5-Aroyl-3,4-dihydropyrimidin-2-one Library Generation via Automated Sequential and Parallel Microwave-assisted Synthesis Techniques

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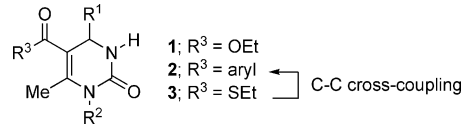
An efficient two-step synthetic pathway toward the preparation of diversely substituted 5-aroyl-3,4-dihydropyrimidin-2-ones is realized. The protocol involves an initial trimethylsilyl chloride-mediated Biginelli multicomponent reaction involving *S*-ethyl acetothioacetate, aromatic aldehydes, and ureas as building blocks to generate a set of 3,4-dihydropyrimidine-5-carboxylic acid thiol esters. These thiol esters serve as starting materials for a subsequent Pd-catalyzed Cu-mediated Liebeskind−Srogl cross-coupling reaction with boronic acids to provide the desired 5-aroyl-3,4-dihydropyrimidin-2-one derivatives. Both steps were performed using microwave heating in sealed vessels, either in an automated sequential or parallel format using dedicated microwave reactor instrumentation. A diverse library of 30 5-aroyl-3,4-dihydropyrimidin-2-ones was prepared with commercially available aldehyde, urea, and boronic acid building blocks as starting materials.

Introduction

Modern drug discovery progressively relies on high-speed organic synthesis and combinatorial/parallel chemistry techniques for the efficient generation of compound libraries. Microwave-assisted organic synthesis[1,2] and combinatorial chemistry, together with high-throughput screening methods, have been instrumental for the rapid synthesis, screening, and identification of compounds with new and improved biological activities.[3] In this context, interest in multifunctionalized 3,4-dihydropyrimidin-2(*1*H)-ones (DHPMs, Chart 1) synthesized via the one-pot Biginelli three-component condensation[4] has surged rapidly because of the pharmacological properties associated with many derivatives of this privileged heterocyclic core.[5−8] Reports have described several DHPMs that have been identified, for example, as calcium channel modulators[6] or small molecules targeting the mitotic machinery.[7] Notably, 4-aryldihydropyrimidinone heterocycles of type **1** possessing a C5 ester moiety have proven to be excellent templates for selective α_{1a} receptor subtype antagonists to warrant further consideration for the treatment of benign prostatic hyperplasia (BPH).[8] In contrast to the readily available DHPM C5 esters **1**, the corresponding C5-aroyl derivatives **2** have received little attention in the literature so far.[9] The pharmacological potential of these bis(hetero)aryl ketones therefore is largely unexplored.

Although a large number of DHPM derivatives can be prepared directly via one-pot Biginelli multicomponent protocols,[4,5] a much larger number of very interesting heterocycles possessing the DHPM scaffold can be obtained by chemical functionalization of the six diversity points around the DHPM core.[10] In a series of recent publications,

Chart 1



we have disclosed several high-speed methods for the scaffold decoration of DHPMs involving microwave-assisted transformations.[11] In continuation of our interest in the generation of diversely substituted and novel types of privileged scaffolds of the 3,4-dihydropyrimidin-2-one type (DHPMs), we herein report the efficient solution-phase synthesis of a 30-member library of 5-aroyl-dihydropyrimidinones **2**.[12] Our two-step method utilizes DHPM-5-carboxylic acid thiol esters **3** as key intermediates, which subsequently undergo a Pd-catalyzed Liebeskind−Srogl carbon−carbon cross-coupling with boronic acids[13] to furnish DHPMs **2** using automated sequential and parallel microwave-assisted processing.

Results and Discussion

Synthesis of DHPM C5 Thiol Esters via Biginelli Condensation. Over the years a large variety of protocols have been developed to synthesize 3,4-dihydropyrimidin-2-ones of the DHPM type on the basis of Biginelli multicomponent chemistry.[4,5] This cyclocondensation generally involves the acid-catalyzed condensation of an aldehyde, a CH-acidic carbonyl compound, and an urea component. In our previous work, we have described the use of Lewis acids such as $Yb(OTf)_3$ (10 mol %) as efficient catalysts for microwave-assisted Biginelli reactions.[14] Because of the high cost of the involved lanthanide salts we were interested to find alternative catalysts or reaction mediators that could be applied with equal or even higher efficiency under high-speed microwave conditions.

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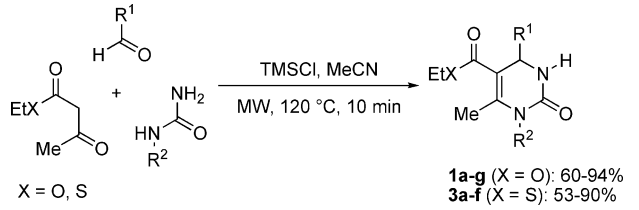
Table 1. Microwave-Assisted Biginelli Reactions Mediated by Trimethylsilyl Chloride[a]



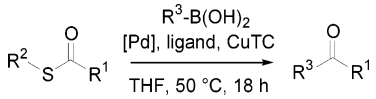
DHPM	R^1	R^2	X	yield (%)[b]
1a	Ph	H	O	94
1b	Ph	Me	O	80
1c	Ph	Et	O	68
1d	thiophen-2-yl	Me	O	60
1e	4-NO_2-C_6H_4	Et	O	73
1f	3,4-$(F)_2$-C_6H_3	Me	O	79
1g	3,4-$(F)_2$-C_6H_3	Et	O	62
3a	Ph	H	S	90
3b	3-Br-C_6H_4	H	S	86
3c	2-CF_3-C_6H_4	H	S	66
3d	3,4-$(OMe)_2$-C_6H_3	H	S	76
3e	thiophen-2-yl	Me	S	62
3f	3,4-$(F)_2$-C_6H_3	Et	S	53

[a] Single-mode microwave irradiation under sealed vessel conditions. For more details, see the Experimental Section. [b] Isolated yield of pure products.

In this context, we have evaluated the use of trimethylsilyl chloride (TMSCl) as a reaction mediator for the Biginelli reaction using microwave heating (Table 1). In the past few years, several publications have described the use of this reagent in stoichiometric quantities as an efficient mediator for the Biginelli[15] and closely related[16] multicomponent reactions at room temperature. All our optimization work was performed in a sequential single-mode automated process in sealed vessels using controlled microwave heating.[14] The protocol was initially optimized for the condensation of ethyl acetoacetate with benzaldehyde and urea leading to DHPM **1a** (Table 1) looking at the following parameters: reaction temperature, solvent, reaction time, and molar ratios of the building blocks and TMSCl reagent.

To our delight, TMSCl proved to be a very effective mediator for the synthesis of both N1-unsubstituted and the more difficult to prepare N1-alkyl-substituted DHPMs, providing short reaction times and high yields equal to those of the considerably more expensive lanthanide-based Lewis acid salts. In our hands, the solvent of choice was acetonitrile because of its capability of dissolving all the starting materials at the elevated temperatures used for the condensation process. At the same time, the low solubility of the reaction products in most instances allowed direct precipitation of pure DHPMs from the crude reaction mixture at room temperature or by the addition of crushed ice. In this respect, acetonitrile was a more favorable choice than THF or a mixture of DMF and acetonitrile that had been previously used.[15,16] After some optimization, the most effective temperature was found to be 120 °C which proved to be a good compromise between the degradation of the urea building blocks at higher temperatures (giving rise to undesired byproducts)[14] and the achieving of short reaction times (10 min) in combination with high yields (94% for DHPM **1a**). Longer reaction times did not provide any significant yield increases. The cleanest conversions and highest product yields were typically obtained applying 3.0 equiv of the urea component and equimolar amounts of the CH-acidic carbonyl compound, aldehyde, and TMSCl. The current protocol was applicable to a range of different Biginelli reactions involving N-alkyl ureas and electron-rich and electron-poor aromatic aldehydes providing DHPMs **1a**−**g** in a 60−94% isolated yield (Table 1).

Scheme 1. Pd-Catalyzed Liebeskind−Srogl Protocol for the Synthesis of Ketones

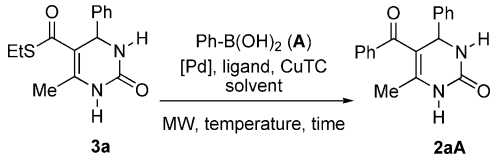


Having an optimized general protocol for a high-speed TMSCl-mediated Biginelli condensation in hand, we next proceeded to apply this method to the synthesis of the required DHPM-5-carboxylic acid thiol esters **3**. Without any modification, our protocol delivered a 90% isolated yield of DHPM **3a** when *S*-ethyl acetothioacetate was used in place of ethyl acetoacetate. It is interesting to note that only one single reference for the synthesis of a DHPM-5-carboxylic acid thiol esters **3** exists in the literature.[17] As with the corresponding oxygen analogs **1**, the TMSCl protocol was applied toward the synthesis of a small collection of DHPM thiol esters **3** involving sterically hindered aromatic and heterocyclic aldehydes, in combination with unsubstituted and alkyl-substituted ureas (Table 1).

While the required key *S*-ethyl acetothioacetate building block is not commercially available, it can be prepared on a large scale via Claisen self-condensation of *S*-ethyl thioacetate as described in the literature.[18]

Liebeskind−Srogl Coupling of DHPM Thiol Esters 3 with Boronic Acids. Although several methods for the preparation of ketones from thiol esters have been described in the literature,[19] it has to be noted that none of those can be performed under neutral conditions or can be considered to be generally applicable since the reaction partners are often too sensitive under the employed reactions conditions. The Liebeskind−Srogl ketone synthesis represents a novel Pd-catalyzed carbon−carbon cross-coupling procedure that allows the preparation of ketones from thiol esters under mild and base-free conditions (Scheme 1). The protocol requires a stoichiometric amount of a Cu(I) carboxylate, such as Cu(I) thiophene-2-carboxylate (CuTC),[20] acting as a metal cofactor. Although the mechanism of this and related cross-couplings is not completely understood at the moment, the crucial role of the cofactor seems to be that CuTC simultaneously polarizes the Pd−S bond through Cu(I) coordination to S while activating the trivalent boron through coordination of the carboxylate.[13,21] For all these mechanistic reasons the protocol requires an inert atmosphere to prevent the oxidation of the Cu(I) salt to an ineffective Cu(II) species, with reaction times typically ranging from 12 to 18 h at 50 °C in inert solvents such as THF or dioxane. The advantage of this ketone synthesis is the use of commercially available boronic acids as reaction partners which exhibit a broad range of functional group tolerance, are air and moisture-stable, are easy to handle, and have relatively low toxicity in comparison to other heavy metal organometallic reagents. Despite these

Table 2. Optimization Studies for the Microwave-Assisted Coupling of Thiol Ester **3a** to Ketone **2aA** Using the Liebeskind−Srogl Protocol[a]



entry	concentration[b]	(pre)catalyst/ligand	$PhB(OH)_2$/CuTC (equiv)	solvent	time (min)	temp (°C)	yield (%)[c]
a	0.07	$Pd(PPh_3)_4$ (5 mol %)	1.2/3	THF	45	100	41
b	0.07	$Pd(PPh_3)_4$ (10 mol %)	2/4	THF	60	130	66
c	0.07	$Pd(dba)_2$ (5 mol %) + PPh_3 (10 mol %)	2/4	dioxane	60	130	27
d	0.07	$Pd_2dba_3 \cdot CHCl_3$ (5 mol %) + TFP (15 mol %)	2/4	THF	60	130	43
e	0.07	$PdCl_2$(dppf) (20 mol %) + TFP (40 mol %)	2/4	dioxane	60	130	38
f	0.07	$PdCl_2$(dppf) (20 mol %) + PPh_3 (40 mol %)	2/4	dioxane	60	130	33
g	0.07	Herrmann catalyst (20 mol %) + dppf (40 mol %)	2/4	dioxane	60	130	22
h	0.07	$Pd(OAc)_2$ (10 mol %) + P(*t*Bu)$_3$ (20 mol %)	2/4	dioxane	60	130	29
i	0.07	$Pd(OAc)_2$ (10 mol %) + PPh_3 (20 mol %)	3/4	dioxane	60	130	71
j	0.07	$Pd(OAc)_2$ (10 mol %) + PPh_3 (20 mol %)	2/4	dioxane	120	100	58
k	0.07	$Pd(OAc)_2$ (10 mol %) + PPh_3 (20 mol %)	1.5/3	dioxane	60	130	56
l	0.07	$Pd(OAc)_2$ (10 mol %) + PPh_3 (20 mol %)	2/3	dioxane	60	130	72
m	0.07	$Pd(OAc)_2$ (10 mol %) + PPh_3 (20 mol %)	2/3	dioxane	30	130	51
n	0.07	$Pd(OAc)_2$ (5 mol %) + PPh_3 (15 mol %)	2/3	dioxane	60	130	55
o	0.07	$Pd(OAc)_2$ (10 mol %) + PPh_3 (20 mol %)	2/3	dioxane	90	130	59
p	0.15	$Pd(OAc)_2$ (10 mol %) + PPh_3 (20 mol %)	2/3	dioxane	60	130	86
q	0.30	$Pd(OAc)_2$ (10 mol %) + PPh_3 (20 mol %)	2/3	dioxane	60	130	75
r	0.15	$Pd(OAc)_2$ (10 mol %) + PPh_3 (20 mol %)	2/3	dioxane	90	130	71
s	0.15	$Pd(OAc)_2$ (10 mol %) + PPh_3 (20 mol %)	2/3	THF	60	130	76

[a] Single-mode microwave irradiation in sealed vessels (Biotage Initiator Eight EXP). [b] Molar concentration of DHPM **3a**. [c] Isolated product yield after column chromatography. For more details, see the Experimental Section.

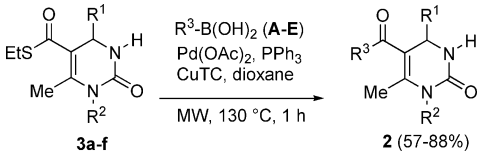
advantages, we are not aware of any application of the Liebeskind−Srogl ketone synthesis in a high-throughput synthesis/combinatorial context.

As a suitable model for reaction optimization, we decided to investigate the coupling of DHPM-5-carboxylic acid thiol ester **3a** (0.3 mmol scale) with phenylboronic acid under sealed-vessel microwave-heating conditions using a single-mode instrument (see Table 2). The screening of the reaction conditions was performed by tuning all the main factors: solvents, molar ratio of reactants, percentage of catalyst and of the CuTC metal cofactor, catalytic systems (namely, palladium(0) sources and ligands), reaction time, temperature, and effect of additives. With respect to the solvent, our studies support earlier investigations by Liebeskind and co-workers[13,21] that the use of solvents with coordinating properties such as DMF or DMA is not suitable for these types of cross-coupling. In addition, the use of protic solvents such as MeOH is not successful, despite the favorable coupling properties of these solvents with microwave irradiation. Somewhat surprisingly, the use of acetonitrile as a solvent did not furnish the desired reaction product ketone **2a** at all. Ethereal solvents such as THF and dioxane proved to be the best solvents for this coupling protocol. In our hands, dioxane provided slightly higher product yields (entries p and s in Table 2) and therefore was used for all future studies. In the refinement of the protocol in terms of the catalytic system, we found that the use of comparatively inexpensive $Pd(OAc)_2$ as a precatalyst in combination with PPh_3 as a ligand proved to be the most effective system. The best results were obtained with 10 mol % of $Pd(OAc)_2$ and 20 mol % of PPh_3 (entry p, Table 2). A reduced catalyst loading led to significantly lower yields (entry n, Table 2). Apart from the $Pd(OAc)_2/PPh_3$ system, a variety of other catalysts and different combinations of palladium precatalysts/ligands were tested (Table 2). All of these proved to be effective for this transformation but furnished lower isolated product yields. The reaction temperature of choice proved to be 130 °C, since lower values led to incomplete conversions using the identical 60 min time frame. We also discovered that the molar concentration of the starting material is critical for the success of this transformation. The best results were achieved with an initial concentration of 0.15 M of the DHPM thiol ester (compare entries l, p, and q, Table 2). The highest conversions were typically seen after a reaction time of 60 min. Reaction times longer than 60 min (entry r, Table 2) did not result in increased yields, and shorter irradiation periods (entry m, Table 2) led to reduced conversions. The use of additives such as a coordinating metal salt (i.e., 1.5 equiv of $Zn(OAc)_2$)[13,21] or of molecular sieves as water scavengers was not effective in further increasing the product yields.

The most effective experiment (entry p, Table 2) was performed with an excess of both phenylboronic acid (2 equiv) and of the CuTC metal cofactor (3 equiv), providing the desired ketone product **2aA** in a reproducible 86% isolated yield. Importantly, the reaction could be scaled directly from 0.3 mmol to 2.0 mmol using a 20 mL reaction vessel in a suitable single-mode microwave system. In fact, by maintaining the previously optimized reaction parameters, we obtained nearly identical results (86 versus 82%).

To simplify the purification protocol and to make the reaction more attractive for the preparation of combinatorial libraries (see below), we have also investigated the use of polymer-supported catalytic systems. While the use of

Table 3. Thirty Member Library of 5-Aroyl-DHPMs **2** Obtained from DHPM Thiol Esters **3a**−**f** and Boronic Acids **A**−**E** Using Liebeskind−Srogl Ketone Synthesis[a]



DHPM **2**	R^1	R^2	R^3	yield (%)[b]
2aA	Ph	H	Ph	86
2aB	Ph	H	3-Cl-C_6H_4	80
2aC	Ph	H	4-Me-C_6H_4	78
2aD	Ph	H	3-OMe-C_6H_4	74
2aE	Ph	H	3,4-$(F)_2$-C_6H_3	88
2bA	3-Br-C_6H_4	H	Ph	66
2bB	3-Br-C_6H_4	H	3-Cl-C_6H_4	64
2bC	3-Br-C_6H_4	H	4-Me-C_6H_4	61
2bD	3-Br-C_6H_4	H	3-OMe-C_6H_4	58
2bE	3-Br-C_6H_4	H	3,4-$(F)_2$-C_6H_3	68
2cA	2-CF_3-C_6H_4	H	Ph	65
2cB	2-CF_3-C_6H_4	H	3-Cl-C_6H_4	70
2cC	2-CF_3-C_6H_4	H	4-Me-C_6H_4	64
2cD	2-CF_3-C_6H_4	H	3-OMe-C_6H_4	57
2cE	2-CF_3-C_6H_4	H	3,4-$(F)_2$-C_6H_3	66
2dA	3,4-$(OMe)_2$-C_6H_3	H	Ph	71
2dB	3,4-$(OMe)_2$-C_6H_3	H	3-Cl-C_6H_4	74
2dC	3,4-$(OMe)_2$-C_6H_3	H	4-Me-C_6H_4	63
2dD	3,4-$(OMe)_2$-C_6H_3	H	3-OMe-C_6H_4	59
2dE	3,4-$(OMe)_2$-C_6H_3	H	3,4-$(F)_2$-C_6H_3	74
2eA	thiophen-2-yl	Me	Ph	82
2eB	thiophen-2-yl	Me	3-Cl-C_6H_4	77
2eC	thiophen-2-yl	Me	4-Me-C_6H_4	68
2eD	thiophen-2-yl	Me	3-OMe-C_6H_4	62
2eE	thiophen-2-yl	Me	3,4-$(F)_2$-C_6H_3	69
2fA	3,4-$(F)_2$-C_6H_3	Et	Ph	73
2fB	3,4-$(F)_2$-C_6H_3	Et	3-Cl-C_6H_4	70
2fC	3,4-$(F)_2$-C_6H_3	Et	4-Me-C_6H_4	66
2fD	3,4-$(F)_2$-C_6H_3	Et	3-OMe-C_6H_4	57
2fE	3,4-$(F)_2$-C_6H_3	Et	3,4-$(F)_2$-C_6H_3	65

[a] Single-mode microwave irradiation on a 0.30 mmol scale in sealed vessels (Biotage Initiator Eight EXP). [b] Isolated product yield after column chromatography. For more details, see the Experimental Section.

polymer-supported PPh_3 or of supported Pd catalysts, such as FibreCat (FibreCat 1001, 1007 and 1026),[22] did simplify product purification to some extent, both methods furnished significantly lower product yields (22−47%) and were therefore not further investigated. The application of fluorous PPh_3 in combination with fluorous solid-phase extraction (F-SPE)[23] proved to be somewhat more effective, allowing the isolation of the desired product in a 56% yield without extensive purification by column chromatography. Although not used for the current library protocol (see below), this method could prove useful in the synthesis of larger compound libraries in an automated fashion.

Library Production Using Automated Sequential Processing. Having an optimized and robust protocol for the microwave-assisted Liebeskind−Srogl ketone synthesis in hand, we next set out to prepare a small library of 30 5-aroyl DHPMs of type **2** from six diversely substituted DHPM thiol esters **3a**−**f** (Table 1) and five commercially available arylboronic acids (**A**−**E**, Table 3). The synthesis of the library was performed using automated sequential processing in a dedicated single-mode microwave reactor in sealed vessels following exactly the protocol optimized for DHPM **2aA** on a 0.30 mmol scale. The microwave-assisted library generation furnished all the desired ketones **2** in good to high yields (57−88%), tolerating both electron-rich and electron-poor aryl boronic acids (Table 3). The results shown in Table 3 also demonstrate the suitability of a range of DHPM thiol esters **3** as building blocks in this reaction, both involving N1-unsubstituted and N1-alkyl derivatives.

Of particular interest are Liebeskind−Srogl transformations involving DHPM scaffolds with "Suzuki-active" aryl halides such as DHPM **3b**, which because of the base-free conditions exhibit complete selectivity[24] for ketone synthesis as opposed to Suzuki biaryl coupling.[25] The neutral Liebeskind−Srogl protocol proved to be generally applicable, tolerating a variety of different functional groups such as halides, methoxy groups, and heterocycles like the thiophene moiety. All 30 library compounds were isolated by silica gel column chromatography and fully characterized by ^1H NMR and MS analysis.

Library Production Using Parallel Processing in Rotor Systems. While automated sequential microwave synthesis has been a very successful concept for the construction of small compound libraries,[3] this method becomes impractical if one considers the generation of larger compound libraries. For the preparation of the comparatively small 30 member 5-aroyl-DHPM **2** library described above, the overall microwave irradiation time (1 h per individual reaction) would already be 30 h. We have therefore considered the synthesis of the same library in a parallel format in one microwave irradiation experiment using multivessel rotor technology. Several publications have already described the successful preparation of compound libraries in multivessel rotor systems employing suitable multimode microwave reactors with comparatively large microwave cavities.[26−29] Here, we describe the use of a novel 48-vessel rotor system (filling volume of 6.0−25 mL per vessel, see Figure S1 in the Supporting Information) in combination with a commercial multimode microwave reactor (Synthos 3000, Anton Paar)[28] for the preparation of a 16-member subset of the above DHPM library.

An important issue in parallel microwave processing is the homogeneity of the electromagnetic field in the microwave cavity. Inhomogeneities in the field distribution may lead to the formation of so-called hot and cold spots resulting in different reaction temperatures in individual vessels, and therefore different conversions. We therefore initially investigated the reaction homogeneity in the 48-vessel rotor system by looking at a suitable, easy-to-monitor model reaction. For this purpose, we have chosen the acid-catalyzed esterification of benzoic acid with ethanol as a model reaction (EtOH/1 M aq H_2SO_4 = 2:1 v/v, 140 °C, 20 min). Initial optimization experiments in a single-mode microwave instrument demonstrated that this esterification proved to be somewhat sensitive to the reaction temperature.[30] Any significant temperature differences between individual vessels of the rotor would therefore translate to differences in conversion. Gratifyingly, we found that when the esterification reaction was performed in the 48-vessel rotor at an internal temper-

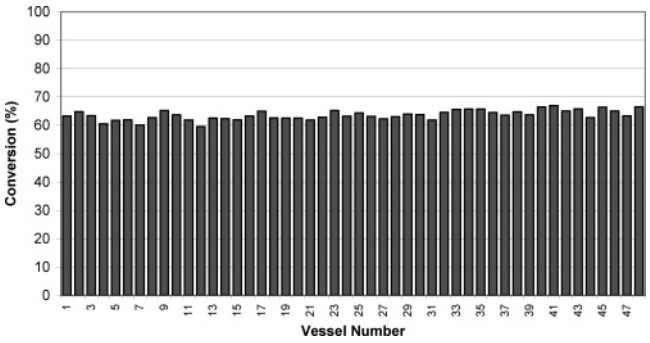


Figure 1. Graphical analysis of conversions in the individual vials of the 48-vessel rotor system for the esterification of benzoic acid with ethanol. The conversions to ethyl benzoate in all 48 vials were very similar (59.5−66.9%, average conversion 63.6%, SD = 1.7). Conversions were measured by HPLC analysis (215 nm).

Table 4. Comparison of Yields of 5-Aroyl-DHPMs **2** (Table 3) Obtained via Single-Mode and Multimode Synthesis[a]

				sequential	parallel
DHPM **2**	R^1	R^2	R^3	yield (%)[b]	yield (%)[b]
2aA	Ph	H	Ph	86	80
2aB	Ph	H	3-Cl-C_6H_4	80	83
2aC	Ph	H	4-Me-C_6H_4	78	74
2aD	Ph	H	3-OMe-C_6H_4	74	71
2aE	Ph	H	3,4-$(F)_2$-C_6H_3	88	85
2bA	3-Br-C_6H_4	H	Ph	66	69
2bB	3-Br-C_6H_4	H	3-Cl-C_6H_4	64	62
2cA	2-CF_3-C_6H_4	H	Ph	65	67
2cB	2-CF_3-C_6H_4	H	3-Cl-C_6H_4	70	69
2cE	2-CF_3-C_6H_4	H	3,4-$(F)_2$-C_6H_3	66	63
2dA	3,4-$(OMe)_2$-C_6H_3	H	Ph	71	68
2dB	3,4-$(OMe)_2$-C_6H_3	H	3-Cl-C_6H_4	74	71
2dC	3,4-$(OMe)_2$-C_6H_3	H	4-Me-C_6H_4	63	64
2dE	3,4-$(OMe)_2$-C_6H_3	H	3,4-$(F)_2$-C_6H_3	74	72
2eA	thiophen-2-yl	Me	Ph	82	86
2eC	thiophen-2-yl	Me	4-Me-C_6H_4	68	66

[a] Single-mode microwave irradiation on a 0.30 mmol scale in sealed vessels (Biotage Initiator Eight EXP), results from Table 3. Multimode microwave synthesis on a 0.30 mmol scale in a 48-vessel rotor system (Synthos 3000, Anton Paar). [b] Isolated product yield after column chromatography. For more details, see the Experimental Section.

ature of 140 °C for 20 min, the conversions in all 48 vials were very similar, ranging from 60 to 67% (Figure 1). Similar results were also obtained for a 64-vessel rotor system (see Figures S2 and S3 in the Supporting Information).

Having confirmed temperature and reaction homogeneity in the rotor system, we next set out to synthesize the 16-member subset library via the Liebeskind−Srogl reaction (Table 4) to see how yields from the single-mode runs would compare with the multimode experiment. For the realization of this small parallel library synthesis, the 16 vessels of the middle ring of the 48-vessel rotor (Figure S1) were filled with the appropriate reaction mixtures (0.30 mmol scale) and then irradiated for 60 min at 130 °C. Gratifyingly, in comparison with the automated sequential single-mode process, nearly identical product yields were obtained for the 16 studied examples (Table 4). The total microwave irradiation time for the preparation of the 16 compounds was 1 h, demonstrating the successful concept and time savings achieved by application of microwave-assisted processing in a parallel format.

Conclusion

In conclusion, we have developed a two-step protocol for the synthesis of 5-aroyl-3,4-dihydropyrimidine-2-ones libraries of type **2**, combining a trimethylsilyl chloride-mediated Biginelli multicomponent approach with the transition metal-catalyzed Liebeskind−Srogl ketone synthesis. This novel method uses commercially available building blocks (aldehydes, boronic acids, and ureas) to generate diversity on the 5-aroyl-DHPM scaffold that is otherwise not easily available. Both reaction steps can be efficiently carried out with controlled microwave irradiation. For the second step, the Pd-catalyzed Liebeskind−Srogl cross coupling, the results obtained from automated sequential microwave processing in single-mode instruments were comparable with those from parallel processing in multimode instruments. While the sequential treatment of individual reaction vessels allows better control over the reaction conditions, the throughput is significantly higher for parallel processing.

Experimental Section

General Methods. All building blocks were purchased from commercial sources and were used without any further purification. TLC analysis was performed on Merck precoated 60 F_{254} plates. ^{1}H NMR spectra were recorded on a Bruker AM360 in $CDCl_3$ or DMSO-d_6, operating at 360 MHz. Mass spectra were taken on a Hewlett-Packard LC/MSD 1100 series instrument in the atmospheric-pressure chemical-ionization positive APCI mode. HPLC analysis was performed on a Shimadzu LC-10 system that included LC10-AT(VP) pumps, an autosampler (SIL-10AXL), and a dual wavelength UV detector set at 215 and 254 nm. The separation was carried out using a C 18 reversed-phase analytical column, LiChrospher 100 (E. Merck, 100 × 3 mm, particle size 5 μm) at 25 °C and a mobile phase from (A) 0.1% TFA in 90:10 water/MeCN and (B) 0.1% TFA acid in MeCN (all solvents were HPLC grade, Acros; TFA was analytical reagent grade, Aldrich). The following gradients were applied at a flow rate of 0.5 mL/min: linear increase from solution 30% B to 100% solution B in 8 min and a hold at 100% solution B for 2 min.

Microwave Irradiation Experiments. Single-mode microwave irradiation experiments were carried out using an Emrys Synthesizer or Initiator Eight EXP model from Biotage AB (Uppsala, Sweden).[14] Experiments were carried out in sealed microwave process vials using the standard absorbance level (300 W maximum power). Reaction times under microwave conditions reflect total irradiation times rather than actual reaction times at a given temperature. Multimode microwave irradiation was performed in a Synthos 3000 reactor using a dedicated 48-vessel rotor system both from Anton Paar GmbH, Austria.[28]

***S*-Ethyl Acetothioacetate.**[18] A solution of 16.67 g (160 mmol) of *S*-ethyl thioacetate in 50 mL of dry ether was added dropwise to 80 mL of a 2 M solution of isopropylmagnesium chloride in 120 mL of dry THF at −20 °C. The mixture was then stirred at 0 °C for 4 h. Fifteen milliliters of concentrated HCl and 15 g of ice were added to the solution at 0 °C. The layers were separated and the organic phase was extracted with 45 mL of 5% sodium bicarbonate solution

and then dried over sodium sulfate. The solvent was evaporated, and the product was distilled under high vacuum (bp 88 °C, 5 mbar), yielding 9.95 g (85%) of the desired product (keto/enol form 75/25) as a colorless oil with a purity of greater than 98% (detected by HPLC). ^{1}H NMR ($CDCl_3$, 360 MHz) of keto form: δ 3.67 (s, 2H), 2.95 (q, $J = 7.4$ Hz, 2H), 2.28 (s, 3H), 1.29 (t, $J = 7.4$ Hz, 3H).

General Procedure for the Microwave-Assisted Biginelli Protocol (Table 1). The appropriate aldehyde (2.0 mmol), urea (6.0 mmol), 1,3-dicarbonyl compound (2.0 mmol), and acetonitrile (3 mL) were placed in a 10 mL Pyrex microwave process vial. After the addition of TMSCl (2.0 mmol), the vessel was sealed and subsequently irradiated for 10 min at 120 °C. After it was cooled to ambient temperature, the mixture was poured onto crushed ice (30 g) and allowed to stand at 4 °C for 18 h. The resulting precipitated solid was collected by filtration and washed with a cold 1:1 mixture of ethanol/water, providing the desired DHPM products **1a**−**g** and **3a**−**f** as off-white solids in 53−90% yields and high purity (>98% detected by HPLC analysis). For ^{1}H NMR and MS data, see the Supporting Information.

General Procedure for Microwave-Assisted Liebeskind−Srogl Cross-Couplings. Single-Mode Reactor (Table 3). A dry microwave process vial was charged with the corresponding C5-DHPM thiol ester **3a**−**f** (0.30 mmol), the appropriate boronic acid **A**−**E** (0.6 mmol), CuTC (171 mg, 0.90 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol, 10 mol %), and PPh_3 (16 mg, 0.06 mmol, 20 mol %). Then the reaction vessel was sealed and flushed with argon. Through the septum of the microwave vessel, anhydrous, degassed dioxane (2 mL) was added, and the mixture was subsequently heated for 1 h at 130 °C with microwave irradiation. After the mixture was cooled to ambient temperature, the solvent was evaporated, and the crude mixture was diluted with ethyl acetate (80 mL) and extracted with 10% aqueous ammonia (3 × 30 mL). The organic layer was dried over $MgSO_4$ and then concentrated under reduced pressure to afford a semisolid that was subsequently purified by silica gel column chromatography using a 5:1 mixture of $CHCl_3$/acetone (Table 3, entries **2aA**−**2dE**) or a 1:2 mixture of ethyl acetate/petroleum ether (Table 3, entries **2eA**−**2fE**) as an eluent. This procedure provides the pure ketones **2** as solids in 57−88% yields (Table 3) and high purity (>98% detected by HPLC analysis). For ^{1}H NMR and MS data, see the Supporting Information.

Microwave-Assisted Liebeskind−Srogl Cross Coupling. Parallel Processing in a Multimode Reactor (Table 4). Sixteen dry 50 mL Teflon vessels were charged with a magnetic stirring bar. This was followed by the addition of the appropriate DHPM thiol esters **3b**−**f** (0.30 mmol), the appropriate boronic acids **A**−**E** (0.6 mmol), CuTC (172 mg, 0.9 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol, 10 mol %), and PPh_3 (16 mg, 0.06mmol, 20 mol %). The vessels were sealed with a septum and subsequently flushed with Ar. Anhydrous, degassed dioxane (2 mL) was added through the septum. In the same way, the reference vessel (where the temperature was measured with a direct probe) was charged with 249 mg (0.90 mmol) of DHPM **3a**,[31] 219 mg (1.80 mmol) of phenylboronic acid, 515 mg (2.70 mmol) of CuTC, 20 mg (0.09 mmol, 10 mol %) of $Pd(OAc)_2$, 47 mg (0.18 mmol, 20 mol %) of PPh_3, and 6 mL of anhydrous, degassed dioxane. All the vessels were closed and placed in the center circle of the rotor, which was subsequently moved into the microwave cavity. After a ramp of 10 min to heat the system up to 100 °C and another 5 min to reach 130 °C, the vessels were subsequently irradiated for 1 h to 130 °C. After they were cooled to 40 °C (10 min), the crude reaction mixtures were worked up as described above for the sequential procedure. Yields are given in Table 4.

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Supporting Information Available. ^{1}H NMR spectral data, MS analysis, and systematic names of all library compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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