ChemComm

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2021, 57, 8328

Received 7th June 2021,
Accepted 21st July 2021

DOI: 10.1039/d1cc02984c

rsc.li/chemcomm

Four component Passerini polymerization of bulky monomers under high shear flow†

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We introduce a four component Passerini polymerization utilizing sterically bulky isocyanide monomers. Under typical Passerini conditions, bulky isocyanides do not react within standard Passerini reaction timescales (hours). We overcome this challenge *via* the unique physiochemical conditions present in a vortex fluidic device, reducing the reaction time to 2 h on average. Under these high-shear thin-film conditions, bulky isocyanides are readily incorporated into the multicomponent polymerization without the need of high-pressure or temperature. Finally, we demonstrate that the four component approach using functional cyclic anhydrides allows for post-polymerization modification.

The Passerini reaction is one of the most versatile reactions in modern macromolecular chemistry,[1] finding utility in post-polymerization modification,[2] multicomponent polymerization techniques,[3] soft matter materials design,[4] single-chain polymer nanoparticle formation,[5] and biocompatible materials.[6] With simple reagents, fast reaction times, 100% atom economy and high yields, the Passerini reaction has become an invaluable synthetic tool. Classically consisting of three components–isocyanides, aldehydes (and less commonly ketones), and carboxylic acids–the barrier to entry for polymer chemists is very low from a synthetic point of view. However, there are more exotic iterations of the Passerini reaction–emerged in recent years–involving either alternative functional groups such as acidic phenols (the Passerini–Smiles reaction),[7] thiocarboxylic acids,[8] and recently from our team, thioaldehydes.[9] By changing the nature of the functional group, the resulting ester/amide linkage can be tuned to incorporate other linking combinations such as thioester/amide, or ester/thioamides. In addition to modifying the functional group, there has been focus on introducing additional components into the traditional three component framework. The first major advance for higher component Passerini reactions in the realm of polymer science was pioneered by Meir and coworkers, employing alcohols in a pressurized CO_2 atmosphere to generate carbonic acids as the acid component, thereby directly incorporating CO_2 into polymeric materials.[10] One major drawback of Passerini-based multicomponent polymerizations is that sterically bulky components drastically decrease their reaction rate.[11] Typically, these obstacles are only overcome with increased temperature and/or pressure.[12] A rapidly emerging area of research which overcomes the typically inconvenient methods of high temperatures and high pressures is the use of thin films under high shear conditions, pioneered by Raston and team with the development of the vortex fluidic device (VFD).[13] The standard VFD instrument consists of a 20 mm outside diameter quartz tube (*ca.* 17.5 mm internal diameter) with a hemispherical base, which is spun at high speeds (up to 9000 rpm) at a set tilt angle, typically at 45° as the optimal angle for a diverse range of applications. Operating under the unique conditions of the VFD offers many key advantages unavailable to standard reaction flasks, for example in controlling protein folding and photoredox reactions, or accelerating enzymatic reactions.[13] The VFD can also be used as a flow chemistry system, further enhancing its utility.[14]

At high RPMs and at a 45° degree tilt angle, the thin film in the VFD is generated down to a thickness of *ca.* 200 μm, leading to high mechanical shear forces arising from the Coriolis force from the hemispherical base of the tube and twisted eddies from the Faraday waves. These are manifested as topological fluid flows to submicron dimensions, as spinning top and double helical flows, respectively[15] Within this environment of high shear and intense micro mixing, the traditional kinetic barrier of sterically bulky substituents can be overcome without the need for high temperatures and/or increased pressures.[16] Indeed, the topological fluid flows in the VFD generate arrays of high temperature (> 200 °C) and likely high pressure a few μm in diameter on the surface of the tube with molecules rapidly streaming through them.[15] This new phenomena has exciting potential for controlling reactions which would otherwise

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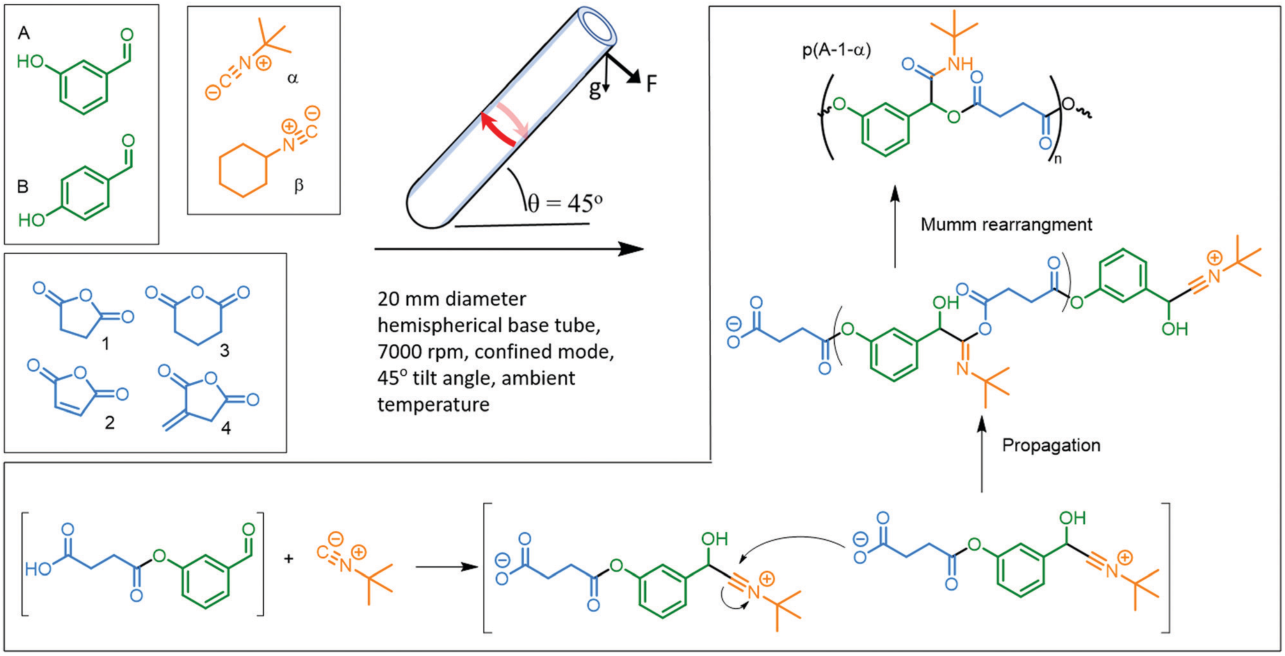
† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1cc02984c



Scheme 1 Overview of the hydroxybenzaldehydes (green), cyclic anhydrides (blue), and isocyanides (orange) explored in VFD-enabled four component Passerini polymerizations in the current study as well as the proposed reaction mechanism.

require high temperature and pressues, with the VFD achieving the equivalent conditions when operating under ambient temperature and pressure. Another advantage to the synthesis of macromolecules in the VFD is the absent risk of tube blockage, observed in classical flow chemistry instruments.[15b,17]

Herein, we introduce a four component (alcohol, anhydride, aldehyde, and isocyanide) Passerini multicomponent polymerization (MCP), using various hydroxy benzaldehyde isomers, cyclic anhydrides, and isocyanides. The combination functions due to the hydroxy moiety ring opening the anhydride, generating the carboxylic acid *in situ*, which can subsequently proceed with the standard Passerini reaction mechanism. Critically, this MCP can be carried out with a bulky isocyanide at ambient temperature in a VFD, whereas it is not feasible under standard reaction conditions.

Scheme 1 displays a selection of the broad range of components that can be utilized in this four component Passerini MCP. Starting with commercially available cyclohexyl isocyanide, 3-hydroxybenzaldehyde and cyclic anhydrides, we initially explored the electronic effects of the various hydroxybenzaldehydes to determine if the phenol p*K*a effected the MCP. Wishing to avoid the potential for parasitic Passerini–Smiles type reactions (where phenols participate as the acid component), we commenced with a less acidic phenol by way of 3-hydroxybenzaldehyde and the less bulky cyclohexyl isocyanide. For the control reactions, all components were added to a 1 mL vial, dissolved in 0.1 mL of acetonitrile and the mixture allowed to stand for 16 h before being precipitated into diethyl ether. All control polymers in this series (samples p(A-1-β), p(A-2-β), p(A-3-β), and p(A-4-β)) polymerized well (refer to Fig. S4–S7 and S21–S24, ESI†). For our VFD conditions, we operated in 'confined mode', implying that all the reaction components were added to the quartz tube and dissolved in 0.1 mL of acetonitrile, which was subsequently sealed with a modified rubber septum (refer to Scheme S1, ESI†). The volume in our MCPs did not exceed 0.3 mL in order to avoid the thin film touching the septum at the top, which would disturb the fluid mechanics of the set-up.[15a] The tubes were all held at 45° tilt angle and rotated at 7000 rpm for 2 h, followed by precipitation into diethyl ether. Both in the VFD and under normal reaction conditions, the reactions proceeded at ambient temperature and without the need for a base as evidenced by both NMR spectroscopy and size exclusion chromatography (SEC, Fig. S1–S32, ESI†). The decrease in the aldehyde proton resonance and the addition of the characteristic ester/amide α proton resonance of the Passerini product are characteristic NMR signals highlighting conversion. Additionally, the SEC traces for all samples highlight the characteristic shape for a step-growth polymerization (refer to Fig. S1–S16, ESI†). Subsequently, we switched the hydroxybenzaldehyde to the more acidic 4-hydroxybenzaldehyde. Again, the reaction both in the VFD and under regular conditions proceeded smoothly at ambient temperature and without the need for a base, demonstrating that indeed the Passerini–Smiles type reaction is not taking place. It should be noted that while the aldehyde ^{1}H NMR resonance is drastically reduced in all samples, the nature of step-growth polymerization implies the presence of polymer chains with aldehyde end groups. These two polymerization series with hydroxybenzaldehydes A and B, cyclic anhydrides 1 to 4, and cyclohexyl isocyanide ("β") highlight the utility of our four component multicomponent polymerization strategy, particularly with the addition of functional cyclic anhydrides, which are directly incorporated into the polymer backbone.

Repeating the above two experimental matrices, yet with *tert*-butyl isocyanide ("α"), produced markedly different results (Table 1). Upon switching to the bulkier isocyanide, no reactions with either the 3-hydroxybenzaldehyde or the 4-hydroxybenzaldehyde under

Table 1 Four component Passerini polymerization results of *tert*-butyl isocyanide *via* VFD and non-VFD methods

Method[a]	Sample	M_n[b] (g mol^{-1})	Đ	Yield[c] (%)
VFD	p(A-1-α)	2510	1.7	54
VFD	p(A-2-α)	2220	1.8	71
VFD	p(A-3-α)	3900	3.6	91
VFD	p(A-4-α)	1620	1.5	27
Control	p(A-1-α)	N/A	N/A	0
Control	p(A-2-α)	N/A	N/A	0
Control	p(A-3-α)	N/A	N/A	0
Control	p(A-4-α)	N/A	N/A	0
VFD	p(B-1-α)	1030	1.5	34
VFD	p(B-2-α)	915	1.5	69
VFD	p(B-3-α)	1830	1.9	82
VFD	p(B-4-α)	1020	1.6	80
Control	p(B-1-α)	N/A	N/A	0
Control	p(B-2-α)	N/A	N/A	0
Control	p(B-3-α)	N/A	N/A	0
Control	p(B-4-α)	N/A	N/A	0

[a] VFD method was conducted at 7000 rpm for 2 h at 45° tilt angle in a sealed quartz test tube. The control experiment was carried out in 1.2 mL SEC vial for 16 h at ambient conditions. [b] M_n are determined *via* SEC in THF based on PMMA standards. [c] Yield determined by polymer recovered after precipitation.

standard conditions produced sufficient polymer to analyze after precipitation (<1 mg, 24 h reaction time). Bulky monomers and side groups have often been challenging entities in polymer chemistry.[18] With the exception of some highly reactive ring opening metathesis polymerizations (ROMP), which are able to polymerize at mild temperatures, there are limited examples of defect-free polymerizations with bulky constituents.[19] Due to this issue, either a grafting-to or grafting-from approach onto a pre-existing polymer backbone is typically employed. Thus, we turned to the unique physiochemical conditions present in high shear thin-films in the VFD. With the intense micro mixing and high mechanical shear forces, we can address the challenges of overcoming the high kinetic barrier posed by bulky monomers such as *tert*-butyl isocyanide. Our approach utilizing the VFD proved successful. We attribute the ability to successfully overcome this kinetic barrier in the VFD to the high shear topological fluid flows in the film.[15] These micro-sized spinning top and double helical vortices generate localized high temperature (and pressure) pockets on the surface of the tube, producing an environment where the thermodynamic product is strongly preferred over the kinetic product, leading to the successful incorporation of the bulky *tert*-butyl isocyanide (Fig. 1).

To address the possibility of whether or not parasitic Passerini–Smiles events were taking place during VFD polymerizations, we synthesized a simple non-phenolic benzaldehyde monomer. By adding two methylene units as a spacer for the hydroxy group, we bypass the ability for the hydroxy group to function as the Passerini–Smiles acidic phenol. With this control monomer, the bulky *tert*-butyl isocyanide, and under VFD conditions, we were easily able to synthesize polymeric material (refer to Fig. S33 and S34, ESI†).

With the development of a new four component Passerini based MCP as well as the conditions required to synthesize these materials with bulky side-groups, we have demonstrated that they can be readily equipped with various functional handles depending on the cyclic anhydride utilized. In our case, we selected the commercially available maleic anhydride which, after VFD polymerization, was used in a post-polymerization modification reaction utilizing a Michael Addition with thiol terminated poly(ethylene glycol) (PEG) to generate a PEG-ylated brush polymer (Fig. 2 and Fig. S33, ESI†). The multimodal peak shape of p(A-2-α)-thio, while non-intuitive, is to be expected when a low dispersity, low molecular

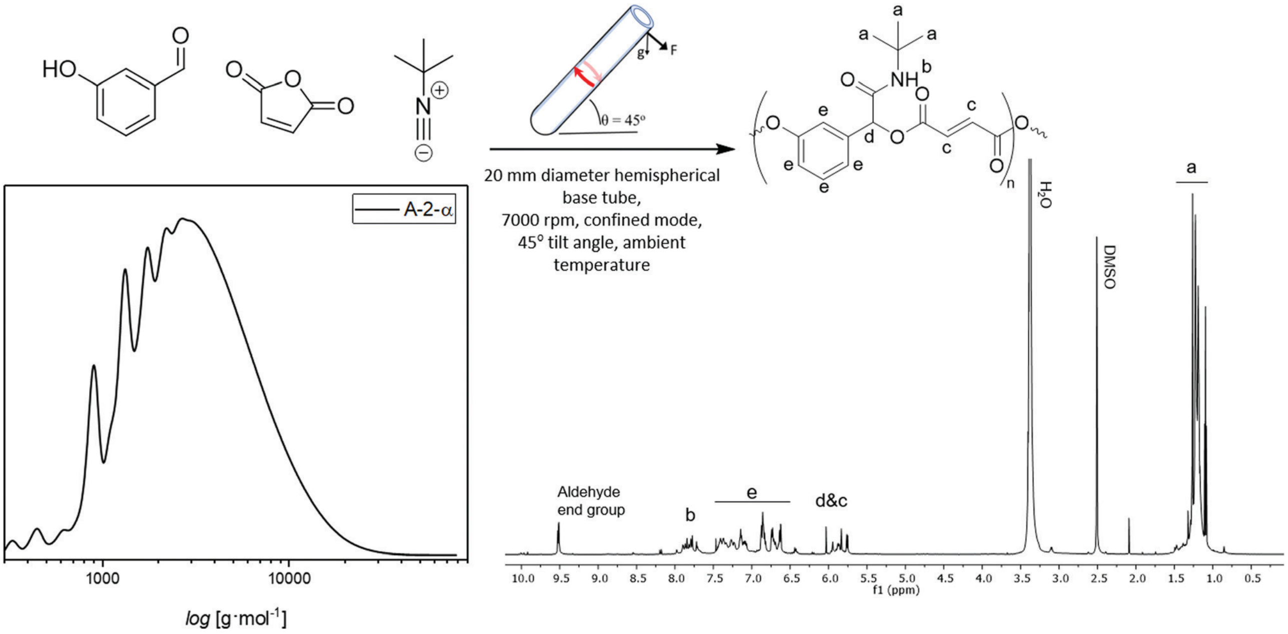


Fig. 1 Representative SEC chromatograms (THF as eluent solvent and PMMA standards) and ^{1}H NMR spectra of VFD-enabled polymerization with 20 mm diameter hemispherical base tube, 7000 rpm for 2 h at a tilt angle of 45° at ambient temperature.

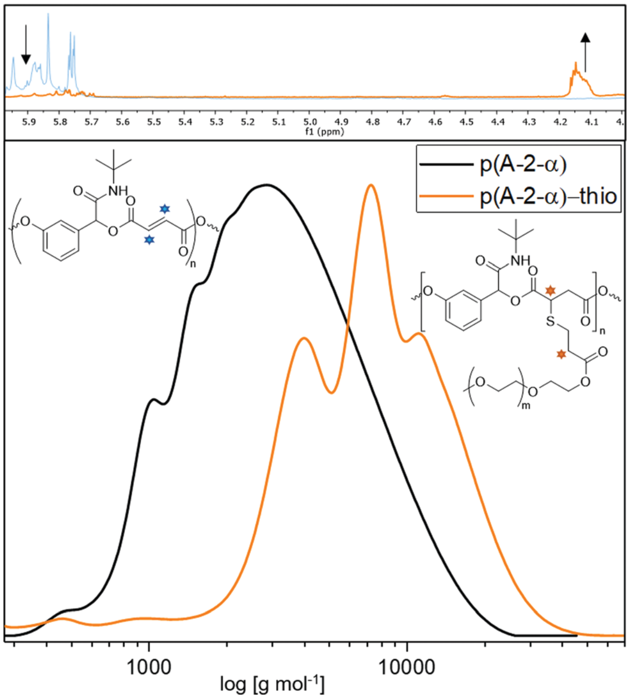


Fig. 2 Post-polymerization modification of p(A-2-α) backbone *via* thio-Michael addition PEG-thiol (SEC eluent solvent DMAc, PMMA standards).

weight polymer (PEG) is ligated to a larger dispersity, larger molecular weight polymer (p(A-2-α)).[20]

In summary, we introduce a very simple four component Passerini-based MCP, enabling access to step-growth polymers with functional backbones. Importantly, we highlight that the VFD provides ready access to step-growth polymers, which can directly incorporate bulky monomers without the need of using high temperatures or pressures. Lastly, our method demonstrates that numerous functional cyclic anhydrides can be incorporated in order to tune the properties of these soft matter materials. Moreover, the recently established high shear topological fluid flows in the VFD[15] provide an understanding of the ability for the device to prepare material that is otherwise not possible using conventional flask processing. Our approach provides strong support for the utility of the VFD in organic and polymer synthesis, where processes are not limited to diffusion control.

B. T. T. and C. B.-K. acknowledge support from the Queensland University of Technology (QUT). B. T. T. acknowledges support by the Australian Research Council (ARC) in the form of DECRA followship and C. B.-K. acknowledges support by the ARC in the form of a Laureate Fellowship enabling his photochemical research program. C. L. R. acknowledges the ARC and the Government of South Australia for generous funding.

Conflicts of interest

There are no conflicts to declare.

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