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A Simple and Efficient Synthesis of Functionalized Cyclic Carbonate Monomers Using a Versatile Pentafluorophenyl Ester Intermediate

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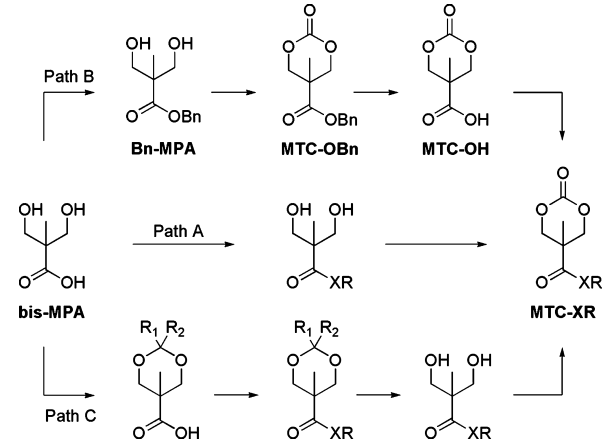
Abstract: An improved two-step synthetic route to functionalized cyclic carbonate monomers that features a novel cyclic carbonate intermediate with an active pentafluorophenyl ester group (MTC-$OPhF_5$) has been developed. The versatile pentafluorophenyl ester intermediate can be synthesized on the gram to kilogram scale in one high-yielding step and is easy to store and handle on the benchtop. The active pentafluorophenyl ester of MTC-$OPhF_5$ is amenable to further substitution with suitable nucleophiles such as alcohols and amines to generate functionalized cyclic carbonates in high yields. The substitution reaction is tolerant of a wide variety of functionalities, including various hydrophobic and hydrophilic groups, reactive functionalities (via thiol−ene click chemistry or alkyl halides), and protected acids, alcohols, thiols, and amines. In view of the ever-increasing need for biodegradable and biocompatible polymers, this new methodology provides a simple and versatile platform for the synthesis of new and innovative materials.

Aliphatic polycarbonates and polyesters have received considerable attention as biocompatible materials for drug delivery, polymer-based therapeutics, and imaging contrast agents.[1] Suitable polymers can be prepared by ring-opening polymerization (ROP) of cyclic carbonates or cyclic esters by cationic, anionic, coordination−insertion, organocatalytic, and enzymatic methods.[2] In order to expand their versatility, access to cyclic monomers having a wide variety of functional groups in a simple and cost-effective manner is essential. While functionalized cyclic esters have been reported, steric and ring-strain issues have limited the utility of this approach.[3] Alternatively, many groups have focused on functionalized cyclic carbonate monomers[4] derived from 1,3-diols.

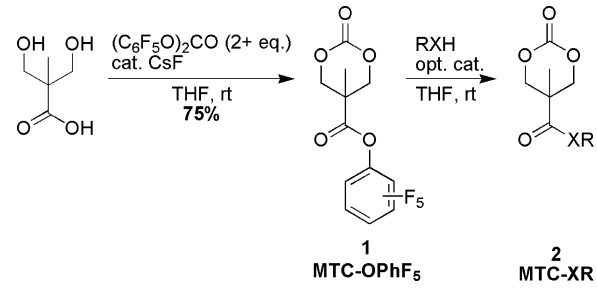
A number of synthetic pathways for the preparation of functionalized cyclic carbonates starting from 2,2-bis(hydroxymethyl)-propionic acid (bis-MPA) have been reported (see Scheme 1). The most direct synthetic route involves functionalization of the carboxylic acid group under acidic or basic conditions prior to installation of the cyclic carbonate (path A).[5] Alternate pathways B and C enable coupling of more sensitive functional groups via more tedious and complicated protection/deprotection schemes. In path B, the free carboxylic acid must be activated, typically by use of dicyclohexylcarbodiimide or conversion to the acyl chloride, prior to reaction with an alcohol or amine nucleophile.[6] In path C, the diols are protected (commonly as an acetonide) prior to functionalization of the carboxylic acid.[7] Unfortunately, these reported schemes do not employ a common intermediate for the functionalization step. Finally, the use of phosgene to install the cyclic carbonate suffers from its toxicity and labor intensity (e.g., reactions are performed at −78 °C with exhaustive workups). The use of phosgene alternatives, such as various chloroformates, nitro-substituted diphenylcarbonates, and carbonyl diimidazole,[5−8] suffers from unwanted side reactions, low reactivity, or difficult workups.

Scheme 1. Reported Synthetic Routes to Functionalized Cyclic Carbonate Monomers



The lack of a simple and efficient synthetic route to functionalized cyclic carbonate monomers constitutes a significant barrier to the widespread practical application of this cyclic monomer platform in the production of tailored functional biodegradable polymers. In particular, a versatile synthetic scheme based on a common intermediate would be beneficial.

Scheme 2. General Synthetic Route to Functionalized Cyclic Carbonate Monomers Using Pentafluorophenyl Ester Intermediate **1**



Scheme 2 shows an improved two-step synthetic route to functionalized cyclic carbonate monomers that features a novel cyclic carbonate intermediate with an active pentafluorophenyl ester group, MTC-$OPhF_5$ (**1**). In contrast to an *N*-succinimidyl ester variant reported by Zhou et al.,[9] the versatile intermediate **1** and

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its ethyl analogue ETC-OPhF$_5$ (see the Supporting Information) are easily synthesized on the gram to kilogram scale in one high-yielding step. Reaction of bis-MPA with 2 equiv of commercially available bis(pentafluorophenyl)carbonate (PFC) results in the one-pot transformation of the carboxylic acid into a pentafluorophenyl ester group and ring-closure of the 1,3-diol to generate a cyclic carbonate (see the Supporting Information for individual model reactions). Intermediate **1** is easy to store and handle on the benchtop, and its active pentafluorophenyl ester group can be reacted with suitable nucleophiles such as alcohols and amines to generate functionalized cyclic carbonates in high yields.

As opposed to phosgene, PFC is a crystalline solid that is easy to handle and store. Ring closure of the 1,3-diol with PFC requires a catalyst such as CsF to affect the ring closure without facilitating concomitant polymerization. THF was found to be the most effective solvent, likely because of the partial solubility of the CsF, although acetonitrile was effective as well. During the initial stages of the reaction, a significant amount of gas, presumably carbon dioxide from formation of the pentafluorophenyl ester, was evolved with a slight exotherm (~5 °C). Upon completion (~20 h), the reaction mixture was concentrated and redissolved in methylene chloride, where the much of the pentafluorophenol byproduct precipitated and could be recovered. The product was then rinsed with saturated aq. NaHCO$_3$ then water, dried over MgSO$_4$, and concentrated. The crude product was recrystallized from an ethyl acetate/hexane (1:1) mixture to afford **1** as a white crystalline powder in 75% yield. The structure of MTC-OPhF$_5$ was confirmed by ^{13}C, ^{1}H, and ^{19}F NMR spectroscopy as well as mass spectrometry.

A large number of functional carbonate monomers are easily prepared by the direct reaction of the common intermediate **1** with various nucleophiles. A series of alcohols and amines were surveyed to generate monomers **2a**−**o** (Figure 1) with a wide range of functional groups, including various hydrophobic and hydrophilic groups, reactive functionalities (via thiol−ene and triazole click chemistry or alkyl halides), and protected acids, alcohols, thiols, and amines. As before, the concern is accomplishing the functionalization without opening the ring or effecting polymerization. Use of weaker nucleophiles such as alcohols required a catalyst such as CsF to facilitate the reaction. Selective reaction of amines with the pentafluorophenyl ester group was accomplished without the use of a catalyst by lowering the reaction temperature. This transformation was accomplished in nearly quantitative conversions with minimal, if any, carbonate ring opening.

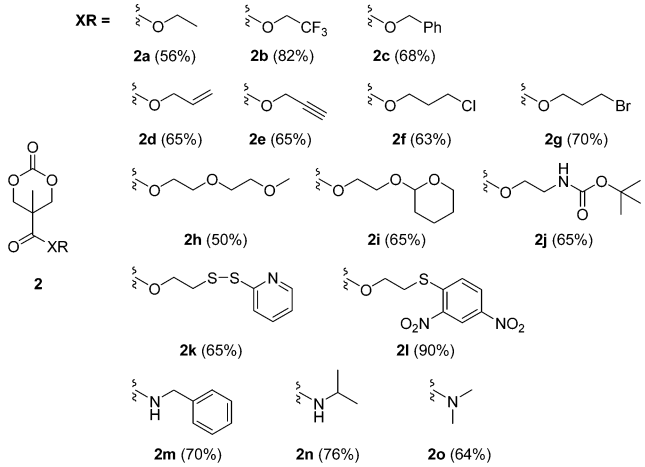

Figure 1. Functionalized cyclic carbonates **2** synthesized from **1**.

Selected functionalized carbonate monomers were polymerized using a catalyst system[6b] comprising 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexyl-2-thiourea (TU) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) to generate polymers **3a**−**f** with predictable molecular weights and narrow polydispersities (Scheme 3 and Table 1).

Scheme 3. Ring-Opening Polymerization of Selected Monomers To Form Functionalized Polycarbonates **3**

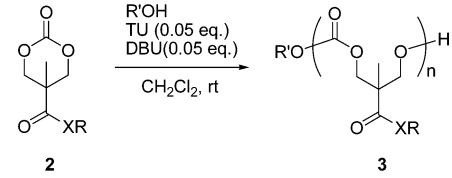

Table 1. Polymerization of Functionalized Cyclic Carbonates

polymer	monomer	initiator	[M]/[I]	M_n (g/mol)	PDI	yield (%)
3a	**2a**	Bn-MPA	108	17100	1.27	86
3b	**2b**	Bn-MPA	54	11500	1.26	76
3c	**2f**	Bn-MPA	102	4400	1.32	64
3d	**2g**	Bn-MPA	101	7300	1.42	84
3e	**2i**	Bn-MPA	99	6600	1.24	60
3f	**2o**	pyrenebutanol	63	10500	1.32	71

In conclusion, we have reported a novel two-step synthesis that enables a broad range of functionality to be incorporated into cyclic carbonate monomers using a common and versatile pentafluorophenyl ester intermediate. Subsequent polymerizations of the various cyclic carbonates have demonstrated fidelity and control consistent with previous reports[6b] and thus will permit higher-order architectures (such as cross-linking, block copolymers, graft polymers, etc.) to be constructed. In view of the ever-increasing need for biodegradable and biocompatible polymers, along with new breakthroughs in self-assembly and nanotechnology, it is envisioned that this improved route to functionalized cyclic carbonates will provide a synthetically facile platform for the synthesis of new and innovative materials, including a new class of polymeric activated esters.[9,10]

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Supporting Information Available: Synthetic procedures and characterization data for pentafluorophenyl ester **1**, functionalized cyclic carbonates **2**, and functionalized polycarbonates **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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