# Multicomponent Polymerization System Combining Hantzsch Reaction and Reversible Addition−Fragmentation Chain Transfer to Efficiently Synthesize Well-Defined Poly(1,4-dihydropyridine)s

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S *Supporting Information*

ABSTRACT: A novel multicomponent system has been constructed through the combination of Hantzsch reaction and reversible addition−fragmentation chain transfer (RAFT) polymerization in a one-pot manner. Compared to traditional stepwise methods, this one-pot system exhibits much more advantages to facilely and efficiently prepare well-defined poly(1,4-dihydropyridine)s (poly(1,4-DHP)s). A series of poly(1,4-DHP) derivatives have also been successfully prepared through this Hantzsch−RAFT system using different aldehydes as reactants, suggesting this system is a general and versatile approach to prepare well-defined functional polymers with 1,4-DHPs as side groups. Since 1,4-DHP derivatives are an important class of bioactive molecules in the pharmaceutical field, this simple method to prepare poly(1,4-DHP)s might have potential to prepare related functional polymers for biological and pharmaceutical applications.
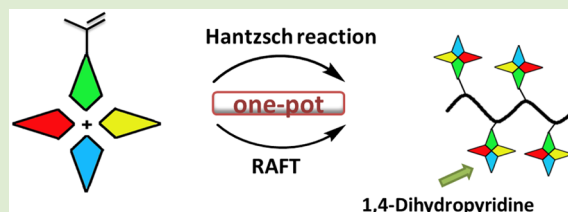
In recent decades, multicomponent reactions (MCRs) have drawn great attention and been utilized in the fields of synthetic organic chemistry, pharmaceutics, and life sciences[1] because of their high efficiency to decrease the laborious operations and save solvents, chemicals, and time.[2] Furthermore, MCRs can introduce some special functional groups which largely enrich the functions and diversities of compounds.[3−8] Recently, since Meier's pioneering research of introducing the Passerini three-component reaction (3CR) into polymer chemistry,[9−11] more and more MCRs, such as Ugi, Biginelli, Kabachnik-Fields (KF), Asinger reactions etc.,[8,12−19] have been exploited to synthesize new functional polymers, and a series of polymers with new main chains, side groups, and topologies have thereof been successfully prepared,[7,20−22] indicating the vitality of MCRs in polymer science.

Our group has recently developed a new strategy to perform MCRs during controlled radical polymerization (CRP) to construct one-pot MCR−CRP systems (Scheme 1a),[14,15,23,24] where MCRs could occur simultaneously with CRPs to modify monomers or polymers to finally produce new side-functionalized polymers in a one-pot manner. CRPs have been chosen due to their excellent regulable characters, which guarantee MCRs to proceed smoothly within the time scale of polymerization in order to in situ modify monomers or polymers. In our recent work, we have successfully achieved tricomponent (enzymatic reaction/click reaction/CRP)[25] and tetracomponent (Biginelli/CRP, KF/CRP)[14,15] MCR−CRP systems. In order to further expand the scope of the one-pot system, we hope to introduce other MCRs into the MCR−CRP family. The chosen MCR should be highly efficient and robust under radical polymerization conditions and contain as much

Scheme 1. (a) One-Pot MCR−CRP System Combining Multicomponent Reaction (MCR) and Controlled Radical Polymerization (CRP) and (b) the Hantzsch−RAFT Process to One-Pot Synthesis of Well-Defined Poly(1,4-DHP)s
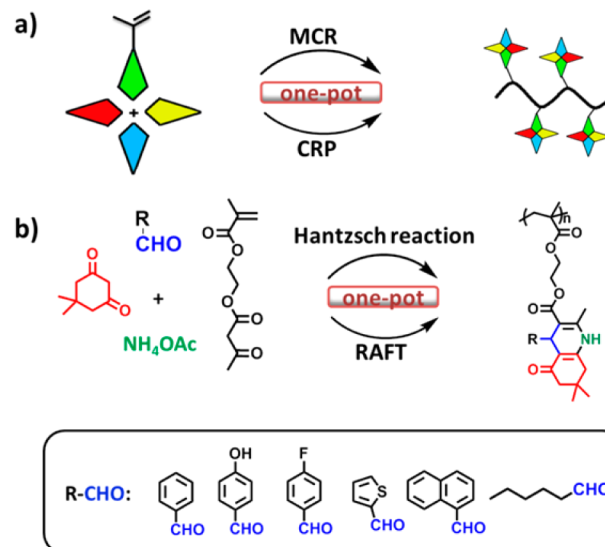
components to bring in more functions while forming unique structural monomers. Hantzsch reaction, a green and efficient

four-component reaction to synthesize 1,4-dihydropyridines (1,4-DHPs) with excellent yields,[26−29] has therefore been investigated. 1,4-DHP derivatives are an important class of bioactive molecules in pharmaceutics.[30,31] They possess anti-inflammatory, antimicrobial, antioxidant, and antiulcer activities. DHPs are also commercially used as calcium channel blockers for the treatment of cardiovascular diseases such as hypertension.[32] In addition, 1,4-DHP-type compounds are also excellent starting synthons for the development of antituber-cular agents.[33] However, to our knowledge, Hantzsch reaction has been rarely utilized in polymer science in spite of its huge progress in organic chemistry since its birth in 1882.[26] The Hantzsch reaction contains four common starting materials, namely, an aldehyde, 2 equiv of β-ketoester, ammonia, to generate a 1,4-DHP derivative. This reaction is efficient and highly atom-economic with only water as the byproduct. Besides, Hantzsch reaction can be carried out under benign conditions. On the basis of all the facts (facile operations, common reactants, potential products), we believe it is worthwhile to establish a Hantzsch−CRP system to facilitate functional polymer synthesis. Herein, we report for the first time the facile preparation of well-defined poly(1,4-dihydropyridine)s (poly(1,4-DHP)s) through the combination of Hantzsch reaction and RAFT polymerization (Scheme 1b). RAFT polymerization is chosen for its good reputation of tolerance to various functional groups, facile operation, and excellent control of polymerization.[34−36] Through this new one-pot concurrent system, the Hantzsch reaction was found to collaborate well with the RAFT process to facilely achieve a series of well-defined polymers with different 1,4-DHPs as side groups (Scheme 1b).

Commercially available 2-(acetoacetoxy)ethyl methacrylate (AEMA) was used as the vinyl monomer for RAFT polymerization as well as the 1,3-dione functional group source for the Hantzsch reaction. Benzaldehyde, dimedone, and ammonium acetate were used as the other three model components for the Hantzsch−RAFT system (Scheme 1b). The Hantzsch reaction and RAFT polymerization were performed simultaneously in a one-pot manner. A series of reaction conditions, including the ratio of reactants, catalyst, reaction time, temperature, and solvents, have been explored to optimize the Hantzsch−RAFT system, and the optimal Hantzsch−RAFT process is performed at 70 °C in acetonitrile. An excess amount of ammonium acetate (1.5 equiv to AEMA) is added to guarantee the complete conversion of monomer AEMA to target monomer. Glycine[27] has been screened as the catalyst to ensure Hantzsch reaction proceeds to high conversion. For the RAFT polymerization, azodiisobutyronitrile (AIBN) and 4-cyano-4-(ethylthiocarbonothioylthio) pentanoic acid were used as the initiator and chain transfer agent (CTA), respectively. In a typical Hantzsch−RAFT system, monomer AEMA, benzaldehyde, dimedone, ammonium acetate, glycine (10% equiv to ammonium acetate), AIBN, and CTA were added orderly in a Schlenk tube (acetonitrile as solvent). The Schlenk tube was sealed with a rubber septum and purged by nitrogen flow for 20 min, and the tube was then kept in a 70 °C oil bath for 12 h. Samples were withdrawn periodically under N_2 atmosphere for NMR (Supporting Information, Figure S1) and gel permeation chromatography (GPC) analyses (SI, Figure S2). The final polymer was obtained after dialysis against methanol (MWCO: 7000).

Conversions calculated from ^{1}H NMR versus time and the corresponding kinetic curve were presented to evaluate reaction features of the Hantzsch−RAFT system (Figure 1a).
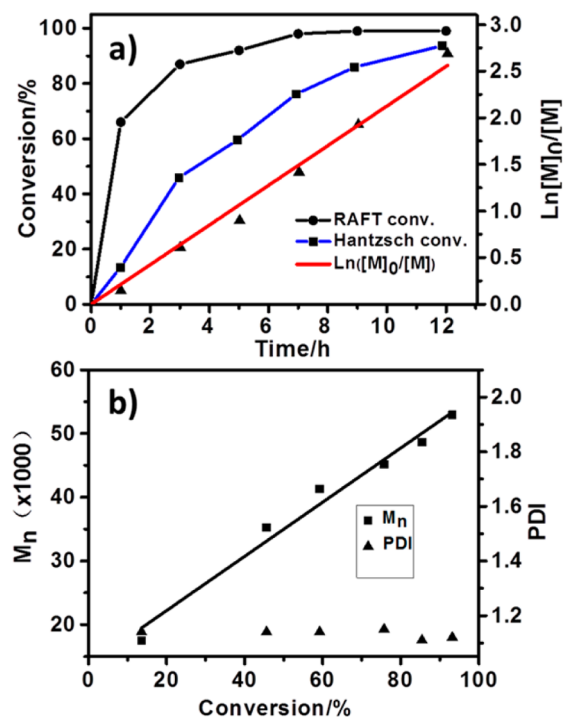

Figure 1. One-pot Hantzsch−RAFT system. (a) Conversions of Hantzsch reaction and RAFT separately and the kinetic curve versus time of the RAFT process. (b) Molecular weights and PDIs of the polymers during polymerization versus monomer conversions. [AEMA]/[CTA]/[AIBN]/[dimedone]/[benzaldehyde]/[ammonium-acetate]/[glycine] = 100/1/0.2/100/100/150/15, [AEMA] = 1.0 M in 2.0 mL of CH_3CN, 70 °C.

Under the optimal conditions, the four components generated target 1,4-DHP in situ efficiently in about 3 h (∼90% conversion), while RAFT polymerization also processed smoothly (∼45% conversion in terms of vinyl groups). Then, the RAFT process continued to proceed smoothly and finally reached ∼90% conversion in 12 h following a linear pseudo-first-order kinetic curve (Figure 1a). The obtained polymers have controlled molecular weights and narrow polydispersity indices (PDIs ∼ 1.20) (Figure 1b and Figure S2, SI), indicating the controllable feature of this Hantzsch−RAFT system.

The homopolymer poly(AEMA) was synthesized as the control. The specific methylene protons in the dione group (3.60 ppm) and the ester group (4.06−4.45 ppm) could be clearly observed in the ^{1}H NMR spectrum (Figure 2a). However, in the ^{1}H NMR spectrum of the one-pot obtained poly(1,4-DHP)s (Figure 2b), the sharp peak of the methylene group (3.60 ppm) nearly disappeared, while the signal of the ester group in the poly(1,4-DHP) became a broad peak. The characteristic peaks of the 1,4-DHP group, the protons of CH (4.92 ppm, marked as C) and NH (8.85 ppm, E), and the aromatic ring (6.90−7.40 ppm, D) could be clearly identified, indicating almost complete conversion of the Hantzsch reaction was achieved during this one-pot polymerization.

To synthesize new functional polymers, there are usually two main stepwise methods, namely, the traditional monomer−polymer method and postpolymer modification (PPM) of a
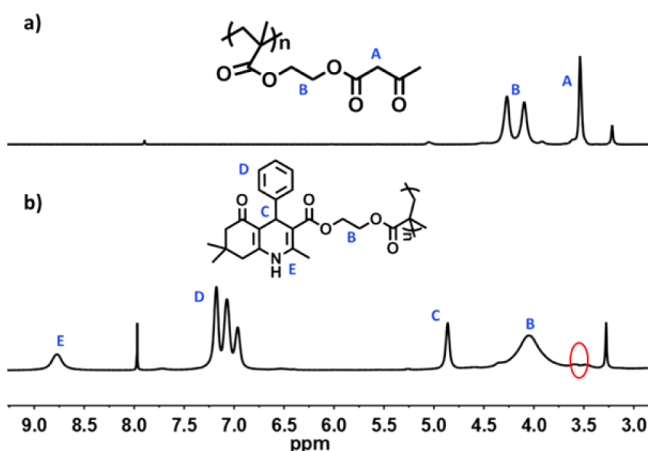
Figure 2. ^{1}H NMR (chloroform-d/dmso-d_6 = 7/3) of (a) the poly(AEMA) and (b) the poly(1,4-DHPs) through the Hantzsch−RAFT system.

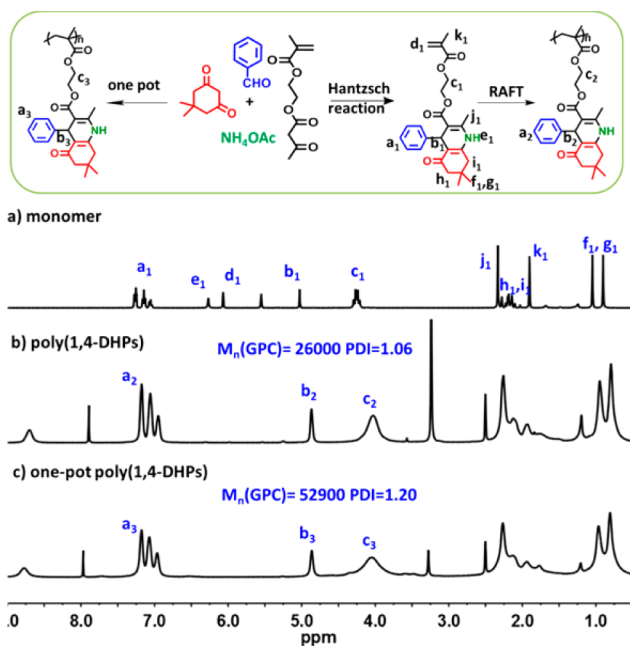**Figure 3.** Preparations of poly(1,4-DHP)s from the traditional monomer−polymer method and one-pot strategy and ^{1}H NMR spectra of (a) synthesized monomer (chloroform-d), (b) "pure" poly(1,4-DHP)s, and (c) poly(1,4-DHP)s via a one-pot Hantzsch−RAFT system (chloroform-d/dmso-d_6 = 7/3).

precursor polymer.[7,8,37,38] For the monomer−polymer method, a small molecule functional monomer is first synthesized and then subjected to polymerization to get the target polymer. For the PPM method, the reactive groups on a polymer precursor take part in a subsequent reaction to get target functional polymers. In this work, we also prepared the functional poly(1,4-DHP)s via traditional stepwise methods to make a comparison to the newly developed one-pot Hantzsch−RAFT system.

The "pure" poly(1,4-DHP) was first synthesized through the monomer−polymer method. The 1,4-DHP monomer was synthesized by Hantzsch reaction (Figure 3a). The obtained monomer was subjected to polymerization through a similar RAFT process to get the target "pure" poly(1,4-DHP)s (Figure 3b).

From the ^{1}H NMR spectrum (Figure 3b and 3c), it can be seen that the positions of characteristic peaks in both polymers by different approaches are the same. The integral ratios of a, b, and c are nearly 5:1:4 for both poly(1,4-DHP)s and one-pot poly(1,4-DHP)s, although they were prepared through different routes, indicating the Hantzsch−RAFT strategy is also an effective way to prepare well-defined poly(1,4-DHP)s.

The PPM strategy is also a powerful tool to synthesize functional polymers, especially with the development of efficiently modern modification reactions.[7,8,14,22] Therefore, the PPM method has also been performed. Poly(AEMA) was first synthesized through RAFT polymerization and then was modified using the Hantzsch reaction under the optimal conditions of the Hantzsch model reaction to form predesigned poly(1,4-DHP)s. The PPM process was monitored by GPC, and the reaction seemed to occur rapidly; however, some unwanted higher molecular weight shoulder was clearly observed (SI, Figure S3), implying the current conditions (glycine as catalyst and CH$_3$CN as solvent) might be not suitable for the PPM process to prepare the desired polymer, and it is necessary to further optimize conditions for the PPM route.

To show the versatility of the one-pot Hantzsch−RAFT system, we have demonstrated the advantages in terms of simple operation, high efficiency, and time saving provided by the one-pot Hantzsch−RAFT system in preparation of functional poly(1,4-DHP)s. To further explore the versatility and expand applications of this one-pot system, we also tried to

prepare a series of new structural poly(1,4-DHP)s derived from different aldehydes under the above-mentioned reaction conditions (Table 1).

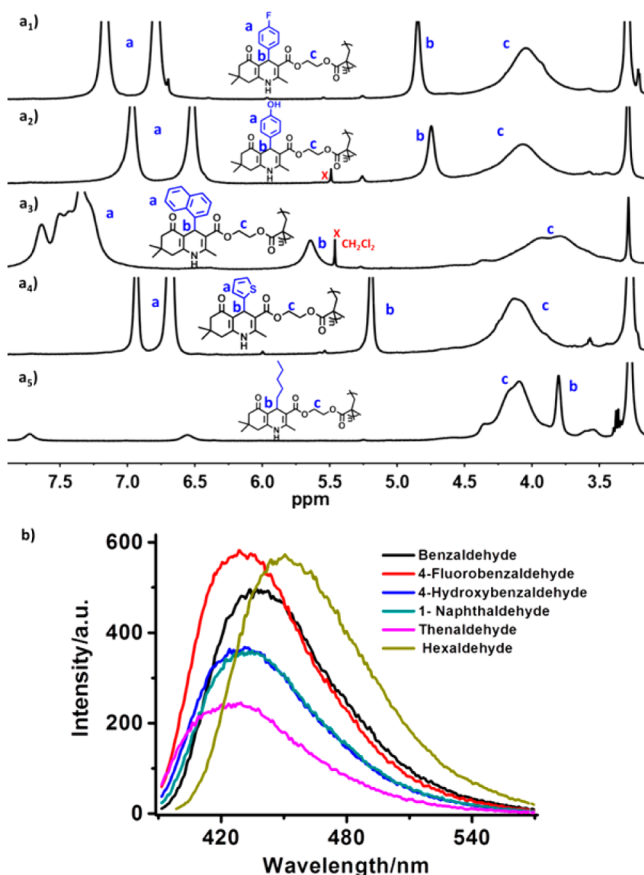**Table 1. One-Pot Hantzsch−RAFT of Various Aldehydes^a**

no.	aldehyde	RAFT conv. (%)^b	Hantzsch conv. (%)^c	M_n(GPC)^d	PDI^d
1	benzaldehyde	93	95	52900	1.20
2	4-fluorobenzaldehyde	91	94	53000	1.15
3	4-hydroxybenzaldehyde	87	93	57400	1.16
4	1-naphthaldehyde	77	92	46000	1.16
5	2-thenaldehyde	89	95	53700	1.15
6	hexaldehyde	69	89	41000	1.23

^{a}[AEMA]/[CTA]/[AIBN]/[Dimedone]/[Aldehyde]/[Ammonium acetate]/[Glycine] = 100/1/0.2/100/100/150/15, [AEMA] = 1.0 M in 2.0 mL of CH$_3$CN, 70 °C. ^{b}Calculated by ^{1}H NMR. ^{c}Calculated by ^{1}H NMR. ^{d}Determined by GPC.

All the aldehydes went on well in the Hantzsch−RAFT system in a controllable way, and corresponding 1,4-DHP-functionalized polymers have been successfully prepared. The ^{1}H NMR spectrum of these poly(1,4-DHP)s (Figure 4a$_1$−a$_5$) illustrated that all the obtained polymers were mainly constructed by different 1,4-DHP compositions (>89% conversions) and possessed controlled molecular weights with narrow PDIs (∼1.20), indicating that the Hantzsch−RAFT system was facile as well as general for the preparation of various well-defined poly(1,4-DHP)s.

The polymer side groups determine the physical/chemical properties and the functions of the polymers. In current research, the preliminary function, i.e., fluorescent feature, of the obtained poly(1,4-DHP)s has been analyzed. All the obtained poly(1,4-DHP)s show strong fluorescence in the

Figure 4. (a) ^{1}H NMR spectra (400 MHz, chloroform-d/dmso-d_6 = 7/3) of polymers prepared from a one-pot Hantzsch−RAFT system with various aldehydes: (a_1) 4-fluorobenzaldehyde, (a_2) 4-hydroxybenzaldehyde, (a_3) 1-naphthaldehyde, (a_4) 2-thenaldehyde, (a_5) hexanaldehyde. (b) Emission spectrum of poly(1,4-DHP)s with different aldehydes substituted via one-pot Hantzsch−RAFT process (the excitation wavelength is 365 nm).

visible-light region (Figure 4b and Figure S4, SI), primarily demonstrating the specific feature of this new type of polymers.

In conclusion, we present a "new" horizon of the "old" Hantzsch reaction in polymer chemistry, and a novel one-pot Hantzsch−RAFT method is successfully developed by combining Hantzsch reaction and RAFT in the same reactor. The various well-defined poly(1,4-DHP)s could be therefore prepared simply and efficiently in one shot. Considering the simple operation, common starting materials, and the important features of 1,4-DHP derivatives, the well-defined poly(1,4-DHP) polymers prepared through this one-pot system might have potential applications in polymer chemistry, biology, and material science.

ASSOCIATED CONTENT

ⓢ Supporting Information

Detailed experimental procedures, GPC and ^{1}H NMR of the polymers, ^{1}H NMR spectrum of polymerization versus time, and emission and excitation spectrum of poly(1,4-dihydropyridine)s with different aldehydes substituted via the one-pot Hantzsch−RAFT process. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions
All authors have given approval to the final version of the manuscript.

Notes
The authors declare no competing financial interest.

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