Ugi–Smiles Coupling of Thiouracil Derivatives towards 2,4-Diamino Pyrimidines

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Abstract: Diaminopyrimidines could be synthesized via a multicomponent coupling starting from *S*-alkyl thiouracil derivatives. The synthetic strategy based upon an Ugi–Smiles coupling, and subsequent oxidation of the adducts affords a versatile platform for the preparation of various diaminopyrimidines with five points of diversity. The whole sequence may be performed as a one-pot process.

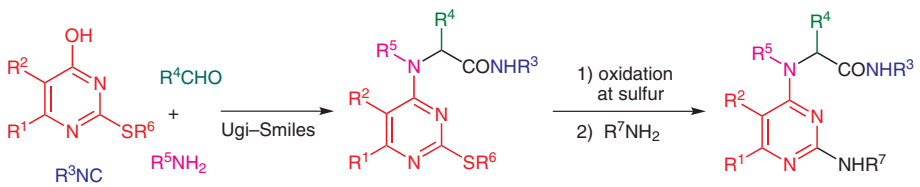
Key words: Ugi–Smiles, thiouracil, isocyanide, diaminopyrimidines, S_NAr

Diaminopyrimidines, which are involved in many biochemical pathways including DNA biosynthesis, have the ability to inhibit a large variety of protein kinases[1] displaying a wide range of biological activities such as anticancer,[2] antispychotic,[3] or anti-inflammatory.[4] Their syntheses generally rely on nucleophilic aromatic substitution performed on chloropyrimidines. The latter are prepared by the transformation of hydroxy derivatives using activating agents such as $POCl_3$. A few years ago, we disclosed a new Ugi-type coupling for the synthesis of anilines[5] and heteroaromatic amines[6] from an electron-deficient phenol in one step. An appropriate choice of reagent could allow the synthesis of 2,4-diaminopyrimidines,[7] with a structure close to cytosine and uracil derivatives. For instance, this reaction performed using thiouracil would afford 4-amino-2-mercaptopyrimidines which could be further transformed into the corresponding diaminopyrimidines via an activation of the thio functionality and subsequent nucleophilic aromatic substitution.[8] Herein, we wish to present a sequential multicomponent access to diaminopyrimidines starting with *S*-alkyl thiouracils (Scheme 1).

S-Benzyl thiouracil, chosen as a model for this study, was prepared through benzylation of thiouracil with benzyl and fluorobenzyl chlorides under standard conditions. The presence of the electron-donating thioether moiety on the pyrimidine ring does not disrupt the Ugi–Smiles couplings as shown by the various aminopyrimidines **1** prepared from a series of amines, aldehydes, and isocyanides (Table 1). Good yields are obtained except with isocyanoesters (Table 1, entries 4–6) in agreement with their lower reactivity.

The ability of the thioether group of **1** to serve as a platform for diaminopyrimidines was next examined. For this purpose, the thioethers could be transformed into the corresponding sulfones, which are good leaving groups. Various oxidizing agents have been reported for the conversion of thioethers into sulfones. Conditions allowing a one-pot oxidation–substitution sequence were required in order to construct the fastest possible means of access to diaminopyrimidine scaffolds. In terms of side-product formation, hydrogen peroxide appears to be the best choice.[9] However, its use generally requires lengthy optimization due to the need for a metal catalyst, and so MCPBA was selected for its broad scope and simple use;[10] the resulting benzoic acid not being expected to compete with the amines added in the subsequent step.

This oxidation step was then tested with thioether **1g** using three equivalents of MCPBA. Various solvents were evaluated for this purpose: methanol, toluene, and dichloromethane. The latter gave the best results with 95% isolated yield in 30 minutes at room temperature compared to 90% over five hours in methanol and 70% over six hours in toluene. A reductive workup is generally required when using MCPBA in order to destroy the remaining oxidizing agent and to suppress explosive hazards. However,



Scheme 1 Attempted Ugi–Smiles couplings of thiouracil

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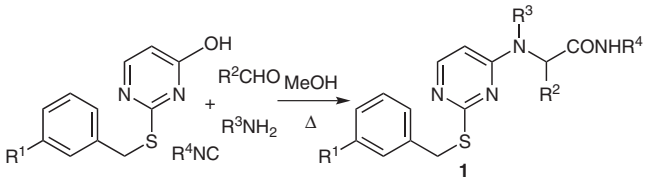
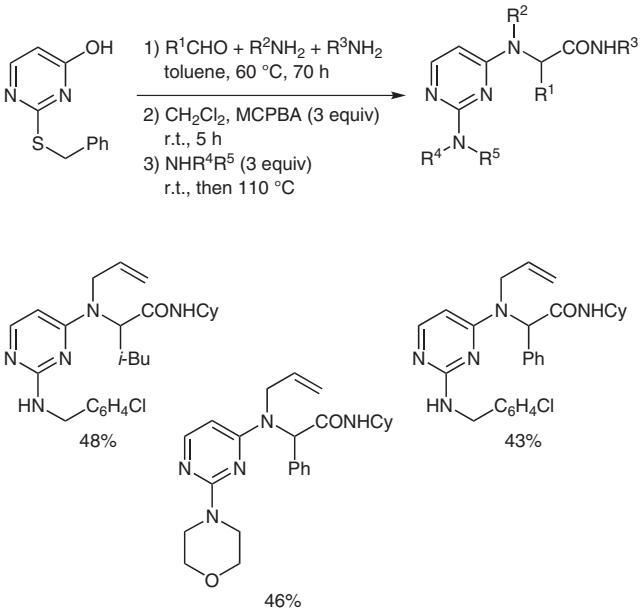
Table 1 Synthesis of Aminopyrimidines **1**



Entry	R^1	R^2	R^3NH_2	R^4NC	Product	Yield (%)
1	H	*i*-Bu	$AllNH_2$	4-ClBnNC	**1a**	91
2	H	*i*-Bu	$AllNH_2$	CyNC	**1b**	86
3	H	H	$AllNH_2$	CyNC	**1c**	72
4	H	H	$AllNH_2$	MeO_2C–NC	**1d**	45
5	H	H	MeO–NH_2	MeO_2C–NC	**1e**	47
6	H	H	MeO–NH_2	MeO_2C–NC	**1f**	51
7	H	Ph	$AllNH_2$	CyNC	**1g**	72
8	F	*i*-Bu	MeO–NH_2	4-ClBnNC	**1h**	72
9	F	Ph	$AllNH_2$	CyNC	**1i**	85
10	F	Ph	MeO–NH_2	4-MeOBnNC	**1j**	77
11	F	*i*-Bu	$AllNH_2$	CyNC	**1k**	87
12	F	*i*-Pr	$AllNH_2$	CyNC	**1l**	98
13	F	Et	$AllNH_2$	*t*-BuNC	**1m**	53

MCPBA oxidizes primary and secondary amines to hydroxylamines at room temperature. Therefore, the amine used as the nucleophile in the last step was added in excess for prior decomposition of the unreacted peroxide. Three equivalents of morpholine were added to the former reaction mixture (in dichloromethane) but the substitution of the sulfone group was sluggish either at room temperature or under heating. However, heating the isolated sulfone with the amine in refluxing toluene gave the expected diaminopyrimidine in satisfactory yields. In order to find a compromise for both steps, the sulfone formation was performed in a 1:1 mixture of toluene and dichloromethane. Under these conditions, the oxidation is slightly longer but still high yielding (over 90%). After the morpholine addition, the mixture was left at room temperature for 20 minutes, and then refluxed with distillation of the dichloromethane to afford the diaminopyridine **2a** in a 74% isolated yield over two steps. A wide range of Ugi–Smiles adducts behave similarly with primary and secondary amines as shown by the results displayed in Table 2.

Searching for an even simpler experimental protocol, a one-pot version was tested starting directly from the *S*-benzylthiouracil and using two different amines in the sequence. For this purpose, the Ugi–Smiles step was performed in toluene, a solvent more suited to the following steps. Before the addition of MCPBA, a small amount of dichloromethane was introduced. Under these conditions, a sequential formation of 2,4-diaminopyrimidines with

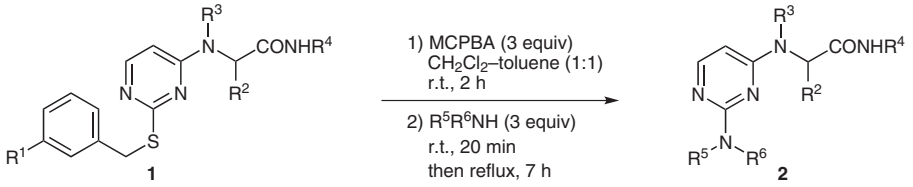


Scheme 2 One-pot synthesis of diaminopyrimidines

five points of diversity could be designed; albeit with moderate yields (Scheme 2).

To conclude, we have disclosed a one-pot multicomponent access to diaminopyrimidines. This methodology opens the way to the preparation of libraries of pyrimidine analogues related to DNA biosynthesis. This synthetic strategy could be further applied to the formation of other derivatives using carbon nucleophiles in place of the amine; we are currently working towards this.

Table 2 Synthesis of Diaminopyrimidines **2**



1 **2**

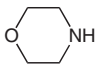
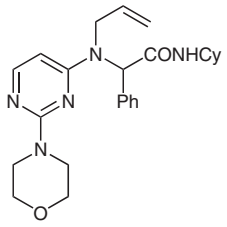
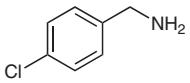
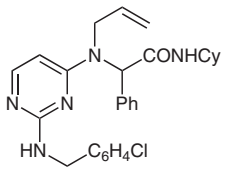
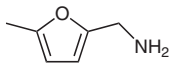
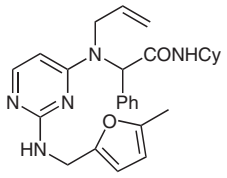
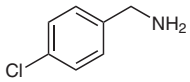
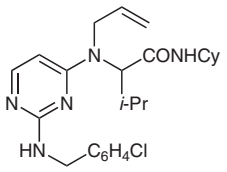
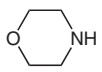
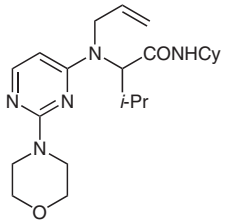
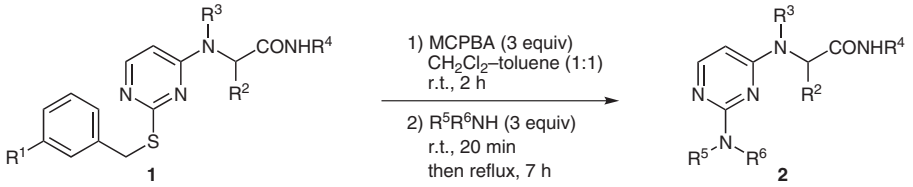
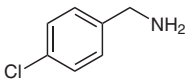
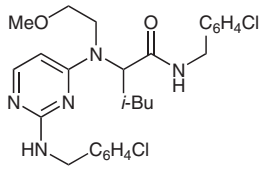
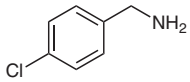
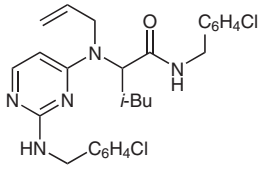
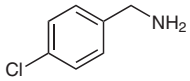
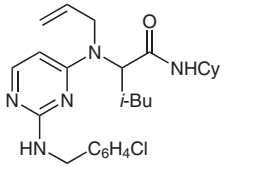
Entry	**1**	R^5R^6NH	Product	Yield (%)
1	**1g**		 **2a**	74
2	**1g**		 **2b**	57
3	**1g**		 **2c**	68
4	**1l**		 **2d**	74
5	**1l**		 **2e**	60

Table 2 Synthesis of Diaminopyrimidines **2** (continued)



1 **2**

Entry	1	R^5R^6NH	Product	Yield (%)
6	**1h**		 **2f**	51
7	**1a**		 **2g**	81
8	**1b**		 **2h**	73

Ugi–Smile Procedure for 1g

To a 1 M solution of the benzaldehyde (1 mmol) in MeOH was successively added allylamine (1 mmol), cyclohexylisocyanide (1 mmol), and 2-(benzylthio)pyrimidin-4-ol (1 mmol) under an inert atmosphere. The resulting mixture was heated at 60 °C for 48 h. After evaporation of the solvent, the mixture was purified by flash chromatography to give **1g** (340 mg, 72% yield) as a yellow solid (mp 166–168 °C). R_f = 0.5 (EtOAc–PE = 60:40). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, 1 H, *J* = 6.1 Hz, H-12), 7.30 (d, 2 H, *J* = 7.1 Hz, H-16), 7.27–7.16 (m, 7 H, H-ar), 7.15–7.10 (m, 1 H, H-ar), 6.30 (br s, 1 H, H-2), 6.10 (d, 1 H, *J* = 6.1 Hz, H-11), 5.79 (d, 1 H, *J* = 7.3 Hz, NH), 5.43–5.31 (m, 1 H, H-8), 4.88 (d, 1 H, *J* = 9.6 Hz, H-9), 4.86 (d, 1 H, *J* = 17.4 Hz, H-9), 4.29 (d, 1 H, *J* = 13.9 Hz, H-14), 4.23 (d, 1 H, *J* = 13.9 Hz, H-14), 3.93–3.80 (m, 2 H, H-7), 3.75–3.64 (m, 1 H, H-cy), 1.84–1.71 (m, 2 H, H-cy), 1.60–1.44 (m, 3 H, H-cy), 1.29–1.15 (m, 2 H, H-cy), 1.06–0.89 (m, 3 H, H-cy). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 170.0 (C-13), 168.9 (C-1), 161.5 (C-10), 155.7 (C-12), 137.9 (C-15), 135.5 (C-3), 133.4 (C-8), 129.6 (C-ar), 128.8 (C-ar), 128.8 (C-ar), 128.5 (C-17), 128.5 (C-6), 127.1 (C-18), 116.9 (C-9), 100.7 (C-11), 62.2 (C-2), 48.7 (C-7), 48.6 (C-cy), 35.2 (C-14), 32.9 (C-cy), 25.5 (C-cy), 24.9, 24.8 (C-cy). HRMS: *m/z* calcd for $C_{28}H_{32}N_4OS$: 472.2297; found: 472.2298. IR (thin film): 3300, 2933, 1653, 1474, 1169 cm^{-1}.

Synthesis of Diaminopyridine 2a

To a 0.1 M solution of Ugi–Smiles adduct **1g** in a CH_2Cl_2–toluene solvent mixture (50:50) was added MCPBA (3.0 equiv, 3 mmol) under argon. The mixture was stirred at r.t. for 2 h, then morpholine (3 equiv) was added. After stirring at r.t. for 20 min, the mixture was heated at 110 °C for 7 h. After evaporation of the solvent and flash chromatography, compound **2a** was obtained as a yellow solid (mp 137–139 °C) in 74% isolated yield (322 mg). R_f = 0.3 (EtOAc–PE = 40:60). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, 1 H, *J* = 6.1 Hz, H-12), 7.28–7.23 (m, 5 H, H-7, H-8, H-9), 6.14 (s, 1 H, H-2), 5.87 (d, 1 H, *J* = 6.1 Hz, H-11), 5.57–5.44 (m, 1 H, H-4), 4.98–4.90 (m, 2 H, H-5), 3.90–3.73 (m, 3 H, H-3, H-cy), 3.69–3.60 (m, 8 H, H-14, H-15), 1.86–1.77 (m, 2 H, H-cy), 1.65–1.48 (m, 3 H, H-cy), 1.36–1.21 (m, 2 H, H-cy), 1.12–0.90 (m, 3 H, H-cy). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 169.4 (C-1), 162.4 (C-10), 160.7 (C-13), 156.0 (C-12), 135.6 (C-6), 133.7 (C-4), 129.6 (C-7), 128.7 (C-8), 128.4 (C-9), 117.1 (C-5), 95.1 (C-11), 66.9 (C-15), 63.8 (C-2), 49.0 (C-3), 48.4 (C-cy), 44.4 (C-14), 33.2, 33.0 (C-cy), 25.5 (C-cy), 24.8, 24.7 (C-cy). HRMS: *m/z* calcd for $C_{25}H_{33}N_5O_2$: 435.2634; found: 435.2629. IR (thin film): 3309, 2932, 2850, 1658, 1239 cm^{-1}.

Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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