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Dewar Heterocycles as Versatile Monomers for Ring-Opening Metathesis Polymerization

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Abstract

We report the utility of readily available heterocycles as precursors to unique ring-opening metathesis polymerization (ROMP) monomers. Photochemical valence isomerization reactions of pyridones, dihydropyridines, and pyrones dearomatize the parent heterocycles to their highly strained Dewar isomers, which readily engage in controlled ROMP reactions using Grubbs catalysts. This strategy is used to access polymer backbones that contain strained β-lactam and azetidine cores, which can be further derivatized using post-polymerization chemistries. We demonstrate this through the synthesis of water-soluble β-amino acid polymers that have potential applications as biomedical materials, along with the synthesis of highly-soluble poly(acetylene) derivatives, which have potential applications as organic conductive materials derived from bio-feedstock chemicals.

Abstract

The conversion of Dewar heterocycles to polymers bearing strained β-lactam and azetidine moieties is disclosed. These monomers are derived from their parent heterocycles (pyridones, pyridines, and pyrones) *via* photochemical valence isomerization. Post-polymerization modification of these polymers allow for the synthesis of β-amino acid polymers and soluble poly(acetylene) derivatives.

Aromatic compounds make up a vast portion of our feedstock chemicals given their wide abundance in nature and ease of accessibility. However, due to the inherent stability imparted by these molecules' resonance energy, their reactivity is often poor.[1–2] To this end, dearomative functionalization has attracted the attention of the synthetic chemistry community as a potent strategy for accessing complex three-dimensional functionality from readily available "flat" compounds that are typically thought to be too inert to undergo productive chemical transformations.[2–4] Aromatic heterocycles have long been known to undergo photochemical valence isomerization reactions to generate their dearomatized

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ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization, NMR spectra, GPC traces (pdf)

The Supporting Information is available free of charge on the ACS Publications website.

The authors declare no competing interests.

Dewar isomers (Scheme 1).[5–6] These bicyclic photoproducts are often quite reactive given the strained nature of their cyclobutene substructures. Hence, the valence isomerization of these compounds effectively unveils new reactive functional group handles, providing an attractive platform for generating densely functionalized building blocks for organic synthesis. Some Dewar heterocyclic compounds have been used in the context of total synthesis, by our laboratory and others.[7–11] However, their utility as substrates for polymerization reactions is highly underexplored. We reasoned that various heterocycles such as pyridones, pyridines, and pyrones could be converted to their high-energy Dewar isomers by light irradiation, thereby introducing a strained cyclobutene moiety as a reactive handle for ring-opening metathesis polymerization (ROMP). Moreover, we recognized that the resulting polymers would have significant structural novelty in their backbone, and potential for unique physical properties given their structural rigidity, chirality, and capacity to undergo post-polymerization modification.

Dewar aromatics have recently found potent utility in polymer synthesis. Swager and co-workers demonstrated in 2018 that Dewar *o*-xylylene can undergo radical polymerization to yield high molecular weight poly(*o*-xylylene) *via* post-polymerization isomerization.[12] Accessing poly(*o*-xylylene) has previously been a formidable challenge, highlighting the strategic use of *o*-xylylene's Dewar isomer as the monomer. Bielawski and co-workers demonstrated in 2019 that a dibromo derivative of a Dewar benzene-type substrate could be polymerized and subsequently modified in two steps to access poly(acetylene).[13] More recently, Bielawski and co-workers reported the polymerization of cyclobutene substrates derived in two steps from photopyrone, which were then converted to substituted poly(acetylene) derivatives using post-polymerization chemistry.[14] These highly strained monomers are, however, challenging to access, often involving many synthetic steps and harsh conditions. We reasoned that direct polymerization of the Dewar heterocycles could generate unique polymers bearing strained heterocycles, which would enable further modification and impart interesting material properties. Here we report the successful direct polymerization of Dewar heterocycles derived from cheap and abundant sources, including bio-feedstock.

We initiated our investigation by targeting pyridones, which are known to undergo photochemical valence isomerization to yield β-lactam-fused cyclobutenes (Figure 1a).[5] N-functionalized Dewar pyridones, derived photochemically from their aromatic precursor, could be readily polymerized using Grubbs 3rd generation (G3) catalyst in DCM solvent to afford novel poly(β-lactam) polymers with low dispersity ($Đ < 1.30$), following termination with ethyl vinyl ether (Figure 1a, entries 1–2). Furthermore, unprotected lactams (Figure 1a, entry 3) could also be readily polymerized in DMF solvent to maintain solubility during the polymer chain growth process (other common solvents resulted in immediate precipitation, and incomplete polymerization, upon initiation). In all cases, the strained β-lactam functionality is preserved with no sign of ring opening, as confirmed by IR and NMR spectroscopy. To study the effect of catalyst loading on the molecular weight of this new class of polymers, monomer **1** was selected as a model substrate. The initial monomer-to-catalyst ratio ($[1]_o/[G3]_o$) was varied from 25 to 200, which showed a linear increase in molecular weight from 4.3 to 33.3 kDa, as determined by GPC (Figure 1b). Additionally, the

dispersity of these polymers remained low regardless of the feed ratio (Đ between 1.05 to 1.09), demonstrating the controlled nature of these polymerization reactions. The resulting poly(β-lactam) polymers could be further diversified through post-polymerization functionalization (Scheme 2). Hydrolysis of the β-lactam under acidic conditions cleanly yields a water-soluble polymer bearing a β-amino acid motif, making them an attractive material for biomedical applications.[15–17] β-lactams have traditionally been viewed as reactive functional groups for ring-opening polymerization to generate polyamide-type polymers.[18–22] However, the synthesis of polymers with incorporated β-lactam functionality directly in the backbone is more rare, with limited examples in the literature.[23] These results demonstrate that β-lactam incorporated polymer backbones can be readily accessed from cheap, simple pyridone heterocycles.

Another related class of Dewar heterocycles is that derived from pyridine. Unlike pyridones, the formation of the azetine-fused cyclobutene structure in Dewar pyridine renders these intermediates highly reactive, with a half-life of only 2.5 minutes at room temperature (Scheme 1).[6] Attempts to polymerize these intermediates directly, or conduct the photo-isomerization and polymerization in one pot, were met with failure. We reasoned that instead pyridinium dearomatization chemistry could be used to access protected dieneamines, which could be photochemically isomerized to yield protected bicyclic azetidines, formally the Dewar isomer of dihydropyridine (Figure 2a).[24–25] We found that these strained molecules also readily engage in ROMP chemistry, yielding poly(azetidine)-type polymer backbones in a controlled fashion, with polydispersity index values ranging from 1.07 to 1.09 (Figure 2a, entries 1–2). The initial monomer-to-catalyst ratio ($[5]_o/[G3]_o$) was varied from 25 to 200, which showed a linear increase in molecular weight from 5.0 to 26.0 kDa, with minimal change in the dispersity (Figure 2b). These results represent another example of unique materials that could be derived from cheap and abundant compounds, like pyridine. While azetidine functional groups have frequently been used in ring-opening polymerization reactions to yield polyamine-type polymers,[26] the direct incorporation of the strained four-membered azacyclic ring in the polymer backbone is rare.[27–28]

The final class of monomers we targeted were those derived from pyrones, many of which can be accessed from biofeed-stock chemicals. For example, α-pyrone **8** can be derived from malic acid, which is generated from glucose fermentation.[29–30] Initial attempts to polymerize Dewar pyrone **9** directly were unfruitful – exposing a solution of freshly prepared monomer to Grubbs 3 catalyst led to rapid precipitation of an insoluble material, with recovered unreacted monomer in the filtrate (Scheme 3a). We assigned this insoluble precipitant to be oligomeric product **10** on the basis of solid state NMR and IR (observe strong β-lactone C=O stretch at 1822 cm-1). Both the insolubility of the resulting oligomerized material and high instability of the Dewar pyrone monomer to polar solvents limited exploration of solvent conditions to help facilitate the desired polymerization. Attempts to synthesize a more soluble polymer by decorating the precursor pyrone with various substituents at either C3 or C5 were also met with difficulty, as no polymerization was observed. Instead, we opted to open up the β-lactone ring, generating an ester moiety that could help solubilize the resulting polymer. Cyclobutene **11** was synthesized in two steps.[31] We found that the *cis* isomer of β-chloro ester **11** polymerized using Grubbs

generation 2 catalyst (the *trans* isomer was found to be unreactive in our hands) to give polymer **12** after 24 hours at room temperature. We attribute this difference in reactivity to steric contributions. In the case of the *trans* isomer of the β-chloro ester monomer, the ester and chlorine substituents on the cyclobutene ring are both individually blocking a face of the cyclobutene olefin, thereby diminishing accessibility by the ruthenium complex due to steric interactions on both sides. The *cis* orientation of these two groups allows one face of the cyclobutene moiety to interact with the ruthenium complex to engage in ROMP chemistry. The lack of ROMP reactivity with Grubbs generation 3 catalyst might be a result of the two basic pyridine ligands on the ruthenium complex (which dissociate to generate the active catalyst) reacting with the acidic α-proton on the ring-opened monomer. Deprotonation of this acidic C–H bond and subsequent chelation of the enolate oxygen to the metal center could potentially deactivate the catalyst.[35–36] Grubbs generation 2 catalyst lacks the pyridine ligands, and is able to catalyze the polymerization chemistry, which is in line with this hypothesis.

We reasoned that polymer **12** could be converted to a substituted poly(acetylene) through a base-mediated elimination reaction (Scheme 3b). Indeed, exposing polymer **12** to triethylamine at room temperature resulted in the generation of a highly soluble poly(acetylene) derivative **13** and triethylammonium chloride, as determined by NMR. A shift in the C=O IR absorption from 1732 cm^{-1} to 1708 cm^{-1} is consistent with the formation of an α,β-unsaturated carbonyl system, which would be expected from the elimination of the β-chloride (Scheme 3b). Interestingly, the resulting polymer has a vibrant burgundy color in solution, with a strong absorption at 425 nm, as determined by UV-Vis spectroscopy (see Supporting Information). Given the notoriously challenging synthesis of substituted poly(acetylene) derivatives[32–34] – particularly those that are soluble in organic solvents – these results present a promising avenue towards accessing soluble conjugated materials that could be readily derived from pyrones. We note here that a similar approach was also reported recently by Bielawski and co-workers for accessing ester-substituted poly(acetylene)s.[35] Interestingly, the authors also observed poor polymerization using Grubbs 3 catalyst, and opted to use Hoveyda-Grubbs generation 2 catalyst to obtain high conversion in an hour on a similar β-chloroester monomer. Our experimental observations and recorded spectra are also consistent with their reported results (see Supporting Information).

In conclusion, we demonstrate that Dewar heterocycles are versatile monomers for ring-opening metathesis polymerization, giving access to unique, unprecedented polymer backbones. These ROMP monomers can be easily obtained *via* photochemical valence isomerization reactions of the corresponding aromatic heterocycle. In the case of Dewar pyridones and Dewar dihydropyridines, polymers with strained four-membered azacyclic rings such as β-lactam and azetidine motifs can be accessed. Pyrone-derived monomers can also be polymerized to give β-chloroester polymers, which can be readily converted to soluble poly(acetylene) derivatives. Further applications of these polymers are currently being explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

GPC	Gel Permeation Chromatography

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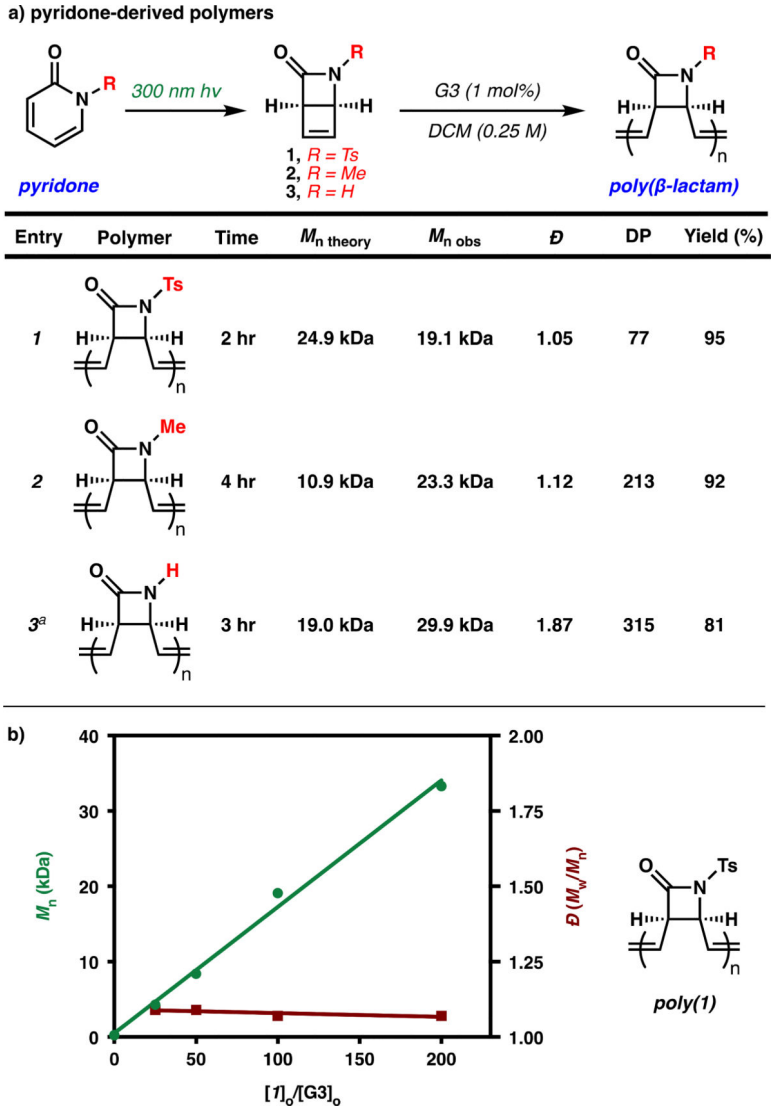


Figure 1.

(a) Dewar pyridone substrates tested for polymerization activity. All polymerization reactions were carried out at room temperature in 0.25 M DCM with a [monomer]:[G3] ratio of 100:1 unless otherwise noted. M_n and $Đ$ values were determined by GPC (see Supporting Information). All polymerization reactions were allowed to progress to >95% completion. Reported yields are isolated yields of polymers from the Dewar pyridone monomer. [a]Polymerization was conducted with a [monomer]:[G3] ratio of 200:1 in 0.25 M DMF solvent. (b) Change in M_n (green) and $Đ$ (red) as a function of monomer-to-catalyst ratio, $[\mathbf{1}]_0/[G3]_0$ for the polymerization of monomer **1**.

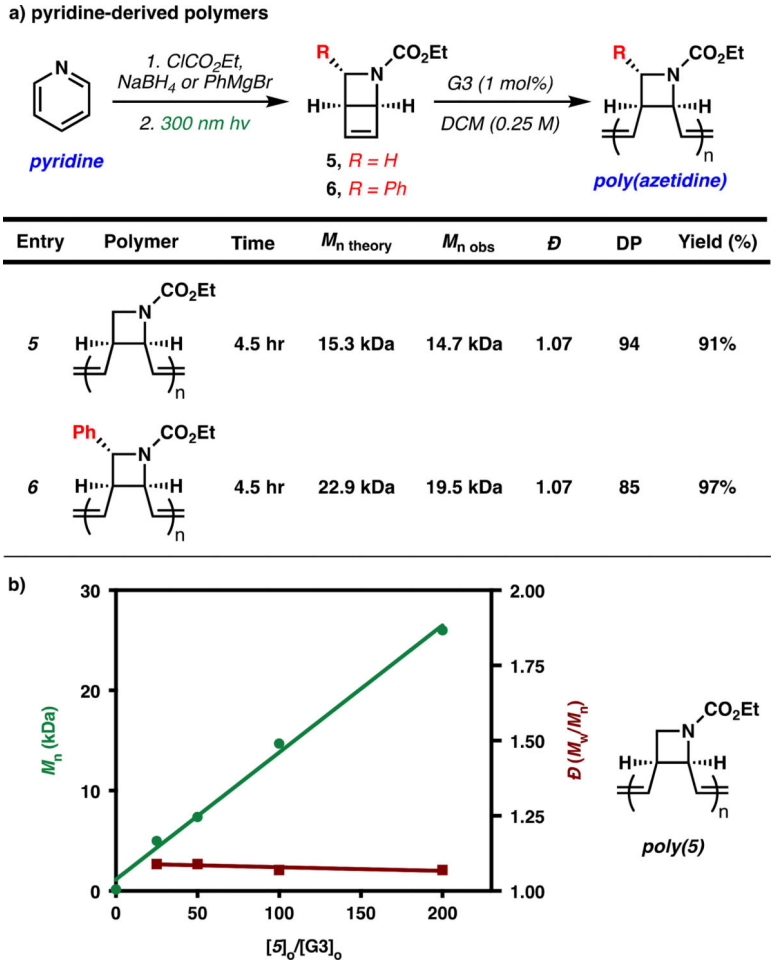
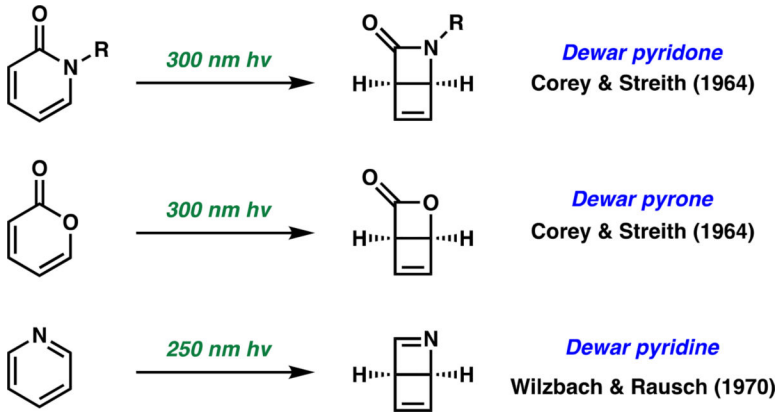


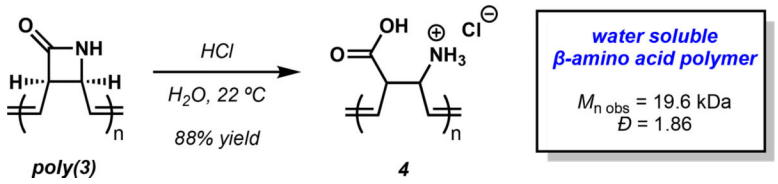
Figure 2.

(a) Dewar dihydropyridine substrates tested for polymerization activity. All polymerization reactions were carried out at room temperature in 0.25 M DCM with a [monomer]:[G3] ratio of 100:1. M_n and $Đ$ values were determined by GPC using poly(styrene) standards. All polymerization reactions were allowed to progress to >95% completion. Reported yields are isolated yields of polymers from the Dewar dihydropyridine monomer. (b) Change in M_n (green) and $Đ$ (red) as a function of monomer-to-catalyst ratio, $[\mathbf{5}]_o/[G3]_o$ for the polymerization of monomer **5**.

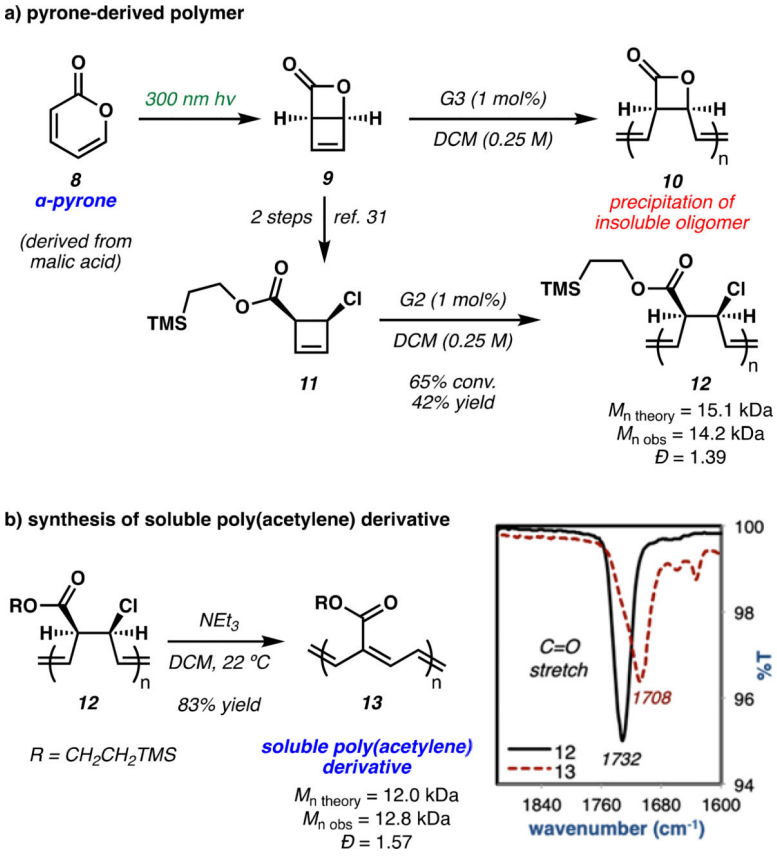


Scheme 1.

Examples of Dewar heterocycles accessed *via* photochemical valence isomerization reactions



Scheme 2.
Synthetic modification of poly(β-lactam)



Scheme 3.

(a) Synthesis of β-chloroester polymer from Dewar pyrone. Polymerization conducted at room temperature and was stopped after 24 hours (65% conversion). Reported yields are isolated yields of polymers from the Dewar pyridone monomer. (b) Conversion of β-chloroester polymer to ester-functionalized, soluble poly(acetylene) derivative *via* base-mediated elimination.