The Generation of Dihydropyrimidine Libraries Utilizing Biginelli Multicomponent Chemistry

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Abstract

With the emergence of high-throughput screening in the pharmaceutical industry over a decade ago, synthetic chemists were faced with the challenge of preparing large collections of molecules to satisfy the demand for new screening compounds. The unique exploratory power of multicomponent reactions such as the Ugi four-component reaction was soon recognized to be extremely valuable to produce compound libraries in a time- and cost effective manner. The present review article summarizes strategies for the construction of libraries through another multicomponent reaction, the Biginelli dihydropyrimidine synthesis. In this three-component condensation dating back to 1893, CH-acidic carbonyl compounds, aldehydes and urea-type building blocks combine to assemble a multifunctionalized dihydropyrimidine scaffold. Due to the interesting pharmacological properties associated with the privileged DHPM structures, the Biginelli reaction and related procedures have received increasing attention in recent years. This review details synthetic advances for the construction of Biginelli libraries via solution phase and solid-phase strategies that are amenable to a high-throughput or combinatorial format.

Introduction

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry. In times where a premium is put on speed, diversity, and efficiency in the drug discovery process, MCR strategies offer significant advantages over conventional linear-type syntheses. 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. In an ideal case, the individual building blocks are commercially available or are easily synthesized, and cover a broad range of structural variations. MCRs are providing products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry techniques. Multicomponent reactions leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of "drug-like" molecules for biological screening, since the combination of three or more small molecular weight building blocks in a single operation leads to high combinatorial efficacy. Over the last decade, industrial and academic researchers have made such powerful MCR strategies into one of the most efficient and cost-effective tools for combinatorial and parallel synthesis [1].

One prominent MCR that produces an interesting class of nitrogen heterocycles is the venerable Biginelli dihydropyrimidine synthesis (Scheme 1). In 1893, P. Biginelli reported on the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate (**1**), benzaldehyde (**2**) and urea (**3**) [2]. 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 as 3,4-dihydropyrimidin-2(1*H*)-one **4** (Scheme 1) [3], and this reaction is nowadays referred to as "Biginelli reaction", "Biginelli condensation" or as "Biginelli dihydropyrimidine synthesis" [4, 5].

While the early examples of this cyclocondensation process typically involved a β-ketoester, aromatic aldehyde, and urea, the scope of this heterocycle synthesis has now been extended considerably by variation of all three building blocks, allowing access to a large number of multifunctionalized pyrimidine derivatives (see below).[4, 5] For this particular heterocyclic scaffold the acronym DHPM has been adopted in the literature and is also used throughout this review. Due to the importance of multicomponent reactions in combinatorial chemistry there has been a renewed interest in the Biginelli reaction, and the number of publications and patents describing the synthesis of novel DHPM analogs is constantly growing. In the present review article we focus on synthetic methods that are suitable for the generation of DHPM libraries in a high-throughput or combinatorial format.

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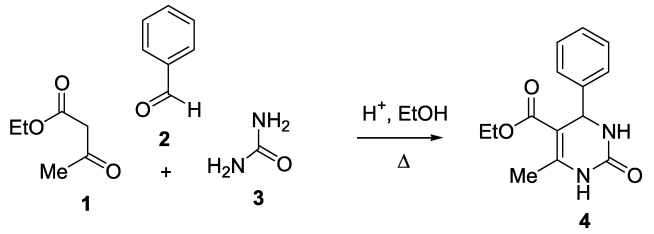


Scheme 1. The original Biginelli dihydropyrimidine synthesis (1893).

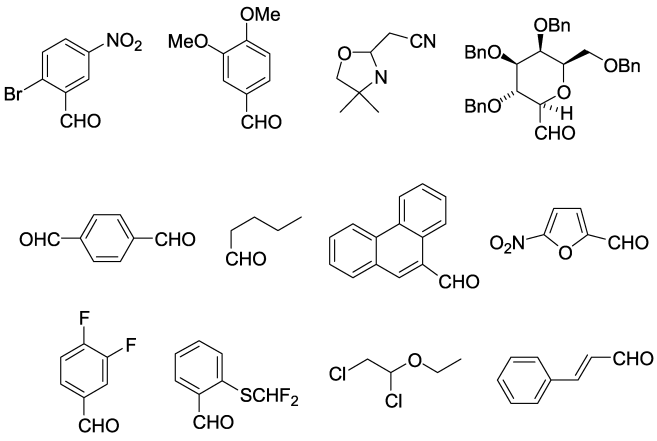


Figure 1. Aldehyde and protected aldehyde building blocks used in the Biginelli reaction.

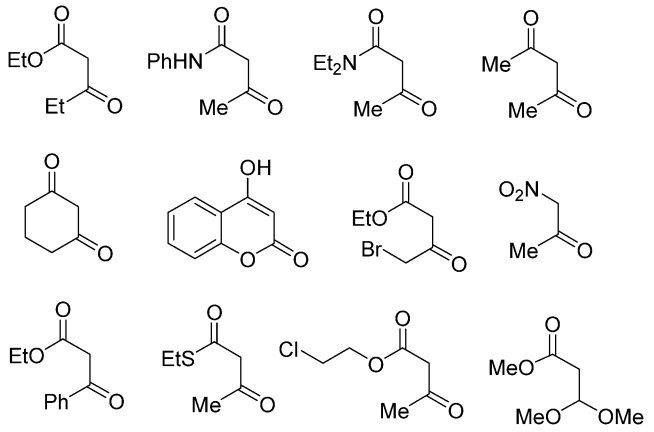


Figure 2. CH-Acidic carbonyl building blocks used in the Biginelli reaction

Building Blocks and Diversity

Out of the three building blocks in the Biginelli reaction it is the aldehyde component, which can be varied to the largest extent. In general, the reaction works best with aromatic aldehydes. These can be substituted in the *o*-, *m*- or *p*-position with either electron-withdrawing or -donating groups. Good yields are usually obtained with *m*- or *p*-substituted aromatic aldehydes carrying electron-withdrawing substituents. For *o*-substituted benzaldehydes having bulky substituents, yields can be significantly lower. Heterocyclic aldehydes derived from furan, thiophene, and pyridine rings also generally furnish acceptable yields of DHPM products [4].

Aliphatic aldehydes typically provide only moderate yields in the Biginelli reaction unless special reaction conditions are employed, *i.e.* Lewis acid catalysts/solvent-free methods, or using the aldehydes in protected form [6]. The C4 unsubstituted DHPM can be prepared in a similar manner employing suitable formaldehyde synthons [6]. Of particular interest are reactions where the aldehyde component is derived from a carbohydrate. In such transformations, DHPMs having a sugar-like moiety in position 4 (*C*-nucleoside analogs) are obtained (see also Figure 7) [7]. In a few cases, bisaldehydes have been used as synthons in Biginelli reactions [8].

Traditionally, simple alkyl acetoacetates are employed as CH-acidic carbonyl building blocks, but other types of 3-oxoalkanoic esters or thioesters can also be used successfully [4].

With methyl 4-chloroacetoacetate, for example, the corresponding 6-chloromethyl-substituted DHPMs which can serve as valuable templates for further synthetic transformations are obtained [9]. Benzoylacetic esters react analogously, but yields are usually significantly lower and the overall condensation process is more sluggish [4]. Primary, secondary, and tertiary acetoacetamides can be used in place of esters to produce pyrimidine-5-carboxamides [4]. In addition, β-diketones serve as viable substrates in Biginelli reactions. Condensations can also be achieved employing cyclic β-diketones such as cyclohexane-1,3-dione [10], and other cyclic β-dicarbonyl compounds (Figure 2) [11].

If a C6-unsubstituted DHPM derivative needs to be synthesized, the corresponding 3-oxopropanoic ester derivative in which the aldehyde function is masked as an acetal can be employed [12]. Apart from ester-derived CH-acidic carbonyl compounds, nitroacetone also serves as a good building block, leading to 5-nitro-substituted DHPM derivatives in generally high yields [13].

The urea is the component in the Biginelli reaction that faces the most restrictions in terms of allowed structural diversity (Figure 3) [4]. Therefore, most of the published examples involve urea itself as building block. However, simple monosubstituted alkyl ureas generally react equally well, in a regiospecific manner, to provide good yields of *N*1-substituted DHPMs.

Thiourea and substituted thioureas follow the same general rules as ureas, although longer reaction times are required to achieve good conversions. Yields are typically lower when compared to the corresponding urea derivatives. In some instances it is also possible to react protected urea or thioureas (isoureas), or guandidines of type **6** under weak basic conditions with the aldehyde and CH-acidic

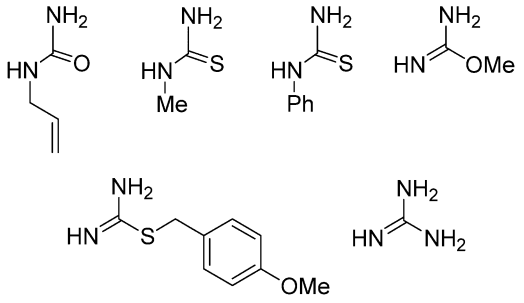
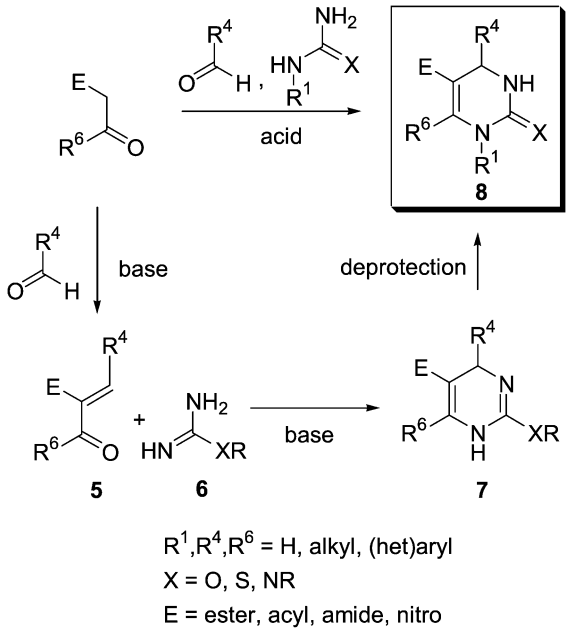


Figure 3. Urea-type building blocks used in the Biginelli reaction.



Scheme 2. Comparison and diversity analysis of the Biginelli and Atwal dihydropyrimidine syntheses.

carbonyl component (or with a precondensed Knoevenagel-type enone) to yield the corresponding protected DHPMs [14, 15]. This latter method, using precondensed enones of type **5** has been frequently referred to as the "Atwal modification" of the Biginelli reaction (Scheme 2) [4, 5, 16].

Given the diversity in building block selection that is tolerated in the Biginelli reaction it is evident that a large number of DHPM derivatives of the general formula **8** can be synthesized by combination of a relatively small number of (commercially available or proprietary) individual building blocks. Employing 20 aldehydes (point of diversity R^4), 10 CH-acidic carbonyl derivatives (points of diversity E and R^6) and 5 (thio)urea analogs (points of diversity X and R^1) in a Biginelli- or Atwal type condensation would lead to a library of 1.000 DHPM compounds, with a total of five diversity points around the dihydropyrimidine core [17]. It is therefore not surprising that a literature search for the general DHPM structure **8** in the Chemical Abstracts Registry database led to well over 10.000 hits [18]. It is interesting to note however, that only a small fraction of these compounds has been published in the chemical literature (<1.000) [19]. On the other hand, more than half the 10.000 structures of type **8** are commercially available, typically from companies specializing in chemical library generation.

Solution Phase Library Synthesis

Since the experimental conditions for the traditional Biginelli three-component reaction are rather straightforward, libraries of DHPMs are readily accessible by parallel or automated solution phase synthesis. Today there is a great variety of suitable reaction conditions for carrying out Biginelli condensations in solution. For the condensation of ethyl acetoacetate with benzaldehyde and urea (Scheme 1), more than 60 different experimental conditions have been reported [19]. In general, Biginelli condensations are carried out in a solvent such as ethanol or methanol, but more recently aprotic solvents such as tetrahydrofuran or acetonitrile have also been used successfully. The Biginelli condensation is strongly dependent on the amount of acidic catalyst present in the reaction medium. Traditionally, strong Bronsted acids such as hydrochloric or sulfuric acid have been employed [4], but nowadays the use of Lewis acids such as BF_3OEt_2 and CuCl [20], $FeCl_3$ [21], or $Yb(OTf)_3$ [22] is preferred. In fact a plethora of different methods and conditions for synthesizing DHPMs according to the Biginelli principle is known today, ranging from mg to kg scale [19].

Biginelli condensations generally proceed rather slowly at room temperature, and involve an *N*-acyliminium ion intermediate formed by initial acid-catalyzed condensation of the aldehyde and urea building blocks [5, 23]. Therefore it is necessary to activate these processes by heating. Apart from traditional heating methods, microwave dielectric heating employing some of the solvent/catalyst systems mentioned above has been used to shorten reaction times significantly [19]. As far as the molar ratio of building blocks is concerned, Biginelli reactions generally employ an excess of the CH-acidic carbonyl or the urea components, rather than an excess of the aldehyde. As DHPM products are usually only sparingly soluble in solvents such as methanol or ethanol at room temperature, work-up in many cases simply involves isolation of the product by filtration. It is also possible to precipitate the product by addition of water.

Along these lines Fréchet and coworkers have described the generation of a >140 member single compound DHPM library by combination of 25 aldehydes, 6 ureas/thioureas, and 9 acetoacetates or acetoamides under standard Biginelli reaction conditions [24]. This synthesis involved heating a mixture of the urea component with 1 equiv of the aldehyde and 1.5 equiv of the CH-acidic carbonyl building block in the presence of catalytic HCl in ethanol for 3 h (Scheme 2). The

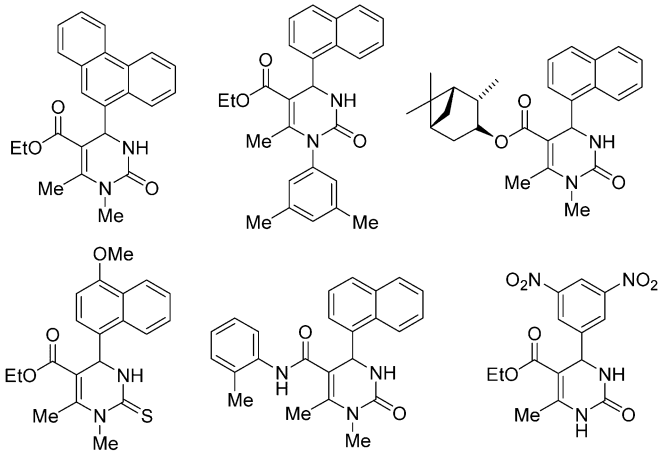


Figure 4. Examples of DHPM library compounds prepared by conventional solution phase synthesis [24].

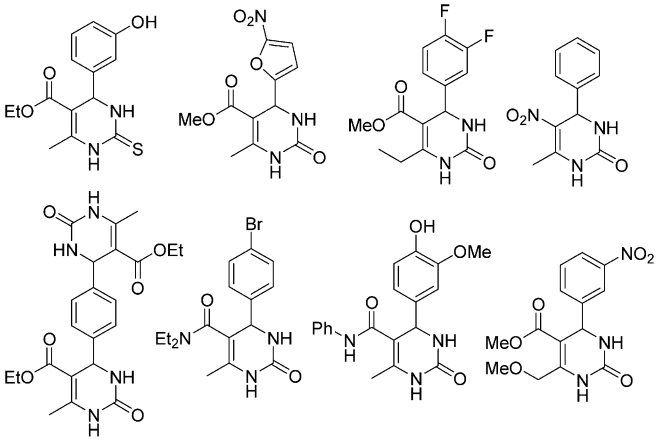


Figure 5. Examples of DHPM library compounds prepared by automated sequential microwave-assisted synthesis [8].

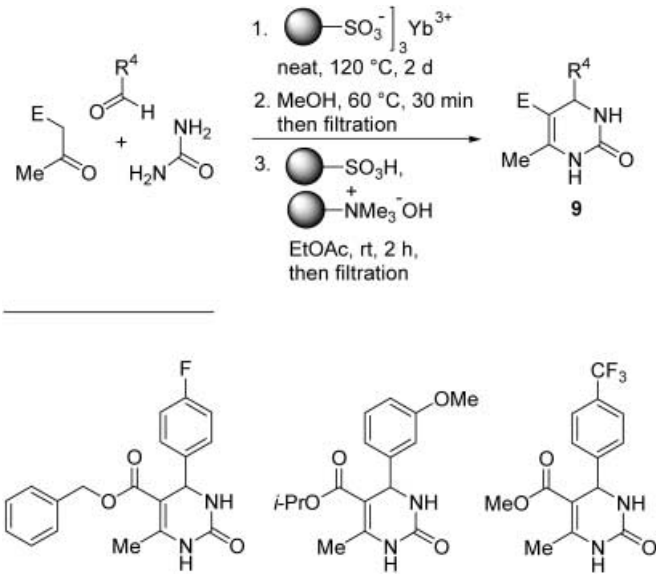
products were isolated from the crude reaction mixture by simple crystallization and provided DHPMs in 20–60% yield and >80% purity. Since this library was synthesized with the aim of preparing selectors for chiral HPLC separation, a variety of bulky π-acidic and π-basic groups were introduced at the C4 position (Figure 4) in order to interact with a corresponding chiral stationary phase (see below).

One major drawback of the classical Biginelli procedure, apart from the long reaction times involving reflux temperatures, is the moderate yields that are frequently obtained when using more complex building blocks. Recently, several groups have reported on microwave-assisted protocols for the Biginelli reaction that allow the preparation of DHPMs in a more rapid fashion [19]. For example, the automated generation of a library of 48 DHPM analogs was achieved by employing robotic dispensing of individual building block solutions into microwave reaction vials that were then irradiated in a microwave cavity under sealed vessel conditions [8]. This work employed a commercially available single-mode microwave reactor with a robotics interface including a liquid handler and a gripper. The liquid handler allows dispensing of reagents into the Teflon sealed reaction vials, while the gripper moves each sealed vial in an out of the microwave cavity after irradiation. Here, a diverse set of 25 aldehydes, 8 urea/thioureas and 17 CH-acidic carbonyl compounds was used in the preparation of the DHPM library. Out of the full set of 3400 possible DHPM derivatives, a representative subset of 48 analogues was prepared using automated mixing of building blocks (Figure 5). For most building block combinations 10 min of microwave heating at 120 °C using AcOH/EtOH (3:1) and 10 mol% $Yb(OTF)_3$ as solvent/catalyst system proved successful, leading to an average isolated yield of 52% of DHPMs with >90% purity. Given the unattended automation capabilities of the microwave synthesizer a library of this size was synthesized in 12 h [8].

A similar set of DHPMs was also synthesized in a parallel fashion using the EtOH/HCl conditions, employing a 36 vessel rotor system in dedicated multimode microwave instruments [25]. While a parallel reaction setup has the advantage of higher throughput that can be achieved in a microwave experiment, irradiating each vessel separately not only gives better control over the reaction parameters but also allows for the rapid optimization of reaction conditions. In contrast to the parallel mode, not all reaction vessels are exposed to the same irradiation conditions [26].

Polymer-Assisted Solution Phase Synthesis

In order to simplify some of the purification and workup issues involved in the Biginelli condensation for those cases where precipitation is not feasible, Dondoni and Massi have introduced a variation of the classical Biginelli solution phase protocol, employing a polymer-supported Yb(III) reagent as Lewis acid catalyst, and a mixture of acidic and basic ion exchange resin for workup [27]. In this procedure, equimolar amounts of aldehyde and CH-acidic carbonyl component are treated with a threefold excess of urea in the presence of an Amberlyst 15 supported Yb catalyst. The reaction was carried out in the absence of any solvent at 120 °C for 2 days with gentle stirring. In order to avoid an aqueous or chromatographic workup, MeOH was added to the 60 °C reaction mixture. After filtration from the supported Lewis acid catalyst, a mixed-resin bed containing the strongly acidic Amberlyst 15 (A 15) sulfonic acid ion exchange resin and the strongly basic Ambersep 900 OH resin was used to scavenge excess urea and by-products derived from 1,3-dicarbonyl component condensation (Scheme 3). A range of CH-acidic carbonyl compounds and aldehydes was tested to produce a library of 32 DHPM derivatives **9** in 63–80% yield and ca. 90% average purity [27].



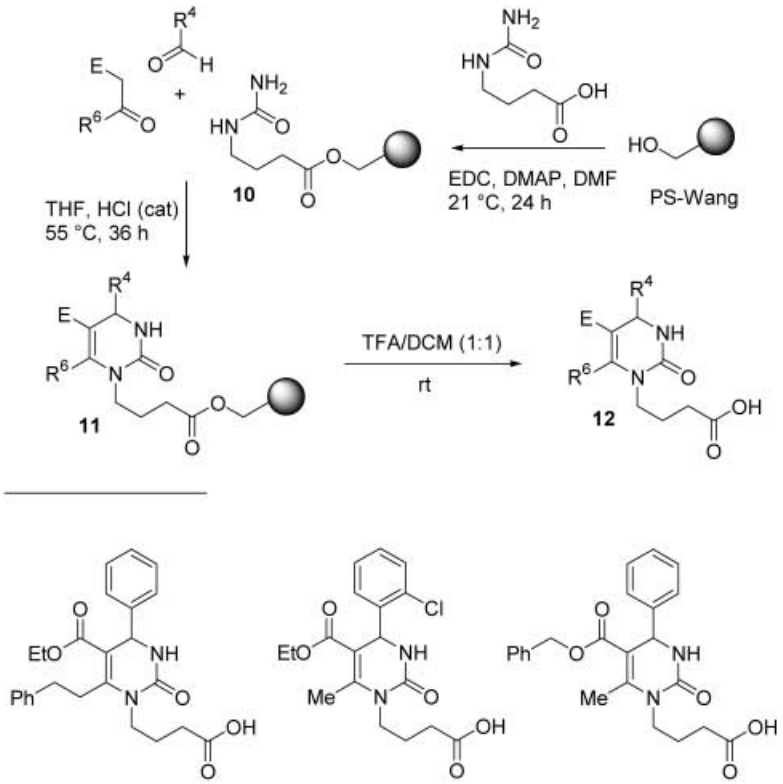
Scheme 3. Biginelli condensation using polymer-supported catalysts/scavengers and examples of library compounds [27].

Solid Phase Strategies

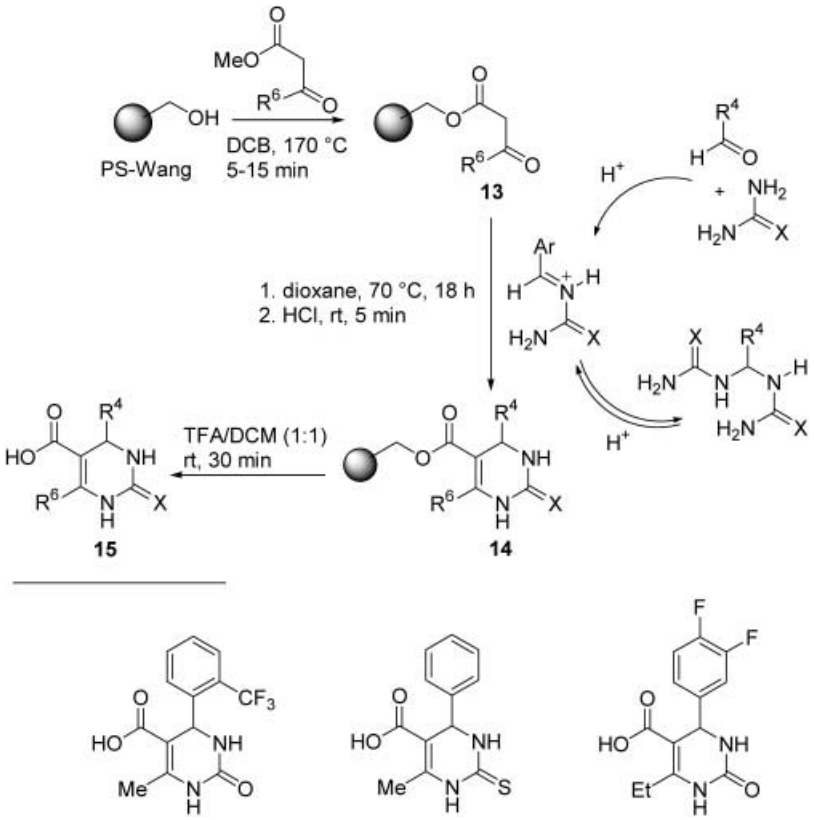
Solid phase organic synthesis remains one of the cornerstones of combinatorial chemistry, since this technique allows the chemist to take full advantage of the powerful principles (*i.e.* split-and-mix synthesis) offered by combinatorial technologies [28]. For a multicomponent reaction such as the Biginelli condensation, various solid-phase strategies can be envisaged and in fact a number of different approaches have been disclosed in recent years, utilizing different resin-bound building blocks and linker combinations. Given the regioselectivity encountered in using *N*-substituted urea building blocks in the Biginelli condensation (see above), a solid phase modification where the urea component is linked to the solid support via the amide nitrogen is an obvious choice. This strategy was first described by Wipf and Cunningham in 1995 (Scheme 4) [29]. In this sequence, a β-aminobutyric acid (GABA)-derived urea (4 equiv) was attached to standard Wang resin using EDC (N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide) as coupling reagent under standard reaction conditions. The resulting polymer-bound urea **10** was then condensed with 2 equiv each of an aromatic aldehyde and a β-ketoester in THF at 55 °C in the presence of catalytic HCl. After cleavage of the benzylic bond with trifluoroacetic acid/dichloromethane (TFA/DCM 1:1) the *N*1-functionalized DHPMs of type **12** were isolated by simple filtration in 67–98% yield based on the urea loading of the resin. No further purification was necessary, since all DHPMs were >95% pure by NMR and excess reagents were easily removed by rinsing the resin with THF before the deprotection step. Using a set of 5 different β-ketoesters and 6 aldehydes, a small collection of 10 DHPM derivatives with the hydrophilic GABA anchor at the N1-DHPM position was prepared [29]. The influence of various solvents (DMF, DMA, methoxyethyl ether) on the solid phase Biginelli condensation step was further studied and optimized with the aid of an automated synthesizer [30].

A conceptually different solid phase approach was reported in 2001 (Scheme 5) [31]. In contrast to the previous strategy employed by Wipf and Cunningham, here the acetoacetate building block was linked to the solid support. Acetoacetates could either be attached by treatment of Wang resin with diketene (R^6 = Me), or by transesterification of Wang resin with β-ketoesters (R^6 = alkyl, aryl). This latter procedure can be conveniently carried out by parallel high-speed microwave-assisted chemistry at 170 °C in 1,2-dichlorobenzene (DCB) and obviously offers a higher degree of diversity (R^6) in terms of the number of different polymer bound β-ketoester building blocks that can be generated [32]. The resin-bound β-ketoesters **13** were then reacted with 3 equiv each of urea/thiourea and an aldehyde building block in dioxane/HCl at 70 °C. Within minutes after the addition of the reagents a colorless bisureide precipitate formed resulting from trapping of the initially formed *N*-acyliminium ion intermediate [23] by excess urea present in the reaction medium. Upon longer reaction times and under acidic catalysis the iminium ion intermediates are regenerated from the bisureides and subsequently are intercepted (irreversibly) by the resin bound β-ketoesters resulting in the formation of polymer bound DHPMs **14** (Scheme 5). Treatment with concd HCl at room temperature dissolved any remaining bisureide by-product and allowed clean filtration of the resin. No release of DHPM product was observed under these conditions. Subsequent cleavage with TFA/DCM (1:1) led to the desired DHPM-5-carboxylic acids **15** (11 examples) in 52–81% yield and high purity (>95%). Biginelli condensations involving thiourea needed considerable longer reaction times in accordance with solution phase reactions (see above) and required the presence of a suitable scavenger such as thiophenol in the cleavage step [31].

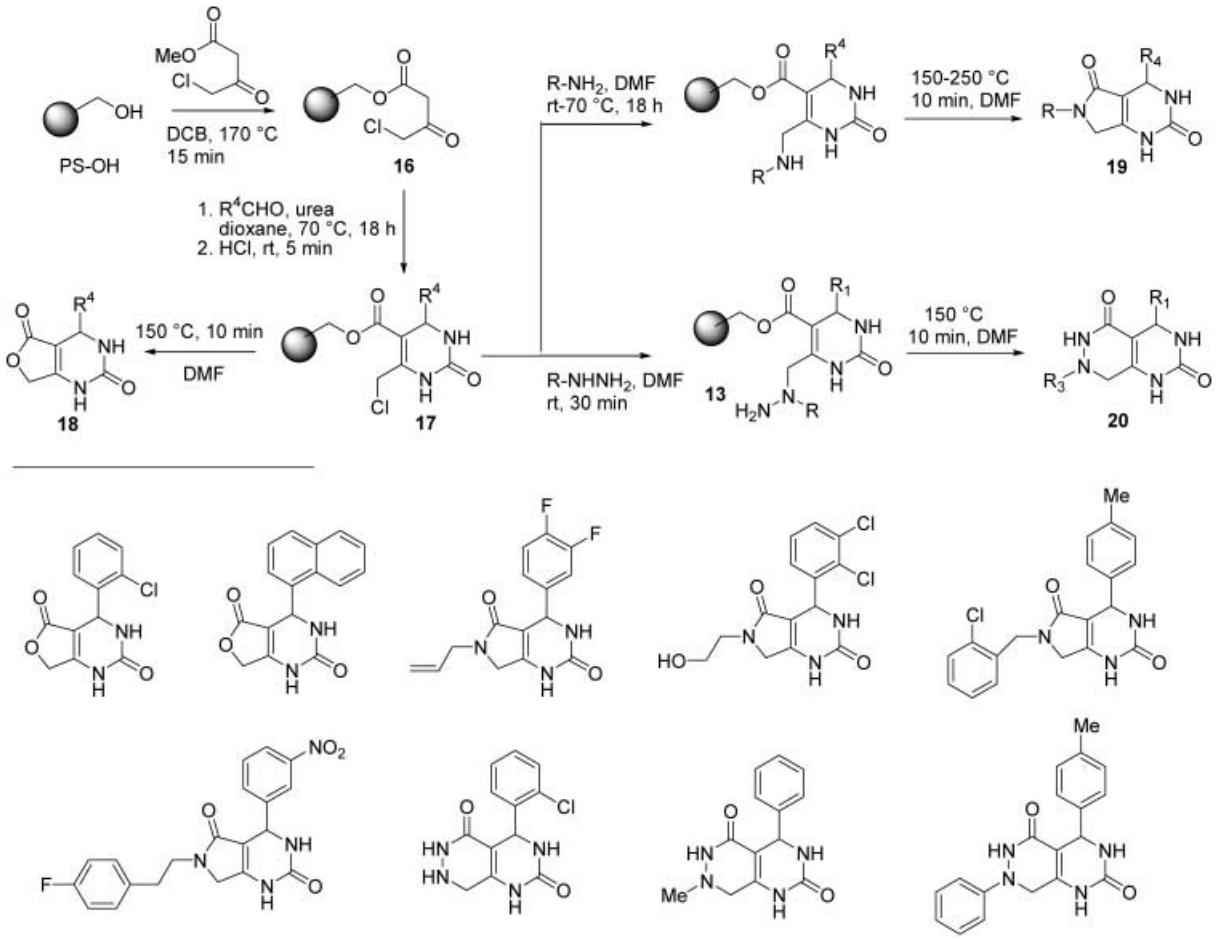
In the context of increasing the complexity generating-power of the classical Biginelli approach an extension of the solid-phase strategy highlighted in Scheme 5 toward the synthesis of bicyclic DHPM scaffolds was recently disclosed, employing commercially available methyl 4-chloroacetoacetate as a β-ketoester building block (Scheme 6) [9]. The 4-chloroacetoacetate precursor immobilized on hydroxymethyl polystyrene (PS-OH) **16** was subjected to a Biginelli-type three-component condensation employing urea and 12 diverse aromatic aldehydes (3 equiv each) utilizing the same reaction conditions as described above. The resulting 6-chloromethyl-functionalized resin-bound DHPMs **17** served as common chemical templates for the generation of three different heterobicyclic scaffolds using three different traceless cyclative cleavage strategies (Scheme 6) [9]. The corresponding furo[3,4-d]pyrimidines **18** were obtained by microwave flash heating in a rapid,



Scheme 4. Solid phase synthesis of DHPMs according to Wipf and Cunningham and examples of library compounds [29].



Scheme 5. Solid phase synthesis of DHPM-5-carboxylic acids and examples of library compounds [31].

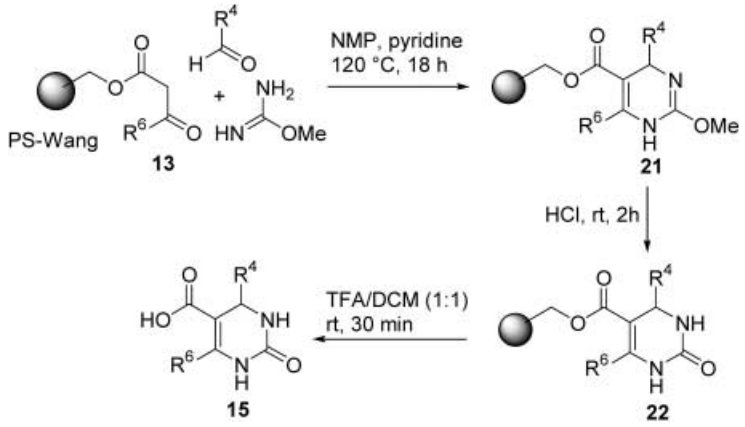


Scheme 6. Solid phase synthesis of bicyclic DHPM derivatives and examples of library compounds [9].

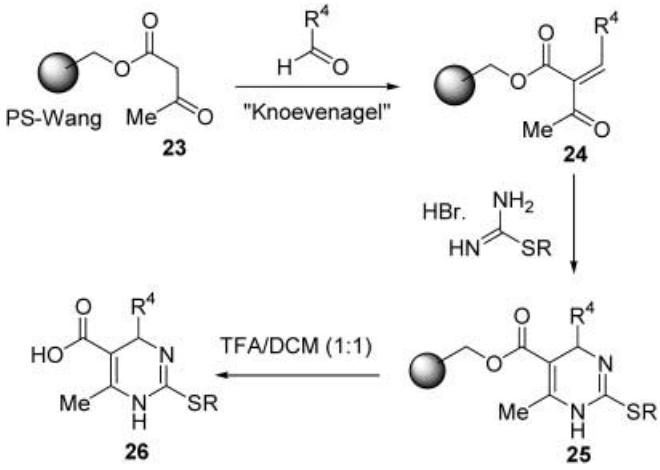
thermally triggered cyclative release. Complete cleavage of material from the resin was achieved within 10 min at 150 °C utilizing DMF as a solvent. These heterocycles (12 examples) were obtained in 10–77% overall yield over the three solid phase reaction steps in >95% purity (LC-MS). Treatment of the chloromethyl DHPM intermediates with a variety of primary amines (5 equiv, 11 examples) followed by high-temperature microwave heating furnished the anticipated pyrrolo[3,4-d]pyrimidine scaffolds **19** via nucleophilic cyclative cleavage. A small library of 22 examples was prepared in 25–55% overall yield (4 steps) and generally ca 85% LC-MS purity. For aromatic amines cleavage temperatures of 250 °C were necessary in order to release the desired products from the polymer support. In a similar way, reaction with monosubstituted hydrazines resulted in the formation of pyrimido[4,5-d]pyridazines **20**, although here yields and purities were considerable lower (7 examples, 32–41% yield, ca 50% LC-MS purity). The same strategy could also be utilized in a solution-phase synthesis [9].

In addition to solid-phase adaptations of the traditional three-component Biginelli condensation, solid-phase variations of the so-called "Atwal modification" of the Biginelli reaction (see Scheme 2) have also been reported. Thus, as an alternative to the acid-catalyzed Biginelli three-component assembly of the DHPM ring system outline in Scheme 5, an "orthogonal" strategy, where an *O*-methylisourea salt is condensed with CH-acidic carbonyl and aldehyde components under *mildly basic* conditions has been introduced (Scheme 7) [31]. Polymer-bound ketoesters (R^6 = Me, Et) were treated with *O*-methylisourea hydrogensulfate and an aromatic aldehyde (8 examples, 3 equiv) in *N*-methylpyrrolidone (NMP) at 120 °C using pyridine (10 equiv) as a base. After hydrolysis of the initially formed resin-bound *O*-methyl-1,4-dihydropyrimidine intermediates **21** with a large excess of aqueous HCl, standard cleavage from Wang resin furnished the desired DHPM-5-carboxylic acids **15** (10 examples) in acceptable overall yields (30–66% over four steps) and high purity (>95% by 1H NMR). The yields in this base-catalyzed version of the Biginelli condensation were however somewhat lower than utilizing the classic acid-catalyzed pathway (see Scheme 5).

A closely related approach has been reported by Robinett et al. (Scheme 8) [33]. Here, the supported acetoacetate was



Scheme 7. Solid phase synthesis of DHPM-5-carboxylic acids employing a base-catalyzed variation of the Biginelli condensation [31].

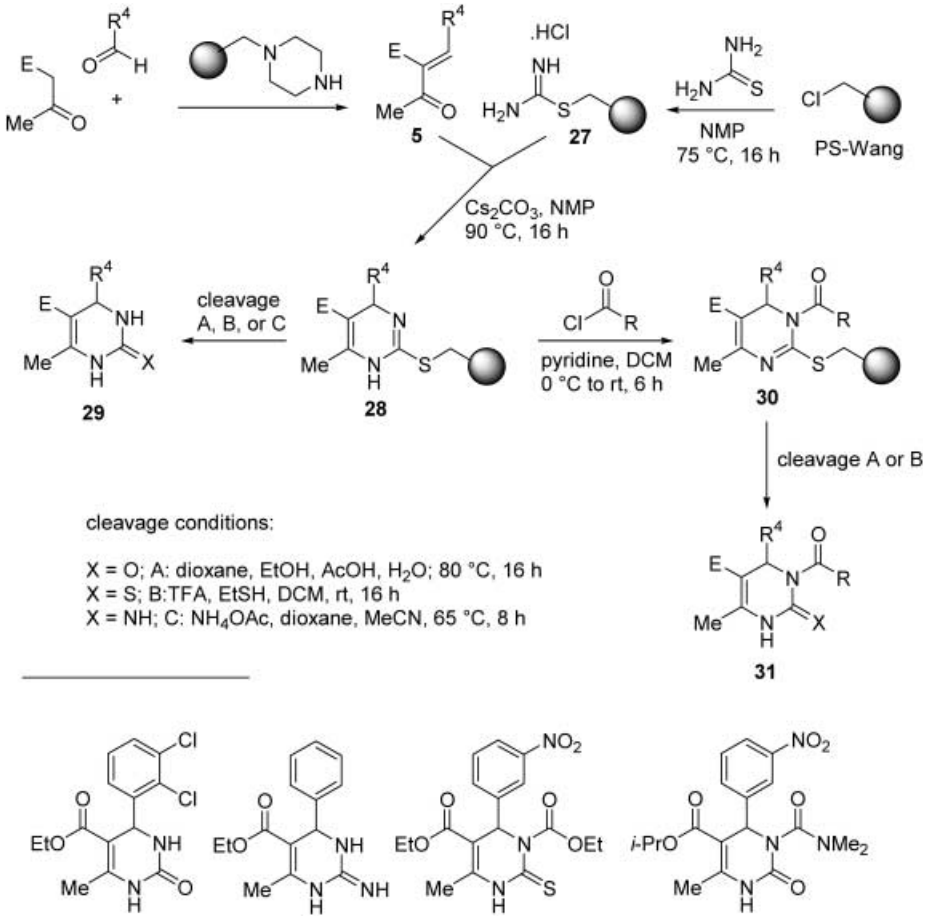


Scheme 8. Solid phase synthesis of 1,4-dihydropyrimidine-5-carboxylic acids employing the Atwal modification of the Biginelli condensation [33].

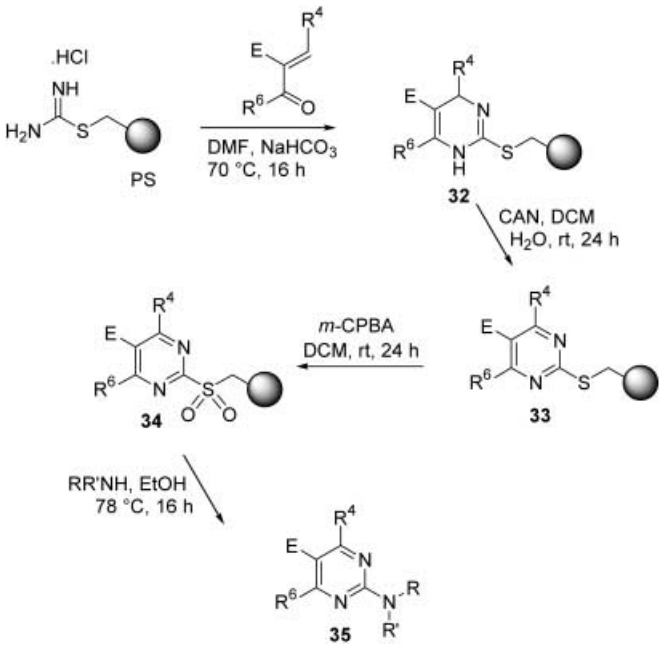
first subjected to a Knoevenagel condensation on the resin [32] with a variety of aldehydes, followed by reaction with S-alkylisothioureas to produce 1,4-dihydropyrimidines on solid support. Rather than hydrolyzing the protected urea/thiourea functionality (see Scheme 7), these intermediates were directly cleaved with TFA/DCM 1:1 to furnish a 648 member combinatorial library **26** (no further details available) [33].

In an effort to increase the molecular diversity that can be achieved in solid phase syntheses of DHPM scaffolds utilizing the Atwal concept, an alternative approach – reversing the linking strategy of Robinett et al. (Scheme 8) – was elaborated, where initially an isothiourea building block was attached to resin-bound 4-(benzyloxy)-benzyl chloride ("chloro Wang resin") by treatment of the functionalized polymer with thiourea (5 equiv) in NMP at 75 °C (Scheme 9) [34]. The resin bound isothiouronium salt **27** was then condensed with enones **5** (1.5 – 2.5 equiv), which themselves can be readily prepared in high-throughput fashion by modified Knoevenagel condensation involving a polymer supported piperazine catalyst [35]. The key condensation step leading to resin-bound 1,4-dihydropyrimidines **28** was carried out in NMP at 90 °C in the presence of Cs_2CO_3 as a base utilizing 1.5 – 2.5 equiv excess of the enone. The polymer bound dihydropyrimidine can then be directly cleaved from the resin employing different cleavage strategies (multidirectional resin cleavage). Thus, three types of DHPMs **29** (X = O, S, and NH) can be obtained applying the appropriate cleaving conditions A (hydrolytic), B (benzylic cleavage), or C (aminolysis). The DHPM derivatives **29** (9 examples) were produced in 55 – 71% overall yield (3 steps) and showed > 95% purity by ^{1}H NMR. A key feature of this method is the multidirectional cleavage of the thiouronium derived Wang linker, allowing the introduction of an additional element of diversity in the cleavage step, which multiplies the number of DHPMs that can be generated via this pathway by three. Furthermore, another diversity element can be attached onto the pyrimidine nucleus by regioselective *N*3-acylation of the polymer bound DHPM intermediate with suitable electrophiles (*e.g.* acyl chlorides, RCOCl). Applying different cleavage strategies on this substrate (**30**) the corresponding *N*3-functionalized DHPMs **31** were obtained in moderate yields (41 – 55% yield after chromatographic purification). This solid phase approach is therefore particularly attractive for the preparation of pharmacologically active *N*3-acylated analogues [5], and should be useful for the generation of targeted libraries of this heterocyclic scaffold.

An interesting variation of the strategy shown in Scheme 9 involving a safety-catch linker was elaborated by Vanden Eynde and coworkers (Scheme 10) [36]. Oxidation of the resin-bound 1,4-dihydropyrimidine **32** with cerium ammonium nitrate (CAN) produced the corresponding fully conjugated pyrimidine species **33**, which did not allow displacement of the sulfide by amines. Activation through oxidation of the sulfide to the sulfone with *m*-chloroperbenzoic acid (*m*-CPBA) [37], however, produced a linked pyrimidine derivative that could readily by



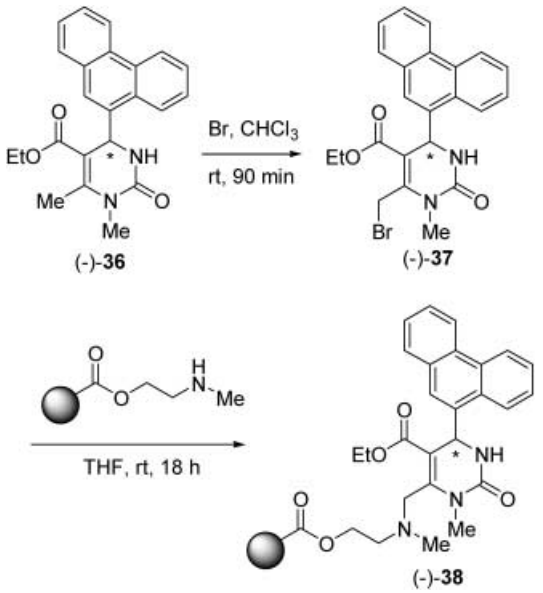
Scheme 9. Solid phase synthesis of DHPM derivatives based on multidirectional resin cleavage and examples of library compounds [34].



Scheme 10. Solid phase synthesis of 2-aminopyrimidine-5-carboxylates based on the safety-catch linker principle ($R^4 = CO_2Et$, $R^6 = Ph$) [36].

liberated from the resin (PS-Merrifield) by treatment with various aliphatic or aromatic primary/secondary amines. Again, diversity is here introduced in the final cleavage step of the solid-phase synthesis to provide 2-aminopyrimidine-5-carboxylates **35** [36].

In addition to the three points of attachment of the DHPM core to a functionalized polymer support that were described above (Schemes 4 – 10), there are other possibilities to immobilize the DHPM skeleton on a resin. In this context, Fréchet and coworkers have described an interesting strategy where the DHPM is linked via its C6 methyl group onto a macroporous polymethacrylate support (Scheme 11) [24]. Enantiomeric resolution of racemic 9-phenanthryl- DHPM **36** by semipreparative chiral HPLC allowed the preparation of the optically pure DHPM (−)-**36** which was subsequently brominated with elemental bromine at the C6 position. Coupling of the reactive bromomethyl-DHPM (−)-**37** to the amino functionalized support in THF provided resin-bound enantiomerically pure DHPM **38** that was used as a chiral stationary phase (CSP) in HPLC-based separations (see below).



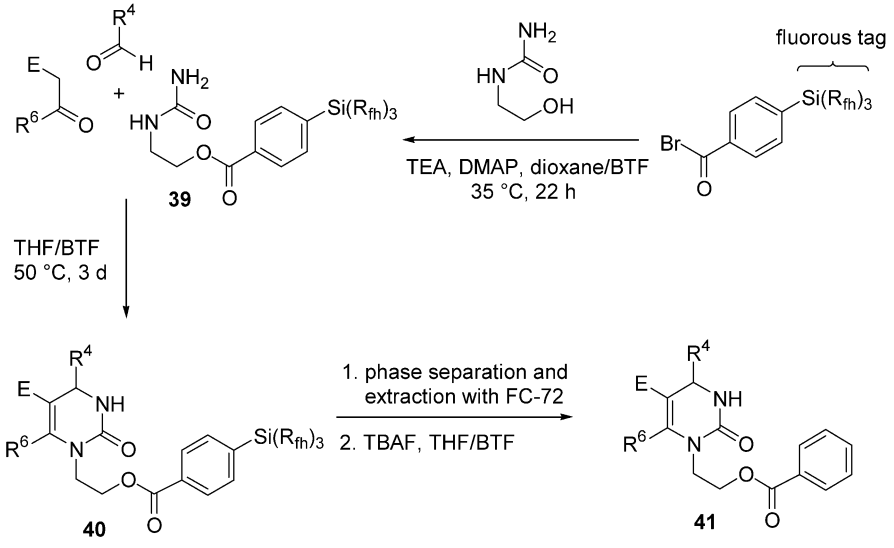
Scheme 11. Preparation of a DHPM-based chiral stationary phase on macroporous aminomethacylate beads [24].

Fluorous Synthesis

In fluorous synthesis an organic molecule is attached to a "fluorous label", which is of sufficient structure, size, and fluorine content to render the attached organic molecule "fluorous", *i.e.* soluble in fluorocarbon solvents. 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. Unlike solid phase synthesis, fluorous synthesis allows the routine use of standard reagents and reaction conditions [38]. The fluorous Biginelli (or Fluginelli) reaction was introduced by the Wipf and Curran groups in 1997 (Scheme 12) [39]. In fluorous Biginelli reaction a fluorous urea derivative **39** was prepared by attachment of a suitable fluorous tag (derived from 1*H*,1*H*,2*H*,2*H*-perfluorododecane) to hydroxyethylurea. The fluorous urea was then condensed with 10 equiv each of the corresponding acetoacetates (3 entries) and aromatic aldehydes (3 entries) in THF-benzotrifluoride (BTF) containing HCl. A large excess of the reagents was used to drive the reaction to completion. Optimal solubility of all the reaction components and a homogeneous solution were achieved in a 2:1 mixture of THF/BTF. After extraction of the fluorous DHPMs **40** with fluorous solvent (perfluorohexanes, FC-72), desilylation with tetrabutylammonium fluoride (TBAF) followed by extractive purification provided the "organic" Biginelli products DHPMs **41** (6 examples) in 47–71% overall yield and >90% purity (^{1}H NMR). Considering the simple experimental techniques used in this fluorous chemistry, automation should be feasible, thus allowing the preparation of DHPM libraries.

Soluble Polymer-Supported Synthesis

In recent years, the synthesis of small molecules supported on soluble polymers has received renewed interest [40]. This technique couples the advantages of homogeneous solution phase chemistry (high reactivity, lack of diffusion phenomena and ease of reaction monitoring) with those of solid phase chemistry (use of excess reagents and easy isolation

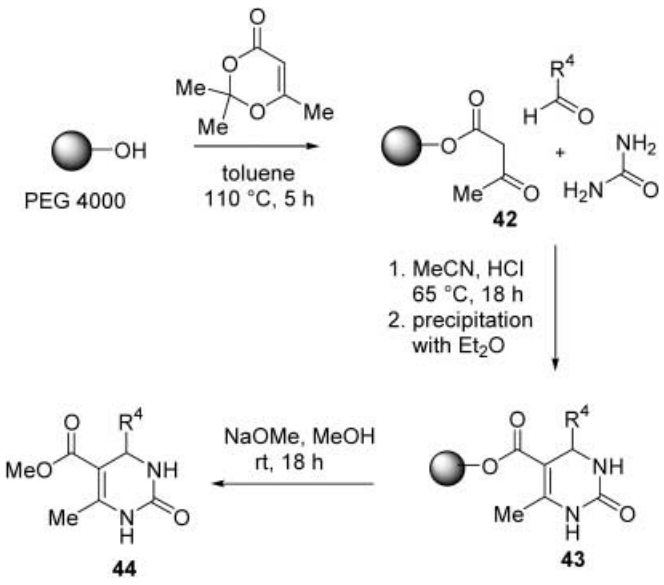


R_{fh} = $C_{10}F_{21}CH_2CH_2$-, BTF = benzotrifluoride ($C_6H_5CF_3$), TBAF = tetrabutylammonium fluoride

Scheme 12. Fluorous Biginelli (Fluginelli) reaction [39].

and purification of products). Several examples of soluble polymer-supported Biginelli chemistry have been reported in the literature. In a recent study Xia and Wang have employed polyethylene glycol (PEG) as a soluble support for the CH-acidic carbonyl component [41]. As shown in Scheme 13, PEG-linked acetoacetate **42** was prepared by reacting PEG 4000 with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (*i.e.* diketene acetone adduct) in refluxing toluene for 5 h. The homogeneous Biginelli condensation of the supported acetoacetate with 4 equiv each of the aldehyde (9 examples) and urea building blocks was performed in acetonitrile in the presence of catalytic amounts of HCl. After evaporation of solvent, the PEG-bound DHPMs **43** were precipitated from the reaction mixture with diethyl ether. Cleavage of the DHPMs was afforded with 1 N NaOMe in methanol to furnish the DHPM methyl esters **44** in 70 – 91% yield (9 examples) and > 92% purity (HPLC). It is worth mentioning that this is the only example of a nucleophilic cleavage of the DHPM C5-ester bond reported so far. Even under conventional solution-phase conditions this ester is difficult to hydrolyze [42].

In a further modification of their strategy, the same authors reported that reaction times for the Biginelli condensation step could be reduced to 1 – 2 min by carrying out the process without solvent in the presence of polyphosphoric acid (PPA) as catalyst and by applying microwave heating. Apparently, here PEG acts simultaneously as a solvent and as a polymer support [41].



Scheme 13. Soluble polymer-assisted Biginelli condensation [41].

An inherent problem of soluble polymers of the PEG-type is their comparatively low loading of typically 0.1 – 1.0 mmol functionality per gram polymer. A way to overcome this issue is to employ dendritic or hyperbranched polymers as high loading supports for organic synthesis [43]. Vanden Eynde and coworkers have utilized hyperbranched star polymers of the Boltorn type [44] as supports in Biginelli-type condensations (Scheme 14) [45]. These polyols have loadings of up to 9 mmol/g with an average molecular weight of *e.g.* 7200 for the Boltorn H40 polymer. In their study, the 64 hydroxyl groups on the H40 polymer were initially derivatized with an appropriate acid in order to mimic a Merrifield-type linker. Esterifications were performed in the presence of dicyclohexylcarbodiimide (DCC) and a catalytic amount of DMAP in dioxane. Analogous to the related solid phase protocols described above (Schemes 9 and 10) treatment with thiourea in refluxing ethanol for 4 h provided the polymer-supported isothiouronium salt, which was subsequently condensed with an enone under mildly basic conditions to furnish a supported 1,4-dihydropyrimidine **46.** Applying the hydrolytic cleavage conditions A detailed in Scheme 9 led to the desired DHPM structures **47** in ca. 60% overall yield. Isolation of the final compounds was made by filtering the ethanol-insoluble polymer, and concentration of the filtrate. A study comparing the reaction kinetics between standard microporous polystyrene resin (Merrifield resin), and various soluble supports (PEG, MeOPEG, Boltorn polymers) clearly demonstrated the superior kinetic behavior of reactions carried out on soluble supports.

Figure 6 summarizes the possible anchoring strategies that have been described for attaching DHPMs to a polymeric or fluorous support. These are the result of either employing the corresponding supported acetoacetate or urea/isothiourea building blocks in a Biginelli or Atwal type condensation (A – C), or are derived from anchoring an existing DHPM core to a polymeric support by suitable derivatization strategies (D). In terms of linking and cleaving methods, acid-labile linkers (*i.e.* Wang linker) have been used most frequently, but other strategies such as traceless cyclative cleavage, safety-catch release, or cleavage by nucleophiles have also been reported by some authors.

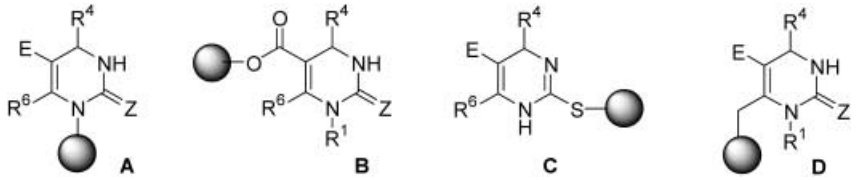
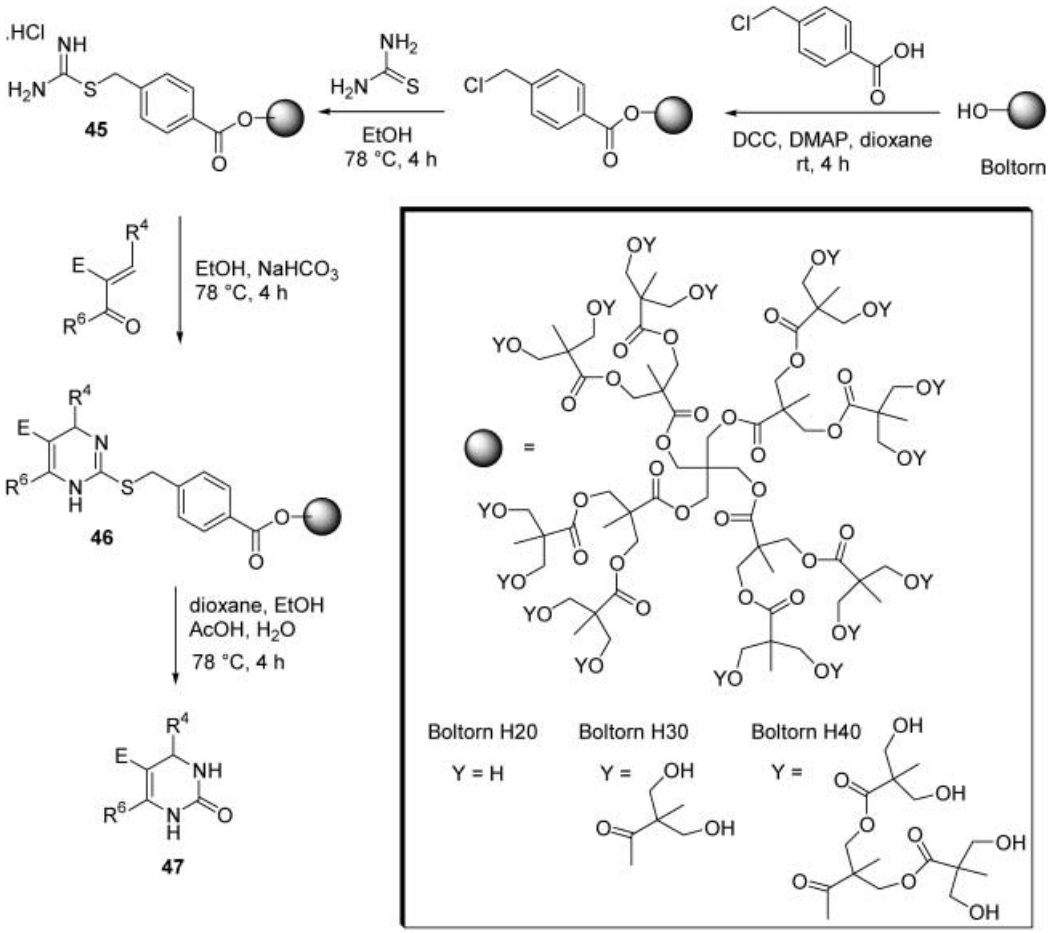


Figure 6. Possible attachment points of DHPM scaffolds to solid-, soluble polymer-, or fluorous supports.



Scheme 14. Soluble polymer-assisted Biginelli condensation using hyperbranched star polymers [45].

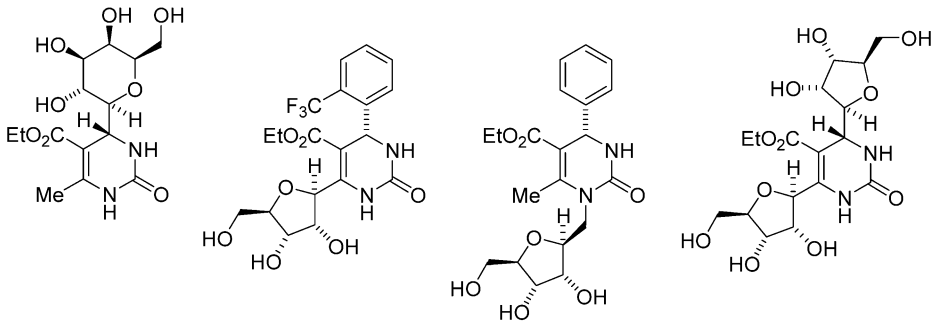
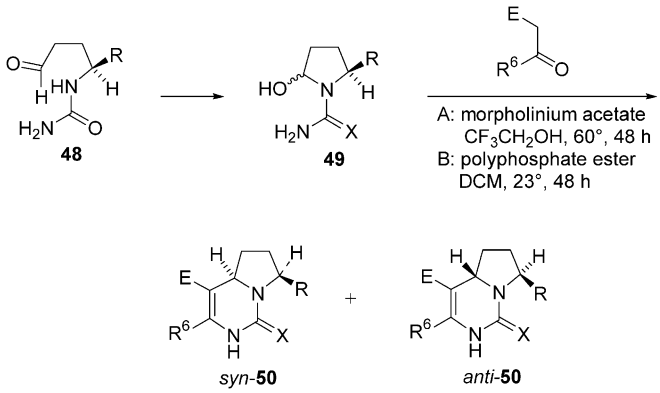


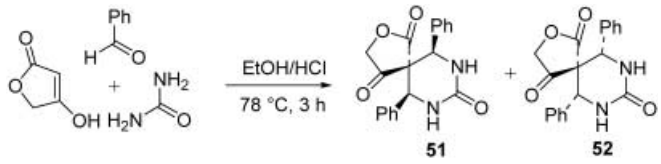
Figure 7. Mono- and bisglycosylated DHPM derivatives (major diastereoisomers shown) [7].

Unusual Biginelli-Type Condensations

Apart from the traditional Biginelli three-component condensation, there are a number of related processes where similar building blocks are employed, but the structure of the final product differs from a Biginelli DHPM. Alternatively, uncommon building blocks have been used by some authors which will be also covered in this section. One example of the latter category is the use of C-glycosylated substrates in the Biginelli condensation. Dondoni and coworkers have prepared a number (13 examples) of dihydropyrimidone glycoconjugates where the sugar residue was installed at N1, C4, or C6 in the monoglycosylated derivatives and at both the C4 and C6 positions in the bisglycosylated products (Figure 7) [7]. The mono- and bisglycosylated products were obtained as mixtures of diastereomers with good to excellent selectivities due to asymmetric induction by the sugar residue in the formation



Scheme 15. Enantioselective intramolecular ("tethered") Biginelli condensations for the synthesis of hexahydropyrrolo[1,2-c]pyrimidines.



Scheme 16. Pseudo four-component cyclocondensation leading to spiroheterobicycles.

of the C4 stereocenter of the dihydropyrimidine ring. Given the availability of various glycosylated aldehydes, ureas, and ketoesters, this methodology should permit access to combinatorial libraries of glycosylated DHPM derivatives with a wide range of structural and stereochemical elements of diversity.

A special variant of the Biginelli reaction are intramolecular or so-called tethered Biginelli condensations developed by Overman and co-workers, where the aldehyde and urea component are linked together in one building block (Scheme 15) [46, 47]. The "tethered Biginelli strategy" has been used in the synthesis of various polycyclic guanidinium alkaloids that all have the hexahydropyrrolo[1,2-c]pyrimidine fragment **50** in common and display a range of interesting biological activities.[47, 48] For example, condensation of the chiral hemiaminal precursor **49** with a suitable β-ketoester leads to the desired hexahydropyrrolo[1,2-c]pyrimidine scaffold [47]. Importantly, depending on the reaction conditions (A or B), both the *syn* and *anti* stereoisomers of **50** can be obtained with high selectivities.

As mentioned above cyclic β-diketones such as cyclohexane-1,3-dione and other cyclic β-dicarbonyl compounds are known to function well in Biginelli condensations. However, for tetronic acid the reaction takes an entirely different course, following a pseudo four-component pathway to furnish spiro heterobicyclic products in good yields (Scheme 16) [49]. The reaction proceeds by a regiospecific condensation of two molecules of aldehyde with the other reagents to afford products **51** and **52** having the C-4 and C-6

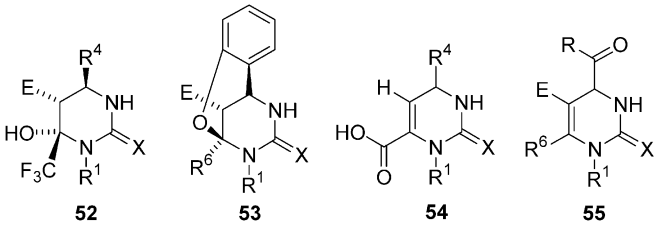


Figure 8. Uncommon pyrimidine scaffolds derived from Biginelli-type condensations.

substituents exclusively in *cis* configuration. The classical Biginelli product was not detected.

A number of other "unusual" Biginelli-type structures are displayed in Figure 8. For 1,3-dicarbonyl building blocks having a strong electron-withdrawing substituent (R^6) such as a trifluoromethyl group, the Biginelli sequence generally provides a hexahydropyrimidine derivative of type **52** [50]. In fact, a variety of hexahydropyrimidines can be synthesized in this way using perfluorinated 1,3-dicarbonyl compounds or β-ketoesters as building blocks [22, 50]. The steric proximity of an OH substituent in the *ortho* position of the aromatic ring and the C6 carbon of the pyrimidine ring in DHPMs [51] enables the formation of a six-membered ring via intramolecular Michael addition [24, 52]. For example, with aromatic aldehydes such as salicylaldehyde, the expected product of a Biginelli condensation is not a simple DHPM but rather the 8-oxa-10,12-diazatricyclo[7.3.1.$0^{2,7}$]-tridecatriene derivative **53** (Figure 8) [24, 52]. Several examples of these unusual domino Biginelli condensation/Michael addition sequences have been reported. Another interesting variation of the standard Biginelli reaction involves the use of β-ketocarboxylic acids as CH-acidic carbonyl compounds. Under suitable reaction conditions, oxalacetic acid is an excellent substrate in such condensations [53] Cyclization and in-situ decarboxylation cleanly yields 5-unsubstituted 3,4-dihydropyrimidin-2(1*H*)-ones **54**. By using trifluoroacetic acid (TFA) as the acidic catalyst and 1,2-dichloroethane (DCE) as the solvent, excellent yields of products can be obtained. The use of β-ketoaldehydes in the Biginelli condensation was reported to yield dihydropyrimidines with an additional carbonyl group (**55**) which provides an additional site for further derivatization [54].

Chirality and Biological Activity

DHPMs 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 [55]. In the calcium channel blocker SQ 32926, for example, it is exclusively the (*R*)-enantiomer that carries the therapeutically desired antihypertensive effect (Figure 9) [56]. In some related DHPM analogs, the individual enantiomers were in fact demonstrated to have opposing

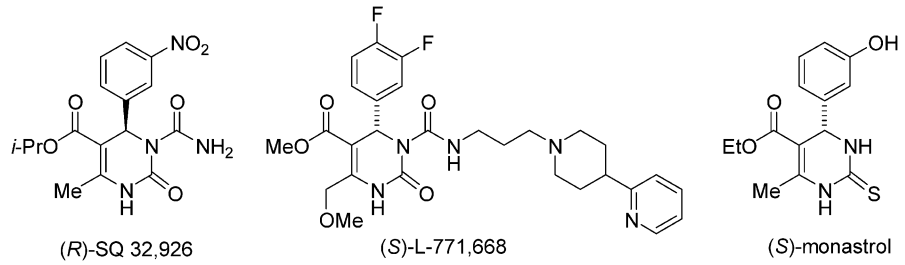


Figure 9. Examples of biologically active DHPM derivatives (more active enantiomer shown).

antagonist/agonist pharmacological activity [57]. For the β_{1A}-selective adrenoceptor antagonist L-771,688 the (*S*)-enantiomer is significant more active than the (*R*)-enantiomer [12], and recent work on the mitotic kinesin Eg5 inhibitor monastrol [58] has shown that the (*S*)-enantiomer is the more potent inhibitor of Eg5 activity [59].

Access to enantiomerically pure DHPMs is therefore of considerable interest and a prerequisite for the development of any drugs in this field. By employing any of the combinatorial strategies summarized above, libraries of DHPMs can be generated in a relatively straightforward fashion. However, all these products would still be racemic and therefore an initial screening will not address possible enantioselective effects on molecular activity. 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 rapidly obtain enantiomerically pure DHPMs. These methods include fractional crystallization techniques involving diastereomeric α-methylbenzylammonium salts [60] or covalently linked derivatives [12, 56, 61], or rely on biocatalytic resolution [62]. Analytically, separation of DHPM derivatives can be readily achieved by enantioselective HPLC using a variety of different chiral stationary phases (CSPs) [63], including "designer-made" CSPs that are based on the principle of "reciprocal" recognition of chirality using the immobilized DHPM derivative **38** (Scheme 11) [24]. Alternatively, chiral separation can also be performed by capillary electrophoresis (CE) with chiral modifiers and buffers [64]. The absolute configuration of enantiomerically pure DHPMs is easily derived from circular dichroism (CD) spectra [65]. Despite the advances made in resolution strategies over the past years rapid access to enantiomerically pure DHPM derivatives for high-throughput screening, *i.e.* by a general asymmetric variation of the Biginelli dihydropyrimidine synthesis has still not been achieved.

Conclusion

In its 110 years of existence, the Biginelli dihydropyrimidine synthesis has evolved from a little-known name reaction developed in the late 19th century, to one of the most often used multicomponent strategies today, successfully making the transition from academic research laboratories to the high-throughput labs of many pharmaceutical and biotech companies. In this context, the reader should be aware that the present review is limited to the published work on the Biginelli reaction, and can not take into account the certainly very large body of innovative unpublished work developed in industrial laboratories. 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 (HTS) techniques.

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