JOC Article

Synthesis of 2-Amino-4-pyrimidinones from Resin-Bound Guanidines Prepared Using Bis(allyloxycarbonyl)-Protected Triflylguanidine

Christoph W. Zapf and Murray Goodman*

Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, California, 92093-0343

mgoodman@ucsd.edu

Received August 15, 2003

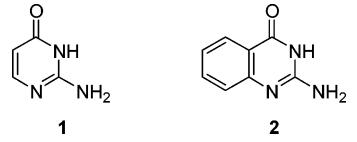
We have synthesized novel heterocyclic compounds from resin-bound guanidines. For this purpose, an amine immobilized on a solid support was acylated with protected amino acids. Following the deprotection, the liberated amines were guanidinylated utilizing a new member of the family of diurethane-protected triflyl guanidine reagents, *N*,*N*′-bis(allyloxycarbonyl)-*N*″-triflylguanidine. The deprotected guanidines were subsequently regioselectively cyclized with β-keto esters yielding novel compounds containing heterocyclic structures in high purities.

Introduction

Modern drug design cannot be imagined without the chemistry of heterocycles. These molecules offer unique advantages over linear or carbocyclic structures, a fact which has been recognized by medicinal chemists for decades. Heterocycles are commonly regarded as interesting scaffolds which can be synthesized readily and which are able to incorporate substituents. The cyclic nature of heterocycles provides an inherent constraint arraying the substituents in the desired orientation. For these and other reasons, many pharmaceuticals contain heterocyclic groups.[1,2]

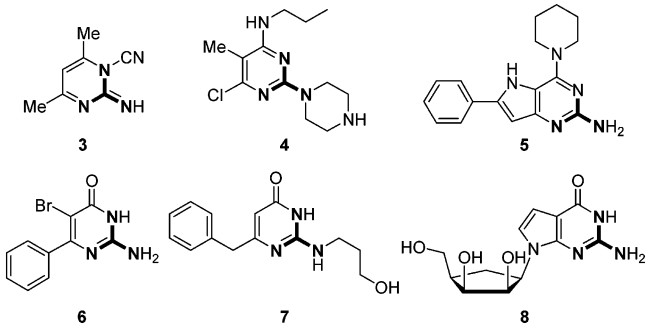
Results and Discussion

A substantial body of work has been reported on the synthesis of 2-aminopyrimidinones **1** and bicyclic analogues such as 2-aminoquinazolinones **2** shown in Figure 1.



1 **2**

FIGURE 1. Isocytosine **1** and 2-aminoquinazolinones **2**.



3 **4** **5** **6** **7** **8**

FIGURE 2. Biologically interesting 2-aminopyrimidine-derived compounds.

Compounds derived from the parent structures **1** and **2** have provided a basis for different medicinal applications (Figure 2). Cyano-substituted aminopyrimidine **3** has been shown to act as a potential antimycotic,[3] while the piperazine-substituted pyrimidine structure **4** shows remarkable selectivity for the α2-adrenoceptors[4] whereas piperidine-substituted aminopyrrolopyrimidine **5** serves as a Y5 receptor antagonist.[5] Bromo-substituted 2-amino-4-pyrimidinone structure **6** displays anti-inflammatory properties,[6] while compound **7** acts as a reverse-transcriptase inhibitor[7,8] and pyrrolopyrimidinone **8** has been shown to possess antiherpetic activities.[9]

The structural nature of this class of pyrimidines lends itself to condensation chemistry. Cyclizations have been a dominant approach for the synthesis of pyrimidines with modifications determined by the specific structures of the target molecules.[10] For this purpose, a 1,3-dicarbonyl compound **10** can be allowed to react with guani-

(1) *Annual Reports in Medicinal Chemistry*; Doherty, A. M., Ed.; Academic Press: New York, 2001; Vol. 36.
(2) *Annual Reports in Medicinal Chemistry*; Doherty, A. M., Ed.; Academic Press: New York, 2002; Vol. 37.
(3) Kreutzberger, A.; Sellheim, M. *J. Heterocycl.. Chem.* **1985**, *22*, 721−723.
(4) Guérémy, C.; Audiau, F.; Renault, C.; Benavides, J.; Uzan, A.; Le Fur, G. *J. Med. Chem.* **1986**, *29*, 1394−1398.
(5) Norman, M. H.; Chen, N.; Chen, Z.; Fotsch, C.; Hale, C.; Han, N.; Hurt, R.; Jenkins, T.; Kincaid, J.; Liu, L.; Lu, Y.; Moreno, M.; Santora, V. J.; Sonnenberg, J. D.; Karbon, W. *J. Med. Chem.* **2000**, *43*, 4288−4312.
(6) Skulnick, H. I.; Ludens, J. H.; Wendling, M. G.; Glenn, E. M.; Rohloff, N. A.; Smith, R. J.; Wierenga, W. *J. Med. Chem.* **1986**, *29*, 1499−1504.
(7) Nizi, E.; Botta, M.; Corelli, F.; Manetti, F.; Messina, F.; Maga, G. *Tetrahedron Lett.* **1998**, *39*, 3307−3310.
(8) Botta, M.; Corelli, F.; Maga, G.; Manetti, F.; Renzulli, M.; Spadari, S. *Tetrahedron* **2001**, *57*, 8357−8367.
(9) Legraverend, M.; Bisagni, E. *Tetrahedron Lett.* **1985**, *26*, 2001−2002.

10.1021/jo035201a CCC: $25.00
Published on Web 12/03/2003

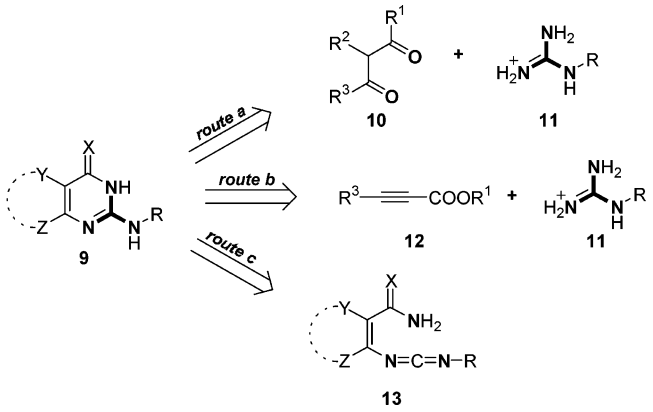


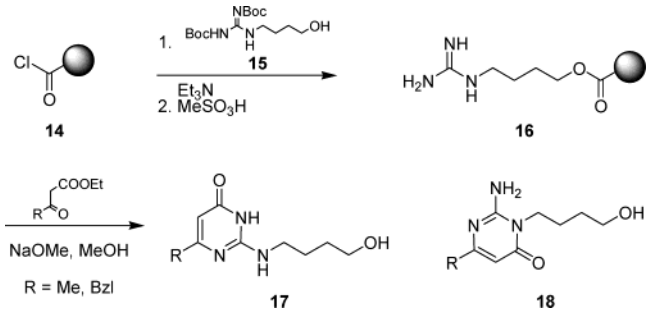
FIGURE 3. 2-Aminopyrimidines can be synthesized through different approaches.

dine, a substituted guanidine **11,** or a precursor thereof (route a, Figure 3). During the reaction, the heterocycle is formed as well as a byproduct such as a molecule of water or alcohol. The 1,3-dicarbonyl compounds generally utilized are substituted malonic esters, 1,3-diketones, and β-keto esters.[9,11−23]

Furthermore, route b in Figure 3 illustrates how substituted propiolates **12** can be utilized in a manner similar to β-keto esters to cyclize a substituted guanidine **11** yielding 2-aminopyrimidinones **9**. Propiolates **12** can be regarded as dehydrated analogues of β-keto esters and therefore have been utilized as well in the design and synthesis of heterocyclic compounds.[24−27]

Other methods to synthesize heterocyclic structures **9** have been reported in the literature. For instance, the aminopyrimidine system can also be obtained by intramolecular reaction of an amine functionality with a substituted aromatic carbodiimide (route c).[28]

SCHEME 1. Solid-Phase Synthesis of Hydroxybutyl Regioisomers 17 and 18



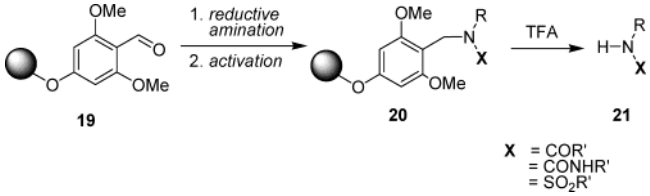
The utility of reactions on solid support was initially demonstrated in peptide chemistry.[29] Chemical transformations on solid supports have now been extended to many important organic reactions.[30−32] Substantial progress has been achieved toward the synthesis of heterocycles on a solid-support. The methods employed and the structures prepared in this manner are varied. Recent reviews describe the syntheses of heterocyclic structures utilizing solid-phase chemistry.[33,34]

There have been several reports on the solid-phase synthesis of heterocycles related to the 2-aminopyrimidinones noted above.[35,36] Scheme 1 illustrates a very interesting approach to prepare 2-aminopyrimidines via resin-bound guanidines which was reported by Botta and co-workers.[7,8] For this purpose, immobilized acid chloride **14**, which was derived from a Merrifield resin, was allowed to react with *N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*″-4-hydroxybutyl guanidine **15** to immobilize the guanidine on the solid support via an ester linkage. Subsequent removal of the protecting groups with methanesulfonic acid generated the resin-bound guanidine **16**. Exposure of the terminal guanidine to ethyl acetoacetate and ethyl-3-oxo-4-phenylbutanoate in refluxing methanol in the presence of sodium methoxide resulted in the formation and simultaneous removal of the heterocycle from the solid support. As indicated in Scheme 1, the β-keto ester did not react regiospecifically but led to the formation of two regioisomers **17** and **18** in a ratio of about 3:1.

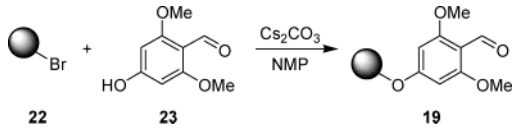
The encouraging results from Botta et al. to prepare heterocyclic structures from resin-bound guanidines prompted us to design novel target structures based on our experience with guanidinylation chemistry[37−40] and

(10) Kenner, G. W.; Todd, A. In *Heterocyclic Compounds*; Elderfield, R. C., Ed.; John Wiley and Sons: New York, 1957; Vol. 6, pp 234−323 and references therein.
(11) Legraverend, M.; Nia Ngongo-Tekam, R.-M.; Bisagni, E.; Zerial, A. *J. Med. Chem.* **1985**, *28*, 1477−1480.
(12) Miller, D. J.; Ravikumar, K.; Shen, H.; Suh, J.-K.; Kervin, S. M.; Robertus, J. D. *J. Med. Chem.* **2002**, *45*, 90−98.
(13) Alberola, A.; Antolín, L. F.; Gonzáez, A. M.; Laguna, M. A.; Pulido, F. J. *Heterocycles* **1987**, *25*, 393−397.
(14) Gangjee, A.; Yu, J.; McGuire, J. J.; Cody, V.; Galitsky, N.; Kisliuk, R. L.; Queener, S. F. *J. Med. Chem.* **2000**, *43*, 3837−3851.
(15) Cho, H.; Shima, K.; Hayashimatsu, M.; Ohnaka, Y.; Mizuno, A.; Takeuchi, Y. *J. Org. Chem.* **1985**, *50*, 4227−4230.
(16) Nugent, R. A.; Murphy, M. *J. Heterocycl. Chem.* **1986**, *23*, 245−247.
(17) Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G. *J. Med. Chem.* **1989**, *32*, 2381−2388.
(18) Troxler, F.; Weber, H. P. *Helv. Chim. Acta* **1974**, *57*, 2356−2364.
(19) Wade, J. J.; Hegel, R. F.; Toso, C. B. *J. Org. Chem.* **1979**, *44*, 1811−1816.
(20) Nair, M. D.; Sudarsanam, V.; Desaj, J. A. *Indian J. Chem.* **1982**, *21B*, 1030−1032.
(21) Miyamoto, Y.; Yamazaki, C. *J. Heterocycl. Chem.* **1994**, *31*, 1445−1448.
(22) Vasudevan, A.; Mavandadi, F.; Chen, L.; Gangjee, A. *J. Org. Chem.* **1999**, *64*, 634−638.
(23) Jones, T. R.; Betteridge, R. F.; Newell, D. R.; Jackman, A. L. *J. Heterocycl. Chem.* **1989**, *26*, 1501−1507.
(24) Härter, H. P.; Lichti, H.; Stauss, U.; Schindler, O. *Helv. Chim. Acta* **1976**, *59*, 1203−1212.
(25) Al-Jallo, H. N.; Muniem, M. A. *J. Heterocycl. Chem.* **1978**, *15*, 849−853.
(26) Acheson, R. M.; Wallis, J. D. *J. Chem. Soc., Perkin Trans. 1* **1981**, *2*, 415−422.
(27) Campbell, M. M.; Campbell, A. C.; Peace, A.; Pick, J.; Woods, G. F. *J. Chem. Soc., Chem. Commun.* **1985**, 1164−1165.
(28) Okawa, T.; Kawase, M.; Eguchi, S.; Kakehi, A.; Shiro, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2277−2285.
(29) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149−2154.
(30) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4537−4554.
(31) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1997**, *53*, 5643−5678.
(32) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1998**, *54*, 15385−15443.
(33) Franzén, R. G. *J. Comb. Chem.* **2000**, *2*, 195−214.
(34) Krchnák, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61−91.
(35) Hamper, B. C.; Gan, K. Z.; Owen, T. J. *Tetrahedron Lett.* **1999**, *40*, 4973−4976.
(36) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *J. Org. Chem.* **2002**, *67*, 5831−5834.
(37) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804−3805.
(38) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432−8439.
(39) Baker, T. J.; Goodman, M. *Synthesis* **1999**, *No SI*, 1423−1426.
(40) Baker, T. J.; Luedtke, N. W.; Tor, Y.; Goodman, M. *J. Org. Chem.* **2000**, *65*, 9054−9058.

SCHEME 2. Amides, Ureas, and Sulfonamides 20 Can Be Linked to a Resin via the Nitrogen Atom Utilizing Aldehyde Resin 19 and Subsequently Cleaved in a Traceless Fashion



SCHEME 3. Synthesis of Aldehyde Resin 22



in the context of solid-phase chemistry.[41,42] We also envisioned possibilities of incorporating amino acids into the design of novel heterocyclic compounds.[43]

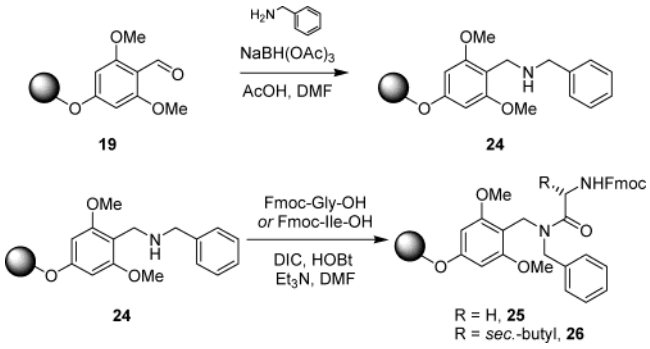
Synthesis of Resin-Bound Guanidines on Solid Support To Prepare Novel Heterocycles. Over the last several years, methoxy-substituted benzaldehyde linkers **19** (Scheme 2) have become popular because of their robust nature toward a large variety of reagents and chemical transformations.[44,45] After reductive amination and subsequent activation, the amine can be converted into an immobilized acyl-, urea or sulfonyl derivative **20**. It is possible to cleave these structures from the electron-rich benzylic position by treatment with strong acid such as TFA. The "traceless" nature of this resin is a useful feature, as the linkage to the solid support is converted to a proton as seen in substrate **21**.

We chose to employ the trimethoxybenzyl group as a suitable linkage to the solid support. Structural diversity can be derived from structure **21** since a wide variety of primary amines is readily available for the reductive amination of resin **19**, as well as reactions with carboxylic acids, isocyanates, and sulfonic acids. Employing these reagents in a combinatorial manner can lead to the generation of amides, ureas, or sulfonamides **21** with a large degree of structural diversity. At the outset of the project, we sought a synthetic route to obtain heterocyclic compounds which would incorporate as much structural diversity as possible and would not limit the possible chemical reactions.

To prepare linker **19**, we utilized a tentagel-grafted polystyrene resin which terminated in a bromoalkyl group **22**. The bromide was displaced successfully by readily available 2,6-dimethoxy-4-hydroxybenzaldehyde **23** in the presence of cesium carbonate at elevated temperature as shown is Scheme 3.

Resin **19** was prepared on a multigram scale. A portion was treated with a primary amine under reductive amination conditions to introduce the first point of diversity into the target molecule (Scheme 4). Synthesis of the secondary amine **24** was accomplished by allowing aldehyde resin **19** to react with benzylamine and sodium triacetoxyborohydride, in the presence of acetic acid in DMF. To ascertain the homogeneity of the resin-bound structure, an aliquot of the secondary amine resin **24** was treated with benzoyl chloride in the presence of triethylamine, producing the corresponding benzoylamide which was cleaved with neat TFA. Analysis of this sample by RP-HPLC and ^{1}H NMR indicated high purity of the target compound.

SCHEME 4. Synthesis of Resin-Bound Benzyl Amides 25 and 26 Utilizing Aldehyde resin 19



The secondary amine **24** is ready for the introduction of a second element of diversity by acylation with amine-protected amino acids. A comparison of different coupling reagents revealed that diisopropylcarbodiimide (DIC) and 1-hydroxybenzotriazole (HOBt) represent a highly effective reagent combination for the coupling of amino acids to the resin-bound secondary amine **24**. On the basis of these findings, Fmoc-Gly-OH and Fmoc-Ile-OH were coupled to resin-bound secondary amine **24** utilizing DIC and HOBt as shown in Scheme 4 yielding the Fmoc-protected benzyl amides after their removal from the solid support with TFA.

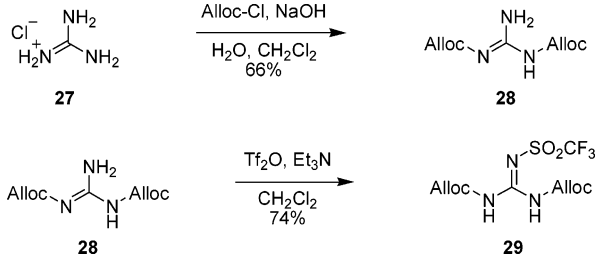
To confirm the completion of the amide bond formation, analytical samples of resin **25** and **26** were treated with 20% piperidine in DMF followed by benzoyl chloride in the presence of triethylamine. Subsequent cleavage with TFA yielded the corresponding diamides. The absence of benzoyl benzamides in the RP-HPLC chromatogram indicated complete amide bond formation and Fmoc deprotection.

The primary amine liberated by the removal of the Fmoc protecting group represents an excellent substrate for resin-bound guanidinylation. As noted above, the linkage to the solid support is acid sensitive. Therefore, the utilization of *N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*″-(trifluoromethylsulfonyl)guanidine to convert the resin-bound amine into the corresponding guanidine could not be employed since the removal of the Boc groups requires acidic conditions. The corresponding *N*,*N*′-bis(benzyloxycarbonyl) derivative of this reagent was also not considered since removal of these protecting groups requires strongly acidic conditions or heterogeneous hydrogenolysis. We therefore sought an alternative protecting group strategy and decided to synthesize *N*,*N*′-bis(allyloxycarbonyl)-*N*″-(trifluoromethylsulfonyl)guanidine **29** (Scheme 5).

As with the previously reported reagents,[37,38,41] the synthesis of this new analogue commenced from guani-

(41) Zapf, C. W.; Creighton, C. J.; Tomioka, M.; Goodman, M. *Org. Lett.* **2001**, *3*, 1133−1136.
(42) Goodman, M.; Zapf, C. W.; Rew, Y. *Biopolymers* **2001**, *60*, 229−245.
(43) Zapf, C. W. Ph.D. Thesis, University of California, 2003.
(44) Boojamra, C. G.; Burow, K. M.; Thompson, L. A.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 1240−1256.
(45) Jensen, K. J.; Alsina, J.; Songster, M. F.; Vagner, J.; Albericio, F.; Barany, G. *J. Am. Chem. Soc.* **1998**, *120*, 5441−5452.

SCHEME 5. Synthesis of *N*,*N*′-Bis(allyloxycarbonyl)-*N*″-trifluoromethylsulfonyl Guanidine 29



dine hydrochloride **27**, which was allowed to react with allyl chloroformate under strongly basic conditions in a two-phase system to produce *N*,*N*′-bis(allyloxycarbonyl)-guanidine **28** in 66% yield. Subsequent conversion of the remaining NH_2 group into the sulfonamide utilizing triflic anhydride yielded reagent **29** in 74% yield. The *N*,*N*′-bis(allyloxycarbonyl)-*N*″-(trifluoromethylsulfonyl)guanidine **29** was characterized by ^{1}H and ^{13}C NMR spectroscopy and was synthesized on a multigram scale.

With this new guanidinylating reagent available and after establishing amide bond formation conditions for coupling protected amino acids, we carried out the synthesis of resin-bound guanidines as outlined in Scheme 6. Removal of the Fmoc group under standard conditions was followed by conversion of the resin-bound primary amine into the corresponding bis-Alloc-protected guanidine **30** utilizing reagent **29**. Subsequently, the protecting groups were removed under palladium-catalyzed conditions. It is presumed that the cleavage occurs via a $\pi-$allylpalladium(II) intermediate, which can act as an alkylating agent.[46] Therefore, the allyl cation must be scavenged by nucleophiles, thus preventing undesired alkylations and simultaneously regenerating the palladium(0) catalyst. Phenylsilane has recently been shown to be an effective scavenger of the π-allyl palladium complexes in solution[47] and on solid support.[48]

Cleavage of small resin quantities of the protected guanidine **30** and the deprotected guanidines **31** and **32** indicated complete conversions and high purities, respectively. Further analysis of compounds **30**−**32** by mass spectrometry and ^{1}H NMR spectroscopy facilitated the identification of the desired compounds.

Conversion of Resin-Bound Guanidines into 2-Amino-4-pyrimidinones. Previously reported literature by Botta and co-workers indicated reactivity of resin-bound guanidines with β-keto esters.[7,8] With these findings, attempts were undertaken to synthesize heterocycles from resin-bound guanidines **31** and **32** using β-keto esters as substrates to accomplish this transformation. After preparation of the free guanidine **31**, we subsequently investigated different solvent conditions to obtain optimal purity for the synthesis of 2-amino-pyrimidinones. We were able to demonstrate that methanol was the best solvent (Table 1) for the clean conversion of the resin-bound guanidine **31** into the corresponding heterocycle utilizing β-keto esters.

(46) Merzouk, A.; Guibé, F.; Loffet, A. *Tetrahedron Lett.* **1992**, *33*, 477−480.
(47) Dessolin, M.; Guillerez, M.-G.; Thieriet, N.; Guibé, F.; Loffet, A. *Tetrahedron Lett.* **1995**, *36*, 5741−5744.
(48) Thieriet, N.; Alsina, J.; Giralt, E.; Guibé, F.; Albericio, F. *Tetrahedron Lett.* **1997**, *38*, 7275−7278.

TABLE 1. Results of Solvent Study To Optimize the Cyclization of Resin-Bound Guanidine 31

solvent	purity of 2-amino-pyrimidinone **33** (%)
1,4-dioxane	80
N,*N*-dimethylformamide/methanol 1:1	80
tetrahydrofuran: methanol 1:1	90
methanol	92

TABLE 2. Results of Study of Required Additives To Optimize Cyclization of Resin-Bound Guanidine 31

additive	purity of 2-amino-pyrimidinone **33** (%)
no additive	0
acetic acid	0
trimethyl orthoformate (TMOF)	0
triethylamine	22
sodium methoxide	93

The solvent study for the cyclization was conducted in the presence of trimethyl orthoformate (TMOF) and sodium methoxide. A further investigation of the additives required for the cyclization of resin-bound guanidine **31** revealed that sodium methoxide is the sole additive necessary for the formation of 2-aminopyrimidinone **33** (Table 2). A strong base is required for the cyclization reaction, presumably giving rise to the guanidine moiety in its deprotonated state. The target structure **33** was obtained under these conditions in high purity after its removal from the solid support (Scheme 7).

Having established a viable protocol for the formation of a desired heterocycle, we investigated the generality of the cyclization reaction utilizing different β-keto esters (Scheme 8). For this purpose, resin-bound guanidines **31** and **32** were treated with three β-keto esters in the presence of methoxide base to form 2-amino pyrimidinones **33**−**36** after removal from the resin. As illustrated below, the final molecules were obtained with high purities which indicate essentially quantitative conversions for all chemical reactions.

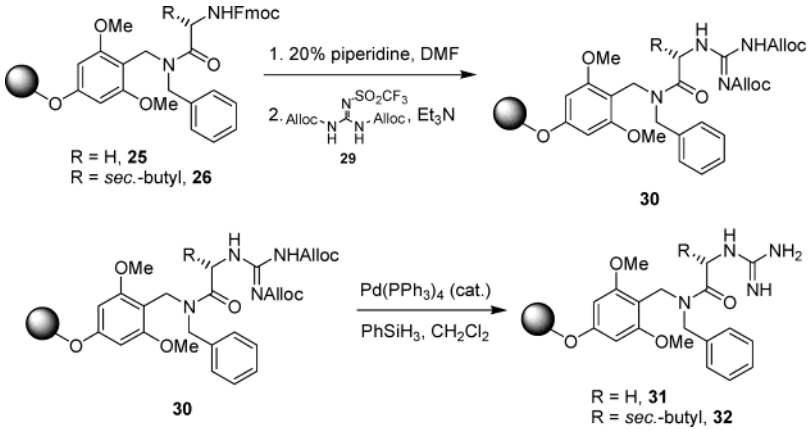
Mass spectrometry, RP-HPLC, and NMR spectroscopy were employed to determine the structure and purity of the desired heterocycles. The results of these studies provide a high level of confidence for the chemistry we employed to prepare the target heterocyclic compounds.

Summary and Outlook

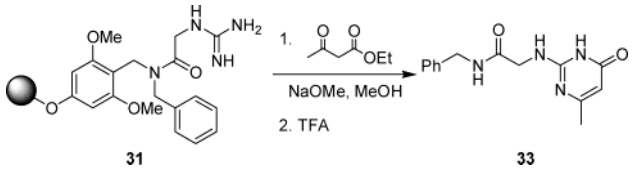
We have successfully synthesized novel heterocyclic compounds from resin-bound guanidines. For this purpose, a secondary amine **24** immobilized on a solid support was acylated with different Fmoc-protected amino acids utilizing diisopropylcarbodiimide (DIC). Following the removal of the protecting group, the liberated primary amines were guanidinylated utilizing *N*,*N*′-bis-(allyloxycarbonyl)-*N*″-triflylguanidine **29**, a new version of our diurethane-protected triflyl guanidines. We have synthesized this reagent in multigram quantities from readily available guanidine hydrochloride in two steps in good overall yield. The deprotected guanidines were subsequently cyclized with β-keto esters producing heterocycles **33**−**36** in high purity.

The design of our novel heterocycles offers several points of diversity. As demonstrated, different amino acids can be incorporated as well as different β-keto

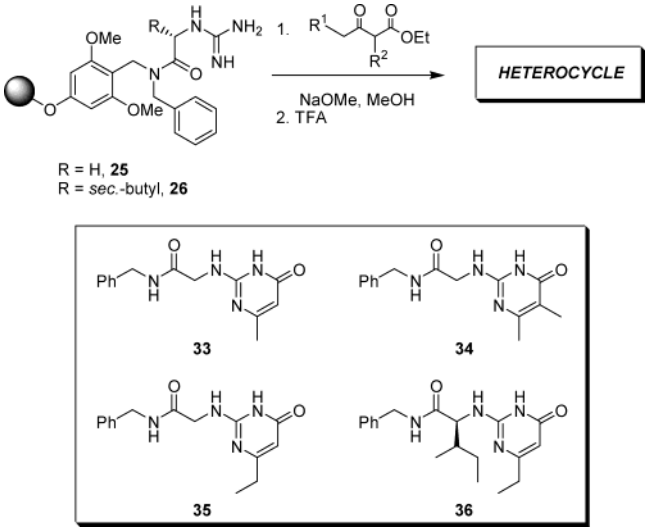
SCHEME 6. Solid-Phase Synthesis of Resin-Bound Guanidines 31 and 32 by Guanidinylation of Immobilized Amino Acids Utilizing *N,N′*-Bis(allyloxycarbonyl)-*N″*-trifluoromethylsulfonyl Guanidine 29



SCHEME 7. Conversion of Resin-Bound Guanidine 31 into *N*-Benzyl-2-(4-methyl-6-oxo-1,6-dihydropyrimidin-2ylamino)acetamide 33



SCHEME 8. Synthesis of Target Heterocycles 33−36 Utilizing Different *β*-Keto Esters



esters. In addition, the primary amine utilized for the reductive amination of aldehyde resin **19** must be regarded as a third point of diversity which lends itself to further structural diversity. Primary amines are abundant, and a wide variety is commercially available.

Taking the three points of diversity into account, large libraries of heterocycles can be constructed. Amines, natural and unnatural amino acids, as well as *β*-keto esters are popular building blocks for combinatorial chemistry which are either commercially available or can be readily synthesized. In utilizing these building blocks, many compounds can be synthesized in a parallel fashion and subsequently evaluated in a high-throughput screening process for biological activity. In this paper, we have shown the way to synthesize these novel heterocyclic structures which could serve as a promising route for drug discovery.

Experimental Section

Reactions in solution were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualization agent. The N−H-containing compounds were visualized by exposing the TLC plates to chlorine gas (freshly generated by concentrated hydrochloric acid and potassium permanganate) for approximately 30−60 s. Subsequently, the TLC plates were dipped into a solution prepared by combining an aqueous KI (500 mg of KI in 50 mL of H_2O) and an aqueous *o*-tolidine (500 mg of *o*-tolidine in 45 mL of H_2O and 8 mL of acetic acid) solution. Alternatively, TLC plates were visualized utilizing a 2% ninhydrin solution in ethanol.

The NMR spectra were obtained on a 400 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual undeuterated solvent as an internal standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet.

Mass spectra were obtained using electrospray and MALDI−FTMS techniques.

For analytical RP-HPLC, the flow rate was set to 1.0 mL/min, using a analytical C18 column (25 × 0.46 cm, 5 μm, 300 Å). Solvents used were as follows: solvent A, 0.1% TFA/H_2O; solvent B, 0.1% TFA/CH_3CN. Analysis of compounds by RP-HPLC was carried out utilizing a gradient condition (solvent A 90−10% over 30 min).

***N,N′*-Di-Alloc-guanidine 28.** In a 250 mL round-bottom flask, guanidine hydrochloride **27** (2.87 g, 30 mmol) and benzyltriethylammonium chloride (137 mg, 0.6 mmol, 0.02 equiv) were dissolved in aqueous NaOH (20 mL, 6 N) and methylene chloride (60 mL). The solution was cooled to 0 °C in an ice bath for 15 min. Allyl chloroformate (12.73 mL, 120 mmol, 4 equiv) was added quickly with vigorous stirring.

The reaction was allowed to proceed for 6 h during which the initially clear two-phase system became a white suspension. A white solid was removed by filtration which was identified as *N*-(allyloxycarbonyl) guanidine. The filtrate was diluted with 50 mL of water and 50 mL of DCM. The organic phase was collected and the aqueous extracted two additional times with 50 mL of DCM. The combined organic phases were dried with $MgSO_4$. The solvent was removed under reduced pressure and the oily residue purified by column chromatography. A solvent mixture of 5% Et_2O in DCM was chosen as the initial solvent condition to elute tri-Alloc guanidine (R_f = 0.59, 10% Et_2O in DCM). To elute the desired product from the column, the solvent mixture was changed to 50% MeOH in DCM. The compound was isolated as a white solid (4.50 g,

65.9%): $R_f = 0.27$ (10% Et_2O in DCM); ^1H NMR ($CDCl_3$, 400 MHz, δ): 5.91 (2H, ddt, $J = 5.8, 10.4, 17.2$ Hz), 5.32 (2H, dd, $J = 2, 17.2$ Hz), 5.24 (2H, dd, $J = 1, 10.6$ Hz), 4.60 (4H, d, $J = 5.6$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 159.0, 131.8, 118.1, 66.3; MS (ESI) 228 $[M + H]^+$, 250 $[M + Na]^+$, 226 $[M - H]^-$, 262 $[M + Cl]^-$.

***N*,*N*′-Di-Alloc-*N*″-triflylguanidine 29.** Thoroughly dried *N*,*N*′-di-Alloc-guanidine **28** (4.50 g, 19.78 mmol) was flushed extensively with argon and dissolved in freshly distilled methylene chloride (70 mL). The solution was cooled to −78 °C in a 2-propanol/dry ice bath. After the mixture was cooled for 10 min, freshly distilled triethylamine (4.14 mL, 29.67 mmol, 1.5 equiv) was added dropwise via syringe and cooled for another 10 min. Triflic anhydride (4.99 mL, 29.67 mmol, 1.5 equiv) was added dropwise over 15 min via a syringe, and the reaction was allowed to warm to rt. The cooling bath reached rt after approximately 5 h, and the reaction was allowed to proceed for an additional 1 h. The reaction mixture was transferred into a separatory funnel, diluted with 70 mL of DCM, and extracted four times with 25 mL of 1 N HCl. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. The brown, oily residue was purified by column chromatography utilizing DCM as eluent. The product was obtained as a clear oil (5.22 g, 73.5%): $R_f = 0.29$ (DCM); ^1H NMR ($CDCl_3$, 400 MHz, δ) 5.91 (2H, ddt, $J = 6.0, 10.8, 17.0$ Hz), 5.40 (2H, dd, $J = 1.2, 17.2$ Hz), 5.34 (2H, dd, $J = 1.2, 10.8$ Hz), 4.72 (4H, d, $J = 6$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, δ) 150.7, 149.8, 129.9, 120.5, 119.0 (q, $J = 317$ Hz), 68.5; MS (ESI) 360 $[M + H]^+$, 382 $[M + Na]^+$, 398 $[M + K]^+$, 358 $[M - H]^-$; HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{10}H_{13}N_3O_6S$ 360.0472, found 360.0478.

2-(*N*′,*N*″-Bis(allyloxycarbonyl)-*N*-guanidino)acylbenzylamide 30. After deprotection of resin **25** and **26** utilizing 20% piperidine in DMF, the benzyl amide resin was allowed to react with *N*,*N*′-di-Alloc-*N*″-triflyl uanidine **29** (5 equiv) for 22 h followed by thorough washing of the resin alternating methylene chloride and methanol. An analytical resin sample (R = H) was cleaved with neat TFA for 2 h: ^1H NMR ($CDCl_3$, 400 MHz, δ) 7.34−7.25 (m, 5H), 6.59 (t, 1H, 4.8 Hz), 5.95−5.84 (m, 2H), 5.38−5.19 (m, 4H), 4.66 (d, 2H, 6.0 Hz), 4.56 (d, 2H, 6.0 Hz), 4.45 (d, 2H, 5.6 Hz), 4.13 (s, 2H); MS (ESI) 375 $[M + H]^+$, 397 $[M + Na]^+$, 413 $[M + K]^+$; analytical RP-HPLC $t_R = 22.28$ min.

2-Guanidinoacetylbenzylamide 31. To remove the Alloc protecting groups, resin **30** (R = H) (2 g, 0.82 mmol) was prewashed with freshly distilled DCM. Subsequently, the resin was suspended in 20 mL of freshly distilled DCM to which phenylsilane (2 mL, 16.4 mmol, 20 equiv) and tetrakis-(triphenylphosphine)palladium(0) (95 mg, 82 μmol, 0.1 equiv) were added. After 3 h, the resin was washed with DCM, methanol, and aqueous NaCN until the resin beads became colorless. Excess cyanide was removed by washing the resin twice with water, followed by two washings with THF to remove residual water. The resin was further rinsed several times alternating methanol and DCM. An analytical resin sample was cleaved with neat TFA for 2 h: ^1H NMR (DMSO-d_6, 400 MHz, δ) 8.62 (t, 1H, $J = 5.8$ Hz), 7.55 (t, 1H, $J = 5.8$ Hz), 7.34−7.22 (m, 9H), 4.31 (d, 2H, $J = 6.0$ Hz), 3.88 (d, 2H, $J = 5.6$ Hz); MS (ESI) 207 $[M + H]^+$; HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{10}H_{15}N_4O$ 207.1246, found 207.1242. analytical RP-HPLC $t_R = 14.74$ min.

(2*S*,3*S*)-2-Guanidino-3-methylpentanoic Acid Benzylamide 32. This compound was prepared in an analogous fashion as carried out for 2-guanidino-acetyl benzyl amide **31**. An analytical resin sample was cleaved with neat TFA for 2 h: ^1H NMR (DMSO-d_6, 400 MHz, δ) 8.63 (t, 1H, $J = 5.8$ Hz), 7.68 (d, 1H, $J = 9.6$ Hz), 7.60−6.90 (m, 9H), 4.31 (m, 2H), 4.00 (dd, 1H, $J = 6.8, 9.6$ Hz), 1.85 (m, 1H), 1.41−1.35 (m, 1H), 1.11−1.03 (m, 1H), 0.87−0.80 (m, 6H); MS (ESI) 263 $[M + H]^+$; analytical RP-HPLC $t_R = 22.94$ min.

***N*-Benzyl-2-(4-methyl-6-oxo-1,6-dihydropyrimidin-2ylamino)acetamide 33.** To resin-bound guanidine **31** (91 mg, 35 μmol) suspended in MeOH (2 mL) were added 6 N NaOMe (58 μL, 0.35 mmol, 10 equiv) and ethyl acetoacetate (44 μL, 0.35 mmol, 10 equiv). The reaction vessel was shaken for 22 h followed by thorough washing of the resin, alternating methanol and methylene chloride. The resin was dried in a desiccator and cleaved with 2 mL of neat TFA for 2 h. After the cleavage solution was collected, the resin was rinsed with methanol and the combined solutions were taken to dryness. On the basis of the initial loading the heterocycle was obtained in quantitative yield: ^1H NMR (DMSO-d_6, 400 MHz, δ) 8.56 (t, 1H, $J = 5.8$ Hz), 7.34−7.21 (m, 6H), 4.31 (d, 2H, $J = 6.0$ Hz), 3.98 (d, 2H, $J = 4.4$ Hz), 2.07 (s, 3H); MS (ESI) 273 $[M + H]^+$, 295 $[M + Na]^+$; HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{17}N_4O_2$ 273.1346, found 273.1342; analytical RP-HPLC $t_R = 18.05$ min.

***N*-Benzyl-2-(4,5-dimethyl-6-oxo-1,6-dihydropyrimidin-2-ylamino)acetamide 34.** To resin-bound guanidine **31** (67 mg, 26 μmol) suspended in MeOH (2 mL) were added 6 N NaOMe (44 μL, 0.26 mmol, 10 equiv) and ethyl 2-methylacetoacetate (37 μL, 0.26 mmol, 10 equiv). The reaction vessel was shaken for 21 h followed by thorough washing of the resin, alternating methanol and methylene chloride. The resin was dried in a desiccator and cleaved with 2 mL of neat TFA for 2 h. After the cleavage solution was collected, the resin was rinsed with methanol and the combined solutions were taken to dryness: ^1H NMR (DMSO-d_6, 400 MHz, δ) 8.63 (t, 1H, $J = 5.6$ Hz), 7.35−7.22 (m, 5H), 4.31 (d, 2H, $J = 5.6$ Hz), 4.06 (d, $J = 5.2$ Hz), 2.19 (s), 1.82 (s); MS (ESI) 287 $[M + H]^+$, 309 $[M + Na]^+$, 285 $[M - H]^-$, 321 $[M + Cl]^-$; HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{19}N_4O_2$ 287.1502, found 287.1501; analytical RP-HPLC $t_R = 14.08$ min.

***N*-Benzyl-2-(4-ethyl-6-oxo-1,6-dihydropyrimidin-2-ylamino)acetamide 35:** To resin-bound guanidine **31** (97 mg, 38 μmol) suspended in MeOH (2 mL) were added 6 N NaOMe (63 μL, 0.38 mmol, 10 equiv) and ethyl propionyl acetate (48 μL, 0.38 mmol, 10 equiv). The reaction vessel was agitated for 21 h followed by thorough washing of the resin, alternating methanol and methylene chloride. The resin was dried in a desiccator and cleaved with 2 mL of neat TFA for 2 h. After the cleavage solution was collected, the resin was rinsed with methanol and the combined solutions were taken to dryness: ^1H NMR (DMSO-d_6, 400 MHz, δ) 8.58 (t, 1H, 5.8 Hz), 7.43−7.20 (m, 6H), 4.30 (d, 2H, 5.6 Hz), 3.99 (s, 2H), 2.35 (s, 2H), 1.10 (t, 3H, 7.2 Hz); MS (ESI) 287 $[M + H]^+$, 309 $[M + Na]^+$, 285 $[M - H]^-$, 399 $[M + TFA]^-$; HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{19}N_4O_2$ 287.1502, found 287.1505; analytical RP-HPLC $t_R = 12.97$ min.

(*S*)-2-(4-Ethyl-6-oxo-1,6-dihydropyrimidin-2ylamino)-(*S*)-3-methylpentanoic Acid Benzylamide 36. To resin-bound guanidine **32** (130 mg, 52 μmol) suspended in MeOH (2 mL) were added 6 N NaOMe (87 μL, 0.52 mmol, 10 equiv) and ethyl propionyl acetate (65 μL, 0.52 mmol, 10 equiv). The reaction vessel was shaken for 24 h followed by thorough washing of the resin, alternating methanol and methylene chloride. The resin was dried in a desiccator and cleaved with 2 mL of neat TFA for 2 h. After the cleavage solution was collected, the resin was rinsed with methanol and the combined solutions were taken to dryness: ^1H NMR (DMSO-d_6, 400 MHz, δ) 8.66 (t, 1H, 5.6 Hz), 7.32−7.19 (m, 6H), 4.43 (m, 1H), 4.30 (t, 2H, $J = 6.2$ Hz), 2.30 (m, 2H), 1.83 (m, 1H), 1.44 (m, 1H), 1.09 (m, 4H), 0.87 (m, 6H); MS (ESI) 343 $[M + H]^+$, 365 $[M + Na]^+$, 341 $[M - H]^-$, 377 $[M + Cl]^-$; analytical RP-HPLC $t_R = 26.54$ min.

Acknowledgment. We thank Dr. Chris Holmes for his comments and suggestions and the Affymax Research Institute for support of this project. We also thank Dr. Christopher Creighton for insightful discussions at the outset of this project.

Supporting Information Available: Detailed experimental procedures and full characterization data for compounds **22**, **25**, **26**, and **28**−**36**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035201A