

The Synthesis of BMPCL (Hedrick REP Inimer/ATRP Initiator)

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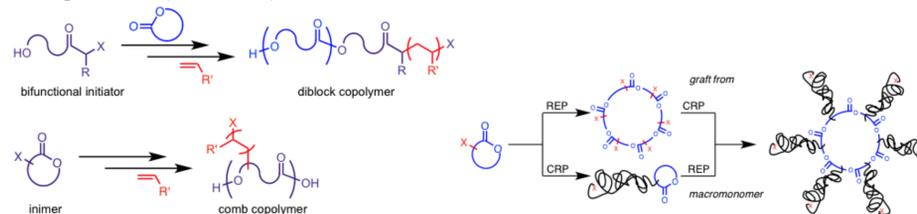
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Abstract

The new synthetic pathway for the creation of γ -(2-bromo-2-methylpropionyl)- ϵ -caprolactone (BMPCL) and its increase in overall yield is described. BMPCL can serve as an inimer, a molecule that can be both a monomer for ring expansion polymerization and an initiator for controlled radical polymerizations. Improvements were made to the method published by Hedrick *et al.* Our method avoids pyridinium chlorochromate (PCC), a reagent with negative environmental impacts from Cr^{VI}, by using the milder Swern oxidation. This reduces environmental issues, while also improving the overall yield from 17% to 28%. Our new synthesis also eliminates the need for chromatography after each step, which reduces waste and helps with yields. The final synthetic step, a Baeyer-Villiger oxidation was also found to take less than the reported 24 hours to run to completion, decreasing both the time required for synthesis and the potential for product degradation. The improvements upon the synthesis of BMPCL allow for the monomer to be made faster and in higher yields, improving the overall quality of the synthesis.

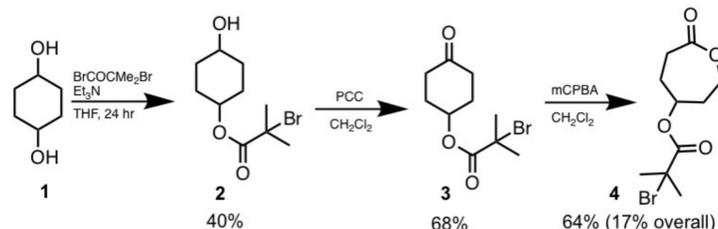
Background

Block copolymers consists of monomers joined together in such a way, that the polymer constituents, blocks, each contain only one type of monomer, so each section is different in composition. They have been shown to have a large diversity in morphologies, and they can be made using lactone ring opening polymerization (ROP) as well as controlled radical polymerizations (CRP). The two processes are typically combined using bifunctional initiators, which form diblock polymers. An inimer, a molecule that can act both as an ROP monomer and as a CRP initiator, can create a polymer with an entirely new architecture—jellyfish, or very large rings with chains growing off of it (Scheme 1).



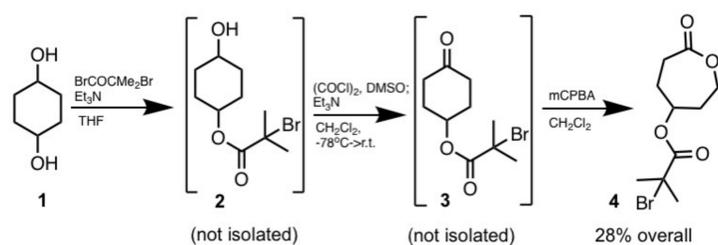
Scheme 1. Bifunctional initiators and inimers in copolymer synthesis and Tandem polymerization of jellyfish/brush polymers.

A New Method of Synthesis



In Hedrick's synthesis of The γ -(2-bromo-2-methylpropionyl)- ϵ -caprolactone (BMPCL, 4), pyridinium chlorochromate (PCC) is used to create intermediate 3. This has high environmental impacts since PCC uses Cr^{VI}.

Scheme 2. Hedrick's synthesis of BMPCL (4)



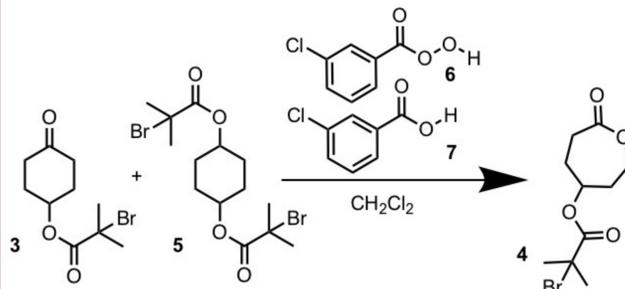
The Getzler lab has improved upon this synthesis, utilizing a Swern oxidation instead of PCC, while also providing a higher overall yield.

Scheme 3. Getzler Lab BMPCL (4) Synthesis

Current and Future Work

Attempts to track the Baeyer-Villiger oxidation at full-scale have resulted in tlc's that do not match those found in microscale trials. It would appear that tlc is less helpful when reaction components are not pure, but it can still be used to check for the correct materials at the beginning and end of each step of the synthesis. Calculations have been done to determine the amount of residual mCBA in purified products in order to determine more accurate yields, but these amounts have been found to be highly variable.

Next steps will include first obtaining new mCPBA that is free of impurities. We will look to see if this solves the issues with excess mCBA after purification. Next, yields will be obtained at various points throughout the 24 hour reaction period for comparison with the ultimate goal of finding a time of maximum yield. At that point, yields will be confirmed so that our work on the new synthesis can be published.



Scheme 6. Baeyer-Villiger oxidation where the starting material is unpurified. The desired starting material (3) is in solution with diacetylated material (5), a byproduct of the first step and reacted with mCPBA (6) and any mCBA (7) to create the desired product (4).

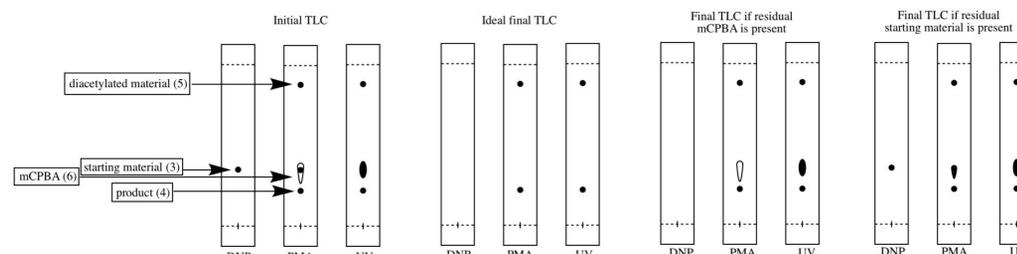
Product Code	Reaction Mass(grams)	% Yield	%impurity (mCPBA)	Calculated Pure BMPCL Mass(grams)	Actual %yield
JMB-1-109 A and B	0.82	35%	5.1	0.78	34%
JMB-1-104B	0.55	24%	16.6	0.46	20%
JMB-1-101	0.33	14%	2.3	0.32	14%
JMB-1-78	0.5	41%	13.7	0.43	35%
JMB-1-116 A and B	0.63	27%	3.4	0.61	26%
JMB-1-119	1.03	44%	5.4	0.97	42%
JMB-1-123	0.54	23%	4.7	0.51	22%
Average Percent Yield					28%

Table 1. BMPCL yields using impure mCPBA.

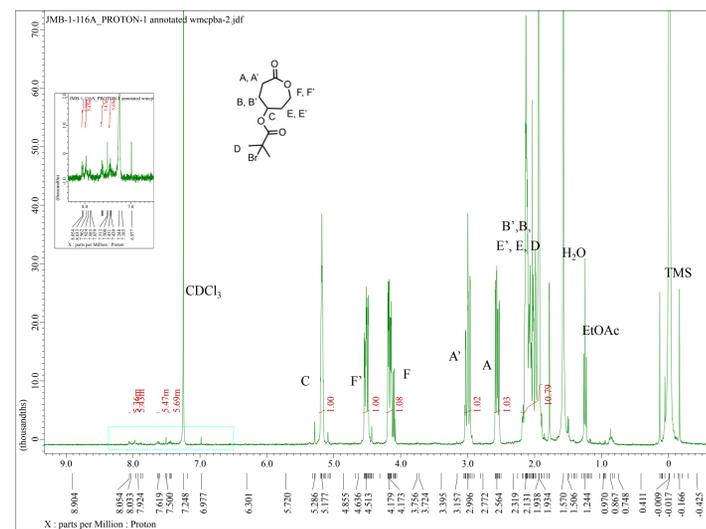
Improving Upon the Baeyer-Villiger

The BV oxidation can be tracked using thin layer chromatography (tlc) with a running solvent of 7:3 (Hex:EtOAc) to determine their respective R_f values. Phosphomolybdic acid (PMA) and dinitrophenylhydrazine (DNP) stains were used along with UV to track each component. Compound 4 is visible under UV at a much lower R_f than compounds 6 and 3, but compounds 6 and 3 run at very similar R_f values, which are indistinguishable using only UV. When DNP is present, only compound 3 produces a stain. Even with a proper tlc tracking system, it began to appear that while there was no compound 3 present, the final column-purified product still had residual amounts of compound 6 that was in such small amounts, it could not be seen via tlc.

When not stored properly, mCPBA (6) can degrade to its more stable acid form, mCBA (7), which cannot perform the BV oxidation. This can pose challenges when running the reaction because when impure, it is difficult to estimate how much oxidant is required to push the reaction to completion. Additionally, once complete, the excess of compounds 6 and 7 can be difficult to separate using a column. It is ideal to have a minimal amount of excess oxidant.



Scheme 4. TLCs at the beginning of the BV compared to different ending options using UV, DNP and PMA stains (7:3 hexanes:EtOAc).



Scheme 5. NMR spectrum of purified BMPCL (4) after the full synthesis (CDCl₃).

References

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