An efficient synthesis of the inimer gamma-(2-bromo-2-methylpropionate)-epsilon-caprolactone (BMPCL)

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ABSTRACT

The original synthesis of gamma-(2-bromo-2-methylpropionate)-epsilon-caprolactone (BMPCL), in use since 1999, has an overall yield of 17% and uses a Cr(VI) reagent for a key oxidation. Despite these liabilities, this synthetic procedure has been reported in all subsequent uses of BMPCL. This is due to BMPCL’s desirable capacity as an inimer – the tertiary alpha-bromo ester functionality allows initiation of controlled radical polymerization while the strained lactone moiety can act as a monomer in ring-opening polymerizations. These orthogonal capacities make BMPCL useful for the synthesis of complex polymer architectures such as combs. This paper reports a higher yielding, telescoped BMPCL synthesis that reduces the use of toxic reagents. Utilizing a mild and near-quantitative activated-DMSO mechanism, the Swern oxidation, in place of pyridinium chlorochromate increases the yield by approximately half to 25% (average of three trials) while eliminating heavy metal usage. In an additional effort for synthetic efficiency, the number of chromatographic purifications was reduced from three to one.

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Introduction

Block copolymers display a broad array of functional morphologies in the solid state, which has been well established for simple linear diblocks (1, 2). More recent investigations of high-χ block copolymer solution dynamics reveal a dramatic diversity of morphologies (3). These soluble nanostructures are being aggressively investigated for high-value applications such as drug
delivery \((4–6)\). Many block copolymer syntheses rely on orthogonal reactivity, often produced through inefficient post-polymerization modification. The efficiency of block copolymer synthesis is increased by the use of monomers with inherent orthogonal reactivity.

Controlled radical polymerizations (CRP) \((7–9)\) and lactone ring-opening polymerization (ROP) \((10–12)\) are ubiquitous. These polymerization techniques have been combined in bifunctional initiators (Scheme 1) \((13–18)\), but it is much harder to find inimers, molecules that can act as both CRP initiators and ROP monomers. In addition to high efficiency synthesis, inimers allow access to different polymer architectures. Bifunctional initiators make diblocks whereas inimers make combs (Scheme 1). An elegant example is Hedrick’s synthesis \((19)\) of gamma-(2-bromo-2-methylpropionate)-epsilon-caprolactone (BMPCL, 4). This work also demonstrated the use of BMPCL in all possible combinations of sequential and simultaneous ROP and CRP. Hedrick’s synthesis begins by reacting diol 1 with a latent CRP initiator to yield alcohol 2, which is sequentially oxidized first to a ketone (3) and finally to BMPCL (Scheme 2). This synthesis uses \(Cr^{VI}\) for a key oxidation and each of its three steps includes a full workup and purification. As is common across chemistry, polymer scientists are often more interested in the final outcomes of their investigations than in developing greener synthetic approaches \((20)\). Better processes thus remain undeveloped, unpublished, and unused. Therefore, it is unsurprising that all subsequent literature uses of BMPCL cite Hedrick’s protocol, with its reported overall yield of 17% \((21–36)\). Our BMPCL synthesis (Scheme 3) significantly increases the efficiency by employing reaction telescoping \((37)\) to eliminate two columns, and replacing PCC with the milder, higher yielding, and dramatically less toxic Swern protocol. The elimination of \(Cr^{VI}\) \((38, 39)\), and the increased overall yield, work in combination to provide a greener route to the BMPCL inimer.

Scheme 1. Bifunctional initiators and inimers in ring-opening polymerization (ROP)/atom transfer radical polymerization (ATRP) copolymer synthesis.

Scheme 2. Hedrick’s synthesis of BMPCL (4).\(^{19}\)
Materials and methods

Chemicals and equipment

Flash chromatography was performed using silica gel (Sili-cycle, Ultra Pure, 230–400 mesh). Et₃N (99%, pure), 2-bromo-2-methylpropionyl bromide (98%), oxalyl chloride (98%), meta-chloroperoxybenzoic acid (mCPBA, 70-75%), and Celite® 545 were used as received from Acros Organics. THF and CH₂Cl₂ were ACS Reagent Grade and used as received from Pharmco-Aaper. Dry DMSO was transferred to a Strauss bomb (Quark glass) when received and dispensed from there. Dry CH₂Cl₂ was dispensed from an mBraun USA MB-SPS. NMR spectra were acquired on a JEOL-ECZS 400 MHz spectrometer in CDCl₃ (Cambridge Isotope Labs, 99.8% D) and referenced to solvent residuals (40). IR spectra were acquired on a PerkinElmer Spectrum Two FT-IR spectrometer with a PIKE Technologies MiRacle ATR solids attachment equipped with a ZnSe crystal. Mass spectrometry performed the Mass Spectrometry Lab of the School of Chemical Sciences at the University of Illinois Urbana-Champaign. All glassware used in Swern oxidations was treated with a mild bleach solution prior to removal from the hood. Unless otherwise specified, thin layer chromatography (tlc) was performed on Supelco TLC Silica Gel 60 F₂₅₄ plates and visualized with UV and/or a 10% w/v solution of phosphomolybdic acid in absolute ethanol.

(4-Ketocyclohexyl) 2-Bromo-2-methylpropionate (3)

In a dry, N₂ flushed 100 mL round-bottom flask equipped with a septum and under pressure of N₂, CH₂Cl₂ (dry, 60 mL) and oxalyl chloride (0.624 mL, 7.15 mmol, 1.22 equiv) were stirred, at −78 °C. DMSO (dry, 0.864 mL, 12.2 mmol, 2.07 equiv) in CH₂Cl₂ (dry, 0.864 mL) was added dropwise to the stirred cooled solution. After 45 min, (4-hydroxycyclohexyl) 2-bromo-2-methylpropionate (19) (1.555 g, 8.87 mmol, 1.00 equiv) in CH₂Cl₂ (dry, 2.97 mL) was added dropwise. After 1 h, Et₃N (3.35 mL, 24.1 mmol, 4.11 equiv) was added, and the solution warmed to RT over 30 min. The pale yellow solution was quenched with H₂O (20 mL), followed by removal of the organic phase, and extraction of the aqueous phase with CH₂Cl₂ (3 × 20 mL). The combined organic phases were washed with 40 mL each of 1% HCl, H₂O, 5% NaHCO₃, and brine. The solution was dried over MgSO₄ and evaporated to yield the crude ketone as a yellow liquid that solidifies if stored overnight in the fridge. The crude mixture is not indefinitely stable even when cool. Flash chromatography (hexanes:EtOAc, 3:2) produces a clear liquid which solidified in the fridge to yield the title compound as a white solid (1.46 g, 5.55 mmol, 94.5% yield; avg. of 3 rxns = 88.5%). ¹H NMR matched that previously reported (see Supporting Information).

Gamma-(2-Bromo-2-methylpropionate)-epsilon-caprolactone (BMPCL, 4)

A reaction vessel was charged with 1,4-cyclohexanediol (mixture of cis and trans) (1.02 g, 8.78 mmol, 1.00 equiv) and Et₃N (1.84 mL, 13.2 mmol, 1.50 equiv) which were stirred until dissolved in THF (17 mL), followed by the dropwise addition of 2-bromo-2-methylpropionyl bromide (1.09 mL, 8.82 mmol, 1.00 equiv) over 10 min. After a minimum of 3 h (or up to 24 h), solvent was evaporated, the residue was dissolved in CH₂Cl₂, washed with 1 M HCl (3 × 5 mL), H₂O/brine (∼4:1 mixture, 2 × 5 mL), dried over MgSO₄, and evaporated to yield a clear, yellow liquid. In a stirred, dry 250 mL round-bottom flask equipped with septum and pressure of N₂, CH₂Cl₂ (dry, ~90 mL) and oxalyl chloride (0.91 mL, 10.4 mmol, 1.20 equiv) were combined, and cooled to −78 °C. DMSO (dry, 1.30 mL, 19.5 mmol, 2.25 equiv) in CH₂Cl₂ (dry, 1.30 mL) were mixed under N₂ in a 5 mL syringe and added dropwise to the cooled solution at 1 mL/min. After 45 min, the crude alcohol in CH₂Cl₂ (dry, 5-10 mL) was added portion wise by cannula. After 75 min, Et₃N (4.90 mL, 35. mmol, 4.0 equiv) was added, the solution was stirred for 10 min, removed from the cold bath, and warmed to RT over 30 min.
The reaction was quenched with H$_2$O (30 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic phase was washed successively with 30 mL each 1% HCl, H$_2$O, 5% NaHCO$_3$ and brine, dried over MgSO$_4$, and evaporated to yield a yellow liquid (product $R_t = 0.32$, 7:3 hexanes:EtOAc). A solution of crude ketone in CH$_2$Cl$_2$ (~8 mL), was added mCPBA (3.35 g, 70-75%, 19.4 mmol, 2.2 equiv) in CH$_2$Cl$_2$ (20 mL) dropwise (1 mL/min). Upon reaction completion, as determined by tlc, the cloudy solution was filtered over Celite. The yellow filtrate was washed with 5%aq. NaHCO$_3$ (3 × 30 mL), brine (1 × 30 mL), dried over MgSO$_4$, and evaporated to yield a pale yellow oil which was purified by gradient flash chromatography [175-200 mL silica gel; (solvent gradient given as: ‘volume % EtOAc in hexanes’) 400 mL 10%, 250 mL 15%, 250 mL 20%, 250 mL 25%, 400 mL 30% EtOAc, 200 mL 50%]. Analytically pure product was isolated as a white crystalline powder (0.704 g, 2.02 mmol, 26.3%; avg. of 3 rxs = 24.9%; $R_t = 0.22$ (hexanes:EtOAc, 7:3)]. Spectroscopy matched that previously reported (see Supporting Information).

Results and discussion

As part of our interests in lactone polymerization (41, 42), we turned to BMPCL as a lactone inimer. Although it is an attractive target, the synthesis seemed ready for modernization, which we undertook. The first step was developing a Swern protocol (43) for oxidation of the alcohol. This proceeded smoothly under relatively common conditions (44), reliably achieving high isolated yields, averaging 88% over three trials of our optimized protocol. This 20% increase over Hedrick’s reported method is the largest contributor to our increased overall yield. Furthermore, utilization of this protocol avoids the use of Cr$^{VI}$ oxidants, a significant environmental benefit (45, 46) not captured directly in the yield calculation. Chromatographic purification of the Swern product is particularly simple. Once the obviously odiferous dimethyl sulfide has eluted, the highly crystalline ketone 3 can be observed collecting on the column tip and test tube sides. Despite the explosion hazard associated with solid peroxides, and literature reports of catalyzed oxidations using the green reagent H$_2$O$_2$ as the terminal oxidant (47), the commercial availability of mCPBA was attractive. Therefore, we made no significant changes to the individual acylation or Baeyer-Villiger protocols and achieved comparable yields for individual transformations.

While we hoped to develop a true one-pot procedure, differences in optimal reaction concentrations and solvents proved insurmountable. Furthermore, an aqueous workup between each synthetic transformation proved necessary, although the workup between the Swern and Baeyer-Villiger can be performed in the reaction flask, if desired. We were able to eliminate two columns, however, and limit inter-reaction procedures to simple aqueous workups (Scheme 3). The single column purification is remarkably simple. The primary impurity is a quickly eluted high $R_t$ material generated in the first step and which persists through the remaining reactions unaffected, presumably diacylated cyclohexanediol.

While developing this protocol we noted that the post-Swern mixture does not store well, even dilute and in a freezer. It is thus important to proceed directly to the aqueous workup and submit the crude ketone to Baeyer-Villiger conditions. Furthermore, given the potential for lactone degradation in the presence of acid, workup and purification of the final product should be initiated as soon as the final oxidation is complete. In light of these factors, one critical component of successfully employing this protocol is to carefully plan reaction timing for the two oxidation steps.

Given the critical importance of eliminating residual mCPBA or its reduced byproduct meta-chlorobenzoic acid (mCBA), close attention was paid to the aromatic region of the $^1$H NMR spectra, and no signals other than the solvent residual are observed (Supporting Information). IR is also provided (Supporting Information), though it is unlikely to be better than NMR in detection of either mCPBA or mCBA given the degree of overlap in major spectra bands. ESI-HRMS (Supporting Information) shows a parent ion peak at 279.0226 m/z which is consistent with BMPCL plus a proton. The expected signal at 281.0204 m/z due to $^{81}$Br is also observed. Importantly, no signals are observed for protonated mCBA (157.01 m/z) or mCPBA (173.00 m/z). Removal of residual water from BMPCL via toluene azeotrope prior to polymerization is not expected to impact yield.

Conclusion

BMPCL is one of a very limited number of molecules that can act as both an initiator for CRP and a monomer for ROP. Since its initial disclosure in the literature in 1999, the reported method of preparation has not changed, despite its length, use of toxic Cr$^{VI}$, and low overall yield. This paper provides a revised experimental procedure allowing for the synthesis of BMPCL more quickly, with a higher overall yield, and using less toxic materials. Rapid adoption of this significantly greener synthesis will be aided by the simplicity and straightforward nature of these changes and the highly detailed experimental protocol. We hope this will increase the use of this otherwise excellent inimer while lowering...
the negative environmental impact of its production. We believe this method provides material suitable for use in polymerization, once dried, and this work is currently underway in our laboratory.

Author contributions

Data available within the article or its supplementary materials. The authors declare no competing interests. S. E. W., A. C., and J. M. K. contributed equally; E. H., L. L., and M. O. contributed equally.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Supporting information

Electronic supporting information includes annotated $^1$H- and $^{13}$C-NMR, and ATR-FTIR spectra for both compounds and HRMS and single mass analysis for BMPCL. $^1$H- and $^{13}$C-NMR, and ATR-FTIR spectra for are also given in mNova format.

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