Multicomponent Reactions

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Multicomponent Reactions in Polymer Synthesis**

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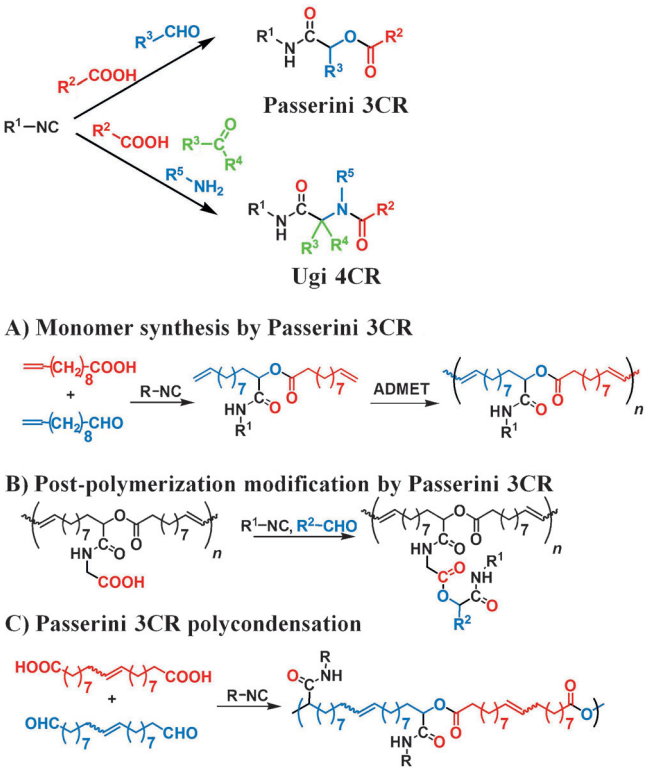
Since Strecker discovered the synthesis of amino acids through the three-component reaction of amines, aldehydes (or ketones), and hydrogen cyanide—the so-called Strecker reaction—multicomponent reactions (MCRs) have been widely explored. Until the middle of the 20th century, a variety of MCRs were reported, including the Biginelli reaction, the Gewald reaction, the Hantzsch reaction, the Kabachnik–Fields reaction, the Mannich reaction, the Passerini reaction, and the Ugi reaction.[1] MCRs fascinate chemists because they combine three or more starting reactants in a one-pot and one-step process to generate single products under mild conditions. The integration of MCRs into combinatorial syntheses for the synthesis of a library of compounds was found to be a very powerful approach to generate diverse organic molecules, leading to the rapid development of drug leads in the pharmaceutical chemistry.

Soft-matter materials science depends fundamentally on polymers and increasing attention is paid to the synthesis of new functional polymers that are specifically designed for specialized applications. In particular, the precise installation of functional groups within a polymer has become indispensable to satisfy the demand for polymers used in interdisciplinary applications. Recently, the happy marriage of polymer chemistry and click chemistry has accelerated the preparation of functional polymers. Time-consuming and exhausting chemical transformations are not necessary and even non-experts can synthesize functionalized materials.[2] This combination has pushed the development of a wide range of interdisciplinary sciences[2] and further easing of the synthetic requirements including milder reaction condition and the direct employment of commercially available chemicals is expected to increase the rate of these advances. Hence, polymer chemists are trying to expand the synthetic portfolio for the preparation of functional polymers and some of their newest toys are MCRs, which have only very recently been appreciated in polymer science. This Highlight will focus on recent achievements obtained with MCRs in the area of polymer chemistry. We will focus on two classes of reactions, one utilizing isocyanides and one utilizing sulfonyl azides.

Isocyanides are frequently used in MCRs, because they show both a nucleophilic and an electrophilic center (Scheme 1).[1] It is therefore not surprising that isocyanide-based MCRs have been intensively explored in the field of polymer synthesis. A first example was reported by Meier et al. in 2011.[3] They showed that the Passerini three-component reaction (Passerini 3CR, Scheme 1A) can be employed to synthesize diverse monomers derived from bio-renewable ricinoleic acid for acyclic diene metathesis (ADMET) polymerizations. Furthermore, they demonstrated the potential of Passerini 3CRs by conducting post-polymerization modification reactions on polymers featuring carboxylic acids (Scheme 1B) with isocyanides and aldehydes as reactants. The reactions proceeded smoothly and resulted in



Scheme 1. Representation of the Passerini 3CR and the Ugi 4CR and the utilization of the Passerini 3CR for polymer synthesis.

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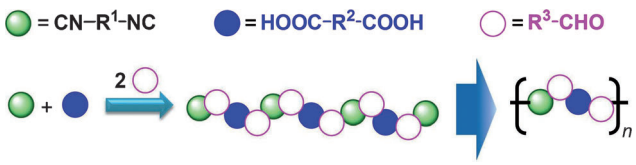
quantitative conversion of the starting carboxylic acids. The high efficiency of the Passerini 3CR was further demonstrated by a polycondensation under step-growth conditions between dialdehydes, dicarboxylic acids, and isocyanides at 40 °C in solution (Scheme 1 C). The resulting polyesters had molecular weights of up to 5.6×10^4 g mol^{-1}. Thus, the Passerini 3CR polycondensation was found to be a very powerful synthetic strategy to produce functionalized polyesters.

The striking efficiency and convergence of the Passerini 3CR was further utilized in the construction of a dendrimer skeleton.[4] In addition to the Passerini 3CR, the Meier group also studied the Ugi four-component reaction (Ugi 4CR) for the preparation of diverse monomers featuring α,ω-dienes for ADMET polymerization to afford a pool of highly functionalized polyamides.[5] These examples impressively demonstrate not only the broad possibilities of Passerini 3CR and Ugi 4CR for the synthesis of polymers, but also how easy these reactions are to conduct.

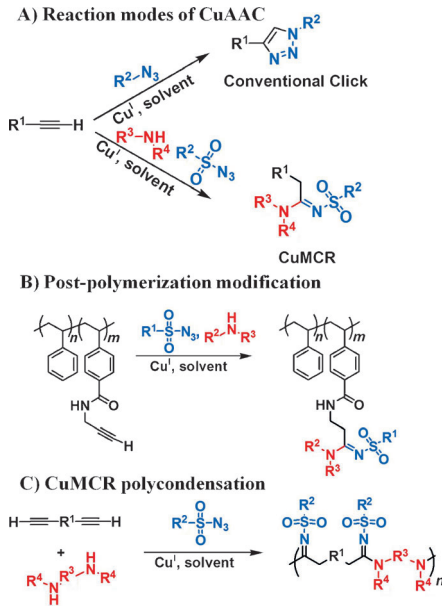
A new aspect of multicomponent polycondensations has been emphasized by Li et al.[6] In MCRs, the composition of the productis strictly governed by the reaction mechanism; this aspect can be taken advantage of to regulate the monomer distribution, in other words to control the monomer sequence. In fact, Li et al. successfully obtained poly(ester amide)s by 3CR polycondensations of dicarboxylic acids, aldehydes, and diisocyanides (Scheme 2). The obtained



Scheme 2. Sequence control of poly(ester amide)s by the Passerini 3CR polycondensation of diisocyanides, dicarboxylic acids, and aldehydes.

poly(ester-amide)s displayed a controlled monomer sequence in the primary structures, which is a challenging but highly desirable task for the synthesis of advanced materials. The importance of sequence-control events during polymerizations was recently emphasized by Lutz et al.[7] and consequently, the employment of MCRs in this newly growing area can provide new synthetic possibilities and easy access to highly functionalized well-defined polymers. MCRs based on isocyanides have been quite successful, but one negative aspect is that isocyanide derivatives are rather difficult to synthesize and possess a penetrating, extremely unpleasant smell, which limits their utilization by non-experts.[8]

An MCR that is easier to conduct, the Cu-catalyzed three-component reaction (CuMCR) between acetylenes, amines, and sulfonyl azides, has found recent application (Scheme 3 A). In 2013, Theato et al. has successfully demonstrated the synthetic utilization of CuMCR in the post-polymerization modification of polymers featuring acetylene moieties in reactions with amines (Scheme 3 B).[8a] At the same time, Choi et al. reported an elegant polycondensation based on CuMCR (Scheme 3 C).[8b] The three-component



Scheme 3. Representation of Cu-catalyzed three-component reactions (CuMCRs) of acetylenes, amines, and sulfonyl azides in polymer chemistry.

polycondensation of diamines, diacetylenes, and sulfonyl azides was conducted in DMF in the presence of CuCl as the Cu^{I} source and triethylamine as an additive at 70 °C to afford poly(*N*-sulfonylamidines) with molecular weights of up to 7.5×10^4 g mol^{-1}. These examples document the advantages of CuMCR reactions in polymer chemistry because they proceed homogenously with high efficiency, can utilize a broad variety of monomers, and yield no structural defects. Noteworthy, the reaction mode of this CuMCR is different from that of the well-established Cu^{I}-catalyzed azide–alkyne cycloaddition (CuAAC). Therefore, the typical reactants from CuAAC, that is, organo azides and terminal alkynes, can be easily used for the synthesis of functionalized polymers in a CuMCR, which makes CuMCR a potential candidate to be used for various applications.

In conclusion, multicomponent reactions have emerged as highly versatile reactions in the area of functional polymer synthesis. To my knowledge, so far only three MCRs, namely the Passerini 3CR, the Ugi 4CR, and CuMCR, have been successfully employed to afford highly functionalized polymeric materials. Certainly, we will see more MCRs for the synthesis of novel polymers in the near future. It is clear that MCRs are not only reactions between three or more reactants yielding single products, but also tandem (or cascade[9]) and sequential[10] reactions, which will become an essential part of the synthetic portfolio in the area of polymer synthesis.

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