Base-catalyzed rearrangement of hemiacetal 3: DBU (3 drops) was added to a solution of hemiacetal **3** (3 mg, 0.011 mmol) in dry benzene (10 mL) under a dry nitrogen atmosphere and the solution stirred for 15 min. After 15 min, the benzene was removed in vacuo and the residue dissolved in ether and filtered through a silica gel SEP-PAK to obtain ester **4** (1.7 mg, 57% yield).

Acknowledgment. We thank Bruce Jenkins for identifying the pulmonate and Dr. M. Taylor for assistance in collecting the organisms. The research was supported by a grant from the National Science Foundation (CHE-8121471).

Registry No. 3, 91466-58-9; 4, 91466-59-0.

Thallium in Organic Synthesis. 62. A Convenient Synthesis of α-Arylsuccinic Acids[1,2]

Edward C. Taylor,* Richard A. Conley, and Alan H. Katz

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

Alexander McKillop

School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, Norfolk, England

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The "acetophenone rearrangement" (eq 1),[3-5] which is carried out by treatment of aralkyl ketones with thallium(III) trinitrate (TTN) in a mixture of methanol and trimethyl orthoformate (TMOF), or with TTN absorbed

$$ArC(O)CH_2R \xrightarrow[MeOH/TMOF]{TTN} R(Ar)CHCO_2Me \quad (1)$$

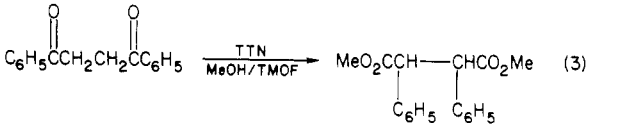
upon K-10 montmorillonite clay,[6] provides a high-yield, mild, one-step procedure for the synthesis of arylacetic acids and α-alkylarylacetic acids (as their methyl esters) which are of considerable interest as antiinflammatory, analgesic, and antipyretic agents.[7] We report in this paper details of a useful extension of the "acetophenone rearrangement" which leads to α-arylsuccinic acids (eq 2).

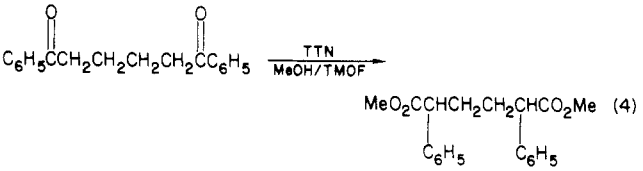
$$ArC(O)CH_2CH_2CO_2H \xrightarrow[MeOH/TMOF]{TTN} MeO_2CC(Ar)HCH_2CO_2Me \quad (2)$$

These latter compounds, which are precursors to the anticonvulsant α-arylsuccinimides,[8] are difficult to prepare in good yield by conventional routes.[9] Our new procedure involves TTN-mediated oxidative rearrangement of β-aroylpropionic acids (readily available by Friedel–Crafts acylation of arenes with succinic anhydride), and thus constitutes a two-step process for α-arylation of succinic acid. The same approach can be applied to the preparation of dimethyl α-phenylglutarate and dimethyl α-phenyladipate by oxidative rearrangement of γ-benzoylbutyric acid and δ-benzoylvaleric acid, respectively. Representative examples of this α-arylation process are given in Table I (method A).[10]

The reaction of β-benzoylpropionic acid with TTN in methanol alone gave only methyl β-benzoylpropionate (i.e., no oxidative rearrangement was observed), whereas the use of TMOF, free of added methanol,[11] led to a much lower yield of dimethyl α-phenylsuccinate, along with substantial amounts of the half-ester $C_6H_5CH(CO_2CH_3)CH_2CO_2H$. Replacement of MeOH/TMOF by aqueous perchloric acid as the reaction medium gave a complex mixture of oxidation products.[12] These results suggest that β-benzoylpropionic acid is first converted to its methyl ester by methanol in the presence of TTN, a strong Lewis acid and an effective esterification catalyst, and that TMOF converts the latter to its enol ether, which then undergoes oxidative rearrangement.[13] In confirmation of this proposed pathway, methyl β-benzoylpropionate (prepared in situ from the acid) was converted with methanol/TMOF/TsOH to its enol ether, which rearranged cleanly to dimethyl α-phenylsuccinate within 15 min at room temperature (77% yield). Analogous results were obtained when this procedure was applied to other ω-aroylalkanoic acids (see Table I, method B).

Oxidative rearrangement of 1,2-dibenzoylethane and 1,4-dibenzoylbutane with 2 equiv of TTN in MeOH/TMOF gave dimethyl α,α′-diphenylsuccinate (65%) (eq 3) and dimethyl α,α′-diphenyladipate (73%) (eq 4), respectively. Unsymmetrical α,α′-diarylsuccinates can also be prepared by this procedure; thus, 1-(*p*-bromobenzoyl)-2-benzoylethane undergoes a double rearrangement under the above conditions to give dimethyl α-(*p*-bromophenyl)-α′-phenylsuccinate (51%). Existing methods for the preparation of α,α′-diarylsuccinic acid derivatives usually involve coupling of arylacetic acids and can only produce symmetrical products.[15]





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(10) A few examples of this process for α-arylation of carboxylic acids were previously reported without experimental details: (a) McKillop, A.; Taylor, E. C. *Endeavour* **1976**, 88. (b) Reference 3.

(11) There is some methanol present as a result of the reaction: $Tl(ONO_2)_3{\cdot}3H_2O + 3HC(OMe)_3 \rightarrow Tl(ONO_2)_3 + 6MeOH + 3HCO_2Me$.

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(14) We have also examined the effectiveness of the TTN/K-10 supported reagent (ref 6) for this transformation. The brown suspension of the reagent in CCl_4 instantly turned white upon addition of the enol ether; results comparable to those reported in Table I were obtained. The TTN/K-10 supported reagent was not as effective, however, for oxidative rearrangement of the β-aroylpropionic acids; in these latter cases, the poor solubility of the substrates in CCl_4 greatly slows the rate of reaction.

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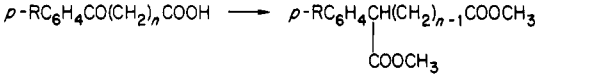
Table I. Oxidative Rearrangement of β-Aroylalkanoic Acids to Dimethyl α-Arylsuccinates, α-Arylglutarates, and α-Aryladipates



starting compound	R	n	method A[a] reactn time, h	method A[a] yield,[c] %	method B[b] reactn time, min	method B[b] yield,[c] %
1	H	2	2.5	82	15	77
2	CH_3	2	2	74	10	66
3	OCH_3	2	1	80	10	71
4	OC_6H_5	2	1	74	15	67
5	F	2	12	76	180	73
6	H	3	3	80	15	78
7	H	4	3	70		

[a] Direct oxidative rearrangement with TTN·$3H_2O$ in MeOH/TMOF (see Experimental Section). [b] Oxidative rearrangement of the in situ prepared methyl ester, enol ether (see Experimental Section). [c] Calculated on pure redistilled or recrystallized material. The conversions appear to be quantitative as judged by GLC.

Experimental Section

Conversion of α-Aroylalkanoic Acids to Dimethyl α-Arylsuccinates, α-Arylglutarates, and α-Aryladipates: General Procedures. Method A. A solution of 10 mmol of the ω-aroylalkanoic acid in 25 mL of a 1:1 mixture of methanol and trimethyl orthoformate was added to 4.44 g (10 mmol) of thallium trinitrate trihydrate, and the mixture was heated under reflux until precipitation of thallium(I) nitrate was complete (see Table I for individual reaction times). The mixture was concentrated and diluted with 25 mL of ether, and the thallium(I) nitrate was removed by filtration. The filtrate was washed successively with 2 × 50-mL portions of water, aqueous sodium bicarbonate, and water and was then dried over anhydrous $MgSO_4$. Concentration of the filtrate and distillation under reduced pressure (or recrystallization) of the crude product yielded the dimethyl α-arylsuccinate, α-arylglutarate, or α-aryladipate. Compounds prepared by this general procedure are listed in Table I. The double rearrangements leading to dimethyl α,α′-diphenylsuccinate, dimethyl α-phenyl-α′-(p-bromophenyl)succinate, and dimethyl α,α′-diphenyladipate were carried out by the same procedure but with 2 equiv of TTN·$3H_2O$.

Method B. The ω-aroylalkanoic acid was converted to its methyl ester by treatment with methanol/H_2SO_4, and the ester was then converted to the corresponding enol ether by treatment with refluxing trimethyl orthoformate and p-toluenesulfonic acid.[16] The crude enol ether was dissolved in a 1:1 mixture of methanol and trimethyl orthoformate and added to 1 equiv of TTN·$3H_2O$, and the mixture was allowed to stir at room temperature until precipitation of thallium(I) nitrate was complete (see Table I for individual reaction times). The reaction mixture was then worked up as described above under method A.

Dimethyl α-phenylsuccinate: obtained in 82% yield from β-benzoylpropionic acid (1) according to method A, and 77% by method B: mp 57.5–58.5 °C; NMR ($CDCl_3$) δ 7.28 (s, 5 H), 3.9–4.20 (m, 1 H), 3.65 (s, 6 H), 2.5–3.4 (m, 6 H), 2.5–3.4 (m, 2 H); IR ($CHCl_3$) 1738 cm^{-1}. Spectral data and mp were identical with those of authentic material.[17]

Dimethyl α-(p-methylphenyl)succinate: obtained in 74% yield from β-(p-methylbenzoyl)propionic acid (2)[18] according to method A, and 68% by method B: bp 119–121 °C (0.2 mm); NMR ($CDCl_3$) δ 7.11 (s, 4 H), 3.92 (m, 1 H), 3.60 (s, 6 H), 2.45–3.40 (m, 2 H), 2.28 (s, 3 H); IR ($CHCl_3$) 1736 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.62; H, 6.85.

Dimethyl α-(p-methoxyphenyl)succinate: obtained in 80% yield from β-(p-methoxybenzoyl)propionic acid (3)[19] according to method A, and 71% yield by method B: bp 135–140 °C (0.7 mm); NMR ($CDCl_3$) δ 7.19 (d, 2 H), 6.83 (d, 2 H), 3.90–4.10 (m, 1 H), 3.73 (s, 3 H), 3.62 (s, 3 H), 2.5–3.40 (m, 2 H); IR ($CHCl_3$) 1735 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found: C, 61.83; H, 6.36.

Dimethyl α-(p-phenoxyphenyl)succinate: obtained in 74% yield from β-(p-phenoxybenzoyl)propionic acid (4) according to method A, and 67% by method B: mp 70.5–71.5 °C; NMR ($CDCl_3$) δ 6.86–7.43 (m, 9 H), 3.95–4.20 (m, 1 H), 3.68 (s, 6 H), 2.5–3.40 (m, 2 H); IR (KBr) 1738 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.89; H, 5.79.

Dimethyl α-(p-fluorophenyl)succinate: obtained in 76% yield from β-(p-fluorobenzoyl)propionic acid (5)[17] according to method A, and 73% by method B: bp 94–96 °C (0.01 mm) [lit.[20] bp 146–147 °C (8 mm)]; NMR ($CDCl_3$) δ 6.9–7.60 (m, 4 H), 4.02–4.28 (m, 1 H), 3.69 (s, 3 H), 2.52–3.38 (m, 2 H); IR ($CHCl_3$) 1735 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}FO_4$: C, 60.00; H, 5.54; F, 5.64. Found: C, 59.85; H, 5.64; F, 7.68.

Dimethyl α-phenylglutarate: obtained in 80% yield from γ-benzoylbutyric acid (6) according to method A, and 78% by method B: bp 173–175 °C (6.5 mm); NMR ($CDCl_3$) δ 7.28 (s, 5 H), 3.62 (s, 6 H), 3.0–3.30 (m, 1 H), 2.05–2.38 (m, 4 H); IR ($CHCl_3$) 1737 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.85; H, 6.54.

Dimethyl α-phenyladipate: obtained in 70% yield from δ-benzoylvaleric acid (7) according to method A: bp 130–133 °C (0.5 mm); NMR ($CDCl_3$) δ 7.20 (s, 5 H), 3.7–4.40 (m, 1 H), 3.81 (s, 6 H), 1.5–2.55 (m, 6 H); IR ($CHCl_3$) 1736 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 66.92; H, 7.00.

Dimethyl α,α′-diphenylsuccinate: obtained in 65% yield from 1,2-dibenzoylethane according to method A (2 equiv of TTN): mp 173.5–175 °C [lit.[21] mp 177–178 °C]; NMR ($CDCl_3$) δ 7.08 (s, 10 H), 4.25 (s, 2 H), 3.68 (s, 6 H); IR (KBr) 1738 cm^{-1}.

Dimethyl α-phenyl-α′-(p-bromophenyl)succinate: obtained in 51% yield from 1-(p-bromobenzoyl)-2-benzoylethane[22] according to method A (2 equiv of TTN): mp 152–153.5 °C; NMR ($CDCl_3$) δ 6.85–7.95 (m, 9 H), 4.30 (s, 2 H), 3.68 (s, 6 H).

Anal. Calcd for $C_{18}H_{17}O_4Br$: C, 57.31; H, 4.54; Br, 21.18. Found: C, 57.51; H, 4.73; Br, 20.95.

Dimethyl α,α′-diphenyladipate: obtained in 73% yield from 1,4-dibenzoylbutane according to method A (2 equiv of TTN): mp 120–132 °C [lit.[23] mp 125–132 °C]; NMR ($CDCl_3$) δ 7.28 (s, 10 H), 3.58 (s, 8 H), 2.69–3.20 (m, 4 H); IR (KBr) 1736 cm^{-1}.

Registry No. 1, 2051-95-8; 1 methyl ester, 25333-24-8; 1 enol ether, 91266-20-5; 2, 4619-20-9; 2 methyl ester, 57498-54-1; 2 enol ether, 91266-21-6; 3, 3153-44-4; 3 methyl ester, 5447-74-5; 3 enol ether, 91266-22-7; 4, 36330-86-6; 4 methyl ester, 91266-23-8; 4 enol ether, 91266-24-9; 5, 366-77-8; 5 methyl ester, 39560-31-1; 5 enol ether, 91266-25-0; 6, 4144-62-1; 6 methyl ester, 67173-95-9; 6 enol ether, 91266-26-1; 7, 4144-62-1; dimethyl α-phenylsuccinate, 15463-92-0; dimethyl α-(p-methylphenyl)succinate, 36265-44-8; dimethyl α-(p-methoxyphenyl)succinate, 22248-26-6; dimethyl α-(p-phenoxyphenyl)succinate, 91266-19-2; dimethyl α-(p-fluorophenyl)succinate, 1496-23-7; dimethyl α-phenylglutarate, 10436-86-9; dimethyl α-phenyladipate, 81631-72-3; dimethyl α,α′-diphenylsuccinate, 19020-59-8; dimethyl α-phenyl-α′-(p-bromophenyl)succinate, 91280-66-9; dimethyl α,α′-diphenyladipate, 7300-04-1; 1,2-dibenzoylethane, 495-71-6; 1-(p-bromobenzoyl)-2-benzoylethane, 51908-41-9; 1,4-dibenzoylbutane, 3375-38-0; trimethyl orthoformate, 149-73-5; thallium trinitrate, 13746-98-0.

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