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Dakin−West Synthesis of β-Aryl Ketones

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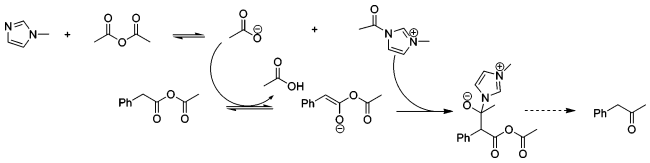

Triethylamine and 1-methylimidazole were found to be selective catalysts for the Dakin−West synthesis of diaryl ketones and aryl methyl ketones, respectively. In the 1-methylimidazole-catalyzed reaction, catalysis is due to the simultaneous formation of both an effective acylating agent, 1-acyl-3-methylimidazolium, and a base, carboxylate anion. Hydrocinnamic acid, a compound previously reported to be unreactive under Dakin−West conditions, forms 4-phenyl-2-butanone when the reaction is catalyzed by 1-methylimidazole.

The Dakin−West reaction, originally carried out in acetic anhydride and pyridine, is the best known route for the synthesis of β-acetoamido ketones from α-amino acids (Figure 1).[1,2]

Among other applications,[3,4] Woodward used the Dakin−West reaction in his classic synthesis of strychnine,[5] and more recently, Fu used a modified Dakin−West reaction to asymmetrically C-acylate acyclic silyl ketene acetals.[6] The Dakin−West reaction also has been used successfully to make ketones from aryl acetic acids (Figure 2),[7−9] and this reaction is the subject of our study.

Application of the Dakin−West reaction to aryl acetic acids has had two important limitations: (1) it required that the carboxylic acid form an anhydride with an acidic α-CH group,[7] and (2) the reaction yielded two ketone products; for example, phenylacetic acid **(1)** and acetic anhydride **(2)** with pyridine (entry 1) give phenyl-2-propanone (**3**) and 1,3-diphenyl-2-propanone (**5**).[10,11]

In this work we show that the major product can be determined by the choice of catalyst, and that by using

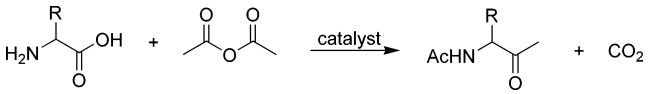

FIGURE 1. The reaction of amino acids with acetic anhydride reported by Dakin and West[1].

1-methylimidazole (MIM), the scope of the Dakin−West reaction can be extended to compounds previously believed to be unreactive. We also suggest an alternative to the previously proposed mechanisms for this reaction.[12,13]

The most efficient catalyst identified to date for this reaction is probably 4-(dimethylamino)pyridine (DMAP),[14,15] but as shown below, several compounds can be used to catalyze the acid-ketone transformation (Table 1). Of these, we found that MIM has several advantages. It is less expensive and less toxic than DMAP and, as a liquid, often easier to use. Like DMAP, it permits the Dakin−West reaction to proceed at room temperature with excellent overall yields. With MIM, hydrocinnamic acid (entry 6), a compound that is unresponsive to pyridine catalysis,[11] was converted to 4-phenyl-2-butanone in ∼50% yield, and phenylacetic acid (entry 2), 4-nitrophenylacetic acid (entry 9), and 4-methoxyphenylacetic acid (entry 10) gave almost quantitative yields. In contrast, 2-phenylbutanoic acid (entry 11) showed only 6% conversion to 3-phenyl-2-pentanone, and ethyl 2-phenylacetate (entry 12) showed no reaction even with prolonged heating.

Although we found 1-benzylimidazole (entry 3) to be an effective, if somewhat slower, catalyst than MIM, 1,2-dimethylimidazole (entry 4) was much less efficient, giving only 12% product yield and poorer selectivity than MIM and 1-benzylimidazole under the same reaction conditions.

For phenylacetic acid (**1**), the ratios of products **3** and **5** differed with the catalyst employed. Using MIM or 1-benzylimidazole, the ratios of products **3** and **5** were 94:6 and 90:10, respectively (entry 2 and entry 3). Using 1,2-dimethylimidazole or triethylamine (TEA), the ratios of products **3** and **5** were 72:28 and 6:94, respectively (entry 4 and entry 5). No reaction was observed for hydrocinnamic acid with TEA alone (entry 8). However, reactions carried out with both TEA and MIM present produced more 1,5-diphenyl-3-pentanone than did reactions with only MIM present (entry 6 and entry 7).

In some trials, reactions with **1** gave product mixtures containing over 30% of **3** and **5** as their enol esters (Figure 3). Surprisingly, although the enol esters were sometimes a large fraction of the product mixture, little or no enol ester was detected in the ^{1}H NMR or ^{13}C NMR spectra of the reaction medium during the course of the reaction. Instead, it appears that the enol ester formed during the workup from residual acetic acid and the ketone products. The enol ester content could be reduced to <2% of the total product by thoroughly washing the initial organic phase with aqueous potassium bicarbonate before removing the solvent.

We used ^{1}H NMR to monitor the disappearance of phenylacetic acetic anhydride (**20**) and **1** and the formation of **3** and **5**. The time course of reaction showed apparent first-order

(1) Dakin, H. D.; West, R. *J. Biol. Chem.* **1928**, *78*, 91.
(2) Khodaei, M.; Khosropour, A.; Fattahpour, P. *Tetrahedron Lett.* **2005**, *46*, 2105.
(3) Casimir, J. R.; Turetta, C.; Ettouati, L.; Paris, J. *Tetrahedron Lett.* **1995**, *36*, 4797.
(4) Kawase, M.; Hirabayashi, M.; Koiwai, H.; Yamamoto, K.; Miyamae, H. *Chem. Commun.* **1998**, 641.
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(6) Mermerian, A.; Fu, G. *J. Am. Chem. Soc.* **2005**, *127*, 5604.
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(8) Nicholson, J. *J. Chem. Educ.* **2004**, *81*, 1362.
(9) Smith, G. G. *J. Am. Chem. Soc.* **1952**, *75*, 1134.
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(14) Hofle, G.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981.
(15) Scriven, E. F. *Chem. Soc. Rev.* **1983**, *12*, 129.

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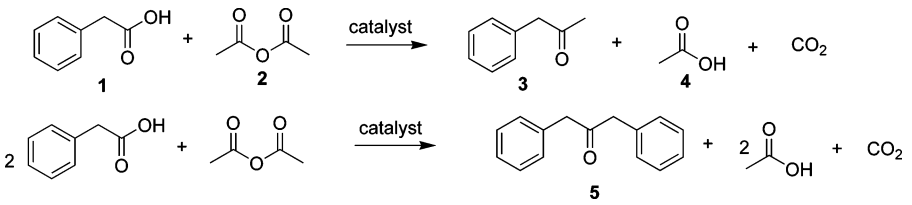
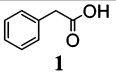
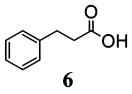
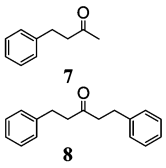
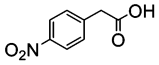
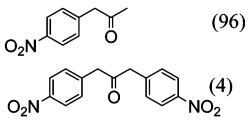
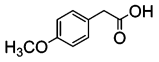
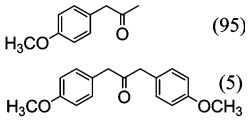
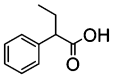
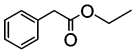


FIGURE 2. The Dakin−West reaction of phenylacetic acid.

TABLE 1. Reaction Conditions, Yields, and Product Ratios for Dakin−West Syntheses of *β*-Aryl Ketones

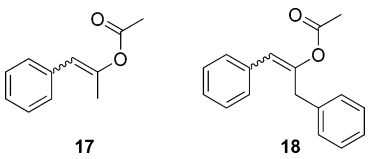
Entry	Carboxylic Acid[a]	Catalyst[b]	Catalyst: Acid Ratio	Time (h)	Yield[c] (%)	Products[d]
1	 **1**	pyridine[11]	6:1	6	80[e]	**3, 5** (70:30)
2	**1**	MIM	0.5 - 2 : 1	12	93	**3, 5** (94:6)
3	**1**	1-benzyl-imidazole	0.5 : 1	48	98	**3, 5** (90:10)
4	**1**	1,2-dimethyl-imidazole	0.5 : 1	48	12	**3, 5** (72:28)
5	**1**	TEA	1 : 1	48	73	**3, 5** (6:94)
6	 **6**	MIM	2 : 1	48	48[e]	 **7** (96) **8** (4)
7	**6**	MIM + TEA	1 + 1 : 1	48	57[e]	**7, 8** (90:10)
8	**6**	TEA	2 : 1	48	0[e]	-
9		MIM	0.5 : 1	12	100	 (96) (4)
10		MIM	0.5 : 1	12	83	 (95) (5)
11		MIM	2 : 1	48	6[e]	
12		MIM	2 : 1	48	0[e]	-

[a] The reaction medium contained 5 equiv of acetic anhydride. See experimental procedure for other details. [b] MIM = 1-methylimidazole; TEA = triethylamine. [c] Yields were calculated based on the isolated product mixture, except entry 9 which was determined by ^{1}H NMR. [d] The numbers in parentheses indicate the relative mole percentage of that compound in the isolated product mixture. [e] The reaction mixture was refluxed for the duration of the reaction.

kinetics with respect to **20** with rate constants of $(4.2 \pm 0.4) \times 10^{-3}$ min^{-1} and $(1.7 \pm 0.2) \times 10^{-3}$ min^{-1} for the 1-methylimidazole- and 1-benzylimidazole-catalyzed reactions, respectively (Figure 4). This reaction order is consistent with that reported by other investigators using pyridine to catalyze the Dakin−West reaction.[12,13]

Pyridine catalysis of the Dakin−West reaction requires the catalyst to be present in large excess, typically 6 or more times the carboxylic acid concentration.[11,16] This suggested to previous investigators that pyridine was acting as a general base, catalyzing the reaction by removing a proton from the α-carbon of the *β*-aryl acetic anhydride. However, we found this assumption to be less tenable after observing effective catalysis with

(16) Godfrey, A.; Brooks, D.; Hay, L.; Peters, M.; McCarthy, J.; Mitchell, D. *J. Org. Chem.* **2003**, *68*, 2623.



17 **18**

FIGURE 3. Enol esters **17** and **18**, formed by reaction of acetic acid with **3** and **5**, respectively.

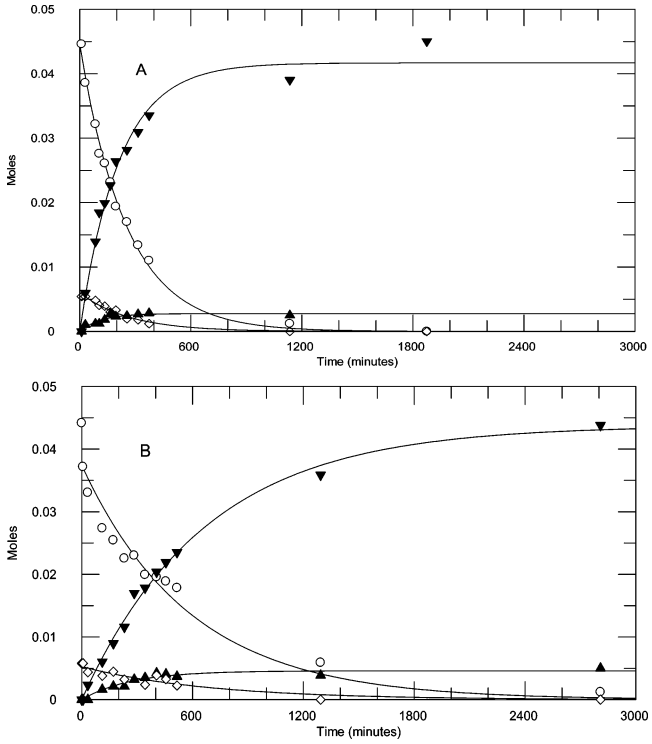


FIGURE 4. Concentrations of reactants and products over the course of the reaction: (A) MIM catalyzed; (B) 1-benzylimidazole catalyzed. Data shown are for (◊) phenylacetic acid (**1**), (○) phenylacetic acetic anhydride (**20**), (▼) phenyl-2-propanone (**3**), and (▲) 1,3-diphenyl-2-propanone (**5**). After equilibration of the phenylacetic acid and acetic anhydride, the reaction was initiated by the addition of 0.5 equiv of catalyst. Samples of the reaction mixture were removed at regular intervals after initiation, and the reactants' and products' relative concentrations were determined by ^{1}H NMR, and normalized to the initial concentration of phenylacetic acetic anhydride and phenylacetic acid.

MIM even when its concentration was half that of the carboxylic acid present in the reaction mixture. Moreover, although a general base catalyst must be able to abstract a proton from the α-carbon of **20** to make **20a** (Scheme 1), we found no correlation between the effectiveness of the catalyst and the pK_a of its conjugate acid. For example, MIM is a better catalyst than TEA, but its conjugate acid has a lower pK_a.

MIM, 1-benzylimidazole, DMAP, and to a lesser extent, pyridine, give a methyl ketone as their major product with acetic anhydride (Table 1). These catalysts can all react with an anhydride to generate a powerful acylating agent and a carboxylate anion. In keeping with this, we propose that for aryl acetic acids, the Dakin−West reaction occurs as shown in Scheme 1.

In this mechanism, MIM is actually a pre-catalyst, that upon reaction with **2** produces the true catalysts of the reaction, acylimidazolium cation (**19a**) and carboxylate anion (**4a**). The pK_a of acetic acid is between 12 and 22 in aprotic organic solvents such as DMSO and acetonitrile,[17,18] suggesting that **4a** would be capable of abstracting the α-hydrogen of **20** to form **20a** in acetic anhydride. The subsequent reaction of **20a** with **19a** forms the tetrahedral intermediate **21** (Scheme 1).

It is possible to predict the rate-limiting step in Scheme 1. The first step of this mechanism is unlikely to be rate limiting because the reaction is first order with respect to **20.** The second step is also unlikely because the anhydride transfer is relatively rapid, reaching equilibrium within a few minutes in our reaction conditions. Later steps f, g, and h are probably not rate limiting because the transient formation of **22**, **23**, or **24** was not observed in the NMR spectra of the reaction medium during the reaction. By elimination, either the formation or breakdown of **21** is likely to be the rate-limiting step (steps d or e of Scheme 1). Previous studies have shown that for acyl transfer reactions in aprotic solvents, the formation or breakdown of a tetrahedral intermediate is frequently rate limiting.[17,19,20] In either case, the reaction rate would depend on the concentrations of the enolate and the acyl-imidazolium precursors.[6] This is consistent with our observation that both nitro and methoxy groups promote the reaction (entries 9 and 10), presumably by stabilizing the enolate by resonance or induction, and with our observation that the reaction is first order with respect to **20**. With reactants that are less able to form an enolate, such as ethyl phenylacetate, the reaction proceeds poorly or not at all. The poor yield of 3-phenyl-2-pentanone from phenylbutyric acid probably reflects the steric hindrance at the α-carbon as well as the relative instability of the tertiary carbanion formed as an intermediate.

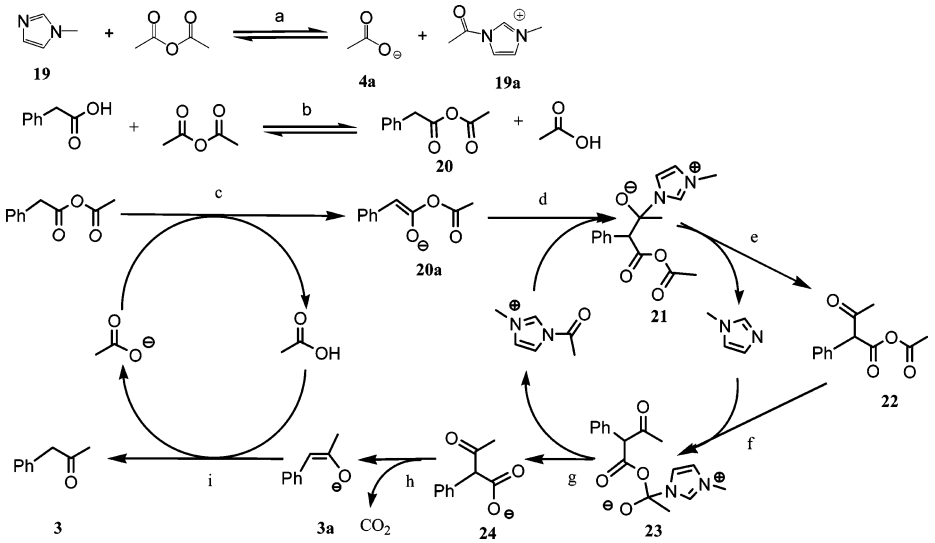
In contrast to catalysis with MIM, TEA catalysis gives a diaryl ketone as the major product. Results similar to those with TEA have been observed using sodium acetate as the catalyst,[11,21] suggesting that these catalysts promote a different mechanism of acid-ketone conversion. We propose that TEA and acetate may act by general base catalysis rather than nucleophilic catalysis. The difference is notable; for the reaction of **1**, nucleophilic (MIM) catalysis gives a product ratio of **3** to **5** of 94:6 while base (TEA) catalysis gives a **3** to **5** ratio of 6:94. Previously, Smith and Fahey proposed a general base mechanism for pyridine catalysis.[12] In this broadly accepted mechanism, the Dakin−West reaction is a base-catalyzed condensation of anhydrides that forms a methyl aryl ketone as the major product. Our results suggest that the predominant reaction Smith and Fahey observed was actually nucleophilic catalysis by pyridine rather than base catalysis and that base catalysis alone leads to the diaryl ketone as the major product.

Base catalysis may follow a similar reaction sequence to that shown in Scheme 1, but with the critical tetrahedral intermediate formed from **20a** and **20** (Figure 5). Alternatively, as has been previously suggested, this reaction may occur by a mechanism involving either an intramolecular O−C migration (Figure 5) or the bimolecular equivalent.[5,11,22] Whatever the mechanism, for reasons that remain unclear, base catalysis generates the diaryl ketone (**5)** as the major product.

Compared to MIM and 1-benzylimidazole, 1,2-dimethylimidazole catalyzes the reaction of **1** much less effectively. This implies that the methyl group on the 2-position of 1,2-

(17) Hajdu, J.; Smith, G. *J. Am. Chem. Soc.* **1981**, *103*, 6192.
(18) Kolthoff, I. M.; Chantooni, M. K.; Bhowmik, S. *J. Am. Chem. Soc.* **1967**, *90*, 23.
(19) Fersht, A.; Jencks, W. *J. Am. Chem. Soc.* **1970**, *92*, 2622.
(20) Fersht, A.; Jencks, W. P. *J. Am. Chem. Soc.* **1970**, *92*, 5432.
(21) Hurd, C.; Thomas, C. *J. Am. Chem. Soc.* **1936**, *58*, 1240.
(22) Buchanan, G. L.; McArdle, J. *J. Chem. Soc.* **1952**, 2944.

SCHEME 1. Mechanism for Nucleophilic Catalysis[a] of the Dakin−West Reaction by 1-Methylimidazole



[a] Reaction steps are (a) formation of the acyl-imidazolium, **19a,** and the carboxylate anion, **4a**; (b) acid-anhydride acetyl transfer; (c) abstraction of an α-hydrogen from the *β*-aryl anhydride **20** to form the enolate **20a**; (d) nucleophilic attack on **19a** by **20a** to form a tetrahedral intermediate **21**; (e) breakdown of **21** by the loss of **19** to form **22**; (f) attack on the acetyl carbonyl of **22** by **19** to form **23**; (g) formation of **24** by the transfer of an acetyl group to **19**; (h) the subsequent decarboxylation of **24** to release CO_2; and (i) protonation of the enolate **3a** to form phenyl-2-propanone, **3**.

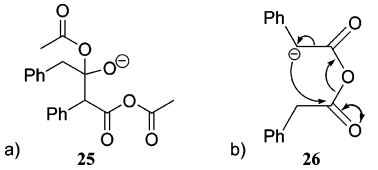


FIGURE 5. (a) Tetrahedral intermediate (**25**) proposed for a stepwise mechanism for base catalysis similar to the mechanism for nucleophilic catalysis shown in Scheme 1; (b) mechanism for base catalysis via a concerted O−C transfer.[5,11,22]

dimethylimidazole hinders the formation or reaction of the acyl-imidazolium ion, thus limiting nucleophilic catalysis without affecting base catalysis. These results are consistent with reports that 2-methyl substituted pyridines are much less effective as nucleophilic reagents.[15,23]

Simple general base catalysis is less efficient than nucleophilic catalysis. For **1**, the reactions were slower and had lower yields when catalyzed by TEA than by MIM. Hydrocinnamic acid with acetic anhydride showed no reaction when treated with TEA but underwent an acid-ketone transformation with MIM. King and McMillan reported that hydrocinnamic acid remained unchanged using pyridine catalysis.[10,11] Our results suggest that with an appropriate catalyst, this reaction can be applied to a broader range of compounds than previously believed.

In conclusion, we show that by choosing the right catalyst it is possible to obtain either a methyl aryl ketone or a diaryl ketone as the major product of the Dakin−West reaction. A catalyst that can generate an effective acylating agent and a strong base in aprotic solvents (such as MIM and DMAP) will convert anhydrides with only mildly acidic α-carbons to aryl methyl ketones. In contrast, catalysts that cannot facilitate nucleophilic catalysis (such as TEA or sodium acetate) require more acidic C−H groups for reaction and give diaryl ketones as their major products.

(23) Butler, A. R.; Gold, V. *J. Chem. Soc.* **1961**, 4362.

Experimental Section

General Procedure. In a typical reaction, an aryl carboxylic acid (0.05 mol, 1 equiv) was dissolved in **2** (0.25 mol, 25 mL, 5 equiv), at room temperature, and the solution was stirred and purged with N_2 for several minutes. The reaction was initiated by the addition of catalyst (0.025 mol, 0.5 equiv), and the reaction was continuously purged with a slow flow of N_2 over the course of the reaction. At regular intervals during the reaction, 100 μL samples of the reaction mixture were transferred to an NMR tube containing $CDCl_3$, and their ^1H and ^{13}C NMR spectra were immediately recorded. Reactions were typically allowed to run for 12 or 48 h, depending on the catalyst and reactants. For the reactions using MIM, NMR results showed that in most cases the reaction reached completion in 10 h or less.

Reactions with hydrocinnamic acid, 3-phenylbutyric acid and ethyl phenylacetate (entries 6−8, 11, and 12) followed the procedure described above except the reaction mixture contained more catalyst (0.1 mol, 2 equiv) and was heated to reflux over the course of the reaction.

^{1}H NMR Kinetics. The relative concentrations of **1**, **3**, **5**, and **20** in the reaction mixture were determined using their ^1H NMR peak areas. This information was used to generate a best-fit curve for the reaction time course and to determine the reaction order for **20.**

Workup. After completion, water (10 mL) was added to the reaction flask to hydrolyze **2**. The reaction mixture was extracted with ethyl acetate (3 × 50 mL), and the extracts combined and washed with saturated potassium bicarbonate (2 × 50 mL) followed by water (2 × 50 mL), then dried over magnesium sulfate and filtered. Removing the solvent by rotary evaporation gave the product mixture, which was characterized by ^1H NMR, ^{13}C NMR, and GC/MS.

Acknowledgment. We thank the Howard Hughes Medical Institute and Smith College for funding and Charles Amass for technical assistance in this project.

Supporting Information Available: ^1H NMR and ^{13}C NMR of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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