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ARTICLE

From Drug to Adhesive: A New Application of Poly(Dihydropyrimidin-2(1H)-one)s via the Biginelli Polycondensation

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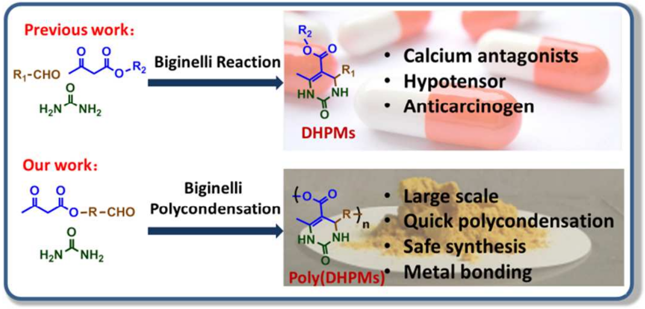
The reactions for polymer synthesis should be simple and efficient using easy available raw materials. A new difunctional monomer containing benzaldehyde and beta-keto ester groups (monomer AB) has been successfully prepared in a medium scale, and the corresponding poly(dihydropyrimidin-2(1H)-one)s (DP ~ 84) can be synthesized via the Biginelli polycondensation in short time (~ 1 h). The in situ generated polycondensates could glue two metal sheets, demonstrating the interesting metal bonding property which can't be observed in small molecules. The optimized multifunctional monomers (AB_2, A_2B_2 monomers) were subsequently used for the in situ polycondensation between metal sheets, and metal bonding strength could be improved to the similar level of commercial cyanoacrylate glue. Since the monomers could be easily prepared in a large scale and the polymeriztion could be simply performed, the Biginilli polycondensation might have potential as a new strategy to synthesize new functional polymers.

Introduction

As the cousin of organic chemistry, polymer chemistry is also the art of chemical reactions. However, different from organic chemists who devote themselves to the exploration of new reactions, polymer chemists mainly focus on how to use the extant reactions to prepare applicable polymers. Therefore, polymer chemists tend to choose the chemical reactions which are suitable for large scale manufacture, low cost and highly efficient with negligible side products to generate target valuable polymers. For example, polycondensate, such as nylon and polyester, might be one of the most useful members in the polymer family although the reactions are very simple using common reagents.

As the modern synthetic strategy, some new emerged efficient reactions are being introduced into polymer chemistry to synthesize whole new condensation polymers. For example, some click reactions, like Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC)[1-3], thiol-ene addition reactions[4-6], (hetro) Diels-Alder (D-A) reactions[7, 8], have been employed to prepare new functional condensation polymers. For another example, as a milestone of new polycondensation methodology, Meier et al. introduced tricomponent Passerini reaction into polymer chemistry to prepare multicomponent polycondensates, opening a door for synthesizing new condensed polymers[9-12]. Subsequently, more and more multicomponent reactions (MCRs)[13-18], such as the Ugi reaction[19-23], thiolactone based MCR[4, 24-26] and metal catalyzed MCRs[27, 28], have been explored for polycondensate syntheses. All those pioneering attempts using modern efficient reactions result in a series of distinctive polymers and new concepts in polymer field although there are still some flaws, such as using laboriously synthesized monomers or unsafe (toxic, smelly or explosive) chemicals, which more or less limit the large scale manufacture and application of those sophisticated polymers. Therefore, further research is still necessary to build the bridge between modern efficient reactions and real applicable polymers.



Scheme 1. Features of Biginelli polycondensation.

Recently, our group detailed studied the tricomponent Biginelli reaction and introduced it into polymer chemistry[29]. Only using very common and safe reactants, namely beta-keto ester, benzaldehyde and urea, the Biginelli reaction could highly

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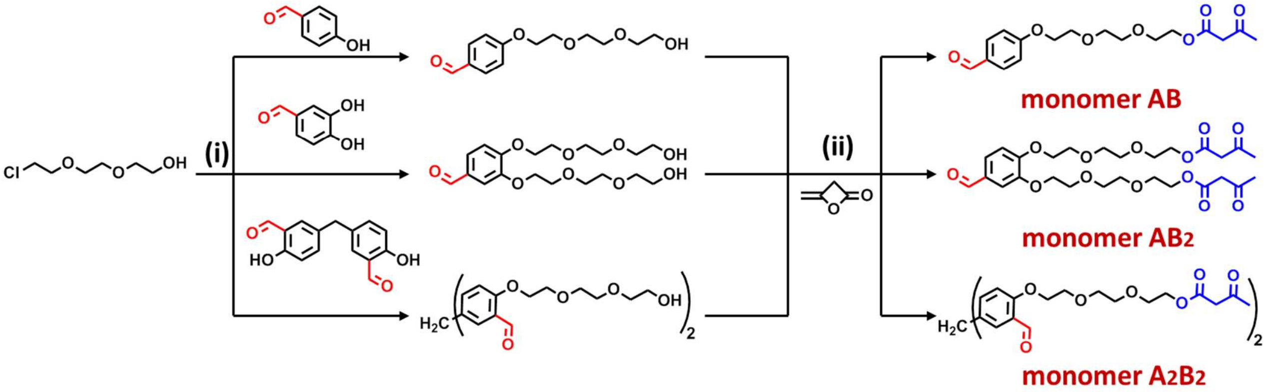
efficiently stitch two polymer chains together to generate a copolymer like other click reactions, demonstrating the new vitality of this 'old' reaction (> 120 years) in polymer chemistry. Traditionally, the Biginelli reaction has been studied as an excellent method to prepare dihydropyrimidin-2(1H)-ones (DHPMs) which have outstanding pharmacological activity as calcium antagonists[30, 31], hypotensor[32, 33] and anticarcinogen[34, 35] (**Scheme 1**). However, the physical features of DHPMs have been ignored for a long period, perhaps because they are difficult to be reflected by the small molecules. Herein, we synthesized a difunctional monomer (monomer AB) containing benzaldehyde and beta-keto ester groups with high yield (> 90%) in a medium scale (~ 60 g), followed by polycondensation in the presence of urea to prepare poly(DHPMs) (DP ~ 84, M_{nGPC} ~ 22300) within short polymerization time (~ 1 h).

Encouraged by the successful rapid Biginelli polycondensation, the in situ polymerization between two metal sheets was subsequently performed to quickly glue metal sheets together (130 °C, ~ 20 min), demonstrating the interesting metal bonding function when the small molecular 'drug' grows up as a high molecular weight polymer. The optimized monomers (AB_2, A_2B_2 monomers) were also synthesized (**Scheme 2**) to improve the polymer bonding strength to the similar level of the instant glue (2 ~ 8 MPa). Considered the easy available and safe reactants, simple operation and distinctive function, this Biginelli-type polycondensate might have potential to be used as an applicable adhesive material.



Scheme 2. Optimized monomers. (i) K_2CO_3, NaI, DMF, 110 °C, 8 h. (ii) TEA, DCM, 40 °C, 6 h.

Experimental

Synthesis of 2-(2-(2-(4-formylphenoxy)ethoxy)ethoxy)ethyl 3-oxobutanoate (monomer AB)

4-Hydroxybenzaldehyde (24.4 g 0.20 mol) was dissolved with 2-(2-(2-chloroethoxy)ethoxy) ethanol (37.1 g, 0.22 mol) in 100 mL of dry DMF. Potassium carbonate (55.2 g, 0.40 mol) and sodium iodide (30 g, 0.20 mol) were added to the mixture. The system was stirred at 110 °C for 8 h. After removing most of the solvents by rotavapor, 50 mL of water was added and the mixture was extracted by CH_2Cl_2 three times. The organic layer was dried over $MgSO_4$ and then evaporated to get a brown oil followed by mixing with trimethylamine (30.3 g, 0.30 mol) in 50 mL of CH_2Cl_2. 4-Methyleneoxetan-2-one (18.5 g, 0.22 mol) was added to the mixture slowly with rapidly stirring at room temperature. Then, the system was stirred at 40 °C for 6 h. After removing the solvents, the residue was dissolved in 50 mL of ethyl acetate, washed by diluted hydrochloric acid (0.1 M) and saturated sodium chloride solution three times. The organic layer was dried over $MgSO_4$ and then evaporated to get the product as an orange oil (61.2 g, 90.5%). The AB_2 and A_2B_2 monomers were synthesized through similar route using different benzaldehyde derivatives (**Scheme 2**).

^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 9.82 (s, 1H, $C\underline{H}O$), 7.81 (d, 2H, J = 8.4 *Hz*, $C\underline{H}CCHO$), 7.08 (d, 2H, J = 8.4 *Hz*, $C\underline{H}CO$), 4.04-4.25 (m, 4H, $C\underline{H}_2OAr$, $C\underline{H}_2OCO$), 3.48-3.77 (m, 10H, $OCH_2C\underline{H}_2OC\underline{H}_2C\underline{H}_2OC\underline{H}_2CH_2O$, $COC\underline{H}_2CO$), 2.14 (s, 3H, $COC\underline{H}_3$).

^{13}C NMR (100 MHz, DMSO-d_6, δ/ppm): 201.94, 191.70, 167.75, 163.97, 132.27, 130.18, 115.39, 70.43, 70.28, 69.23, 68.70, 68.16, 64.31, 50.03, 30.41.

IR (ν/cm-1): 2874, 1738, 1734, 1646, 1599, 1577, 1262, 1045, 950, 832.

ESI-MS: observed (expected): 361.1259 (361.1258) [$M+Na^+$].

Polycondensation of monomer AB in acetic acid

Typically, monomer AB (10.1 g, 30 mmol) and urea (3.6 g, 60 mmol) were dissolved in acetic acid (15 mL). Then magnesium chloride (0.28 g, 3 mmol) was added to the mixture. The system was stirred at 100 °C for 4 h. Samples were taken periodically for ^{1}H NMR and GPC analyses for conversion and molecular weight determination, respectively. The final polymer was simply purified by precipitation into cold water, then washed for three times by water and diethyl ether as a yellow powder (8.9 g, ~ 81%).

Metal bonding through the neat Biginelli polycondensation

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Two thin urea films (7.5 mg, 0.125 mmol) were formed separately through volatilization of concentrated urea aqueous solution on two metal sheets. Monomer (~ 40 mg, ~ 0.12 mmol) was added on either urea film before clamping the two metal sheets. The contact area was 1 cm × 1 cm. After heated at 130 °C for 20 minutes, the metal plates were cooled down to room temperature, and used for the tensile shear strength analysis by a microcomputer control electronic universal testing machine.

Results and discussion

Medium scale preparation of AB monomer and the Biginelli polycondensation in acetic acid.

The difunctional AB monomer can be easily synthesized in a medium scale for subsequent polycondensation, meeting the prerequisite for possible real application. The Biginelli polycondensation (**Fig. 1a**) was carried out in acetic acid/$MgCl_2$ (solvent/catalyst) system as our previous report. Different conditions including temperature, catalyst amount and urea amount have been evaluated **(Fig. S1, Fig. S2, Fig. S3**), and the typical condition for polycondensation was chosen as 100°C, [AB monomer]/[urea]/[$MgCl_2$] = 1/2/0.1. Equal amount of benzaldehyde and beta-keto ester groups in monomer AB meets the requirement of polycondesation, and right amount of catalyst and excess urea which can be easily removed after polymerization guarantee the rapid polycondesation. The GPC and ^{1}H NMR were utilized to monitor the polymerization. The monomer conversion was calculated by comparing the integral ratio of the aldehyde group protons to the new formed methine protons (PhCH, ~ 4.95-5.10 ppm), and a time-dependent increase of molecular weight could be clearly observed. Oligomers formed rapidly at the beginning of the polymerization (5 min, ~ 80%) (**Fig. 1c, Fig. S4**). Afterwards, the conversion reached maximum (~ 100%) in 40 min (**Fig. 1c**). The viscosity of the polymerization system increased continuously. At the later stage of the polymerization, the molecular weight increased rapidly (**Fig. 1d**), confirming the mechanism of conventional step-growth polymerization. A polymer with quite high molecular weight (M_{nGPC} ~ 22300, PDI ~ 1.59) was generated and the polycondensation almost finished in an hour. The extension of polymerization time to 4 h has slight influence on the molecular weight, which is attributed to the difficult Biginelli reaction with low concentration of reactive moieties (**Fig. 1d**). Through simple precipitation into cold water and washing with water and diethyl ether, the final polymer (yellow powder, Fig. 1b) with high glass transition (T_g ~ 96.5 °C) and good thermal stability (**Fig. S5, Fig. S6**) could be easily obtained. In the ^{1}H NMR spectrum of the purified polymer (**Fig. 2**), the aldehyde group (9.82 ppm) almost completely disappeared, while the characteristic PhCH peak and two NH peaks of Biginelli cyclization product (5.04 ppm, 7.65 ppm, 9.15 ppm) could be clearly identified. The integral ratio between the methine PhCH peak and NH groups ($I_{5.04}/I_{7.65}/I_{9.15}$) was 1/1/1, suggesting the efficient and thorough Biginelli polycondensation. The degree of polymerization (DP) was calculated through the integral ratio between the aldehyde residue (9.82 ppm) at the polymer chain end and the amide group in the polymer main chain (9.15 ppm) as approximate 84, and the molecular weight is therefore calculated as about M_{nNMR} ~ 30400 g/mol.

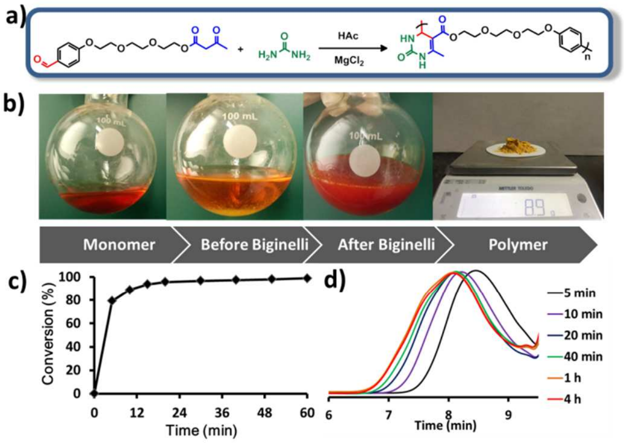

Fig. 1. The Biginelli polycondensation of monomer AB and urea. a) Reaction conditions: [monmer AB]/[urea]/[magnesium chloride] = 1/2/0.1, acetic acid as solvent, 100 °C. b) The photos of monomer (10.1 g), the polymerization system before and after the Biginelli reaction, and the obtained polymer. c) The conversions of Biginelli reaction. d) GPC tracking of the condensation polymerization.

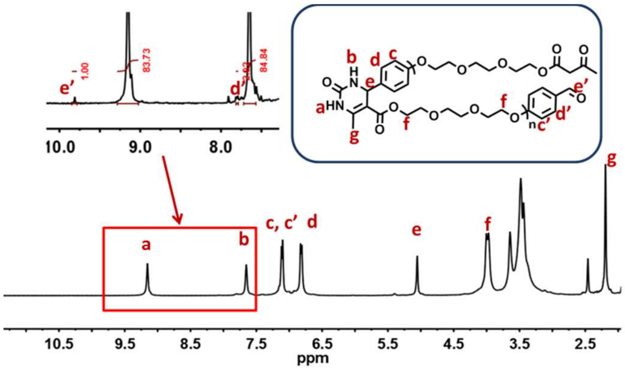

Fig. 2. ^{1}H NMR spectrum (DMSO-d6, 400 MHz) of the final polymer.

Quick neat Biginelli polycondensation of monomer AB under heat

The polycondensation kinetic reveals that the Biginelli reaction occurred quite fast in solvent. Actually, the reaction rate of MCRs is highly concentration-dependent, implying the multicomponent polycondensation without solvent might proceed even faster. Therefore, the neat polycondensation of monomer AB and urea without catalyst was tested. Urea was added on glass surface, then covered with the monomer AB, equal amount of monomer AB was dropped on the other zone on same glass as the control. Both zones were simultaneously heated by an electric heat gun, and the mixture of monomer AB and urea quickly produced plenty of bubbles due to the dehydration Biginelli reaction. After 30 seconds, filament was formed by pulling up the mixture, indicating the generation of polymer only by heating under catalyst free condition (**Fig. 3a,**

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Video in SI). From the ^1H NMR spectrum of the mixture, the characteristic PhCH (5.04 ppm) and NH (9.23 ppm) peaks of Biginelli products could be clearly observed, confirming the Biginelli polycondensation. The residual aldehyde group in the ^1H NMR spectrum suggested only part of monomers took part in the polymerization (**Fig. 3b**), which is attributed to the heterogeneous mixing between the liquid monomer and solid urea, leading to incomplete polymerization. Meanwhile, the ^1H NMR analysis showed nothing happened in the control group (**Fig. S7**), confirming the presence of three functional groups is crucial for the polymerization. The GPC analysis also suggested the generation of Biginelli polycondensate, the broad GPC trace indicated the polymer is a mixture containing high molecular weight polymers, low molecular weight oligomers and unpolymerized monomer (**Fig. 3c**).

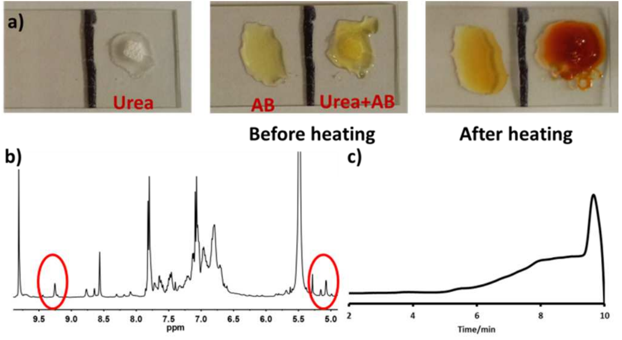

Fig. 3. Quick neat Biginelli polycondensation of monomer AB and urea with electric heat gun. a) Photos of glass with urea, before and after heated by an electric heat gun for 30 seconds. b) ^1H NMR spectrum (DMSO-d_6, 400 MHz) of the mixture after heating. c) GPC tracking of the mixture after heating.

Metal bonding with the Biginelli polycondensation of monomer AB

Compared with small molecular DHMPs, interesting properties were discovered in poly(DHMPs). In the Single-Molecule Force Spectroscopy (SMFS) measurement (**Fig. S8**), the single chain of Biginelli polycondensates showed stronger metal interaction than the polyester counterpart (the control polymer), implying the polar Biginelli structure might has specific interaction with metals and the Biginelli polycondensate might be a possible metal adhesive. Three kinds of metal sheets (stainless steel, aluminium, and brass) were therefore chosen to investigate the metal bonding capability of the Biginelli polycondensates (**Fig. 4a**). The in situ generated Biginelli polycondensate can well glue all three metal sheets, and shows the best bonding effect on the brass surface (tensile shear strength: ~ 2.8 Mpa) (130 °C, 20 minutes, **Fig. 4b, Fig. S9**). The influence of polycondensation time on the bonding effect has been studied (brass as the model), and a bonding strength plateau (~ 2.8 Mpa) was observed (~ 20 min) after a gradual increase period (5-15 min), indicating the complete polycondensation in the limited space between two brass sheets. (**Fig. 4c**).

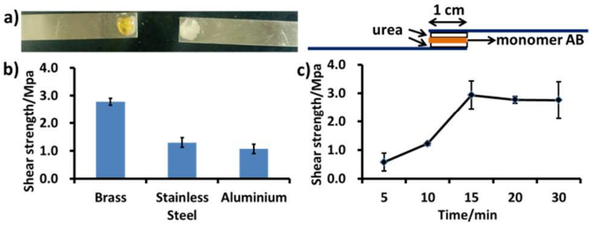

Fig. 4. Metal bonding capability of the Biginelli polycondensation from monomer AB. a) Schematic diagram of metal bonding operation. b) Tensile shear strength of Biginelli polycondensation on different metals (130 °C, 20 minutes). c) Tensile shear strength versus polymerization time between two brass sheets, 130 °C (mean ± SD, three tests).

Metal bonding with the optimized monomers (monomer AB_2 and monomer A_2B_2)

Cross-linked network usually provides higher molecular weight as well as stronger structure to polymers. For example, epoxy resin glue tends to form cross-linked network to increase its bonding strength through the reaction between epoxy and amine groups. Therefore, we synthesized two optimized monomers (monomer AB_2 and monomer A_2B_2) containing more functional groups in the monomer structure, and used them to perform the in situ Biginelli polycondensated between two brass sheets under the same condition (130 °C, 20 minutes). The Biginelli polycondensation of monomer AB_2 demonstrated stronger tensile shear strength (~ 3.6 MPa) as expected, indicating the cross-linked polymer network has positive effect on the bonding strength. Furthermore, polymerization of monomer A_2B_2 showed even better bonding effect (~ 5.9 MPa) which is similar to the commercial cyanoacrylate glue (2~8 MPa). Although similar amount of aldehyde and beta-keto ester were used, the A_2B_2 monomer showed obviously stronger adhesive effect than the AB monomer, confirming the potentiation of bonding strength by increased molecular weight and crosslinking degree (**Fig.5**).

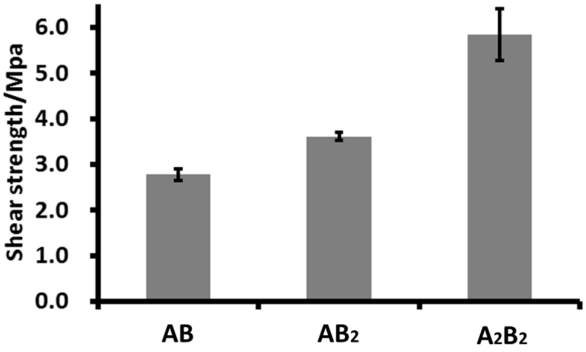

Fig.5. Tensile shear strength of Biginelli polycondensation of different monomers on brass (130 °C, 20 minutes) (mean ± SD, three tests).

Rapid metal-sticking with electric heat gun

The Biginelli polycondensation can be easily performed even only using an electric heat gun. Therefore, rapid metal-sticking might be realized using this new multicomponent polymer. A preliminary experiment was performed to evaluate the metal-

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sticking effect through the Biginelli polycondensation of monomer A_2B_2 (**Fig. 6a**). After heated by an electric heat gun for 40 seconds and cooled down to room temperature, the bonding strength has been tested as ~ 5.5 Mpa, and the bonded brass sheets can serve as a connection between a spring scale and a barrel of DCM (20 L, ~ 27 kg) (**Fig. 6b**). It is inspiring that such a small bonding area (1 cm × 1 cm) can readily bear such a heavy object (**Fig. 6c**).

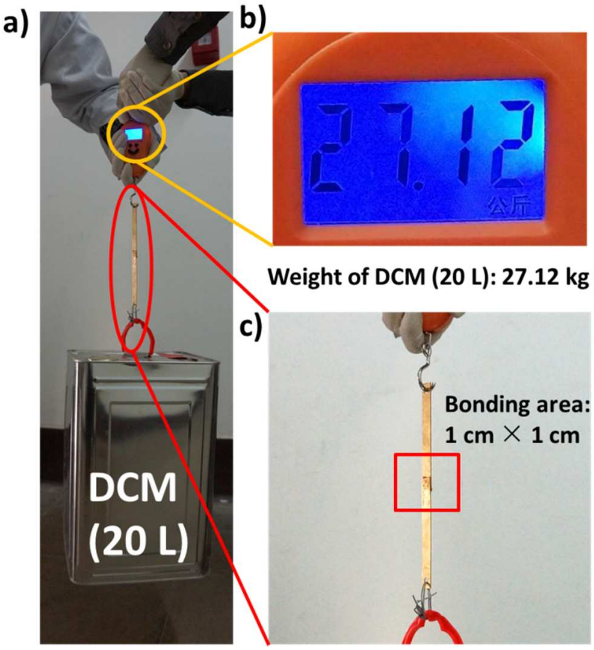

Fig. 6. Using bonded brass to lift heavy objects. a) Photo of lifting a barrel of DCM (20 L, ~ 27 kg) with bonded brass sheets. b) The enlarged photo of spring balance readings. c) The enlarged photo of bonded brass sheets.

Conclusions

Through the Biginelli reaction, a new structural multicomponent polycondensate, poly(DHPMs) was successfully prepared in solution rapidaly (~ 1 hour) on a large scale. The polycondensation is so efficient that it can happen merely with the heating of an electric heat gun under neat condition (catalyst free). The new generated DHPM groups in the polymer structure can act as a glue to stick different metals together, especially effective on brass. Furthermore, the optimized monomers have been prepared to improve the tensile shear strength via cross-linked network. Due to the simple synthesis of the monomers, easy polymerization, and excellent metal bonding performance, the Biginelli polycondensation and the thereof obtained polymers might have potential for future industrial application.

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