Training the old dog new tricks: the applications of the Biginelli reaction in polymer chemistry

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Recently, the Biginelli reaction, one of the most famous multicomponent reactions, has been introduced into the polymer chemistry to highly efficiently synthesize some interesting functional polymers. In this mini-review, several applications of the Biginelli reaction in polymer chemistry have been summarized, including polycondensation, post-polymerization modification, one-pot synthesis of well-defined polymer, etc. Meanwhile, the utilization of the Biginelli reaction in material science and chemical biology, and the future development of the Biginelli reaction in polymer chemistry have also been discussed.

Biginelli reaction, functional polymer synthesis, polycondensation

1   Introduction

Polymer chemistry was born when people looked at an ordinary organic reaction, the condensation reaction between phenol and formaldehyde, from the perspective of material. The therefore obtained phenolic resin achieved huge market success, and opened up the new era of synthetic polymers. Since then, a bridge between laboratorial organic reactions and practical applications has been built up, and more and more types of polymers were synthesized via different organic reactions. The new appeared polyester, polyurethane polyamide, etc. enrich the family of polymeric products, and greatly improve people's life.

Different from organic chemists who are keen on finding new reactions or improving reactions, polymer chemists tend to choose existing efficient chemical reactions to large-scalely prepare valuable polymeric materials for application. Nowadays, various efficient organic reactions have been introduced into polymer chemistry to synthesize new functional polymers through different polymerization strategies, such as polycondensation [1–3], post-polymerization modification (PPM) [4–6], one-pot synthesis [7–12], and polymer coupling [13,14]. As a trend of modern polymer chemistry, screening organic reactions for polymer synthesis is a feasible strategy to solve some thorny synthesis problems in polymer chemistry. For example, the high temperature and high vacuum are usually unavoidable when common coupling reactions are used to prepare polycondensates. However, polycondensation can be carried out much easier under relatively mild conditions via some click reactions, like Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction [15–17], thiol-ene addition reactions [18–20], (hetro) Diels-Alder (D-A) reactions [21,22], suggesting the organic chemistry a great treasure to bring fresh opinion and technology to polymer chemistry.

Encouraged by the success of click reactions in polymer

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chemistry, many other organic reactions have also been reassessed from the angle of polymer synthesis. Among them, multicomponent reactions (MCRs) show distinctive attractions.

MCRs have a long history since Strecker's synthesis of amino acids in 1850 [23,24]. Reactions starting from three or more reactants to generate a single product which contains most atoms of substrates are defined as MCRs. Since Meier *et al*. [25] firstly used the famous tri-component Passerini reaction in monomer synthesis and polycondensation, more and more MCRs, such as the Ugi reaction [26–30], the Biginelli reaction [31–33], the Hantzsch reaction [34–36], the Kabachnik-Fields (K-F) reaction [37–39], the Mannich reaction [40–43], the thiolactone-based reaction [44–47] have been developed for functional polymer syntheses. As more than two functional groups can be combined together and new functional group can be formed via MCRs, MCRs have unique superiority in the synthesis of sophisticated structural or multi-functional polymers.

As one of the most famous MCRs, the Biginelli reaction has been detailed studied for more than a century, and its efficiency, selectivity and easy operation have been repeatedly verified. Biginelli reaction is named by Pietro Biginelli [48,49] who firstly reported the reaction in 1891. The Biginelli reaction is a tri-component reaction involving an aldehyde, a β-ketoester and a urea or a thiourea to form a 3,4-dihydropyrimidin-2(1*H*)-ones (DHPM) while only losing two molecules of water as the byproduct (Figure 1(a)). The Biginelli reaction has wide range of substrates and usually occurs under mild heating condition with Lewis acids as catalysts [50,51]. Both aromatic aldehyde and aliphatic aldehyde can be used as excellent aldehyde substrates, and electron rich aromatic aldehyde can facilitate the reaction [52]. β-Ketoester and its variants, such as 1,3-cyclohexanedione derivatives [53], some keto-enol tautomerization derivatives [54] and β-ketoester derivatives with heteroatom [55] have high reactivity as the module of the Biginelli reaction. The third component has some limitation and usually is urea, isourea, thiourea, guanidine or their derivatives [56]
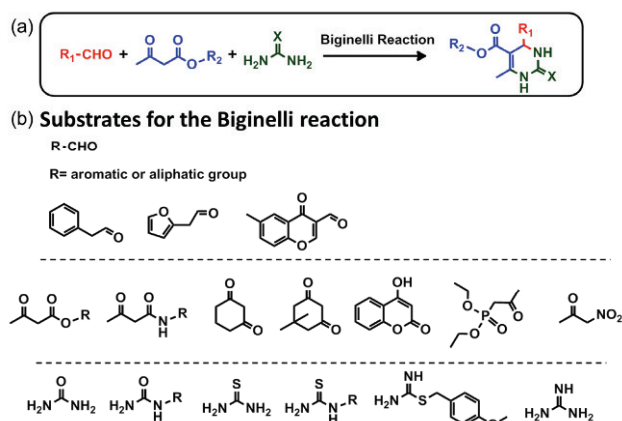
(Figure 1(b)).

Since its appearance, the Biginelli reaction has been applied for drug discovery due to the pharmaceutical activity of DHPM structure. The DHPM derivatives generated from the Biginelli reaction have potentials as calcium antagonists [57,58], hypotensors [59,60] and anticarcinogens etc. [61,62], some of them have also been found the activities against virus and bacteria [63–65]. However, the efficient and robust Biginelli reaction used to be appreciated by organic chemists during the facile synthesis of small molecules. It is ignored that the Biginelli reaction has great value in functional polymer synthesis, a new field where the Biginelli reaction may achieve other successes. Here, in this mini review, we summarize the recent progress on the utilization of the Biginelli reaction in polymer chemistry, including polycondensation, PPM, one-pot synthesis, and we also make a brief introduction on the applications of new functional polymers synthesized via the Biginelli reaction and discuss about the future development of the Biginelli reaction in polymer chemistry.

2 Polycondensation and the properties of DHPM group

Polycondesation is a common method to get polymers with high molecular weights. Nowadays, most well-developed polycondensations are dehydration reactions, i.e. two molecules join together with water losing. As abovementioned, the highly efficient click reactions enrich the reaction family for polycondensation. Also, some MCRs have also been used for the syntheses of new functional polycondensates, such as the Passerini reaction, the Ugi reaction, the K-F reaction and the Biginelli reaction [26,66–69].

As its substrates are abundant and easily obtained, the Biginelli reaction is suitable for polycondensation and the following probable industrial production. In 2015, Tao *et al*. [32] demonstrated a very efficient polycondensation to synthesize poly(DHPMs) in a medium scale via the Biginelli reaction for the first time. The AB-type monomer can be synthesized in a quite large scale (~60 g), meeting the prerequisite for probable manufacture. From the gel permeation chromatography (GPC) trace, the Biginelli polycondesation of the AB-type monomer was found to almost finish in only 1 h. The degree of polymerization (DP) of final polymer is calculated by ^{1}H NMR as about 84, indicating the Biginelli an efficient coupling tool to successfully generate polycondensates (Figure 2).

Through the Biginelli polycondensation, a new functional polymer containing DHPM group in the main chain has been prepared. The DHPM moiety gives some interesting properties to the polymer. For example, Tao *et al*. [32] discovered their poly(DHPM)s have the ability to glue metals. The polymer with DHPM group showed much stronger metal interaction than the common polyester counterpart via
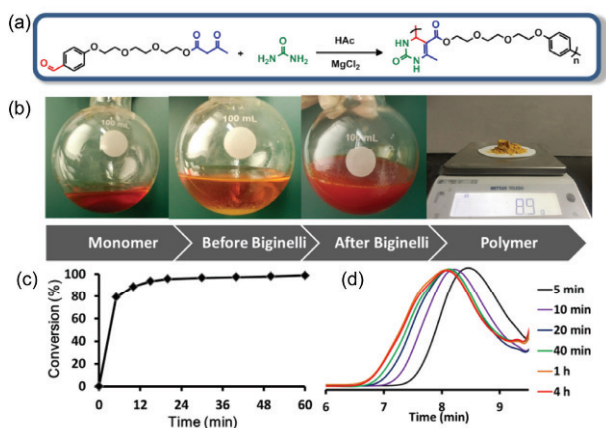

Figure 1 (a) The Biginelli reaction; (b) substrates for the Biginelli reaction.

Figure 2 The Biginelli polycondensation of monomer AB and urea. (a) Reaction conditions: [monmer AB]/[urea]/[magnesium chloride]=1:2:0.1, acetic acid as solvent, 100 °C; (b) the photos of monomer (10 g), the polymerization system before and after the Biginelli reaction, and the obtained polymer; (c) the conversions of Biginelli reaction; (d) GPC tracking of the condensation polymerization. Reprinted with permission from Ref. [32] Copyright © 2015, Royal Society of Chemistry (color online).

single-molecule force spectroscopy (SMFS) measurement. They optimized the reaction conditions, and found when an A_2B_2 monomer (with two aldehyde groups and two β-ketoester groups) was used, two brass sheets can be bonded together via the *in situ* Biginelli polycondensation while the crosslinked network helps increase the adhesion strength. As a surprising result, 1 cm^2 bonding area with 40 mg polymer can easily bear an object with the weight of 27 kg or more (Figure 3).
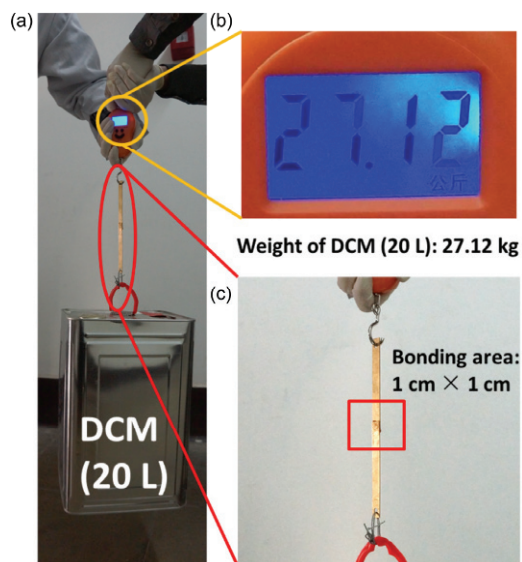
The DHPM group is rigid; therefore, the polycondensates

Figure 3 Using bonded brass to lift heavy objects. (a) Photo of lifting a barrel of DCM (20 L, ~27 kg) with bonded brass sheets; (b) the enlarged photo of spring balance readings; (c) the enlarged photo of bonded brass sheets. Reprinted with permission from ref. [32] Copyright © 2015, Royal Society of Chemistry (color online).

constructed through the DHPM linkage have high glass transition temperature (T_g). In 2016, Meier *et al.* [70] used some renewable resources to prepare two bifunctional monomers for the following Biginelli polycondensation. A series of poly(DHPMs) were synthesized and the T_gs have been investigated, and the T_g of some polymers can be up to 203 °C (Figure 4), also suggesting the new function stemming from the new molecular structure.

3　PPM of the Biginelli polycondensates

Post-polymerization modification (PPM) is one of the most important methods to prepare functional polymers, and it is usually performed by the modification of main chain, side chain or end group of polymers [71,72]. When the thiourea instead of urea participates in the Biginelli reaction, the generated DHPM group contains thiourea moiety, thus can be used as a reactive site for following PPM. In 2015, Tao *et al.* [33] synthesized a Biginelli polycondensate with thiourea and an AB monomer. The parent poly (DHPM) (**P1**, Figure 5) can be modified by halogen compounds to generate new functional polymers as the daughter polymers (**P2**, **P3**, **P4**, Figure 5). Furthermore, those daughter polymers also have reactivity for next PPM to get other functional polymers [33] (**P2′**, **P3′**, Figure 5). The efficiency of PPM is almost 100%, indicating the Biginelli polycondensates can be regarded as versatile platform for the synthesis of functional polymers. The PPM of the Biginelli polycondensate successfully adds new functional groups to the original polymers. Also, it alters some physical characteristics of polymers, such as T_g, which is attributed to flexible chains modified to the parent polymer. Optical properties of polymer can be changed by PPM as well. For example, a new
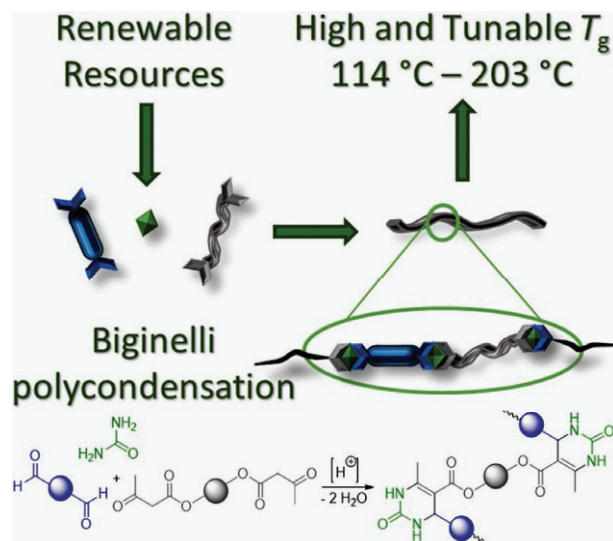

Figure 4 Biginelli polycondensation with renewable resources and the high T_g of polymers. Reprinted with permission from ref. [70] Copyright © 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim (color online).
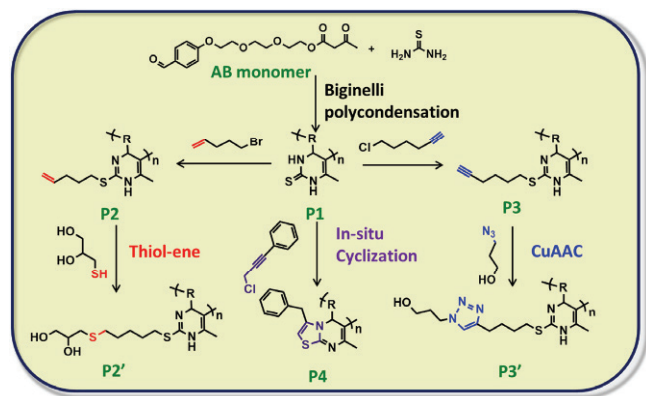
Figure 5 Preparation of new functional polymers through successive PPM of Biginelli polycondensate. Reprinted with permission from ref. [33] Copyright © 2015, American Chemical Society (color online).

fluorescent heterocycle can form by PPM via *in-situ* cyclization (**P4**, Figure 5), which changed the wavelength of UV absorption (from 310 to 390 nm) and emission wavelength (from 480 to 518 nm) of the parent polymer.

Besides, the Biginelli reaction has also been utilized to modify the side chain of polymers as well as the conjugation between two polymers [31], verifying the unrivalled efficiency of the Biginelli reaction.

4 One-pot strategy to synthesize functional polymers via Biginelli reaction and RAFT polymerization

One-pot synthesis is an important strategy which can observably improve the efficiency of synthesis. By combining two or more successive reactions into one procedure to avoid the laborious separation and the purification of intermediate chemical compounds, one-pot synthesis strategy can always save time and increase the reaction yield compared to the multi-step procedure. In polymer chemistry, some elegant researches suggested the monomer synthesis and polymerization can sometimes be subjected in one reactor to omit the monomer purification, which requires both reactions (monomer synthesis, polymerization) compatible and non-interfering.

The Biginelli reaction is the first MCR applied in one-pot synthesis of functional polymer [31]. In 2013, Tao *et al.* [31] chose the commercial 2-(acetoacetoxy)ethyl methacrylate (AEMA) as the monomer and the β-ketoester module for the Biginelli reaction, thus combined the Biginelli reaction and the reversible addition-fragmentation chain-transfer (RAFT) polymerization in one-pot to synthesize Biginelli-type polymer. From the kinetics study, the Biginelli reaction almost finished in 2 h. Meanwhile, the molecular weights of the polymers increased linearly versus monomer conversions and the polydispersity indices (PDIs) kept narrow. All those indicate the RAFT polymerization is unaf-

fected by the Biginelli reaction. The final polymer has well-controlled structure (predesigned molecular weight, narrow PDI), and the β-ketoester side group has been completely converted to DHPM group, suggesting the successful construction of Biginelli-RAFT system (Figure 6).

Moreover, some other MCRs, such as the Hantzsch reaction, the K-F reaction, the enzymatic-CuAAC reaction, have been introduced to combine with controlled radical polymerization (CRP), leading to a series of MCR-CRP systems [9,11,73].

5 Other applications

Besides generation of the specific DHPM group, the highly efficient and robust Biginelli reaction can also been used as a reliable coupling tool and has various applications in polymer science, material science and even chemical biology.

In 2015, the Biginelli reaction was applied in the surface modification of carbon nanotubes (CNTs) by Tao *et al.* [74]. As a famous one-dimensional nano-material, CNTs have light weight, perfect hexagon structure connection, and many superb mechanical, electrical and chemical properties [75,76]. In recent years, with the deeper research of the CNTs and nano-materials, broader application prospects of CNTs also constantly emerge. However, the poor solubility
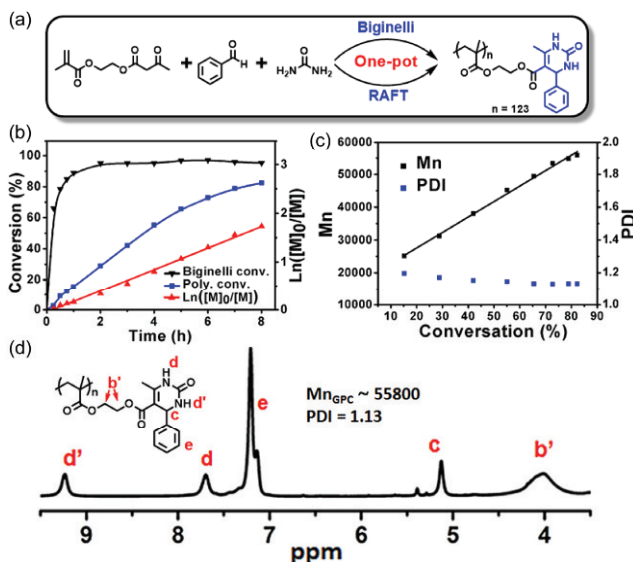

Figure 6 One-pot synthesis of Biginelli-type polymer. (a) Reaction condition: [AEMA]/[benzaldehyde]/[urea]/[MgCl$_2$]=1:1.5:1.5:0.1, [AEMA]/[CTA]/[AIBN]=150:1:0.3, acetic acid as solvent, 70 °C, 8 h. CTA: chain transfer agent, 4-cyano-4-(ethylthiocarbonothioylthio) pentanoic acid; AIBN: 2,2′-azodiisobutyronitrile; (b) the conversions of Biginelli reaction (black) and RAFT polymerization (blue), and the kinetic plots (red) of RAFT polymerization during the one-pot process; (c) molecular weights and PDIs versus monomer conversions; (d) ^{1}H NMR spectra (DMSO-d_6, 400 MHz, portion) of the final polymer. Reprinted with permission from ref. [31] Copyright © 2013, Royal Society of Chemistry (color online).

of CNTs in both aqueous and organic solvents limits their application. Therefore, many methods have been developed to prepare polymer-CNT nanocomposites to solve that problem. Normally, "grafting to" and "grafting from" are common methods to prepare polymer-CNTs nanocomposites [77–81]. In Tao's research, "grafting to" was chosen because of its easy operation and suitability for large scale manufacture. Polymers (poly(ethylene glycol) (PEG) and poly(*N*-isopropylacrylamide) (PNIPAM)) with β-ketoester end group were synthesized by PPM and RAFT polymerization, respectively. Then, noncovalent π-π stacking and the Biginelli reaction were simultaneously performed to obtain polymer-CNT complexes in a shot. The following Fourier translation infrared spectroscopy (FT-IR), thermal gravimetric analysis (TGA) and transmission electron microscopy (TEM) image confirmed the successful preparation of polymer-CNT nanocomposites. Both polymer-CNTs nanocomposites have excellent solubility in different solvents. Besides, PNIPAM-CNT nanocomposite remains the thermosensitivity of PNIPAM. Thus, it can repeatedly dissolve in cold water and precipitate in hot water (Figure 7). This one-pot strategy combining "grafting to" and polymer chain end modification is easy for operation, and may be a general method to modify different carbon-based nanomaterials.

For another example, the Biginelli reaction is also applied in chemical biology. Live cell imaging can provide important information about cell physiological state. Some covalently attaching fluorescent probe can make visual glucans on cell surface. Because of their high efficiency and bioorthogonality, click reactions such as strain-promoted alkyne-azide cycloadditions (SPAAC) [82], CuAAC [83], have been used as splicer between fluorescent probe and glycans. In 2013, Tao *et al.* [31] introduced the Biginelli reaction into this area. β-Ketoester modified glucosamine

(dione-Glu) was introduced onto A549 cell surface. Whereafter, a water-soluble fluorescent probe with aldehyde group (NBD-CHO) and urea were added into the cell culture media and the Biginelli reaction occurred under catalyst-free condition to conjugate the fluorescent probe onto cell surface (Figure 8(c)). Meanwhile, none fluorescent signal was observed in the controls (without urea or dione-Glu) (Figure 8(d, e)), further confirming the existence of the Biginelli reaction on the cell surface. The excellent cell survival and the bright cell imaging result indicate the Biginelli reaction is a bioorthogonal reaction and might be applied in the modification of other biomolecules, such as proteins, DNA/RNAs.

6 Conclusions and perspectives

MCRs have been regarded as the "click 2.0 reactions" to synthesize new functional polymers [84]. Actually, some highly efficient MCRs, the Biginelli reaction for example, are modular, facile, highly efficient, atom-economical, and only generate environment-friendly byproducts, highly similar with traditional two-component click reactions. Those MCRs could also be recognized as new members of click reactions.

In this mini review, we summarize some applications of Biginelli reaction in polycondensation, PPM, one-pot synthesis strategy, etc. The high efficiency of Biginelli reaction ensures the successful synthesis of these functional polymers. Besides, the new generated DHPM group attaches some new excellent features to the polymers. Some primary applications of Biginelli reaction are described as well to show its unique charm in material science and chemical biology.
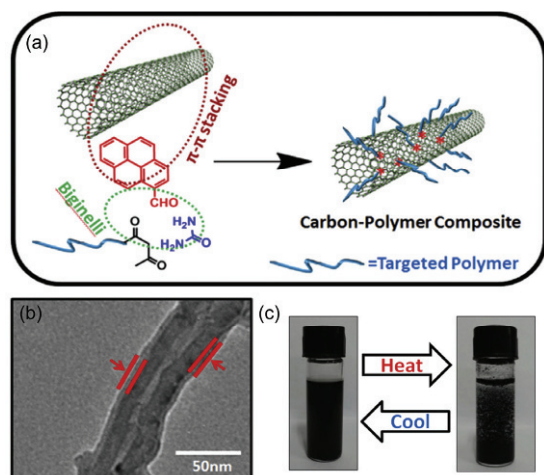
Since aldehydes, β-ketoesters and urea are all common

Figure 7 (a) One-pot polymer modification of CNTs through Biginelli reaction and π-π stacking; (b) TEM characterization of CNT-PNIPAM; (c) Influence of temperature on the water dispersity of CNT-PNIPAM. Reprinted with permission from ref. [74] Copyright © 2015 Elsevier Ltd. All rights reserved (color online).
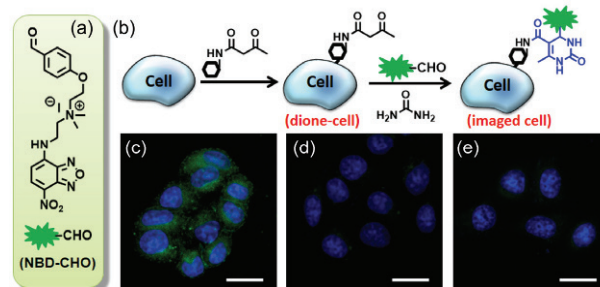

Figure 8 Bioorthogonal cell fluorescence imaging performed via Biginelli reaction. (a) Fluorescent tag: NBD-CHO; (b) cell-imaging through Biginelli reaction: the native cells are incubated with dione-Glu to get dione-labeled cells (dione-cells), then treated with urea and NBD-CHO to achieve imaged cell; (c–e) confocal laser scanning microscopy (CLSM) images of cells through different treatment. (c) Dione-cells treated with urea and NBD-CHO; (d) control 1: dione-cells treated with NBD-CHO only; (e) control 2: native cells treated with urea and NBD-CHO. Green=NBD-CHO channel; Blue=Hoechst 33258 channel; Scale bar=20 μm. Reprinted with permission from ref. [31] Copyright © 2013, Royal Society of Chemistry (color online).

raw materials, the efficient Biginelli reaction may be easy to be applied in further large scale manufacture and play important roles in many fields. Polymers with different functional groups or complex architectures will be considered by using this fantasy MCR. However, some limitations make Biginelli reaction not omnipotent. Due to the limited choices of urea derivatives, it is difficult to directly obtain multifunctional polymers via Biginelli reaction. Luckily, some other MCRs also can be chosen to prepare functional polymers, such as mercaptoacetic acid locking imine (MALI) reaction [85,86] and the Ugi reaction, etc. For example, the Ugi reaction has been applied in multifunctional polymers synthesis, (co)polymers with different functional groups can be easily obtained through polymer conjugation via the Ugi reaction [27]. Besides, other MCRs have different applications in polymer chemistry with their unique features, affording people more choices to synthesize novel functional polymers [87–90].

Preparing polymers through MCRs is growing as a new hotspot in polymer chemistry, we believe the application of MCRs in polymer science will prompt the new understanding and application of those "old" reactions, and plenty of new functional polymers based on MCRs will appear in the near future.

Conflict of interest   The authors declare that they have no conflict of interest.

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