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Note

Synthesis of *N*-tetra-*O*-acetyl-β-D-glucopyranosyl-*N*′-(4′,6′-diarylpyrimidin-2′-yl)thioureas

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ABSTRACT

Some 2-amino-4,6-diarylpyrimidines **2** have been prepared from substituted benzylideneacetophenones and guanidine hydrochloride in the presence of alkali by conventional heating in alcoholic medium and microwave heating in solvent-free conditions. *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4′,6′-diarylpyrimidin-2′-yl)thioureas **4** have been synthesized by reaction of per-O-acetylated glucopyranosyl isothiocyanate **1** and substituted 2-amino-4,6-diarylpyrimidines **2**. Two different methods have been used, namely, refluxing in anhydrous dioxane and solvent-free microwave-assisted coupling. The second procedure afforded higher yields in much shorter reaction times. The compounds **2** and **4** were tested for their antibacterial and antifungal activities in vitro against *Staphylococcus epidermidis*, *Enterobacter aerogenes* and *Candida albicans* by disc diffusion method.

The pyrimidine structural motif is a fundamental part of nucleic acids and has been associated with a number of biological activities.[1,2] Aminopyrimidine derivatives have displayed interesting antibacterial, antitumour and HIV-I inhibiting activities.[2] Both pyrimidine and aminopyrimidine moieties occur in commercially available drugs such as the anti-atherosclerotic Aronixil®, the anti-histaminic Thonzylamine®, the anti-anxiolytic Buspirone®, and in other medicinally relevant compounds as well.[3]

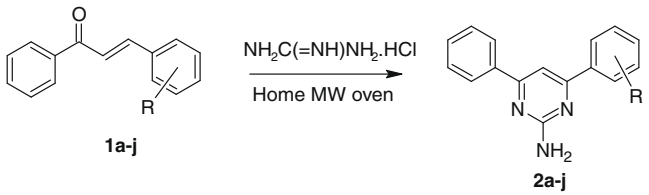
In an other hand, sugar isothiocyanates are among the most versatile synthetic intermediates in carbohydrate chemistry.[4] They play a pivotal role in the preparation of a broad series of functional groups such as amide, isonitrile, carbodiimide and *N*-thiocarbonyl derivatives allowing, simultaneously, the covalent coupling of a quite unrestricted variety of structures to the saccharide part.[5] Moreover, isothiocyanates are important reagents in heterocyclic chemistry, which may be exploited in the synthesis of nucleosides and other *N*-glycosyl structures.[6,7]

One of the most popular and interesting approach in the context of 'green chemistry' is employing microwave energy for conducting chemical transformations, which allows a higher speed of heating, shorter reaction times, is compatible with solvent-free conditions and very often lead to higher selectivities.[8–11]

Thioureas and derivatives are biologically important compounds and are useful fungicides, herbicides[12] and antibacterial agents.[13] They have also found use in organocatalysis.[14,15] Thioureas have been synthesized by the reaction of primary and secondary amines with thiophosgene and isothiocyanates.[4,5,16–19]

Glucopyranosyl thioureas containing heterocycles (such as thiazole, benzothiazole[20] and thiadiazole[21]) were synthesized using conventional heating method. We report herein the preparation of some peracetylated glucopyranosyl thioureas containing the pyrimidine nucleus both under classical heating and solvent-free microwave irradiation conditions.

2-Aminopyrimidines were prepared previously by the reaction of substituted benzylideneacetophenones[22] with guanidine under reflux in ethanol.[3,23] For the purpose of this work, we have prepared new 2-amino-4,6-diarylpyrimidines **2a–j** by ring-closure condensation of substituted benzylideneacetophenones and guanidine hydrochloride in the presence of sodium hydroxide under microwave-assisted conditions and compare the results with the classical procedures (Scheme 1 and Table 1). *N*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4′,6′-diarylpyrimidin-2′-yl)thioureas **4a–j** were subsequently synthesized by the condensation of tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate and the corresponding 2-aminopyrimidines **2a–j**. We performed



1a-j and **2a-j:** R= H (**a**), *p*-F (**b**), *p*-Cl (**c**), *m*-Cl (**d**), *p*-Br (**e**), *p*-Me (**f**), *p*-iPr (**g**), *o*-OH (**h**), *p*-OMe (**i**), *m*-OMe (**j**)

Scheme 1. Synthetic pathway for 2-amino-4,6-diarylpyrimidines (**2a–j**).

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Table 1
2-Amino-4,6-diarylpyrimidines (**2a–j**)

Entry	R	Yield (%)		Microwave irradiation time (min)
		A	B	
2a	H	72	89	1
2b	*p*-F	—	86	2
2c	*p*-Cl	76	85	2
2d	*m*-Cl	75	83	2
2e	*p*-Br	71	80	2
2f	*p*-Me	—	85	1
2g	*p*-iPr	—	85	1
2h	*o*-OH	70	85	1
2i	*p*-OMe	73	80	1
2j	*m*-OMe	—	83	1

A: by refluxing; B: under solvent-free condition in modified domestic microwave oven.

this reaction by using two methods: by refluxing in anhydrous dioxane for 8–10 h and by irradiation in a domestic microwave oven for a few minutes in solvent-free condition (Scheme 2 and Table 2). The last method accelerated the reactions and gave higher yields.

We realized that 2-amino-4,6-diphenylpyrimidines with electron-withdrawing group (such NO_2, except halogens) cannot be formed; we tried to perform the reaction of benzylideneacetophenones having nitro-group with guanidine, but the reactions were unsuccessful.

In the refluxing cases, 2-aminopyrimidines **2** and peracetylated glucopyranosyl isothiocyanate **3** were dissolved in anhydrous dioxane. After the reaction, the solvent was distilled off, and the resultant sticky residue was triturated with ethanol to afford thioureas **4a–j** that were recrystallized with 1:1 ethanol–toluene. Using MW irradiation, a mixture of 2-aminopyrimidine and peracetylated glucopyranosyl isothiocyanate was grinded together and irradiated in domestic MW oven (750 W). After first several minutes of microwave irradiation (MWI), the reaction mixture became pastry. The reaction yields increased using MW oven from 60–68% to 68–80%. All the obtained thioureas were soluble in common organic solvents (such as ethanol, methanol, toluene, benzene and DMF). Their structures have been confirmed by spectral (IR, NMR and MS) data.

The IR spectra showed characteristic bands at 3522–3410 (ν_{NH}), 1754–1748 ($\nu_{C=O}$), 1594, 1578, 1526, 1495 ($\nu_{C=C}$), 1364–1362 ($\nu_{C=S}$), 1232–1222 and 1070–1041 cm^{-1} (ν_{COC}). The ^1H NMR spectra showed resonance signals which are specific for protons in thiourea-NH groups at δ = 11.16–12.04 ppm. Proton H-1 has its chemical shift at δ = 6.19–6.21 ppm (in triplet) with couple constants J_{12} = 9.0–9.5 Hz. The resonance signal of H-2 appeared as a triplet at δ = 5.02–5.06 ppm with J_{12} = 9.0–9.5 Hz. The coupling constant values for the pyranose ring agreed with *trans*-axial H–H disposition and a β-anomeric configuration. The ^{13}C NMR spectra showed signals for the thiocarbonyl group at δ = 181.3–181.4 ppm.[24] The mass spectra showed M^+ peak at the respective molecular weights of the compounds. Some of them were subjected to HREIMS to obtain respective molecular weights.

Compounds **2** and **4** were screened for their antibacterial and antifungal activities in vitro against *Staphylococcus epidermidis*, *Enterobacter aerogenes* and *Candida albicans* by the disc diffusion method. All amines **2** have significant biological activities against *E. aerogenes*, *S. epidermidis* and *C. albicans*. Compounds **2a–j** showed highest antibacterial activity against *S. Epidermidis* (Table 3). Almost all compounds **4** have remarkable biological activity, except compound **4b** which exhibited no antifungal activity against *E. aerogenes* and compound **4g** against *C. albicans*. Especially, the antibacterial activity against *S. epidermidis* was proved significantly in these compounds (Table 4).

In summary, the present new method of formation of 2-amino-4,6-diarylpyrimidines **2** and *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4′,6′-diarylpyrimidin-2′-yl)thioureas **4** under microwave irradiation offers several advantages: faster reaction rates (1–2 min for **2** and 5–7 min for **4**) and high yields (80–89% for **2** and 72–83% for **4**), while the conventional method of formation of these thioureas involves longer reaction times (8–10 h and 60–68% for **4**).

1. Experimental

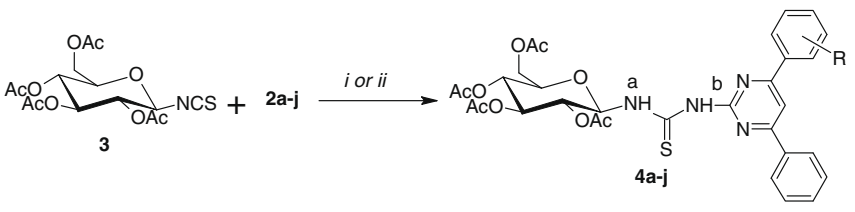
1.1. General methods

Melting points were determined on a STUART SMP3 apparatus (BIBBY STERILIN-UK). The FTIR-spectra were recorded on a Magna

Table 2
N-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4,6-diarylpyrimidin-2-yl)thioureas (**4a–j**)

Entry	R	Yield[a] (%)	Refluxing time (h)	Yield[b] (%)	Microwave irradiation time (min)
4a	H	60	8	75	5
4b	*p*-F	—	—	87	5
4c	*p*-Cl	68	9	76	6
4d	*m*-Cl	67	10	72	7
4e	*p*-Br	66	9	76	5
4f	*p*-Me	60	8	80	7
4g	*p*-iPr	68	8	79	6
4h	*o*-OH	60	9	80	6
4i	*p*-OMe	68	8	77	6
4j	*m*-OMe	—	—	83	6

[a] By refluxing.
[b] By using microwave oven.



2a-j and **4a-j:** R= H (**a**), *p*-F (**b**), *p*-Cl (**c**), *m*-Cl (**d**), *p*-Br (**e**), *p*-Me (**f**), *p*-iPr (**g**), *o*-OH (**h**), *p*-OMe (**i**), *m*-OMe (**j**)

i: anhydrous dioxane, reflux 8-10 h
ii: solvent-free, MW irradiation 5-7 min

Scheme 2. Synthetic pathway for *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-*N*′-(4,6-diarylpyrimidin-2-yl)thioureas (**4a–j**).