Reaction of 1-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-(Pyridin-3-yl)pyrimidin-2-yl) urea with Methyl Iodide and X-ray Crystallographic Structure of Its Derivative

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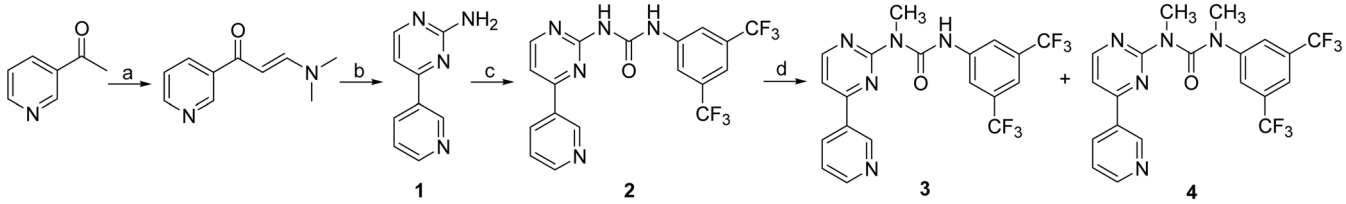
The 2-aminopyrimidine moiety is a well-known structural subunit in a large number of both natural products[1] and synthetic compounds with important biological activities. 2-Aminopyrimidine derivatives substituted at *N*- or 4-positions are of particular importance since they show versatile biological and pharmacological activities. These activities include antifungal,[2] pesticidal activities,[3] an enzyme inhibitory activity against a number of kinases, such as Bcr-Abl kinase,[4] rho-associated protein kinase[5] and glycogen synthase kinase (GSK3).[6] They are active also as inhibitors for *N*-type Ca-channels,[7] endotheline receptors,[8] human methionine aminopeptidase,[9] and as potential drug candidates for treatment of prion diseases.[10] A well-known example of such substituted 2-aminopyrimidines is imatinib, a highly selective Bcr-Abl kinase inhibitor, which has been used successfully for treatment of chronic myeloid leukemia. Furthermore 4-pyridinylpyrimidines are widely used as ligands for metal complexation.[11]

During the course of our work for the synthesis of inhibitors for b-RAF kinase enzyme which plays a key role in tumorigenesis and cancer progression,[12] it is important to synthesize the dimethylated urea **4** and the monomethylated ureas in order to investigate the mode of action of the synthesized urea derivatives. Herein, we describe a detailed synthesis for pyrimidine urea derivatives and their structure elucidation by FT-NMR and X-ray diffractometer.

The reaction of 3-acetylpyridine with *N*,*N*-dimethylformamide dimethylacetal to yield 3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one is reported in a variety of solvents such as toluene[13] and DMF.[14] However, it was most convenient when applied without the use of any solvent, by direct fusion of 3-acetylpyridine with 1.4 equivalents of *N*,*N*-dimethylformamide dimethylacetal, where it proceeded smoothly in 4 hours and in a good yield of 82% (Scheme 1).[15] By refluxing 3-(dimethylamino)-1-(pyridin-3-yl)prop-2-en-1-one with guanidine hydrochloride in absolute ethanol and in the presence of sodium ethoxide, 4-(pyridin-3-yl)-pyrimidin-2-amine (**1**) was obtained in a good yield of 73%. The preparation of urea derivatives from the corresponding amines using isocyanates is reported in a variety of solvents such as dioxane,[16] THF[17] and pyridine.[18] In our case, pyridine was used as a solvent, and the reaction of 4-(pyridin-3-yl)pyrimidin-2-amine (**1**) with 3,5-bis(trifluoromethyl)phenyl isocyanate gave 1-(3,5-bis(trifluoromethyl)phenyl)-3-(4-(pyridin-3-yl)pyrimidin-2-yl)urea (**2**) in good yield of 66%. The urea derivative **2** was *N*-methylated through the reaction of excess (10 equivalents) of methyl iodide in anhydrous THF in the presence of sodium hydride at room temperature under nitrogen atmosphere to obtain two compounds in yield of 22% and 35%, while the unreacted starting compound **2** was recovered in 40%.

By investigating two resulted products, one of them was found to be the dimethylated urea **4** by FT-NMR and FT-IR, while another one was found to be the monomethylated urea **3** by X-ray diffractometer. By repeating the methylation reaction for several times, the same products were obtained in every time, and the only above-mentioned monomethylated derivative **3** was obtained, while another monomethyl regio-isomer, 3-(3,5-bis(trifluoromethyl)phenyl)-3-methyl-1-(4-(pyridin-3-yl)pyrimidin-2-yl)urea could not be obtained. Although we do not precisely know the reason why 3-(3,5-bis(trifluoromethyl)phenyl)-3-methyl-1-(4-(pyridin-3-yl)pyrimidin-2-yl)urea could not be obtained, this might be probably due to the higher stability of *N1*-anion in compound **2** compared to the *N3*-anion, since *N1*-anion is stabilized more by the resonating structure of the pyrimidine



Scheme 1. *Reaction conditions*: a) *N*,*N*-dimethylformamide dimethylacetal, fusion, 4 h, 82% yield, b) guanidine HCl, NaOEt, abs. EtOH, reflux, 6 h, 73% yield, c) 3,5-bis(trifluoromethyl)phenyl isocyanate, pyridine, reflux, 24 h, 66% yield, d) CH_3I, NaH, THF, rt, 24 h, 22% for compound **3** and 35% yield of compound **4**.

Table 1. Crystal data and structural refinement of compound **3**[22]

Diffractometer	Rigaku RAXIS-RAPID	Radiation	MoK$_\alpha$(λ = 0.71075 Å) Graphite monochromated
Formula	$C_{19}H_{13}F_6N_5O$	Detector position	127.40 mm
Formula weight	441.33	Pixel size	0.100 mm
Crystal color, habit	yellow, platelet	*a* (Å)	14.739(1)
		b (Å)	8.5265(6)
		c (Å)	15.863(1)
		β (^{o})	107.291 (2)
		V (Å^3)	1903.4(2)
Crystal dimensions	0.40 × 0.30 × 0.05 mm	Space group	$P2_1/n$ (#14)
Crystal system	monoclinic	Z value	4
Goodness of fit indicator	1.070	Dcalc	1.540 g/cm^3
μ(MoKα)	1.40 cm^{-1}	F(000)	896.00
Final *R*1, *wR*2[I > 2.0σ(I)]	0.105, 0.354	Reflection collected	29876

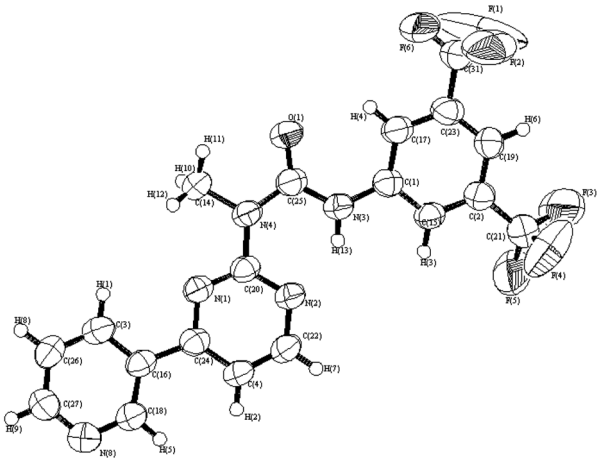


Figure 1. Molecular structure of compound **3**.

moiety. The highly electron withdrawing effect exerted by the pyrimidine ring nitrogens could also explain for the higher acidity of *N1*-proton relative to the other *N3*-proton.

A yellow platelet crystal of compound **3** having approximate dimensions of 0.40 × 0.30 × 0.05 mm was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-K radiation. The data were collected at a temperature of 25 ± 1 ^{o}C to a maximum 2q value of 55.0^o. The structure was solved by direct methods and expanded using Fourier techniques.[19] All calculations were performed using the crystal structure crystallographic software package[20] except for refinement, which was performed using SHELXL-97 (Table 1).[21]

In summary, we prepared some pyrimidine urea derivatives in good yields and in 4 steps and elucidated the structure of the monomethylated urea **3** by X-ray diffractometer. The studies on anticancer activities and mode of action of these synthesized compounds are currently underway.

Experimental Section

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-(pyridin-3-yl)-pyrimidin-2-yl)urea (2). To a solution of 4-(pyridin-3-yl)pyrimidin-2-amine (**1**) (1.0 g, 5.81 mmol) in anhydrous pyridine (30 mL) was added 3,5-bis(trifluoromethyl)phenyl isocyanate (1.0 mL, 5.81 mmol) and the resulted mixture was refluxed for 24 hr under N_2 atmosphere. The reaction mixture was evaporated under reduced pressure and the residue was suspended in methanol, filtered by suction filtration, and dried under vacuum to yield the pure product. 1.64 g (66%); mp 248-249 ^{o}C (methanol); IR (KBr): 3436, 1717, 1577, 1448, 1285, 803 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.99 (s, 1H), 10.62 (s, 1H), 9.37 (s, 1H), 8.77-8.84 (m, 2H), 8.55 (d, 1H, *J* = 7.5 Hz), 8.33 (s, 2H), 7.84 (d, 1H, *J* = 5.2 Hz), 7.75 (s, 1H), 7.58-7.62 (m, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 162.94, 159.38, 158.28, 152.63, 152.22, 148.95, 141.15, 135.22, 131.77, 131.50, 131.06, 125.54, 124.41, 119.72, 111.83.

Procedure for *N*-methylation: preparation of compounds 3 and 4. To a solution of **2** (0.2 g, 0.47 mmol) in anhydrous THF (10 mL) was added sodium hydride (56 mg, 1.4 mmol, 60% dispersion in mineral oil) at 0 ^{o}C and stirred under N_2 atmosphere at room temperature for 1 hr. To the reaction mixture was added methyl iodide (0.3 mL, 4.68 mmol) and stirred overnight at room temperature. Excess of sodium sulfate decahydrate was added to the reaction mixture while stirring is maintained for 30 min and filtered by sintered glass crucible. The filtrate was dried over anhydrous $MgSO_4$, evaporated under reduced pressure and purified by column chromatography (silica gel, ethylacetate:hexane = 4:1) to obtain the pure products **3** and **4**.

3-(3,5-Bis(trifluoromethyl)phenyl)-1-methyl-1-(4-(pyridin-3-yl)pyrimidin-2-yl)urea (3). It was obtained as a white powder. 46 mg (22%); mp 194-195 ^{o}C (methanol); IR (KBr) 3437, 1687, 1580, 1437, 1280, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.14 (s, 1H), 9.33 (s, 1H), 8.84 (s, 1H), 8.76, (d, 1H, *J* = 5.3 Hz), 8.43-8.46 (m, 1H) , 8.12 (s, 2H), 7.53-7.58 (m, 2H), 7.49 (d, 1H, *J* = 5.3 Hz), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.07, 159.89, 157.36, 153.29, 152.16, 148.41, 140.35, 134.89, 132.46, 132.01, 125.08, 124.04, 119.62, 116.58, 110.21, 32.22.

3-(3,5-Bis(trifluoromethyl)phenyl)-1,3-dimethyl-1-(4-

(pyridin-3-yl)pyrimidin-2-yl)urea (4). 75 mg (35%); mp 225-226 °C (THF); IR (KBr) 1677, 1573, 1277, 1142, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.18 (s, 1H), 8.74 (s, 1H), 8.40 (d, J = 5.15 Hz, 1H), 8.26 (d, J = 7.95 Hz, 1H), 7.56 (s, 2H), 7.47-7.41 (m, 2H), 7.12 (d, J = 5.15 Hz, 1H), 3.50 (s, 3H), 3.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.09, 160.39, 158.75, 158.28, 151.81, 148.27, 145.38, 134.30, 132.09, 131.64, 124.69, 123.72, 120.87, 118.94, 109.42, 37.90, 34.83.

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