Tetrahedron Letters 56 (2015) 674–676

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of poly β ketoesters via double acylketene trapping

Aniello Palma, James M. Serginson, Anthony G. M. Barrett *

Department of Chemistry, Imperial College London, London SW7 2AZ, UK

ARTICLE INFO

Article history:
Received 9 October 2014
Revised 27 November 2014
Accepted 9 December 2014
Available online 13 December 2014

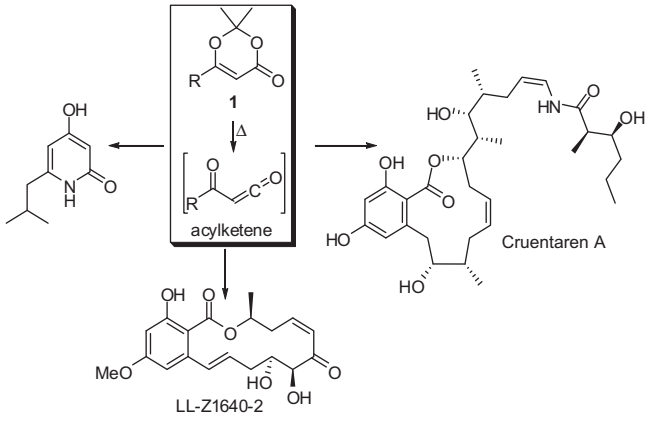
Keywords:
Poly β ketoesters
Acylketene
Dioxinone
Polyesters
Thermolysis

ABSTRACT

The synthesis and characterization of polymeric β ketoesters is herein reported. These polymers were prepared by allowing highly electrophilic acylketenes, generated in situ via thermolysis of stable 6-substituted-2,2-dimethyl-4*H*-1,3-dioxin-4-ones, to react with diol co-monomers. A relationship between polymer molecular weights and reaction conditions was established.

Polyesters are important synthetic biodegradable polymers with applications in many different fields ranging from biomedical uses, such as drug delivery, to new materials such as in food container fabrication.[1,2] This class of polymers are usually prepared by ring-opening polymerizations or via polycondensation reactions.[3,4] Poly β ketoesters in particular have applications as coating components and additives in adhesives. Such polymers are of particular interest as the carbonyl of the ketone and the CH_2 α to the carbonyls represent excellent chemical handles for cross-linking reactions.[5] A mild and tunable method to synthesize this class of compounds is highly desirable. Hawker and co-workers recently reported the reaction of ketenes with a series of diols in order to yield polyesters.[1] Inspired by the early work of Harris and Hyatt on the thermolysis of ambient temperature stable 6-substituted-2,2-dimethyl-4*H*-1,3-dioxin-4-one derivatives to generate the corresponding acylketenes,[6,7] we have developed a methodology which uses the acylketenes generated from dioxinones **1** as key synthetic intermediates in the total synthesis of natural products containing resorcylate units and other biologically active molecules (Scheme 1).[8–12] Herein we report the synthesis of poly β ketoesters, exploiting the high reactivity of acylketenes toward nucleophiles such as alcohols and phenols. Our approach involved the thermolysis of double-dioxinones **2a** and **2b**, thereby generating an acylketene at each terminus and thus acting as equivalents of double-acylketenes **3a**,**b**.[13] These were found to react with a range of diols yielding poly β ketoesters.[14] Since, we have established that the onset temperature of keto-ketene generation can be tuned by replacement of one or both of the methyl substituents in dioxinone **1** by phenyl groups, the polymerization reaction herein described should be tunable for the synthesis of poly β ketoesters (Scheme 2).[15]

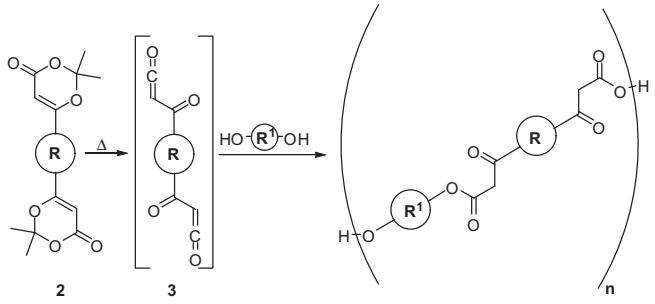
Conversion of the commercially available di-acid **4a** into the di-imidazolyl derivative **5** using carbonyl diimidazole (CDI) and subsequent reaction with the lithium enolate of *tert*-butyl acetate, which was generated with lithium di-*iso*-propylamide (LDA), gave diketo-diester **6a** (100%). Subsequent reaction of diketo-diester **6a** with a mixture of acetic anhydride, acetone and concentrated



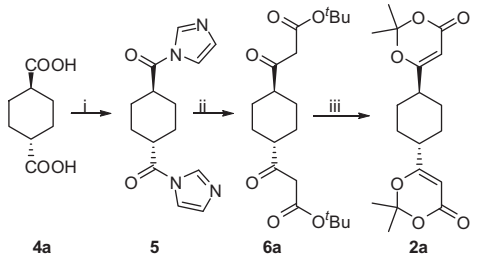
Scheme 1. Example of acylketenes employed in the synthesis of natural products and biologically active molecules.

* Corresponding author. Tel.: +44 020 7594; fax: +44 020 7594 5805.
E-mail address: agm.barrett@imperial.ac.uk (A.G.M. Barrett).

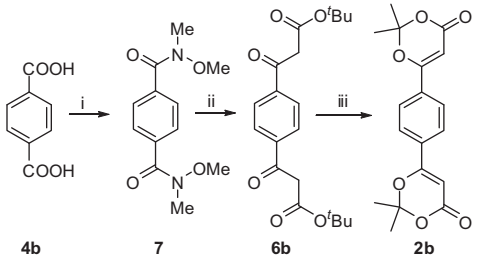
http://dx.doi.org/10.1016/j.tetlet.2014.12.036
0040-4039/



Scheme 2. General reaction scheme for the synthesis of poly β ketoesters.



Scheme 3. Synthesis of **2a**. Reagents and conditions: (i) CDI, THF, 100%; (ii) LDA, ^{t}BuOAc, THF, −30 °C, 100%; (iii) Me_2CO (20 equiv), Ac_2O (30 equiv), H_2SO_4, 0–20 °C, 60% yield over 2 steps.



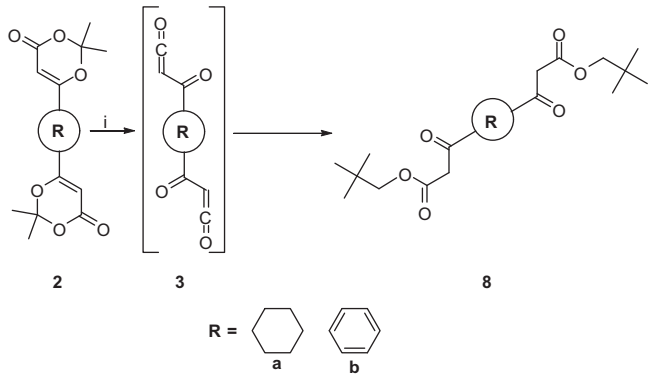
Scheme 4. Synthesis of **2b**. Reagents and conditions: (i) a) ClCOCOCl, CH_2Cl_2, DMF (catalyst); (b) $MeNH_2OMe{\cdot}Cl$, pyridine, CH_2Cl_2, 0–20 °C, 85% yield over 2 steps; (ii) LDA, ^{t}BuOAc, THF, −30 °C, 100%; (iii) Me_2CO (20 equiv), Ac_2O (30 equiv), H_2SO_4, 0–20 °C, 65% yield over 2 steps.

sulfuric acid gave the double dioxinone **2a** in 60% yield over the two steps (Scheme 3).

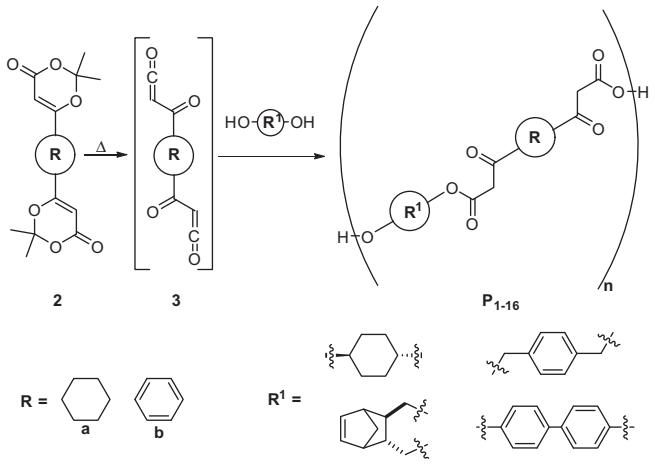
Double dioxinone **2b** was readily prepared starting from terephthalic acid (**4b**), which was converted into the diamide **7** in 85% yield over two steps. The lithium enolate prepared by deprotonation of *tert*-butyl acetate with LDA, was allowed to react with diamide **7** yielding diketo-diester **6b**. Subsequent reaction of diketo-diester **6b** with a mixture of acetic anhydride, acetone and concentrated sulfuric acid gave the double dioxinone **2b** in 65% yield over two steps (Scheme 4).

Generation of acylketenes **3a**,**b** via the thermolysis of double-dioxinones **2a**,**b** at 100 °C, and trapping with 2,2-dimethylpropan-1-ol was next examined (Scheme 5).[15]

Since we considered that solvent polarity would have a major impact on polymer M*w* and M*w*D, both toluene (bp 110 °C) and 1,4-dioxane (bp 104 °C) were examined, as the reflux temperature of each is appropriate for the generation of the acylketenes. These test reactions were carried out in parallel where the other reaction conditions were kept constant (concentration, temperature and reaction time). After evaporation of the solvent, the crude residues were analyzed by ^{1}H NMR spectroscopy. Pleasingly, under both



Scheme 5. Synthesis of diketo-diesters **8a**,**b**. Reagents and conditions: (i) Solvent in a sealed tube (PhMe or 1,4-dioxane), 2,2-dimethylpropan-1-ol (2 equiv), 100 °C.



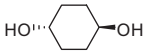
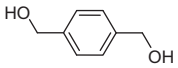
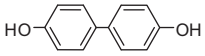
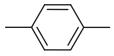
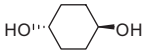
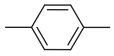
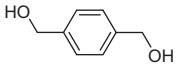
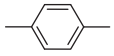
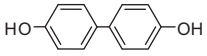
Scheme 6. Synthesis of poly β ketoesters $\mathbf{P_{1-16}}$.

sets of conditions, the conversion yields of double dioxinones **2a**,**b** into the double β ketoesters **8a**,**b** were greater than 95%. Both sets of conditions were subsequently applied to generate a variety of different poly β ketoesters by employing a number of different diols (Scheme 6).

Polymers $\mathbf{P_{1-16}}$ (Table 1) were characterized using ^{1}H NMR and IR spectroscopy, mass spectrometry and GPC techniques. The ^{1}H NMR spectra showed broad peaks in the expected regions characteristic of polymeric material. ^{1}H NMR peaks at 5.21 ppm and 1.65 ppm corresponding respectively to the proton on the sp^2 carbon of the dioxinone unit and the methyl groups in the starting materials **2a**,**b** were not present in all products $\mathbf{P_{1-16}}$. GPC analyses of the polymers $\mathbf{P_{1-16}}$ were performed in order to acquire structural information about the size of the polymers. This was carried out with a Polymer Labs PL-GPC 50 with two PL-Gel 5 μm MIXED-D columns at 40 °C using DMF with 1% v/v triethylamine and 1% v/v acetic acid as the eluent at a flow rate of 0.5 ml/min. Solutions of all samples were filtered using Whatman Puradisc 13 200 nm PTFE syringe filters. These GPC analyses showed a clear relationship between the size of the polymers and the reaction conditions employed with M*w* values significantly increasing when 1,4-dioxane was used as the solvent compared to toluene (Table 1 and Fig. 1).[16]

In conclusion, syntheses of several prototype poly β ketoesters from double dioxinones and diols are reported. The key polymerization process was the generation of acyl ketene intermediates via retro-Diels Alder fragmentation of 6-substituted-2,2-dimethyl-4*H*-1,3-dioxin-4-ones **2a**,**b** and trapping with a range of diols. Further

Table 1
Solvents used, Mw and polydispersity index (PDI) for polymers $\mathbf{P_{1-16}}$

Entry	R	R^1	Toluene	Mw (g/mol)	PDI	1,4-Dioxane	Mw (g/mol)	PDI
1			$\mathbf{P_1}$	1.03×10^3	1.46	$\mathbf{P_2}$	2.20×10^3	1.35
2			$\mathbf{P_3}$	1.22×10^3	1.28	$\mathbf{P_4}$	2.31×10^3	1.41
3			$\mathbf{P_5}$	1.30×10^3	1.25	$\mathbf{P_6}$	2.60×10^3	1.46
4			$\mathbf{P_7}$	1.60×10^3	1.22	$\mathbf{P_8}$	2.60×10^3	1.48
5			$\mathbf{P_9}$	1.75×10^3	1.40	$\mathbf{P_{10}}$	2.27×10^3	1.27
6			$\mathbf{P_{11}}$	1.09×10^3	1.21	$\mathbf{P_{12}}$	2.28×10^3	1.45
7			$\mathbf{P_{13}}$	1.44×10^3	1.17	$\mathbf{P_{14}}$	2.00×10^3	1.32
8			$\mathbf{P_{15}}$	1.38×10^3	1.11	$\mathbf{P_{16}}$	1.84×10^3	1.20

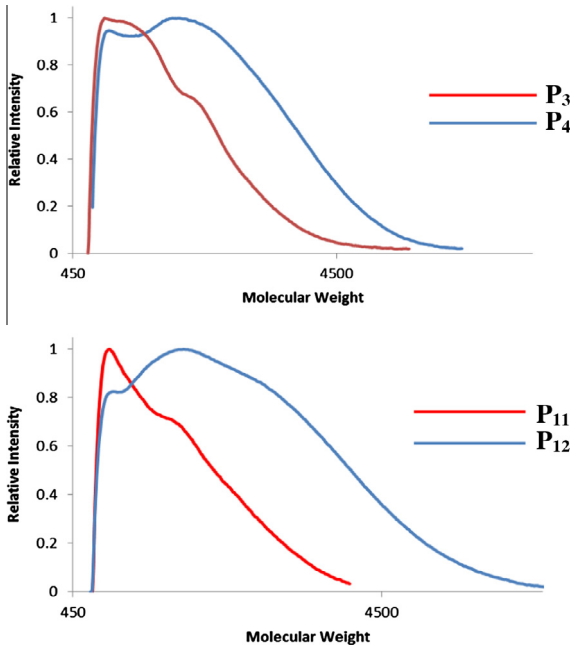


Figure 1. GPC analysis of polymers $\mathbf{P_3}$ versus $\mathbf{P_4}$ and $\mathbf{P_{11}}$ versus $\mathbf{P_{12}}$. The shift toward higher molecular weight for $\mathbf{P_4}$ and $\mathbf{P_{12}}$ compared to $\mathbf{P_3}$ and $\mathbf{P_{11}}$, respectively, demonstrates the solvent effects on the polymer size. The molecular weight axis is logarithmic ($\log_{10}$).

applications of these polymerization reactions will be reported in due course.

Acknowledgments

The authors thank the European Research Council (ERC) for research support, GlaxoSmithKline for the generous financial endowment (to A.G.M.B.). P.R. Haycock and R.N. Sheppard (both from Imperial College London) are thanked for the high-resolution NMR spectroscopy.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.12.036.

References and notes

1. Wolffs, M.; Kade, M. J.; Hawker, C. J. *Chem. Commun.* **2011**, 10572–10574.
2. Kim, Y.; Kim, H. K.; Nishida, H.; Endo, T. *Macromol. Mater. Eng.* **2004**, 923–926.
3. Jeske, R. C.; DiCiccio, A. M.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 11330–11331.
4. Nagai, D.; Sudo, A.; Endo, T. *Macromolecules* **2006**, 8898–8900.
5. Esser, R. J.; Devona, J. E.; Setzke, D. E.; Wagemans, L. *Prog. Org. Coat.* **1999**, *36*, 45–52.
6. Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* **1984**, 5105–5108.
7. Harris, T.; Harris, M. *Tetrahedron* **1977**, 2159–2185.
8. Patel, B. H.; Mason, A. M.; Barrett, A. G. M. *Org. Lett.* **2011**, *13*, 5156–5159.
9. Blencowe, P. S.; Barrett, A. G. M. *Eur. J. Org. Chem.* **2014**, 4844–4853.
10. Fouché, M.; Rooney, L.; Barrett, A. G. M. *J. Org. Chem.* **2012**, *77*, 3060–3070.
11. Miyatake-Ondozabal, H.; Barrett, A. G. M. *Org. Lett.* **2010**, *12*, 5573–5575.
12. Cookson, R.; Pöverlein, C.; Lachs, J.; Barrett, A. G. M. *Eur. J. Org. Chem.* **2014**, 4523–4535.
13. The intermediates **3** are drawn as double ketenes for convenience but it is highly likely, given the high reactivity of ketenes, that the concentration of any ketene intermediate is very low and the concentration of a double ketene effectively zero.
14. All the ketoesters exist as a mixture of keto and enol tautomers. However, for convenience, they are drawn as single entities.
15. Navarro, I.; Schlingmann, G.; Christoph, P.; Barrett, A. G. M. *J. Org. Chem.* **2009**, *74*, 8139–8142.
16. Higashimura, T.; Suzuoki, K.; Kato, H.; Okamura, S. *Die Makromol. Chem.* **1967**, *108*, 129–137.