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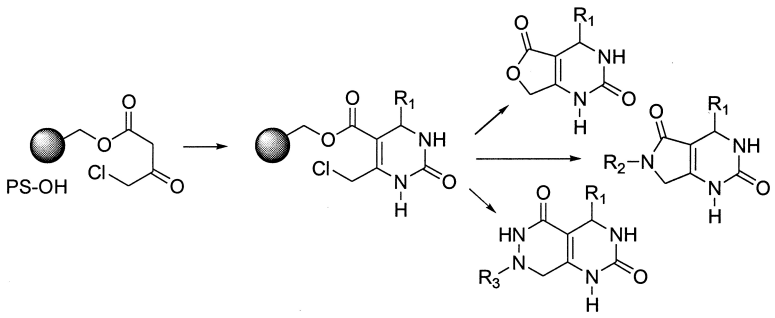

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Traceless Solid-Phase Synthesis of Bicyclic Dihydropyrimidones Using Multidirectional Cyclization Cleavage

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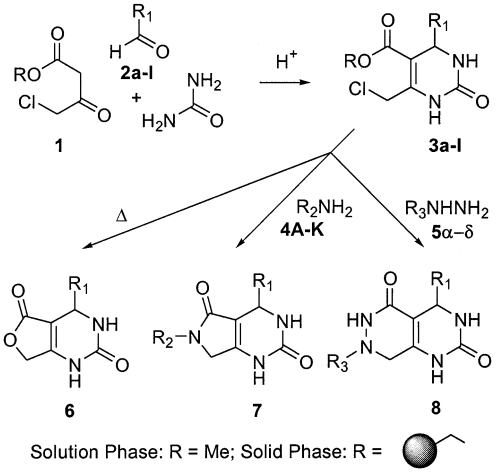
Solid-phase and solution-phase protocols for the synthesis of furo[3,4-*d*]pyrimidines, pyrrolo[3,4-*d*]-pyrimidines, and pyrimido[4,5-*d*]pyridazines are reported. The multistep solid-phase sequence involves the initial high-speed, microwave-promoted acetoacetylation of hydroxymethylpolystyrene resin with methyl 4-chloroacetoacetate. The immobilized 4-chloroacetoacetate precursor was subsequently subjected to three-component Biginelli-type condensations employing urea and a variety of aromatic aldehydes. The resulting 6-chloromethyl-functionalized resin-bound dihydropyrimidones served as common chemical platforms for the generation of the desired heterobicyclic scaffolds using three different traceless cyclative cleavage strategies. The corresponding furo[3,4-*d*]pyrimidines were obtained by microwave flash heating in a rapid, thermally triggered, cyclative release. Treatment of the chloromethyl dihydropyrimidone intermediates with a variety of primary amines followed by high-temperature microwave heating furnished the anticipated pyrrolo[3,4-*d*]pyrimidine scaffolds via nucleophilic cyclative cleavage. In a similar way, reaction with monosubstituted hydrazines resulted in the formation of pyrimido[4,5-*d*]pyridazines. All compounds were obtained in moderate to good overall yields and purities.

Introduction

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.[1] In times where a premium is put on speed, diversity, and efficiency in the drug discovery process, MCR strategies offer significant advantages over conventional linear-type syntheses.[2] The Biginelli three-component protocol is particularly attractive,[3] since the resulting dihydropyrimidone (DHPM) scaffold displays a wide range of biological activities, which has led to the development of a number of lead compounds based on that structural core.[4] In recent years a variety of different combinatorial protocols based on the classical Biginelli MCR have been advanced.[3] Those include solution-phase methods,[5,6] the use of polymer-supported reagents,[7] fluorous-phase conditions,[8] and several solid-phase protocols in which different resin-bound building blocks and linker combinations have been utilized.[9−12] Although a large number of functionalized DHPMs can potentially be prepared employing the above-mentioned procedures, the synthesized heterocyclic scaffold in all these cases remains a structurally relatively simple dihydropyrimidone derivative.[13]

In the context of increasing the complexity-generating power[14] of the classical Biginelli approach, we have considered the use of the 4-chloroacetoacetate building block **1** (R = Me; Scheme 1) in a Biginelli-type condensation. The resulting functionalized DHPM **3** (R = Me) appeared to be an ideal common chemical template for the generation of a variety of interesting bicyclic scaffolds such as furo[3,4-*d*]-pyrimidines **6**, pyrrolo[3,4-*d*]pyrimidines **7**, and pyrimido-[4,5-*d*]pyridazines **8**.[15] In addition, the overall synthetic strategy seemed particularly well-suited for adaptation to the solid-phase, employing a resin-bound 4-chloroacetoacetate building block of type **1** (R = resin) and taking advantage of the inherent benefits of a traceless, cyclative cleavage approach (Scheme 1).[16] Herein, we describe the facile and rapid solid-phase generation of small libraries of the hitherto scarcely reported heterobicyclic scaffolds **6**, **7**, and **8** from one common chemical platform, employing microwave-assisted cyclative cleavage strategies.

Scheme 1



Results and Discussion

Validation of Concept in Solution Phase. Only a few publications in the literature refer to the synthesis of

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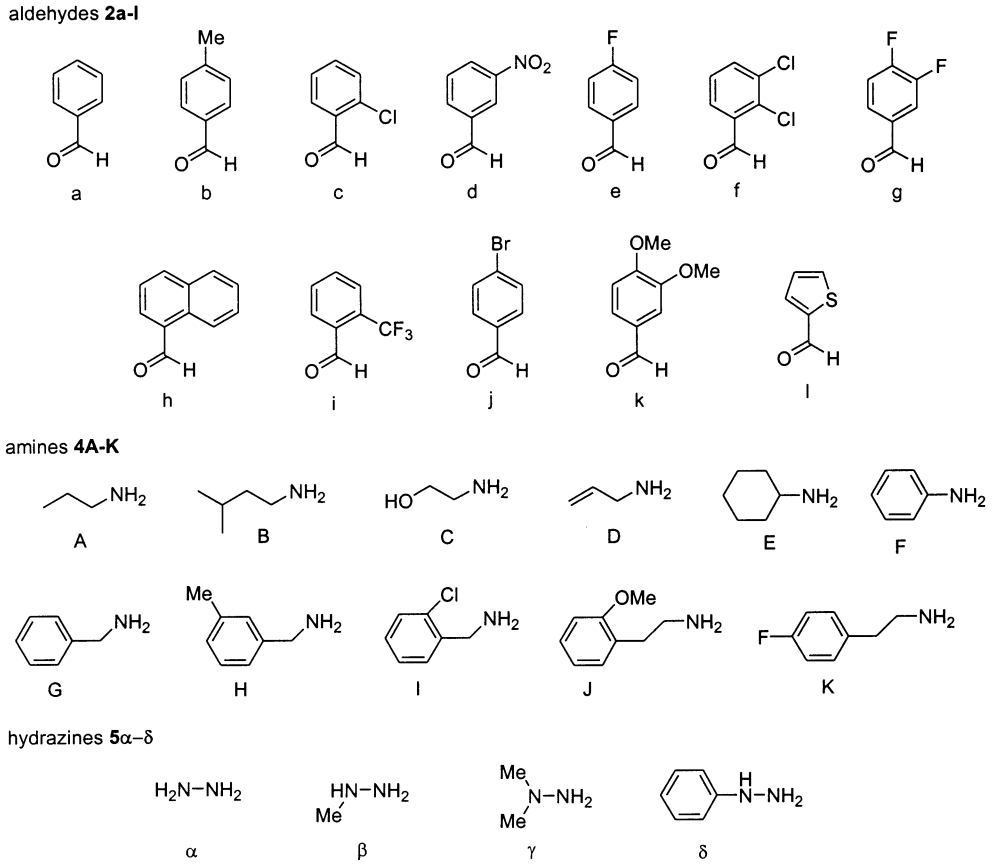
Table 1. Building Blocks for the Generation of Scaffold Libraries **6**−**8**

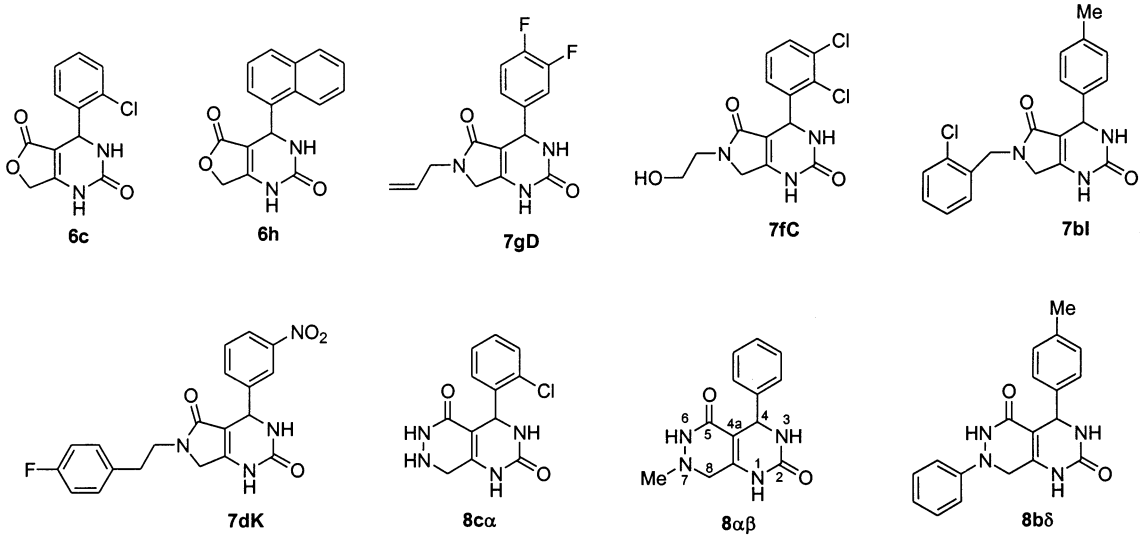


heterocyclic systems of type **6**−**8**.[17,18] In contrast to our planned strategy outlined in Scheme 1, all published synthetic routes are derived from the corresponding 6-bromomethyl-DHPM derivatives, which are readiliy available by careful bromination of the corresponding parent 6-methyl-DHPM analogues with stoichiometric amounts of elemental bromine.[17,18] We have chosen not to utilize this approach, since in the anticipated solid-phase protocol such a bromination step would invariably also lead to *gem*-dibromo derivatives when employing excess bromine.[17d] Therefore, we have opted to directly incorporate an appropriate reactive halomethyl group into DHPMs **3** by employing a suitable functionalized *β*-ketoester building block, i.e., methyl 4-chloroacetoacetate **1** (R = Me), in the Biginelli condensation step. Since *β*-ketoester **1** (R = Me) is a perfectly stable, commercially available, and inexpensive reagent, we have decided to use this building block rather than the somewhat unstable and noncommercial bromo analogue.[17b]

We were delighted to find that the acid-catalyzed Biginelli condensation of methyl 4-chloroacetoacetate **1** (R = Me) with urea and a variety of substituted aromatic aldehydes (e.g., **2a**−**h**; see Table 1) provided the desired 6-chloromethyl-functionalized DHPMs **3a**−**h** (R = Me) in moderate to good yields (27−70%; see Table 2), either employing polyphosphate ester (PPE) in THF as reaction medium[19] or (preferably) utilizing a solventless protocol using concentrated HCl as catalyst.[20] Workup of the crude reaction mixtures with MeOH/H_2O at room temperature provided DHPMs **3a**−**h** with sufficient purity (>90%, ^{1}H NMR) for further synthetic manipulations. Samples of analytical purity were obtained by flash chromatography (see Experimental Section). We next turned our attention to the thermal cyclization of chloromethyl-DHPMs **3** to the desired furo[3,4-*d*]pyrimidines **6**. For the cyclization of the corresponding bromo analogues (typically performed by simply heating the neat samples in an oil bath), reaction temperatures between 130 and 230 °C have been reported in the literature.[17] Similarly, chloromethyl-DHPMs **3a**−**h** underwent cyclization by heating of the neat substances in an oil bath at 200−215 °C for 7 min, resulting in the clean formation of the corresponding furo[3,4-*d*]pyrimidines **6a**−**h**. The isolated yields after recrystallization were 58−72% (see Table 2). Since these thermal cyclizations formed an integral part of the intended solid-phase cyclative cleavage strategy (Scheme 1), a careful analysis of the thermal properties of neat chloromethyl-DHPM **3a** by differential scanning calorimetry (DSC) was carried out, establishing a required cyclization temperature of 185 °C (see Figure S1 in the Supporting Information; a cyclization temperature of 170 °C was found for the bromo analogue).

Having confirmed the feasibility of synthesizing the hitherto unreported chloromethyl-DHPMs **3** (R = Me) and their usefulness in the preparation of furo[3,4-*d*]pyrimidines **6**, we next considered the reaction of DHPMs **3** with primary amines **4** (see Table 1 for building blocks). Similarly to the published protocols involving the analogous bromo precursors,[18] we discovered that treatment of DHPMs **3** with an excess of primary amine (2.0−3.0 equiv) in methanol provided the anticipated pyrrolo[3,4-*d*]pyrimidines **7** in moderate to good yields (33−74%, Table 2). The best results

Table 2. Yields of Dihydropyrimidones **3** and Heterobicycles **6**−**8** Prepared by Solution-Phase Synthesis (Scheme 1)[a]



product	yield[b] (%)	product	yield[b] (%)	product	yield[b] (%)	product	yield[b] (%)
3a	60	**6a**	71	**7aA**	50	**8aα**	58
3b	72	**6b**	58	**7fC**	74	**8cα**	63
3c	65	**6c**	68	**7aG**	64	**8gα**	43
3d	27	**6d**	64	**7dK**	41	**8a*β***	82
3e	68	**6e**	61	**7dH**	39	**8a*δ***	60
3f	32	**6f**	66	**7gJ**	33	**8c*β***	32
3g	70	**6g**	72	**7gD**	63	**8e*β***	26
3h	64	**6h**	59	**7bI**	64	**8b*δ***	35
				7bH	54		
				7eE	45		

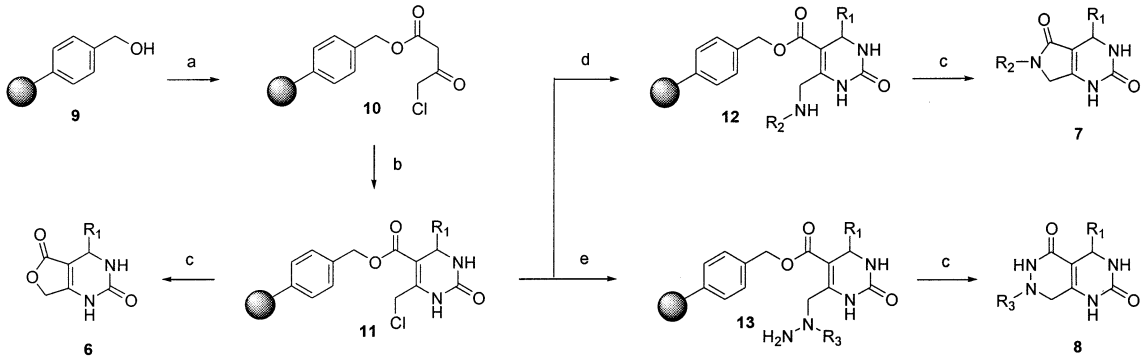
[a] For structures and building blocks, see Scheme 1 and Table 1. Selected examples are displayed below the title of the table. [b] Yields are isolated yields of analytically pure compounds obtained by recrystallization or chromatographic purification. For details, see Experimental Section.

were obtained by first allowing the corresponding amine **4** to react with the appropriate chloromethyl-DHPM **3** at ambient or a slightly elevated temperature for 1−2 h, followed by a period of heating under reflux conditions (5−6 h). In most cases the solid pyrrolo[3,4-*d*]pyrimidines **7** directly precipitated from the solution upon cooling to 4 °C. Using such a protocol, we have synthesized a small number of selected products derived from simple aliphatic amines (**7aA**, **7fC**, **7gD**), substituted benzylamines (**7aG**, **7dH**, **7bI**, **7bH**), and phenylethylamines (**7dK**, **7gJ**) (see Table 2 for yields and structural representations of selected examples). Sterically hindered amines such as cyclohexylamine (**4E**) only provided the initial open-chain substitution product, which could, however, be cyclized to the desired pyrrolopyrimidine **7eE** by heating in an oil bath at 240 °C (neat) for a few minutes. In contrast, aromatic amines (e.g., aniline, **4F**) proved to be too unreactive to undergo lactam formation even at 250 °C (oil bath, neat) and only noncyclized substitution products could be isolated. On the other hand, for very reactive amines (e.g., *n*-propylamine, **4A**), it was possible to isolate the corresponding open-chain substitution products by carrying out the reaction at room temperature (24 h). However, these 6-aminomethyl-DHPMs readily cyclized upon warming.

When hydrazine and monosubstituted hydrazines **5** were employed as 1,2-binucleophiles under similar reaction conditions, the formation of the expected[18a] pyrimido[4,5-*d*]-pyridazines **8** in 26−82% yield (see Table 2) was observed. In the case of monosubstituted hydrazines (*N*-methylhydrazine, *N*-phenylhydrazine), the position of the substituent at N-7 of the bicyclic scaffold **8** was confirmed for compounds **8a*β*** (R_3 = Me) and **8a*δ*** (R_3 = Ph) by the presence of a characteristic C-4a/H-(N6) long-range coupling derived from HMBC NMR experiments (see structural representation in Table 2). Interestingly, *N*,*N*-dimethylhydrazine provided only the corresponding open-chain hydrazino-substituted DHPM; cyclization, even under forcing conditions (250 °C, DMF, microwave irradiation), could not be achieved. All compounds synthesized in these solution-phase studies were fully characterized by spectroscopic and analytical data (see Experimental Section). The main purpose of the solution-phase work was to obtain reference data for the construction of the solid-phase-derived library described below. However, it is pointed out that the two-step solution-phase synthesis of scaffolds **6**−**8** is considerably more efficient than the previously reported methods,[17,18] although no attempts were made to fully optimize the reaction conditions or to develop a suitable high-throughput purification strategy.

Development, Validation, and Application of Solid-Phase Strategy. For a suitable polymer support for the planned solid-phase protocol, we have chosen hydroxymethylpolystyrene resin (**9**, PS−OH, Scheme 2). Since our strategy did not rely on any acidic cleavage conditions, the use of this "linker system" (rather than the use of more conventional Wang resin) seemed appropriate. To increase the amount of material that could be generated, a relatively

Scheme 2[a]



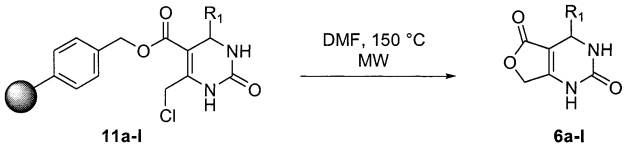
[a] Reaction conditions: (a) methyl 4-chloroacetoacetate (10 equiv), 1,2-dichlorobenzene, microwave irradiation (170 °C), 15 min; (b) R_1CHO (3 equiv), urea (3 equiv), dioxane, HCl (cat.), 70 °C, overnight, then concentrated HCl, room temp, 5 min; (c) DMF, microwave irradiation (150 or 200 °C), 10 min; (d) R_2NH_2 (5 equiv), DMF, room temp, 50 °C, or 70 °C, overnight; (e) R_3NHNH_2 (5 equiv), DMF, room temp, 30 min.

high-loading form (2.80 mmol/g) was selected. The required key support-bound ester **10** was prepared by rapid, microwave-assisted "acetoacetylation" of the hydroxy-functionalized resin **9** with methyl 4-chloroacetoacetate in 1,2-dichlorobenzene (bp 180 °C) (Scheme 2). This process formally constitutes a transesterification involving a highly reactive α-oxoketene intermediate. We have recently reported analogous transesterifications involving a variety of *β*-ketoesters and PS Wang resin.[21] In the particular case reported herein, complete conversion (>99%) was achieved within 15 min at 170 °C, as confirmed by on-bead FTIR analysis (1748 and 1730 cm^{-1} for C═O absorptions; see Figure S2 in Supporting Information) and calculated from the weight gain of the scrupulously washed and dried resin **10**. It is important to note that these microwave-assisted transesterifications need to be carried out under *open-vessel* conditions[22] so that the formed methanol is removed from the equilibrium. In a *closed-vessel* system, the process is significantly less effective (conversions between 70 and 80% after 15 min, depending on the scale of the reaction).[22]

With the required immobilized 4-chloroacetoacetate precursor **10** at hand, the subsequent three-component Biginelli-type condensations were carried out in dioxane at 70 °C (18 h), closely following our recently disclosed solid-phase Biginelli protocol.[12] An amount of 3 equiv of both the aromatic aldehyde building block **2** and urea was used in the HCl-catalyzed synthesis. As previously observed,[12] the presence of excess aldehyde/urea led to the (reversible) formation and precipitation of the corresponding insoluble bisureides, i.e. $R_1CH(NHCONH_2)_2$.[23] To ensure an effective conversion **10** → **11**, it was therefore essential to stir the reaction mixture; shaking was significantly less effective.[12] After completion of the condensation step, the remaining bisureide precipitate was dissolved by addition of concentrated HCl to the reaction mixture. For the production of a small collection of polymer-bound DHPM templates of type **11**, all 12 aldehyde building blocks displayed in Table 1 (**2a**−**l**) were employed. The progress of the conversion **10** → **11** was monitored for selected examples by on-bead FTIR (disappearance of the 1748 cm^{-1} C═O absorption) and estimated from the weight gain of the dried resins to be generally in the range of 45−85%. Any attempted increase of reaction temperature or time or the use of more reagent equivalents did not enhance the conversion.

Our approach to the furo[3,4-*d*]pyrimidine scaffold **6** relied on a novel type of thermally triggered, cyclative release of a lactone moiety from a resin-bound ester intermediate.[24] Because of the confirmed high temperatures required for this process in solution (see above), we were initially concerned about the practicality of performing such transformations on polymer support. On the basis of our recent encouraging experiences in the area of high-temperature microwave-assisted solid-phase chemistry,[21,25,26] we also considered the use of this technology here.[27] After some experimentation, we discovered that the desired furopyrimidine products **6a**−**l** could be efficiently released from the resin by controlled single-mode microwave irradiation of chloromethyl-DHPMs **11a**−**l** in sealed vessels for 10 min at 150 °C using DMF as solvent (see Experimental Section). Increasing the reaction time to 15 min or resubjection of the reisolated resin to those conditions did not provide any additional product. With irradiation at 100 °C for 10 min, only small amounts of furopyrimidine products were detected in solution; at 175 or 200 °C, the purity of the isolated cleaved products was somewhat lower. At the optimum cleavage temperature of 150 °C, furopyrimidines **6a**−**l** were obtained in very high purity (>95%) as judged by HPLC−UV_{220}/MS measurements (see Table 3 for details). The chemical identity and HPLC−UV homogenity of a selection of these samples were further corroborated by comparing their ^1H NMR data with the spectra obtained from conventional solution-phase experiments described above. Yields were determined by weighing the isolated solid materials after evaporation of solvent and were generally in the range 40−80% (over three steps, based on the initial loading of PS−OH resin **9**; see Table 3). The only exceptions were examples derived from ortho-substituted aromatic aldehydes (**6f**, 14%; **6i**, 10%). In these cases, the low yields are most likely a consequence of the rather poor solubility and reactivity of the corresponding bisureides $R_1CH(NHCONH_2)_2$, which make the desired Biginelli condensations on polymer support troublesome.[12,23] More efficient agitation or a different solvent/catalyst system would probably be required to increase the conversion rates for those reactions. In any event, the isolated yields of furopyrimidines (Table 3) corresponded nicely to the initial measured weight gain of the resin-bound chloromethyl-DHPMs **11a**−**l** (data not shown). Investigation of the reisolated resin by FTIR confirmed that Merrifield resin (*ν*-

Table 3. HPLC−UV_{220}/MS Purity and Masses Found for Furo[3,4-*d*]pyrimidines **6**



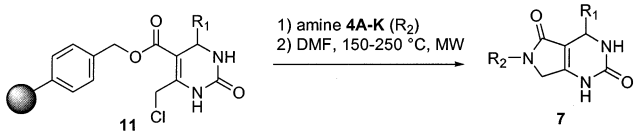
product[a]	yield[b] (%)	purity[c] (%)	MW (calcd)	MW $(M-H)^-$
6a	77	>95	230.1	229.0
6b	69	>95	244.1	243.0
6c	41	>95	264.0	263.0
6d	44	>95	275.1	274.0
6e	62	>95	248.1	247.0
6f	14	>95	298.0	297.0
6g	40	>95	266.1	265.0
6h	44	>95	280.1	279.0
6i	10	>95	298.1	297.0
6j	52	>95	308.0	307.0
6k	50	>95	290.1	289.0
6l	54	>95	236.0	235.0

[a] For structures (R_1) and building blocks, see Table 1. [b] Yields are isolated yields and are based on the initial loading of PS−OH resin **9** (2.80 mmol/g). [c] Crude homogenity was determined from the relative peak areas (%) of HPLC chromatograms at 220 nm; see Experimental Section.

(C−Cl): 1265 cm^{-1}) was formed during the cyclative cleavage process, supporting the assumption that the cleavage of the benzyl−oxygen bond is the key step in this mode of cyclative release.[17d]

To explore and validate the solid-phase approach to the second target scaffold, i.e., the pyrrolo[3,4-*d*]pyrimidines **7**, the resin-bound chloromethyl precursor **11a** was initially treated with a representative selection of four primary amines (**4A**, **4E**, **4I**, and **4J**). In contrast to the cyclative release **11** → **6**, here a two-step protocol was implemented. In the first step, the chloro group was displaced by excess amine nucleophile (**11** → **12**). After the resin was washed, cyclative nucleophilic cleavage (lactam formation)[16] to release the target heterobicyclic system (**12** → **7**) was carried out. On the basis of the different reactivity of the primary amines (Table 1), the nucleophilic displacement **11** → **12** was carried out either at room temperature (alkylamines and phenylethylamines) or at 50 °C (benzylamines and sterically hindered amines). These substitution reactions were conveniently carried out overnight in DMF, employing 5 equiv of the corresponding amine. It was imperative to drive these substitution reactions to completion; otherwise, the subsequently released pyrrolopyrimidines (**12** → **7**) were invariably contaminated with furopyrimidines derived from the cleavage pathway **11** → **6**. This principle was strictly followed even at the expense of losing some material from the resin. We discovered that in some cases, traces (<5%) of the desired pyrrolopyrimidines were already released from the resin during the nucleophilic displacement step at room temperature. Similarly, the formation of small amounts of furopyrimidines was observed during these nucleophilic displacements when the reaction was carried out at 50 °C. Both processes, however, had only a small effect on the overall isolated yields of the pyrrolopyrimidine products (Table 4). Proper cleavage of the desired pyrrolo[3,4-*d*]pyrimidines was

Table 4. HPLC−UV_{220}/MS Homogenity and Masses Found for Pyrrolo[3,4-*d*]pyrimidines **7**

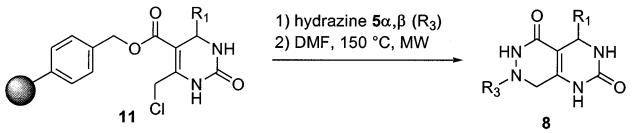


product[a]	yield[b] (%)	homogenity[c] (%)	MW (calcd)	MW $(M-H)^-$
7aA	52	>95	271.1	270.0
7aE	41 [63][d]	>95 [>95][d]	311.2	310.2
7aI	30 [50][d]	90 [86][d]	353.1	352.1
7aJ	35	94	363.2	362.2
7aF	[15][d] {32}[e]	[69][d] {65}[e]	305.1	304.4
7bB	43	88	313.2	312.2
7bH	45	89	347.2	346.2
7cD	48	94	303.1	302.0
7dA	38	>95	316.1	315.2
7dJ	27	69	408.1	407.2
7eE	41	93	329.2	328.2
7eJ	37	83	381.1	380.2
7gC	37	89	309.1	308.0
7gG	25	92	355.1	354.4
7hB	35	86	349.2	348.2
7hH	30	81	383.2	382.2
7jA	41	88	349.0	348.0
7jI	35	85	431.0	430.0
7kE	31	>95	371.2	370.4
7kJ	29	93	423.2	422.2
7lK	43	>95	357.1	356.0
7lC	55	>95	279.1	278.0

[a] For structures and building blocks (R_1 and R_2), see Table 1. [b] Yields are isolated yields and are based on the initial loading of PS−OH resin **9** (2.80 mmol/g). [c] Crude homogenity was determined from the relative peak areas (%) of HPLC chromatograms at 220 nm; see Experimental Section. [d] Yields and homogenities in brackets refer to 200 °C cyclative cleavage conditions (see text). [e] Yields and homogenities in braces refer to 250 °C cyclative cleavage conditions (see text).

performed under identical conditions as described for furopyrimidine cleavage, i.e., by microwave irradiation at 150 °C for 10 min in DMF. Under those conditions, all four products were completely released from the resin with the exception of the cyclohexyl derivative **7aE**, which in solution-phase experiments did undergo lactam formation only under forcing conditions (240 °C, see above). In this particular case, a better yield was obtained when the microwave-assisted cleavage was carried out at 200 °C (DMF, 10 min, sealed vessel; see Table 4). The same was also the case for the somewhat sterically hindered 2-chlorobenzylamine **4I**. The isolated yields of the four initially selected pyrrolopyrimidines corresponded to overall yields of 35−63% over four steps based on the initial loading of PS−OH resin **9**. The chemical identity and homogenity (>86%) of those compounds was established by HPLC−UV_{220}/MS measurements (see Table 4) and was confirmed by comparison of ^1H NMR data with reference samples obtained from solution-phase experiments. Although the solution-phase work discussed above did not allow the preparation of the desired pyrrolopyrimidine product **7aF**, we have also tested aromatic amines (e.g., aniline **4F**) in the solid-phase protocol. Here, it was necessary to work at 70 °C (20 equiv, 18 h) in order to obtain complete nucleophilic displacement of chlorine by the comparatively

Table 5. HPLC−UV_{220}/MS Purity and Masses Found for Pyrimido[4,5-*d*]pyridazines **8**



product[a]	yield[b] (%)	purity[c] (%)	MW (calcd)	MW $(M + H)^+$
8aα	37	39	244.1	245.2
8a*β*	41	54	258.1	259.2
8j*β*	30	53	336.0	337.2
8gα	35	45	280.1	281.2
8c*β*	37	50	292.1	293.2
8k*β*	32	41	318.1	319.2
8l*β*	35	61	264.2	265.2

[a] For structures and building blocks (R_1, R_3), see Table 1. [b] Yields are isolated yields and are based on the initial loading of PS−OH resin **9** (2.80 mmol/g). [c] Crude homogenity was determined from the relative peak areas (%) of HPLC chromatograms at 220 nm; see Experimental Section.

nonnucleophilic aniline. Cyclative cleavage in DMF was attempted at 200 and 250 °C for 10 min, and it did indeed provided the desired product **7aF** albeit in somewhat lower yield and homogenity (Table 4).

For the preparation of a larger set of pyrrolopyrimidines **7**, we have chosen 10 out of the available 12 resin-bound chloromethyl-DHPM templates **11a**−**l**. Not selected were the low-conversion substrates **11f** and **11i** so that the quality of the library is not compromised. The resin-bound chloromethyl-DHPMs **11** were treated with 5 equiv of the corresponding amines **4A**−**K**. In general, 2 different amines were chosen for each of the selected 10 chloromethyl-DHPM templates, leading to a library of 22 pyrrolopyrimidines **7** in total (see Table 4). As described above, nucleophilic displacement **11** → **12** was carried out either at room temperature (alkyl- and phenylethylamines) or at 50 °C (benzylamines and sterically hindered amines) in DMF, followed by a 10 min microwave-assisted cyclative cleavage step at 150 °C. Since in general purity is more important than yield in a combinatorial synthesis, we have used those cleavage conditions although cleavage at 200 °C (or even 250 °C for **7aF**) did result in markedly higher yields in some cases (Table 2). The purity of all library compounds was assessed by HPLC−UV/MS as shown in Table 2. In general, purities were excellent (>85%) with very few exceptions. The masses found corresponded in all cases to the expected product. The overall isolated yields of pyrrolopyrimidines (over four steps based on initial loading of resin **9**) were in the range 25−55%.

For the solid-phase synthesis of the pyridazino[4,5-*d*]-pyrimidine scaffold **8**, analogous validation experiments were attempted involving selected chloromethyl-DHPM resins **11** (see Table 5) and hydrazines **5α** (R_3 = H), **5*β*** (R_3 = Me), and **5*δ*** (R_3 = Ph). Because of the high nucleophilicity of unsubstituted hydrazine and *N*-methylhydrazine, reaction times for the substitution step **11** → **13** at room temperature were reduced to 30 min. Longer reaction times led to appreciable amounts of pyridazinopyrimidines already being released from the resin at this undesired stage (TLC monitoring). For all pyridazinopyrimidine examples, cyclative cleavage was carried out using the standard microwave-heating conditions (DMF, 10 min, 150 °C). Arylhydrazines, i.e., **5*δ***, proved to be problematic in that higher reaction temperatures (70 °C, 18 h) were required to carry out the initial displacement of chlorine by the substituted hydrazine nitrogen. Here, concomitant cyclization could not be avoided, which led to very low overall yields of isolated products. Therefore, aromatic hydrazines could not be used in the solid-phase protocol. In addition, the use of hydrazine **5α** itself let to major byproducts, apart from the expected pyrimidopyridazine **8**. In some cases, these byproducts, presumably derived from a dehydrogenation process according to MS measurements, were the major products. Therefore, the purities of the pyrimidopyridazine products **8** were not as high as in the other two libraries. Note that in the above experiments, an excess of the hydrazine was employed. Alternatively, it may be possible to use the hydrazine component as the limiting reagent, which could result in somewhat cleaner reactions. However, this modification of the protocol was not investigated. Because of the low purities in these solid-phase transformations, a postcleavage purification or the use of the solution-phase method outlined above for the preparation of these compounds may be preferable.

Concluding Remarks

In conclusion, we have developed both a solution- and solid-phase method for the construction of bicyclic dihydropyrimidone libraries. The heterocyclic systems **6**−**8** have hitherto been scarcely reported in the literature, and therefore, with the exception of some furo[3,4-*d*]pyrimidines,[17a] their biological properties have not been evaluated. The novel protocol described herein allows for the synthesis of a number of heterobicyclic scaffolds using either solution-phase or solid-phase methods. Further decoration of the pyrimidine moieties on those heterobicycles using well-established chemistry[15] may potentially lead to a larger number of derivatives for high-throughput evaluation of their biological properties.

Key steps in the solid-phase protocols include rapid high-temperature, microwave-promoted coupling (**9** → **10**) and cleavage (**11** → **6**−**8**) reactions. On the basis of our previous experience in microwave-assisted solid-phase synthesis,[21,25,26] we believe that the high-speed conversions here are a consequence of the direct rapid and intense heating (microwave flash heating) of the polar solvents (1,2-dicholorobenzene or DMF), coupled with the unconventionally high reaction temperatures (150−200 °C). Although similar high conversion rates for solid-phase processes may, in principle, also be achieved by conventional thermal heating at high temperatures,[28] the convenience of using superheated solvents in sealed vessels and the rapid heating/cooling cycles offered by modern microwave reactors makes conventional oil-bath heating a less attractive alternative. The stability of the polystyrene support itself under these rather drastic conditions deserves further comments. We[25] and others[29] have recently observed that relatively short exposures (20 min) of cross-linked polystyrene resins to controlled microwave heating at 200 °C (on-line temperature measurement) did not seem to affect the polymer support. To further corroborate these

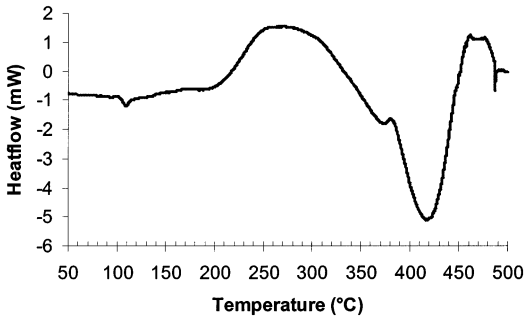


Figure 1. Differential scanning calorimetric measurements (DSC) monitoring the decomposition of standard Merrifield resin (2% DVB, 2.3 mequiv Cl/g, 200−400 mesh, neat).

observations, we have carried out a differential scanning calorimetry experiment (DSC) on a sample of standard, 2% DVB-cross-linked Merrifield resin (Figure 1). DSC, which is widely used in materials science, quality inspection, polymer and biopolymer chemistry, and pharmacy, has been shown to provide useful information and hints in the planning of thermolytical reactions such as ring closure and rearrangement reactions (see above and Figure S1 in the Supporting Information).[30] This information, which can be obtained before the reaction itself is performed, includes (i) the range of temperature where the planned reaction can or must be performed, (ii) knowledge of subsequent rearrangement or decomposition temperatures, and (iii) safety precautions in exothermic processes.[30] Although here being only a crude estimate not involving any solvent, the DSC experiment on Merrifield resin shown in Figure 1 seems to confirm that cross-linked polystyrene resins are thermally stable just up to 200 °C. Therefore, these supports seem ideally suited for carrying out microwave-heated transformations.

Experimental Section

General Methods. Building blocks **1**, **2**, **4**, and **5** were purchased from commercial sources and used without further purification. All solid-phase experiments were carried out with hydroxymethylpolystyrene resin **9** (Advanced ChemTech, Louisville, KY, , 2.8 mmol/g, 100−200 mesh, catalog no. SA5024, lot no. 14325-1, 1% DVB). TLC analysis was performed on Merck precoated 60 F_{254} plates. Flash column chromatography was performed using silica gel 60 (0.040−0.063 mm, Merck) with ethyl acetate/toluene mixtures as eluent. Melting points were obtained on a Gallenkamp melting point apparatus, model MFB-595, in open capillary tubes. ^{1}H NMR spectra were recorded on a Bruker AMX360 or AMX500 instrument in $CDCl_3$ or DMSO-d_6, operating at 360 or 500 MHz, respectively. On-bead FTIR spectra were recorded on a Unicam Galaxy series FTIR 7000 (Mattson Instruments Inc.) using mashed resin beads in KBr pellets. Conventional IR spectra were taken on a Perkin-Elmer 298 spectrophotometer in KBr pellets. Mass spectra were taken on a Hewlett-Packard LC/MSD series 1100 instrument in the atmospheric pressure chemical ionization (negative or positive APCI) mode. Microanalyses were performed on a Carlo Erba 1106 elemental analyzer. The differential scanning calorimetry experiments were performed with a Rheometric Scientific DSC-Plus instrument with the DSC software version 5.42 or with Orchestrator 6.2.2. The DSC plots were recorded without solvents between 50 and 500 °C with a heating rate of 5 °C/min and ca. 2 mg of compound in open aluminum crucibles.

Quality Assessment Using HPLC−UV/MS. Homogenity and molecular parent ion identity of the synthesized library compounds (solid phase) were determined on a Hewlett-Packard (HP) 1100 LC/MSD system, which included a solvent degas unit, a quaternary pump, an autosampler, a variable-wavelength detector set at 220 nm, and a single quadrupole mass spectrometer equipped with an atmospheric pressure chemical ionization (APCI) source. The separations were carried out using a C_8 reversed-phase analytical column (Zorbax Eclipse XDB-C8, 150 mm × 4.6 mm, particle size 5 μm) at 30 °C and a mobile phase from (A) 0.1% formic acid in water, (B) 0.1% formic acid in acetonitrile, and (C) methanol (all solvents were HPLC grade, Merck; formic acid was analytical reagent grade, Fluka). The two following gradients were applied at a flow rate of 1 mL/min (solution C is constant at 4%): linear increase from 18% to 78% solution B in 10 min, hold at 78% solution B for 4 min, then back to the initial settings to reequilibrate the column for 6 min (gradient I, used for analyzing furo[3,4-*d*]-pyrimidines **6** and pyrrolo[3,4-*d*]pyrimidines **7**); linear increase from 0% to 78% solution B in 20 min, hold at 78% solution B for 4 min, reequilibration for 6 min (gradient II, used for analyzing pyrimido[4,5-*d*]pyridazines **8**). The APCI-MS conditions were as follows: negative-ion mode (NIM, applied when using gradient I), positive-ion mode (PIM, applied when using gradient II), nitrogen as nebulizer gas (40 psig) and as drying gas (5 L/min, 300 °C), vaporizer temperature at 350 °C, corona current at 26 (NIM)/5 (PIM) μA, capillary voltage at 6000 (NIM)/2500 (PIM) V, and fragmentor voltage at 90 (NIM)/60 (PIM) V. Spectra were obtained in the mass range *m*/*z* 100−500. Sample preparation was done by diluting approximately 30 μL of the DMF cleavage solution with 1 mL of 0.1% formic acid in water/0.1% formic acid in acetonitrile/methanol, 78:18:4 v/v/v (for **6**, **7**), and 0.1% formic acid in water/methanol, 96/4 v/v (for **8**) (corresponding to the initial conditions of the gradients described above). An amount of 5 μL of the solutions was injected onto the HPLC−UV/MS system. The purity of the synthezised compounds was determined by applying the area normalization technique to analyze the LC−UV data. The strong solvent signals (DMF) as well as the rather small signals also obtained from a blank run involving microwave irradiation of resin **9** for 10 min at 150 °C in DMF were excluded from integration.

Microwave Irradiation Experiments. All microwave irradiation experiments were carried out using the Smith synthesizer from PersonalChemistry AB (Uppsala)[31] in the standard configuration. A detailed description of this single-mode microwave reactor with integrated robotics was recently published.[6] For the preparation of resin-bound β-ketoester **10** (see below), the system was operated under *open-vessel* conditions.[22]

Solution-Phase Synthesis of Dihydropyrimidones 3a−h. General Procedure. A mixture of the appropriate aldehydes **2a−h** (3.0 mmol), methyl 4-chloroacetoacetate (452 mg, 3.0 mmol), urea (210 mg, 3.5 mmol), and HCl in

dioxane (4 M solution, Aldrich, 40 μL) was stirred in a sealed flask at 85−90 °C for ca. 1 h. The crude products were stirred with a 1:2 water/MeOH mixture (2−3 mL) for 2 h, filtered, and dried. Analytically pure samples were obtained by flash chromatography (silica gel).

Methyl 6-Chloromethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (3a). Yield 60%, mp 171 °C. IR (KBr): ν 3360, 3220, 3105, 1670, 1650 cm^{-1}. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 3.67 (s, 3H), 4.77−4.84 (m, 2H), 5.43 (d, J = 2.8 Hz, 1H), 6.05 (br s, 1H), 7.28−7.33 (m, 5H), 8.14 (br s, 1H). ^{13}C NMR ($CDCl_3$, 90 MHz): δ 39.6, 51.7, 55.5, 103.1, 126.5, 128.3, 128.9, 142.6, 143.7, 153.1, 165.0. MS (pos APCI): *m*/*z* 281 (M + 1). Anal. Calcd for $C_{13}H_{13}N_2O_3Cl$ (280.71): C, 55.62; H, 4.67; N, 9.98. Found: C, 55.30; H, 4.42; N, 9.60.

Analytical and spectroscopic data for DHPMs **3b**−**h** are presented in the Supporting Information.

Synthesis of Furo[3,4-*d*]pyrimidines 6a−h from Dihydropyrimidones 3a−h. General Procedure. Samples of the corresponding dihydropyrimidones **3a**−**h** (1.0 mmol) were heated neat in an oil bath at 210 °C (bath temperature) for ca. 7 min. The resulting solids were purified by recrystallization from EtOH to afford furopyrimidines **6a**−**h** in analytical purity.

4-Phenyl-4,7-dihydro-1*H*,3*H*-furo[3,4-*d*]pyrimidine-2,5-dione (6a). Yield 71%, mp 284 °C (lit.[17d] mp 272 °C). IR (KBr): ν 3200, 3150, 1730, 1690, 1670 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.80−4.90 (m, 2H), 5.22 (s, 1H), 7.30−7.36 (m, 5H), 7.81 (br s, 1H), 10.0 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 53.0, 65.3, 96.9, 126.9, 128.1, 128.8, 142.9, 151.2, 159.9, 170.1. MS (neg APCI): *m*/*z* 229 (M − 1). Anal. Calcd for $C_{12}H_{10}N_2O_3$ (230.22): C, 62.60; H, 4.38; N, 12.17. Found: C, 62.75; H, 4.29; N, 12.18.

Analytical and spectroscopic data for furo[3,4-*d*]pyrimidines **6b**−**h** are presented in the Supporting Information

Synthesis of Pyrrolo[3,4-*d*]pyrimidines 7 from Dihydropyrimidones 3 and Amines 4. General Procedure. A mixture of the appropriate DHPM **3** (1.0 mmol) and amine **4** (Figure 1) (3.0 mmol) in MeOH (5−10 mL) was stirred at 25−30 °C for 1−2 h. Then the mixture was heated at reflux temperature for an additional 5−6 h. After cooling to ambient temperature, the solid product was filtered and washed with cold MeOH to provide a sample of the desired pyrrolopyrimidine **7**. Analytically pure samples were obtained by recrystallization from suitable solvents.

4-Phenyl-6-propyl-3,4,6,7-tetrahydro-1*H*-pyrrolo[3,4-*d*]-pyrimidine-2,5-dione (7aA). Yield 50%, mp 173−174 °C. IR (KBr): ν 3420, 3240, 3105, 1685 cm^{-1}. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 0.71−0.80 (m, 3H), 1.42 and 1.46 (2 d, J = 7.5 Hz, 2H), 3.07−3.24 (m, 2H), 3.91 and 3.97 (2 d, J = 18.5 Hz, 2H), 5.16 (s, 1H), 7.23−7.36 (m, 5H), 7.51 (br s, 1H), 9.52 (br s, 1H). MS (neg APCI): *m*/*z* 270 (M − 1). Anal. Calcd for $C_{15}H_{17}N_3O_2$ (271.31): C, 66.34; H, 6.27; N, 15.48. Found: C, 66.31; H, 5.83; N, 15.35.

4-(2,3-Dichlorophenyl)-6-(2-hydroxyethyl)-3,4,6,7-tetrahydro-1*H*-pyrrolo[3,4-d]pyrimidine-2,5-dione (7fC). Yield 74%, mp 284−285 °C. IR (KBr): ν 3410, 3250, 3140, 1675, 1630 cm^{-1}. ^{1}H NMR (DMSO-d_6, 360 MHz): δ 3.15−3.29 (m, 2H), 3.41−3.46 (m, 2H), 4.07 (s, 1H), 4.72 (br s, 1H), 5.66 (s, 1H), 7.30−7.39 (m, 2H), 7.49 (br s, 1H), 7.56−7.59 (m, 1H), 9.64 (br s, 1H). ^{13}C NMR (DMSO-d_6, 90 MHz): δ 43.8, 48.3, 52.0, 59.8, 101.6, 128.4, 128.8, 129.7, 130.1, 132.0, 142.6, 151.0, 151.4, 167.7. MS (neg APCI): *m*/*z* 342. Anal. Calcd for $C_{14}H_{13}Cl_2N_3O_3$ (341.03): C, 49.12; H, 3.83; N, 12.28. Found: C, 49.22; H, 3.80; N, 12.28.

Analytical and spectroscopic data for pyrrolo[3,4-*d*]pyrimidines **7aG**, **7dK**, **7dH**, **7gJ**, **7gD**, **7bI**, **7bH**, **7eE**, and related compounds are presented in the Supporting Information.

Synthesis of Pyrimido[4,5-*d*]pyridazines 8. General Procedure. A mixture of the appropriate DHPM **3** (1.0 mmol) and the corresponding hydrazine derivative **5** (Figure 1) (3.0 mmol) was heated under reflux in 1,4-dioxane (7 mL) for 5−10 h. The colorless precipitate that was formed during the reaction was filtered and subsequently washed with cold water. For reactions involving aromatic hydrazines, EtOH was used as a solvent. Purification was performed by extracting the sparingly soluble products with boiling MeOH.

4-Phenyl-4,6,7,8-tetrahydro-1*H*,3*H*-pyrimido[4,5-*d*]pyridazine-2,5-dione (8aα). Yield 58%, mp >320 °C. IR (KBr): ν 3240, 1700, 1670 cm^{-1}. ^{1}H NMR (DMSO-d_6, 360 MHz): δ 3.37−3.57 (m, 2H), 5.35 (d, J = 2.8 Hz, 1H), 7.27−7.81 (m, 5H), 7.88 (br s, 1H), 8.27 (br s, 1H), 9.73 (br s, 1H), 12.70 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 45.2, 52.3, 99.7, 126.8, 127.5, 128.7, 144.9, 146.6, 152.3, 166.3. MS (neg APCI): *m*/*z* 243 (M − 1). Anal. Calcd for $C_{12}H_{12}N_4O_4$ (244.25): C, 59.01; H, 4.95; N, 22.94. Found: C, 59.11; H, 5.03; N, 22.87.

Analytical and spectroscopic data for pyrimido[4,5-*d*]-pyridazines **8cα**, **8gα**, **8a*β***, **8a*δ***, **8c*β***, **8e*β***, **8b*δ***, and related compounds are presented in the Supporting Information

Resin-Bound 4-Chloroacetoacetate (10) by Microwave-Assisted Transesterification. To 200 mg (0.56 mmol) of hydroxymethylpolystyrene resin (2.80 mmol/g) in a large Smith process vial was added 4 mL of 1,2-dichlorobenzene. After the mixture was stirred for 10 min at room temperature to allow complete swelling of the resin, 840 mg (5.6 mmol, 10 equiv) of methyl 4-chloroacetoacetate (Acros, Belgium) was added. The open, noncapped process vial[22] was irradiated in the single-mode cavity of the Smith synthesizer with magnetic stirring for 15 min at 170 °C. After cooling to ambient temperature, the resin was filtered, washed with acetone (3 × 5 mL), THF (2 × 5 mL), MeOH (2 × 5 mL), and dichloromethane (3 × 5 mL) and dried (40 °C, 10 mbar, 14 h). The yield was 266 mg (>99% conversion relative to a loading of 2.80 mmol/g; resulting loading 2.10 mmol/g). FTIR (KBr pellets): 1748 and 1730 (C═O) cm^{-1} (Figure S2). Alternatively, larger quantities (>1 g) of the resin could be prepared using a multimode microwave reactor in open PFA vials in analogy to our recently published method.[21]

Biginelli Condensations on Solid Phase (10 → 11a−l). General Procedure. A sample of the above resin-bound β-ketoester **10** (238 mg, 0.5 mmol) was suspended in dry dioxane (4 mL) at room temperature. Then, the corresponding aldehydes **2a**−**l** (1.5 mmol, see Figure 1 for building blocks), urea (90 mg, 1.5 mmol) and a 2:1 mixture of dioxane/HCl_{concd} (10 μL) were added and the reaction mixture was gently

stirred at 70 °C for 18 h. After the mixture was cooled to room temperature, a 1:1 mixture of dioxane/HCl_{concd} (2 mL) was added and the mixture was stirred for an additional 5 min at room temperature in order to dissolve the precipitated bisureide. The suspension was filtered, and the resulting resin-bound DHPMs **11a**−**l** were washed with dioxane (3 × 5 mL), EtOH (2 × 5 mL), dichloromethane (2 × 5 mL), dioxane (2 × 5 mL), and dichloromethane (2 × 5 mL) and were subsequently dried (40 °C, 10 mbar, 14 h).

Furo[3,4-*d*]pyrimidines 6a−l from DHPMs 11a−l. General Procedure. Sample aliquots (ca. 100 mg) of the appropriate resin-bound chloromethyl-DHPMs **11a**−**l** were suspended in dry DMF (3 mL) and irradiated in large Smith process vials for 10 min at 150 °C (closed-vessel conditions) in the cavity of the Smith synthesizer. After cooling to ambient temperature, the resins were filtered and washed twice with DMF (1 mL each). From the combined DMF solutions (ca. 5 mL), amounts of 30 μL were taken for HPLC−UV/MS determination of purity and identity (see above). The rest of the sample was evaporated to dryness under reduced pressure to yield the desired furopyrimidines **11a**−**l** in 10−77% overall yield (based on the initial loading of resin **9**; see Table 1), which in most cases crystallized directly after evaporation of the solvent. Pure crystalline material (ca. 20 mg, ^{1}H NMR) was obtained by trituration with diethyl ether.

Pyrrolo[3,4-*d*]pyrimidines 7 from DHPMs 11a−l. General Procedure. Sample aliquots (ca. 100 mg) of the appropriate resin-bound chloromethyl-DHPMs **11a**−**l** were suspended in dry DMF (3 mL) and treated with 5 equiv of the corresponding amine building block (see Table 2 and Figure 1). Depending on the reactivity of the amine, the suspension was stirred for 18 h at room temperature (for reactive amines **4A**−**D**,**J**,**K**), at 50 °C (for amines **4E**−**I**), or at 70 °C (for amine **4F**, 20 equiv). The resulting resins **12** were filtered and washed with DMF (3 × 5 mL), THF (2 × 5 mL), EtOH (2 × 5 mL), and DMF (2 × 5 mL). The purified resins **12** were resuspended in DMF (3 mL) and irradiated sequentially[6] in large Smith process vials for 10 min at 150, 200 (for sterically bulky amines **4E**−**I**), or 250 °C (for amine **4F**) in the cavity of the Smith synthesizer. After cooling to ambient temperature, the resins were filtered off and washed twice with DMF (1 mL each). From the combined DMF solutions (ca. 5 mL), amounts of 30 μL were taken for HPLC−UV/MS determination of purity (see above). The rest of the sample was evaporated under reduced pressure to yield the desired pyrrolopyrimidines **7** in 25−55% overall yield (based on initial loading of resin **9**; see Table 2), which in most cases crystallized directly after evaporation of solvent. Pure crystalline material (20 mg, ^{1}H NMR) was obtained by trituration with diethyl ether.

Pyrimido[4,5-*d*]pyridazines 8 from DHPMs 11. General Procedure. Sample aliquots (ca. 100 mg) of the appropriate resin-bound chloromethyl-DHPMs **11** were suspended in dry DMF (3 mL) and treated with 5 equiv of the corresponding hydrazine building block (see Table 3 and Figure 1) for 30 min at room temperature. The resulting resins **13** were filtered and washed with DMF (3 × 5 mL), THF (2 × 5 mL), EtOH (2 × 5 mL), and DMF (2 × 5 mL). The purified resins **13** were resuspended in DMF (3 mL) and irradiated in large Smith process vials for 10 min at 150 °C in the cavity of the Smith synthesizer. After cooling to ambient temperature, the resins were filtered off and washed twice with DMF (1 mL each). From the combined DMF solutions (ca. 5 mL), amounts of 30 μL were taken for HPLC−UV/MS determination of purity (see below). The rest of the sample was evaporated under reduced pressure to yield the desired pyrimidopyridazines **8** in 30−41% overall yield (based on the initial loading of resin **9**; see Table 3), which in most cases crystallized directly after evaporation of solvent. Because of the moderate purity of these compounds, no attempts were made to obtain pure solid materials by trituration with the appropriate solvent.

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Supporting Information Available. Analytical and spectroscopic data for furo[3,4-*d*]pyrimidines **6**, pyrrolo[3,4-*d*]pyrimidines **7**, and pyrimido[4,5-*d*]pyridazines **8** obtained from solution-phase studies, differential scanning calorimetry (DSC) measurements (Figure S1), and on-bead FTIR spectra (Figure S2). This material is available free of charge via the Internet at http://pubs.acs.org.

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