Microwave-Assisted Solution- and Solid-Phase Synthesis of 2-Amino-4-arylpyrimidine Derivatives

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An efficient and rapid microwave-assisted solution-phase method for the synthesis of 2-amino-4-arylpyrimidine-5-carboxylic acid derivatives has been developed. The five-step linear protocol involves an initial Biginelli multicomponent reaction leading to dihydropyrimidine-2-thiones which are subsequently S-alkylated with methyl iodide. The resulting 2-methylthiodihydropyrimidines are sequentially oxidized first with manganese dioxide and then with Oxone to provide 2-methylsulfonyl-pyrimidines which serve as excellent precursors for the generation of a variety of 2-substituted pyrimidines via displacement of the reactive sulfonyl group with nitrogen, oxygen, sulfur, and carbon nucleophiles. A modified protocol using a solid-phase method has also been developed.

Introduction

The 2-aminopyrimidine structural subunit is contained in a growing number of both natural products and synthetic compounds with interesting biological properties.[1] This structural motif, representing a heterocyclic guanidine moiety, has consequently been extensively used as a druglike scaffold in medicinal chemistry.[1−7] Of particular interest are derivatives possessing an aryl ring at the C4 position and an electron-withdrawing substituent such as an ester or amide group at C5 (see structure **C**, Nu = NR_2, Figure 2).[2−5] Several 2-aminopyrimidines of this type show interesting biological activities, for example as inhibitors of rho-associated protein kinase 1,[2] glycogen synthase kinase 3 (GSK3),[3] and of N-type calcium channels.[4] Notably, the 2-amino-4-arylpyrimidine subunit is also found in important drugs such as the hypocholesterolemic agent rosuvastatin (an HMG-CoA reductase inhibitor)[5,6] and the potent anticancer drug Gleevec (a tyrosine kinase inhibitor)[7] (Figure 1).

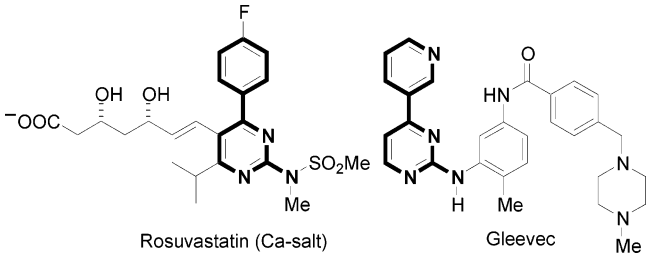

Figure 1. Important drug molecules containing the 2-amino-4-(het)aryl-pyrimidine structural motif.

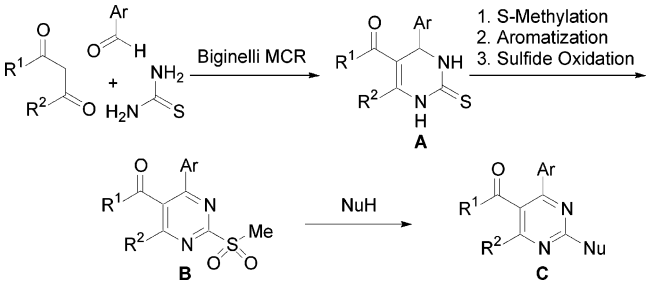

Figure 2. Design of 2-amino-4-arylpyrimidine libraries with four diversity points.

In general, 2-aminopyrimidine heterocycles are often constructed by condensation reactions of enones with suitable guanidine or related nitrogen-containing building blocks.[8] This approach, however, is of restricted use for the efficient preparation of compound libraries in a combinatorial fashion because of the limited availability of substituted guanidines. Alternatively, the 2-amino group on the pyrimidine can be introduced by displacement of a good leaving group at the C2 position (for example a sulfone) with a primary or secondary amine.[5,9,10] From the standpoint of combinatorial chemistry and library diversity, this latter approach clearly is the preferred option.

Herein, we describe the rapid and efficient synthesis of 2-amino-4-aryl-pyrimidines of type **C** by taking advantage of the high diversity initially generated on the pyrimidine core through a Biginelli multicomponent (MCR) approach[11] using differently substituted β-ketoesters, aldehydes, and thiourea as starting materials (Figure 2). In a three-step sequence, the initially formed dihydropyrimidine-2-thione **A** is subsequently converted to a 2-methylsulfonylpyrimidine **B**, in which the sulfonyl group can be displaced with a variety of nucleophiles leading to the desired target structures **C** (Nu = NR_2). In contrast to the previously published related approaches for the synthesis of 2-aminopyrimidines of type **C**,[5,10] our method allows for considerable diversity in all building blocks, and every step in the five step sequence has been demonstrated to operate under high-speed microwave irradiation conditions.[12]

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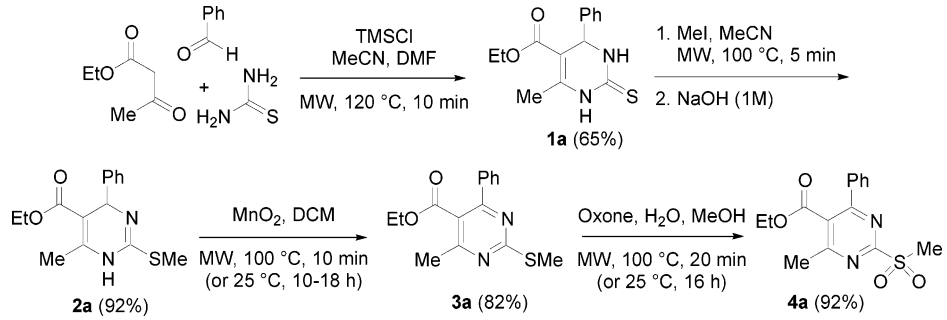
Scheme 1



Results and Discussion

Optimization of Reaction Conditions for the Synthesis of 2-Sulfonylpyrimidine 4a. According to the general strategy outlined in Figure 2, our synthesis of the required sulfone precursor commenced with the preparation of dihydropyrimidine-2-thione (DHPM) **1a** via Biginelli condensation (Scheme 1).

For this well-known multicomponent process involving treatment of thiourea with an aldehyde and β-ketoester building block, a plethora of synthetic methods are available in the literature,[11] including protocols that make use of controlled microwave irradiation.[13] In contrast to many of the recently reported methods involving the use of an expensive Lewis acid catalyst such as $Yb(OTf)_3$,[11] we utilized trimethylsilyl chloride (TMSCl) as an inexpensive mediator of the Biginelli reaction.[14] Gratifyingly, a 65% yield of dihydropyrimidine-2-thione (DHPM) **1a** was obtained by microwave heating (120 °C, 10 min) of a mixture of ethyl acetoacetate, benzaldehyde, and thiourea, (1:1:1.2) in a MeCN/DMF solvent combination (2:1) with 1 equiv of TMSCl (Scheme 1). The isolated yield obtained from these optimized conditions compared favorably with microwave experiments using 10 mol % $Yb(OTf)_3$ as catalyst[13] and with a run using the TMSCl method at room temperature for 1−3 h.[14] The high-speed microwave method proved applicable for a variety of different substrates (see below).

For the required subsequent S-methylation **1a** → **2a**, our original 1989 protocol using methyl iodide in methanol as solvent was transformed from open-vessel reflux conditions (65 °C, 2 h)[15] to a sealed-vessel microwave heating process (100 °C, 5 min), providing the desired 2-methylthio-1,4-dihydropyrimidine **2a** in a 92% isolated yield after treatment of the reaction mixture with dilute aqueous sodium hydroxide solution. Other alkylation reagents such as dimethylsulfate or dimethylcarbonate were also successful but provided slightly lower product yields, and the reactions were not as easy to work up.[16]

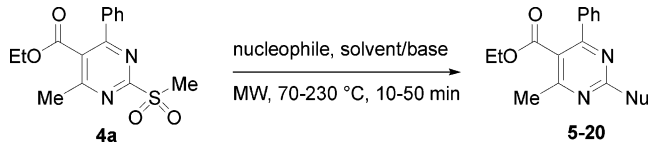
For the oxidation/aromatization of the DHPM nucleus (**2a** → **3a**), different reaction conditions were investigated.[17] In our hands, the most suitable protocols in terms of product yield and purity made use of either activated MnO_2 or cerium ammonium nitrate (CAN) in DCM as solvent. Both methods could either be run at room temperature for several hours (10−18 h) or be performed under microwave irradiation conditions at 100−120 °C. In the latter case, full conversion was typically achieved within less than 20 min. Both the room temperature and the microwave protocols showed similar purity profiles and allowed the isolation of 2-methylthiopyrimidine **3a** in a 76−82% yield. For ease of workup and general applicability (see below), we decided to use the MnO_2 procedure for all subsequent studies. Optimized conditions involved microwave heating of a solution of 2-methylthiodihydropyrimidine **2a** with 5 equiv of MnO_2 in anhydrous DCM under sealed-vessel conditions at 100 °C for 10 min[18]

The oxidation of sulfide **3a** to the sulfone **4a** was studied using a range of typical sulfide-oxidizing reagents such as *m*-chloroperbenzoic acid (*m*-CPBA),[5] AcOH−H_2O_2,[19] SeO_2−H_2O_2,[20] Oxone,[21] and tetra-*n*-butylammonium Oxone under anhydrous conditions.[22] For substrate **3a**, the use of inexpensive Oxone (3 equiv) in a H_2O/MeOH solvent mixture was most convenient. Again, complete oxidation of sulfide to sulfone could be accomplished either at room temperature within 16 h or under microwave heating at 100 °C for 2 × 10 min (after the first 10 min, an additional 1.5 equiv of Oxone was added to the reaction mixture). In an effort to eliminate an unnecessary workup step, we additionally developed a rapid one-pot protocol in which the dihydropyrimidine ring was first aromatized in the presence of 1 equiv of CAN in a DCM/H_2O mixture (**2a** → **3a**, MW, 120 °C, 15 min). The subsequent addition of Oxone in MeOH into the same reaction vessel and resubjection to microwave irradiation at 100 °C for 2 × 10 min (**3a** → **4a**) provided, after a simple extractive workup, the desired target sulfone **4a** in a 74% overall isolated yield.

In summary, we have elaborated the synthesis of pyrimidine sulfone precursors of type **4a** via a rapid four-step all-microwave synthetic sequence from readily available building blocks and inexpensive alkylation and oxidation reagents. The overall yield of sulfone **4a** over the four steps is 45%. The total reaction time under high-temperature sealed-vessel microwave conditions is 45 min, compared to ∼2−3 days using conventional methods (reflux or room temperatures).

Displacement of the 2-Methylsulfonyl Group in Pyrimidine 4a with Nucleophiles. There are only a few publications that report the displacement of a reactive C2 sulfonyl group in pyrimidines of type **B** (Figure 2) with nucleophiles.[5,10] Furthermore, the published examples of nucleophiles are limited to reactive primary or secondary amines.[5,10] We were interested in expanding the scope of this valuable transformation, which would allow the introduction of considerable diversity at C2 of the Biginelli MCR-derived pyrimidine cores (**B** → **C**), and therefore, we have studied the reaction of sulfone **4a** with a variety of nitrogen,

Table 1. Microwave-Assisted Displacement of the C2 Methylsulfonyl Group in **4a** with Nucleophiles[a]



compound	nucleophile (**A**−**X**)	solvent/base	temp (°C)	time (min)	yield (%)[b]
5aA	pyrrolidine (**A**)	THF	140	10	72
5aB	piperidine (**B**)	THF	140	10	68
5aC	ethanolamine (**C**)	THF	140	10	74
5aD	benzylamine (**D**)	THF	140	10	73
5aE	4-fluorophenethylamine (**E**)	THF	140	10	45
5aF	2-methoxyphenethylamine (**F**)	THF	140	10	80
5aG	ammonia[c] (**G**)	DMSO	100	15	82
5aH	dimethylamine[d] (**H**)	DMF	200	20	81
5aI	aniline (**I**)	dioxane	230	50	67
5aJ	*p*-anisidine (**J**)	dioxane	230	50	73
5aK	*N*-methyl-methanesulfonamide (**K**)	THF/K_2CO_3	140	10	45
5aL	phenol (**L**)	MeCN/Cs_2CO_3	70	15	83
5aM	*p*-thiocresol (**M**)	THF/K_2CO_3	140	30	82
5aN	malononitrile (**N**)	MeCN/Cs_2CO_3	70	10	85

[a] Reaction conditions: single-mode sealed-vessel microwave irradiation. For details, see the Experimental Section. [b] Yields refer to isolated yields of pure products after column chromatography. [c] Ammonium acetate as substitute for NH_3. [d] Dimethylamine was generated in situ by decomposition of DMF.

oxygen, sulfur, and carbon nucleophiles under microwave irradiation conditions (Table 1).

Our investigations began with the use of reactive primary and secondary aliphatic amines **A**−**F**. The treatment of sulfone **4a** with 1.2 equiv of the corresponding amine in anhydrous THF at 140 °C (MW) for 10 min showed full conversion by HPLC and provided the desired 2-aminopyrimidines **5aA**−**F** in a 45−80% isolated yield after purification by column chromatography (Table 1). It was also possible to introduce a free-NH_2 group at C2 using ammonium acetate (2 equiv) in DMSO solution as a substitute for gaseous NH_3. Microwave heating at 100 °C for 15 min provided 2-aminopyrimidine **5aG** in an 82% yield. Similarly, the 2-dimethylamino derivative **5aH** was most conveniently prepared in a good yield by taking advantage of the in situ decomposition of DMF to dimethylamine at the comparatively high reaction temperature of 200 °C.

In contrast to aliphatic amines, aromatic amines such as aniline (**I**) and *p*-anisidine (**J**) proved to be considerably less reactive. Under the standard reaction conditions used for aliphatic amines (MW, 140 °C, 10 min), no conversion was seen by HPLC monitoring. Taking advantage of the expanded temperature range offered by controlled sealed-vessel microwave heating,[12] we found that irradiating sulfone **4a** with 1.2 equiv of an aromatic amine in dioxane at 230 °C for 50 min did allow full conversion to the desired 2-arylaminopyrimidines **5aI** and **5aJ** which were isolated in 67 and 73% yields, respectively, after column chromatography.

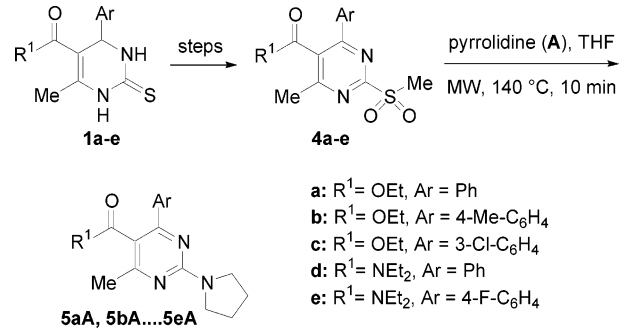
In view of the importance of the methanesulfonamide moiety in the HMG-CoA reductase inhibitor rosuvastatin (Figure 1), we also attempted the direct displacement of the 2-methylsulfonyl group with commercially available *N*-methyl-methanesulfonamide, HN(Me)SO_2Me (**K**). Application of the standard reaction conditions (MW, 140 °C, 10 min, THF) provided a 45% isolated yield of the corresponding *N*-methanesulfonylamino-pyrimidine **5aK**, with a number of unidentified byproducts. No attempt was made to further optimize this protocol. Traditionally, this moiety is introduced by a 2-step procedure involving initial displacement of the sulfone with methylamine, followed by *N*-sulfonylation with methanesulfonyl chloride.[5]

We next turned out attention to oxygen, sulfur, and carbon nucleophiles. Good product yields were obtained by treatment of sulfone **4a** with the phenolate anion (1.1 equiv), generated directly from phenol and cesium carbonate in MeCN as solvent.[23] Microwave heating at 70 °C for 15 min provided an 83% isolated yield of 2-aryloxypyrimidine **5aL** after purification by column chromatography. Similarly, the sulfone group could also be displaced with sulfur nucleophiles such as thiophenolate anions, for example *p*-thiocresol. Thus, the reaction of sulfone **4a** with 1.5 equiv of *p*-thiocresol in THF/K_2CO_3[24] at 140 °C for 30 min provided an 82% yield of the corresponding 2-arylthiopyrimidine **5aM**. Gratifyingly, it was also possible to use carbon nucleophiles (carbanions) for the displacement of the methylsulfonyl group in pyrimidine **4a**. Treatment of **4a** with malononitrile in MeCN/Cs_2CO_3 rapidly provided the expected pyrimidin-2-yl-malononitrile derivative **5aN**.[25]

We have thus shown that by applying microwave irradiation in sealed vessels, the 2-methylsulfone group on pyrimidine **4a** can be displaced with a variety of different nitrogen, oxygen, sulfur, and carbon nucleophiles, in most cases providing excellent yields of the anticipated 2-functionalized pyrimidines **5** in very short reaction times.[26] The use of high-temperature microwave heating is particularly valuable for those cases were unreactive nucleophiles such as aromatic amines need to be reacted.

Introducing Diversity on the Pyrimidine Core. Synthesis of Sulfones 4a−f. Having successfully demonstrated the concept (see Figure 2) of 2-aminopyrimidine synthesis from Biginelli-type dihydropyrimidines (DHPMs) with one model substrate (sulfone **4a**), we next looked at increasing the structural diversity on the pyrimidine core to synthesize potentially larger more-diverse compound libraries. Toward

Scheme 2



this end, an additional four dihydropyrimidine-2-thiones **1b**−**e** (Scheme 2) were prepared via Biginelli MCRs involving thiourea, a set of two 1,3-dicarbonyl compounds (ethyl acetoacetate and *N*,*N*-diethyl acetoacetamide), and four aromatic aldehydes (benzaldehyde, 3-chlorobenzaldehyde, 4-fluorobenzaldehyde, and 4-methylbenzaldehyde) as building blocks. In all cases, the general microwave-assisted TMSCl-based protocol outlined above was employed for DHPM synthesis, providing the desired compounds **1b**−**e** in 73−83% yields.

For the generation of the desired sulfone precursors **4a**−**e,** a modified and general procedure was developed that allowed the rapid transformation of thiones **1a**−**e** to the corresponding sulfones according to the three-step strategy detailed in Scheme 1. However, in the present protocol (see the Experimental Section for details), the intermediate *S*-methylthio-1,4-dihydropyrimidines **2a**−**e** and 2-methylthiopyrimidines **3a**−**e** were not isolated, and the reaction carried on directly without purification to the sulfone stage. Purification of the crude sulfones **4a**−**e** by column chromatography provided an excellent overall 82−95% yield of pure products over the three steps (**1a**−**e** → **2a**−**e** → **3a**−**e** → **4a**−**e**).

As a complimentary data set to the displacement of the sulfone group in **4a** with six aliphatic amines **A**−**F** described in Table 1, we were now interested in investigating the reaction of the five sulfones **4a**−**e** with a single representative amine, namely, pyrrolidine (**A**), under reaction conditions identical to those used before (MW, THF, 140 °C, 10 min). To our delight, as in the case of **4a,** the remaining four 2-methylsulfonylpyrimdines **4b**−**e** reacted smoothly with 1.2 equiv of pyrrolidine in THF at 140 °C to provide complete conversion to the corresponding aminopyrimidines, which were isolated in 72−91% yields after chromatographic purification (Scheme 2). The generation of a full set of 6 × 5 = 30 diverse aminopyrimidine library compounds **5aA**−**5eF** employing a novel microtiter platform under multimode microwave irradiation conditions is described in the accompanying publication.[27]

Solid-Phase Synthesis of 2-Aminopyrimidines. In addition to the solution-phase protocol outlined above, we also considered a microwave-assisted solid-phase method to be able to prepare large compound libraries using combinatorial principles in a high-speed format. While several reports describe the construction of Biginelli dihydropyrimidines on a solid support by immobilizing one of the three building blocks to the support,[10,28] we chose to prepare the starting dihydropyrimdine-2-thiones of type **A** in solution-phase using our optimized high-speed microwave protocol (Scheme 1), and to subsequently attach the purified thiones **A** to Merrifield resin. This would allow us to perform "multidirectional resin cleavage" in the final step of the synthesis with a potentially large number of nucleophiles, simplifying product purification in particular if the nucleophile was used in substoichiometric quantities.

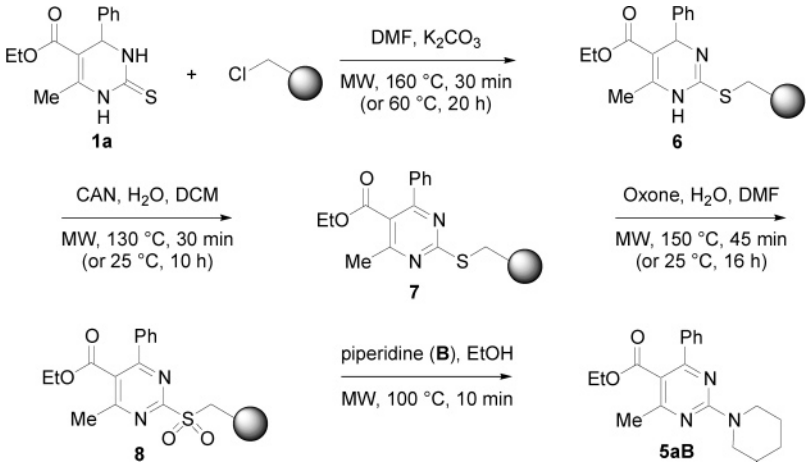
Toward this end, dihydropyrimidine-2-thione **1a** was immobilized on standard polystyrene Merrifield resin (2.30 mequiv cl/g) by irradiating the preswollen resin in DMF at 160 °C for 30 min with an excess of thione **1a** (3 equiv) and K_2CO_3 as a base (Scheme 3).[29,30] Under these conditions, complete conversion was achieved as judged by on-bead FT-IR monitoring (disappearance of the C−Cl stretch at 1265 cm^{-1}) and from the mass of reisolated excess thione **1a**. We have also performed this transformation under conventional heating conditions (60 °C, 20 h) leading to identical results.

The formed resin-bound 2-alkylthio-1,4-dihydropyrimidine **6** was subsequently treated with aqueous CAN (1.5 equiv) in DCM[10] to aromatize the dihydropyrimidine; the use of solid MnO_2 utilized in the solution-phase method (Scheme 1) being incompatible with the solid-phase reaction conditions. The oxidation was either performed at room temperature within 10 h or under microwave irradiation at 130 °C for 30 min. For the sulfide to sulfoxide oxidation **7** → **8**, we relied again on the Oxone method (see Scheme 1) which worked equally well as in the solution-phase protocol. Microwave irradiation at 150 °C of resin-bound sulfide **7** in aqueous DMF with 1.5 equiv of Oxone for 3 × 15 min (with additional 1.5 equiv of the oxidizing agent being added after each cycle) provided the immobilized sulfone **8**. The progress of the oxidation was followed by on-bead FT-IR spectroscopy monitoring the intensity of the characteristic SO_2 vibrations at 1077 and 1221 cm^{-1}.

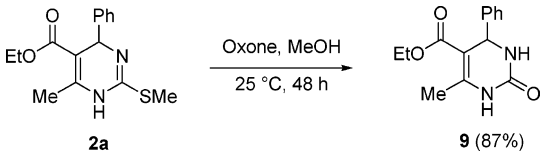
On the basis of earlier reports in the literature,[23,29] we assume that any nonaromatized sulfide **7** would be released at this stage from the resin since the corresponding sulfone (not shown) would be very labile toward nucleophiles such as water and immediately be transformed into the corresponding cyclic urea. This was confirmed by solution-phase studies on the oxidation of 2-methylthio-1,4-dihydropyrimidine **2a** with Oxone or other chemoselective sulfide−sulfone oxidizing reagents. Even under anhydrous conditions, the only isolable product was the 3,4-dihydropyrimidine-2-one **9** (Scheme 4).

Finally, treatment of resin-bound sulfone **8** with a variety of nucleophiles was evaluated. Among the many conditions that were investigated, microwave heating at 100 °C for 10 min with the appropriate nucleophile in ethanol as solvent[10] typically provided the best results. In case of piperidine (**B**), for example, the corresponding 2-piperidinopyrimidine **5aB** was formed in a 43% isolated overall crude yield (based on the initial loading of the Merrifield resin). However, the ^1H NMR purity of the isolated crude final products in all cases, regardless of microwave or conventional conditions being applied in the sequence, was lower than 85% (typically between 70 and 80%). Since this comparatively low purity (over 4 steps) required subsequent chromatographic purification from unidentified byproducts, the solution-phase method

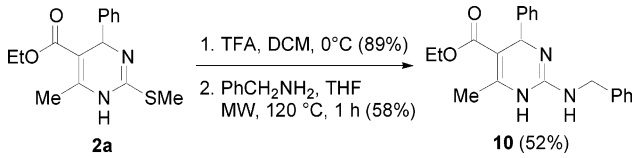
Scheme 3



Scheme 4



Scheme 5



at this stage seems more practical, although the possibility of the application of multidirectional resin cleavage[9] in a combinatorial fashion makes the solid-phase protocol still attractive for the preparation of larger compound libraries.

Preparation of 2-Amino-1,4-dihydropyrimidines. Finally, since we had access to a variety of 2-methylthio-1,4-dihydropyrimidines of type **2**, we also investigated the possibility to displace the methylthio group in the dihydroheterocycles directly with amines. This would lead to 2-amino-1,4-dihydropyrimidine-5-carboxylates, an important structural subunit in many biologically active guanidinium alkaloids of the batzelladine and crambine families.[31] Surprisingly, this approach to "2-amino-DHPMs" has never been described in the literature, and our own attempts in this area remained fruitless for many years.[32] Indeed, treatment of 2-methylthio-1,4-dihydropyrimidine **2a** with, for example, benzylamine under a variety of different conditions failed to provide the expected 2-amino-1,4-dihydropyrimidine product **10** (Scheme 5).

On the bais of a recent report in the literature on a different series of cyclic isothioureas,[30] we realized that no reaction takes place on the isothiourea in its deprotonated form because of the reduced electrophilicity and that standard nucleophilic counterions, such as iodide, often lead to undesired side reactions. Following arguments made in the literature,[30] we therefore converted the free base to its trifluoroacetate salt. The use of the less nucleophilic trifluoroacetate counterion ultimately allowed the synthesis of 2-amino-1,4-dihydropyrimidine **10** by microwave irradiation of a mixture of the 2-methylthio-1,4-dihydropyrimidine TFA salt **2a** and 1.2 equiv of benzylamine in THF at 120 °C for 1 h. The cyclic guanidine **10** was isolated in a 58% yield after column chromatography.

Conclusions

In conclusion, we have demonstrated that readily available 2-methylsulfonyl-pyrimidines, derived from a Biginelli multicomponent strategy, are excellent precursors for the generation of a variety of 2-substituted pyrimidines of type **C** via displacement of the reactive sulfonyl group with different nitrogen, oxygen, sulfur, and carbon nucleophiles. The use of high-temperature sealed-vessel microwave irradiation allows the preparation of the desired target structures in high yields and comparatively short reaction times. All five synthetic steps required for the synthesis of the target structures were carried out under microwave irradiation, both in solution phase and on solid phase.

Experimental Section

General. TLC analysis was performed on pre-coated plates. ^{1}H NMR spectra were recorded on a Bruker AMX 360 at 360 MHz in the solvents indicated. Chemical shifts (δ) are expressed in parts per million downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. All melting points were recorded on a Gallenkamp melting point apparatus. On-bead FT-IR spectra were recorded on a Unicam Galaxy Series FTIR 7000 (Mattson Instruments Inc.) using mashed resin beads in KBr pellets. Solid-phase reactions were carried out on an Advanced Chemtech Synthesizer PL 4 × 6 in Teflon frits or in appropriate 10 mL sealed-glass vials. Low-resolution mass spectra were obtained in the atmospheric pressure chemical ionization (positive or negative APCI) mode. Analytical HPLC analysis was carried out on a C18 reversed-phase analytical column (119 × 3 mm, particle size 5 μm) at 25 °C using mobile phases A (water/acetonitrile 90:10 (v/v) + 0.1% TFA) and B (acetonitrile + 0.1% TFA) at a flow rate of 0.5 mL/min. The following gradient was applied: linear increase from solution 30% B to 100% B in 7 min, hold at 100% solution B for 2 min.

Microwave Irradiation Experiments. Microwave-assisted synthesis was carried out in an Emrys Synthesizer or Initiator Eight EXP single-mode microwave cavity producing

controlled irradiation at 2450 MHz (Biotage AB, Uppsala). Reaction times refer to hold times at the temperatures indicated, not to total irradiation times. The temperature was measured with an IR sensor on the outside of the reaction vessel.

Materials. Merrifield resin (2.3 mmol g^{-1}, Lot&Filling Code 20126 PR) was purchased from Aldrich Chem. Co. All reactions were performed without protection gas atmosphere. All solvents were distilled using standard procedures. Commercial reagents were used without further purification.

Ethyl 6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1a). TMSCl (108 mg, 127 μL, 1 mmol) was added to a mixture of ethyl acetoacetate (130 mg, 127 μL, 1 mmol), thiourea (91 mg, 1.2 mmol), and benzaldehyde (106 mg, 102 μL, 1 mmol) in 3 mL of DMF/CH_3CN (1:2). After irradiation in a microwave reactor at 120 °C for 10 min, the reaction mixture was poured onto crushed ice. The resulting solid precipitate was isolated by filtration and washed with cold H_2O/CH_3CN (1:1). After it was dried, 180 mg (65%) of DHPM **1a** was obtained as a white solid in >98% purity (HPLC at 215 nm). mp: 205−207 °C (lit.[33] 204−206 °C). ^{1}H NMR (360 MHz, DMSO-d_6) :δ 1.09 (t, J = 7.1 Hz, 3H), 2.28 (s, 3H), 4.00 (q, J = 7.1 Hz, 2H), 5.17 (d, J = 3.6 Hz, 1H), 7.20−7.36 (m, 5H), 9.64 (s, 1H), 10.33 (s, 1H). MS (positive APCI, *m/z*): 277 [13, (M + 1)], 276 (100, M).

Ethyl 6-Methyl-4-phenyl-2-methylthio-1,4-dihydropyrimidine-5-carboxylate (2a). Methyl iodide (184 mg, 81 μL, 1.3 mmol) was added to a solution of thione **1a** (276 mg, 1 mmol) in dry MeOH (3 mL), and the reaction mixture was irradiated in a a microwave reactor at 100 °C for 10 min. The reaction mixture was poured onto a mixture of crushed ice and 5 mL of 1 M NaOH (5 equiv) and was allowed to crystallize overnight at 4 °C. The precipitate was filtered off, washed with water, followed by cold Et_2O, and then dried to give 267 mg (92%) of compound **2a** as a pale yellow solid. mp: 165−167 °C (lit.[34] 165−166 °C). ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.20 (t, J = 7.1 Hz, 3H) 2.36 (s, 3H) 2.46 (s, 3H) 4.11 (q, J = 7.0 Hz, 2H) 5.66 (s, 1H) 7.24−7.34 (m, 5H). MS (positive APCI, *m/z*): 291 [15, (M + 1)], 290 (100, M), 218 [15, (M−73)].

Ethyl 6-Methyl-4-phenyl-2-methylthio-pyrimidine-5-carboxylate (3a). Activated manganese(IV) oxide (MnO_2, Fluka, catalog no. 63548) (217 mg, 2.5 mmol) was added to a solution of 1,4-dihydropyrimidine **2a** (145 mg, 0.5 mmol) in anhydrous DCM (3 mL). The reaction mixture was irradiated in a microwave reactor at 100 °C for 10 min (or stirred for 8 h at room temperature, full conversion in both conditions according to HPLC monitoring at 215 and 254 nm). The crude mixture was filtered through a plug of silica (3 g) and washed with DCM (3 × 4 mL). The combined organic layers were evaporated to give 118 mg (82%) of pyrimidine **3a** in >98% purity (HPLC at 215 nm) without any further purification as a yellow oil.[35] ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.03 (t, J = 7.1 Hz, 3H) 2.56 (s, 3H) 2.60 (s, 3H), 4.15 (q, J = 7.1 Hz, 2H) 7.42−7.65 (m, 5H). MS (positive APCI, *m/z*): 289 [15, (M + 1)], 288 (100, M).

Ethyl 6-Methyl-4-phenyl-2-methylsulfonyl-pyrimidine-5-carboxylate (4a). Potassium hydrogen persulfate (Oxone) (461 mg, 0.75 mmol dissolved in 3 mL of water) was slowly added to a solution of sulfide **3a** (72 mg, 0.25 mmol) in DMF (2 mL) at 0 °C. The reaction mixture was irradiated in a microwave reactor at 100 °C for 2 × 10 min (after the first 10 min, an additional 1.5 equiv of Oxone was added to the reaction mixture) or stirred at room temperature for 16 h. The crude reaction mixture was subsequently diluted with water and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with water and brine and were dried over $MgSO_4$. All solvent was removed in vacuo, and petroleum ether was added to the remaining oil. The white solid precipitate was filtered off, washed with petroleum ether, and dried to give 74 mg (92%) of sulfone **4a** as a white solid. mp: 77−79 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.12 (t, J = 7.1 Hz, 3H), 2.74 (s, 3H), 3.41 (s, 3H), 4.27 (q, J = 7.0 Hz, 3H), 7.74−7.48 (m, 5H). MS (positive APCI, *m/z*): 320 (20, M), 258 [100, (M − 62)]. IR (KBr): ν_{max} 1728, 1550, 1525, 1320, 1247, 1150, 1127, 1083, 469 cm^{-1}.

General Procedure for the Displacement of Sulfone in 4a with Amines A−F (Table 1). To a solution of sulfone **4a** (64 mg, 0.2 mmol) in THF (3 mL) in a 10 mL microwave vial, 1.2 equiv of the appropriate amine **A**−**F** (1.2 equiv) was added. The vial was sealed and irradiated in a microwave reactor at 140 °C for 10 min. The solvent was removed under reduced pressure, and the residue was then purified by silica gel column chromatography to afford 2-aminopyrimidines **5aA**−**F** as colorless oils or solids.

Ethyl 6-Methyl-4-phenyl-2-(pyrrolidin-1-yl)-pyrimidine-5-carboxylate (5aA). mp: 74−75 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.94 (s, 3H), 1.99 (s, 4H), 2.53 (s, 3H), 3.67 (s, 4H), 4.03 (s, 2H), 7.27−7.59 (m, 5H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 13.6, 23.2, 25.4, 46.7, 60.1, 13.5, 128.1, 129.2, 139.8, 159.2, 165.7, 166.8, 169.4. MS (positive APCI, *m/z*): 313 [35, (M + 2)], 311 (100, M).

Ethyl 6-Methyl-4-phenyl-2-(piperidin-1-yl)-pyrimidine-5-carboxylate (5aB). ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.94 (t, J = 7.1 Hz, 3H), 1.61−1.69 (m, 6H), 2.50 (s, 3H), 3.89−3.92 (m, 4H), 4.04 (q, J = 7.2 Hz, 2H), 7.38−7.59 (m, 5H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 13.6, 23.3, 24.9, 25.9, 44.7, 60.8, 113.3, 128.0, 128.1, 129.2, 139.8, 160.3, 165.8, 167.0, 169.3. MS (positive APCI, *m/z*): 325 (100, M).

Ethyl 6-Methyl-4-phenyl-2-(2-hydroxyethylamino)-pyrimidine-5-carboxylate (5aC). mp: 91−93 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.94 (s, 3H), 2.50 (s, 3H), 3.58 (s, 2H), 3.77 (s, 2H), 4.06 (s, 3H), 6.26 (s, 2H), 7.27−7.52 (m, 5H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 13.5, 22.6, 44.5, 61.2, 63.0, 115.6, 127.09, 128.4, 129.8, 138.5, 168.2. MS (positive APCI, *m/z*): 302 [23, (M + 1)], 301 (100, M), 283 [15, (M − 18)].

Ethyl 6-Methyl-4-phenyl-2-benzylamino-pyrimidine-5-carboxylate (5aD). mp: 72−73 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.97 (t, J = 7.1 Hz, 3H), 2.50 (s, 3H), 4.07 (q, J = 7.1 Hz, 2H), 4.72 (d, J = 5.9 Hz, 2H), 5.72 (s, 1H), 7.27−7.56 (m, 10H). MS (positive APCI, *m/z*): 348 [23, (M + 1)], 347 (100, M).

Ethyl 6-Methyl-4-phenyl-2-(4-fluorophenethylamino)-pyrimidine-5-carboxylate (5aE). mp: 113−115 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.97 (t, J = 7.1 Hz, 3H), 2.49 (s, 1H), 2.88 (t, J = 6.9 Hz, 2H), 3.70 (q, J = 6.9 Hz, 2H),

4.07 (q, $J = 7.1$ Hz, 2H), 5.63 (s, 1H), 6.96−7.56 (m, 9H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 13.5, 22.9, 35.0, 42.7, 61.0, 115.2, 115.4, 128.0, 128.2, 129.5, 130.2, 130.3, 134.8, 139.2, 161.1, 166.1, 168.8. MS (positive APCI, *m/z*): 380 [20, (M + 1)], 379 (87, M).

Ethyl 6-Methyl-4-phenyl-2-(2-methoxyphenethylamino)-pyrimidine-5-carboxylate (5aF). mp: 87−89 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.96 (t, $J = 7.1$ Hz, 3H), 2.49 (s, 3H), 2.46 (t, $J = 6.8$ Hz, 2H), 3.74 (q, $J = 6.7$ Hz, 2H), 3.84 (s, 3H), 4.06 (q, $J = 7.1$ Hz, 2H), 5.48−5.50 (m, 1H), 6.85−7.56 (m, 9H). MS (positive APCI, *m/z*): 392 [20, (M + 1)], 391 (100, M), 313 [70, (M −78)].

Ethyl 6-Methyl-4-phenyl-2-amino-pyrimidine-5-carboxylate (5aG). Ammonium acetate (31 mg, 0.4 mmol) was added to a solution of sulfone **4a** (64 mg, 0.2 mmol) in DMSO (3 mL) in a microwave vial. The vial was sealed and irradiated in a microwave reactor at 100 °C for 15 min. The solvent was removed under reduced pressure, and the residue was then purified by silica gel column chromatography (ether/ethyl acetate = 7:1) to give 42 mg (82%) of 2-aminopyrimidine **5aG** as a white solid. mp: 119−121 °C. ^{1}H NMR (360 MHz, DMSO-d_6): δ 0.88 (t, $J = 7.1$ Hz, 3H), 2.35 (s, 3H), 3.98 (q, $J = 7.1$ Hz, 2H), 7.12 (s, 2H), 7.44 (s, 5H). MS (positive APCI, *m/z*): 258 [20, (M + 1)], 257 (100, M).

Ethyl 6-Methyl-4-phenyl-2-dimethylamino-pyrimidine-5-carboxylate (5aH). A solution of sulfone **4a** (64 mg, 0.2 mmol) in DMF (3 mL) contained in a 10 mL sealed microwave vial was irradiated in a microwave reactor at 200 °C for 10 min. The solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (ether/ethyl acetate = 9:1) to give 50 mg (81%) of 2-aminopyrimidine **5aH** as a colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.95 (t, $J = 7.1$ Hz, 3H), 2.53 (s, 3H), 3.28 (s, 6H), 4.05 (q, $J = 7.1$ Hz, 2H), 7.41−7.60 (m, 5H). MS (positive APCI, *m/z*): 286 [15, (M + 1)], 285 (85, M), 257 [100, (M − 28)].

Ethyl 6-Methyl-4-phenyl-2-phenylamino-pyrimidine-5-carboxylate (5aI). Aniline (22 mg, 0.24 mmol) was added to a solution of sulfone **4a** (64 mg, 0.2 mmol) in dioxane (3 mL) in a 10 mL microwave vial. The vial was sealed and irradiated in a microwave reactor at 230 °C for 50 min with the aid of a silicon carbide passive heating element.[36] The solvent was removed under reduced pressure, and the residue was then purified by silica gel column chromatography (petroleum ether/ethyl acetate = 7:3) to give 45 mg (67%) of 2-anilinopyrimidine **5aI** as a colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.01 (t, $J = 7.1$ Hz, 3H), 2.58 (s, 3H), 4.12 (q, $J = 7.1$ Hz, 2H), 7.33−7.22 (m, 11H). MS (positive APCI, *m/z*): 335 [35, (M + 1)], 333 (100, M).

Ethyl 6-Methyl-4-phenyl-2-(4-methoxyphenylamino)-pyrimidine-5-carboxylate (5aJ). *p*-Anisidine (30 mg, 0.24 mmol) was added to a solution of sulfone **4a** (64 mg, 0.2 mmol) in dioxane (3 mL) in a 10 mL microwave vial. The vial was sealed and irradiated in a microwave reactor at 230 °C for 50 min with the aid of a silicon carbide passive heating element.[36] The solvent was removed under reduced pressure, and the residue was then purified by silica gel column chromatography (petroleum ether/ethyl acetate = 7:3) to give 53 mg (73%) of 2-anilinopyrimidine **5aJ** as a colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.99 (t, $J = 7.1$ Hz, 3H), 2.55 (s, 3H), 3.80 (s, 3H), 4.11 (q, $J = 7.1$ Hz, 2H), 6.87−7.63 (m, 10H). ^{13}C NMR (90 MHz, $CDCl_3$): δ 13.6, 23.0, 55.5, 61.2, 114.2, 116.7, 121.4, 128.1, 128.3, 129.6, 132.3, 138.8, 155.6, 159.0, 166.0, 167.3, 168.6. MS (positive APCI, *m/z*): 364 [15, (M + 1)], 363 (100, M).

Ethyl 6-Methyl-4-phenyl-2-(*N*-methyl-*N*-methanesulfonylamino)-pyrimidine-5-carboxylate (5aK). *N*-methyl methanesulfonamide (26 mg, 21 μL, 0.24 mmol) was added to a mixture of sulfone **4a** (64 mg, 0.2 mmol) and K_2CO_3 (30 mg, 0.22 mmol) in THF (3 mL) in a 10 mL microwave vial. The vial was sealed and irradiated in a microwave reactor at 140 °C for 10 min. The reaction mixture was filtered, and the inorganic solid was washed with THF (2 × 5 mL). The filtrates were combined and concentrated under reduced pressure, and the residue was then purified by silica gel column chromatography (petroleum ether/ethyl acetate = 7:3) to give 32 mg (45%) of compound **5ak** as a pale-yellow oil. ^{1}H NMR (360 MHz, DMSO-d_6): δ 1.01 (t, $J = 7.1$ Hz, 3H), 2.53 (s, 3H), 3.47 (s, 3H), 3.56 (s, 3H), 4.16 (q, $J = 7.1$ Hz, 2H), 7.53−7.63 (m, 5H). MS (positive APCI, *m/z*): 351 [10, (M + 2)], 350 [15, (M + 1)], 349 (100, M), 271 [15, (M −78)].

Ethyl 6-Methyl-4-phenyl-2-phenoxy-pyrimidine-5-carboxylate (5aL). Phenol (21 mg, 0.22 mmol) was added to a solution of sulfone **4a** (64 mg, 0.2 mmol) and Cs_2CO_3 (72 mg, 0.22 mmol) in MeCN (3 mL) in a 10 mL microwave vial. The vial was sealed and irradiated in a microwave reactor at 70 °C for 15 min. The reaction mixture was filtered, and the inorganic solid was washed with MeCN (2 × 5 mL). The filtrates were combined and concentrated under reduced pressure, and the residue was then purified by silica gel column chromatography (petroleum ether/ethyl acetate = 7:3) to give 56 mg (83%) of 2-phenoxypyrimidine **5aL** as a colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.07 (t, $J = 7.2$ Hz, 3H), 2.58 (s, 3H), 4.19 (q, $J = 7.2$ Hz, 2H), 7.24−7.61 (m, 10H). MS (positive APCI, *m/z*): 335 [25, (M + 1)], 334 (100, M).

Ethyl 6-Methyl-4-phenyl-2-(*p*-tolylthio)-pyrimidine-5-carboxylate (5aM). *p*-Thiocresol (32 mg, 0.26 mmol) was added to a solution of sulfone **4a** (64 mg, 0.2 mmol) and K_2CO_3 (30 mg, 0.22 mmol) in THF (3 mL) in a 10 mL microwave vial,. The vial was sealed and irradiated in a microwave reactor at 140 °C for 30 min. The reaction mixture was filtered, and the inorganic solid was washed with THF (2 × 5 mL). The filtrates were combined and concentrated under reduced pressure, and the residue was then purified by silica gel column chromatography (petroleum ether/ethyl acetate = 7:3) to give 60 mg (82%) of compound **5aM** as a white solid. mp: 62−63 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.06 (t, $J = 7.1$ Hz, 3H), 2.41 (s, 3H), 2.52 (s, 3H), 4.17 (q, $J = 7.1$ Hz, 2H), 7.22−7.43 (m, 5H), 7.53−7.55 (d, $J = 8.0$ Hz, 4H). MS (positive APCI, *m/z*): 366 [10, (M + 2)], 365 [30, (M + 1)], 364 (100, M), 313 [35, (M-51)].

Ethyl 6-Methyl-4-phenyl-2-dicyanomethyl-pyrimidine-5-carboxylate (5aN). Malononitrile (14.5 mg, 0.22 mmol) was added to a solution of sulfone **4a** (64 mg, 0.2 mmol)

and Cs_2CO_3 (72 mg, 0.22 mmol) in MeCN (3 mL) in a 10 mL microwave vial. The vial was sealed and irradiated in a microwave reactor at 70 °C for 10 min. The reaction mixture was poured into water and acidified to pH 2 with 1 M HCl. The precipitate was filtered off, washed with water, and dried to give 55 mg (85%) of compound **5aN** as a yellow solid. mp: >186 °C (dec). IR (KBr): 1111, 1252, 1278, 1414, 1455, 1579, 1602, 1619, 1714, 2195, 2216 cm^{-1}. ^1H NMR (360 MHz, DMSO-d_6): δ 0.88 (t, $J = 7.1$ Hz, 3H), 2.49 (s, 3H), 4.02 (q, $J = 7.1$, 2H), 5.27 (s, 1H), 7.50−7.57 (m, 5H). ^{13}C NMR (90 MHz, DMSO-d_6): δ 13.7, 19.5, 44.3, 61.8, 114.0, 118.5, 128.4, 129.0, 131.3, 137.4, 161.7, 162.8, 165.9. MS (positive APCI, *m/z*): 308 [20, (M + 1)], 306 (100, M), 258 [50, (M − 48)]. Anal. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.66; H, 4.61; N, 18.29. Found: C, 66.50; H, 4.46; N, 18.24.

General Procedure for the Preparation of DHPMs 1b−e (Scheme 2). Thiourea (91 mg, 1.2 mmol) and TMSCl (108 mg, 127 μL, 1 mmol) were added to a mixture of the corresponding 1,3-dicarbonyl compound and aromatic aldehyde (1.0 mmol each) in 3 mL of DMF/CH_3CN (1:2). The mixture was irradiated in a microwave reactor at 120 °C for 20 min and then poured onto crushed ice. The solid precipitates were isolated by filtration and washed with cold H_2O/CH_3CN (1:1) to afford the corresponding DHPM−thiones **1b−e** as colorless solids.

Ethyl 6-Methyl-4-(*p*-tolyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1b). Yield: 73%. mp: 190−192 °C (lit.[37] 192−194 °C). ^1H NMR (360 MHz, DMSO-d_6): δ 1.10 (t, $J = 7.1$ Hz, 3H), 2.25 (s, 3H), 2.27 (s, 3H), 3.40 (q, $J = 7.1$ Hz, 2H), 5.1 (d, $J = 3.3$ Hz, 1H), 7.08−7.15 (m, 4H), 9.61 (s, 1H), 10.30 (s,1H). MS (positive APCI, *m/z*): 291 [20, (M + 1)], 290 (100, M), 256 [45, (M − 34)].

Ethyl 6-Methyl-4-(3-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1c). Yield: 86%. mp: 187−189 °C. ^1H NMR (360 MHz, DMSO-d_6): δ 1.10 (t, $J = 7.1$ Hz, 3H), 2.29 (s, 3H), 4.02 (q, $J = 7.2$ Hz, 2H), 5.18 (s, 1H), 7.16−7.42 (m, 4H), 9.69 (s, 1H), 10.43 (s,1H). MS (positive APCI, *m/z*): 312 [30, (M + 2)], 311 [15, (M + 1)], 310 (100, M).

***N,N*-Diethyl 6-Methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1d).** Yield: 68%. mp: 221−223 °C. ^1H NMR (360 MHz, DMSO-d_6): δ 0.50 (s, 3H), 0.92 (s, 3H), 1.67 (s, 3H), 3.02 (s, 4H), 4.98 (s, 1H), 7.13−7.37 (m, 5H), 9.13 (s, 1H), 9.86 (s, 1H). MS (positive APCI, *m/z*): 303 (100, M), 244 [100, (M − 59)], 161 [45, (M − 142)].

***N,N*-Diethyl 6-Methyl-4-(4-fluorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1e).** Yield: 69%. mp: 238−240 °C. ^1H NMR (360 MHz, DMSO-d_6): δ 0.59 (s,3H), 0.92 (s,3H), 1.68 (s, 3H), 3.06 (s, 4H), 5.00 (s, 1H), 7.18 (s, 2H), 7.20 (s, 2H), 9.15 (s,1H), 9.89 (s, 1H). MS (positive APCI, *m/z*): 321 (100, M), 317 [60, (M − 4)].

General Procedure for the Conversion of DHPMs 1a−e to Sulfones 4a−e (Scheme 2). Methyl iodide (184 mg, 81 μL, 1.3 mmol) was added to a solution of the corresponding DHPM **1a−e** (1.0 mmol) in dry MeOH (3 mL), and the reaction mixture was subsequently irradiated at 120 °C for 15 min. The resulting mixture was neutralized by the addition of NEt_3 (695 μL, 5 mmol), and then all volatiles were removed in vacuo. The crude residue containing the corresponding 2-methylthio-1,4-dihydropyrimidines **2a−e** was extracted with a chloroform/water mixture, and after concentration of the organic extracts to ~10 mL, activated MnO_2 (435 mg, 5.0 mmol) was added. The reaction mixture was irradiated in a microwave reactor at 120 °C for 10−20 min. The mixture was filtered through a plug of silica and washed with $CHCl_3$ (3 × 4 mL). The solvent of the combined organic layers was removed in vacuo. To the crude 2-methylthiopyrimidines **3a−e**, MeOH (5 mL) and potassium hydrogen persulfate (Oxone) (1.8 g in 8 mL water, 3 mmol) were added. The reaction mixture was irradiated in a microwave reactor at 100 °C for 2 × 10 min (after the first 10 min, an additional 1.5 equiv of Oxone was added to the reaction mixture); then they were diluted with water and subsequently extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$ to give the sulfones **4a**, **4b**, and **4d** without any further purification (crude yield of 91−95%, HPLC purity at 215 nm 96−99%). The sulfones **4c** and **4e** were purified by silica gel column chromatography (petroleum ether: ethylacetate = 7:1) to provide pure products (82−86%).

Ethyl 6-Methyl-4-(*p*-tolyl)-2-methylsulfonyl-pyrimidine-5-carboxylate (4b). Yield: 95%. Pale yellow solid. mp: 91−93 °C. ^1H NMR (360 MHz, $CDCl_3$): δ 1.17 (t, $J = 7.1$ Hz, 3H), 2.42 (s, 3H), 2.71 (s, 3H), 3.40 (s, 3H), 4.29 (q, $J = 7.1$ Hz, 2H), 7.29 (d, $J = 8.1$ Hz, 2H), 7.64 (d, $J = 8.1$ Hz, 2H). MS (positive APCI, *m/z*): 335 [15, (M + 1)], 334 (100, M).

Ethyl 6-Methyl-4-(3-chlorophenyl)-2-methylsulfonyl-pyrimidine-5-carboxylate (4c). Yield: 86%. Colorless oil. ^1H NMR (360 MHz, DMSO-d_6): δ 1.09 (t, $J = 7.1$ Hz, 3H), 2.69 (s, 3H), 3.47 (s, 3H), 4.28 (q, $J = 7.1$ Hz, 2H), 7.61−7.72 (m, 4H). MS (positive APCI, *m/z*): 355 [35, (M + 1)], 354 (100, M), 292 [75, (M − 62)].

***N,N*-Diethyl 6-Methyl-4-phenyl-2-methylsulfonyl-pyrimidine-5-carboxylate (4d).** Yield: 91%. Colorless solid. mp: 95−97 °C. ^1H NMR (360 MHz, $CDCl_3$): δ 0.68 (t, $J = 7.1$ Hz, 3H), 1.11 (t, $J = 7.1$ Hz, 3H), 2.67 (s, 3H), 2.66−2.72 (m, 1H), 2.82−2.88 (m, 1H), 3.33−3.38 (m, 1H), 3.41 (s, 3H), 3.60−3.66 (m, 1H), 7.45−7.53 (m, 3H), 7.91 (d, $J = 7.5$ Hz, 2H). MS (positive APCI, *m/z*): 348 [10, (M + 1)], 347 (35, M), 285 [100, (M − 62)].

***N,N*-Diethyl 6-Methyl-4-(4-fluorophenyl)-2-methylsulfonyl-pyrimidine-5-carboxylate (4e).** Yield: 82%. Colorless oil. ^1H NMR (360 MHz, $CDCl_3$): δ 0.73 (t, $J = 7.1$ Hz, 3H), 1.15 (t, $J = 7.1$ Hz, 3H), 2.68 (s, 3H), 2.70−2.78 (m, 1H), 2.82−2.92 (m, 1H), 3.36−3.45 (m, 1H), 3.41 (s, 3H), 3.58−3.68 (m, 1H), 7.18 (t, $J = 8.6$ Hz, 2H), 7.95−7.99 (m, 2H). MS (positive APCI, *m/z*): 365 (100, M), 303 [100, (M − 62)].

General Procedure for the Displacement of the Sulfone Group in 4a−e with Pyrrolidine (Scheme 2). Freshly distilled pyrrolidine (17 mg, 20 μL, 0.24 mmol) was added to a solution of the corresponding sulfone **4a−e** (0.2 mmol) in THF (2 mL) in a 10 mL microwave vial,. The vial was sealed and irradiated in a microwave reactor at 100 °C for 10 min. The solvent was removed under reduced pressure, and the residue was then purified by silica gel column

chromatography to afford the 2-(pyrrolidine-1-yl)-pyrimidines **5aA**−**5eA** as colorless oils in 71−92% yields.

Ethyl 6-Methyl-4-(*p*-tolyl)-2-(pyrrolidin-1-yl)-pyrimidine-5-carboxylate (5bA). Yield: 92%. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.01 (t, J = 7.1 Hz, 3H), 1.97−2.01 (m, 4H), 2.39 (s, 3H), 2.50 (s, 3H), 3.64−3.68 (m, 4H), 4.08 (q, J = 7.1 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H). MS (positive APCI, *m/z*): 326 [30, (M + 1)], 325 (100, M).

Ethyl 6-Methyl-4-(3-chlorophenyl)-2-(pyrrolidin-1-yl)-pyrimidine-5-carboxylate (5cA). Yield: 75%. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.01 (t, J = 7.1 Hz, 3H), 1.98−2.02 (m, 4H), 2.52 (s, 3H), 3.64−3.68 (m, 4H), 4.08 (q, J = 7.1 Hz, 2H), 7.27−7.60 (m, 4H). MS (positive APCI, *m/z*): 348 [20, (M + 3)], 346 [35, (M + 1)], 345 (100, M).

***N,N*-Diethyl 6-Methyl-4-phenyl-2-(pyrrolidin-1-yl)-pyrimidine-5-carboxamide (5dA).** Yield: 78%. ^{1}H NMR (360 MHz, DMSO-d_6): δ 0.60 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H), 1.93 (br s, 4H), 2.65−2.71 (m, 1H), 2.85−2.91 (m, 1H), 3.15−3.20 (m, 1H), 3.42−3.48 (m, 1H), 3.52 (b, 4H), 7.42−7.73 (m, 5H). MS (positive APCI, *m/z*): 339 [20, (M + 1)], 338 (100, M).

***N,N*-Diethyl 6-Methyl-4-(4-fluorophenyl)-2-(pyrrolidin-1-yl)-pyrimidine-5-carboxamide (5eA).** Yield: 71%. ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.71 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.12 Hz, 3H), 1.98−2.02 (m, 4H), 2.38 (s, 3H), 2.71−2.76 (m, 1H), 2.91−2.97 (m, 1H), 3.25−3.31 (m, 1H), 3.55−3.62 (m, 1H), 3.62−3.69 (m, 4H), 7.05−7.87 (m, 4H). MS (positive APCI, *m/z*): 357 [20, (M + 1)], 356 (100, M).

Solid-Phase Synthesis of 2-(Piperidin-1-yl)-pyrimidine 5aB (Scheme 3). Merrifield resin (200 mg, 2.3 mmol/g of chlorine, 200−400 mesh, 2% DVB) was suspended in DMF (15 mL) and swollen for 20 min in a 20 mL microwave vial. Thione **1a** (380 mg, 1.4 mmol, 3 equiv) and K_2CO_3 (190 mg, 1.4 mmol) were added, and the suspension was irradiated in a microwave reactor at 160 °C for 20 min. The resin was filtered, washed successively with DMF (3 × 6 mL), THF (3 × 6 mL), MeOH/H_2O (3 × 6 mL), and MeOH (3 × 6 mL), and dried in vacuo to give resin-bound S-alkyl intermediate **6** (267 mg). A sample of resin-bound **6** (100 mg, 0.19 mmol) was suspended in CH_2Cl_2 (10 mL) and allowed to swell in the solvent for 20 min at room temperature. A solution of ceric ammonium nitrate (CAN) (131 mg, 0.23 mmol) in water (6 mL) was slowly added to the suspension. The mixture was irradiated at 130 °C for 30 min. After filtration, the resin was washed successively washed with DCM (3 × 5 mL), THF (3 × 5 mL), MeOH/H_2O (3 × 5 mL), MeOH (3 × 5 mL), and DMF (4 × 5 mL). The suspension of the resulting resin in DMF (**7**) was cooled to 0 °C, and potassium hydrogen persulfate (Oxone) (367 mg, 0.6 mmol in water) was slowly added. The reaction mixture was irradiated at 150 °C for 3 × 15 min (after the first and second 15 min, an additional 1.5 equiv of Oxone was added to the reaction mixture). The resin was filtered, washed successively with DCM (3 × 5 mL), THF (3 × 5 mL), MeOH/H_2O (3 × 5 mL), and MeOH (3 × 5 mL), and dried in vacuo to give resin-bound sulfone **8.** The resin-bound sulfone **8** (100 mg, 0.19 mmol) was suspended in EtOH (10 mL). Freshly distilled piperidine (20 mg, 24 μL, 0.24 mmol) was added to the suspension, and the suspension was irradiated in a microwave reactor at 100 °C for 10 min. The resin was filtered and washed with EtOH (3 × 10 mL). The filtrates were combined and concentrated under reduced pressure to give pyrimidine **5aB** (43% in overall yield based on the initial loading of Merrifield resin) and ∼75% purity (HPLC at 215 nm). Subsequent purification by silica gel chromatography provided a sample of pure **5aB** which was in all respects identical to a sample prepared by solution-phase methods (see above).

Preparation of Dihydropyrimidone 9 (Scheme 4). Potassium hydrogen persulfate (Oxone) (461 mg, 0.75 mmol) was slowly added to a solution of 2-methylthio-1,4-dihydropyrimidine **2a** (73 mg, 0.25 mmol) in MeOH (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 48 h; then it was diluted with water and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with water and brine and dried over $MgSO_4$. All solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 7:1) to give 56 mg (87%) of known DHPM **9**.

Preparation of 2-Benzylamino-1,4-dihydropyrimidine 10 (Scheme 5). Trifluoroacetic acid (285 mg, 192 μL, 2.5 mmol) was carefully added to a solution of 2-methylthio-1,4-dihydropyrimidine **2a** (145 mg, 0.5 mmol) in DCM (3 mL) at room temperature. The mixture was stirred for 15 min; then all volatiles were removed, and the residue was crystallized from diethyl ether to give 180 mg (89%) of the trifluoroacetate salt of **2a** as a white solid that was dried in vacuo. Benzyl amine (48 mg, 49 μL, 0.52 mmol) was added to a solution of the salt (180 mg, 0.44 mmol) in THF (3 mL), and the mixture was subsequently irradiated in a microwave reactor at 120 °C for 1 h. All solvent was removed in vacuo, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 7:1) to give 91 mg (52%) of 2-amino-1,4-dihydropyrimidine **10** as a white semisolid.^{1}H NMR (360 MHz, $CDCl_3$): δ 1.14 (t, J = 7.1 Hz, 3H), 2.36 (s, 3H), 3.99 (m, 2H), 4.32 (m, 2H), 7.19−7.27 (m, 10H). MS (positive APCI, *m/z*): 350 [35, (M + 1)], 349 (100, M).

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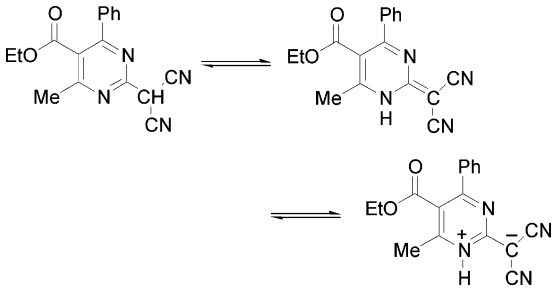

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