Palladium-Catalyzed Chemoselective Protodecarboxylation of Polyenoic Acids

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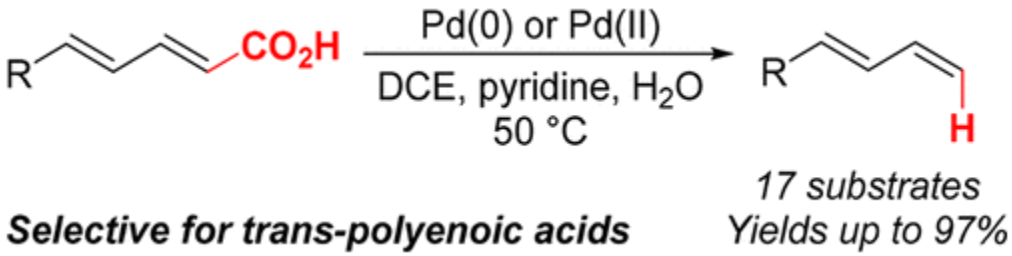
Abstract:

Conditions for the first palladium-catalyzed chemoselective protodecarboxylation of polyenoic acids to give the desired polyenes in good yields are presented. The reactions proceed under mild conditions using either a Pd(0) or Pd(II) catalyst and tolerate a variety of aryl and aliphatic substitutions. Unique aspects of the reaction include the requirement of phosphines, water, and a polyene adjacent to the carboxylic acid.

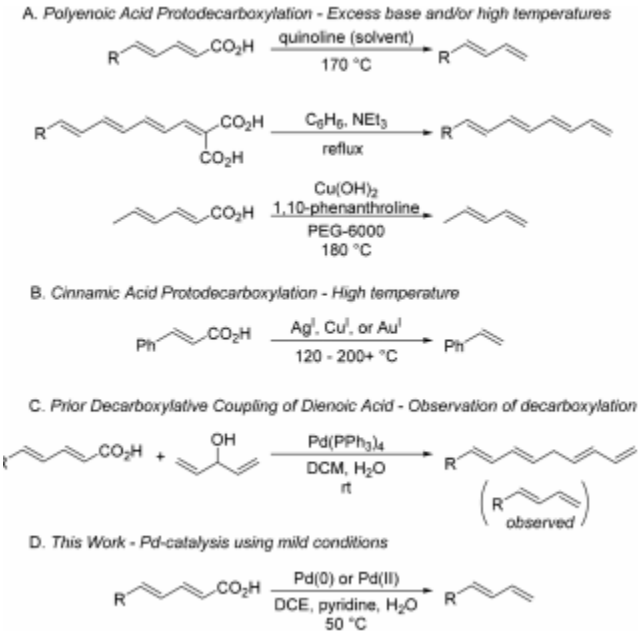


Keywords: Polyenoic Acids | Protodecarboxylation

Article:

Dienes and polyenes are typically prepared using olefination reactions(1) or metal-catalyzed couplings.(2) However, because of the relative instability of conjugated π-systems, their large-scale preparation and storage are not typically viable without the incorporation of a stabilizer. Polyenoic acids could serve as a concealed form of polyenes if mild methods existed for their protodecarboxylation. The existing acid-catalyzed protodecarboxylation methods are not typically compatible with polyenes due to possible polymerization issues.(3) In recent years, metal-catalyzed protodecarboxylations and decarboxylative coupling reactions have received much attention.(4) Unlike protodecarboxylation of aryl(4a−c,f,j,k,o,5) carboxylic acids, few methods have been reported for transition-metal-catalyzed protodecarboxylation of cinnamic acids (Scheme 1B).(4i,k,6) Metal-catalyzed dienoic acid protodecarboxylation protocols have

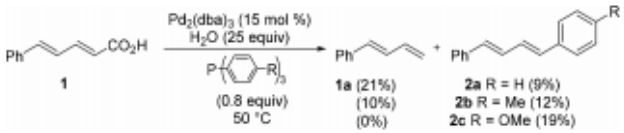
been scarcely reported. The current methods require excess base and high temperatures(7) or give low yields (Scheme 1A).(8) Additionally, modern aryl protodecarboxylation conditions are highly optimized for this motif; thus, vinylic acids are unreactive(5) without modification of the conditions.(9)



Scheme 1. Current Dienoic and Polyenoic Acid Protodecarboxylation Methods

During our study of the decarboxylative coupling of dienoic acids and pentadienyl groups (Scheme 1C),(10) we observed the protodecarboxylation of dienoic acids. Because of the limited methods of protodecarboxylation, we aimed to develop a mild method which would allow for quick access to polyenes from shelf stable starting materials (Scheme 1D). This would be a valuable process since the conjugated polyene motif is widely used in organic synthesis(11) and can be found in several bioactive natural products,(12) such as navenone B, amphotericin B, rapamycin, and retinoic acid.

We began our investigation by exploring the reactivity of 5-phenyl-2,4-pentadienoic acid (1) in the presence of AgOAc at 140 °C(9) or copper oxide at 170 °C.(13) Although both of the conditions successfully protodecarboxylated cinnamic acid, only the silver-catalyzed reaction showed the desired product (6% yield, Supporting Information, SI). We subsequently explored the protodecarboxylation of 1 using conditions similar to our decarboxylative coupling process (Scheme 2).(10c) Initially, a palladium catalyst in the absence of solvent was examined since the polarity difference between the acids and desired products could minimize the reaction workup. Reactions using Pd(II) acetate or Pd(0) complexes at 50 °C led to no reaction. However, Pd(PPh3)4 in the presence of water gave a mixture of diene 1a and unanticipated diaryl diene 2a in a moderate overall yield. To explore the formation of product 2a, we executed the reaction using 15 mol % of Pd2(dba)3 in the presence of different phosphine ligands. Tris-p-tolyl- and tris-p-anisylphosphines yielded 1,4-diarylbutadienes 2b and 2c, respectively. These reactions clearly indicated the source of the second phenyl group in compound 2 was the phosphine ligand.(14)



Scheme 2. Initial Solvent-Free Protodecarboxylation

Encouraged by the greater formation of diene 1a with the reaction using triphenylphosphine, we decided to use this ligand for optimization. Thus, reactions were performed using Pd(PPh3)4 as a catalyst under acidic or basic conditions in the absence of water (Table 1, entries 1 and 2). Under these conditions, neither product 1a nor 2a was isolated. Using the same conditions in the presence of water, decomposition was observed with formic acid, but a 22% yield of diene 1a was isolated with no observed formation of 2a when Et3N was added (entries 3 and 4). Further optimization studies of these solventless conditions indicated a reproducibility problem due to the inconsistency in mixing the heterogeneous reaction mixture. Thus, we continued the optimization using DMF, MeOH, THF, and DCE. Only the reaction performed in DCE gave the desired product when water was added to the reaction mixture (Table 1, entry 7). The addition of organic bases led to an improvement in yield to greater than 60% (entries 9 and 10), whereas the sodium carboxylate of 1a was poorly soluble and less reactive. Increasing the catalyst loading to 15 mol % gave the desired product with 80% yield (entry 11). Surprisingly, the oxidation state of the palladium catalyst precursor did not have a major effect on the reaction efficiency, as long as triphenylphosphine and water were added (entries 12–15). No exogenous base was required for Pd(OAc)2-catalyzed reactions, presumably due to the basicity of the acetate ligand. A side-by-side comparison determined that the reaction with Pd(OAc)2 was slightly faster but in some cases yielded product 2a. We further confirmed the necessity of palladium in this transformation by examining the reactivity of other transition metal catalysts (i.e., Cu(I), Cu(II), Zn(II), Ir(I), and Rh(I), SI), all of which were unreactive.

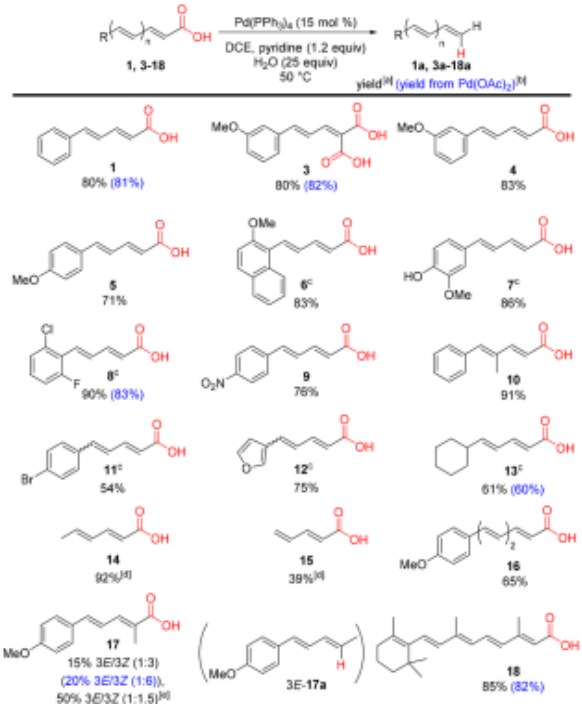
Table 1. Optimization of Dienoic Acid Protodecarboxylation

entry	$Pd(PPh_3)_4$ (mol %)	solvent (0.1 M)	additive (1.2 equiv)	H_2O (equiv)	yield[a] (%)
1	10	none	NEt_3	0	0[b]
2	10	none	formic acid	0	dec
3	10	none	formic acid	25	dec
4	10	none	NEt_3	25	22[b]
5	10	MeOH	none	25	0[b]
6	10	DCE	none	0	0[b]
7	10	DCE	none	25	28
8	10	DCE	formic acid	25	dec
9	10	DCE	NEt_3	25	61
10	10	DCE	pyridine	25	64
11	**15**	**DCE**	**pyridine**	**25**	**80 (88)**
12	10[c]	DCE	PPh_3/ pyridine[d]	25	81
13	10[c]	DCE	PPh_3/ pyridine[d]	0	0[b]
14	10[c]	DCE	PPh_3 (0.4 equiv)	25	78
15	10[c]	DCE	pyridine	25	0[b]
16	5[c]	DCE	pyridine	25	(97)

[a]Isolated yield with parenthetical NMR yield using dimethyl terphthalate as internal standard. [b]Starting material was recovered. [c]Pd(OAc)2 used in place of Pd(PPh)4. [d]Reaction was performed using PPh3 (0.4 equiv) and pyridine (1.2 equiv). [e]Reaction run on 1-g scale.

The optimization reactions in Table 1 were typically run using 20–50 mg of starting material (0.08–0.2 mmol of acid), but the reaction was scaled up nicely to 1 g (5.7 mmol) with an increase in yield while using only 5 mol % catalyst loading (entry 16). For the ease of material usage, all subsequent reactions were performed on a smaller scale (0.08–0.2 mmol of acid) using pyridine (1.2 equiv) as a base and Pd(PPh3)4 (15 mol %) as the catalyst (Table 1, entry 11).

With these optimal conditions, the scope of the reaction was evaluated using other dienoic and polyenoic acids (Scheme 3). For comparison, protodecarboxylation using Pd(OAc)2 (Table 1, entry 14) was also examined with various substrates. The yields were comparable to Pd(0) conditions (within 10%). Methoxyaryl dienoic acid derivatives (3–6) were efficiently converted to their respective dienes with yields ranging from 71% to 83%. Similarly, good to excellent yields were observed with arenes possessing free phenolic (7), chloro (8), and nitro (9) groups (86%, 90%, and 76%, respectively). When 4-bromophenyl derivative 11 (mixture of 4Z/4E) was subjected to protodecarboxylation conditions, a mixture of protodecarboxylative products (1Z/1E) were isolated in a moderate yield (54%). Remarkably, under these mild conditions, no products were observed from palladium insertion into any carbon–halogen bonds. Furyl and cyclohexyl dienoic acids 12 and 13 reacted under the same conditions to give their corresponding butadienes in 75% and 61% yields, respectively. Sorbic and pentadienoic acids reacted to give their decarboxylated diene derivatives 14a and 15a (1H NMR yields due to the volatility of 1,3-butadiene and 1,3-pentadiene).



Scheme 3. Protodecarboxylation of Various Polyenoic Acids

With the exception of furyl and 4-bromophenyl derivatives (11a and 12a), all of the isolated butadiene derivatives adopted the thermodynamically more stable E-geometry, although the stereochemistry correlates to that of the starting material (dienoic acids 6–8 and 11–13 were prepared as a mixture of 4Z/4E). Protodecarboxylation of α-methylpentadienoic acid derivative (17) at 50 °C resulted in a 15% yield of a mixture of products (3Z/3E ratio 1:3) and 20% yield using Pd(II) catalyst (3Z/3E ratio 1:6). Running the reaction with Pd(0) at 80 °C increased the yield of 17a, but with lessened selectivity (50%, 3Z/3E 1:1.5).

Further extension of the unsaturated acid, by the insertion of an additional vinyl group, led to the efficient formation of triene 16a upon protodecarboxylation. Based on the success of hexatrienoic acid 16, the quintessential polynoic acid, retinoic acid, was evaluated. all-trans-Retinoic acid (18) yielded the desired product in 85% yield, but its 13-cis analogue (19, Figure 1) failed to react. It has been reported that under basic conditions, 13-cis-retinoic acid undergoes lactonization (δ-lactone), which would hinder the protodecarboxylation.(7b) However, 1H NMR analysis of the reaction mixture and purified compounds did not indicate the formation of a δ-lactone product under the mild conditions of our process. Similar selectivity was observed from the reaction of Z-dienoic acid 20 (Figure 1), even at 80 °C, despite the reactivity of its E-analogue (17). On the basis of these data, it is surprising that protodecarboxylation of compound 3 proceeded smoothly to give the desired doubly decarboxylated product instead of only removing the E-carboxylic acid group (Scheme 3). These results suggest that compound 4 (1E-isomer) is selectively formed in situ after the first decarboxylation step, which was confirmed by 1H NMR analysis of the reaction mixture after 8 h.

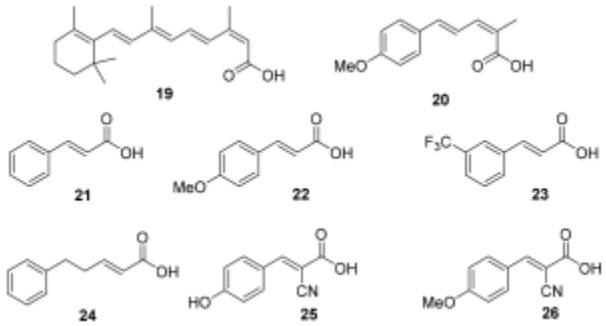
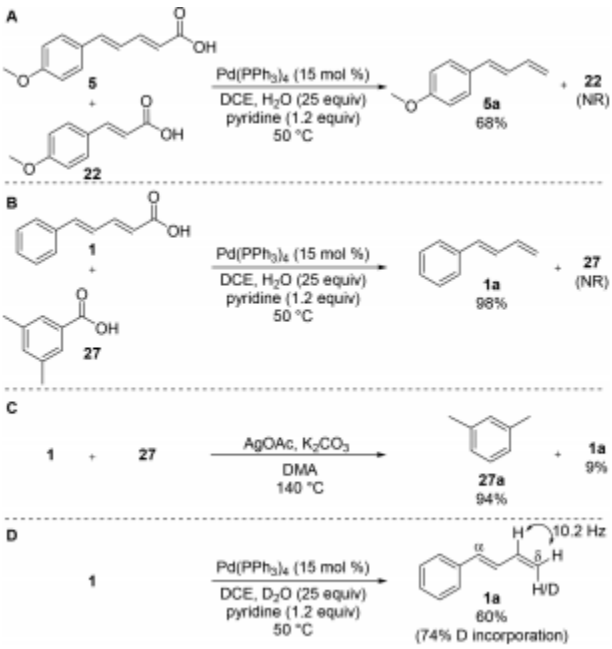


Figure 1. Unreactive carboxylic acids with protodecarboxylation reaction conditions.

Acrylic and cinnamic acids 21–26 (Figure 1) failed to react under our conditions. The lack of reactivity for these compounds suggests that dienoic acids have unique reactivity under these conditions.(15) Fortunately, increasing the reaction temperature to 100 °C and replacing DCE with trifluoromethylbenzene resulted in the decarboxylation of cinnamic acid derivatives 22 and 26 (72% and 55% yield, respectively, SI). Under these harsher conditions, 13-cis-retinoic acid (19) gave a mixture of decomposition products, and no reactivity was observed for benzoic acids.

To exemplify the selectivity of our mild conditions, we subjected an equimolar mixture of p-methoxycinnamic acid (22) and 4-(p-methoxyphenyl)-2,4-pentadienoic acid (5) to our standard reaction conditions (Scheme 4A). The only isolated product was diene 5a, and cinnamic acid 22 was completely recovered. This result shows that cinnamic acids do not poison the catalyst, nor do dienoic acids modify the catalyst to enable the reactivity of 22. Similarly, 1a was isolated from the reaction of 1 in the presence of benzoic acid 27 (Scheme 4B). To show the

complementarity of our conditions, the same benzoic and dienoic acids were reacted with a silver catalyst, and the opposite chemoselectivity was observed (Scheme 4C). It is noteworthy that C(sp2)-carboxylic acids react under silver or copper protocols in a pattern where benzoic acids are much more reactive than cinnamic acids,(9,13) and dienoic acids are negligibly reactive. This reactivity pattern is inverted using our palladium conditions.



Scheme 4. Selectivity of Protodecarboxylation Reactions

A possible mechanistic pathway for this Pd(II)-catalyzed process is shown in Figure 2. Triphenylphosphine attacks(16) the β-position of the electophilic π-complex (A), initially formed from Pd(II) and diene, to generate phosphonium intermediate B. The elimination of CO2 and PPh3 from this intermediate yields vinyl palladium species C. Protodepalladation in the presence of water furnishes the diene product. A similar 1,2-addition, 1,2-elimination mechanism has been proposed previously.(17)

The E versus Z selectivity for starting materials can be rationalized by analyzing the secondary interactions in phosphonium carboxylate intermediates (B′ and B″, Figure 2). In both intermediates, the conformers positioning the carboxylate and phosphonium in antiperiplanar orientations can be achieved. However, in B′, resulting from trans acid, Pd−π secondary interactions are feasible. This interaction could lower the energy requirement for the elimination step, allowing for low-temperature protodecarboxylation. In contrast, in B″, resulting from the cis-acid, the antiperiplanar conformation of phosphonium and carboxylate does not allow for coordination of the palladium to the π-system. Presumably, the preferred pathway for B″, under the reaction conditions, is the reformation of the cis-dienoate.

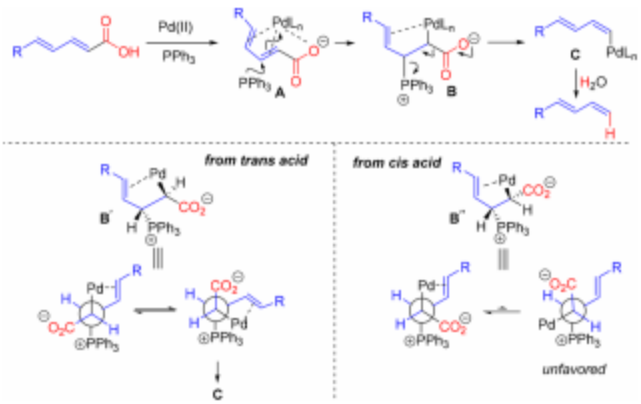


Figure 2. Proposed mechanism for Pd(II)-catalyzed protodecarboxylation.

The elimination step from B′ yields the Z-vinylpalladium intermediate (C) that undergoes protodepalladation to form the 3E-isomer. This result is in alignment with the observed reactivity of diacid 3 and dienoic acid 17. Further corroboration of the Z-vinylpalladium intermediate was accomplished by running the reaction of 1 with D2O in place of H2O (Scheme 4D). Compound 1a was isolated from this reaction with 74% deuterium incorporation at the δ-position (SI). The stereochemistry of the terminal alkene was determined by the H–H coupling constant of 10.2 Hz for the observed terminal H. Higher D-incorporation was observed (95% D, 22% yield) when the poorly soluble potassium salt of 1 was used. It is possible that the allylic phosphonium intermediate (B) could undergo SN2′ attack at the δ position by another phosphine or dissociate at higher temperature, which would decrease the stereoselectivity, as observed for dienoic acid 17. Overall, the proposed mechanism (Figure 2) serves to explain the necessity for phosphines and the diene. Reactions catalyzed by Pd(0) possibly proceed by similar mechanism after being protonated in situ to generate Pd(II)H complexes.(18) These Pd(II) complexes might explain the formation of 2a–c (Scheme 2), which was reported to be catalyzed by Pd(II).(14b)

In this study, we developed the first palladium-catalyzed chemoselective protodecarboxylation of dienoic and polyenoic acids. The very mild reaction conditions can tolerate various functional groups, allowing for the isolation of dienes and polyenes in synthetically useful yields. The proposed mechanism, which involves stereoinversion of the α-carbon, involves a Pd–π secondery interaction that can be used to rationalize the E/Z selectivity. Further studies are ongoing to make use of the potential intermediates on the pathway.

Associated Content

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03016.

1D and 2D NMR spectra for all new compounds (PDF)

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Notes
The authors declare no competing financial interest.

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