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Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from an Old Dog

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ABSTRACT

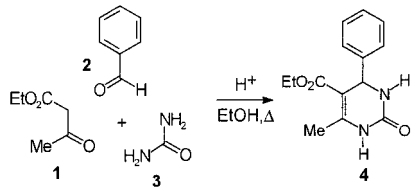
In 1893, P. Biginelli reported the synthesis of functionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) via three-component condensation reaction of an aromatic aldehyde, urea, and ethyl acetoacetate. In the past decade, this long-neglected multicomponent reaction has experienced a remarkable revival, mainly due to the interesting pharmacological properties associated with this dihydropyrimidine scaffold. In this Account, we highlight recent developments in the Biginelli reaction in areas such as solid-phase synthesis, combinatorial chemistry, and natural product synthesis.

Introduction

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.[1−5] In times where a premium is put on speed, diversity, and efficiency in the drug discovery process,[6] MCR strategies offer significant advantages over conventional linear-type syntheses.[1−5] In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components.[1−5] In an ideal case, the individual building blocks are commercially available or are easily synthesized and cover a broad range of structural variations. MCRs can provide products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry techniques.[2−6] The search and discovery for new MCRs on one hand,[7] and the full exploitation of already known multicomponent reactions on the other hand, is therefore of considerable current interest.

One such MCR that belongs in the latter category is the venerable Biginelli dihydropyrimidine synthesis. In 1893, Italian chemist Pietro Biginelli reported on the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate (**1**), benzaldehyde (**2**), and urea (**3**).[8] The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1*H*)-one **4** (Scheme 1).[8] Apart from a series of publications by the late Karl Folkers[9] in the mid 1930s, the "Biginelli reaction" or "Biginelli condensation" as it was henceforth called was largely ignored in the early part of the 20th century. The synthetic potential of this new heterocycle synthesis therefore remained unexplored for quite some time. In the 1970s and 1980s, interest slowly increased, and the scope of the original cyclocondensation reaction shown in Scheme 1 was gradually extended by variation of all three building blocks (Figure 1), allowing access to a large number of multifunctionalized dihydropyrimidines of type **4**.[10]

Scheme 1. Biginelli Dihydropyrimidine Synthesis



Our own involvement in the Biginelli reaction started in the mid-1980s, when the author was an undergraduate student at the University of Graz, Austria. Together with Peter Roschger, a fellow student and long-time high school friend, we synthesized the first DHPMs in our home laboratories. Even at that time—well before the advent of combinatorial chemistry—the simplicity of the approach and the synthetic potential appealed to us (apart from the easy access and inexpensiveness of the required starting materials). Our first research paper on the subject appeared in 1989,[11] and a comprehensive review article with 120 references on the Biginelli reaction was published in 1993.[10] Since this first review article, a tremendous increase in activity has occurred, as evidenced by the growing number of publications and patents on the subject. This is mainly due to the fact that the multifunctionalized dihydropyrimidine scaffold **4** (DHPMs, "Biginelli compounds") represents a heterocylic system of remarkable pharmacological efficiency. In the past decades, a broad range of biological effects, including antiviral, antitumor, antibacterial, and antiinflammatory activities, has been ascribed to these partly reduced pyrimidine derivatives.[10] More recently, appropriately functionalized DHPMs have emerged as, e.g., orally active antihypertensive agents (**5**, **6**)[12−14] or α_{1a} adrenoceptor-selective antagonists (**7**).[15] A very recent highlight in this context has been the identification of the structurally rather simple DHPM monastrol (**8**) as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest.[16] Monastrol specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for

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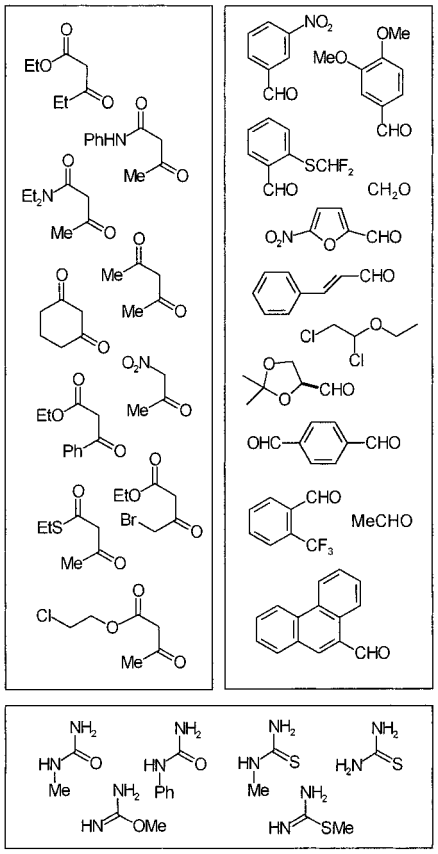


FIGURE 1. Building blocks in Biginelli MCRs.

the development of anticancer drugs.[16] Furthermore, apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have recently been isolated.[17] Most notable among these are the batzelladine alkaloids A and B (e.g., **9**), which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy.[18]

The intense activity in the field of dihydropyrimidine chemistry during the past decade, from both academic and industrial laboratories, has prompted us to revive our early interest in the Biginelli reaction again in 1996, after the author returned to the University of Graz following Ph.D. and postdoctoral work at the University of Queensland (Brisbane) and at Emory University (Atlanta). In this Account, recent developments in the long-neglected Biginelli reaction are reviewed, with special emphasis placed on novel synthetic methodology from our laboratory, in addition to solid-phase and stereoselective DHPM synthesis.

Mechanistic Studies and Improved Protocols

The mechanism of the Biginelli reaction has been the subject of some debate over the past decades. Early work by Folkers and Johnson suggested that bisureide **14**, i.e., the primary bimolecular condensation product of benzaldehyde (**2**) and urea (**3**), is the first intermediate in this reaction.[9] In 1973, Sweet and Fissekis proposed a different

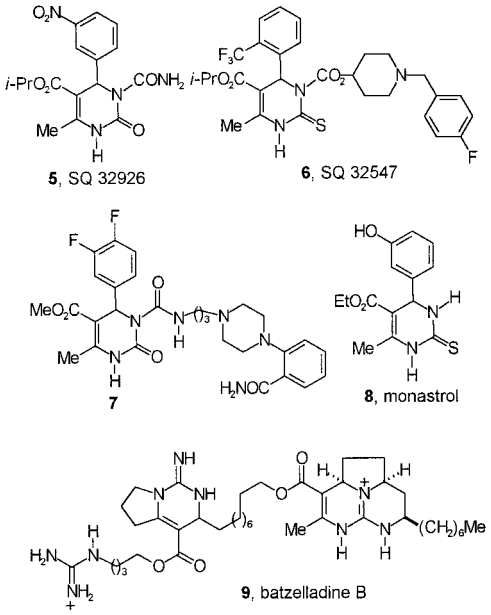
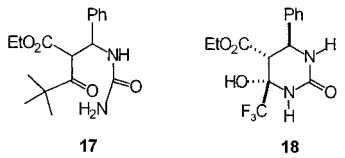


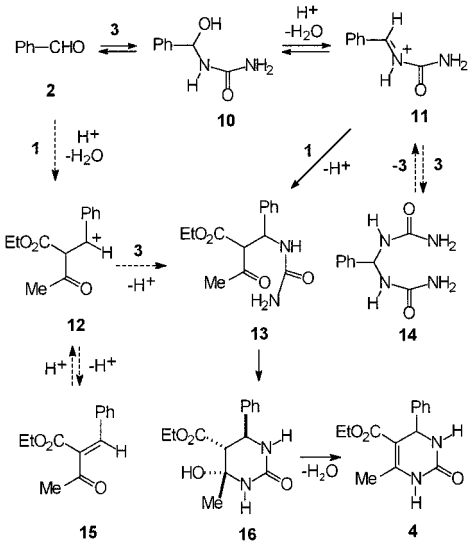
FIGURE 2. Examples of biologically active DHPMs.

pathway and suggested that carbenium ion **12**, produced by an acid-catalyzed aldol reaction of benzaldehyde (**2**) with ethyl acetoacetate (**1**), is formed in the first and limiting step of the Biginelli condensation (**2** → **12** → **13**).[19] We reinvestigated the mechanism in 1997 using $^1H/^{13}C$ NMR spectroscopy and trapping experiments and have established that the key step in this sequence involves the acid-catalyzed formation of an *N*-acyliminium ion intermediate of type **11** from the aldehyde (**2**) and urea (**3**) precursors.[20] Interception of the iminium ion **11** by ethyl acetoacetate (**1**), presumably through its enol tautomer, produces an open-chain ureide **13** which subsequently cyclizes to hexahydropyrimidine **16**. Acid-catalyzed elimination of water from **16** ultimately leads to the final DHPM product **4**. The reaction mechansim can therefore be classified as an α-amidoalkylation, or more specifically as an α-ureidoalkylation.[21] The alternative "carbenium ion mechanism" **2** → **12** → **13**[19] does not constitute a major pathway; however, small amounts of enone **15** are sometimes observed as byproduct.[20]

Although the highly reactive *N*-acyliminium ion species **11** could not be isolated or directly observed, further evidence for the proposed mechanism was obtained by isolation of intermediates **17** and **18**, employing sterically bulky[22] or electron-deficient acetoacetates,[23] respectively. The relative stereochemistry in hexahydropyrimidine **18** was established by an X-ray analysis.[23] In fact, a number of hexahydropyrimidines closely related to **18** could be synthesized by using perfluorinated 1,3-dicarbonyl compounds or β-keto esters as building blocks in the Biginelli condensation.[24]



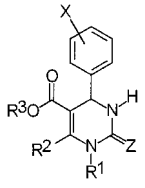
Scheme 2. Mechanism of the Biginelli Reaction



The elucidation of the mechanism of the Biginelli MCR has prompted a renewed interest in improving the efficiency of this process. One major drawback of the traditional Biginelli protocols is the low yield that is encountered when some of the building blocks shown in Figure 1 are employed. To promote conditions that would increase the yield by favoring the formation and interception of iminium ion intermediates of type **11** (Scheme 2), we have investigated a variety of reaction conditions more appropriately suited for *N*-acyliminium ion-based amidoalkylations. After some experimentation we have found that polyphosphate ester (PPE) is an excellent reaction mediator for the Biginelli dihydropyrimidine synthesis, because it specifically stabilizes the iminium ion intermediate **11**.[25] High yields of DHPMs were obtained using THF as solvent in the presence of PPE under reflux conditions, improving the yields compared to those obtained with the traditional protocols by 20−50%. Not surprisingly, Lewis acids such as boron trifluoride etherate (in combination with transition metal salts and a proton source),[22] ferric chloride (with catalytic HCl),[26] indium(III) chloride,[26] or ytterbium triflate (under solvent-free conditions)[26] have recently also been used as highly effective catalysts in this cyclocondensation process. As with PPE, stabilization of the corresponding iminium ion intermediates here is probably responsible for the increased efficiency. Other conditions that were demonstrated to promote the Biginelli reaction—in particular with the otherwise troublesome aliphatic aldehydes—employed *p*-toluenesulfinic acid[27]or trimethylchorosilane[28] as reaction mediators.

Significant rate and yield enhancements were also reported for Biginelli reactions carried out under microwave irradiation.[29,30] We have recently demonstrated that, by using neat polyphosphate ester (PPE) as reaction mediator coupled with microwave irradiation, excellent yields of variously substituted DHPMs of type **19** can be obtained (Table 1).[30] This protocol can be performed on a 1−50 mmol scale with reaction irradiation times of less than 2 min in any domestic microwave oven. For the majority of cases, the products obtained using this procedure had at least >95% purity following a simple aqueous workup protocol.

Table 1. Microwave/PPE-Mediated Synthesis of DHPMs 19[30]

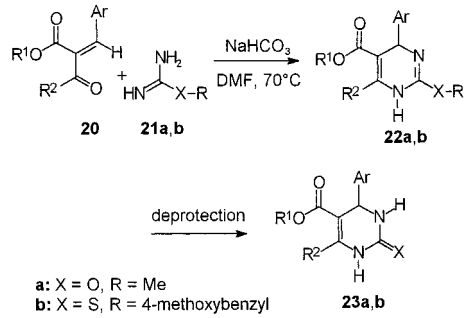


DHPM	X	Z	R^1	R^2	R^3	yield (%)
19a	H	O	H	Me	Et	85
19b	3-NO_2	O	H	Me	Et	93
19c	2-Cl	O	H	Me	Et	95
19d	2-CF_3	O	H	Me	Et	76
19e	2,3-$(Cl)_2$	O	H	Me	Et	91
19f	3,4-$(F)_2$	O	H	Me	Et	87
19g	2-Me	O	H	Me	Me	86
19h	4-NO_2	O	H	Me	Me	86
19i	3-NO_2	O	H	Me	*i*-Pr	94
19j	H	O	H	Me	*t*-Bu	81
19k	3,4-$(F)_2$	O	H	Et	Me	65
19l	H	O	Me	Me	Et	89
19m	H	S	H	Me	Et	82
19n	3-NO_2	S	H	Me	Et	71
19o	H	S	Me	Me	Et	78

An alternative solvent-free procedure for the Biginelli reaction using montmorillonite KSF clay as a solid acid catalyst has been described by Bigi et al.[31] Furthermore, Singh et al. have demonstrated that aldehydes protected as cyclic hemiaminals (oxazinanes or oxazolidines) furnish high yields of DHPMs when acetonitrile/trifluoroacetic acid is used as as reaction medium.[32]

Alternative Synthetic Strategies

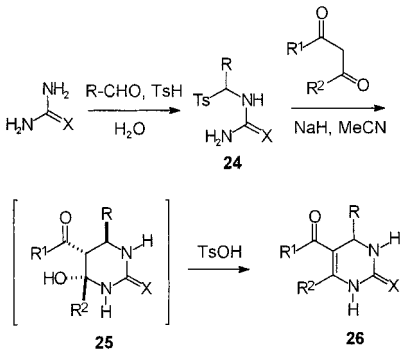
Apart from the traditional Biginelli condensation, there are only a few other synthetic methods available that lead to DHPMs. Since most of these protocols lack the experimental and conceptual simplicity of the Biginelli one-pot, one-step procedure, none of these have any significance today or can compete with the original Biginelli MCR approach. One noticeable exception is the so-called "Atwal modification" of the Biginelli reaction.[33−35] Here, an enone of type **20** is first condensed with a suitable protected urea or thiourea derivative **21** under almost neutral conditions.



Deprotection of the resulting 1,4-dihydropyrimidine **22** with HCl (for **22a**) or TFA/EtSH (for **22b**) leads to the

desired DHPMs **23**. Although this method requires prior synthesis of enones **20**, its reliability and broad applicability make it an attractive alternative to the traditional one-step Biginelli condensation. In addition, 1,4-dihydropyrimidines **22** can be acylated regiospecifically at *N*3, thereby making the pharmacologically important DHPM analogues **5**−**7** readily accessible.[35]

One other novel approach to DHPMs has been described by Shutalev et al. and is outlined below.[36] This synthesis is based on the condensation of readily available α-tosyl-substituted (thio)ureas **24** with the (in situ prepared) enolates of acetoacetates or 1,3-dicarbonyl compounds. The resulting hexahydropyrimidines **25** need not



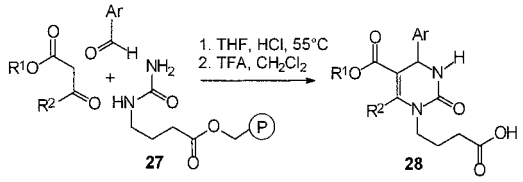
to be isolated and can be converted directly into DHPMs **26**. This method works particularly well for aliphatic aldehydes and thioureas and produces high overall yields of the desired target compounds.

Solid-Phase and Combinatorial Procedures

Solid-phase modifications of MCRs are rapidly becoming one of the cornerstones of combinatorial synthesis of small-molecule libraries.[2−4] Multicomponent reactions such as the Biginelli condensation leading to heterocycles are particularly useful for the creation of diverse chemical libraries, since the combination of $n \geq 3$ small-molecular-weight building blocks (see Figure 1) in a single operation leads to high combinatorial efficacy.[37,38]

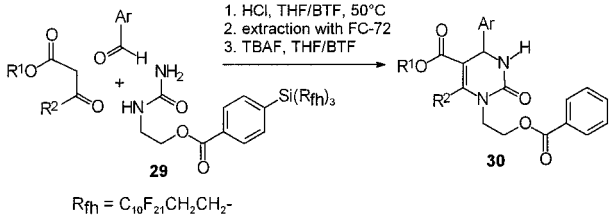
Since the experimental conditions for the traditional Biginelli reaction are rather straightforward, small libraries of DHPMs are readily accessible by parallel synthesis. Along these lines, Fréchet and co-workers have described the generation of a 140-member single-compound DHPM library by combination of 25 aldehydes, 6 ureas/thioureas, and 7 acetoacetates or acetoamides under standard reaction conditions (EtOH/HCl).[39,40] Likewise, we have shown that small single-compound DHPM libraries can be obtained in high yield by parallel synthesis employing the solventless microwave-enhanced variation of the Biginelli reaction described above.[30] In a single microwave irradiation experiment, the 15 DHPMs **19a**−**o** (Table 1) can be generated within 2−3 min, employing the principles of microwave-assisted combinatorial chemistry.[41] Since all five variable substituents around the DHPM scaffold (R^1−R^3, X, Z) can be modified, a significant structural diversity in DHPM analogues can be generated expeditiously.

The first actual solid-phase modification of the Biginelli condensation was reported by Wipf and Cunningham in 1995.[42] In this sequence, γ-aminobutyric acid-derived urea was attached to Wang resin using standard procedures. The resulting polymer-bound urea **27** was condensed with excess β-ketoesters and aromatic aldehydes in THF at 55 °C in the presence of a catalytic amount of HCl to afford the corresponding immobilized DHPMs. Subsequent cleav-



age of product from the resin by 50% trifluoroacetic acid (TFA) provided DHPMs **28** in high yields and excellent purity. The key condensation step was further studied and optimized with the aid of an automatic synthesizer demonstrating the solvent dependence of this process.[43]

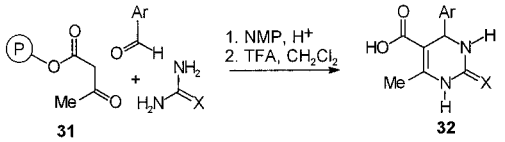
In an interesting variation of this protocol, the Biginelli reaction was also adapted to fluorous-phase conditions by the Wipf and Curran groups.[44,45] In fluorous synthesis, an organic molecule is rendered soluble in fluorocarbon solvents by attachment of a suitable fluorocarbon group ("fluorous tag"). Fluorocarbon solvents are usually immiscible with organic solutions, and fluorous molecules partition out of an organic phase and into a fluorous phase by standard liquid−liquid extraction. At the desired stage of the synthesis, the fluorous label is cleaved and the product is rendered "organic" again.[44] In the fluorous Biginelli reaction, the fluorous urea derivative **29** was prepared by attachment of a suitable fluorous tag to hydroxyethylurea. The fluorous urea **29** was then condensed with 10 equiv each of the corresponding acetoacetates and aldehydes in THF−benzotrifluoride (BTF) containing HCl. After extraction of the fluorous DHPMs



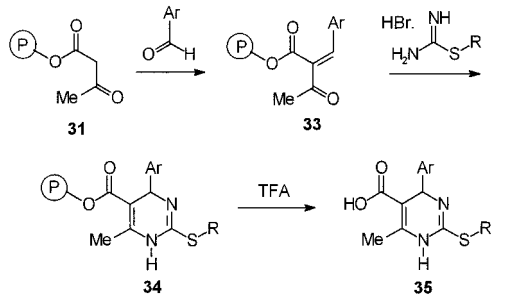
with fluorous solvent (perfluorohexanes, FC-72), desilylation with tetrabutylammonium fluoride (TBAF) followed by extractive purification provided the "organic" Biginelli products DHPMs **30** in good overall yields. Considering the simple experimental techniques used in this fluorous chemistry, automation should be feasible, thus allowing the preparation of DHPM libraries.[45]

In both the solid- and fluorous-phase modifications of the Biginelli condensations described above, the urea component is linked to the solid (or fluorous) support via the amide nitrogen, which invariably leads to the formation of *N*1-functionalized DHPMs of type **28** or **30**. To access pharmacologically active *N*1-unsubstituted DHPMs

(Figure 2), we have developed an alternative protocol, where the acetoacetate building block is linked to the solid support.[46] Thus, Biginelli condensation of Wang-bound acetoacetate **31** with excess aldehydes and ureas/thioureas in NMP/HCl provided the desired DHPMs on solid support. Subsequent cleavage with 50% TFA furnished the free carboxylic acids **32** in high overall yield.[46]

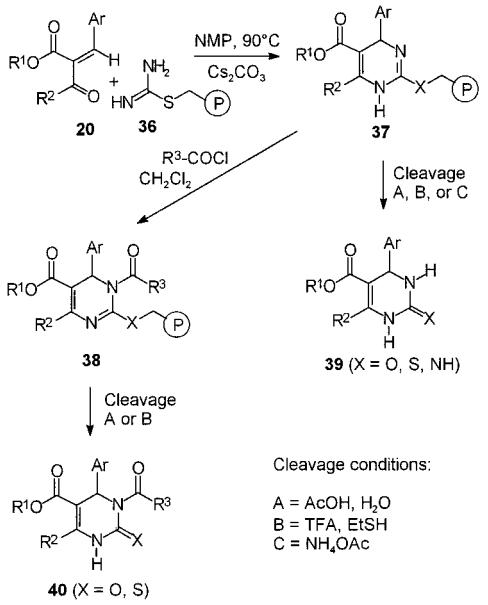


In addition to solid-phase adaptions of the traditional three-component Biginelli condensation, solid-phase variations of the "Atwal modification" of the Biginelli reaction (see above) have also been reported. Robinett et al. have disclosed the synthesis of a 648-member combinatorial library of 1,4-dihydropyrimidines **35**.[47] Toward this end, polymer-bound acetoacetate **31** was subjected to Knoevenagel condensation with aromatic aldehydes, followed by condensation with isothioureas. The resulting polymer-bound 1,4-dihydropyrimidines **34** were cleaved from the resin with 50% TFA to produce carboxylic acid **35**.



In an effort to increase the molecular diversity in solid-phase syntheses of DHPM scaffolds, we have recently developed a novel and versatile solid-phase approach where an isourea building block is attached to the solid support (Scheme 3).[48] In the key step, polymer-bound (Wang) isothiourea **36** is condensed with enones **20** in *N*-methylpyrrolidone (NMP) in the presence of base. The polymer-bound dihydropyrimidine can then be directly cleaved from the resin (**37** → **39**) by employing different cleavage strategies. Therefore, three types of DHPMs **39** (X = O, S, and NH) can be obtained by applying the appropriate cleaving conditions A, B, or C. On the other hand, an additional element of diversity can be introduced onto the pyrimidine nucleus by regioselective *N*3-acylation of the polymer-bound intermediate **37** with suitable electrophiles (e.g., acyl chlorides, R^3COCl). By applying different cleaving strategies to **38**, the corresponding *N*3-functionalized DHPMs **40** were obtained in moderate to high overall yields. This solid-phase approach is therefore particularly attractive for the preparation of pharmacologically active *N*3-acylated analogues such as DHPMs **5**−**7** (Figure 2) and should be useful for the generation of targeted libraries of this heterocyclic scaffold.

Scheme 3. Diversity in Solid-Phase DHPM Synthesis



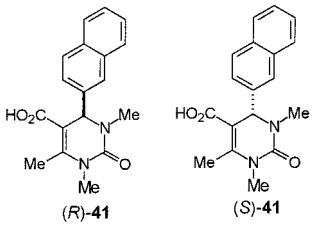
By employing any of the solid-phase synthesis methods described above, libraries of DHPMs can be generated in a relatively straightforward fashion. Biginelli products are therefore contained in many commercially available small-molecule libraries or compound collections and have undoubtely been subjected to many high-throughput screening (HTS) processes. However, all of these products would still be racemic, and therefore screening will not address possible enantioselective effects on molecular activity.

Enantiomerically Pure Dihydropyrimidines

Dihydropyrimidines of the Biginelli type are inherently asymmetric molecules, and the influence of the absolute configuration at the stereogenic center at C4 on biological activity is well documented.[12−15,49] In SQ 32926 (**5**), for example, it is exclusively the (*R*)-enantiomer that carries the therapeutically desired antihypertensive effect.[12] In other DHPM analogues, individual enantiomers were demonstrated to have opposing pharmacological activities.[49] Access to enantiomerically pure DHPMs is therefore of considerable interest and a prerequisite for the development of any drugs in this field.

In the absence of any known general asymmetric synthesis for this heterocyclic target system, resolution strategies have so far been the method of choice to obtain enantiomerically pure DHPMs. Some years ago, we obtained optically pure DHPMs by resolution of the corresponding racemic 5-carboxylic acids (i.e., **41**) via fractional crystallization of the corresponding diastereomeric α-methylbenzylammonium salts.[50] The absolute configuration of acid (*S*)-**41** was proven by single-crystal X-ray analysis of a suitable diastereomeric salt. This method may lead to both enantiomers (*R*)- and (*S*)-**41** but, unfortunately, is not applicable to DHPMs in general.

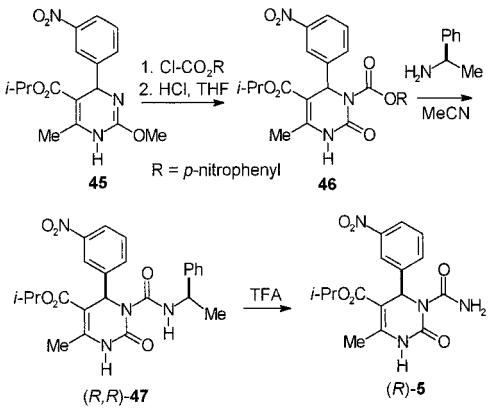
Due to recent advances in preparative chromatographic enantioseparation techniques, enantioselective HPLC and



related methods have gained importance in the synthesis of single-enantiomer drugs and intermediates. In a recent study, we reported the chromatographic enantioseparation of DHPM derivatives accomplished by using a variety of commercially available chiral stationary phases (CSPs) in normal- and reversed-phase analytical HPLC.[51] Out of 29 diverse racemic DHPM analogues, all but one were separated on at least one of the eight CSPs tested, with separation coefficients α ranging from 1.08 to 8.67. In subsequent work, Fréchet and co-workers reported the separation of DHPMs on a standard Pirkle-type 3,5-dinitrobenzoylated CSP and the "reciprocal" preparation of a π-basic DHPM-based CSP.[39,40] Using a combinatorial approach toward the recognition of chirality, out of a library of 108 racemic DHPMs, the 4-(9-phenanthryl) derivative **42** was identified as a lead structure with a separation coefficient of $\alpha = 5.2$ on a Pirkle-type CSP. Resolution of the enantiomers of **42** using semipreparative chiral HPLC, followed by attachment of (−)-**42** to monodisperse macroporous aminomethacrylate beads (Scheme 4), provided the novel polymer-based CSP **44**. Such "designer CSPs" could prove extremely useful for the efficient separation of not only DHPMs but other structurally related compounds as well.

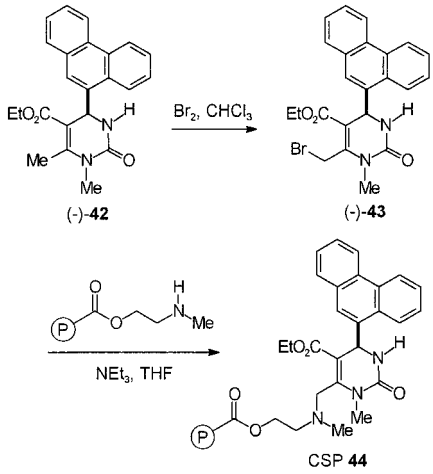
The chiral separation of DHPMs by capillary electrophoresis (CE) using quaternary ammonium-β-cyclodextrin as chiral buffer additive has also been reported.[52]

A preparatively useful synthetic approach to the enantiomerically pure antihypertensive agent (*R*)-SQ 32926 (**5**) was disclosed by Atwal et al.[12] In the first step, the 1,4-dihydropyrimidine intermediate **45** is acylated at *N*3 with 4-nitrophenyl chloroformate followed by hydrolysis with HCl in THF to give DHPM **46**. Treatment with (*R*)-α-methylbenzylamine provided a mixture of diastereomeric ureas from which the (*R*,*R*) isomer **47** was separated by crystallization. Cleavage with trifluoroacetic acid (TFA)



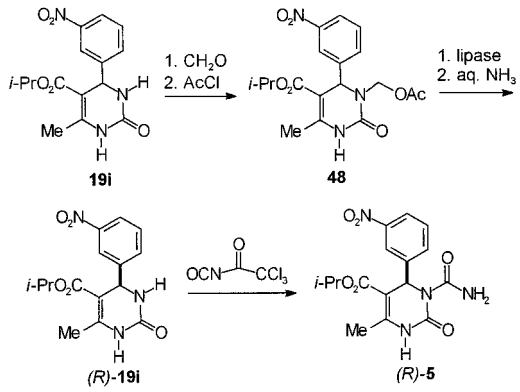
provided SQ 32926 (**5**) in high enantiomeric purity. Similar

Scheme 4. Preparation of a DHPM-Based Chiral Stationary Phase



strategies have been used to obtain a number of pharmacologically important DHPM derivatives in enantiomerically pure form.[12,13,15]

As an alternative to the chemical resolution methods described by Atwal et al., we have developed a biocatalytic strategy toward the preparation of enantiopure (*R*)- and (*S*)-SQ 32926 (**5**). The key step in the synthesis is the enzymatic resolution of an *N*3-acetoxymethyl-activated dihydropyrimidone precursor by *Thermomyces lanuginosus* lipase.[53] Readily available racemic DHPM **19i** (see Table 1)[30] was hydroxymethylated at *N*3 with formaldehyde, followed by standard acetylation with acetyl chloride. The resulting *N*3-acetoxymethyl-activated DHPM **48**



was then cleaved enantioselectively by *Thermomyces lanuginosus* with excellent selectivity ($E > 200$). Degradation of unreacted (*R*)-**48** with aqueous ammonia produced (*R*)-**19i**, which was converted into the desired target structure (*R*)-**5** in one step by *N*3-carbamoylation with trichloroacetyl isocyanate.

A critical point in every preparation of enantiomerically pure materials, regardless of the method, is the assignment of absolute configuration. For the DHPM series, a simple protocol for absolute configuration assignment based on the combination of enantioselective HPLC and circular dichroism (CD) spectroscopy has been developed.[54] By comparison of the characteristic CD spectra of individual DHPM enantiomers with reference samples of known absolute configuration (i.e., (*R*)- and (*S*)-**41**,

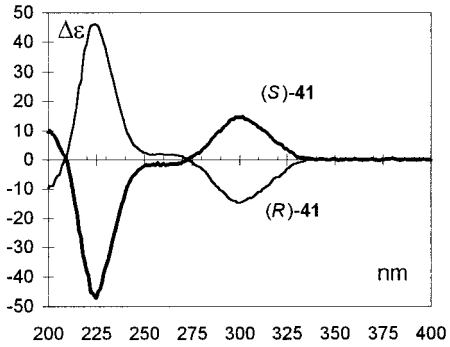
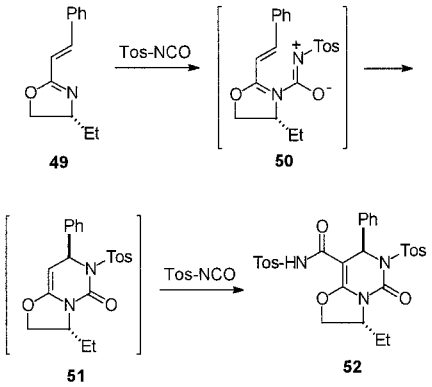


FIGURE 3. Circular dichroism (CD) spectra of (*R*)- and (*S*)-**41**.

Figure 3), the absolute configuration of 4-aryl-DHPMs, such as monastrol (**8**),[55] or SQ 32926 (**5**)[53] could be established. The enantiomers were obtained by semi-preparative HPLC separation of racemic DHPMs on chiral stationary phases.[53] The characteristic CD activity of the enamide chromophor around 300 nm allows the assignment of absolute configuration in this series of dihydropyrimidine derivatives.[54]

As mentioned above, a generally applicable asymmetric synthesis of DHPMs has not been reported yet. However, fused DHPMs of type **52** have recently been obtained by Elliott et al. in diastereomerically pure form by asymmetric hetero-Diels–Alder addition of chiral alkenyloxazolines **49** with isocyanates.[56] Mechanistic investigations suggest that



the reaction proceeds in a stepwise manner (**49** → **50** → **51** → **52**).[57] It remains to be seen if this strategy can be adapted toward a more general synthesis of enantiopure DHPMs.

Efforts to develop a practical asymmetric version of the Biginelli reaction itself have failed so far. While chiral acetoacetates, e.g., (−)-menthyl acetoacetate, show no diastereoselectivity at all,[50] chiral aldehydes derived from carbohydrates apparently can induce chirality at C4 of the pyrimidine ring.[58] The latter approach, however, is of little use due to the low chemical yields and selectivities that have been reported.[58] The only known asymmetric variations of the Biginelli reaction are of intramolecular nature and have been developed for natural product synthesis (see below).

Natural Product Synthesis

Over the last 10 years, a variety of structurally novel and complex guanidine alkaloids have been isolated from

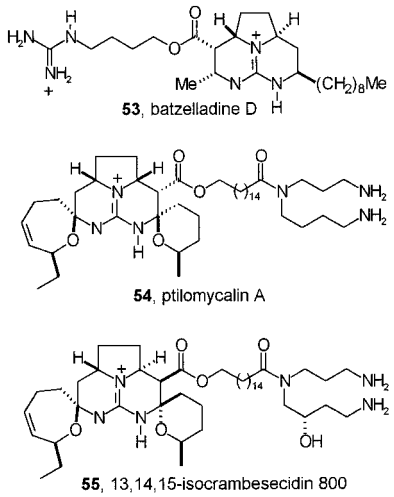


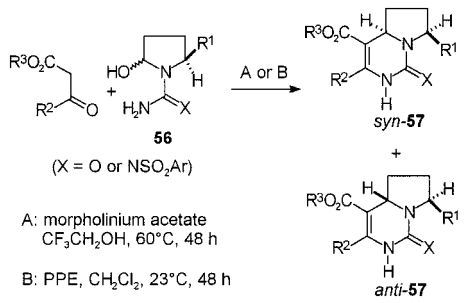
FIGURE 4. Polycyclic guanidinium alkaloids synthesized via intramolecular Biginelli reaction.

marine sources, such as the Caribbean sponges *Ptilocaulis spiculifer* or *Batzella* sp.[17] Among these are the batzelladine alkaloids A-I (i.e., B (**9**) and D (**53**, Figure 4)), ptilomycalin A (**54**, Figure 4), and the alkaloids crambescidin A, 800, and 816.[17] A closely related alkaloid, 13,14,15-isocrambescidin 800 (**55**, Figure 4), was subsequently isolated from the Mediterranean sponge *Crambe crambe*.[17] Many of these alkaloids display a remarkable range of biological activities, including antiviral (HSV-1, HIV-1), antifungal, and antitumor activities.[17] Their unique structures and their potential therapeutic significance have made many of these alkaloids synthetic targets for several research groups. In a very recent and extensive review by the Murphy group, the biological properties and synthetic advances toward these alkaloids have been summarized.[17] Although several strategies to assemble the tricyclic or pentacyclic cores of these guanidinium alkaloids have been realized, one of the most efficient protocols relies on an intramolecular Biginelli condensation as the key step. In fact, the "tethered Biginelli strategy" developed by Overman and co-workers has so far proven to be the only method that has allowed the enantioselective total synthesis of alkaloids in this family.[58–62]

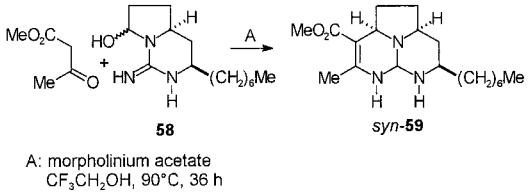
Apparent in all the alkaloids shown in Figures 2 and 4 is the occurrence of the tricyclic guanidinium core with either the *syn* (e.g., in **9** and **54**) or *anti* (e.g., in **53** and **55**) relationship of the hydrogens flanking the pyrrolidine nitrogen. The Overman group has shown that the stereoselectivity in tethered Biginelli condensations can be tuned efficiently to address this problem (Scheme 5).[59] To construct the hexahydropyrrolo[1,2-*c*]pyrimidine fragment common to all alkaloids, the chiral hemiaminal precursor **56** was condensed with a suitable β-ketoester. When typical Knoevenagel conditions (morpholinium acetate) were employed, cis stereoselection (4–7:1) was observed (→ *syn*-**57**). In contrast, when the condensation was carried out in the presence of polyphosphate ester (PPE),[25] trans stereoselection (4–20:1) was observed (→ *anti*-**57**).[59]

With the possibility of accessing both stereoisomers of type **57** by simply changing the reaction medium in the Biginelli condensation step, a number of total syntheses

Scheme 5. Tuning Stereoselectivities in Tethered Biginelli Reactions

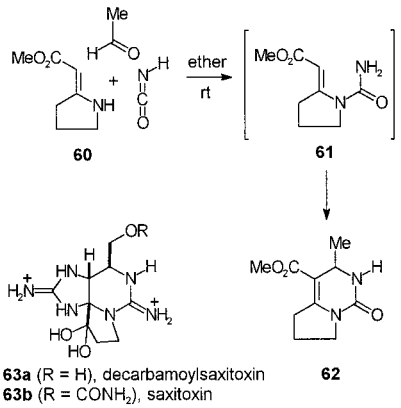


have been carried out by the Overman group.[60−65] To construct the tricyclic portion of the anti-HIV alkaloid batzelladine B (**9**), for example, the hemiaminal precursor **58** (nine steps from 2-nonanone) was subjected to Biginelli condensation with methyl acetoacetate under Knoevenagel conditions (morpholinium acetate).[60] The tricyclic



guanidine *syn*-**59** was obtained in 82% isolated yield and is identical with the methanolysis product of the naturally occurring batzelladine B (**9**).[18] Similar strategies based on enantioselective tethered Biginelli reactions were employed in the total synthesis of batzelladine D (**53**),[61] ptilomycalin A (**54**),[62,65] 13,14,15-isocrambescidin 800 (**55**),[63,64] 13,14,15-isocrambescidin 657,[64] crambescidin 657,[65] and crambescidin 800.[65]

In the context of an enantioselective total synthesis of the highly potent neurotoxin saxitoxin (**63b**), the Kishi group has developed a novel trimolecular cyclization reaction that is somewhat reminiscent of the Biginelli condensation.[66] In its simple racemic version, vinylogous carbamate **60** was condensed with acetaldehyde and isocyanic acid to provide bicyclic dihydropyrimidone **62** in good yield.[67] With some modification, this strategy was



initially employed toward a highly stereospecific but racemic synthesis of saxitoxin (**63b**).[68] In its asymmetric version, (*R*)-glyceraldehyde acetonide was used instead of acetaldehyde and provided, after extensive manipulation of the initially formed pyrrolopyrimidine skeleton, (−)-decarbamoylsaxitoxin (**63a**), which constitutes a formal enantioselective total synthesis of saxitoxin (**63b**).[66] From the mechanistic point of view, an ureidocrotonate species of type **61** has been discussed as an intermediate in this trimolecular cyclization.[69] It is interesting to note that corresponding enamides have also been considered as intermediates in the classical Biginelli reaction.[9,19,20]

Conclusion

The Biginelli dihydropyrimidine MCR has come a long way since its discovery in 1893. From the preparation of simple pyrimidine heterocycles in the late 19th century, to the generation of targeted compound libraries of biofunctional DHPMs and the enantioselective total synthesis of complex natural products, the Biginelli MCR has been adapted successfully to the needs and expectations of modern organic chemistry. Because of the pharmacological potency of the DHPM scaffold, novel dihydropyrimidines with important biological properties will undoubtedly be discovered by combining combinatorial synthesis and high-throughput screening techniques. A continuing exciting future for the Biginelli reaction in the 21st century is therefore secured.

I thank my former and present co-workers, whose names appear in the references below, for their essential contributions to the work described herein. Our work in the area of dihydropyrimidine chemistry since 1996 was generously supported by the Austrian Academy of Sciences (APART 319), the Austrian Science Fund (P-11994-CHE), and the "Jubiläumsfonds der Österreichischen Nationalbank" (Project 7904).

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