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Methods for the Synthesis of Functionalized Pentacarboxycyclopentadienes

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Abstract

Protocols for the synthesis of diverse PCCPs are described. Starting from readily available pentacarbomethoxycyclopentadiene, transesterification offers single-step access to aliphatic ester derivatives, while treatment with amines produces mono- or diamides. For less nucleophilic alcohols, an alternative procedure involving the in situ generation and esterification of a putative cyclopentadiene penta-acid chloride has been developed.

Graphical Abstract

Cyclopentadiene is a hydrocarbon that is canonically known for its unusually high acidity [$pK_a(H_2O) = 16$], which results from aromatic stabilization of its conjugate base.^{1,2} This remarkable acidity can be greatly enhanced by the incorporation of electron-withdrawing substituents at each of the five carbons of the conjugated system. Indeed, the pentacarbomethoxy derivative has been reported to be as acidic as HCl (Figure 1a),³ while the pentanitride compound has a level of acidity on par with perchloric acid.⁴ Such extreme carbanion stability offers intriguing fodder for chemical investigation,^{5–7} yet relatively few practical applications of these species have been reported. Primarily the pentacarboxycyclopentadienes (PCCPs) have been used as ligands, which typically bind to metal centers via the carboxylate oxygens in an “acac-type” fashion or the classic η^5 -binding mode (Figure 1a).^{8,9}

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental details, characterization data, spectra, HPLC traces. (PDF) and .cif files.

We recently introduced PCCPs as a novel class of enantioselective Brønsted acid catalysts.¹⁰ The motivation for this work was a desire to identify a catalytic platform that would be trivial to synthesize and simple to diversify, and that might offer unique opportunities for transition state stabilization. In the course of this work, we found that while 1,2,3,4,5-pentacarbomethoxycyclopentadiene (**2**) was readily available on a preparative scale (Figure 1b), there was a dearth of synthetic procedures to access derivatives of this core material. Crucially, direct hydrolysis to the penta-acid is infeasible due to facile decarboxylation,^{11,12} leaving transesterification or amidation as the most logical synthetic possibilities. While straightforward in conception, such transformations of PCCPs were poorly represented in the literature,¹³ and thus we sought to identify robust procedures to access the desired derivatives. Herein, we describe broadly flexible protocols for the synthesis of functionalized PCCP derivatives.

The pentamethyl ester **2** is readily available by the procedure originally reported by Diels¹⁴ and modified by LeGoff,¹⁵ in which dimethyl malonate and three equivalents of dimethyl acetylenedicarboxylate are combined to produce octacarbomethoxycycloheptadiene **1** as a mixture of diene regioisomers (Figure 1b). Subjection of this material to refluxing aqueous potassium acetate results in ring contraction and fragmentation to yield **2** as a crystalline solid after protonation with HCl. Because this procedure is easily scaled (>50 g), we were keen to identify means to transesterify or amidate **2** that would allow simple access to chiral PCCP ester **3** or amide **4** derivatives.

In this regard, we found that refluxing L-menthol (**5**) with **2** in the presence of *N*-methylimidazole (NMI) resulted in the production of the pentamenthol ester **6** in 96% yield (Figure 1c), albeit with a reaction time of several days to weeks depending on the scale. Other additives such as DMAP, Et₃N, NaH, or *p*-TSA produced inferior results and/or decomposition (see supporting information). Importantly, a stream of N₂ directed just above the solvent was found to greatly decrease reaction times to 48–72 h and in general improved the efficiency of the process, presumably due to the mass-action removal of MeOH.

Using this procedure, we found that PCCPs that incorporated straight-chain, primary alkyl (entry 1), alkenyl (entry 2) and alkynyl (entry 3) alcohols could be prepared in high yield (Figure 2). The engagement of the chiral terpenol (1*S*,2*S*,5*S*)-(-)-Myrtanol was also efficient (entry 4). Cyclic alcohols, including cyclohexanol (entry 5) and dicyclohexylmethanol (entry 6) were also readily installed, as were chiral secondary homobenzylic alcohols (entries 7 and 8). Even a large alcohol such as cholesterol could be incorporated with modest efficiency (entry 9). On the other hand, a number of important substrate classes were not compatible with this procedure, including tertiary alcohols such as *tert*-butanol and 1-adamantol, or electron-deficient alcohols such as benzyl alcohol, phenol, and 2,2,2-trifluoroethanol, all of which failed to cleanly lead to the desired product. The failure of these latter classes of alcohols was particularly disappointing in the context of developing enantioselective Brønsted acid catalysts, and so we sought an alternative procedure that would allow for the incorporation of these less nucleophilic substrates.

After much experimentation, we found that **2** could be converted to the putative penta-acid chloride **16** by treatment with thionyl chloride and catalytic DMF (Figure 3). Addition of an

alcohol in excess to this intermediate then furnished the corresponding PCCP in reasonable yield. Other reagents commonly used to prepare acid chlorides (e.g. PCl_3 , oxalyl chloride) did not lead to complete conversion of all five carboxyl groups, and addition of DMF was found to be critical. Utilizing this strategy, various alcohols that were not compatible with the transesterification strategy could be successfully installed. Benzyl alcohol (entry 1), (*R*)-1-phenylethanol (entry 2), and (*S*)-benzylmandelate (entry 3) gave rise to the corresponding PCCPs. Ethyl L-lactate (entry 4) also proved to be a competent partner, as was phenol (entry 5). Tertiary alcohols such as *t*-butanol could also be incorporated, (entry 6), albeit in low yield, when the reaction was buffered with sodium carbonate to prevent degradation of the acid-sensitive esters. Notably, access to PCCPs derived from fluorinated alcohols such as trifluoroethanol (entry 7), hexafluoroisopropanol (entry 8), and even pentafluorophenol (entry 9) was achieved by utilizing these alcohols in the presence of sodium carbonate. These fluorinated PCCP derivatives represent exceptionally stable anions that do not appear to be protonated by hydrochloric acid or concentrated H_2SO_4 .¹⁶

With an eye toward application of these materials to catalysis, we wished to demonstrate the execution of these methods to furnish functionalized PCCPs on a preparative scale. For the transesterification method, we found that the menthol-derived PCCP **6·NBu₄** could be prepared on >5 g scale in 88% yield (eq 1) without column chromatography. Meanwhile, the second method involving acid chloride formation allowed for the synthesis of 2.52 g of PCCP **20·NMe₄** in 59% yield (eq 2).

(1)

(2)

Given the widespread availability of amines, particularly in enantioenriched form, we were interested to develop the capability of synthesizing amide PCCP derivatives. Toward this goal, we found that in general refluxing a slight excess of acid **2** with a primary amine furnished the corresponding monoamide product rapidly and in good yield, and a survey of

several monoamide PCCPs that were prepared by this method is shown in Figure 4. Simple aliphatic amines such as octylamine, 2-phenethyl amine, and cyclohexyl amine (entries 1–3) led to the corresponding PCCPs in good yields. Bulkier amines such as *t*-butylamine (entry 4) and 1-adamantylamine (entry 5) also produced the monoamides efficiently. In terms of chiral derivatives, (*R*)-(+)-1-(1-naphthyl)ethylamine (entry 6) and L-phenylalanine methyl ester (entry 7) were found to participate well in this process. Notably, even the much less nucleophilic aniline led to the corresponding monoamide PCCP in good yield (entry 8). It was also possible to incorporate ammonia, although only in very low yield (entry 9). Secondary amines such as pyrrolidine failed to react by this procedure to produce any amidation derivative.

Interestingly, when two equivalents of an amine such as (*R*)-(+)-1-(1-naphthyl)ethylamine were used, the 1,2-diamide derivative **36** could be isolated (eq 3). Although the yield of this reaction was modest, **36** was produced as the only observable regioisomer.

We were able to obtain X-ray structures of several amide derivatives, which revealed some key structural features of these materials (Figure 5). Similar to the reported X-ray structure of **2**,¹⁷ monoamide **31** exists in the hydroxyfulvene form (Figure 5a). The acidic proton is hydrogen-bonded to an adjacent carboxyl oxygen atom, which explains its substantial downfield chemical shift (δ 17.7) in the ¹H NMR spectrum. Additionally, there is a hydrogen bond of 1.78 Å found between the amide N-H proton and a neighboring carbonyl oxygen, which represents a potentially useful organizing element. The X-ray structure of the diamide **36** (Figure 5b) also shares many of these structural features. Cocrystallized with a molecule of CHCl₃, the hydroxyfulvene form shows the acidic proton equally shared between the two amide oxygens in a low-barrier hydrogen bond (O...H distances of 1.16 and 1.23 Å). Each of the amide N-H groups is engaged in a hydrogen bond with a neighboring carbonyl group with distances of 1.60 and 1.97 Å respectively.

(3)

Lastly, we explored how various equivalents of octylamine affects the yield and chemoselectivity of the amide products formed (Figure 6). When a slight excess of acid **2** is refluxed in toluene for 0.5 h with octylamine, monoamide PCCP **26** is produced as previously described. However, extending the reaction time to 24 h results in an unusual disproportionation of **26** to furnish imide **39** in moderate yield. On the other hand, treatment of **2** with 6.0 equivalents of octylamine led to production of triamideimide **37** in excellent yield. It should be noted that use of intermediate equivalents of octylamine (1.1–5.0

equivalents of amine to 1.0 equivalent of PCCP **2**) simply led to imide **37** and starting material acid **2**. Finally, the addition of 6.0 equivalents octylamine and AlMe_3 to **2** resulted in the efficient production of pentaamide **38**.

In conclusion, we have developed multiple procedures to access a variety of novel PCCP derivatives from alcohols and amines. The ability to prepare a sterically and electronically diverse collection of these materials should enable exploration of functional PCCPs in areas such as organocatalysis, metal catalysis, and materials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 2. Synthesis of PCCPs via transesterification. Yields are based on isolated and purified materials.

Figure 3.

Synthesis of PCCPs derived from lower-nucleophilicity alcohols via penta-acid chloride 7. Yields are based on isolated and purified materials. For entries 6–9, Na_2CO_3 was added in the esterification step.

Figure 4. Synthesis of monoamide derivatives. Yields are based on isolated and purified material.

Figure 5. Molecular structures of (a) monoamide 11 and (b) diamide 10·CHCl₃ obtained by single crystal X-ray diffraction. Implied hydrogen bond interactions are indicated by dashed lines.

Figure 6.
Impact of amine equivalents on the synthesis of PCCP derivatives.