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Revised mechanism and improved methodology for the Perkin condensation. Resuscitation of the mechanism involving benzal acetate and the improbability of the enolate of acetic anhydride

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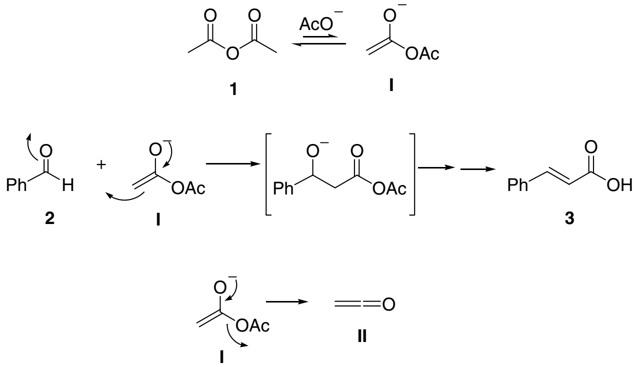
Abstract—The Perkin condensation most likely occurs via the initial formation of a *gem*-diacetate from the aromatic aldehyde and acetic anhydride reactants. The key reactive nucleophile appears to be the enolate of the *gem*-diacetate rather than of acetic anhydride. The diacetate from PhCHO may be converted to cinnamic acid under a variety of (relatively) mild basic conditions.

Although the venerable Perkin condensation reaction has retained its practical importance to this day,[1–3] an analysis of its accepted mechanism raises serious doubts. The reaction is generally believed to occur via the initial addition of the enolate (**I**) of acetic anhydride (**1**) to benzaldehyde (**2**) (Scheme 1), and yet this key step seems unlikely considering that the weakly basic acetate ion is employed to generate **I**. [The pK_a of acetic anhydride is apparently unknown, but may be estimated at ~20, rather lower than that of the analogous carboxylic ester (~25.0);[4a] and that of acetic acid[4b] is ~4.5.] Importantly, the enolate **I**—even were it to be generated—is expected to be highly unstable, fragmenting rapidly to ketene **II** and an acetate ion under the relatively high temperatures employed in the Perkin reaction (~180 °C).[5] (Although the enolates of cyclic anhydrides, e.g., homophthalic anhydride,[3] are reportedly stable, in these the fragmentation to ketene is presumably rapidly reversed intramolecularly.)



Scheme 1.

In fact, a preliminary study indicated that acetic anhydride (**1**) was stable per se to the conditions of the Perkin reaction, i.e. in the absence of benzaldehyde, thus ruling out the possibility that **I** could be formed under these conditions. (It is noteworthy that acetic anhydride is purified by distillation from sodium acetate![6]) Also, treating **1** with potassium *tert*-butoxide (at room temperature) led to its rapid decomposition, strongly indicating the instability of the enolate **I**—when it is indeed generated.

The essential mechanistic problem with the Perkin reaction, therefore, lies in proposing a viable two-carbon nucleophilic species—formally, an acetic acid dianion equivalent—under the conditions employed. Although an alternative to **I** is not obvious, it is noteworthy that benzaldehyde is known to react readily with excess

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Keywords: Acetic anhydride; *gem*-Diacetate; Cinnamic acid; Enolate; Perkin condensation.

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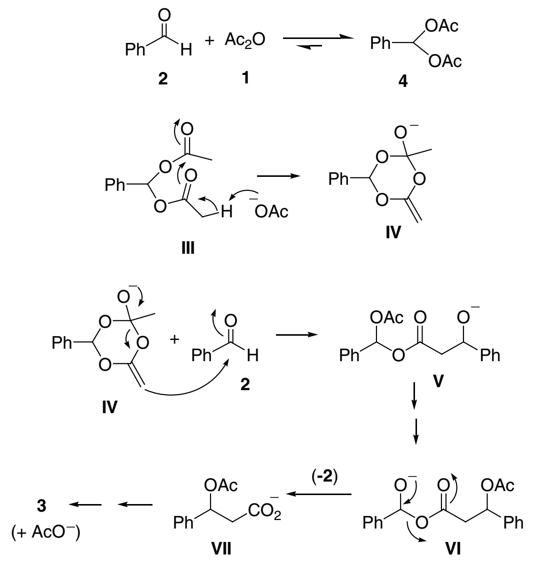


Scheme 2.

Table 1. Yields of cinnamic acid (**3**) produced from the following reactants under the conditions indicated:[a,b,c,d] Ac$_2$O (**1**), PhCHO (**2**), PhCH(OAc)$_2$ (**4**)[b]

Entry	Reactants	Conditions	% Yield of **3**
1[a]	**1**+**2**+KOAc	Reflux	60
2	**1**+**4**+KOAc	Reflux	30
3	**2**+**4**+KOAc	Reflux	75
4[c]	**4**+KOAc+DMF	Reflux	70
5[e]	**4**+*t*-BuOK+THF	Room temperature	70

[a] Entry 1 refers to the classical Perkin reaction; the base and the solvent employed in the other cases are indicated with the reactants. All the above reactions were carried out for the same period of time (5 h).

[b] Diacetate **4** was prepared in 80% yield as reported,[8] from **1**, **2** and anhydrous FeCl$_3$ at 0 °C; **4** was identified from its mp 44–46 °C (lit.[8] 44–46 °C), and by IR and NMR (^{1}H and ^{13}C) spectroscopy.

[c] *Typical procedure (with DMF)*—A mixture of diacetate **4** (1.0 mmol), fused potassium acetate (1.0 mmol) and dry dimethyl formamide (5 ml) was heated at 180 °C in a 10 ml round bottom flask carrying a water condenser and guard tube (CaCl$_2$). After being heated for 5 h, the reaction mixture was cooled to room temperature, treated with saturated NaHCO$_3$ (2 ml) to ensure alkalinity and concentrated by evaporation in vacuo. The mixture was then taken into a mixture of diethyl ether and 6 N HCl, and the organic layer separated and washed with water. The ether extract was dried (Na$_2$SO$_4$) and distilled in vacuo to remove the volatiles. The residue of crude cinnamic acid (**3**) was purified by column chromatography over silica gel to give pure **3** (0.66 mmol, 66%), identified by comparison with an authentic sample employing the mp (132 °C, lit.[d] 133 °C), IR and 300 MHz ^{1}H NMR spectra.

[d] *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Addison Wesley Longman: Harlow, 1989; p 1038.

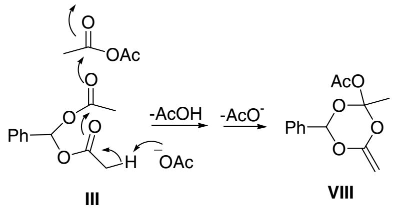
[e] *t*-BuOH may be substituted for THF as the solvent.

acetic anhydride to furnish the *gem*-diacetate **4** in high yields (Scheme 2):[7,8] this then could well be the de facto substrate in the Perkin reaction. Interestingly, this possibility had indeed been considered very early but only to be abandoned, apparently because of the poor yields of cinnamic acid (**3**) obtained.[3] In the present study, we have shown that the yields of **3** can indeed be vastly improved with **4** as the substrate if appropriate conditions are employed. Thus, employing excess benzaldehyde, or DMF as the solvent, or potassium *tert*-butoxide (KO-Bu^t) as the base, led to excellent yields of cinnamic acid (**3**) (Table 1, entries 3–5). Intriguingly, an excess of **1** leads to poor yields (Table 1, entry 2); this is explained further below. (Higher yields indicate that a relatively favourable pathway exists for the transformation.) These considerations lead to the following reasonable mechanistic conclusions which, although perhaps tentative, are at least compatible with the available evidence, and can also form the basis of further work.

The fact that employing excess benzaldehyde (**2**) leads to vastly improved yields, suggests that **2** is the electrophilic species involved. Furthermore, the high yields of **3** obtained from the reaction of diacetate **4** with KOBu^t prove that it is possible to generate the enolate anion of **4**, and effect the Perkin reaction with it. Of course, this is not necessarily valid under the conditions of the original Perkin reaction: clearly, the weakly basic acetate ion normally employed therein could not normally deprotonate **4** (estimated $\mathrm{p}K_\mathrm{a} \sim 24$).[4] However, an interesting assisted mechanism is possible, in which the 'spectator' acetate moiety in **4** participates electrophilically in the deprotonation as shown in **III**, leading to the orthoformate anion **IV** (Scheme 2).

Interestingly, in **IV** the enolate moiety would gain thermodynamic stability by covalent bonding of its oxygen atom to the orthoformate carbon atom. In fact, **IV** may be estimated to possess a $\mathrm{p}K_\mathrm{a}$ of ~11, a value closer—than that of **1** ($\mathrm{p}K_\mathrm{a}$ possibly >20)—to the $\mathrm{p}K_\mathrm{a}$ of acetic acid (~4.5). (The estimated $\mathrm{p}K_\mathrm{a}$ of **IV** is based on the reported $\mathrm{p}K_\mathrm{a}$ of ~12 for the analogous hemiacetal grouping in the sugars, e.g., 12.34 for D-glucose;[9] alcohols possess $\mathrm{p}K_\mathrm{a}$'s ~17,[4b] so the inclusion of additional β oxygen atoms substantially lowers the $\mathrm{p}K_\mathrm{a}$. Note also that the electron withdrawing enol ether moiety in **IV** would lower the $\mathrm{p}K_\mathrm{a}$ further.) Thus, the process shown in **III** would be relatively favoured thermodynamically, and possibly lead to 'viable' amounts of the incipient **IV**. (In fact, additional electrophilic assistance by **1** itself could provide a further kinetic advantage to the above deprotonation of **4** (cf. Scheme 3); this would lead to the *O*-acetyl derivative **VIII**, which could be O-deacetylated with acetate to yield **IV** for further reaction with **2**.)

The final formation of **3** follows from the initial addition of **IV** to **2** yielding **V**, and the succeeding reactions via **VI** and **VII** in Scheme 2. It is interesting and noteworthy that the formation of **VII** from **VI** is accompanied by the



Scheme 3.

release of a molecule of benzaldehyde (**2**), which thus apparently acts as both substrate and catalyst. This indicates that the reaction would slow down markedly as it progresses, and also explains the improved yields obtained with excess benzaldehyde.

Clearly, the above mechanism requires the presence of both benzaldehyde (**2)** and diacetate **4**, which presumably exists in equilibrium under the reaction conditions (cf. Scheme 2). The poor yields with excess acetic anhydride (**1**), mentioned above, most likely result from a shift of this equilibrium towards **4**, with a corresponding depletion of **2**. In fact, since **4** is quite stable and easily isolable, this equilibrium would largely favour **4** under normal conditions, only to be reversed to form viable amounts of **2** (and **1**) at the high temperatures employed in the Perkin reaction. The higher yields obtained with excess benzaldehyde (**2**) are compatible with the possibility that the addition of **IV** to **2** is the rate determining step in the overall reaction. However, the dependence of the overall rate on [**2**] is likely to be complex, in view of the catalytic role for **2** (proposed above).

The interesting formation of **3** from **4** and $KOBu^t$ (Table 1, entry 5) possibly occurs via an alternative mechanism, and is apparently only obliquely relevant to the present discussion. In addition, the formation of **3** from **4** under a variety of relatively mild conditions (Table 1, entries 3–5), is noteworthy. As **4** is readily prepared and isolated from **1** and **2** under relatively mild conditions, this (effectively) defines a considerable improvement in methodology for the Perkin condensation: this essentially avoids high temperatures in excess acetic anhydride, and should suit relatively sensitive substrates.

In conclusion, the available evidence indicates that the accepted mechanism of the Perkin reaction needs to be substantially revised. Essentially, it appears that the enolate of the *gem*-diacetate derived from the aromatic aldehyde and acetic anhydride—rather than the enolate of acetic anhydride itself—adds to the aldehyde in the key step. The deprotonation of the diacetate to the enolate appears to be electrophilically assisted by the neighbouring acetate group. An important practical consequence of these studies is the development of relatively mild conditions for effecting the overall transformation of the Perkin condensation (employing the diacetate as the substrate).

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