Graphical Abstract

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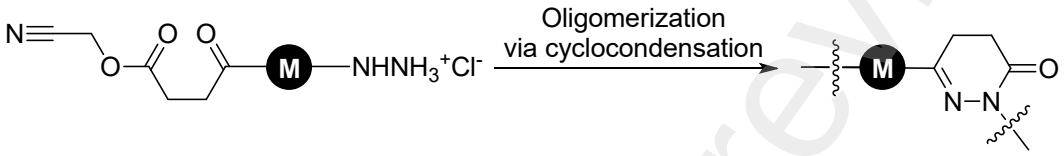

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Cyclocondensation reactions of a bifunctional monomer bearing a nucleophilic hydrazine and electrophilic ketoester pair

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ABSTRACT

An approach to combine monomer units forming heterocyclic linkages is described. A bifunctional monomer bearing a nucleophilic hydrazine and electrophilic ketoester pair was designed and synthesized. The monomer was employed to construct oligomeric products containing pyridazinone linkages via cyclocondensation reactions. The cyclocondensation oligomerization yielded up to pentamers including macrocycles. Regiochemical studies with model compounds revealed that the cyclocondensation occurred via a hydrazone intermediate when conducted under acidic conditions.

Introduction

Condensation reactions are a common class of organic reactions used to link two or more molecules, resulting in the release of small molecules such as water, alcohols, and hydrogen halides. Many naturally occurring and synthetic macromolecules are produced via condensation reactions including cellulose, polyamides (proteins, nylon, and Kevlar®), polyesters (polyethylene terephthalate(PET)), polyurethanes, and polycarbonate.[1,2] However, the linkages between monomer units produced by condensation reactions are largely limited to amides or esters. As a result, there has been a growing interest in the development of methodologies to ligate monomer units with other functional linkages, resulting in heterocycles. The heterocyclic moiety of numerous organic compounds has been often a key structural element to display desirable characteristics for drug discovery, renewable resources, and organocatalysis.[3-6] With the advent of Cu (I) catalyzed "click" reactions, triazole heterocycles are now routinely used in polymerization schemes.[7-9]

Various heterocyclic polymers including polypyrrole, polythiophenes, polypyrazoles, and polypyridazines have been extensively investigated for their mechanical,[10] thermal resistant, electronic,[11-13] conductive,[14-16] and photophysical[17] properties. Such heterocyclic polymers are often prepared electrochemically or through pericyclic pathways. An alternative approach is to perform cyclocondensation reactions between two bifunctional monomers, A-A and B-B.[18] Generally, one bifunctional monomer (A-A) contains two nucleophilic functional groups, while the other bifunctional monomer (B-B) contains two compatible electrophilic functional groups.[3,19] However, few studies have investigated the efficacy of using single bifunctional monomers (A-B) in cyclocondensation oligomerizations.

Pyrazolones (5-membered heterocycles) and pyridazinones (6-membered heterocycles) have been of particular interest in medicinal chemistry as they often exhibit a broad spectrum of pharmacological properties, including anti-inflammatory, analgesic, antimicrobial, and antitumor activities.[20-24] One common approach toward their synthesis is the cyclocondensation reaction between a hydrazine and a β or γ-keto ester to form pyrazolones and pyridazinones, respectively.

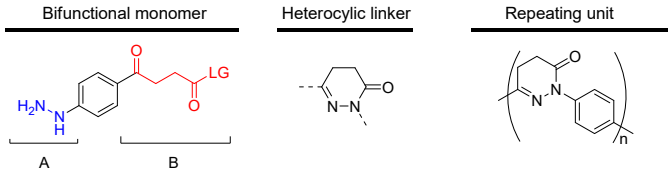


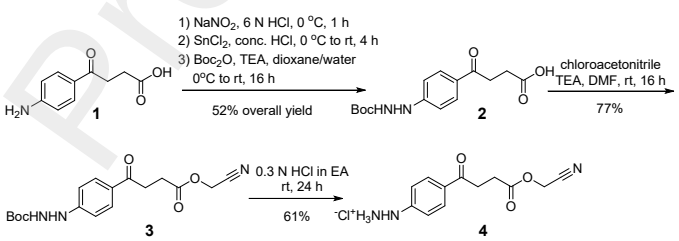
Figure 1. Design of a bifunctional monomer bearing a nucleophilic (hydrazine) and electrophilic (ketoester) pair.

Herein, we describe an A-B type monomer bearing a nucleophilic hydrazine (A) and electrophilic keto ester (B) pair (Figure 1). As shown, pyridazinone linkages are formed from a cyclocondensation reaction with a nucleophilic hydrazine from one monomer and an electrophilic keto ester from an additional, identical, monomer. The ester leaving group (LG) facilitates an effective cyclization when using methyl, ethyl, or cyanomethyl esters. The oligomerization reactions via cyclocondensation are also described. A serious complication that limits the utility of such polymerizations arose due to a radical mechanism that results in the loss of the hydrazine group from the aryl ring.

Results and Discussion

The cyclocondensation reaction of hydrazines and β/γ-keto esters to form pyrazolones and pyridazinones is well-established.[21,25,26] To take advantage of this precedent for oligomerizations, the monomers we designed and synthesized employ a single nucleophilic hydrazine and an electrophilic keto ester pair to effectively achieve linear chain elongation via cyclocondensation reactions. Although the ester leaving group can be any ester not sterically hindered, the cyanomethyl ester was chosen as it has been proven effective for flexizyme catalyzed tRNA charging, thus being expandable to ribosome mediated polymerization and genetic code expansion if desired.[27,28] In this study, the chemical facet of cyclocondensation reactions using the new bifunctional monomers is discussed.

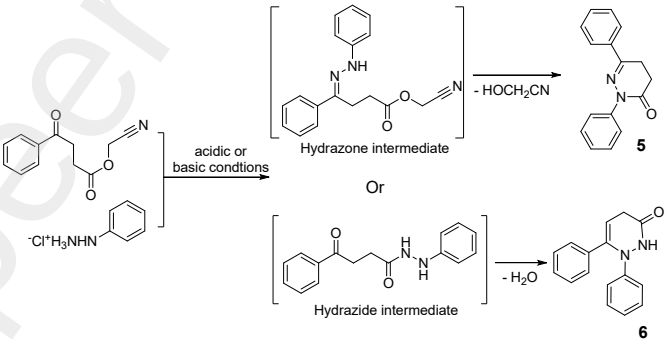
First, 4-(4-aminophenyl)-4-oxobutanoic acid (**1**) was prepared from acetanilide via Friedel-Crafts acylation and subsequent removal of the acetyl group as previously reported.[29,30] As shown in Scheme 1, the amine was converted to a diazonium salt using sodium nitrite in 6 N HCl (aq) and reduced by stannous chloride in concentrated HCl. The resulting hydrazine was allowed to react with di-tert-butyl dicarbonate in the presence of triethylamine to provide a Boc-protected acid (**2**) in 52% overall yield over three steps. The acid was activated using chloroacetonitrile in the presence of triethylamine. The Boc group of cyanomethyl ester (**3**) was then removed with 0.3 N HCl in ethyl acetate. The resulting hydrochloride salt (**4**) is stable enough to be stored in a freezer for extended periods of time (> 3 months).



Scheme 1. Synthesis of a bifunctional monomer bearing a nucleophilic hydrazine and electrophilic ketoester pair.

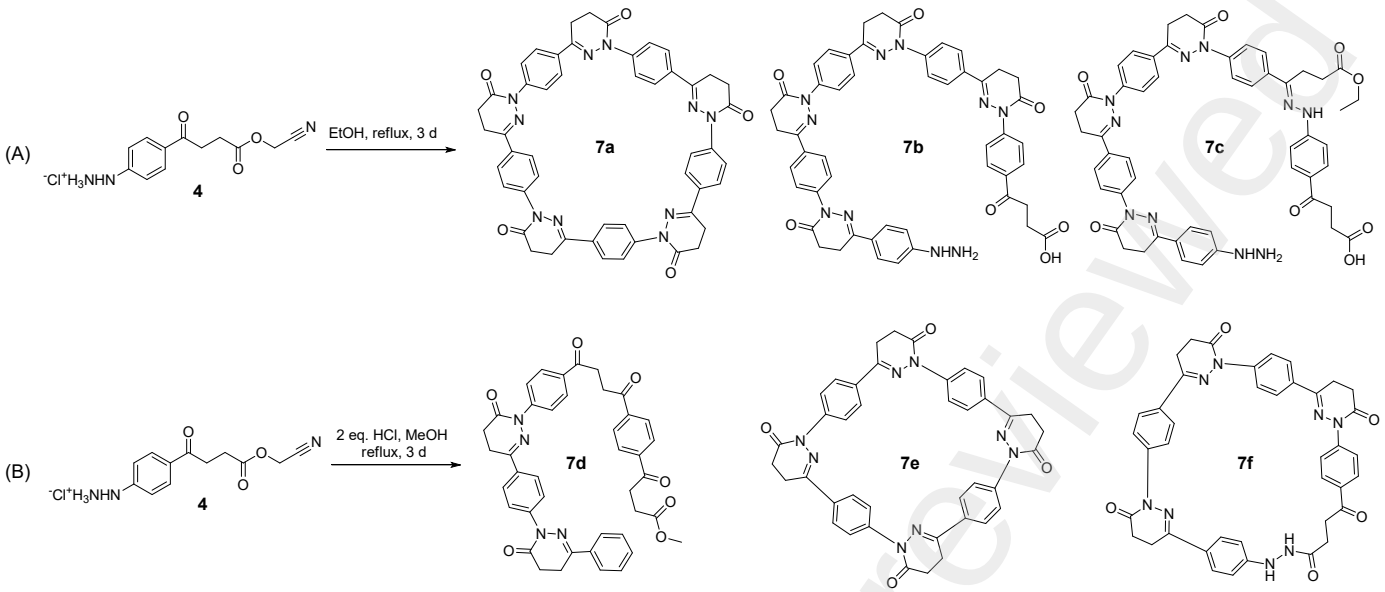
The arylhydrazine monomer (**4**) carries a γ-keto ester group. The heterocyclic products can be produced via two pathways differing in regiochemistry. In the first case, initial intermolecular hydrazone formation is followed by subsequent intramolecular cyclization. In the second case, a hydrazide intermediate forms first by intermolecular coupling, and is followed by intramolecular cyclization. The regiochemistry of cyclocondensation was investigated using two types of model compounds, a hydrazine and a keto ester (Scheme 2). First, phenylhydrazine and cyanomethyl 4-oxo-4-phenylbutanoate were condensed in acidic or basic conditions, respectively (Scheme 2). The acidic conditions employed 2 mole equivalents of HCl in refluxing ethanol. Under basic conditions, the hydrazine and the γ-keto ester was treated with 2 mole equivalents of triethylamine in refluxing THF. The reaction in basic conditions gave a mixture of products including the intermediates of hydrazone and hydrazide, as well as the two regioisomeric pyridazinones (**5** and **6**). Interestingly, the cyclocondensation reaction in acidic conditions exclusively afforded the regioisomer (**5**), via a hydrazone intermediate, in 82% isolated yield, which was characterized by LC-MS and NMR (Figure S1 in S.I.). Similar acidic conditions were employed in the oligomerization reaction of the monomer (Scheme 3).

Scheme 2. Regioselectivity in cyclocondensation to form the pyridazinone.



The oligomerization of the bifunctional monomer (**4**) bearing a hydrazine and γ-ketoester pair was monitored by MALDI-TOF mass spectrometry (Figures S2 and S3 in S.I.). As shown in Scheme 3A, the reaction was first conducted in refluxing ethanol without any additional reagents. The largest oligomers observed by MALDI-TOF MS were a cyclic pentamer (**7a**) and linear pentamers (**7b** and **7c**). The oligomerization was terminated primarily by hydrolysis of the active ester group, or the formation of macrocycles by the intramolecular reaction of the terminal functional groups.

Another approach we investigated was Fischer esterification conditions to prevent the active ester from becoming hydrolyzed (Scheme 3B). For this purpose, the reaction was performed in the presence of an acid catalyst (2 mole eq. HCl). Although the hydrolysis of the active ester was not observed when monitored by LC-MS and MALDI-TOF MS, the oligomerization stopped at the stage of tetramers (**7d**, **7e**, and **7f**) due to the loss of hydrazine group via a radical mediated termination. Such generation of radicals has been reported for arylhydrazine derivatives when reactions are conducted under basic conditions in air.[31-33] However, similar loss of the hydrazine was observed even with mildly acidic conditions under an inert atmosphere, thus terminating the elongation of oligomeric chain. As a result, attempts to increase oligomer length beyond tetramer were unsuccessful. The tetramer was also accompanied with significant decomposition byproducts via hydrazine loss (Figure S3 in S.I.).



Scheme 3. Oligomerization of the bifunctional monomer (**4**) via cyclocondensation reaction: The potential oligomerized structures (**7a-f**) derive from the spectra of MALDI-TOF MS.

Conclusion

We report the formation of oligomeric pyridazinones using a single monomer with an electrophilic γ-ketoester and nucleophilic hydrazine pair. The regioselectivity was successfully controlled in acidic reaction conditions. The oligomerization is limited by early termination of condensation reactions due mainly to either radical formation or hydrolysis of the activated ester. Even though we failed to achieve high molecular weight products by using this bifunctional monomer, the concept may be useful to make bioactive small oligomers.

Declaration of Competing Interest

The authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at …….

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