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Concise and highly efficient approach to three key pyrimidine precursors for rosuvastatin synthesis

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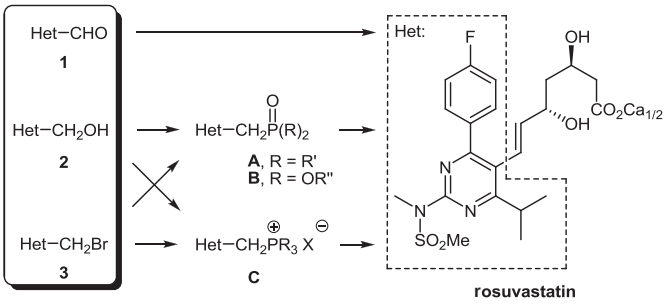
ABSTRACT

We report the synthesis of 5-formyl-, 5-(hydroxymethyl)-, and 5-(bromomethyl) substituted *N*-[4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl]-*N*-methylmethanesulfonamide. The presented synthetic approach is based on highly efficient three step preparation of functionalized 5-methylpyrimidine. The methyl group is selectively brominated by NBS with irradiation into the bromomethyl derivative, which is then transformed into the hydroxymethyl or formyl groups in nearly quantitative yields. This approach is superior to the existing methodologies for the preparation of the key pyrimidine precursors used in the synthesis of rosuvastatin since no metal catalysis and no cryogenic reaction conditions are involved.

1. Introduction

The synthesis of rosuvastatin has been the subject of intense research in recent years.[1,2] This compound is one of the most important antilipidemic[3] agents from both therapeutic[4] and marketing[5] point of view. The structure of rosuvastatin consists of a functionalized pyrimidine ring attached to a chiral dihydroxy heptenoic acid residue (Scheme 1). Several strategies have been conceived for its synthesis. Most of them include different Wittig or Horner–Wadsworth–Emmons reactions between aldehyde **1**[1,6] or phosphorous derivatized precursors **A**–**C**,[7–10] prepared from alcohol **2** or bromide **3**, with the appropriately functionalized chiral chain reaction partners.[2] Having recently developed a highly efficient preparation of one of these functionalized chiral chain residues, (2*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-6-oxotetrahydro-2*H*-pyran-2-carbaldehyde,[11] and demonstrated its application in the construction of rosuvastatin,[12] we focused on the synthesis of the pyrimidine substrates **1**–**3**. Although a great number of procedures are reported in the literature for the generation of compounds **1**–**3**,[2] they suffer from reproducibility problems on a large scale (pilot or industrial scale),[1] the application of hazardous DIBAL-H at cryogenic conditions,[1,8] the use of toxic CO in the presence of high loads of transition metal catalysts and expensive ligands,[13] the application of hazardous tin salts[7a] as well as other corrosive and environmentally unsustainable reagents, such as cyanogen chloride,[7a] copper salts, concentrated HNO_3,[7b] concentrated HBr,[9] and PBr_3,[10] to name just a few.



Scheme 1. Application of three key pyrimidine precursors **1**–**3** for the synthesis of rosuvastatin.

2. Results and discussion

2.1. Synthetic background and our plan

Several methods are reported for the synthesis of aldehyde **1**, alcohol **2**, and bromide **3**. Briefly, Knovenagel, Claisen or other Aldol-type condensations at *p*-fluorophenyl carbonyl derivatives **D**

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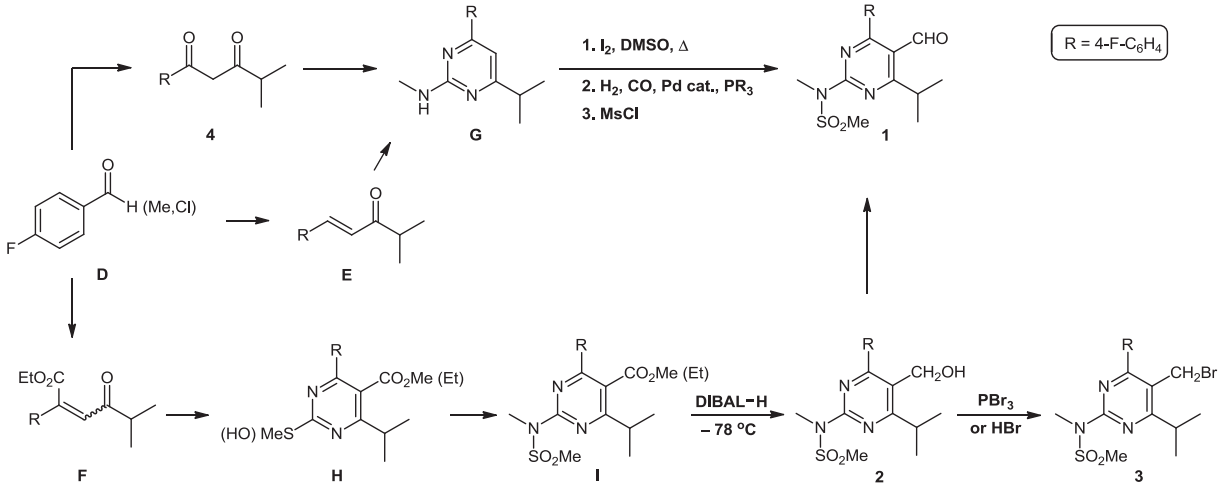
were applied to produce diketone **4**[13,14] or olefins **E**[13] and **F**[1] (Scheme 2). Upon cyclization with the appropriate (thio)urea, or guanidine derivatives these afforded substituted pyrimidines **G** and **H**. Alternatively, pyrimidines **H** and **I** can be obtained from **D** with methyl 4-methyl-3-oxopentanoate either by tin-catalyzed reaction and the use of cyanogen chloride[7a] or by copper(I) catalyzed three component cyclization.[7b] Unfortunately, cumbersome functional group interconversions, which are extremely undesired in scale-up and industrial processes are required to reach the final products **1** and **2**. These include iodination of C-5 unsubstituted pyrimidine derivative **G** followed by formylation with CO/H_2 at 50 bar, 100 °C, in the presence of palladium catalysts,[13] or by cryogenic DIBAL-H reduction of the ester group at **I** into alcohol **2**.[1,8] Bromide **3** is obtained only from alcohol **2** by industrially inconvenient bromination with PBr_3 or concentrated HBr.[9,10]

the undesired late C-5 functionalization of the pyrimidine ring (**G**→**1**, Scheme 2), DIBAL-H reduction of the ester group (**I**→**2**, Scheme 2) as well as toxic and corrosive bromination (**2**→**3**, Scheme 2).

2.2. The synthesis of the pyrimidine ring

α-Methyl-β-diketone **5** was easily prepared[15] from β-diketone **4**[13,14] by methylation with methyl iodide in K_2CO_3/acetone suspension in 96% yield of the isolated product.

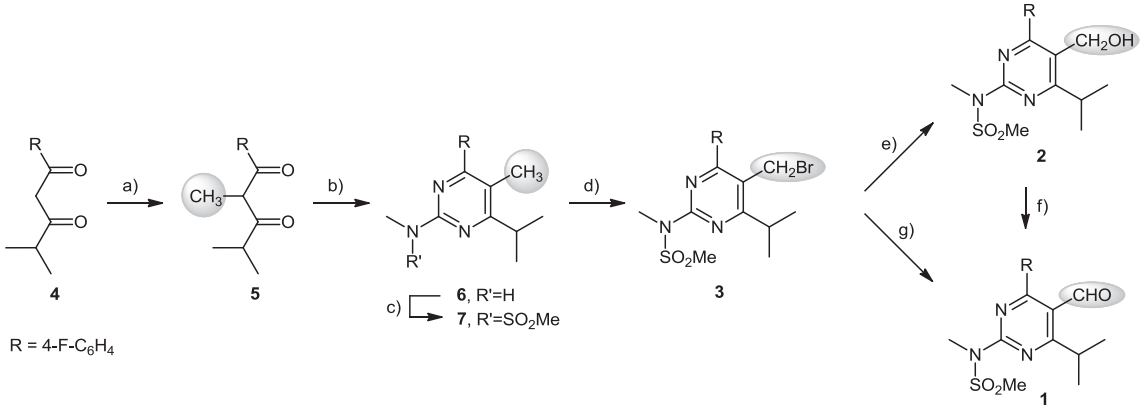
Cyclocondensation of β-diketones with substituted guanidine or guanidinium hydrochloride derivatives is known to provide pyrimidines in moderate to high yields.[16] It has been recently demonstrated that the condensation of compound **4** with urea provides 2-hydroxypyrimidine in moderate 64% yield.[17] More basic guani-



Scheme 2. An overview of the previously reported approaches to generate aldehyde **1**, alcohol **2**, and bromide **3**.

Our synthetic plan toward pyrimidine derivatives **1**–**3** is shown in Scheme 3. It starts with the introduction of α-methyl group at β-diketone **4** into α-methyl-β-diketone **5**, which should after condensation with *N*-methyl guanidine and mesylation of exocyclic amino moiety afford 5-methylpyrimidine derivative **7**. Selective benzylic bromination of **7** should afford bromide **3**, which should then easily be transformed into alcohol **2** and/or aldehyde **1**. In contrast to the chemistry shown in Scheme 2, this approach avoids

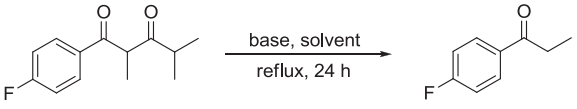
dine derivatives afforded 2-aminopyrimidines also in moderate 51–65% yield.[13,16a] One of the major problems of this method is degradation of starting β-diketone via a retro-Claisen reaction,[18] most commonly in the presence of water and alcohols. This side reaction is mediated by base additives, required to freebase guanidinium hydrochloride or even with guanidine alone. Unfortunately, in comparison to α-unsubstituted analogues, the α-alkyl-β-diketones are even more susceptible to the retro-Claisen reaction.[18]



Scheme 3. Our approach to pyrimidine derivatives **1**–**3**. Reaction conditions: (a) MeI, K_2CO_3, acetone, rt, 48 h, 96%; (b) *N*-methyl guanidinium hydrochloride, Cs_2CO_3, MeTHF, 70 °C, 24 h, 92%; (c) MsCl, Et_3N, CH_2Cl_2, −5 °C, 11 h, 91%; (d) NBS, irradiation, CH_3CN, rt, 16 h, 80%; (e) H_2O, THF, reflux, 6 h, 100%; (f) Ac_2O, DMSO, 85 °C, 17 h, 31%; (g) $NaHCO_3$, NaI, DMSO, rt, 68 h then Ac_2O, DMSO, 70 °C, 7 h, 94%.

Before attempting the pyrimidine **6** formation we decided to screen for an optimal solvent/base combination that would preserve the starting α-methyl-β-diketone **5** from retro-Claisen decomposition during the cyclocondensation reaction with *N*-methyl guanidine. Unless a drying agent is introduced into the reaction mixture, the presence of water cannot be avoided and thus it was essential to use it as a co-solvent in these screening experiments. As demonstrated in Table 1 compound **5** was subjected to different reaction conditions and its stability in terms of resistance to *p*-fluoropropiophenone (**8**) formation was monitored by ^{1}H NMR spectroscopy.

Table 1
Monitoring retro-Claisen reaction of **5**[a]



5 **8**

Entry	Base (equiv)	Solvent	**5**/**8** ratio (%)[b]
1	NaOH (0.1)	90% THF in water	100:0
2	NaOH (1.0)	90% THF in water	100:0
3	MeONa (0.1)	MeOH	0:100
4	Sodium acetate (1.0)	90% THF in water	100:0
5	NaH (1.0)	Dry THF	92:8
6	Diethylamine (1.0)	90% THF in water	100:0
7	Benzylamine (1.0)	90% THF in water	100:0
8	Hünig's base (1.0)	90% THF in water	100:0
9	TMG[c] (1.0)	Dry THF	100:0
10	TMG[c] (1.0)	90% THF in water	59:41
11	Cs_2CO_3 (1.0)	THF[d]	92:8
12	Cs_2CO_3 (1.0)	90% THF in water	81:19

[a] Experimental procedure: 1.0 mmol of **5** and base in 10 mL of the solvent was stirred at reflux temperature for 24 h and analyzed by ^{1}H NMR.
[b] Determined by ^{1}H NMR integration.
[c] 1,1,3,3-Tetramethylguanidine.
[d] Water (1.0 mmol) was added.

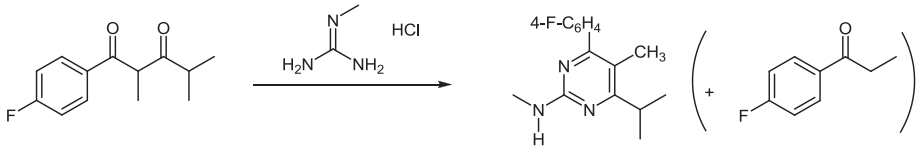
Out of several different organic and inorganic bases, MeONa in methanol proved to be the most detrimental to compound **5**, leading to complete decomposition into propiophenone **8** (Table 1, entry 3). Some decomposition was also observed with Cs_2CO_3 in aq THF (entries 11 and 12) and NaH in dry THF (entry 5). Compound **5** was stable in aq THF solution in the presence of NaOH and sodium acetate (entries 1, 2, and 4) as well as organic bases, such as diethylamine, benzylamine, and *N*,*N*-diisopropylethylamine (Hünig's base) (entries 6–8). Whereas no formation of propiophenone **8** could be detected with 1,1,3,3-tetramethylguanidine in dry THF (entry 9), this was no longer the case if water was used as a co-solvent (entry 10).

Next, we examined the cyclization of α-methyl-β-diketone **5** into pyrimidine **6** (Table 2). Based on the above results with 1,1,3,3-tetramethylguanidine and pK_a considerations, *N*-methyl guanidine is expected to mediate the undesired retro-Claisen reaction of α-methyl-β-diketone **5**. This prompted us to test *N*-methyl guanidinium hydrochloride in combination with different bases. The former is relatively insoluble in organic solvents and providing the base/solvent system is appropriate to allow slow dosing of *N*-methyl guanidine into the reaction mixture, this should suppress the undesired formation of propiophenone **8**.

The experiments are presented in Table 2. In contrast to the results from Table 1, entries 1 and 2, NaOH gave very poor results, largely leading to the formation of **8** (Table 2, entries 1–3). Sodium or potassium alkoxides in the corresponding alcohol gave unsatisfactory results (entries 4–8) as did NaH in different solvents, such as DMSO, DMF, THF, and 2-methyltetrahydrofuran (MeTHF) (entries 9–12). Interestingly, Hünig's base and DBU resulted in no or negligible reaction (entries 13 and 14). Finally we examined carbonate bases in apolar solvent, MeTHF (entries 15–17) and identified Cs_2CO_3 as the base of choice.

In a preparative experiment, employing Cs_2CO_3 in the cyclization of α-methyl-β-diketone **5** with *N*-methyl guanidinium hydrochloride in MeTHF as a solvent afforded the desired pyrimidine **6** in 92% isolated yield.

Table 2
Cyclization of α-methyl-β-diketone 5 with *N*-methyl guanidinium hydrochloride[a]



5 **6** **8**

Entry	Base (equiv)	Solvent	Temperature (°C)	Time (h)	**6**/**8** ratio[b]	Conversion[b]
1	NaOH (1.0)	MeOH/H_2O (9:1)	25	1	4:96	57
2	NaOH (1.0)	MeOH/H_2O (9:1)	25	24	3:97	>99
3	NaOH (2.0)	THF/H_2O (8:2)	25	24	3:97	>99
4	NaOMe (1.0)	MeOH	70	24	33:67	>99
5	EtONa (1.0)	EtOH	70	24	55:45	>99
6	^{i}PrONa (1.0)	^{i}PrOH	70	24	81:19	>99
7	^{t}BuOK (1.0)	^{t}BuOH	70	24	78:22	>99
8	^{t}BuONa (1.0)	^{t}BuOH	70	24	53:47	>99
9	NaH (1.0)	DMSO	70	24	76:24	96
10	NaH (1.0)	DMF	70	24	82:18	92
11	NaH (1.0)	THF	70	24	84:16	>99
12	NaH (1.0)	MeTHF	70	24	79:21	96
13	Hünig's base (2.0)	MeTHF	70	24	—	<1
14	DBU (2.0)	MeTHF	70	24	78:22	5
15	Na_2CO_3 (2.0)	MeTHF	70	24	73:27	6
16	K_2CO_3 (2.0)	MeTHF	70	24	90:10	58
17	Cs_2CO_3 (2.0)	MeTHF	70	24	94:6	99

[a] Reactions performed by batch addition of all reagents: **5** (1.0 g), *N*-methyl guanidinium hydrochloride (1.0 equiv), the base and the solvent (10 mL).
[b] Determined by ^{1}H NMR integration.

2.3. Functional-groups interconversion at the pyrimidine ring

Having the pyrimidine **6** in hand, the C-2 methylamine group was easily mesylated with methanesulfonyl chloride in 91% isolated yield of **7**.

Bromide **3** was previously prepared by the action of HBr[9a] or PBr_3[10] at alcohol **2**. In our case, according to Scheme 3, bromide **3** should be accessed by selective benzylic bromination of the C-5 methyl group at compound **7**.[19] For this we selected *N*-bromosuccinimide (NBS) under irradiation conditions. The initial reactions were conducted using low pressure Hg-lamp (P=4 W, λ=predominantly 254 nm). Applying 1.1 molar equivalents of NBS and solvents, such as acetonitrile, acetone, dichloromethane or ethyl acetate, within 48 h the desired bromide **3** was generated but quantitative conversion of starting **7** could not be achieved. The complete consumption of **7** was achieved in 68 h by using 2.1 molar equivalents of NBS in acetonitrile. The bromide **3** was isolated in up to 74% yield from the reaction mixture by simple precipitation with water, followed by methanol/water wash of the filter cake. Reaction time was significantly shortened to 16 h by applying medium pressure Hg-lamp (P=150 W, λ=predominantly >300 nm) with the bromide **3** isolated from the reaction in up to 80% yield.[20]

Whereas bromide **3** is suitable for the preparation of the corresponding phosphine oxides **A** phosphonate esters **B**, and phosphonium salts **C**, these intermediates have also been obtained from alcohol **2** (Scheme 1). We were delighted to find out that bromide **3** can be quantitatively transformed into alcohol **2** by refluxing in water/THF mixture for 6 h.

For the preparation of aldehyde **1** we first attempted the Swern-type oxidation of alcohol **2** using DMSO as a solvent/reactant and Ac_2O as a hydroxyl group activator. A complex reaction mixture was obtained, with aldehyde **1** isolated in moderate 31% yield. Alternatively, Kornblum oxidation[21] of bromide **3** in alkaline DMSO resulted in the formation of aldehyde **1** with alcohol **2** being the major side product. The latter was without isolation converted into aldehyde **1** by simple addition of acetic anhydride to the reaction mixture (the Swern oxidation). This combined Kornblum/Swern-type oxidation resulted in the formation of pure aldehyde **1** in excellent 94% isolated yield.

3. Conclusion

We report a new, simple, and highly efficient protocol for the synthesis of 5-bromomethyl, 5-hydroxymethyl, and 5-formyl substituted heteroaromatic precursors of rosuvastatin. Our approach is based on incorporation of 5-methyl substituent to the pyrimidine ring in an early phase of the synthesis, at the acyclic β-diketone precursor. Its cyclocondensation with *N*-methyl guanidine under controlled reaction conditions and efficient transformation of the 5-methyl group into bromomethyl, hydroxymethyl, and formyl functionalities makes this protocol superior to the existing methodologies.

4. Experimental section

4.1. General

Reagents, *p*-fluoropropiophenone (**8**) and solvents were used as purchased. NMR spectra were recorded at 298 K on a Bruker Avance III 500 and Varian VNMRS 400 spectrometers operating at 500 MHz (^{1}H), 125 MHz (^{13}C) and 470 MHz (^{19}F), and 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively. Proton and carbon spectra were referenced to TMS as internal standard or residual solvent signals. Chemical shifts are given on the δ scale (ppm). Coupling constants (J) are given in hertz. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), sep (septet), m (multiplet), or br (broadened). High-resolution mass spectra were obtained with Agilent 6224 Accurate Mass TOF LC/MS system. Infrared spectra were recorded on a Thermo Nicolet Nexus spectrometer or BIORAD Excalibur Series spectrophotometer using samples in potassium bromide disks. Melting points were determined on Mettler Toledo DSC apparatus 822^e (heating rate 10 °C/min). For flash chromatography, Fluka Silica gel 60, 220–440 mesh was used. Photochemical reactions were conducted in an immersion-type reactor consisting of reactor body fabricated of borosilicate glass with inserted double-walled borosilicate immersion well. A low pressure Hg-lamp (P=4 W, λ=predominantly 254 nm) or medium pressure Hg-lamp (P=150 W, λ=predominantly >300 nm) was inserted into vertically arranged double-walled, water cooled immersion well.

4.2. Preparation of 1-(4-fluorophenyl)-2,4-dimethylpentane-1,3-dione (5)

A mixture of 1-(4-fluorophenyl)-4-methylpentane-1,3-dione (**4**,[13,14] 50.00 g, 0.24 mol), K_2CO_3 (33.20 g, 0.24 mol, 1.0 equiv), and MeI (18.7 mL, 0.30 mol, 1.25 equiv) in acetone (75 mL) was flushed with nitrogen, sealed, and stirred at room temperature for 48 h. Then, *n*-heptane (75 mL) was added to the mixture and the solids were filtered off and washed with acetone/*n*-heptane (1:1, 200 mL). The obtained organic solutions were combined and concentrated by complete evaporation of acetone and *n*-heptane. The residue was re-dissolved in ethyl acetate (100 mL). The resulting solution was washed with HCl (2 M, 3×40 mL), saturated aq $NaHCO_3$ solution (3×30 mL), H_2O (20 mL), brine (2×40 mL), and dried over magnesium sulfate. The solvent was evaporated to give the title β-diketone **5** (51.98 g, 96%) as colorless oil that crystallizes upon standing. Mp=44.0 °C (DSC onset) and 46.4 °C (DSC peak). ^{1}H NMR ($CDCl_3$): δ 0.97 and 1.03 (6H, 2× d, J=6.8 Hz, CH_3 of ^{i}Pr), 1.38 (3H, d, J=7.0 Hz, $COCH(CH_3)CO$), 2.72 (1H, sep, J=6.8 Hz, CH of ^{i}Pr), 4.58 (1H, q, J=7.0 Hz, COCHCO), 7.07–7.12 (2H, m, ArH), 7.93–7.97 (2H, m, ArH). ^{13}C NMR ($CDCl_3$): δ 13.5, 18.4, 18.9, 39.3, 54.2, 115.8 (d, J_{CF}=21.9 Hz), 131.1 (d, J_{CF}=9.3 Hz), 132.4 (d, J_{CF}=2.4 Hz), 165.8 (d, J_{CF}=255.9 Hz), 195.9, 210.6. ^{19}F NMR ($CDCl_3$): δ −104.3 (m). IR (KBr) ν 3399, 2973, 2934, 2873, 1702, 1679, 1598, 1508, 1460, 1229, 1157, 1028, 952, 863, 807, 600, 577 cm^{-1}. HRMS (ESI$^+$) calcd for $C_{13}H_{16}FO_2^+$ ($[M+H]^+$): 223.1129; found: 223.1130.

4.3. Preparation of 4-(4-fluorophenyl)-6-isopropyl-*N*,5-dimethylpyrimidin-2-amine (6)

A mixture of 1-(4-fluorophenyl)-2,4-dimethylpentane-1,3-dione (**5**, 1.00 g, 4.5 mmol), *N*-methyl guanidine hydrochloride salt (0.49 g, 4.5 mmol, 1.0 equiv), and Cs_2CO_3 (2.93 g, 9.0 mmol, 2.0 equiv) in MeTHF (10 mL) was stirred at 70 °C for 24 h. The resulting suspension was cooled to room temperature. Water (10 mL) was added. Layers were separated and the water layer was back-extracted with MeTHF (10 mL). The combined MeTHF fractions were washed with brine (10 mL) and dried over sodium sulfate. Solvent was evaporated under reduced pressure, the resulting solid was washed with 1:1 water/methanol mixture (20 mL) and dried to afford the pyrimidine derivative **6** (1.08 g, 92%) as yellow crystals. Mp=138.4 °C (DSC onset) and 140.0 °C (DSC peak). ^{1}H NMR ($CDCl_3$): δ 1.25 (6H, d, J=6.7 Hz, CH_3 of ^{i}Pr), 2.11 (3H, s, $ArCH_3$), 2.97 (3H, d, J=5.1 Hz, CH_3N), 3.18 (1H, sep, J=6.7 Hz, CH), 4.99 (1H, br s, NH), 7.09–7.15 (2H, m, ArH), 7.46–7.50 (2H, m, ArH). ^{13}C NMR ($CDCl_3$): δ 13.9, 21.1, 28.4, 31.4, 112.9, 115.0 (d, J_{CF}=21.5 Hz), 131.1 (d, J_{CF}=8.2 Hz), 132.4 (d, J_{CF}=2.4 Hz), 161.1, 162.7 (d, J_{CF}=247.6 Hz), 164.9, 175.0. ^{19}F NMR ($CDCl_3$): δ −113.5 (m). IR (KBr) ν 3273, 2970, 2932, 1589, 1560, 1507, 1464, 1400, 1228, 1219, 1008, 844 cm^{-1}.

HRMS (ESI^+) calcd for $C_{15}H_{19}FN_3^+$ ($[M+H]^+$): 260.1558; found: 260.1566.

4.4. Preparation of *N*-[4-(4-fluorophenyl)-6-isopropyl-5-methylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (7)

A solution of 4-(4-fluorophenyl)-6-isopropyl-*N*,5-dimethylpyrimidin-2-amine (**6**, 1.00 g, 3.86 mmol) in dichloromethane (15 mL) was prepared under inert atmosphere (by nitrogen flushing) and cooled to −5 °C. Then Et_3N (2.15 mL, 15.4 mmol, 4.0 equiv) was added and the reaction mixture was stirred for 10 min. A solution of MsCl (750 μL, 9.65 mmol, 2.5 equiv) in dry dichloromethane (1 mL) was prepared and slowly added (flow rate=250 μL/h) into the reaction mixture. The stirring was continued for additional 8 h at −5 °C. After dilution with dichloromethane (5 mL) and gradual warming up to room temperature, the reaction mixture was washed with water (6 mL). Aqueous layer was re-extracted with dichloromethane (5 mL) and the combined organic layers were washed with HCl (1 M, 3×6 mL), saturated aq $NaHCO_3$ solution (3×6 mL) and brine (2×7 mL). The combined organic layers were passed through a thin pad of silica gel-$MgSO_4$, which was subsequently washed with dichloromethane (5 mL). To the combined filtrates *n*-hexane (10 mL) was added. Solvents were evaporated to 1/5 of the initial volume. The addition of MeOH (7 mL) resulted in precipitation of the first crop of the product, which was collected by filtration. After the evaporation of the mother liquors to 1/10, second crop of the product precipitated, which was also collected by filtration and combined with the first crop to give 5-methylpyrimidine **7** (1.18 g, 91%) as colorless crystals after drying. Mp=119.0 °C (DSC onset) and 120.0 °C (DSC peak) (lit.[12] 118 °C). ^1H NMR ($CDCl_3$): δ 1.29 (6H, d, J=6.7 Hz, CH_3 of ^{i}Pr), 2.27 (3H, s, $ArCH_3$), 3.30 (1H, sep, J=6.7 Hz, CH), 3.51 (3H, s, CH_3N), 3.55 (3H, s, CH_3SO_2), 7.12–7.17 (2H, m, ArH), 7.79–7.83 (2H, m, ArH). ^{13}C NMR ($CDCl_3$): δ 14.3, 21.3, 31.9, 33.1, 42.4, 115.2 (d, J_{CF}=21.7 Hz), 118.6, 131.2 (d, J_{CF}=8.7 Hz), 133.9 (d, J_{CF}=2.5 Hz), 157.8, 163.6 (d, J_{CF}=249.2 Hz), 164.7, 175.4. ^{19}F NMR ($CDCl_3$): δ −111.3 (m). This is a known compound with spectroscopic and physical properties consistent with those reported in the literature.[12]

4.5. Preparation of *N*-[4-(4-fluorophenyl)-5-(bromomethyl)-6-isopropylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (3)

4.5.1. Using low pressure Hg-lamp. A solution of *N*-[4-(4-fluorophenyl)-6-isopropyl-5-methylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (**7**, 3.94 g, 11.69 mmol) and NBS (4.37 g, 24.50 mmol, 2.1 equiv) in acetonitrile (70 mL) was poured into the photochemical reactor. The solution was purged with nitrogen gas for 10 min and the reactor was sealed. The reaction mixture was agitated and irradiated for 68 h at ambient temperature. The dark-red colored reaction mixture was diluted with H_2O (70 mL). The precipitate was collected by filtration, and washed with MeOH/H_2O (1:1, 2×15 mL) and then MeOH (20 mL) to afford bromide **3** (3.59 g, 74%) as off-white crystals after drying.

4.5.2. Using medium pressure Hg-lamp. A solution of *N*-[4-(4-fluorophenyl)-6-isopropyl-5-methylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (**7**, 3.94 g, 11.69 mmol) and NBS (4.37 g, 24.50 mmol, 2.1 equiv) in acetonitrile (75 mL) was poured into the photochemical reactor. The solution was purged with nitrogen gas for 10 min and the reactor was sealed. The reaction mixture was agitated and irradiated for 16 h at ambient temperature. The dark-red colored reaction mixture was diluted with H_2O (100 mL). The precipitate was collected by filtration, washed with water (50 mL), and then with MeOH/H_2O (1:9, 3×15 mL) and dried to afford bromide **3** (3.91 g, 80%) as yellowish crystalline solid after drying. Mp=141.8 °C (DSC onset) and 142.9 °C (DSC peak). ^1H NMR ($CDCl_3$): δ 1.36 (6H, d, J=6.6 Hz, CH_3 of ^{i}Pr), 3.47–3.52 (4H, m, CH_3N, CH), 3.56 (3H, s, CH_3SO_2), 4.48 (2H, s, CH_2), 7.18–7.24 (2H, m, ArH), 7.79–7.83 (2H, m, ArH). ^{13}C NMR ($CDCl_3$): δ 21.8, 27.7, 31.5, 33.1, 42.5, 115.6 (d, J_{CF}=21.7 Hz), 119.3, 130.7 (d, J_{CF}=8.4 Hz), 133.7 (d, J_{CF}=2.5 Hz), 158.0, 163.6 (d, J_{CF}=250.6 Hz), 165.6, 177.5. ^{19}F NMR ($CDCl_3$): δ −110.6 (m). IR (KBr) ν 3435, 2971, 1548, 1512, 1450, 1376, 1339, 1238, 1164, 1154, 1132, 955, 847, 815, 773, 510 cm^{-1}. HRMS (ESI^+) calcd for $C_{16}H_{20}BrFN_3O_2S^+$ ($[M+H]^+$): 416.0438; found: 416.0441.

4.6. Preparation of *N*-[4-(4-fluorophenyl)-5-(hydroxymethyl)-6-isopropylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (2)

A solution of *N*-[4-(4-fluorophenyl)-5-(bromomethyl)-6-isopropylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (**3**, 0.50 g, 1.20 mmol) in THF (10 mL) and water (10 mL) was stirred and heated under reflux for 6 h. The reaction mixture was cooled to room temperature and THF was evaporated under reduced pressure. The product was extracted from the residue with MeTHF (3×6 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to give alcohol **2** in quantitative yield as colorless oil, which crystallized upon standing. Mp=131.5 °C (DSC onset) and 133.6 °C (DSC peak). ^1H NMR ($CDCl_3$): δ 1.32 (6H, d, J=6.7 Hz, CH_3 of ^{i}Pr), 2.27 (1H, br s, OH), 3.47–3.54 (4H, m, CH_3N, CH), 3.55 (3H, s, CH_3SO_2), 4.61 (2H, s, CH_2), 7.12–7.17 (2H, m, ArH), 7.79–7.83 (2H, m, ArH). ^{13}C NMR ($CDCl_3$): δ 22.2, 31.5, 33.0, 42.3, 57.4, 115.3 (d, J_{CF}=21.6 Hz), 120.7, 131.4 (d, J_{CF}=8.4 Hz), 133.9 (d, J_{CF}=2.5 Hz), 157.8, 163.7 (d, J_{CF}=250.0 Hz), 166.1, 175.4. ^{19}F NMR ($CDCl_3$): δ −111.3 (m). IR (KBr) ν 3308, 2979, 2934, 2909, 2875, 1606, 1557, 1513, 1457, 1397, 1379, 1340, 1318, 1234, 1168, 1158, 955, 859, 823, 775, 523 cm^{-1}. HRMS (ESI^+) calcd for $C_{16}H_{21}FN_3O_3S^+$ ($[M+H]^+$): 354.1282; found: 354.1284.

4.7. Preparation of *N*-[4-(4-fluorophenyl)-5-formyl-6-isopropylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (1)

*4.7.1. From alcohol **2**.* A solution of *N*-[4-(4-fluorophenyl)-5-(hydroxymethyl)-6-isopropylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (**2**, 2.00 g, 5.66 mmol) in DMSO (20 mL) was heated to 85 °C Ac_2O (2.15 mL, 22.79 mmol, 4.0 equiv) was slowly added (flow rate 150 μL/h) and the reaction mixture was left to stir for 17 h at 85 °C. Water (15 mL) was added and the resulting precipitate was collected by filtration. The precipitate was dissolved in hot EtOAc (20 mL), cooled to 4 °C and the precipitated solid was collected by filtration and dried to give product **1** (0.62 g, 31%) as colorless crystals.

*4.7.2. From bromide **3**.* A mixture of $NaHCO_3$ (0.40 g, 4.80 mmol, 2 equiv) and NaI (36.0 mg, 0.24 mmol 0.1 equiv) in DMSO (10 mL) was flushed with nitrogen, sealed, and maintained at 20 °C while a solution of *N*-[4-(4-fluorophenyl)-5-(bromomethyl)-6-isopropylpyrimidin-2-yl]-*N*-methylmethanesulfonamide (**3**, 1.00 g, 2.40 mmol) in DMSO (9 mL) was slowly added over 3 h time. The reaction mixture was stirred for 68 h at 20 °C, then warmed to 70 °C and Ac_2O (1.5 mL, 16.4 mmol, 6.6 equiv) was added dropwise in 3 h. The stirring was continued for additional 4 h at 70 °C. Then, the reaction mixture cooled on an ice bath, and the product was precipitated by slow addition of water (20 mL). The precipitate was collected by filtration, washed with water (10 mL) and MeOH (10 mL), and dried under reduced pressure to afford aldehyde **1** (0.79 g, 94%) as colorless solid. Mp=178.2 °C (DSC onset) and 179.1 °C (DSC peak) (lit.[13] 147–148 °C). ^1H NMR ($CDCl_3$): δ 1.32 (6H, d, J=6.7 Hz, CH_3 of ^{i}Pr), 3.55 (3H, s, NCH_3), 3.64 (3H, s, SCH_3), 4.01 (1H, sep, J=6.7 Hz, CH), 7.20–7.27 (2H, m, ArH), 7.61–7.66 (2H, m, ArH), 9.97 (1H, s, CHO). ^{13}C NMR ($CDCl_3$): δ 21.6, 31.9, 33.0, 42.5,

115.9 (d, J_{CF}=22.0 Hz), 119.5, 132.3 (d, J_{CF}=2.5 Hz), 132.6 (d, J_{CF}=8.8 Hz), 158.7, 164.4 (d, J_{CF}=252.7 Hz), 169.7, 179.0, 190.4. ^{19}F NMR ($CDCl_3$): δ −108.6 (m). IR (KBr) ν 3444, 3081, 2977, 2943, 1687, 1600, 1545, 1509, 1445, 1376, 1341, 1230, 1158, 1127, 956, 855, 809, 780 cm^{-1}. HRMS (ESI^+) calcd for $C_{16}H_{17}FN_3O_3S^-$ ($[M-H]^-$): 350.0980; found: 350.0981.

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Supplementary data

This material includes copies of ^{1}H and ^{13}C NMR spectra of compounds **1**–**3**, **5**–**7**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.01.013.

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