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Avermectin-Milbemycin Studies. 4. An Expedient Two-Step Preparation of p-Hydroxybenzoates

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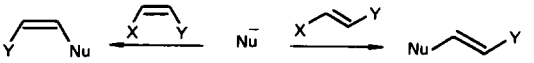
Summary: Dianions derived from a variety of 1,3-diketones react with Z-ethyl-3-bromopropenoate to afford unsaturated diketoesters which upon treatment with base undergo facile cyclization-dehydration to p-hydroxybenzoates.

The conjugate addition-elimination of nucleophiles to activated vinyl halides has been known for many years (Eq. 1).[3] In most cases the geometry of the vinyl halide is retained. Carbon nucleophiles[4] have been utilized; however, without exception simple ketone enolates afford at best poor yields (ca. <20%) of the addition-elimination products.

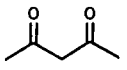
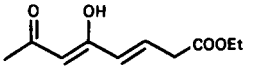
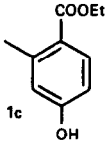
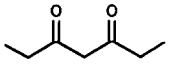
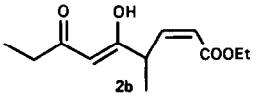
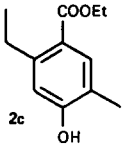
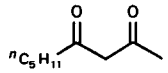
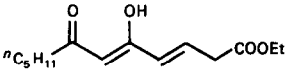
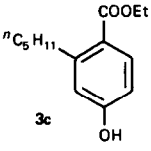
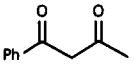
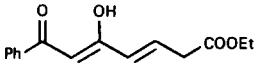
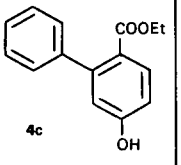
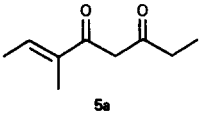
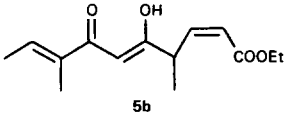
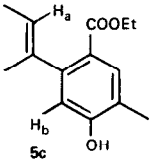
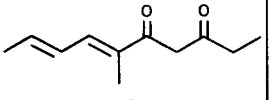
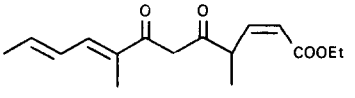
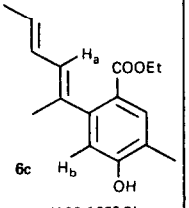


X = Cl, Br; Y = CO_2R, CN, p-$NO_2C_6H_4$, etc.

In connection with our continuing program in the avermectin-milbemycin area,[5] we recently discovered that lithium dianions, derived from 1,3-diketones via treatment with LDA in THF at -78°, react with Z-ethyl-3-bromopropenoate[6] to afford substituted 5,7-dioxoheptenoates in moderate yield.[7] These results are summarized in Table 1. These addition-elimination products, which proved to be unknown, are of interest in that they can be converted efficiently via cyclization-dehydration to substituted p-hydroxybenzoates on treatment with mild protic base.[8]

Several comments concerning both the addition-elimination and cyclization processes are in order. First, only in the case of diketones bearing a terminal ethyl group (2a and 5a) could the expected Z-olefinic ester be isolated. In the other examples, the more stable isomer in which an E-double bond is conjugated to the diketone was obtained. Attempts to intercept the presumed initial Z-isomer by quenching with acid at low temperature were unsuccessful. Second, the reaction failed completely with 2-substituted 1,3-diketones. For example, no identifiable products could be isolated from the reaction with either 3-methyl-2,4-pentanedione or 2-acetylcyclopentanone.

TABLE 1: Preparation of p-Hydroxybenzoates

Diketone	*Dioxoheptenoate* [7]	*Yield* *	*Hydroxybenzoate* [8] *(mp)*	*Method* †	*Yield**
 **1a**	 **1b**	39	 **1c** (89-90° C)	A	64
 **2a**	 **2b**	42	 **2c** (75.5-76° C)	A	80
 **3a**	 **3b**	38	 **3c**	A	58
 **4a**	 **4b**	41	 **4c** (77-78° C)	A B	0 70
 **5a**	 **5b**	55	 **5c** (88.5-89° C)	A B	57 20
 **6a**	 **6b**	41	 **6c** (108-109° C)	A	68

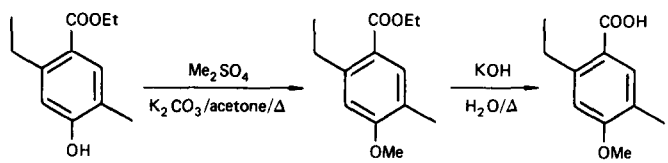
* All yields refer to isolated, homogeneous products.

† Method A: 0.1-0.2M NaOEt in EtOH, 25°C for 1h.
Method B: addition to 5% (v/v) Et_3N/EtOH at reflux.

Third, control experiments employing ethyl propiolate demonstrate that the reaction does not proceed via initial elimination of HBr followed by conjugate addition.

Turning to the cyclization-dehydration process, treatment of the initial addition-elimination products at room temperature with dilute ethanolic sodium ethoxide (0.1-0.2 M) in general afforded the corresponding p-hydroxybenzoates in good yield (ca. 60-80%). Substrate 4b proved to be the exception, being completely destroyed under these conditions. The desired biphenyl 4c was however obtained by slow addition of 4b to a 5% (v/v) solution of triethylamine in ethanol held at reflux; the yield here was 70%. The two step conversion of 1,3-diketones to p-hydroxybenzoates could also be performed in a single flask simply by quenching the dianion reaction with absolute ethanol, and then allowing the mixture to stir at room temperature for 1 h. The overall yields, however, were somewhat deminished; futhermore, this method failed for substrate 4a.

Structural assignments for both the 1,3-diketones and p-hydroxybenzoates were based on spectroscopic properties, in conjunction with elemental composition data derived either by high resolution mass spectrometry and/or elemental analysis. In the case of 2c, a chemical correlation was performed. Towards this end, methylation of the phenolic hydroxyl group (Me_2SO_4, K_2CO_3, acetone, 12 h at reflux)[10] followed by ester hydrolysis (20% aq KOH, 12 h at reflux) afforded 7, which was identical in all respects (i.e., ^1H NMR, IR, TLC, mp and mmp) with an authentic sample kindly provided by Professor Barrett (Northwestern University). Finally, stereochemical assignments for 5c and 6c were secured by observation of nuclear Overhauser effects (ca. 20% and 15%, respectively) between the vinyl and ortho hydrogens (H_a and H_b).[11]



2c 6 7

Two reasonable mechanisms for the cyclization-dehydration reaction can be envisioned. The first involves intramolecular nucleophilic attack of the vinylogous β-ketoester anion on the 7-keto group; alternatively, the mono or dianion of the bis-enol could undergo a 6π-electron cyclization. In both cases, loss of water and subsequent aromatization completes the process. A prerequisite for successful dehydration and/or cyclization appears to be the presence of a proton source. That is, treatment of 2b with dimethylaminopyridine in benzene at reflux resulted only in olefinic bond migration.

In summary, a new, highly expedient two step synthesis of substituted p-hydroxybenzoates has been uncovered. The cyclization-dehydration process, formally a vinylogous polyketide cyclization, finds analogy in the classical biomimetic synthesis of 2,4-dihydroxybenzoates.[12] In conjunction with the addition-elimination process reported here, this approach to unusually substituted p-hydroxybenzoates should have considerable potential.

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References and Notes

1. Camille and Henry Dreyfus Teacher-Scholar Award, 1978-1983; National Institutes of Health (National Cancer Institute) Career Development Award, 1980-1985.

2. NATO Postdoctoral Fellow, Science and Engineering Research Council, 1983-1985.

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7. A typical procedure for this reaction follows: A solution of heptane-3,5-dione 2a (256.0 mg, 2.0 mmol) in dry THF (3 mL) was added dropwise to a solution of LDA (4.2 mmol) in THF (12 mL) under argon at -78°. After 5 min, Z-ethyl-3-bromopropenoate (400 mg, 2.2 mmol) in THF (2 mL) was added in one portion. A mildly exothermic reaction ensued. The reaction mixture was then stirred for an additional 15 min, and then partitioned between ether and dilute aqueous HCl (0.5 M). The organic phase was dried ($MgSO_4$), evaporated and the residue chromatographed on silica [7:3 (v/v) hexane/ether] to give 188 mg (42%) of Z-ethyl-4-methyl-5,7-dioxo-2-nonenoate (2b) as a colorless oil.

8. A typical procedure follows: Method A. Diketoester 2b (124 mg 0.547 mmol) was dissolved in 0.18 M ethanolic sodium ethoxide (20 mL) under argon at room temperature. After 1 h, the mixture was partitioned between ether and dilute aqueous HCl (0.5 M). The organic phase was dried and evaporated, and the residue chromatographed on silica [3:2 (v/v) hexane/ether] to give 91 mg (80%) of 2c. Method B. A solution of 4b (43.2 mg, 0.166 mmol) in absolute ethanol (20 mL) was added dropwise over 4 h to a solution of triethylamine (1.0 mL) in absolute ethanol (20 mL) held at reflux under argon. After 18 h the solution was evaporated and the residue was chromatographed on silica [3:2 (v/v) hexane/ ether] to give 28.1 mg (70%) of 4c as a colorless oil.

9. (a) All new compounds gave 250 MHz ^1H NMR, IR and elemental composition data and/or high resolution mass spectra (parent ion identification) in accord with the structures given; (b) All yields recorded here are based on isolated material which was > 97% pure; (c) The NMR and IR spectra of representative intermediates are given below: 1b: IR (CCl_4) 3500-2500 (m), 1740 (s), 1655 (m), 1590 (s), 1370 (m), 1240 (s), 1150 (s), 1030 (m) cm^{-1}; NMR ($CDCl_3$) δ 6.65 (dt, J = 15, 7 Hz, 1H), 5.95 (bd, J = 15 Hz, 1H), 5.53 (8, 1H), 4.2 (q, J = 7 Hz, 2H), 3.23 (d, J = 7 Hz, 2H), 2.15 (s, 1H), 1.3 (t, J = 7 Hz, 3H). 4b: IR (CCl_4) 3300-2500 (m), 1740 (s), 1650 (m), 1570 (s), 1370 (m), 1260 (m), 1180 (m), 1025 (m), 970 (m) cm^{-1}; NMR ($CDCl_3$) δ 7.8 (m, 2H), 7.5 (m, 3H), 6.97 (dt, J = 15, 7 Hz, 1H), 6.23 (s, 1H), 6.15 (br d, J = 15 Hz, 1H), 4.2 (q, J = 7 Hz, 2H), 3.3 (br d, J = 7 Hz, 2H), 1.3 (t, J = 7 Hz, 3H). 1c: IR (CCl_4) 3600 (m), 3500-3100 (s), 1715 (s), 1690 (s), 1600 (s), 1580 (s), 1270 (s), 1250 (s), 1170 (s), 1130 (s), 1080 (s) cm^{-1}; NMR ($CDCl_3$) δ 7.88 (d, J = 11 Hz, 1H), 6.7 (br s, 2H), 6.1 (br, 1H), 4.33 (q, J = 7 Hz, 2H), 2.55 (s, 1H), 1.36 (t, J = 7 Hz, 3H). 4c: IR (CCl_4) 3600 (m), 3500-3100 (s), 1720-1670 (s), 1605 (s), 1570 (s), 1370 (m), 1290 (s), 1225 (m), 1200 (m), 1140 (m), 1100 (m), cm^{-1}; NMR ($CDCl_3$) δ 7.83 (d, J = 11 Hz, 1H), 7.35 (m, 3H), 7.25 (m, 2H), 6.83 (dd, J = 11, 2 Hz, 1H), 6.77 (d, J = 2 Hz, 1H), 5.6 (br s, 1H), 4.05 (q, J = 7 Hz, 2H), 0.96 (t, J = 7 Hz, 3H).

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