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Efficient photodecarboxylation of aroyl-substituted phenylacetic acids in aqueous solution: a general photochemical reaction

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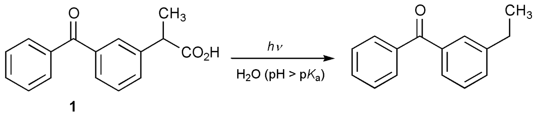
Photolysis (254–350 nm) of a variety of aroyl-substituted phenylacetic acids and *p*-acetylphenylacetic acid in aqueous solution at pH > pK_a resulted in efficient photodecarboxylation (Φ = 0.2–0.7), to give in most cases a single product arising *via* the corresponding arylmethyl carbanion, indicating that photodecarboxylation is an efficient and general reaction for these types of compounds.

The photodecarboxylation of organic carboxylates and carboxylic acids continues to be an area of active research interest.[1–3] This is an example of a simple photochemical extrusion reaction that is comparable to the well-known photodecarbonylation of ketones. However, mechanistically, photodecarboxylation of carboxylic acids is more complex. The mechanism in which carbon dioxide is eliminated from photoexcited (organic) carboxylic acids has been classified into several types with the simple heterolytic and homolytic mechanisms being the most readily visualized.[1] Some recent papers dealing with photodecarboxylation of some non-steroidal anti-inflammatory drugs (NSAIDs) suggest that new insights and potentially new reactive systems await discovery.[2,3a–e] A particular example that attracted our attention is the highly efficiently (Φ = 0.75) photodecarboxylation of ketoprofen [**1**, eqn. (1)] in aqueous solution orginally reported by Costanzo *et al.*[2] At least two groups[3a–e] have studied the mechanism of the photodecarboxylation. The latest report we are aware of is from Scaiano and co-workers[3a] who showed that the reaction proceeds from the singlet excited state of the carboxylate form and that water is not essential (but probably helpful). Singlet state reactivity is unusual for benzophenone photochemistry. The nature of the primary photochemical step remains an issue. It could be either (a) a simple heterolytic cleavage mechanism to generate the carbanion directly or (b) a mesolytic mechanism in which there is an electron transfer from the carboxylate oxygen to the ketone to generate a biradical anion, followed by bond cleavage to give the carbanion.



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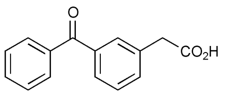
(1)

Ketoprofen (**1**) is an aroyl-substituted phenylacetic acid. Compounds of this general structural type are readily available by routine synthesis. The high (and clean) reactivity of **1** suggested to us that other aroyl-substituted phenylacetic acids might react in a similar manner and that a general type of efficient photodecarboxylation awaits discovery. The availability of compounds of similar structural type that also react will certainly help in the elucidation of the reaction mechanism. We have now made five analogs of **1**, *viz.*, **2**–**6**. Acids **2** and **3** are simple analogs of ketoprofen (**1**). If the photodecarboxylation of **1** is respresentative of a general process, compounds **2** and **3** should react, neglecting of course any dramatic substituent effects on excited state reactivity that we have not taken into account. Compounds **4** and **5** have a different carbonyl chromophore (anthraquinone and acetophenone, respectively). If the reaction is general for other types of carbonyl chromophores, these compounds might be expected to show reactivity as well. Finally, we have changed the nature of the 'leaving group' in **6**. Here, the leaving group is formally formaldehyde, which is much less labile than CO_2. If **6** reacts in an analogous manner (*i.e.* deformylation to give the corresponding carbanion), then the reaction is indeed much more general than ever suspected. In this report, we show that all of **2**–**6** react in the manner anticipated (with varying degrees of efficiency, all generally high) demonstrating that the photodecarboxylation of aroyl and acetoyl-substituted phenylacetic acids is a general reaction. Moreover, less labile leaving groups such as formaldehyde may also be used.



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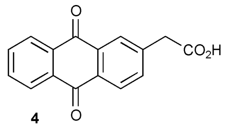

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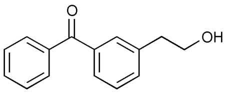
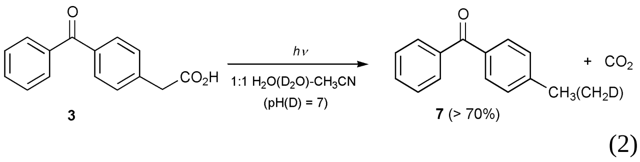


6

Carboxylic acids **2**–**5** were readily made by conversion of the corresponding commercially available methyl-substituted derivative to the α-bromo compound (NBS–CCl_4), followed by reaction with NaCN–EtOH and then hydrolysis using either conc. HCl or aqueous H_2SO_4. All of the acids were purified by repeated crystallization from aqueous EtOH to achieve >98% purity.† Keto-alcohol **6** was readily prepared by BH_3–THF reduction of **2**.

Photolysis of **2**–**4** in 1:1 H_2O–CH_3CN (50 mL total volume; water portion set to pH 7 with dilute NaOH after adding compound to ensure complete dissociation of the acid; $\approx 10^{-3}$ M substrate; Rayonet photochemical reactor; 254, 300 or 350 nm lamps; quartz vessel; solution cooled with a cold-finger to ≈15 °C; purged continuously with argon; 5–20 min) gave cleanly the corresponding photodecarboxylation product [*e.g.*, eqn. (2)] in high yield (up to 100% on sufficiently long photolysis time). No reaction was observed when the solution was kept in the dark. Quantum yields for photodecarboxylation were estimated using the reaction of ketoprofen (**1**) as a secondary standard (Φ = 0.75, in neat water, pH 7)[2] and ^1H NMR to monitor conversions. These experiments gave high quantum yields for the photodecarboxylations for **2**–**4** (in 1:1 H_2O-CH_3CN, pH 7): **2** (Φ = 0.66); **3** (Φ = 0.62); **4** (Φ = 0.22). Photolysis of **2**–**5** in neat CH_3CN under photolysis times used above gave no more than 5% reaction and the compounds could be essentially recovered unchanged.



(2)

It's clear from these results that (efficient) photodecarboxylation is a general photoreaction for aroyl-substituted phenyl-

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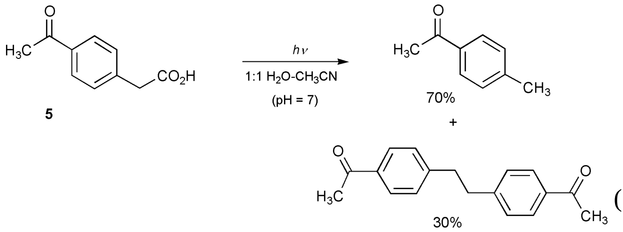
acetic acids. Quantum yields decreased on lowering the pH‡ which is consistent with the carboxylate form being reactive, consistent with the latest findings for ketoprofen (**1**) reported by Scaiano and co-workers.[3a] Furthermore, photolysis of **2** and **3** in D_2O–CH_3CN (as above) gave exclusively the corresponding α-deutero-methyl product, consistent with a carbanion intermediate [eqn. (2)]. Interestingly, photolysis of acetophenone derivative **5** gave two products in a 7 : 3 mole ratio (Φ for loss of substrate ≈ 0.2), respectively [eqn. (3)]: the expected simple decarboxylation product (*p*-methylacetophenone) *via* a simple phenylmethyl carbanion and a 'dimeric' product formally derivable from the phenylmethyl radical *via* coupling. Independent photolysis of *p*-methylacetophenone under identical conditions gave no reaction. Although radical coupling products have not been observed for ketoprofen (**1**) or from any of **2**–**4**, the fact that it is observed for **5** indicates that a radical-type mechanism (*e.g.* initial electron transfer from the carboxylate to the ketone)[3a–c] cannot be excluded for the photodecarboxylation. The reactivity of acetophenone derivative **5** allows for detailed investigations on this reaction pathway.



(3)

The generally high reactivity towards photodecarboxylation of the above aroyl (and acetoyl) substituted phenylacetic acids prompted us to think about the possible driving force for these reactions. A simple rationalization (assuming S_1 reactivity) is that the excited singlet states of these compounds have highly polarized π electron densities, shifted towards the keto oxygen. This would favour loss of CO_2 *via* benzylic C–C bond heterolysis, and subsequent generation of the carbanion. This mechanism bypasses the need for an initial electron transfer from the carboxylate oxygen to the carbonyl group, which appears to be warranted only for **5**. In any event, we wanted to test the former proposal and have made derivative **6** to test whether a similar reaction could operate using a much poorer 'leaving group', *viz.*, formaldehyde, and a moiety incapable of efficient electron transfer to the carbonyl group. To our surprise, photolysis of **6** in 1 : 1 H_2O–CH_3CN gave the anticipated deformylated product [*p*-methylbenzophenone (**7**)] although with yields that are several fold (5–10%) less than observed for the corresponding acid **2**, along with what appears to be major product(s) derived from photoreduction of the ketone. However, photolysis at pH 12 resulted in clean deformylation (> 70% yield) consistent with a hydroxide ion catalyzed process which would be required for deformylation *via* a carbanion intermediate. These initial results suggest that the aroylphenylmethyl group may be thought of as 'photolabile' carbanion leaving group which is able to induce a variety of benzylic C–C bond heterolysis in appropriately designed molecular systems. This is akin to the nitrobenzyl group[4] and selected diarylmethyl systems[5] that are known to have this ability.

In summary, we have shown that the photodecarboxylation of aroyl and acetoyl-substituted phenylacetic acids is a general reaction, all proceeding with high quantum yields. Less labile 'leaving groups' such as formaldehyde may also be used. In this way, one may visualize the aroyl-substituted phenylmethyl group to be a photolabile carbanion leaving group. This type of general reactivity may have application in the design of photolabile protecting groups and other photochemical applications in addition to providing new structural types for the elucidation of detailed reaction mechanism.

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Notes and references

† All compounds had satisfactory ^1H NMR (300 MHz) and mass spectral data.

‡ We have preliminary results indicating that the *meta* isomer **2** becomes increasingly more reactive at acidities greater than pH 2 (and into the Hammett acidity region) suggesting that a new mechanism for photodecarboxylation is available for this compound in acid involving the acid form.

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