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Application of Flow Photochemical Bromination in the Synthesis of a 5-Bromomethylpyrimidine Precursor of Rosuvastatin: Improvement of Productivity and Product Purity

Damjan Šterk,[‡] Marko Jukič,[§] and Zdenko Časar*[,‡,§,⊥]

[‡]Sandoz Development Center Slovenia, API Development, Organic Synthesis Department, Lek Pharmaceuticals, d.d., Kolodvorska 27, 1234 Mengeš, Slovenia

[§]Faculty of Pharmacy, University of Ljubljana, Aškerčeva 7, 1000 Ljubljana, Slovenia

[⊥]Global Portfolio Management API, Sandoz GmbH, Biochemiestrasse 10, 6250 Kundl, Austria

ABSTRACT: In this report we present a flow photochemical bromination of a 5-methyl-substituted pyrimidine precursor of rosuvastatin. The study demonstrated that the reaction productivity can be increased markedly with a flow-mode approach compared to a batch-mode synthesis. Indeed, reaction times can be significantly shortened from a range of hours to a range of minutes. Moreover, in addition to process intensification, the study demonstrated that significantly lower overall levels of side products are obtained when photochemical bromination is conducted in a flow mode.

1. INTRODUCTION

Superstatins[1,2] have recently attracted our attention as interesting synthetic targets due the fact that they maintain a leadership position in high cholesterol management and rank among the most valued pharmaceuticals within the cardiovascular therapeutic category.[3,4] In particular, rosuvastatin[5] has shown some interesting therapeutic advantages over previously known members of the superstatin family.[6,7] Therefore, we have recently developed a lactone pathway to superstatins, exemplified by assembly of rosuvastatin[8] and pitavastatin[9] via a lactonized statin side-chain precursor.[10] Afterwards, we focused our attention on the heterocyclic part of the rosuvastatin molecule and developed a highly efficient four-step procedure to 5-bromomethylpyrimidine **1**.[11] This important rosuvastatin precursor[12−14] was accessed from simple starting materials via photochemical bromination of 5-methylpyrimidine **2** (Scheme 1).[11]

However, 5-methylpyrimidine **2**[11] has a relatively complex structure for the application of photochemical halogenation approaches when functionalization of the 5-methyl position is attempted. A closer look at the structure of **2** reveals a benzylic isopropyl moiety located at position 6 of the pyrimidine core that might also be susceptible to photochemical bromination. This could result in the formation of other regioisomers of the desired intermediate and its analogues with multiple brominated sites such as **3**, **4** and **5** (Scheme 1).[15] In addition, photochemical bromination of the aromatic part of the skeleton is also viable[16] which could provide, in combination with bromination of the benzylic positions, various regiobrominated derivatives **6** (lighter grey-colored brominated positions denote lower likelihood of bromination, Scheme 1). Compounds **3**, **4** and **5** are, due to the bromoalkyl fragment, known to trigger concerns in relation to genotoxic potential, while compounds **6** are less problematic in drug production.[17,18] Therefore, we were prompted to investigate possible formation of these side products in crude **1** after batch photochemical bromination. This would enable us to distinguish whether the predominant side-reaction pathways proceed via bromination of benzylic positions or via bromination of the aryl substituent on position 4 of the pyrimidine ring. Furthermore, although 5-bromomethylpyrimidine **1** was obtained as a principal product in the batch-mode reaction during our primary study and could be obtained as NMR pure material (impurities below ∼2% were not observed) after simple workup by precipitation with water and consecutive aqueous MeOH wash of precipitate,[11] the batch reaction was not completely regioselective, and impurities could indeed already be detected by ^{1}H NMR in the crude product. These impurities were responsible for a lower, 74% yield (4 W low-pressure Hg lamp) to 80% yield (150 W medium-pressure Hg lamp), which is not acceptable for such a simple transformation when the industrial process is considered. Moreover, batch-mode reactions were relatively long (16−64 h) already on millimolar scale (12 mmol).[11] Furthermore, undesirable carryover to the product of impurities such as **3**, **4** and **5** might be possible in the remaining short three to four sequences to the final API.[2] Alternatively, **3** and **4** might partially react with phosphorus precursors (e.g., phosphine or phosphite) in the ensuing step and further in Wittig or HWE coupling with the formyl-substituted side-chain precursors to provide similarly problematic impurity products. Therefore, the objective of the present study was to elaborate an improved process of the key photochemical bromination step in the preparation of 5-bromomethylpyrimidine **1**, which would enable industrial use and provide superior productivity as well as the improved impurity profile of **1**. In addition, this work provides basic understanding about the formation of alkylbromide impurities during the photochemical bromination of the highly substituted pyrimidine core and their influence on the quality of the product.

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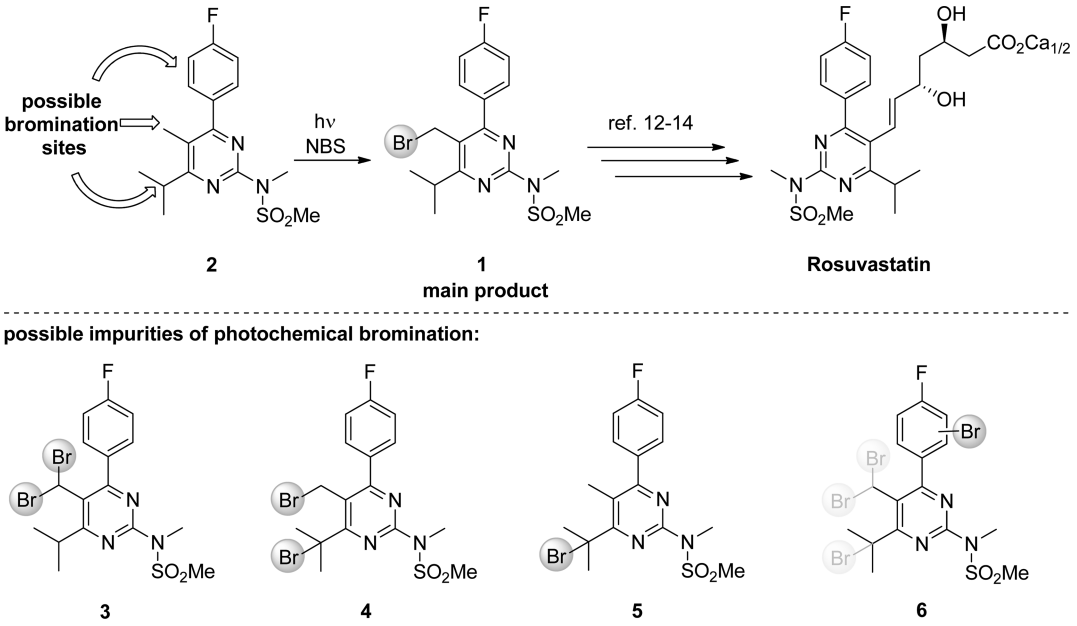
Scheme 1. Application of 5-bromomethylpyrimidine in the synthesis of rosuvastatin and possible impurities formed during its preparation via photochemical bromination of 5-methylpyrimidine



Scheme 2. Flow vs batch photochemical bromination of 5-methylpyrimidine 2

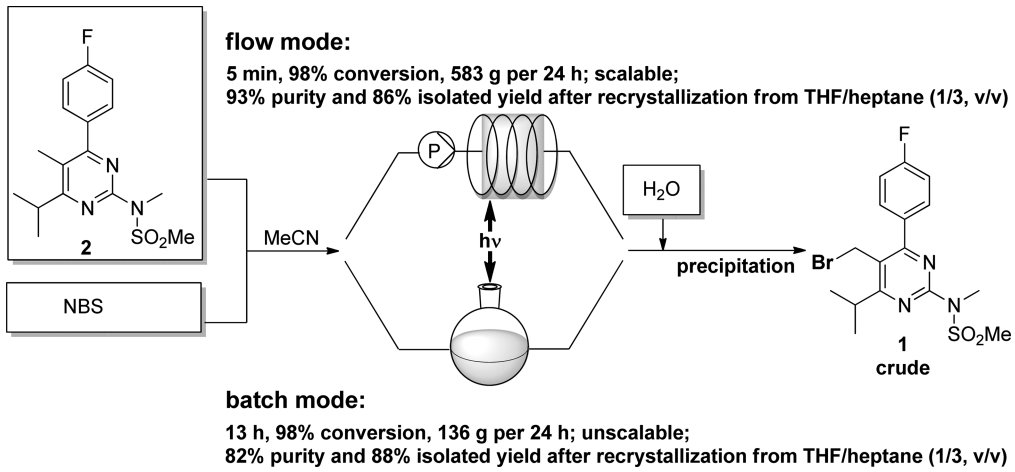


Table 1. Comparison of flow and batch photobromination of 2[a]

entry	reaction type	time	remaining **2** in **1** [area %][d,e]	purity of **1** [area %][d,e]	Σ impurities in **1** [area %][d,e]	productivity [mmol/h]
1	small batch[b]	3 h	0.5	88.0	11.5	8.1
2	large batch[c]	13 h	2.0	80.4	17.6	13.6
3	flow	30 min	<0.2	88.6	11.4	9.7
4	flow	15 min	<0.2	89.1	10.9	19.4
5	flow	10 min	<0.2	89.4	10.6	29.2
6	flow	5 min	2.0	88.0	10.0	58.3

[a]In all cases the temperature of reaction was 22 °C. [b]28 mmol scale based on starting **2**. [c]203 mmol scale based on starting **2**. [d]HPLC purity. [e]Values refer to crude product obtained after precipitation with water (see the Experimental Section).

2. RESULTS AND DISCUSSION

In the quest for more controlled reaction conditions, homogeneous irradiation of the entire volume of the reaction mixture, and simpler scale-up, we attempted to perform the photobromination of **2** in a flow mode.[19] Indeed, flow reactors usually provide better mass transfer through more efficient mixing along with many other advantages including better light dissipation.[20,21] Therefore, we constructed an 18-mL flow reactor coupled to an HPLC pump as described by Hook et al.,[22] which enabled us to vary the residence time by controlling the reaction mixture flow and to achieve better controlled irradiation conditions. The reactor was constructed from a fluorinated polyethylene tube (FEP) of 0.8-mm inner diameter and 36-m length on a quartz cooling jacket support holding the 150 W medium-pressure Hg lamp.

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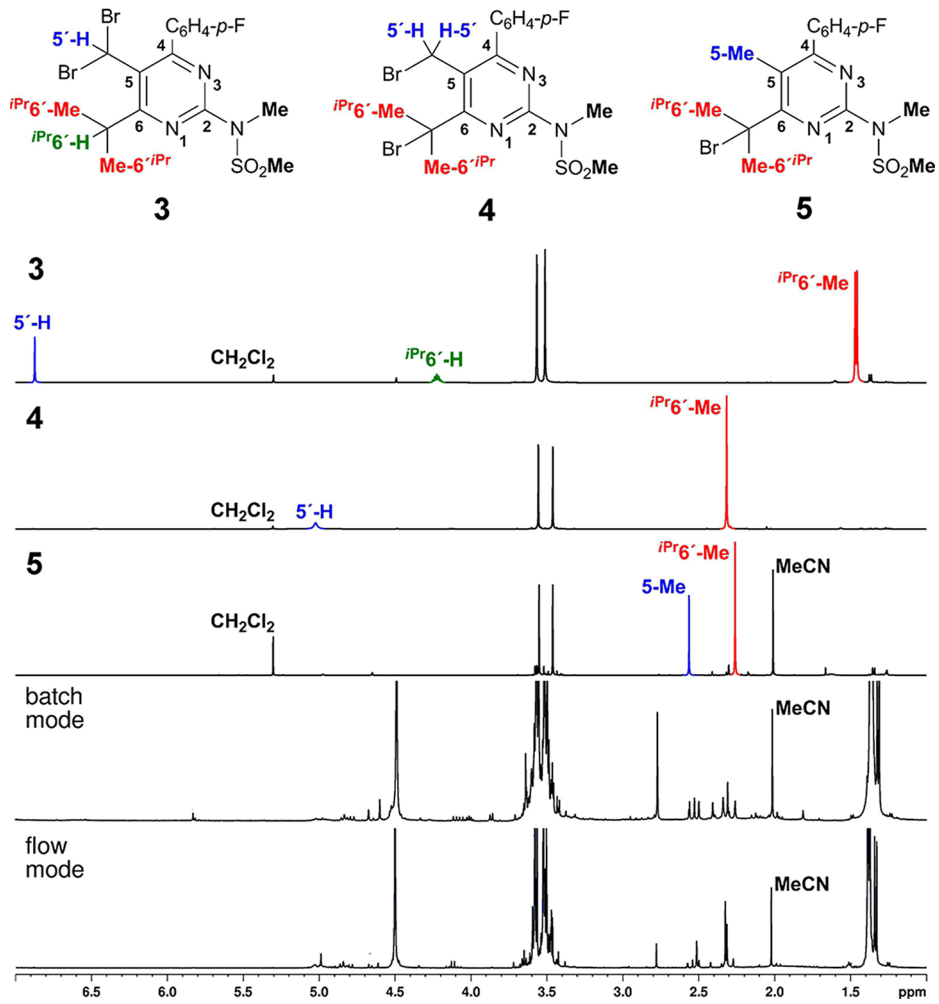

Figure 1. Comparison of impurity profiles by ^{1}H NMR in batch- vs flow-mode photochemical reactions.

For comparison reasons, we started our experiments of bromination with a small-scale batch reaction (28 mmol of **2**), using the 150 W medium-pressure Hg lamp (Scheme 2; Table 1, entry 1). Reaction was completed in 3 h, giving 0.5 area % of the remaining starting material **2** in the reaction mixture (99.5% conversion). Crude product **1**, after precipitation triggered by water addition, had 88 area % purity. When the scale of the reaction was increased to 203 mmol of the starting bromide **2** (7.25-fold increase), the reaction took a significantly longer time to reach near completion under the same reaction conditions. Indeed, 13 h were required to reach 98 area % conversion (2 area % of starting **2** remained in the mixture; Scheme 2; Table 1, entry 2).[23] Moreover, the prolonged reaction time had a markedly deteriorative effect on the product quality. Notably, the crude product obtained after precipitation triggered by water addition was only 80.4 area % pure and contained, in addition to unreacted **2**, a total 17.6 area % of other impurities (highest individual impurity was on the level of ∼2 area %). Recrystallization from THF/heptane (1/3, v/v) provided bromide **1** in 88% overall yield with only 82 area % purity, which did not meet our requirements for subsequent transformations. Moreover, this indicated that the formed impurities are similar in nature and consequently difficult to remove using crystallization as the prime purification method. These results implied that scale-up would be a difficult task to achieve. Because of the prolonged reaction time, the product quality would obviously further decrease significantly beneath the acceptable level. These findings demonstrated that the batch reaction was scale dependent, whereas millimolar experiments produced up to ∼8% fewer impurities and were completed 4.3 times faster in comparison to larger batches already on the lab scale.[24]

Therefore, we turned our attention to flow-mode reactions under identical reaction conditions (same solvent, lamp, and applied temperature). Flow reactions with 10−30 min residence times performed similarly, giving practically full conversion (<0.2 area % of **2** remaining in the reaction mixture) and comparable crude product quality after precipitation with water: 88.6−89.4 area % purity of crude **1** (Scheme 2; Table 1, entries 3−5). The thus obtained quality of **1** was similar to that of small batch-type reactions (88.0 area %, Table 1, entry 1). Nevertheless, productivity of flow reactions was up to 3.6 times higher than that of small-scale batch reaction (Scheme 2, Table 1, entry 1 vs entry 5). When the residence time in the flow reaction was shortened to 5 min (Scheme 2; Table 1, entry 6), a borderline performance of the system was reached, demonstrated by a drop of conversion to 98% (2 area % of **2** remaining in the reaction mixture). Nevertheless, reaction was clean and gave product **1** of 88 area % purity after precipitation with water, which contained the lowest sum of all impurities among all performed reactions. In this case the highest 58.3 mmol/h productivity was obtained.

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The crude bromide **1** was purified by recrystallization from THF/heptane (1/3, v/v) and was recovered in 86% yield as an off-white crystalline solid with chromatographic purity of 93 area %. The largest individual impurity remaining in the recrystallized **1** was **2** at a level of 1.5 area %. Since **2** cannot undergo transformation in the subsequent phosphonium salt formation step[12a,14,25] and can be easily depleted by crystallization, product **1** obtained from the largest flow experiment met our specification requirements.

An interesting feature of both batch- and flow-mode reactions can be observed in Figure 1, where ^{1}H NMR spectra of independently prepared possible benzylic bromination impurities **3**, **4**, and **5** (Scheme 1) are compared with those of crude mixtures of batch- and flow-mode reactions. Compound **3** was obtained by the method of Strekowski et al.,[15] where **1** was heated with NBS at reflux in CCl_4 in the presence benzoyl peroxide followed by chromatographic isolation. Similarly, **4** was obtained by the same approach using **2** as a starting material. The monobrominated derivative **5** was obtained by irradiation of MeCN solution of **2** and NBS with less selective irradiation ranging from 250 to 650 nm. Figure 1 shows that this improved impurity profile is obtained in flow-mode photochemical bromination. Moreover, it suggests that the 5-benzylic site in **2** was not susceptible to additional photochemical overbromination at the applied conditions since 5,5-dibromo derivative **3** is not detectable either in batch- or flow-type photochemical bromination. Similarly, monobromide **5** also could not be observed in the flow reaction. This was confirmed when the batch- and flow-mode products were analyzed by different HPLC or UPLC methods, where **3** and **5** were not clearly distinguished down to the detection limit (verified also with control samples containing pure **3** and **5**). This is a favorable fact since it indicates that potentially genotoxic benzylic bromides **3** and **5** are not present in the product **1**. On the other hand Figure 1 indicates that impurity **4** might be present in both batch and flow reactions (detected as a specific broad singlet at 5.01 ppm). This was also observed by HPLC and UPLC analysis, which revealed **4** in levels up to 2 area % (confirmed also with a control sample containing pure **4**) in the crude product. Therefore, we have assessed the depletion power of this impurity in the subsequent step of the rosuvastatin synthesis where phosphonium salt derivatives, used in Wittig coupling, are formed. For this purpose, we have reacted pure **4** with PBu_3 in THF at 50 °C for 90 min,[25] which resulted in full conversion. LC−MS analysis of the mixture revealed that two compounds in 1:2 ratio were formed. HRMS analysis of these two compounds indicated that neither contains an alkylbromide fragment[26] and can be considered as typical ICH impurities. This data suggest that impurity **4**, albeit being formed in the photochemical bromination step on detectable level, is easily transformed/depleted in the subsequent synthetic steps towards API and is therefore not critical to the quality of the product. Furthermore, the above findings suggest that if the compounds **3** and **5** were not formed there is even a lower likelihood that their analogues with brominated aromatic ring **6** are generated (Scheme 1). On the other hand, analogues of **4** with brominated aromatic moieties, if present, could be easily depleted in the subsequent synthetic steps as was shown in the case of **4**. These findings imply that a majority of formed impurities observed on NMR, HPLC, and UPLC originate either from bromination of different positions of the *p*-F-phenyl substituent[16] or from photochemical degradation products. In both cases these types of impurities can be considered as typical ICH-type impurities and, at formed levels below 1%, do not represent any quality concerns since they can easily be depleted to acceptable levels in the ensuing steps (e.g., phosphonium salt preparation and crystallization) towards the API.[8]

3. CONCLUSION

In summary, we presented a flow photochemical bromination of a 5-methylpyrimidine rosuvastatin precursor. To our knowledge this represents the first report on benzylic bromination performed in a flow mode.[20,21] Our investigation shows favorable effects of the flow-mode reaction on the productivity of the reaction. Moreover, the flow approach proved to be cleaner and provided the desired product with considerably lowers levels of impurities. These are apparently formed by photochemical bromination of an aromatic substituent[16] or photochemical degradation, while benzylic positions within the molecule are less affected by side reactions. Interestingly, no overbromination of the 5-benzylic position was observed,[15] while the 6-isopropyl moiety was prone to bromination to a slight extent. The formed impurities proved to be of no concern for the product quality. We believe that the demonstrated flow approach to the title compound will be suitable for easy scale-up. Due to these facts, we trust that our results will promote the application of flow-mode photochemical brominations in the pharmaceutical industry.

4. EXPERIMENTAL SECTION

4.1. General Considerations. Reagents and solvents were used as purchased. NMR spectra were recorded at 298 K on a Bruker Avance III 500 spectrometer operating at 500 MHz (^{1}H), 125 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 Hz. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), 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 using samples in potassium bromide disks. Melting points were determined on a Mettler Toledo DSC apparatus 822^e (heating rate 10 °C min^{-1}). For flash chromatography, Fluka silica gel 60, 220−440 mesh was used. HPLC analyses were performed on a Waters 2487 instrument with dual λ absorbance detector and a Waters XTerra RP-18 3.5 μm 250 mm × 4.6 mm column was used. HPLC conditions: 40 °C, 0.8 mL min^{-1}, 240 nm, aqueous pH 4.5 buffer (TFA/NH_3)/acetonitrile = 2:8. HPLC analyses were alternatively performed on a Waters 2487 instrument with dual λ absorbance detector and a Waters Symmetry Shield RP-18 5 μm 150 mm × 4.6 mm column. HPLC conditions: 30 °C, 1.0 mL min^{-1}, 220 nm, 0.1% trifluoroacetic acid in water/0.1% trifluoroacetic acid in acetonitrile = 10:0 → 0:10. UPLC analyses were performed on a Waters Acquity instrument and a Waters Acquity HHS T3 1.8 μm 100 mm × 2.1 mm column. UPLC conditions: 25 °C, 0.4 mL min^{-1}, 265 nm, aqueous pH 4.5 buffer (AcOH/NH_3)/acetonitrile = 7:3. Batch photochemical reactions were conducted in an immersion-type reactor consisting of a reactor body fabricated of borosilicate glass with an inserted double-walled quartz immersion well obtained from UV-Consulting Peschl. A medium-pressure Hg lamp TQ 150 from UV-Consulting Peschl (P = 150 W, λ =

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predominantly >300 nm) was inserted into a vertically arranged double-walled, water-cooled immersion well. Flow reactions were conducted in a photochemical reactor as described by Hook et al.[22] with the same lamp as used for the batch reactions.

4.2. Preparation of *N*-(4-(4-Fluorophenyl)-5-(bromomethyl)-6-isopropylpyrimidin-2-yl)-*N*-methylmethanesulfonamide (1). *4.2.1. Batch Mode.* A photochemical reactor with 150 W medium-pressure Hg lamp reactor was equilibrated before reaction for 30 min at 22 °C. Starting *N*-(4-(4-fluorophenyl)-6-isopropyl-5-methylpyrimidin-2-yl)-*N*-methylmethanesulfonamide (**2**)[11] (68.4 g, 0.203 mol, 1.0 equiv) and *N*-bromosuccinimide (NBS) (76.2 g, 0.426 mol, 2.1 equiv) were dissolved in acetonitrile (650 mL) resulting in a 0.27 M solution of **2**. The resulting solution was irradiated in photochemical reactor for 13 h and water (1.3 L) was added. The resulting precipitate was filtered off, washed with water (0.38 L) and dried under reduced pressure to yield 86.5 g of crude **1** that was recrystallized from THF (140 mL) and heptane (420 mL) by evaporation of THF to give 73.9 g (88% yield) of **1** (82 area % HPLC purity) as white powder.

4.2.2. Flow Mode. The flow reactor was equilibrated before reaction for 30 min at 22 °C. Starting *N*-(4-(4-fluorophenyl)-6-isopropyl-5-methylpyrimidin-2-yl)-*N*-methylmethanesulfonamide (**2**)[11] (31.5 g, 93.5 mmol, 1.0 equiv) and *N*-bromosuccinimide (NBS) (35.0 g, 196 mmol, 2.1 equiv) were dissolved in acetonitrile (300 mL), resulting in a 0.27 M solution of **2**. The resulting solution was pumped via a syringe pump through the flow reactor with the flow rate of 3.60 mL min^{-1} (5 min retention time); 50 mL of reaction mixture was collected, and water (100 mL) was added. The resulting precipitate was filtered off, washed with water (20 mL), and dried under reduced pressure to yield 5.53 g of crude **1** that was recrystallized from THF (10 mL) and heptane (30 mL) by evaporation of THF to give 4.80 g (86% yield) of **1** (93 area % HPLC purity) as white powder.

This is a known compound with spectroscopic and physical properties in accordance with those reported in the literature.[11] R_f = 0.45 in hexane/EtOAc = 80:20.

4.3. Preparation of *N*-(5-(Dibromomethyl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-*N*-methylmethanesulfonamide (3). To a stirred solution of *N*-(4-(4-fluorophenyl)-5-(bromomethyl)-6-isopropylpyrimidin-2-yl)-*N*-methylmethanesulfonamide (**1**) (2.08 g, 5.0 mmol, 1 equiv) in tetrachloromethane (35 mL) were added *N*-bromosuccinimide (NBS) (1.78 g, 10.0 mmol, 2 equiv) and benzoyl peroxide (125 mg, 0.5 mmol, 0.1 equiv) at room temperature. Reaction mixture was heated to reflux, stirred for 5 h, and left to cool to room temperature. Solids were filtered off and filtrate was concentrated under reduced pressure to afford oily residue. Product was purified by column chromatography (silica gel; hexane/EtOAc = 90:10 → 70:30; R_f = 0.49 in hexane/EtOAc = 80:20) to afford 0.15 g (6% yield) of compound **3** as a white solid. Mp = 154 °C (DSC onset). ^{1}H NMR ($CDCl_3$): δ 1.39 (6H, d, J = 6.6 Hz, CH_3), 3.45 (3H, s, CH_3N), 3.50 (3H, s, CH_3SO_2), 4.16 (1H, h, J = 6.5 Hz, CH), 6.80 (1H, s, CH), 7.17−7.20 (2H, m, CH_{Ar}), 7.54−7.57 (2H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 21.8, 32.5, 33.1, 33.3, 42.6, 116.2 (d, J_{CF} = 21.8 Hz), 123.9, 130.4 (d, J_{CF} = 8.5 Hz), 133.2, 157.8, 161.6, 163.8 (d, J_{CF} = 251.5 Hz), 179.8. IR (KBr) ν 522, 543, 575, 773, 820, 964, 1152, 1118, 1153, 1236, 1338, 1388, 1540, 1553, 1967, 3444 cm^{-1}. HRMS (ESI^+) calcd for $C_{16}H_{19}Br_2FN_3O_2S^+$([M + H]$^+$): 493.9543; found: 493.9549.

4.4. Preparation of *N*-(5-(Bromomethyl)-4-(2-bromopropan-2-yl)-6-(4-fluorophenyl)pyrimidin-2-yl)-*N*-methylmethanesulfonamide (4). To a stirred suspension of *N*-(4-(4-fluorophenyl)-6-isopropyl-5-methylpyrimidin-2-yl)-*N*-methylmethanesulfonamide (**2**) (1.68 g, 5.0 mmol, 1 equiv) in tetrachloromethane (35 mL) were added *N*-bromosuccinimide (NBS) (1.78 g, 10.0 mmol, 2 equiv) and benzoyl peroxide (125 mg, 0.5 mmol, 0.1 equiv) at room temperature. Reaction mixture was heated to reflux, stirred for 15 h, and left to cool to room temperature. Solids were filtered off and filtrate was concentrated under reduced pressure to afford residual oil. Product was purified by column chromatography (silica gel; hexane/EtOAc = 90:10 → 70:30; R_f = 0.39 in hexane/EtOAc = 80:20) to afford 0.5 g (21% yield) of compound **4** as a white solid. Mp = 146 °C (DSC onset). ^{1}H NMR ($CDCl_3$): δ 2.31 (6H, s, CH_3), 3.45 (3H, s, CH_3N), 3.55 (3H, s, CH_3SO_2), 5.01 (2H, br s, CH_2), 7.18−7.26 (2H, m, CH_{Ar}), 7.56−7.59 (2H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 27.3, 33.4, 34.5, 42.2, 62.1, 115.7 (d, J_{CF} = 21.8 Hz), 122.1, 130.4(d, J_{CF} = 8.4 Hz), 133.6, 156.0, 163.4 (d, (d, J_{CF} = 249.9 Hz), 169.9, 170.4. IR (KBr) ν 575, 844, 954, 969, 1113, 1155, 1332, 1379, 1442, 1509, 1548, 1606, 3445 cm^{-1}. HRMS (ESI^+) calcd for $C_{16}H_{19}Br_2FN_3O_2S^+$([M + H]$^+$): 493.9543; found: 493.9540.

4.5. Preparation of *N*-(4-(2-Bromopropan-2-yl)-6-(4-fluorophenyl)-5-methylpyrimidin-2-yl)-*N*-methylmethanesulfonamide (5). Starting *N*-(4-(4-fluorophenyl)-6-isopropyl-5-methylpyrimidin-2-yl)-*N*-methylmethanesulfonamide (**2**) (3.37 g, 10.0 mmol, 1 equiv) and bromosuccinimide (NBS) (3.73 g, 21.0 mmol, 2.1 equiv) were dissolved in acetonitrile (70 mL) and transferred to the photoreactor. The reactor was sealed and flushed with nitrogen for 10 min. The mixture was stirred and irradiated with a doped medium-pressure Hg lamp, TQ 150 Z3, from UV-Consulting Peschl (P = 150 W, polychromatic emission spectra between 250 and 650 nm) for 4 h. Medium-pressure Hg lamp was in a quartz immersion jacket cooled with water and stabilized at 40 − 45 °C. The obtained solution was diluted with H_2O/methanol = 9:1 (100 mL). Precipitate was filtered off and filtrate collected. Volatiles were evaporated under reduced pressure, and residual water phase was thoroughly extracted with dichloromethane (2 × 10 mL). Organic phases were combined, acetonitrile (10 mL) and $CF_3CO_2NH_4$ buffer (pH = 4.5, 15 mL) were added, and the mixture was stirred at room temperature for 24 h. Volatiles were evaporated under reduced pressure, and the water phase was again thoroughly extracted with dichloromethane (2 × 10 mL). Organic phases were combined, washed with brine (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford residual oil. The product was purified by reverse phase column chromatography (C18; aqueous pH 4.5 buffer (TFA/NH_3)/acetonitrile = 2:8; R_f = 0.38 in hexane/EtOAc = 80:20) to afford 80 mg (2% yield) of **5** as a yellowish solid. Mp = 145 °C (DSC onset). ^{1}H NMR ($CDCl_3$): δ 2.25 (6H, s, CH_3), 2.56 (3H, s, CH_3), 3.46 (3H, s, CH_3N), 3.55 (3H, s, CH_3SO_2), 7.14−7.19 (2H, m, CH_{Ar}), 7.53−7.57 (2H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 17.5, 33.3, 33.7, 42.0, 62.2, 115.3 (d, J_{CF} = 21.6 Hz), 120.7, 131.3 (d, J_{CF} = 8.4 Hz), 134.6, 155.3, 163.3 (d, J_{CF} = 249.8 Hz), 168.12, 169.3. IR (KBr) ν 575, 1113, 1150, 1229, 1332, 1389, 1512, 1546, 2923, 3437 cm^{-1}. HRMS (ESI^+) calcd for $C_{16}H_{20}BrFN_3O_2S^+$([M + H]$^+$): 416.0438; found: 416.0441.

4.6. Reaction of *N*-(5-(Bromomethyl)-4-(2-bromopropan-2-yl)-6-(4-fluorophenyl)pyrimidin-2-yl)-*N*-methylmethanesulfonamide (4) with Tributylphosphine. To a

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solution of *N*-(5-(bromomethyl)-4-(2-bromopropan-2-yl)-6-(4-fluorophenyl)pyrimidin-2-yl)-*N*-methylmethanesulfonamide (**4**) (49 mg, 0.1 mmol) in dry THF under nitrogen atmosphere was added tributylphosphine (55 μL, 0.22 mmol) at 50 °C.[25] The resulting colorless solution was stirred at 50 °C, and after 90 min the HPLC analysis indicated complete conversion of the starting material. The reaction was very clean, and two products were formed: bis- and monophosphonium salts in the ratio of 1:2.[26] The structures of the products were determined by LC−HRMS analysis, and that of monophosphonium salt was determined by comparison of the retention time with with that of an authentic sample.[12a,14,25] Monophosphonium salt might originate from bis-phosphonium salt via hydrolysis with water during sample preparation. Monophosphonium salt: HRMS (ESI^+) calcd for $C_{28}H_{45}FN_3O_2PS^+$([M + H]$^+$): 538.3027; found: 538.3026. Bis-phosphonium salt: HRMS (ESI^+) calcd for $C_{40}H_{70}FN_3O_2P_2S^{2+}$([M + 2H]$^{2+}$): 369.7397; found: 369.7404. Note that the calculated mass for the phosphonium salt is lower for one hydrogen and that for the bis-phosphonium salt is lower for two hydrogens than the actual mass due to the fact that the MS software assumes that the ion is formed by ionization with an additional proton while the compound is already in an ionic form.

AUTHOR INFORMATION

Corresponding Author

*E-mail: zdenko.casar@sandoz.com. Telephone: +43 5338 200 3747. Fax: +43 5338 200 418.

Notes

The authors declare no competing financial interest.

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(23) After 5 h, conversion of **2** was 91.7% (8.3 area % of **2** was present in the reaction mixture), and after 10 h, the conversion of **2** was 97.3% (2.7 area % of **2** was present in the reaction mixture) according to the HPLC analysis.
(24) This effect most likely originates from nonhomogeneous light absorption through the reaction mixture volume, which becomes more pronounced with increased batch/vessel size. Since the transmission of light through the reaction mixture produces the excited molecules,

which are the reacting species in a photochemical reaction, the progress of the photochemical reaction depends essentially on the concentration of such excited molecules. Moreover, photochemical reactions are only apparently homogeneous, since the concentration of excited molecules varies throughout the volume of reaction mixture and decreases according to the distance from the UV lamp immersion unit. This means that photochemical reaction in batch mode is very dependent on the thickness of the irradiated layer and efficiency of the stirring, which is usually far from ideal in any batch vessel. Thus, the energy is not equally adsorbed in the medium, and the excited species are not homogeneously distributed throughout batch vessel volume. Consequently, the photochemical reaction is significantly more intense near the walls of the UV lamp immersion unit than it is near the walls of the batch vessel where the effect of the stirring is usually the least pronounced. Therefore, in a small batch vessel, as in the case of our millimolar reactions, the majority of the reaction mixture is in close proximity to the walls of the UV lamp immersion unit, which assures that reaction conditions are close to being homogeneous and consequently that the yields are the highest. On the other hand, with the increasing batch/vessels size, as in the case of our larger lab-scale reactions (up to 0.2 mol), where the thickness of the layer of the reaction mixture exposed to light increases, nonhomogenous conditions are created, leading to nonhomogenous irradiation in the reaction mixture more distant from the UV lamp immersion unit. This results in lower yields and/or prolonged reaction times. The latter can lead to overexposing the substrate and/or the product to light and consequently can lead to overreaction on less active or more hindered sites, resulting in regiobrominated and degradation side products.

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(26) Structures of the products, obtained in the reaction between *N*-(5-(bromomethyl)-4-(2-bromopropan-2-yl)-6-(4-fluorophenyl)pyrimidin-2-yl)-*N*-methylmethanesulfonamide (**4**) and tributylphosphine[12a,14,25] proposed on the basis of HRMS analysis and also by comparison of HPLC retention time with authentic sample in the case of monophosphonium salt: