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# Biginelli Multicomponent Reactions in Polymer Science

**Lei Tao, Chongyu Zhu, Yen Wei, and Yuan Zhao**

**Abstract** The Biginelli reaction, a three-component cyclocondensation reaction, is an important member of the multicomponent reaction (MCR) family. The Biginelli reaction is so efficient and shares many similar properties as the recent click reactions. In this chapter, we summarised the current applications of the Biginelli reaction in polymer chemistry including polymer coupling, post polymer modification, and new functional polymer synthesis. We expect this 'old' reaction (>120 years) can draw attention from polymer chemists and play new roles in the polymer science.

**Keywords** Biginelli reaction · Click reaction · MCR · Polymer synthesis and modification · PPM

## Contents



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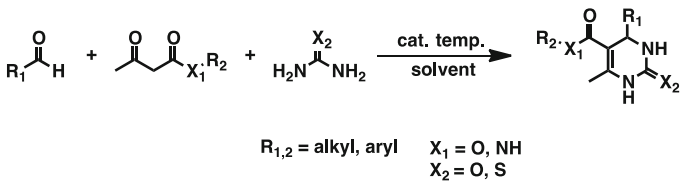



**Scheme 1** The three components of the Biginelli reaction

# 1 The Biginelli Reaction and Its Chemistry

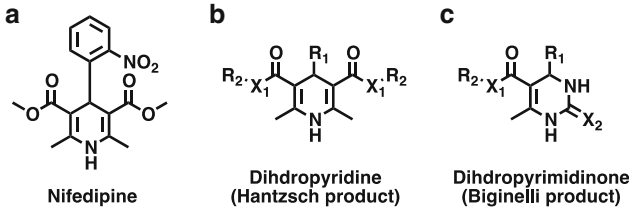
## *1.1 Background of the Biginelli Reaction*

The Biginelli reaction is a member of the multicomponent reaction (MCR) family. It is a three-component cyclocondensation reaction using aldehyde, 1,3-dione, and urea as building blocks and is particularly useful for synthesis of 3,4-dihydro-2(*H*)-pyrimidinone (DHPM) compounds in one pot (Scheme 1).

Although discovered over 100 years ago [1], the Biginelli reaction is still attracting attention because of its potential applications in organic synthesis [2–5] as well as in the pharmaceutical field (especially in drug discovery) [6, 7]. Like other multicomponent reactions, the Biginelli reaction is a powerful tool for synthesis of a large number of compounds because of its easy operation, high efficiency, scalable manufacture, and low cost [4, 5, 8–11]. This robust three-component reaction can produce a complex structure bearing diverse functional groups through a one-pot strategy, with abundant choice of substrates.

Continuing studies of the Biginelli reaction are mainly focused on the synthesis of DHPM compounds and their related pharmaceutical properties [6]. Thanks to its high efficiency, the Biginelli reaction has been applied in the pharmaceutical field to synthesize a library of compounds [12–16]. On the other hand, because the DHPM product contains a heteroaromatic ring structure, it can be used as an aza-analog for other aromatic structures. For example, a derivative of the Biginelli product can be used as an alternative for nifedipine [17, 18], a clinical compound containing a dihydropyridine structure synthesized via the Hantzsch reaction (Scheme 2).

After finding the DHPM structure in some native anti-HIV products (batzelladine A and B) [7, 19], the Biginelli reaction has become popular in drug discovery and drug synthesis. Up to now, the derivatives generated from the Biginelli reaction have shown the potential to treat many diseases [7, 20], such as hypertension [21–23], epilepsy [24], tuberculosis [25], and malaria [26]. Some derivatives were also found to be calcium channel antagonists [6, 18, 21, 23]. Recent data even indicate that Biginelli products and derivatives have activity against viruses [27], bacteria [28, 29], and tumors [30, 31].



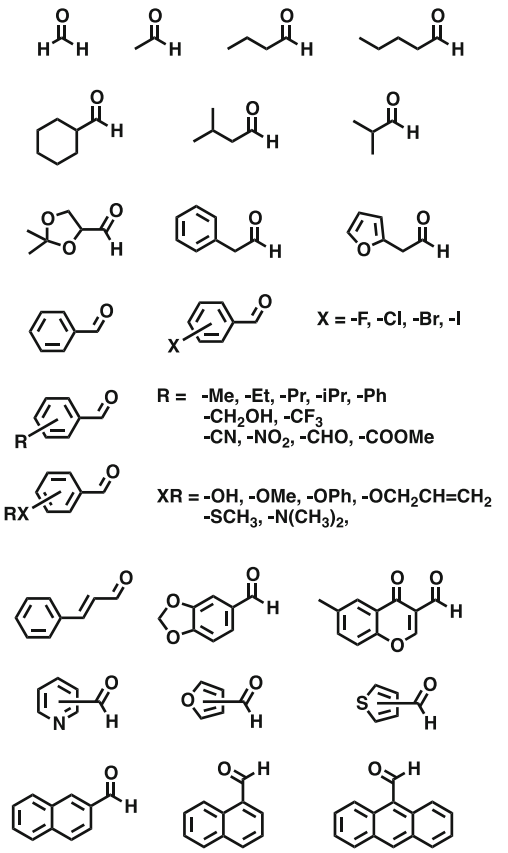

**Scheme 2** The commercial drug nifedipine (**a**) and a comparison between the Hantzsch product (**b**) and the Biginelli product (**c**)

## *1.2 Chemistry of Biginelli Components*

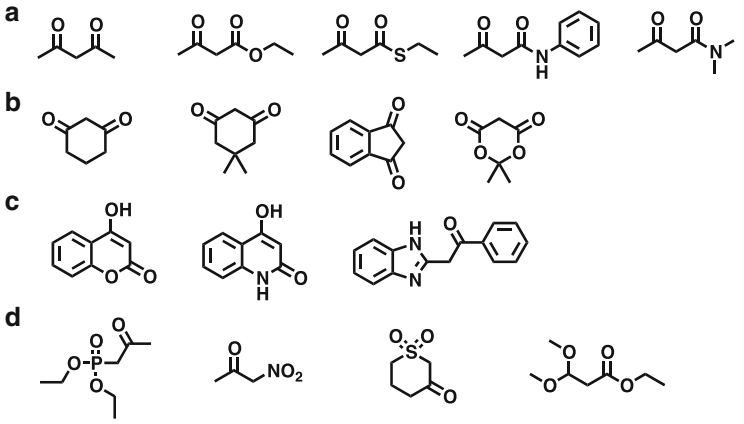
The aldehyde component of the Biginelli reaction can be highly diverse. Both aliphatic and aromatic aldehydes can act as suitable Biginelli components. Apart from the synthetic aldehydes, most of the commercially available aldehyde resources generated from nature (including benzaldehyde [9, 32], cinnamaldehyde [32, 33], and furfural [20, 32]) are proven to be suitable substrates for the Biginelli reaction. A typical library of good aldehyde candidates for the Biginelli reaction is shown in Scheme 3. In addition, the aldehyde group can be easily introduced into some compounds that contain no aldehyde groups through traditional chemistry reactions so that they can be used for the subsequent Biginelli reaction [34].

The rate of the Biginelli reaction can be varied by using different aldehyde substrates. Typically, the reaction rate can be slowed down by a bulky aldehyde under normal conditions [35]. Meanwhile, the functional group on aromatic aldehydes seems to have little effect on the activity of the aldehyde, although an electron-rich aromatic aldehyde might slightly accelerate the reaction rate and increase the yield [36]. Although influenced by various conditions (substrate, catalyst, solvent, and temperature), in general, aromatic aldehydes usually provide a faster reaction rate and a better yield than aliphatic aldehydes [32, 37].

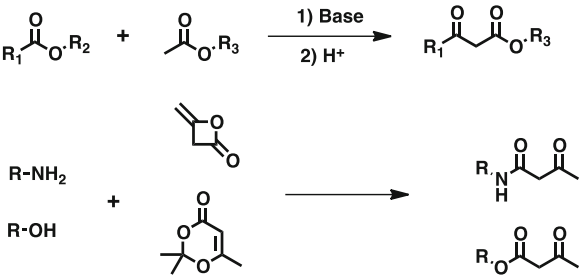
Many compounds can act as the 1,3-dione component of the Biginelli reaction (Scheme 4). Commercially available products such as acetylacetone and ethyl acetoacetate are common 1,3-dione Biginelli components (Scheme 4a). Cyclic 1,3-dione can also participate in the Biginelli reaction. Common examples include 1,3-cyclohexanedione [38], dimedone (5,5-dimethyl-1,3-cyclohexanedione) [39], Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) [40], and 1,3-indanedione [11] (Scheme 4b). Other compounds such as 4-hydroxycoumarin and 4-hydroxyquinolin-2(1*H*)-one can also act as a Biginelli component because they can transform into a 1,3-dione form through keto–enol tautomerization (Scheme 4c) [41, 42]. Apart from normal 1,3-dione compounds and their enol forms, some compounds such as nitroacetone and other ketones with an electron-withdrawing group substituted on the β-position can also perform the Biginelli reaction with high yield (Scheme 4d) [43–46]. Furthermore, the 1,3-dione component can be generated from Claisen condensation or derived from hydroxyl/amine groups by diketene or its alternative acetone adduct, 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (Scheme 5).



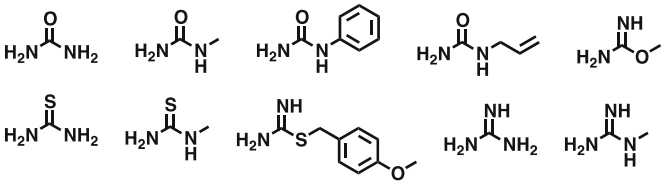

**Scheme 3** Typical aldehydes that are suitable for the Biginelli reactions




**Scheme 4** Suitable 1,3-dione candidates for the Biginelli reaction. (**a**) Linear forms; (**b**) cyclic forms; (**c**) enol forms; and (**d**) ketones with electron-withdrawing group on the β-position




**Scheme 5** Reactions that produce the 1,3-dione unit for the Biginelli reaction



**Scheme 6** Some examples of the urea component for the Biginelli reaction

The choice of the third component is, however, limited in terms of functional variety. In most cases, only urea and thiourea are used as the third component. However, some derivatives, usually monosubstituted, of urea, isourea, and thiourea can also react well in the Biginelli reaction even though they usually require a longer reaction time to provide similar yields [3, 7, 10]. There are some reports that the guanidine group could also be used as reactant to form the Biginelli product under basic conditions [47]. Some urea components used for the Biginelli reaction (urea, isourea, thiourea, guanidine, and their derivatives) are shown in Scheme 6.

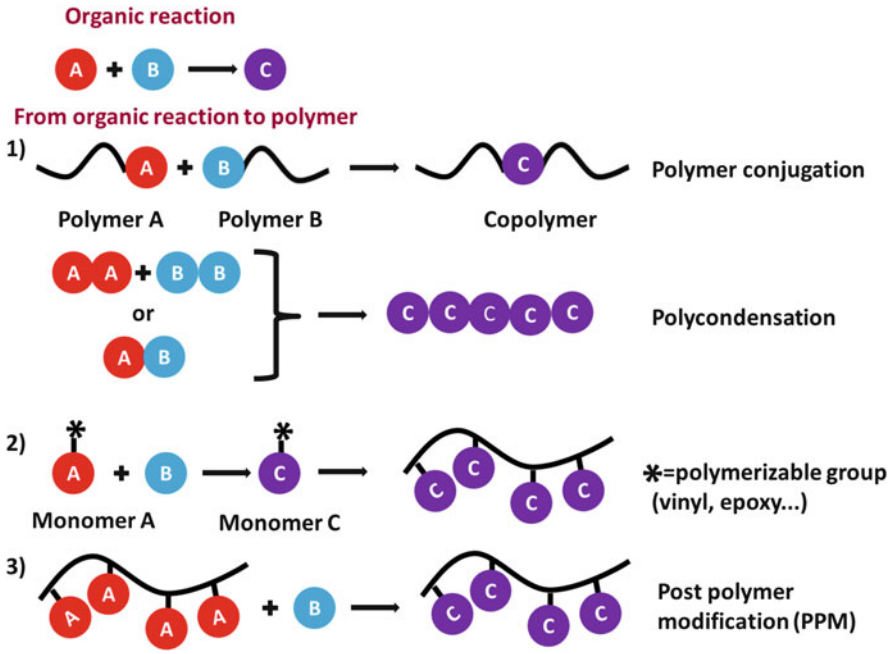
Conditions for the Biginelli reaction have been well studied and developed over the last century [10, 45, 48]. The reaction temperature can be as low as room temperature [49, 50] or as high as heating to reflux [37, 51]. Most solvents, including water [9], ionic liquids [52–54], and low molecular weight polyethylene glycol (PEG) [55], are suitable for the Biginelli reaction. A solvent-free condition is also feasible and can provide higher yield in some circumstances [56–58]. A wide range of organic and inorganic catalysts can catalyze the Biginelli reaction [10]. Other conditions such as ultrasound [59, 60], microwaves [61, 62], or grinding [63, 64] have also been applied to improve this reaction. Recent effort has been focused on the development of more economic and efficient conditions for the Biginelli reaction. With improved conditions (temperature, solvents, catalysts, etc.), a 'greener' Biginelli product can be achieved under environmentally friendly conditions with a high yield [5, 9, 10, 37, 38, 51, 52, 57, 62, 63]. This allows it to work under more biocompatible conditions. A recent report has showed its potential use in biological systems. Under physiological conditions, the Biginelli reaction can smoothly anchor a fluorescence probe onto the cell membrane, indicating the possible application of the Biginelli reaction for cell imaging [34].

Polymer-based catalysts and resins are widely used in many MCRs due to their recyclable and reusable properties. Particularly, use of polymer-supported resins is a powerful tool for organic synthesis because small organic compounds are easily separated from polymers. Therefore, the polymer-support strategy has been widely applied in MCR synthesis, multistep synthesis, and combinatorial synthesis for related pharmaceutical libraries [16, 65, 66]. As a matter of course, polymers have also been applied in the Biginelli reaction. Polymer-based catalysts and polymer-supported resins have been well studied and operated in the synthesis of Biginelli-type products [16, 67–72]. Either insoluble commercial resin (e.g., Wang resin) or soluble polymer (PEG) can act as the polymer support [67, 70]. All three components can be introduced onto the polymers or resins, although 1,3-dione-bound resins and urea-based resins are more commonly used. However, introducing the Biginelli reaction into the polymer field was rarely thought of until now. Therefore, a summary of the applications of the Biginelli reaction in polymer chemistry is given in the next section.

## 2 The Biginelli Reaction in Polymer Chemistry

Introducing organic reactions into polymer chemistry can greatly enrich the polymer family. Through various organic reactions, new structural functional groups can be implanted into the polymer main or side chains, resulting in whole new polymers with distinctive chemical and physical properties, i.e., new functional polymers [73–76]. Generally, there are three approaches to introduction of an organic reaction into the polymer field (Scheme 7): (1) An organic reaction can be performed as a linker. Different polymer chains can be stitched together by an organic reaction into one new polymer, termed a ‘block copolymer.’ Similarly, small molecules (monomers) can be joined together via an organic reaction into a macromolecule, also known as a ‘condensation polymer.’ (2) An organic reaction can be used to synthesize new monomers with both desired functionality and polymerizable groups (vinyl, epoxy groups, etc.). These new monomers can be subsequently polymerized to form a polymer with predesigned side groups. (3) An organic reaction can be used to directly modify the reactive groups on the polymer side chains, adding new functions for the polymer. This process is usually called ‘post-polymerization modification’ (PPM).

Based on the above-mentioned principles, almost all organic reactions could be used for polymer synthesis. However, this is not actually the case. As prerequisites for applicable polymer synthesis (low cost, large scale manufacture, etc.), the chosen organic reactions should have easily available starting materials and high efficiency, with negligible side reactions or side-products, in producing the target functional polymers. Several click reactions such as the thiol–ene/yne reaction, Michael addition, copper-catalyzed azide–alkyne cycloaddition (CuAAC), (hetero) Diels–Alder reaction, and hydroxyl/amine/thiol–isocyanate coupling as well as some enzyme-catalyzed organic reactions such as enzymatic transesterification




**Scheme 7** Three common approaches (*1–3*) for applying an organic reaction in the polymer field

have proved to be powerful tools in the polymer field due to their high efficiency, atom economy, and rapid reaction rate [77–83]. Meanwhile, some MCRs such as the Passerini reaction [84–87], Ugi reaction [88–90], Mannich reaction [91, 92], and Kabachnik–Fields reaction [93–96] have also been introduced into polymer chemistry for synthesis of new functional polymers, demonstrating their potential application in current polymer chemistry.

Of all the MCRs, the Biginelli reaction has been overlooked in the polymer field for a long time. Until now, only a few reports have described this reaction for synthesizing or modifying polymers. As mentioned above, the Biginelli reaction is a highly efficient reaction under mild conditions, with versatile structures and substrates similar to those used in the click reactions, implying that this 'old' reaction could be a useful tool in the polymer field. The high efficiency and yield of the Biginelli reaction can guarantee the quality of the polymer modification. The three components of the Biginelli reaction can be easily introduced and tuned by varying the substrates, offering different choices of modification strategy and product variety. Furthermore, the Biginelli reaction is robust to many other functional groups such as hydroxyl [53], carboxyl [58], alkene [97], alkyne [98, 99], and azide groups [15, 99]. Thus, the Biginelli reaction has the potential to bear with or even cooperate with other reactions to build a one-pot system. In addition, the wide range of reaction temperature and the multiple choices of solvents and catalysts provide an excellent platform to meet the different requirements for polymer

modification and synthesis under various conditions. Some applications of the Biginelli reaction in polymer chemistry are listed as below.

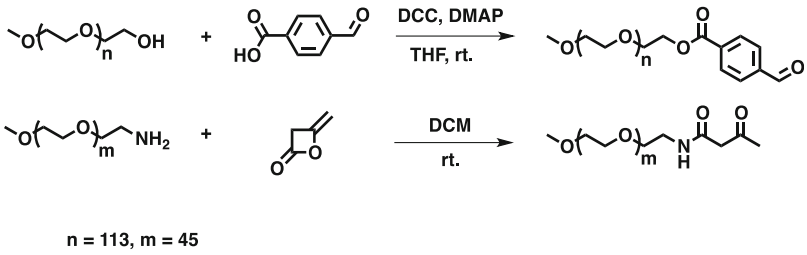
## 2.1 Coupling Reaction

Block copolymers combine different physical or/and chemical properties in one polymer. Hence, some new properties (e.g., amphiphilicity) can be achieved for this type of polymer. Because of their unique properties, copolymers are used everywhere in everyday life. For example, poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) block copolymers (PEO–PPO–PEO, commercially known as Pluronics) are widely used as nonionic surfactants in daily care products. One commercial thermoplastic elastomer is made from styrene–butadiene–styrene (SBS) triblock copolymers.

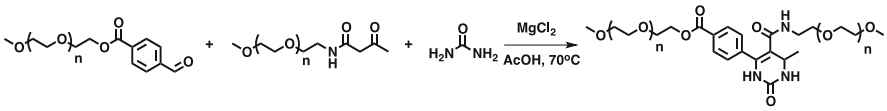
The most straightforward way to make a block copolymer is coupling two different polymers directly through a linkage. However, the direct coupling of different polymer chains is rarely conducted because the reaction often ends up with a mixture of products and unreacted starting polymers. The painful and costly separation of the mixture is usually unavoidable. Therefore, a highly efficient coupling reaction is crucial for successfully stitching different polymers together. The popular click reactions seem to provide a solution [74, 81, 100–102]. Because the Biginelli reaction shows very similar properties to current click reactions, especially under concentrated conditions, it might be able to smoothly conjugate two polymers.

To demonstrate the effective coupling capability of the Biginelli reaction, the linkage of two methyl polyethylene glycol (mPEG) chains via the Biginelli reaction was conducted. Derivatization of the Biginelli units can be easily obtained from either hydroxyl groups or amine groups through traditional reactions. Using commercially available compounds, 4-formylbenzoic acid and diketene, the two Biginelli components aldehyde and 1,3-dione, respectively, were first introduced onto two mPEGs, (Scheme 8).

Afterwards, the two mPEG chains were linked by a coupling agent (in this case, urea) to test the coupling efficiency (Scheme 9). To push the coupling process,




**Scheme 8** Modification of mPEG using a traditional esterification process



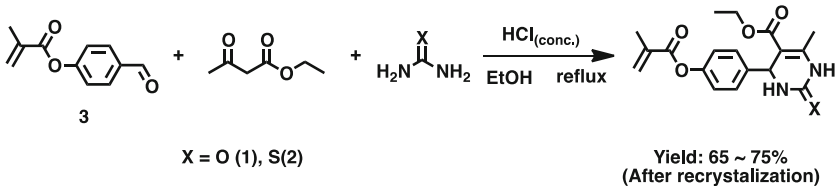

**Scheme 9** Coupling reaction between two mPEG chains

excess urea was used. $MgCl_2$ was chosen as the catalyst and acetic acid (AcOH) was used as the solvent to accomplish the Biginelli reaction according to the literature [37]. The temperature was set at 70°C.

The coupling reaction proceeded smoothly under relatively mild conditions with the aldehyde/1,3-dione ratio near to 1:1. The reaction was monitored by gel permeation chromatography (GPC) and found to be completed within 3 h [33]. As reported in the literature, to produce a similar copolymer from two polymer chains via accepted click reactions (CuAAC, thiol-maleimide, etc.) typically takes from 4 h to 2 days, depending on various conditions such as room temperature [74, 102], heating [81, 100], or photomediation [101]. Thus, the Biginelli reaction can stitch polymer chains together as efficiently as traditional click reactions.

## *2.2 Biginelli Side-Group Polymers*

Biomacromolecules like proteins are the fundamental functional material in nature. Although most proteins share similar backbones, they can act in multiple roles in nature, for example, as catalysts (enzymes), building blocks (collagen), and signal proteins, as a result of differences in the side groups (residues) and in their sequence. Sometimes a small change in a side group on the active site can dramatically change the activity of a protein [103, 104], alter function [105], or cause disorder [106]. Furthermore, the structure of each protein is also affected by the residues on the protein [107]. It can be said that the function of a biomacromolecule is mainly determined by its side groups. This principle is also applicable to synthetic polymers. Functional polymers with different side groups have proved to be useful materials, such as responsive materials [108, 109] and gene delivery materials [110, 111]. Therefore, the easy and effective synthesis of a functional side-chain polymer is a challenging task. So far, the two most widely used approaches are functional monomer polymerization and PPM. Functional monomer polymerization is a two-step approach that requires synthesis of the monomer with predesigned functional group and subsequent polymerization of the monomers. This two-step approach usually provides high functionality for the polymer side chains. PPM, on the other hand, is a one-step approach that can directly modify the side chains of the polymer precursor.




**Scheme 10** Synthesis from pre-monomer (**3**) of two Biginelli monomers, with atom X being oxygen (**1**) or sulfur (**2**)

### 2.2.1 Polymerization of the Biginelli Monomer

Polymerization of synthesized monomers with new functionality is a widely used strategy. The desired functional groups can be introduced accurately and efficiently by the monomers onto the polymer side chains. The Biginelli product DHPM has been well studied in the last few decades and shows some unique properties [6]. Therefore, DHPM polymers were synthesized to obtain a better understanding of the functions of the DHPM structures on the polymer side groups [112]. Two DHPM monomers (**1** and **2** in Scheme 10) were synthesized via the Biginelli reaction, being further polymerized to obtain a polymer with DHPM side groups.

First, a homemade 'pre-monomer', 4-formylphenyl methacrylate **3**, was synthesized to introduce the aldehyde component for conducting the Biginelli reaction. The monomers **1** and **2** were then obtained through reacting the pre-monomers **3** with ethyl acetoacetate and either urea or thiourea, respectively. With the help of a catalytic amount of concentrated hydrochloride (HCl), the two monomers were successfully synthesized in refluxed ethanol at moderate yields by recrystallization.

The DHPM monomers were then polymerized into polymers via conventional radical polymerization initiated by AIBN under argon atmosphere. Both DHPM monomers were successfully polymerized to generate the Biginelli side-group polymers, indicating that the DHPM unit did not interfere with formation of the radicals and had no negative effect on the polymerization process.

The Biginelli side-group polymers, interestingly, showed a pH-dependent color change property. The polymers were white at neutral pH (pH 7) but turned pale yellow at a strongly acidic pH (pH 1) and became yellow in strongly basic conditions (pH 12). The reason for the color change at basic pH is mainly attributed to deprotonation of the NH groups on the DHPM structure. The acid-induced color change, on the other hand, is a result of the formation of hydrogen bonds between the side chains. Because both color changes are reversible, the DHPM polymers could be potential pH detectors or biosensors.

### 2.2.2 Post-polymerization Modification

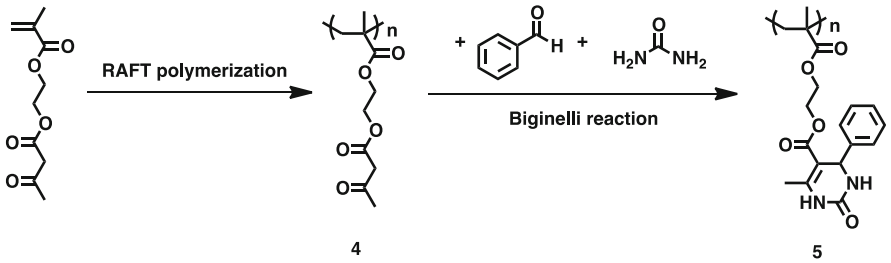
As well as the polymerization of functional monomers, PPM of a readily available polymer is also a well-applied approach. For example, the commercially available polymer poly(vinyl alcohol) (PVA) was synthesized by hydrolysis of the side

chains of synthetic poly(vinyl acetate). Another example is the biomacromolecule derivative chitosan, which is produced by the deacetylation of chitin.

Limited by the bulky size of the polymer and the viscous system caused by the existence of the polymer, PPM using traditional reactions (esterification, oxidation, reduction, etc.) usually ends up with significant unreacted residues, leading to less functionality than obtained by the functional monomer polymerization approach. However, because of its universality, PPM is still a very useful tool, especially for industrial manufacture, for obtaining functionalized polymers or biomacromolecules. PPM can be applied for most polymers, although some functional monomers cannot be directly polymerized to form functional side-group polymers because they act as inhibitors during polymerization. In addition, even if the functional monomers can be polymerized, the final polymer chain length is sometimes limited and cannot be controlled because of hindrance from the size of the monomer or poor solubility of the polymer. However, similar desired functional side-group polymers of a certain length can be achieved through PPM. The chain length of the polymer is sometimes essential for properties such as mechanical properties [113], LCST behavior [114, 115], and bioclearance/degradable lifetime [116, 117].

Recently, scientists have been looking for a better modification motif to improve the functionality of polymer. Modern efficient reactions, such as click reactions, have been chosen and applied to achieve efficient PPM [118]. Because the Biginelli reaction has proved to be a powerful tool for easily achieving complex DHPM structures with high yield, this efficient reaction can also be a potential tool for polymer modification.

A polymer with 1,3-dione side groups was synthesized as the model polymer precursor [34]. The polymer was first synthesized from the commercially available monomer, 2-(acetoacetoxy)ethyl methacrylate (AEMA) through reversible addition–fragmentation chain transfer (RAFT) polymerization. A relatively high molecular weight poly(AEMA) polymer **4** with a degree of polymerization of around 102 was obtained (number-average molecular weight as measured by NMR, $M_{\mathrm{nNMR}} \sim 21{,}900$; as measured by GPC, $M_{\mathrm{nGPC}} \sim 44{,}900$; polydispersity index, PDI ~ 1.18) for the next PPM. To evaluate the efficiency of PPM via the Biginelli reaction, benzaldehyde and urea were chosen as the other two Biginelli components to react with the 1,3-dione side-group polymer (Scheme 11). Slight




**Scheme 11** Sequential synthesis of poly(AEMA) (**4**) and the final Biginelli side-group polymer (**5**)

excess (1.5 equivalents) of these two components were used to accelerate the reaction process and push to completion.

With the help of $MgCl_2$/AcOH catalyst–solvent system, the Biginelli reaction proceeded smoothly on the polymer side groups at 70°C. $^1$H NMR was used to monitor the reaction. The characteristic peaks of the Biginelli structure, two CONH peaks (7.73 and 9.27 ppm), CH (5.16 ppm) on the heteroaromatic ring, and the protons of the benzene ring (7.00–7.40 ppm), formed gradually while the methylene peak of the 1,3-dione group (3.62 ppm) from the polymer precursor disappeared accordingly. Performed similarly to the click reactions, PPM via the Biginelli reaction was nearly complete (>99%) with almost no 1,3-dione left on the side groups after 5 h of reaction. The 1,3-dione groups were transformed successfully into the DHPM Biginelli structures with no visible side reactions. After a simple wash step, the final pure modified polymer **5** was obtained with increased molecular weight and narrow polydispersity ($M_{nGPC}$ ~ 55,300, PDI ~ 1.15), indicating that the backbone of the polymer survived during PPM.

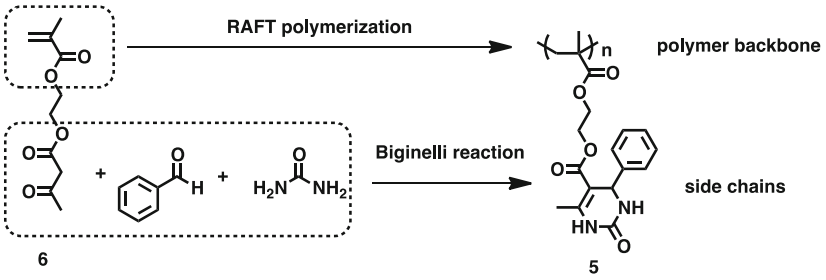
### 2.2.3 One-Pot Polymerization

As well as functional monomer polymerization and PPM, one-pot polymerization has also been used to obtain a highly functionalized polymer. One-pot polymerization combines polymerization with other compatible reactions to achieve the target new polymer in the same reactor. In contrast to functional monomer polymerization, one-pot polymerization can form the functional monomer in situ and thus avoid the purification step necessary with functional monomer synthesis. This approach also avoids hindrance from the polymer backbone, leading to a higher modification yield compared with the normal PPM approach. With less time and cost, the desired polymer can be achieved and functionalized with a high yield in one pot. Some reactions such as the CuAAC click reaction and enzymatic transesterification have been used for construction of a one-pot polymerization system with controlled/living radical polymerization approaches to achieve new functional polymers [119–125].

One-pot polymerization requires the collaborating reactions to proceed smoothly under the polymerization conditions while having negligible or no interference with the polymerization process. In other words, tolerance between the functional groups of each component of the polymerization is essential for this strategy. Therefore, choosing a suitable reaction to cooperate with the polymerization is very important.

The variety of substrate choices for the Biginelli reaction and its good tolerance to many functional groups offers the opportunity to use it in cooperation with other reactions in one pot. In addition, the wide choices of reaction temperature, catalysts, and solvents for the Biginelli reaction are also helpful in matching with the polymerization process.

To demonstrate the advantages of the Biginelli reaction, the RAFT polymerization was again chosen for one-pot polymerization. In this case, thanks to the




**Scheme 12** One-pot polymerization of AEMA monomer (**6**) to form a Biginelli side-group polymer (**5**)

diversity of the Biginelli components, a widely used commercially available monomer, AEMA **6**, was found to be an ideal candidate. The vinyl group of AEMA can be polymerized to form the polymer backbone via RAFT polymerization, and the 1,3-dione can be converted into the DHPM structure through the Biginelli reaction (Scheme 12).

The $MgCl_2$/AcOH catalyst–solvent system was used for the Biginelli reaction because it has proved to be suitable for the Biginelli reaction and harmless to the RAFT polymerization. The temperature was set at 70°C to match the polymerization process while still allows the Biginelli reaction to occur. The Biginelli reaction under these conditions can still proceed rapidly. In the first hour, benzaldehyde and urea reacted with the AEMA monomer, converting most of the AEMA monomers into Biginelli-type monomers; the total polymerization yield of both monomers was below 20%. The subsequent polymerization can be seen as homopolymerization of the newly formed Biginelli-type monomers. The kinetic plot showed that the RAFT polymerization proceeded smoothly and was well controlled with narrow dispersity (PDI ~ 1.13), suggesting that the DHPM structure has no negative effect on the formation or growth of the radical species [33]. In other words, the Biginelli reaction and its product do not inhibit or interrupt the polymerization process.

The purified polymer **5** showed side chains with almost only Biginelli-type structures, suggesting that the AEMA monomers polymerized into the polymer chain during the first hour can still be converted into Biginelli-type structures, as well as the free AEMA in solution.

## 3 Conclusion and Perspective

The Biginelli reaction, as an efficient and green reaction, is ideal for both polymer modification and synthesis. It can serve as a linker to join two polymers together with high yield. PPM using this ‘old’ reaction is also successful, indicating its clickable properties. The Biginelli reaction can even cooperate with the sensitive radical polymerization in one-pot, displaying rapid reaction rate and good

compatibility. All these properties of the Biginelli reaction indicate a similarity to recent click reactions. Furthermore, the Biginelli reaction is a three-component reaction, which could provide an even more complex and functionalized product. The Biginelli reaction could also be useful in synthesizing other functional polymers such as condensation polymers, hyperbranched polymers, and dendrimers. Furthermore, the similarity between the structure of Biginelli product DHPM and nucleobases such as cytosine and thymine could deliver features like self-assembly or biomimicry to the polymers. We believe that with more and more synthesized Biginelli-type polymers, this old reaction will display new vitality in polymer science.

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