d, 1H, J=6.0 Hz), 7.98 (d, 1H, J= 6.0 Hz); ^{13}C NMR ($CDCl_3$): δ 19.8 (t, CH_2), 21.8 (q, 2 CH_3), 24.9, 25.6, 39.6 (3t, 3 CH_2), 52.7 (d, CH), 62.7 (t, CH_2), 68.2 (d, CH), 97.1, 157.4 (2d, 2 CH_{pyrim}), 162.6, 169.0 (2s, 2 C_{pyrim}); MS (EI) m/z: 251 ($[M]^{\cdot+}$, 6). Anal. Calcd for $C_{13}H_{21}N_3O_2$: C, 62.13; H, 8.42; N, 16.72. Found: C, 62.22; H, 8.34; N, 16.54.

4.2.10. [1-(4-Isopropoxy-6-methylpyrimidin-2-yl)-piperidin-2-yl]-methanol (9j). From 900 mg (2.94 mmol) of sulfone **5b** and 672 mg (5.84 mmol) piperidin-2-yl-methanol **8f**, 716 mg (90%) of compound **9j** was obtained as a colorless oil. R_f 0.44 (*n*-hexane/ethyl acetate 1:1). IR (neat): 3400, 1573 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.31 (d, 6H, J=6.2 Hz), 1.50–1.70 (m, 6H), 2.20 (s, 3H), 3.05 (m, 1H), 3.71 (dd, 1H, J=10.7 Hz, J'=4.7 Hz, CH_2N), 4.00 (dd, 1H, J=10.7 Hz, J'=9.0 Hz), 4.15 (br, 1H), 4.60 (m, 1H), 4.90 (m, 1H), 5.25 (sept, 1H, J=6.2 Hz), 5.77 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.6 (t, CH_2), 21.5, 24.4 (2q, 3 CH_3), 25.6, 26.5, 40.3 (3t, 3 CH_2), 53.6 (d, CH), 64.1 (t, CH_2), 68.7 (d, CH), 96.3 (d, CH_{pyrim}), 163.4, 167.9, 170.2 (3s, 3 C_{pyrim}); MS (EI) m/z: 265 ($[M]^{\cdot+}$, 3). Anal. Calcd for $C_{14}H_{23}N_3O_2$: C, 63.37; H, 8.74; N, 15.84. Found: C, 63.09; H, 8.83; N, 15.66.

4.3. General procedure for the hydrolysis of compounds 9 with HCl. Synthesis of pyrimidinones 10

A suspension of the corresponding 4-isopropoxypyrimidine **9** (1 equiv) in concd HCl (2 mL/mmol) was heated at 90 °C for 30 min. After cooling, the mixture was neutralized with aq 5 N NaOH and extracted with CH_2Cl_2 (3×10 mL/mmol). The combined organic layers were washed with brine (1×10 mL/mmol) and the organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude product was purified by flash-chromatography (ethyl acetate/methanol 10:1) to afford pyrimidinones **10**.

4.3.1. 2-(2-Hydroxy-ethylamino)-3*H*-pyrimidin-4-one (10a). From 336 mg (1.7 mmol) of 4-isopropoxipyrimidine **9a**, 226 mg (86%) of compound **10a** was obtained as a colorless solid. Mp: 176–177 °C. R_f 0.17 (dichloromethane/methanol 10:1). IR (neat): 3220–2880, 1681, 1621 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.30 (m, 2H), 3.51 (t, 2H, J= 5.6 Hz), 4.90 (br, 1H), 5.53 (d, 1H, J=6.6 Hz), 6.55 (br, 1H), 7.57 (d, 1H, J=6.6 Hz), 10.60 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 43.4, 59.2 (2t, 2 CH_2), 103.2, 149.2 (2d, 2

CH_{pyrim}), 153.9, 162.0 (2s, 2 C_{pyrim}); MS (ESI) *m/z*: 178 $[M+23]^+$, 156 $[M+1]^+$. Anal. Calcd for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.43; H, 5.96; N, 27.10.

4.3.2. 2-(2-Hydroxyethylamino)-6-methylpyrimidin-4(3*H*)-one (10b). From 446 mg (2.11 mmol) of 4-isopropoxipyrimidine **9b**, 346 mg (97%) of compound **10b** was obtained as a colorless solid. Mp: 192–193 °C. R_f 0.51 (dichloromethane/methanol 3:1). IR (neat): 3250, 1612 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.10 (s, 3H), 3.30 (m, 2H), 3.40 (t, 2H, $J=6.0$ Hz), 3.59 (t, 2H, $J=6.0$ Hz), 4.95 (br, 1H), 5.50 (s, 1H), 6.70 (br, 1H), 10.65 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 24.4 (q, CH_3), 43.1, 60.0 (2t, 2 CH_2), 100.8 (d, CH_{pyrim}), 154.7, 163.0, 166.0 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 192 $[M+23]^+$, 170 $[M+1]^+$. Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.70; H, 6.55; N, 24.84. Found: C, 49.91; H, 6.68; N, 24.56.

4.3.3. 2-(3-Hydroxy-propylamino)-3*H*-pyrimidin-4-one (10c). From 344 mg (1.63 mmol) of 4-isopropoxipyrimidine **9c**, 268 mg (97%) of compound **10c** was obtained as a colorless solid. Mp: 141–142 °C. R_f 0.20 (dichloromethane/methanol 10:1). IR (neat): 3210–2873, 1676, 1609 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.73 (m, 2H), 3.39 (m, 2H), 3.54 (m, 2H), 4.65 (br, 1H), 5.62 (d, 1H, $J=6.6$ Hz), 6.62 (br, 1H), 7.66 (d, 1H, $J=6.6$ Hz), 10.85 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 31.9, 37.6, 58.3 (3t, 3 CH_2), 102.7, 154.4 (2d, 2 CH_{pyrim}), 155.2 162.9 (2s, 2 C_{pyrim}); MS (ESI) *m/z*: 192 $[M+23]^+$, 170 $[M+1]^+$. Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.70; H, 6.55; N, 24.84. Found: C, 49.57; H, 6.80; N, 25.05.

4.3.4. 2-(3-Hydroxy-propylamino)-6-methyl-3*H*-pyrimidin-4-one (10d). From 570 mg (2.53 mmol) of 4-isopropoxipyrimidine **9d**, 403 mg (87%) of compound **10d** was obtained as a colorless solid. Mp: 160–161 °C. R_f 0.60 (dichloromethane/methanol 3:1). IR (neat): 3215–2890, 1675, 1611 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.71 (m, 2H), 2.10 (s, 3H), 3.40 (t, 2H, $J=6.0$ Hz), 3.54 (t, 2H, $J=6.0$ Hz), 4.70 (br, 1H), 5.47 (s, 1H), 6.90 (br, 1H), 10.75 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 23.9 (q, CH_3), 32.0, 37.3, 58.3 (3t, 3 CH_2), 100.2 (d, CH_{pyrim}), 154.4, 162.7, 165.5 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 206 $[M+23]^+$, 184 $[M+1]^+$. Anal. Calcd for $C_8H_{13}N_3O_2$: C, 52.45; H, 7.15; N, 22.94. Found: C, 52.70; H, 7.13; N, 23.11.

4.3.5. 2-(1-Benzyl-2-hydroxy-ethylamino)-6-methyl-3*H*-pyrimidin-4-one (10e). From 410 mg (1.36 mmol) of 4-isopropoxipyrimidine **9e**, 251 mg (71%) of compound **10e** was obtained as a colorless solid. Mp: 145–146 °C. R_f 0.61 (dichloromethane/methanol 6:1). IR (neat): 3215–2890, 1675, 1611 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.10 (s, 3H), 2.90 (m, 2H), 3.51 (d, 2H, $J=4.2$ Hz), 4.15 (m, 1H), 5.48 (s, 1H), 6.57 (d, 1H, $J=7.6$ Hz), 7.25–7.40 (m, 5H); ^{13}C NMR (DMSO-d_6): δ 24.3 (q, CH_3), 37.2 (t, CH_2), 53.8 (d, CH), 61.9 (t, CH_2), 100.8 (d, CH_{pyrim}), 126.5, 128.6, 129.7 (3d, 5 CH_{arom}), 139.3 (s, C_{arom}), 154.4, 163.4, 165.8 (3s, 3 C_{pyrim}); MS (FAB^+) *m/z*: 260 $([M+1]^+$, 100). Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.21. Found: C, 65.06; H, 6.74; N, 15.93.

4.3.6. 2-(*N*-(2-Hydroxyethyl)-*N*-methylamino)-6-phenylpyrimidin-4(3*H*)-one (10f). From 53 mg (0.18 mmol) of 4-isopropoxipyrimidine **9f**, 39 mg (95%) of compound **10f** was obtained as a colorless solid. Mp: 197–198 °C. R_f 0.40 (dichloromethane/methanol 10:1). IR (neat): 3350, 1639 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.26 (s, 3H), 3.75 (m, 4H), 5.00 (br, 1H), 6.26 (s, 1H), 7.50–7.60 (m, 3H), 8.05–8.10 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 36.5 (q, CH_3), 51.8, 58.9 (2t, 2 CH_2), 95.3 (d, CH_{pyrim}), 126.6, 128.4, 130.0 (3d, 5 CH_{arom}), 137.4 (s, C_{arom}), 155.5, 161.9, 165.1 (3s, 3 C_{pyrim}); MS (FAB^+) *m/z*: 246 $([M+1]^+$, 100). Anal. Calcd for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.72; H, 6.03; N, 17.30.

4.3.7. 2-[(2-Hydroxy-ethyl)-methyl-amino]-6-methyl-3*H*-pyrimidin-4-one (10g). From 560 mg (2.49 mmol) of 4-isopropoxipyrimidine **9g**, 387 mg (85%) of compound **10g** was obtained as a colorless solid. Mp: 118–119 °C. R_f 0.26 (dichloromethane/methanol 10:1). IR (neat): 3363–2851, 1647, 1565 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.13 (s, 3H), 3.15 (s, 3H), 3.65 (m, 4H), 4.90 (br, 1H), 5.55 (s, 1H), 10.85 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 23.0, 35.4 (2q, 2 CH_3), 58.0, 50.6, (2t, 2 CH_2), 97.5 (d, CH_{pyrim}), 154.2, 163.6, 164.8 (3s, 3 C_{pyrim}); MS (FAB^+) *m/z*: 206 $[M+23]^+$, 184 $[M+1]^+$. Anal. Calcd for $C_8H_{13}N_3O_2$: C, 52.45; H, 7.15; N, 22.94. Found: C, 52.31; H, 7.23; N, 22.81.

4.3.8. 2-(2-(Hydroxymethyl)pyrrolidin-1-yl)-6-methylpyrimidin-4(3*H*)-one (10h). From 630 mg (2.51 mmol) of 4-isopropoxipyrimidine **9h**, 490 mg (94%) of compound **10h** was obtained as a colorless solid. Mp: 110–111 °C. R_f 0.73 (dichloromethane/methanol 6:1). IR (neat): 3380, 1686 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.95 (m, 4H), 2.38 (s, 3H), 3.40–3.65 (m, 4H), 4.45 (br, 1H), 5.99 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 19.6, (q, CH_3), 23.2, 27.9, 49.8 (3q, 3 CH_2), 61.6 (d, CH), 61.9 (t, CH_2), 100.6 (d, CH_{pyrim}), 151.2, 156.4, 165.6 (3s, 3 C_{pyrim}); MS (FAB^+) *m/z*: 210 $[M+1]^+$. Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.51; H, 7.04; N, 20.11.

4.4. General procedure for the sequential hydrolysis–cyclization of compounds 9. Synthesis of compounds 1

A suspension of the corresponding 4-isopropoxypyrimidine **9** (1 equiv) in concd H_2SO_4 (3 mL/mmol) was heated at 90 °C for 20 min–1 h until the reaction was completed (TLC monitoring). After cooling, the mixture was neutralized with aq 5 N NaOH and extracted with CH_2Cl_2 (3×10 mL/mmol). The combined organic layers were washed with brine (1×10 mL/mmol) and the organic layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to afford imidazo[1,2-*a*]pyrimidinones **1** ($n=1$) or pyrimido[1,2-*a*]pyrimidinones **1** ($n=2$).

4.4.1. 5,6,7,8,8a,9-Hexahydro-4,4b,9a-triaza-fluoren-1-one (1i). From 123 mg (0.49 mmol) of 4-isopropoxipyrimidine **9i**, 92 mg (98%) of compound **1i** was obtained as a colorless solid. Mp: 93–94 °C. R_f 0.38 (dichloromethane/methanol 10:1). IR (neat): 1659, 1579, 1545 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.40–1.90 (m, 6H), 3.00 (m, 1H), 3.60–4.25 (m, 4H), 5.68 (d, 1H, $J=6.4$ Hz), 7.66 (d, 1H, $J=6.4$ Hz); ^{13}C NMR (DMSO-d_6): δ 22.5, 23.9, 41.0, 46.4 (5t, 5 CH_2), 54.6 (d, CH), 102.9, 155.3 (2d, 2 CH_{pyrim}), 155.6, 160.5 (2s, 2 C_{pyrim}); MS (ESI) *m/z*: 192 $[M+1]^+$. Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.92; H, 6.66; N, 22.00.

4.4.2. 3-Methyl-5,6,7,8,8a,9-hexahydro-4,4b,9a-triaza-fluoren-1-one (1j). From 103 mg (0.39 mmol) of 4-isopropoxipyrimidine **9j**, 79 mg (99%) of compound **1j** was obtained as a colorless solid. Mp: 121–123 °C. R_f 0.34 (dichloromethane/methanol 10:1). IR (neat): 1657, 1584, 1553 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.40–1.95 (m, 6H), 2.13 (s, 3H), 2.95 (m, 1H), 3.55–4.20 (m, 4H), 5.58 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 22.6 (t, CH_2), 23.7 (q, CH_3), 23.9, 30.1, 41.0, 46.3 (4t, 4 CH_2), 54.8 (d, CH), 100.6 (d, CH_{pyrim}), 154.7, 160.7, 165.3 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 206 $[M+1]^+$. Anal. Calcd for $C_{11}H_{15}N_3O$: C, 64.37; H, 7.37; N, 20.47. Found: C, 64.15; H, 7.46; N, 20.32.

4.4.3. 1-Methyl-7-phenyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (1f). From 527 mg (1.84 mmol) of 4-isopropoxipyrimidine **9f**, 394 mg (95%) of compound **1f** was obtained as a colorless solid. Mp: 130–131 °C. R_f 0.54 (dichloromethane/methanol 10:1). IR (neat): 1665, 1590, 1553 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.12 (s, 3H), 3.69 (t, 2H, $J=8.8$ Hz), 4.16 (t, 2H, $J=8.7$ Hz), 6.29 (s, 1H), 7.40–7.50 (m, 3H), 7.95–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 32.3 (q, CH_3), 41.0, 47.8 (2t, 2 CH_2), 99.8 (d, CH_{pyrim}), 127.8, 129.1, 130.7 (3d, 5 CH_{arom}), 138.1 (s, C_{arom}), 157.3, 163.2, 164.1 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 228 $[M+1]^+$. Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.49; H, 5.93; N, 18.54.

4.4.4. 7-Methyl-2,3-dihydro-1*H*-imidazo[1,2-a]pyrimidin-5-one (1b). From 50 mg (0.24 mmol) of 4-isopropoxipyrimidine **9b**, 34 mg (95%) of compound **1b** was obtained as a colorless solid. Mp: 233–234 °C. R_f 0.54 (dichloromethane/methanol 6:1). IR (neat): 1658, 1617, 1567 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.09 (s, 3H), 3.69 (t, 2H, $J=8.8$ Hz), 4.05 (t, 2H, $J=8.8$ Hz), 5.53 (s, 1H), 7.90 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 42.9, 62.1 (2t, 2 CH_2), 105.4 (d, CH_{pyrim}), 150.1, 160.0, 164.8 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 152 $[M+1]^+$. Anal. Calcd for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.70; H, 5.77; N, 27.82.

4.4.5. 2-Methyl-6,7,8,9-tetrahydro-pyrimido[1,2-*a*]pyrimidin-4-one (1d). From 420 mg (1.87 mmol) of 4-isopropoxipyrimidine **9d**, 223 mg (73%) of compound **1d** was obtained as a colorless solid. Mp: 204–205 °C. R_f 0.71 (dichloromethane/methanol 6:1). IR (neat): 3262, 1661, 1600, 1580 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.98 (t, 2H, $J=5.6$ Hz), 2.06 (s, 3H), 3.34 (t, 2H, $J=5.4$ Hz), 3.86 (t, 2H, $J=5.7$ Hz), 5.51 (s, 1H), 7.90 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 19.5 (t, CH_2), 23.4 (q, CH_3), 38.3, 38.4 (2t, 2 CH_2), 98.0 (d, CH_{pyrim}), 153.0, 161.5, 164.0 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 166 $[M+1]^+$. Anal. Calcd for $C_8H_{11}N_3O$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.34; H, 6.60; N, 25.66.

4.4.6. 1,7-Dimethyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (1g). From 55 mg (2.44 mmol) of 4-isopropoxipyrimidine **9g**, 39 mg (99%) of compound **1g** was obtained as a colorless solid. Mp: 132–133 °C. R_f 0.40 (dichloromethane/methanol 10:1). IR (neat): 1661, 1591, 1567 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.13 (s, 3H), 2.97 (s, 3H), 3.64 (t, 2H, $J=8.9$ Hz), 4.02 (t, 2H, $J=8.9$ Hz), 5.60 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.7, 32.2 (2q, 2 CH_3), 40.8, 47.7 (2t, 2 CH_2), 102.3 (d, CH_{pyrim}), 157.0, 162.5, 168.8 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 188 $[M+23]^+$, 166 $[M+1]^+$. Anal. Calcd for $C_8H_{11}N_3O$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.27; H, 6.71; N, 25.23.

4.4.7. 5-Methyl-2,3,8,8a-tetrahydro-1*H*-3a,4,7a-triaza-cyclopenta[*a*]inden-7-one (1h). From 300 mg (1.19 mmol) of 4-isopropoxipyrimidine **9h**, 174 mg (76%) of compound **1h** was obtained as a colorless solid. Mp: 77–78 °C. R_f 0.35 (dichloromethane/methanol 10:1). IR (neat): 1661, 1582, 1536 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.30–1.50 (m, 1H), 1.85–2.10 (m, 3H), 2.17 (s, 3H), 3.30–3.40 (m, 1H), 3.65–3.75 (m, 1H), 3.90–4.15 (m, 3H), 5.74 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.0 (q, CH_3), 25.0, 30.9, 45.6, 47.1 (4t, 4 CH_2), 59.1 (d, CH), 103.4 (d, CH_{pyrim}), 159.0, 161.8, 166.1 (3s, 3 C_{pyrim}); MS (ESI) *m/z*: 192 $[M+1]^+$. Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.97. Found: C, 63.08; H, 6.96; N, 22.01.

4.5. General procedure for the intramolecular Mitsunobu cyclization. Synthesis of compounds 1 and 2

Under nitrogen atmosphere, a solution of DEAD (1.1 equiv) in dry THF (5 mL/mmol) was added dropwise to a solution of Ph_3P (1.1 equiv) and the appropriate pyrimidinone **10** (1 equiv) in dry THF (10 mL/mmol) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 5–8 h until the reaction was completed (TLC monitoring). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate/methanol 10:1) to afford compounds **1** and **2**.

4.5.1. Intramolecular cyclization of pyrimdinone 10a. From 197 mg (1.27 mmol) of pyrimidinone **10a**, 19 mg (11%) of compound **1a** and 140 mg (80%) of compound **2a** were obtained.

4.5.1.1. 2,3-Dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-5-one (1a). Isolated as a colorless solid. Mp: 151–153 °C. R_f 0.54 (dichloromethane/methanol 6:1). IR (neat): 3216, 1661, 1605, 1530 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.80 (t, 2H, $J=8.9$ Hz), 4.27 (t, 2H, $J=8.8$ Hz), 5.81 (d, 1H, $J=6.8$ Hz), 7.10 (br, 1H), 7.55 (d, 1H, $J=6.6$ Hz); ^{13}C NMR (DMSO-d_6): δ 42.8, 59.5 (2t, 2 CH_2), 102.7, 155.3 (2d, 2 CH_{pyrim}), 155.7, 162.6 (2s, 2 C_{pyrim}); MS (ESI) *m/z*: 138 $[M+1]^+$. Anal. Calcd for $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.36; H, 5.23; N, 30.71.

4.5.1.2. 2,3-Dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-7-one (2a). Isolated as a colorless solid. Mp: 195–196 °C. R_f 0.14 (dichloromethane/methanol 6:1). IR (neat): 3080, 1649, 1604 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.67 (t, 2H, $J=8.5$ Hz), 4.14 (t, 2H, $J=8.6$ Hz), 5.57 (d, 1H, $J=7.4$ Hz), 7.56 (d, 1H, $J=7.4$ Hz), 7.75 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 40.2, 46.3 (2t, 2 CH_2), 105.1, 138.3 (2d, 2 CH_{pyrim}), 159.2, 171.2 (2s, 2 C_{pyrim}); MS (ESI) *m/z*: 160 $[M+23]^+$, 138 $[M+1]^+$. Anal. Calcd for $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.67; H, 5.22; N, 30.76.

4.5.2. Intramolecular cyclization of pyrimdinone 10e. From 130 mg (0.50 mmol) of pyrimidinone **10e**, 39 mg (33%) of compound **1e** and 54 mg (45%) of compound **2e** were obtained.

4.5.2.1. 2-Benzyl-7-methyl-2,3-dihydro-1*H*-imidazo-[1,2-*a*]pyrimidin-5-one (1e). Isolated as a colorless solid. Mp: 182–183 °C. R_f 0.51 (dichloromethane/methanol 3:1). IR (neat): 3128, 1659, 1564 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.10 (s, 3H), 2.90 (m, 2H), 3.50 (br, 2H), 4.15 (m, 1H), 5.48 (s, 1H), 7.30–7.40 (m, 5H), 7.95 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 19.2 (q, CH_3), 45.6, 49.0 (2t, 2 CH_2), 50.9, (d, CH), 99.1 (d, CH_{pyrim}), 126.9, 128.6, 129.5 (3d, 5 CH_{arom}), 138.1 (s, C_{arom}), 155.4, 160.1, 163.2 (3s, 3 C_{pyrim}); MS (FAB$^+$) *m/z*: 242 ([M+1]$^+$, 100). Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.82; H, 6.12; N, 17.63.

4.5.2.2. 2-Benzyl-5-methyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyrimidin-7-one (2e). Isolated as a colorless solid. Mp: 227–228 °C. R_f 0.12 (dichloromethane/methanol 3:1). IR (neat): 3104, 1673, 1620, 1552 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.03 (s, 3H), 2.97 (dd, 1H, J=13.8 Hz, J'=8.2 Hz), 3.35 (dd, 1H, J=13.7 Hz, J'=4.4 Hz), 3.71 (dd, 1H, J=10.1 Hz, J'=6.4 Hz), 3.99 (dd, 1H, J=10.1 Hz, J'=9.4 Hz), 4.50 (m, 1H), 5.51 (s, 1H), 7.25–7.35 (m, 5H), 9.50 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 17.4 (q, CH_3), 41.0, 48.9 (2t, 2 CH_2), 53.0, (d, CH), 103.7 (d, CH_{pyrim}), 127.1, 128.9, 129.8 (3d, 5 CH_{arom}), 137.0 (s, C_{arom}), 148.1, 158.9, 171.9 (3s, 3 C_{pyrim}); MS (FAB$^+$) *m/z*: 242 ([M+1]$^+$, 100). Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.84; H, 6.24; N, 17.54.

4.5.3. Intramolecular cyclization of pyrimdinone 10d. From 350 mg (1.91 mmol) of pyrimidinone **10d**, 73 mg (25%) of **1d** and 187 mg (66%) of **2d** were obtained. The spectroscopic features of **1d** was identical to those reported above.

4.5.3.1. Spectroscopic data for 4-methyl-6,7,8,9-tetrahydro-pyrimido[1,2-*a*]pyrimidin-2-one (2d). Isolated as a colorless solid. Mp: >300 °C. R_f 0.10 (dichloromethane/methanol 10:1). IR (neat): 3099, 1668, 1618, 1555 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.05 (m, 2H), 2.22 (s, 3H), 3.32 (t, 2H, J=5.6 Hz), 3.88 (t, 2H, J=5.8 Hz), 5.55 (s, 1H), 7.90 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 18.1 (q, CH_3), 20.3, 38.0, 43.0 (t, CH_2), 106.2 (d, CH_{pyrim}), 149.5, 153.5, 169.2 (s, C_{pyrim}); MS (ESI) *m/z*: 166 [M+1]$^+$. Anal. Calcd for $C_8H_{11}N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.74; H, 5.35; N, 30.41.

4.5.4. Intramolecular cyclization of pyrimdinone 10c. From 182 mg (1.08 mmol) of pyrimidinone **10c**, 36 mg (22%) of **1c** and 119 mg (73%) of **2c** were obtained.

4.5.4.1. 6,7,8,9-Tetrahydro-pyrimido[1,2-*a*]pyrimidin-4-one (1c). Isolated as a colorless solid. Mp: 178–179 °C. R_f 0.60 (dichloromethane/methanol 3:1). IR (neat): 3219, 1660, 1603, 1555 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.99 (m, 2H), 3.36 (t, 2H, J=5.7 Hz), 3.90 (t, 2H, J=5.9 Hz), 5.62 (d, 1H, J=6.2 Hz), 7.59 (d, 1H, J=6.2 Hz), 7.95 (br, 1H, N*H*); ^{13}C NMR (DMSO-d_6): δ 19.3, 38.3, 38.6 (3t, 3 CH_2), 99.9 (d, CH_{pyrim}), 154.1 (s, C_{pyrim}), 154.6 (d, CH_{pyrim}), 161.3 (s, C_{pyrim}); MS (ESI) *m/z*: 152 [M+1]$^+$. Anal. Calcd for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.49; H, 6.22; N, 27.86.

4.5.4.2. 6,7,8,9-Tetrahydro-pyrimido[1,2-*a*]pyrimidin-2-one (2c). Isolated as a colorless solid. Mp: 235–236 °C. R_f 0.22 (dichloromethane/methanol 3:1). IR (neat): 3170, 1673, 1621, 1553 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.01 (m, 2H), 3.34 (t, 2H, J=5.3 Hz), 3.88 (t, 2H, J=5.3 Hz), 5.60 (d, 1H, J=7.4 Hz), 7.36 (d, 1H, J=7.4 Hz), 8.10 (br, 1H); ^{13}C NMR (DMSO-d_6): δ 20.0, 37.8, 47.5 (3t, 3 CH_2), 106.2, 142.3 (2d, 2 CH_{pyrim}), 152.8, 169.8 (2s, 2 C_{pyrim}); MS (ESI) *m/z*: 174 [M+23]$^+$, 152 [M+1]$^+$. Anal. Calcd for $C_7H_9N_3O$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.45; H, 6.03; N, 27.75.

4.5.5. Intramolecular cyclization of pyrimdinone 10g. From 230 mg (1.26 mmol) of pyrimidinone **10g**, 197 mg (96%) of **1g** was obtained. The spectroscopic features of this product were identical to those reported above.

4.6. X-ray crystallographic details

4.6.1. Compound 1h. $C_{10}H_{13}N_3O\cdot 3H_2O$, M_r=245.28, trigonal, space group $P3_1$, a=10.185(3) Å, c=10.217(6) Å, V=917.9(7) Å^3, Z=3, D_x=1.331 g cm^{-3}, T=−173 °C, crystal dimensions: 0.01×0.05×0.30 mm, BRUKER SMART APEX-CCD area-detector diffractometer, Mo Kα radiation, λ=0.71073 Å, μ=0.103 mm^{-1}, θ_{max}=28°, 13947 measured reflections, 1489 symmetry-independent reflections, 1459 reflections with $I>2\sigma(I)$, refinement on F^2 with SHELXL-97,[35] 173 parameters, 1 restraint, $R(F)$ [$I>2\sigma(I)$ reflections]=0.043, $wR(F^2)$ [all reflections]=0.101, $S(F^2)$=1.144, $\Delta\rho_{max}$=0.40 e Å^{-3}. The asymmetric unit contains one molecule of **1h** plus three molecules of water. The enantiomer used in the refinement model was chosen arbitrarily.

4.6.2. Compound 2e. $2C_{14}H_{15}N_3O\cdot 3H_2O$, M_r=536.63, monoclinic, space group $P2_1$, a=11.6063(2) Å, b=10.0751(2) Å, c=12.4411(2) Å, β=108.5550(7)°, V=1319.17(4) Å^3, Z=2, D_x=1.292 g cm^{-3}, T=−113 °C, crystal dimensions: 0.15×0.25×0.27 mm, Nonius KappaCCD area-detector diffractometer, Mo Kα radiation, λ=0.71073 Å, μ=0.0905 mm^{-1}, θ_{max}=30°, 36998 measured reflections, 4254 symmetry-independent reflections, 3502 reflections with $I>2\sigma(I)$, refinement on F^2 with SHELXL-97, 387 parameters, 1 restraint, $R(F)$ [$I>2\sigma(I)$ reflections]=0.038, $wR(F^2)$ [all reflections]=0.092, $S(F^2)$=1.037, $\Delta\rho_{max}$=0.15 e Å^{-3}. The asymmetric unit contains two molecules of **2e** plus three molecules of water. The chosen enantiomer was based on the assumption that the chiral centre in the molecule has the *S*-configuration as a result of the known configuration of the reagents used in the reaction.

Acknowledgements

Financial support from MCYT of Spain (Project Nos. PB-94-0509). Dr. David Font thanks the University of Girona for a predoctoral fellowship. Thanks are also due to Mr. Xavier Fontrodona (Serveis Tècnics de Recerca, Universitat de Girona) for recording the X-ray crystallographic data for **1h**.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.11.014. CCDC-276097 and CCDC-287052 contain the supplementary crystallographic data for compounds **1h** and **2e**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

References and notes

1. Nakanishi, K.; Furutani, N.; Funamisu, M.; Grunberger, D.; Weinstein, J. B. *J. Am. Chem. Soc.* **1970**, *92*, 7617–7619.
2. (a) Boryski, J.; Golankiewicz, B.; De Clercq, E. *J. Med. Chem.* **1988**, *31*, 1351–1355. (b) Golankiewicz, B.; Ostrowski, T.; Januszczyk, P.; Zeidler, J.; Baranowski, D.; De Clercq, E. *J. Med. Chem.* **2001**, *44*, 4284–4287.
3. Hardtmann, G. E.; Huegi, B. S.; Gogerty, J. H.; Iorio, L. C.; Barnes, H. W. *J. Med. Chem.* **1971**, *14*, 878–882.
4. Wadw, J. J.; Toso, C. B.; Matson, C. J.; Stelzer, V. L. *J. Med. Chem.* **1983**, *26*, 608–611.
5. (a) Xia, Y.; Chackalamannil, S.; Czarniecki, M.; Tsai, H.; Vaccaro, H.; Cleven, R.; Cook, J.; Fawzi, A.; Watkins, R.; Zhang, H. *J. Med. Chem.* **1997**, *40*, 4372–4377. (b) Gala, D.; DiBenedetto, D. J.; Kugelman, M.; Mitchell, M. B. *Tetrahedron Lett.* **2003**, *44*, 2721–2723. (c) Jiang, M. X.-W.; Warshakoon, N. C.; Miller, M. J. *J. Org. Chem.* **2005**, *70*, 2824–2827.
6. F.R. Patent 2 812 636-A1, 2000.
7. Ahn, H. S.; Bercovici, A.; Boykow, G.; Bronnenkant, A.; Chackalamannil, S.; Chow, J.; Cleven, R.; Cook, J.; Czarniecki, M.; Domalski, C.; Fawzi, A.; Green, M.; Gundes, A.; Ho, G.; Laudicina, M.; Lindo, N.; Ma, K.; Manna, M.; McKittrick, B.; Mirzai, B.; Nechuta, T.; Neustadt, B.; Puchalski, C.; Pula, K.; Silverman, L.; Smith, E.; Stamford, A.; Tedesco, R. P.; Tsai, H.; Tulshian, D.; Vaccaro, H.; Watkins, R. W.; Weng, X.; Witkowski, J. T.; Xia, Y.; Zhang, H. *J. Med. Chem.* **1997**, *40*, 2196–2210.
8. E.P. Patent 1 348 708-A1, 2003.
9. (a) Mai, A.; Artico, M.; Sbardella, G.; Quartarone, S.; Massa, S.; Loi, A. G.; Montis, A. D.; Scintu, F.; Putzolu, M.; Colla, P. L. *J. Med. Chem.* **1997**, *40*, 1447–1454. (b) Mai, A.; Artico, M.; Sbardella, G.; Massa, S.; Novellino, E.; Greco, G.; Loi, A. G.; Tramontano, E.; Marongiu, M. E.; Colla, P. L. *J. Med. Chem.* **1999**, *42*, 619–627.
10. Taylor, E. C.; Zhou, P. *Tetrahedron Lett.* **1997**, *37*, 4339–4342.
11. Lombaert, S.; Doller, D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2497–2500.
12. Ram, V. J.; Singha, U. K.; Guru, P. *Eur. J. Med. Chem.* **1990**, *25*, 533–538.
13. (a) Perreault, D. M.; Cabell, L. A.; Anslyn, E. V. *Bioorg. Med. Chem.* **1997**, *5*, 1209–1220. (b) Hannon, C. L.; Anslyn, E. V. The Guanidinium Group: Its Biological Role and Synthetic Analogs In *Bioorganic Chemistry Frontiers*, *Vol. 3*; Springer: Berlin, Heidelberg, 1993; p 193. (c) Berlinck, R. G. S. *Nat. Prod. Rep.* **2002**, *19*, 617–649.
14. (a) Vaillancourt, L.; Simard, M.; Wuest, J. D. *J. Org. Chem.* **1998**, *63*, 9746–9752. (b) Beijer, F. H.; Sijbesman, R. P.; Hooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761–6769.
15. Liao, R. F.; Lauher, J. W.; Fowler, F. W. *Tetrahedron* **1996**, *52*, 3153–3162.
16. (a) Junyuan, F.; Cheng, C. C. *J. Heterocycl. Chem.* **1993**, 1273–1276. (b) Gibson, C. L.; Ohta, K.; Paulini, K.; Suckling, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3025–3031. (c) Sako, M.; Totani, R.; Hirota, K.; Maki, Y. *Chem. Pharm. Bull.* **1992**, *40*, 235–237.
17. Vlasenko, A. F.; Mandrichenko, B. E.; Rogulchenko, G. K.; Sinyak, R. S.; Mazur, I. A.; Kochergin, P. M. *Chem. Heterocycl. Compd.* **1976**, 13696–13698.
18. Nechev, L. V.; Harris, C. M.; Harris, T. M. *Chem. Res. Toxicol.* **2000**, *13*, 421–429.
19. Seidel, W.; Pischetsrieder, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2017–2022.
20. Golging, B. Y.; Slaich, P. K.; Watson, W. P. *J. Chem. Soc.* **1996**, 515–517.
21. Hornyark, G.; Lempert, K. *Acta Chim. Acad. Sci. Hung.* **1971**, *68*, 277–284.
22. Chowdhury, A. Z. M. S.; Shibata, Y.; Morita, M.; Kaya, K. *J. Heterocycl. Chem.* **2001**, *38*, 1173–1177.
23. (a) Ogura, H.; Kawano, M.; Itoh, T. *Chem. Pharm. Bull.* **1973**, *21*, 2019–2025. (b) Troxler, F.; Weber, H. P. *Helv. Chim. Acta* **1974**, *57*, 2356–2364. (c) Freeman, C. G.; Turner, J. V.; Ward, A. D. *Aust. J. Chem.* **1978**, *31*, 179–186. (d) Wade, J. J.; Hegel, R. F.; Tosa, C. B. *J. Org. Chem.* **1979**, *44*, 1811–1816. (e) Saczewski, J.; Brzozowski, Z.; Gdaniec, M. *Tetrahedron* **2005**, *61*, 5303–5309.
24. (a) Urleb, U.; Stanovnik, B.; Tisler, M. *J. Heterocycl. Chem.* **1990**, *27*, 407–412. (b) Urleb, U.; Stanovnik, B.; Tisler, M. *J. Heterocycl. Chem.* **1990**, *27*, 643–646.
25. Jokic, M.; Raza, Z.; Katalenic, D. *Nucleoside, Nucleotides and Nucleic Acids* **2000**, *19*, 1381–1396.
26. (a) Heras, M.; Ventura, M.; Linden, A.; Villalgordo, J. M. *Synhtesis* **1999**, 1613–1624. (b) Moreno, P.; Heras, M.; Maestro, M.; Villalgordo, J. M. *Synthesis* **2002**, 2691–2700.
27. (a) Font, D.; Heras, M.; Villalgordo, J. M. *J. Comb. Chem.* **2003**, *5*, 311–321. (b) Obrecht, D.; Abrecht, C.; Grieder, A.; Villalgordo, J. M. *Helv. Chim. Acta* **1997**, *80*, 65–72.
28. (a) Brun, V.; Legraverend, M.; Grieson, D. S. *Tetrahedron Lett.* **2001**, *42*, 8161–8164. (b) Brun, V.; Legraverend, M.; Grieson, D. S. *Tetrahedron Lett.* **2001**, *42*, 8165–8167.
29. Parrot, I.; Wermuth, C. G.; Hilbert, M. *Tetrahedron Lett.* **1999**, *40*, 7975–7978.
30. (a) Gibson, C. L.; La Rosa, S.; Suckling, C. J. *Tetrahedron Lett.* **2003**, *44*, 1267–1270. (b) Gibson, C. L.; La Rosa, S.; Suckling, C. J. *Org. Biomol. Chem.* **2003**, *1*, 1909–1918.
31. Font, D.; Heras, M.; Villalgordo, J. M. *Synthesis* **2002**, 1833–1842.
32. Chang, Y.-T.; Gray, N. S.; Rosania, G. R.; Sutherlin, D. P.; Kwon, S.; Norman, T. C.; Sarohia, R.; Leost, M.; Meijer, L.; Schultz, P. G. *Chem. Biol.* **1999**, *6*, 361–375.
33. Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517–5518.
34. (a) Guengerich, F. P.; Persmark, M.; Humphreys, W. G. *Chem. Res. Toxicol.* **1993**, *6*, 635–648. (b) Lagouët, S.; Müller, M.; Guengerich, F. P. *Biochemistry* **1997**, *36*, 6069–6079. (c) Zhang, X. Y.; Elfarra, A. A. *Chem. Res. Toxicol.* **2004**, *17*, 521–528.
35. Sheldrick, G. M. *SHELXL-97*: *Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.