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Unconventional Titania Photocatalysis: Direct Deployment of Carboxylic Acids in Alkylations and Annulations

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Supporting Information

ABSTRACT: Under dry, anaerobic conditions, TiO_2 photocatalysis of carboxylic acid precursors resulted in carbon−carbon bond-forming processes. High yields of dimers were obtained from TiO_2 treatment of carboxylic acids alone. On inclusion of electron-deficient alkenes, efficient alkylations were achieved with methoxymethyl and phenoxymethyl radicals. In reactions with maleic anhydride or maleimides, phenoxyacetic acid produced chromenedione derivatives in addition to adducts. These photocatalytic reactions are simple and cheap to perform, and the TiO_2 is easily removed by filtration. The anaerobic photocatalysis strategy offers a range of synthetic possibilities.

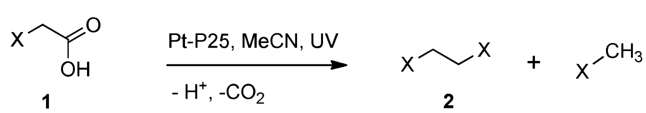
Semiconductor photocatalysis (SCPC) has achieved international prominence for its role in the destructive oxidation of organic molecules during environmental remediation.[1] The electron/hole pair generated when a SC powder is photo-irradiated[2] interacts with water and oxygen to produce reactive oxygen species (hydroxyl radicals, superoxide).[3] These readily convert organic matter to CO_2, water, and mineral acids.[4] Numerous applications of SCPC have been found with sterilizing, deodorizing, and antifouling materials as well as in self-cleaning glass and antifogging coatings. Alternatively, under anaerobic conditions, the TiO_2 electron/hole pair can generate C-centered radicals from certain substrates for use in constructive chemical transformations. However, only a modest number of such molecular assembly applications have been reported.[5]

Two notable examples are the exploratory study of additions of enol ethers to various acceptors[6] and research on the addition of tertiary amines to electron-deficient alkenes.[7] Carboxylic acids also undergo hole oxidation, generating C-centered radicals following decarboxylation. The simplest example is the photo-Kolbé reaction, first studied in the late 1970s.[8] This is potentially an attractive method of radical generation because of the availability of many natural and synthetic carboxylic acids that could then be used without functionalization. Most conventional methods of radical generation from carboxylic acids rely on preparing unappealing precursors such as diacyl peroxides, peresters,[9] Barton esters,[10] or Hunsdieker salts[11] or involve hypervalent iodine.[12]

By analogy with the photo-Kolbé reaction, we anticipated that carboxylic acids might be reductively decarboxylated through photolyses with TiO_2. We used Degussa (Evonik) P25 TiO_2, consisting of a 3:1 anatase/rutile mixture (particle size ∼21 nm, surface area 50 m^2 g^{-1}, anatase excitation wavelength 385 nm, band gap 3.2 eV)[13] as 1−5 mg mL^{-1} dispersions in acetonitrile. Experiments with P25 platinized with 0.1% Pt (Pt−P25)[14] were also carried out. Oxidative/degradative processes were precluded by purging the dispersions with Ar and drying the MeCN over CaH_2. In a typical setup, the dispersion was stirred in a Pyrex tube clamped between two face-to-face sunlamp arrays (UVA).[15] After irradiation, the photocatalyst was simply removed by filtration. We found that a good range of carboxylic acids did indeed react under these conditions. Good yields of dimeric C−C-coupled products could be isolated in the absence of coreactants. On inclusion of electron-deficient alkenes, alkylations proceeded effectively; for aryloxyacetic acids, addition−cyclization cascades supervened.

Photocatalyses of individual carboxylic acids were first investigated. Photolyses of single acids with P25 were inefficient, but the use of Pt−P25 with acids **1a−e** gave very pleasing yields of the homodimerization products **2** derived from C-centered radicals ($XCH_2^\bullet$; Scheme 1). Arylacetic acids

Scheme 1. TiO_2-Promoted Dimerizations of Carboxylic Acids



afforded good to excellent dimer yields (Table 1, entries 1−4). Phenoxyacetic acid (entry 5) and benzyloxyacetic acid (entry 6) also produced useful yields of the corresponding C−C-coupled products. Only in the case of 2-naphthylacetic acid was a significant amount of the reduced byproduct 2-methylnaphthalene observed (entry 2).

To expand the synthetic scope of our TiO_2 chemistry, we examined radical alkylation of alkenes. Since most of the acid-derived radicals had nucleophilic character, alkenes containing electron-withdrawing substituents were chosen.[16] When maleic anhydride was included in the dispersions, photolyses with P25 led to the formation of adducts **3** incorporating the carboxylic

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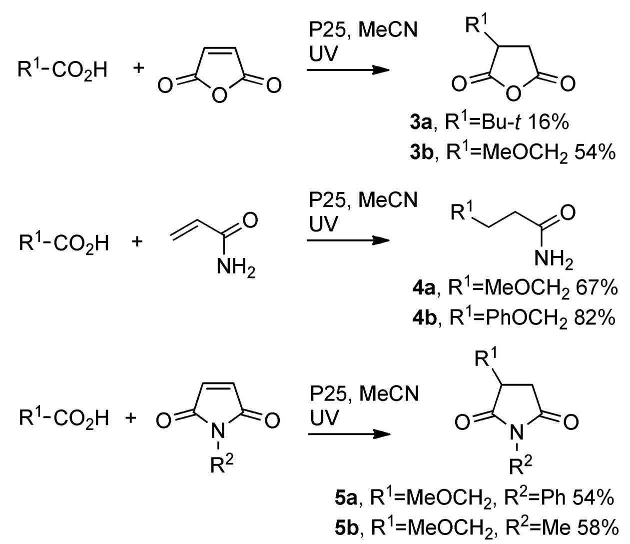
Table 1. Yields of Dimers from SCPC of Carboxylic Acids

entry	acid: X	irrad. time (h)	yield (%) 2	yield (%) XCH_3
1	**1a**: Ph	19	81	0
2	**1b**: 2-naphthyl	52	56[a]	40[a]
3	**1c**: 2-thiophene	20	83	0
4	**1d**: 3-thiophene	20	78	0
5	**1e**: OPh	21	52	0
6	**1f**: OBn	21	38	0

[a]NMR yield.

acid moiety R and an additional H atom (Scheme 2). In each case, significant amounts of succinic anhydride (9–16%)

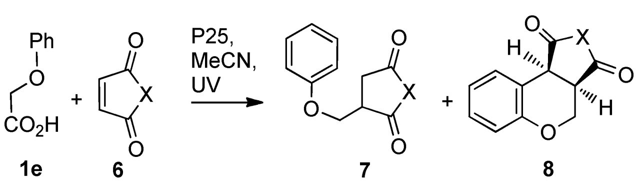
Scheme 2. TiO_2-Promoted Additions of Carboxylic Acids to Alkenes



accompanied products **3**. The yields of the alkyl anhydrides **3** were low for aliphatic carboxylic acids (**3a**) but increased substantially for methoxyacetic acid (**3b**) (Scheme 2). Good yields of the analogous adducts **4** were obtained when acrylamide was used as the substrate, and substantial yields of adducts **5** were isolated from the P25-photocatalyzed reactions of methoxyacetic acid with *N*-phenyl- and *N*-methylmaleimide (Scheme 2). As expected,[17] minor amounts of alkene [2 + 2] photodimers were observed with the maleimides.

The reaction of phenoxyacetic acid (**1e**) with maleic anhydride opened a divergent reaction channel in that adduct **7** was accompanied by a significant amount of dihydrofurochromenedione derivative **8** (X = O) (Scheme 3). This appeared to have formed when the initial adduct radical underwent an intramolecular closure onto the phenyl ring followed by rearomatization. Similar cycloadducts **8** (X = NR) were obtained from TiO_2-photocatalyzed reactions of **1e** with

Scheme 3. Dihydrochromene Derivative Formation



several N-substituted maleimides. Good to excellent overall yields were obtained under all conditions (Table 2). In each case, the adduct **7** and cycloadduct **8** were accompanied by moderate amounts (11–43%) of the corresponding reduced alkene (succinic anhydride or succinimide).

Table 2. Product Yields from Reactions of Phenoxyacetic Acid with Maleic Anhydride and Maleimides[a]

entry	X	time (h)	conditions	yield of 7 + 8 (%)	7:8 ratio
1	O	26	P25	60	1.3:1.0
2	O	18	0.1% Pt–P25	56[b]	6.0:1.0
3	O	45	P25[c]	63[b]	0.3:1.0
4	NH	17	P25	78	0.42:1.0
5	NMe	20	P25	78	0.42:1.0
6	NMe	45	P25[c]	75[b]	0.10:1.0
7	NBu-*t*	12	P25	67	1.0:1.0
8	NPh	11	P25	79	1.0:1.0
9	NPh	16	0.1% Pt–P25	77[b]	0.12:1.0
10	NCO_2Me	12	P25	68	1.1:1.0
11	NCO_2Me	16	0.1% Pt–P25	74[b]	0.5:1.0

[a]In all reactions, **1e** (1 equiv), **6** (2 equiv), and TiO_2 (1.5 equiv) were used. Unless otherwise stated, the TiO_2/MeCN dispersion was 1 mg mL^{-1} and isolated yields are reported. [b]NMR yield. [c]TiO_2/MeCN dispersion was 5 mg mL^{-1}.

Major advantages of our photocatalytic methodology are the inherent opportunities for adjusting and adapting it. The synthetic value of the process in Scheme 3 was enhanced because the selectivity could be tuned in favor of either the furochromene derivative **8** (X = O) or the adduct **7** (X = O). The P25 photocatalyst in a 1 mg mL^{-1} dispersion gave a modest selectivity of **7**:**8** = 1.3:1.0 (Table 2, entry 1). Use of platinized Pt–P25 greatly favored the adduct (**7**:**8** = 6.0:1.0; entry 2), whereas a denser dispersion of P25 inverted the selectivity in favor of the cycloadduct **8** (**7**:**8** = 0.3:1.0; entry 3). The selectivity for the pyrrolochromene derivatives **8** (X = NR) varied to a minor extent depending on the N substituent (compare entries 4, 5, 7, 8, and 10). *N*-Methylmaleimide gave the best selectivity for the cycloadduct **8** (X = NMe), and a denser dispersion of P25 improved this still further (entry 6). In the reaction with *N*-phenylmaleimide, Pt–P25 was selective for the adduct (entry 9). A modest selectivity in favor of the cycloadduct was achieved with Pt–P25 in the case of the *N*-methoxycarbonyl substituent (compare entries 10 and 11).

Platinization provides an electron sink and thus increases the availability of holes by hindering recombination. This modified photocatalyst would therefore be expected to favor the cycloadducts **8** because hole oxidation of the ring-closed radical is a key step (see the mechanism in Scheme 4 below). The increased selectivities for **8** shown in entries 9 and 11 are thus explained. Unexpectedly, Pt–P25 was selective for adduct **7** in the case of maleic anhydride (entry 2). The reason for this inverted selectivity is unknown. However, the same results were obtained when the photolyses were repeated. With the denser P25 dispersion, less light could enter the system, and hence, longer photolysis times were needed. However, the higher reactant concentrations favored encounters between the ring-closed radicals and the P25. Hence, these conditions were also expected to increase the hole availability and favor cycloadduct formation. Entries 3 and 6 do indeed show this.

By analogy with the photo-Kolbé reaction, the first step was expected to be hole capture by the carboxylic acid at the TiO_2 surface to generate the corresponding radical cation.[8] Loss of a proton would then generate an acyloxyl radical, $RCH_2C(O)O^•$, which would rapidly eject CO_2 to produce an alkyl radical, $RCH_2^•$.[18]

The continuous-wave X-band EPR spectrum obtained during UV irradiation (400 nm) of a frozen suspension of P25 with *t*-$BuCO_2H$ in CH_3CN (Figure 1a) showed the 10-line spectrum

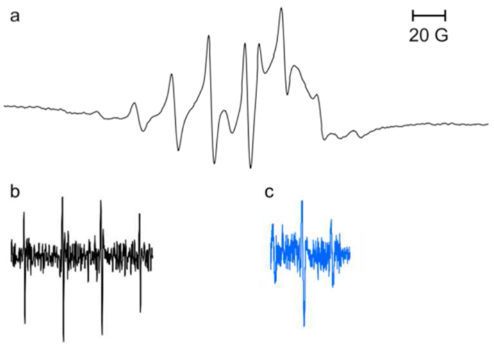
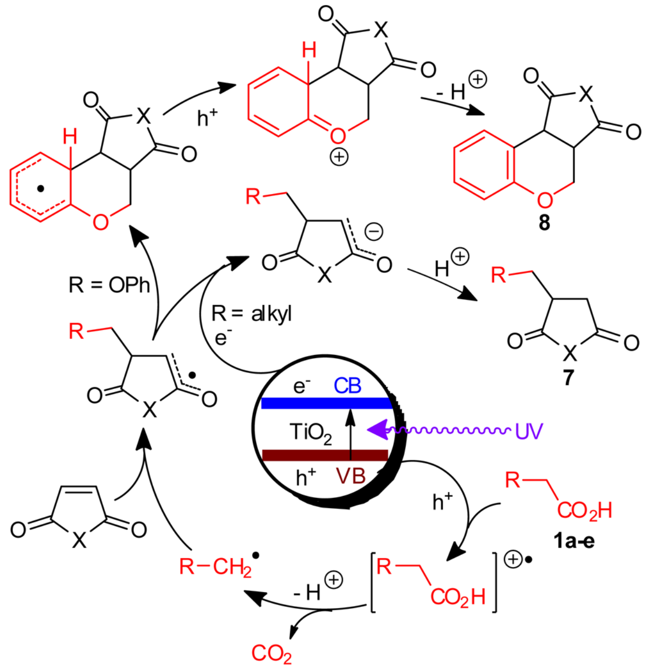


Figure 1. EPR spectra during UV irradiation of TiO_2 with carboxylic acids. (a) EPR spectrum of *t*-$Bu^•$ during UV irradiation of *t*-$BuCO_2H$ and P25 in frozen CH_3CN at 80 K. (b) Isotropic spectrum of *t*-$Bu^•$ (central 4 lines only) during UV irradiation of *t*-$BuCO_2H$ with PC-500 at 300 K in PhH. (c) Isotropic spectrum of $PhOCH_2^•$ during UV irradiation of **1e** and PC-500 in fluid PhH at 300 K.

of the *t*-$Bu^•$ radical superimposed on high-field signals due to trapped electrons (Ti^{3+}) in the titania. Additionally, the same radical was observed as a transient during UV irradiation of the acid with PC-500 in fluid PhH at 300 K (Figure 1b; only the central four lines are shown). UV irradiation of a fluid dispersion of TiO_2[19] with acid **1e** in PhH at 300 K resulted in an isotropic spectrum (Figure 1c). The EPR parameters [g = 2.0024, a(2H) = 17.4 G] were in good agreement with the literature for the $PhOCH_2^•$ radical.[20] Thus, the EPR spectra provided effective support for the first steps of the mechanism. The lack of anisotropy in the solution spectra (Figure 1b,c) demonstrated that at least some of the *t*-$Bu^•$ and $PhOCH_2^•$ radicals were freely tumbling in solution and not bound to the TiO_2 surface.

Additions of the weakly nucleophilic $RCH_2^•$ radicals to the electron-deficient double bonds of the alkenes are expected to be fast.[21] The resulting adduct radicals might abstract H atoms from an endogenous donor. It seems more likely, however, that they pick up electrons from the TiO_2 particles, thus generating the corresponding enolate ions, which are easily protonated[22] to afford adducts **2**, **7**, etc. (Scheme 4). For the electrophilic anhydrido- or imidoalkyl radicals produced on addition of $PhOCH_2^•$ radicals, a competition exists between reduction to adducts **7** or homolytic closure onto the phenyl ring. In the latter case, resonance-stabilized cyclohexadienyl radicals are obtained, which rearomatize to yield the functionalized chromenes **8**. This rearomatization could be the result of hole capture from TiO_2 by the cyclohexadienyl radicals and subsequent proton loss, as shown in Scheme 4. Alternatively, electron transfer to more anhydride or maleimide might take place, as suggested in related work by Hoffmann.[7,23] Protonation of the resulting anhydride or maleimide radical anions, followed by further electron capture and protonation steps, would explain the significant yields of succinic anhydride

Scheme 4. Proposed Mechanism for P25-Photocatalyzed Reactions of Carboxylic Acids with Maleic Anhydride and Maleimides



or succinimide obtained in our reactions. However, this electron transfer route implies that the yield of succinic anhydride or succinimide should equal the yield of the accompanying chromene derivative **8**.[24] In fact, equal yields of **8** and anhydride or succinimide were not observed in any of our reactions. Furthermore, we found that irradiations of TiO_2 dispersions of maleic anhydride and the maleimides in the absence of the carboxylic acids produced anhydride or succinimides in significant yields.[25] We conclude that direct hole capture by the cyclohexadienyl radicals is probably the main process, although of course the alkenes retain their role as electron acceptors.

In conclusion, we have found that UVA irradiations of dispersions of TiO_2 and carboxylic acids under dry anaerobic conditions lead to decarboxylation and free radical generation. In the absence of substrates, the corresponding dimers were prepared in good to excellent yields. On inclusion of electron-deficient alkenes, alkylations occurred quite efficiently. The reaction of phenoxyacetic acid and a maleimide resulted in a cascade process in which a pyrrolochromene derivative accompanied the alkylated succinimide. The process could be tuned by catalyst modification to afford either the alkyl adduct or the pyrrolechromene. These photocatalyses are easily and cheaply carried out in the laboratory, and the heterogeneous catalyst is simply filtered off during workup. Mechanistic aspects and applications of these methods in the synthesis of complex molecules are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, details of EPR spectroscopic experiments, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(24) Provided that the anhydride- or maleimide-derived radicals and ions are not diverted down alternative reaction pathways.

(25) On inclusion of MeOH to mop up holes, the yields of the succinic derivatives increased to 77−91%.