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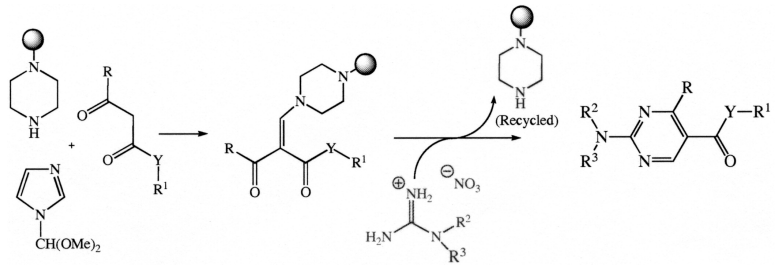

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A "Catch and Release" Strategy for the Parallel Synthesis of 2,4,5-Trisubstituted Pyrimidines

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A resin capture and release strategy for making a combinatorial array of 2,4,5-trisubstituted pyrimidines is demonstrated by capturing β-ketoesters and β-ketoamides on a solid-supported piperazine. Through a cyclocondensation reaction, the solid-supported enaminone is reacted with several guanidines under heating or microwave irradiation affording the corresponding pyrimidines in good yield and chemical purity directly on solution. After this final step, the support can be effectively recycled.

Introduction

Combinatorial chemistry is recognized as a very powerful tool for the acceleration of the drug discovery process.[1] The philosophy behind how combinatorial methods can be employed more effectively has become more refined to allow for such concepts as "privileged structures" and the synthesis of libraries that contain "druglike" characteristics.[2] The design and the synthesis of platforms that possess druglike characteristics and are also amenable to parallel high throughput synthesis methods remain a continuing challenge for contemporary medicinal chemistry.[3]

Recently, we embarked on a development program for the parallel synthesis of several biologically interesting heterocycles.[4] Because heterocycles form the basis of many drug classes, combinatorial libraries derived from known heterocyclic core fragments are attractive targets for identifying lead structures.[5] A relatively little explored class of heterocycles is constituted from pyrimidines bearing an alkylamine substituent on the 2-position. 2-Aminopyrimidine derivatives are found in compounds with potential biological functions as diverse as antipsychotic, cardioprotective, and antimalarial activities.[6]

We were therefore interested in the solid-phase synthesis of pyrimidines libraries. Common approaches for this class of compounds include ring formation reactions and thermal nucleophilic aromatic substitution reactions of halogenated pyrimidines with amines.[7] Nucleophilic aromatic substitution reactions of electron deficient halogenated pyrimidines are usually rapid and high yielding. However, in the case of electron rich or even neutral halogenated pyrimidines (c.a. with alkyl, alkoxyl, or amino substituents), the substitution reactions require prolonged heating for hours or days. One further limitation of these approaches is that one substituent is held invariant in order to anchor the pyrimidine ring to the solid phase.[8]

To avoid this limitation, a "traceless" strategy had to be designed that would be compatible with the synthesis of heterocyclic systems. To prepare a collection of pyrimidines with a high degree of potential diversity and wide utility for drug discovery using solid-phase techniques, it is important to design a pyrimidine synthesis in which at least three components can be independently and readily varied. In that context, sulfur linkers have been attractive for heterocyclic synthesis. The sulfur linker is popular because it can be activated by oxidation and displaced by a wide variety of nucleophiles to introduce new diversity into the molecule (cleavage/diversification).[9] A limitation against this simple approach is that the procedure is not suitable to prepare pyrimidines having substituents susceptible to this oxidant condition (m-CPBA).[10] Moreover, a postsynthetic purification is required if more than 1.0 molar equivalent of reagent is used for the diversification/cleavage step or if the conversion is not totally achieved. Furthermore, at the end of the process, it is not possible to recycle the polymer.

Results and Discussion

As a part of ongoing studies aimed toward the identification of new techniques for a combinatorial pyrimidine synthesis under mild conditions, we have examined new traceless linker methodologies on solid phase. Condensation reactions of 1,3-dicarbonyl compounds or synthetic equivalents with guanidine allow a broad access to 2-amino-substituted pyrimidines.[11] We report herein the successful application of resin-bound β-enaminones, which can be seen both as supported synthetic auxiliaries or novel traceless linkers for the preparation of highly functionalized 2-amino pyrimidine libraries.[12] We were attracted to such a strategy as enaminones should be versatile intermediates too for the preparation of several other heterocyclic derivatives.[13] To design a rapid synthesis of a library of compounds that can be delivered directly onto solution, we decided to anchor the β-enamino ketone on a solid amine-functionalized support. To reach this goal, we first chose the synthetic route depicted in the retrosynthetic Scheme 1, which had been successfully applied to the synthesis of pyrazoles and isoxazoles.[14,15]

The amine group on solid support was an attractive point to realize a "catch and release" approach and to deliver the target libraries with minimal purification steps. Several solid

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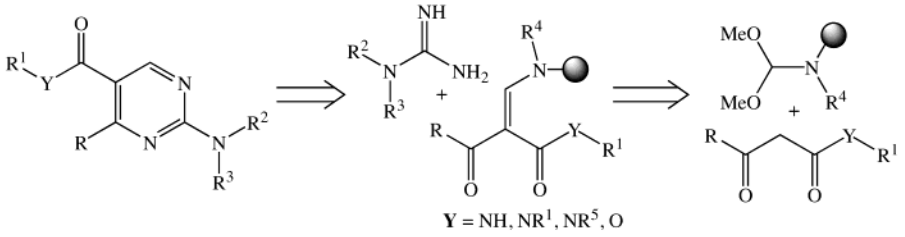
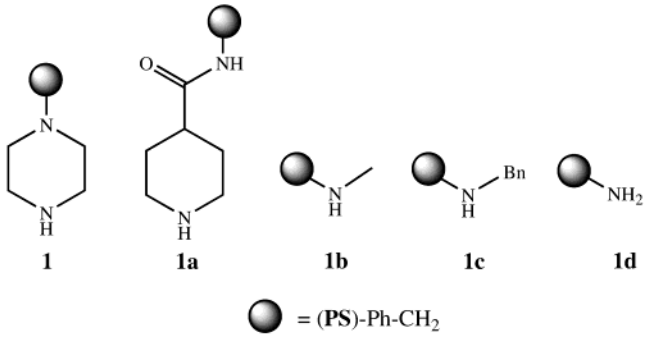
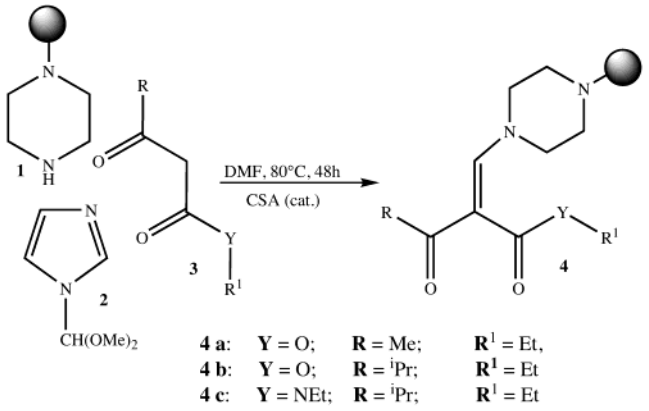
Scheme 1. Retrosyntetic Analysis of a Library of Pyrimidines



Scheme 2. Solid-Support Amines Used To Prepare Support-Bound β-Enaminones



Scheme 3. Preparation of Polymer-Bound Enones[a]



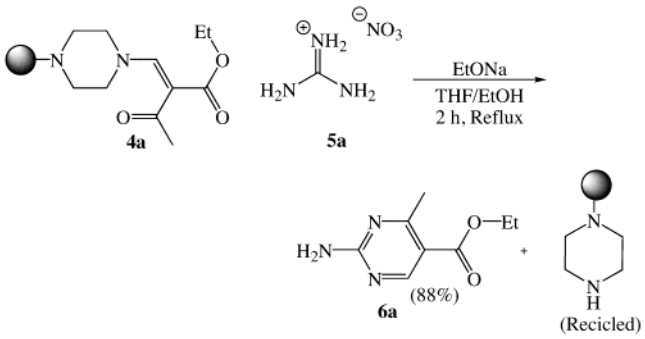
[a] Reagents and conditions: (a) DMF, 80 °C, 48 h. Yields are >99% (as determined by colorimetric assays and elementary analysis of resin beads).

support amines were found to perform well in the synthesis of the support-bound β-enaminone (Scheme 2).

Generally, piperazine **1** and piperidine **1a** provided the cleanest products after cleavage. Moreover, most of the acyclic secondary amines and branched primary amines afforded complex mixtures in the cyclization displacement step. Taking into account that supported piperazine **1** is commercially available, we chose to explore its use for the formation of an anchored β-enaminone. To increase the amount of material that could be generated, a relatively high-loading form (5.60 mmol/g) was selected. Therefore, a mixture of piperazine bound resin **1**, *N*-formylimidazole dimethylacetal **2**, and a β-keto ester **3** was mixed and heated for 48 h in DMF, in the presence of 10% CSA as catalyst (Scheme 3). Filtration from the beads gave β-enaminone **4** in good yield (as determined by colorimetric assays and elementary analysis of resin beads).

This result convinced us to further explore the functionalized polymer **1** in this reaction. Thus, several β-dicarbonyl compounds (**3a**−**c**) were attached to piperazinomethylpolystyrene **1**. The synthetic strategy was initially optimized using commercial β-keto esters and subsequently extended to β-keto esters and β-keto amides prepared according to the classical malonic synthesis.[16]

Scheme 4. Synthetic Route to Substituted Pyrimidine **6a**



The desired 2-aminopyrimidines (**6**) were prepared from the β-enaminone on the resin (**4**) and guanidine (**5**) by refluxing them together in a basic alcoholic media. Thus, the condensation of **4a** with 1 equiv of guanidine nitrate **5a** liberated from its salt with sodium ethoxide in boiling EtOH/THF (4/1) for 2 h resulted in the formation of the chemically pure target heterocyclic species **6a** in 88% yield (Scheme 4).

Initially, our main focus in further derivatizing the enaminone was the conversion to pyrimidines by means of a number of guanidines with different steric and electronic properties. The current literature reveals a growing number of examples of syntheses of guanidines, which utilize several guanilating reagents.[17] Typically, the synthesis of guanidines involves treatment of an amine with an electrophilic amidine species. 3,5-Dimethyl-1-pyrazolylformamidinium nitrate **7** (commercially available) was used to convert primary, secondary, and aromatic amines to their guanidine nitrate derivatives under mild conditions.[18] This protocol allowed the efficient guanylation of complex, thermally labile amines (Scheme 5).

Two β-ketoesters **4a**,**b** and 13 guanidines with potential different reactivity were selected to check the optimized pyrimidine synthesis conditions in the preparation of a 26-membered array (Scheme 4 and Table 1). Another 13-membered array was prepared using the same guanidines (Scheme 6 and Table 1) with the immobilized β-ketoamide **4c** followed by purification of the final compounds. The excess of reagents can be easily removed at the end by means of an aqueous acidic work up or a strong cationic exchange resin capturing for the semiautomated sample purification. This last postsynthetic purification procedure appears to be particularly efficient for the hydrophilic pyrimidines. Pyrimidines were obtained in both good yield and chemical purity

Scheme 5. Preparation of an Array of Guanidines

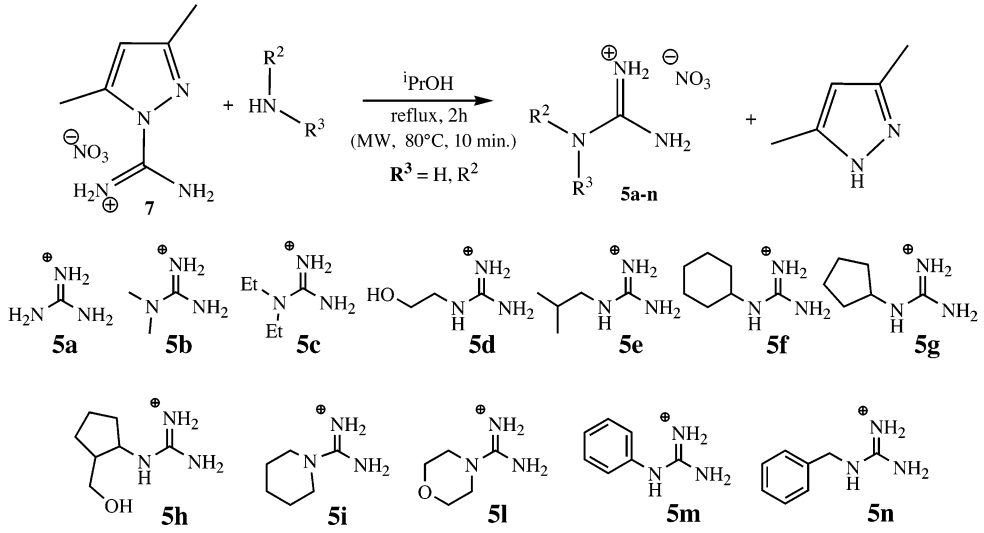
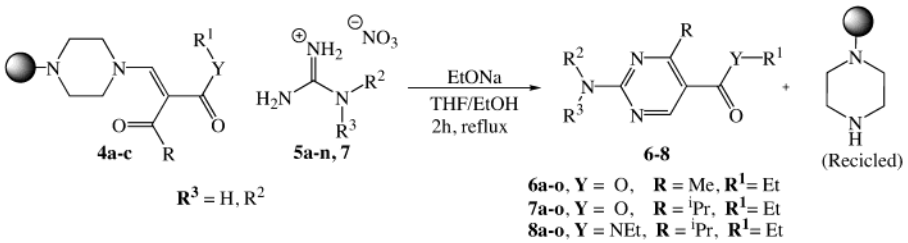


Table 1. Representative Pyrimidine Synthesis Using Enaminone Resins (**4a**−**c**) and Various Guanidines (**5a**−**n**, **7**) under Thermal Conditions



entry	guanidine/ enaminone	% yield[a]/ purity[b]	entry	guanidine/ enaminone	% yield[a]/ purity[b]	entry	guanidine/ enaminone	% yield[a]/ purity[b]
6a	5a/4a	88/91	**7a**	5a/4b	85/87	**8a**	5a/4c	87/89
6b	5b/4a	92/89	**7b**	5b/4b	90/88	**8b**	5b/4c	90/85
6c	5c/4a	91/88	**7c**	5c/4b	89/85	**8c**	5c/4c	91/87
6d	5d/4a	93/87	**7d**	5d/4b	89/86	**8d**	5d/4c	93/85
6e	5e/4a	81/89	**7e**	5e/4b	83/87	**8e**	5e/4c	85/88
6f	5f/4a	94/85	**7f**	5f/4b	92/90	**8f**	5f/4c	94/87
6g	5g/4a	90/90	**7g**	5g/4b	92/88	**8g**	5g/4c	92/89
6h	5h/4a	92/92	**7h**	5h/4b	91/87	**8h**	5h/4c	94/85
6i	5i/4a	91/90	**7i**	5i/4b	90/88	**8i**	5i/4c	91/90
6l	5l/4a	89/87	**7l**	5l/4b	92/89	**8l**	5l/4c	89/88
6m	5m/4a	92/89	**7m**	5m/4b	94/91	**8m**	5m/4c	92/90
6n	5n/4a	89/91	**7n**	5n/4b	92/88	**8n**	5n/4c	91/90
6o	7/4a	94/89	**7o**	7/4b	92/93	**8o**	7/4c	90/92

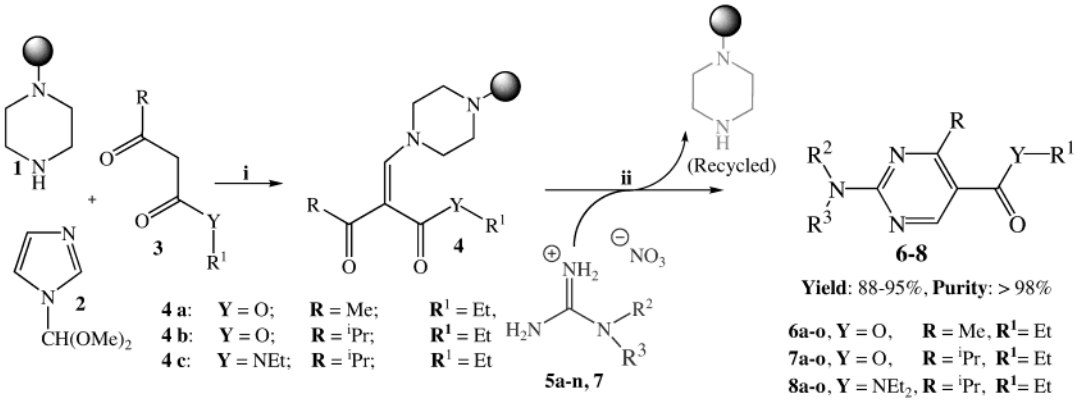
[a] Yields are determined based on mass recovery of crude product. [b] Purity given is determined from crude material based on area of peak corresponding to the correct molecular weight, monitored by HPLC−UV detection, scanning at 254 nm.

(between 85 and 92%, as judged by HPLC−UV 254/MS measurements) independently of the structure of the guanidines and β-keto ester or β-keto amide employed. These data are summarized in Table 1. More details are reported in the Experimental Section.

During the development of this protocol, we used two colorimetric tests to verify the progress of the reactions. The free amine on polymer was monitored using the chloranil test. This rather sensitive assay enables the detection of even small amounts of free secondary amines on the resin, and thereby, a negative test indicates that the enaminone was anchored on the solid support. The presence on the resin (and consequently the delivery from the resin) of enaminones **4** could be monitored with iron(III) test[19] too, which was able to form an intensely colored complex (rust-brown) with enolizable ketones.

On the basis of our recent encouraging experiences in the area of microwave-assisted solid-phase chemistry,[20] we also considered the use of this technology to optimize the timing of developed protocol.[21] Resin-bound enaminone synthesis can be effectively performed in high yield within 30 min using a self-tunable microwave synthesizer at 80 °C.[22] The reaction was carried out in an open vessel to allow the removal of the formed methanol from the equilibrium.[23] After some experiments, we discovered that the desired pyrimidines **6**−**8** could be efficiently released from the resin by controlled single mode microwave irradiation of supported enaminone in the presence of guanidines **5a**−**n** and **7**,

Scheme 6. MWI Capture and Release of Pyrimidines via Solid-Supported Enaminones[a]



[a] Reagents and conditions: (i) DMF, CSA (catalytic), MWI, 80 °C, 30 min. (ii) EtONa, EtOH/THF (4/1), MWI, 130 °C, 10 min.

Table 2. Comparison of Conventional and Microwave Procedures for Pyrimidine Libraries Synthesis

	thermal reaction (2 h, 65 °C)	microwave-assisted reaction (20 min, 80 °C)
pyrimidines	% yield[a]/purity[b]	% yield[a]/purity[b]
6a−o	91/89	92/98
7a−o	90/88	90/99
8a−o	91/88	90/98

[a] Average yield determined based on mass recovery of crude product. [b] Average purity determined by HPLC peak area at 254 nm.

working in a sealed tube for 10 min at 130 °C and using EtOH/THF (4/1) as solvent (Scheme 6) (see Experimental Section).[24]

Increasing the reaction time up to 20 min or resubjecting the recovered resin under the above conditions did not change both yield and purity. On the contrary, irradiating at 180 °C in a sealed tube for 5 min, the yield of the isolated cleaved compounds increased slightly, but the purity was somewhat lower and it was not possible to recycle the restored support.[25] Because of the low purities, in these solid-phase transformations, a further postcleavage purification of these compounds was necessary. At the optimum cleavage temperature of 130 °C and using the same equivalents of reagents as in the thermal reaction, the microwave-assisted release gave similar isolated yields of products. Pyrimidines **6**−**8** were obtained in very high purity (>95%) as judged by HPLC−UV 254/MS measurements (see Table 2 for details). The chemical identity and HPLC−UV homogeneity of a selection of these samples were further corroborated by comparison of their ^{1}H NMR data with the spectra obtained from conventional solution-phase experiments. Yields were determined by weighing the isolated solid materials after evaporation of solvent and were generally in the range of 85−96% (over two steps, based on the initial loading of PS resin **1**). These microwave-assisted reaction conditions also significantly reduced the reaction time for the solid-phase cleavage reactions. In Table 2 are reported some results for the cleavage reactions of resin **2** under MW irradiation (method B), as compared with those of the thermal reaction (method A).

The solid support used can be regenerated in a turnover cycle. The procedure described was in fact repeated using recycled solid support, and high yields of the desired products with high level of purity were always obtained at least for 3−4 cycles.

In summary, we describe an alternative approach to the synthesis of libraries of substituted pyrimidines starting from different β-keto-esters or β-keto-amides, using a low cost and high loading polymer, under very mild conditions and through a microwave strategy. Thermal drawbacks of solid-supported chemistry, such as degradation of the polymer support caused by heating for long times, are so avoided. Additional results of an ongoing effort in our laboratory to develop solid-phase methodologies for the synthesis of other fused ring systems based on the key enaminone intermediate will be reported elsewhere.

General Procedure for Guanidine Nitrate Synthesis. Benzylguanidine Nitrate. To 3,5-dimethyl-lguanylpyrazole nitrate (0.4 g, 2 mmol) in 15 mL of ^{i}PrOH was added benzylamine (0.43 g, 0.44 mL, 4.0 mmol). The mixture was refluxed until the disappearance of guanypyrazole (TLC: DCM/MeOH/NH_3 4/1/2) and allowed to cool. Ether (5 mL) was added, and the resulting sticky solid product was collected, washed with ether, and dried in vacuo. Recrystallization of the crude product from ^{i}PrOH/Et_2O (1/1) yielded 0.3 g (70%) of benzylguanidine nitrate as a white crystalline solid; mp 151−152 °C (lit.[26] mp 150−153 °C). ^{1}H NMR (D_2O): 4.60 (s, 2H). 7.25−7.40 (m, 5H). ^{13}C (D_2O): 45.3, 126.3, 127.5, 128.2, 135.0, 156.8. Anal. Calcd for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.70; N, 26.40. Found: C, 45.30; H, 5.67; N, 26.40.

General Procedure for Conventional and Microwave-Assisted Pyrimidine Synthesis. 1. Conventional Procedure. a. Resin-Bound Enaminone. To a suspension of piperazine resin (0.18 g, 1.00 mmol) swollen in DMF (2 mL) was added a solution of N-formylimidazole dimethylacetal (0.85 g, 6 mmol), ethyl acetoacetate (0.39 g, 0.38 mL, 3 mmol), and camphorsulfonic acid (86.0 mg, 10% w/w) in DMF (8 mL). The resulting mixture was heated to 80 °C for 48 h. The complete conversion of supported secondary amine to enaminone was confirmed using the colorimetric "Chloranil test" (negative). After it was cooled, the mixture was transferred to a polypropylene vessel, and the resin was filtered off and washed with alternating portions of DMF (3 × 10 mL), MeOH (3 × 10 mL), and CH_2Cl_2 (3 × 10 mL).

The resin was dried under reduced pressure. After a sample was taken for IR, the resin was directly used for the next step. The IR spectrum of this sample was compared with the piperazine starting resin (KBr pellet) and showed a strong carbonyl absorption band at 1688, 1643, and 1580 cm^{-1} indicating successful solid support capture of the β-keto ester.

b. Cyclization. 1,1-Dimethylguanidine nitrate (0.15 g, 1.00 mmol) was added at room temperature to a solution of sodium ethoxide in ethanol, prepared from sodium (24 mg, 1.00 mmol) and anhydrous ethanol (4 mL). The suspension was stirred for 10 min, and the sodium nitrate was removed by filtration. The ethanol solution of guanidine was added to the solid-supported enaminone **4a** (from the above experiment) swollen in dry THF (1 mL). The mixture was heated at reflux until disappearance of carbonyl function on the support-bound material (negative to $FeCl_3$ colorimetric test, positive to chloranil test). After it was cooled to room temperature, the resin was collected in a coarse-fritted funnel attached to a jointed Erlenmeyer flask connected to vacuum and successively washed with EtOH (3 × 10 mL) agitating the resin with a wooden spatula to ensure mixing. All of the alcoholic layers were combined and concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (20 mL). Methylene chloride solution was sequentially washed with 5% HCl aqueous solution, aqueous solution, and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated to dryness under reduced pressure to give the pure title pyrimidine **6b** (0.19 g, 92% yield, 89% purity). The identity of the product was controlled by comparison of the ^1H, ^{13}C NMR, and MS spectra with literature data.

2. Microwave Irradiation Procedure. a. Resin-Bound Enaminone. To a piperazine resin (0.18 g, 1.00 mmol) swollen in DMF (2 mL) was added a solution of N-formylimidazole dimethylacetal (0.85 g, 6 mmol), ethyl acetoacetate (0.39 g, 0.38 mL, 3 mmol), and camphorsulfonic acid (86.0 mg, 10% w/w) in DMF (8 mL). The open flask (25 mL round-bottomed glassware with standard condenser) was irradiated at 80 °C (by modulation of the power) for 30 min in a self-tuning single mode CEM Discover Focused Synthesizer. The mixture was cooled rapidly to room temperature by passing compressed air through the microwave cavity for 3 min. The reaction progress was monitored by the Chloranil colorimetric test. After it was cooled to room temperature, the resin sample was collected by filtration using a sintered glass funnel. The resin was thoroughly washed with alternating portions of DMF (3 × 10 mL), MeOH (3 × 10 mL), and CH_2Cl_2 (3 × 10 mL). The resin sample was dried under reduced pressure. The IR spectrum of this resin sample was compared with the piperazine starting resin (KBr pellet) and showed a strong carbonyl absorption band at 1688, 1643, and 1580 cm^{-1} indicating successful solid support capture of the β-keto ester.

b. Cyclization. A suspension of sodium ethoxide, prepared from sodium (24 mg, 1.00 mmol) and anhydrous ethanol (4 mL) and one equiv of 1,1-dimethylguanidine nitrate (0.15 g, 1.00 mmol), was stirred for 10 min, and sodium nitrate was removed by filtration. The neutralized guanidine was then added to the solid-supported enaminone **4a** (from the above experiment) swollen in THF (1 mL). Then, the suspension was placed into an sealed tube (CEM designed 10 mL pressure-rated reaction vial), and the reaction mixture was exposed to microwave irradiation as above for 10 min at 130 °C and monitored for the disappearance of carbonyl function on the support-bound material (negative $FeCl_3$ colorimetric test, positive to chloranil test). After it was cooled to room temperature, the resin was then collected using a sintered glass funnel and successively washed several times with EtOH (3 × 10 mL). All of the alcoholic layers were combined and concentrated in a vacuum, and the residue was dissolved in CH_2Cl_2 (20 mL). Methylene chloride solution was sequentially washed with 5% HCl aqueous solution, aqueous solution, and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated to dryness under reduced pressure to give the pure target pyrimidine **6b** (0.20 g, 95% yield, 99% HPLC purity). The identity of the products was controlled by comparison of the ^1H NMR, ^{13}C NMR, and MS spectra with literature data.

Ethyl 2-(Dimethylamino)-4-methypyrimidine-5-carboxylate (6b). Yield, 92% (95% yield, MWI). White powder, mp 56−58 °C (petroleum ether). ^1H NMR ($CDCl_3$): δ 1.36 (t, J = 6.0 Hz, 3 H, CH_3), 2.65 (s, 3 H, CH_3), 3.24 (s, 6 H, $(CH_3)_2N$), 4.32 (q, J = 6.0 Hz, 2 H, OCH_2), 8.82 (s, 1 H, Ar, H-6). ^{13}C NMR ($CDCl_3$): δ 14.6, 25.7, 34.8, 60.4, 111.0, 158.6, 160.1, 166.5, 170.0. IR ($CHCl_3$): 1705, 1584, 1560, 1415 cm^{-1}. MS (ESI + ve ion): m/z = 210.23 $[M + H]^+$. HPLC analysis: 89% (99% MWI). Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.43; H, 7.20; N, 20.10.

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Supporting Information Available. Synthetic procedures and characterization of new compounds. This material is available free of charge via Internet at http://pubs.acs.org.

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