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The Mechanism of Formation of 6-Aryl-4,6-dioxohexanoic Acids from Arylketones and Succinic Anhydride

William V. Murray*, Praful Lalan and Peter J. Connolly

The R. W. Johnson Pharmaceutical Research Institute,
1000 Route 202, Raritan, NJ 08869-0602

Abstract: Compounds **2a-d** could be synthesized directly from the requisite acetophenone enolate and succinic anhydride. Intermediate O-acylated products **1a-d** were observed. Compounds **1a-d** could be converted to **2a-d** by treatment with at least two additional equivalents of the acetophenone enolate. Evidence indicates that **1** is an intermediate in the synthesis of **2** and that the direct reaction requires at least two equivalents of acetophenone enolate.

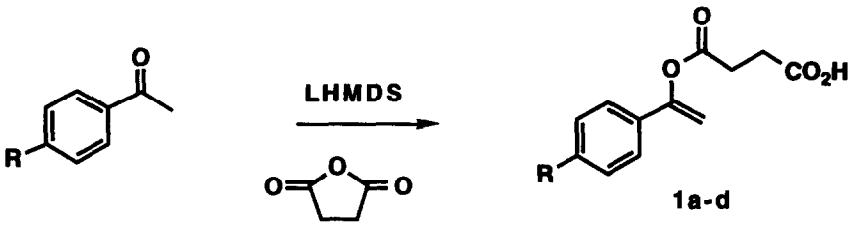
Tepoxalin has emerged as a potentially important therapeutic agent in the treatment of chronic inflammatory disease. We have previously reported the synthesis of 6-aryl-4,6-dioxohexanoic acids in our synthetic studies directed towards tepoxalin and related diarylpyrazolepropionic acids.[1,2] In this study we will show evidence that the acylation reaction described in these reports proceeds through an intermediate enolester which serves as an acylating agent for a second equivalent of aryl enolate.

In our first report, we found that when 2.5 equivalents of 4-methoxyacetophenone was subjected to LDA at -78°C and subsequently treated with one equivalent of succinic anhydride and allowed to warm to room temperature for one hour, only the O-acylated product **1a** was isolated. We later found, that by using lithium hexamethyldisilazide (LHMDS) as base and allowing the reaction mixture to stir for 24 hours complete conversion to the desired C-acylated product **2a** was achieved. We also found that 4-cyanoacetophenone and 4-carbomethoxyacetophenone, when treated as above for one hour at room temperature, afforded exclusively O-acylated products **1b** and **1c**, while 24 hours at room temperature gave the C-acylated products **2b** and **2c**.

We decided to examine this reaction further by isolating the O-acylated intermediates and attempting to rearrange them under a number of different conditions. Compounds **1a-d** were prepared by reacting one equivalent of the substituted acetophenone with one equivalent each of LHMDS and succinic anhydride (Table 1). These compounds were then subjected to a number of conditions intended to rearrange them to the C-acylated products **2a-d**. We attempted to rearrange these compounds thermally either in refluxing xylene or as a melt but were unsuccessful. We tried a number of Lewis acids, including BF_3·OEt, $TiCl_4$, $ZnCl_2$ and TMSOTf without success. We then used

varying amounts of the same acetophenone enolate derivative as was used to form the O-acylated acetophenone in reactions with the enol succinates. We found that 2-3 equivalents of the enolate gave optimal yields of **2a-d**. In a crossover experiment, using 2-3 equivalents of a different acetophenone enolate **3a-d** affords only the product of succinyl transfer to the second enolate. We found that the only product was the C-acylated derivative of the second aryl enolate,[4] suggesting that the succinyl transfer occurs through an intermolecular process and that the original enolate is not liberated during the process. The only by-products we observed in these reactions were the acetophenones, succinamide and succinic acid.

Table 1



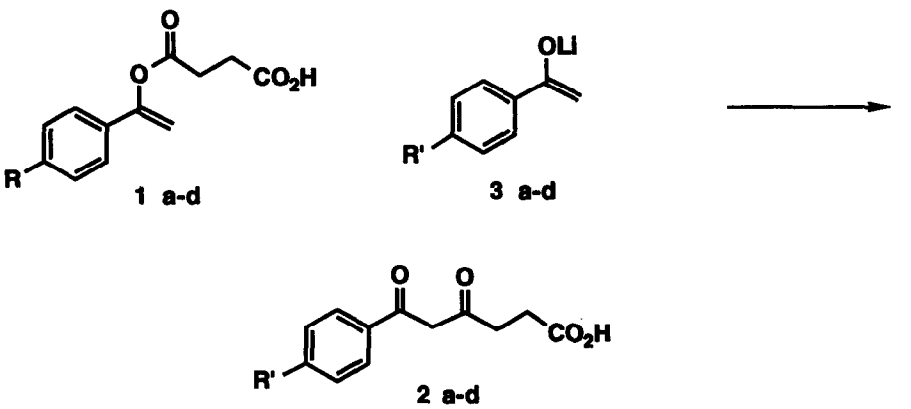
#	R	Yield[3]
1a	OCH_3	44 %
1b	CN	49 %
1c	CO_2CH_3	57 %
1d	Cl	18 %

Several experiments were carried out to test this idea. We thought that if the acetophenone bearing the R substituent were leaving as an enolate, we might be able to generate the O-acylated product with a catalytic amount of the second enolate. We tried this by two routes. The first involved treating 1.1 equivalent of 4-chloroacetophenone with 2.2 equivalents of LHMDS at -78°C followed by one equivalent of succinic anhydride. After stirring overnight at room temperature only a 17% yield of **2d** was isolated.[5] We also attempted this transformation by adding 0.1 equivalent of the enolate of 4-chloroacetophenone (**3d**) to a mixture of 1 equivalent each of **1d** and LHMDS. No **2d** was observed after 24 hours at room temperature.

We believe that this indicates that at least two equivalents of enolate[6] are needed to convert **1** to **2**. It is possible that the the enolate leaving group of **1** is quenched by the resulting diketone and is of no consequence in the product distribution of **2**. Another interesting possibility is that the tetrahedral intermediate **4** forms and undergoes the anion-accelerated electrocyclic reaction shown in Fig. 1. This would unequivocally explain the need for at least two equivalents of anion in this reaction. We also find that additional enolate in solution seems to enhance the solubility of the enol succinates **1a-d** and accelerates their conversion to **2 a-d**. It is also evident that rate of conversion of enol succinate to diketone in our previous examples [1,2] such as 2-acetylthiophene, 4-methyl acetophenone, acetophenone, etc., is much faster than the conversion we observe in enolates **3 a-c**. This originally

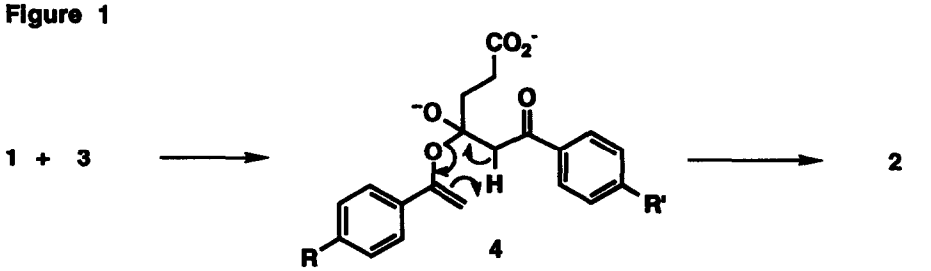
led us to believe that we observed direct C-acylation of the enolate. Since the O to C transfer reactions of these enolates take place in less than an hour, and the by products of the work up are succinic acid and the arylketone, this seemed reasonable. The lability of enolsuccinate **1d** to work up conditions also led us to this interpretation. Now, by careful isolation and conversion of the enolsuccinates to the aryl diketones we believe we have shown the intermediacy of the enol succinates **1a-d**.

Table 2



1	R	3	R'	2	R'	Yield
a	OCH_3	a	OCH_3	a	OCH_3	39 %
b	CN	b	CN	b	CN	44 %
c	CO_2CH_3	c	CO_2CH_3	c	CO_2CH_3	40 %
d	Cl	d	Cl	d	Cl	49 %
a	OCH_3	d	Cl	d	Cl	47 %
a	OCH_3	b	CN	b	CN	51 %
b	CN	d	Cl	d	Cl	22 %
d	Cl	b	CN	b	CN	29 %
c	CO_2CH_3	d	Cl	d	Cl	28 %
d	Cl	a	OCH_3	a	OCH_3	29 %

Figure 1



Preparation of Compound 1b

To a 500 mL round bottom flask equipped with a thermometer, addition funnel and a N_2 inlet, lithium hexamethyldisilazide (1 molar THF, 83 mL, 83 mmoles), followed by 100 mL THF were added and cooled to -75°C. Under stirring, a precooled solution (-70°C) of 4-acetylbenzonitrile (12g, 83 mmoles) in 70 mL THF was added rapidly. The resulting solution was stirred at -75°C for 10 min. A solution of succinic anhydride (8.3 g, 83 mmoles) in 100 mL THF was added and stirred at -70°C for 2 hours. The mixture was allowed to warm to room temperature and stirred for an additional 16 hours . The reaction mixture was partitioned between ether (300 mL) and 2N HCl (200 mL). The ether phase was separated, washed with H_2O (200 mL), brine (200 mL) and dried over sodium sulfate. Removal of solvent and subsequent chromatography on silica gel eluting with hexane / EtOAc 50% gave 10 g (49%) of **1b** as white solid, mp 114-117°C. NMR (300 MHz, $CDCl_3$) δ 2.58 (2H, t, J = 7.0 Hz), 2.83 (2H, t, J = 7.0 Hz), 5.22 (1H, d, J = 2.5 Hz), 5.95 (1H, d, J = 2.5 Hz), 7.75 (2H, d, J = 8.5 Hz), 7.85 (2H, d, J = 8.5 Hz). Mass Spec. (DCI) m/z 246 (MH^+).

Preparation of Compound 2b

To a 200 mL round bottom flask equipped with a thermometer, addition funnel and a N_2 inlet, lithium hexamethyldisilazide (1 molar THF, 6.8 mL, 6.8 mmoles) and 15 mL THF were added and cooled to -75°C. Under stirring, a precooled solution (-70°C) of 4-acetylbenzonitrile (1 g, 6.9 mmoles) in 10 mL THF was added rapidly. The resulting solution was stirred at -75°C for 10 min. A solution of **1b** (0.84g, 3.4 mmoles) in 50 mL THF was added at once. The solution was stirred for 2 hours at -70°C and allowed to warm to room temperature. The reaction was stirred for 16 hours at room temperature. The reaction was partitioned between ether (100 mL) and 2N HCl (250 mL). The ether layer was separated, washed with water and brine as above, dried over sodium sulfate, concentrated and chromatographed on silica gel as above to give 0.371 g (44%) of **2b** as a tan solid, mp 111-114°C. NMR (300 MHz, DMSO-d6) 4:1 mixture of enol:keto tautomers: (Enol) 2.59 (2H, t, J = 6.9 Hz), 2.81 (2H, t, J = 6.9 Hz), 6.71 (1H,s), 8.01 (2H, d, J = 8.2 Hz), 8.09 (2H, d, J = 8.2 Hz): (Keto) 2.5 - 2.8 (4H, obscured resonances), 4.39 (2H, s), 8.01 (2H, d, J = 8.2 Hz), 8.08 (2H, d, J = 8.2 Hz). Mass Spec. (DCI) m/z 246 (MH^+).

References and notes

1. Murray, W.; Wachter, M. *J. Org. Chem.* **1990**,*55*, 3424.
2. Murray, W.; Wachter, M.; Barton, D.; Forero-Kelly, Y. *Synthesis* **1991**,18 .
3. Crude yields were from 75 - 92%. The enolsuccinates (**1**), however, were difficult to purify by chromatography.
4. The only time traces of the C-acylated compound **2** were observed occurred when **1** was not completely purified and some **2** was generated in the first step. When we noted this we repurified **1** and reran the second experiment.
5. Typical yields for this reaction (references 1 & 2) when 2-2.5 equivalents of enolate are used are > 75%.
6. In this study the second equivalent of enolate is used as a base to deprotonate the carboxyl of the enolsuccinate to prevent quenching the active enolate.

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