Studies on Keten and Its Derivatives. Part 89.[1] Ethyl 4-Substituted Acetoacetates: Synthesis and Reaction with Diketen

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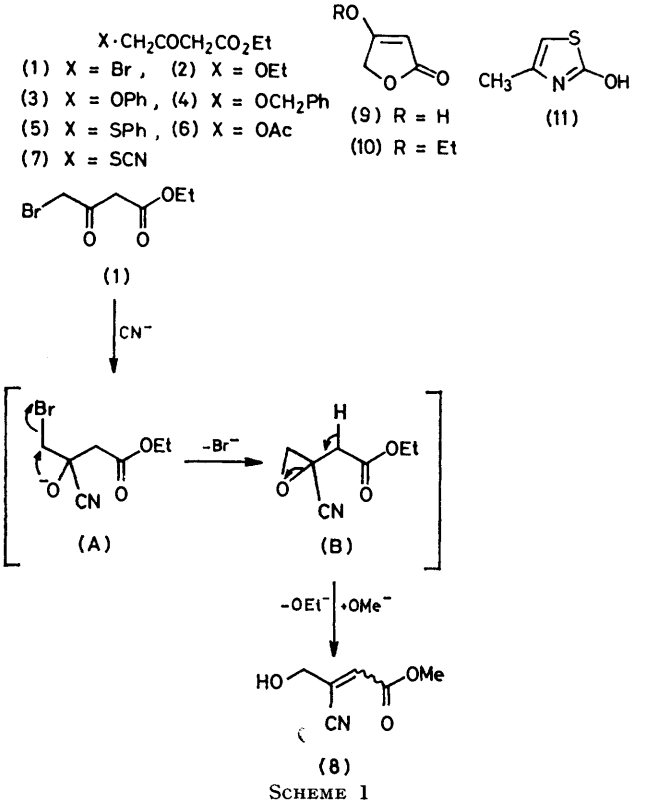
Ethyl 6-substituted 2,4-dihydroxybenzoates (13)—(18) were synthesized by reaction of diketen with 4-substituted acetoacetates (1)—(6). The keto esters (2)—(7) were prepared from ethyl 4-bromoacetoacetate (1).

As part of our investigation of the potential uses of ethyl 4-bromoacetoacetate (1),[2] our attention was focused on its reactivity with nucleophilic reagents.



Scheme 1

This paper reports a convenient method for the preparation of the title compounds (2)—(7), to which little attention has been paid, and the synthesis of 6-substituted 2,4-dihydroxybenzoic acid derivatives applying a method reported previously.[3]

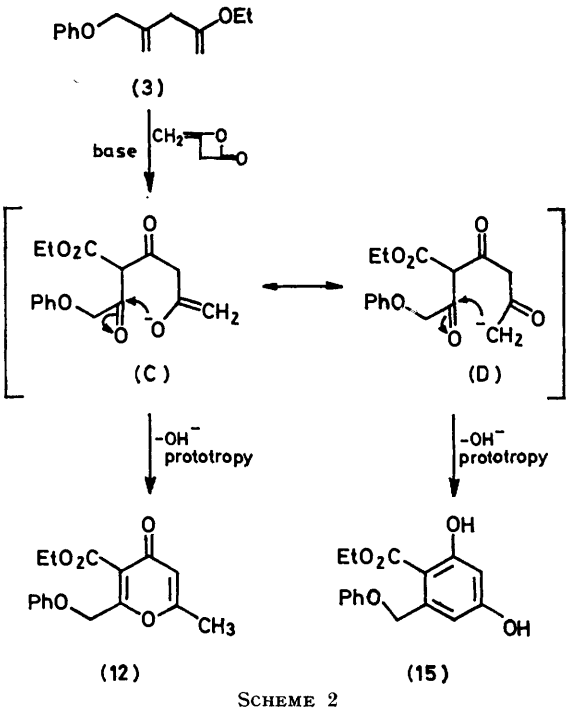
Upon refluxing a solution of ethyl 4-bromoacetoacetate (1) in absolute ethanol in the presence of sodium ethoxide ethyl 4-ethoxyacetoacetate (2) was formed. Similarly, reaction of compound (1) with sodium phenoxide, sodium benzyl oxide, sodium thiophenoxide, sodium acetate, and potassium thiocyanate gave products (3)—(7), respectively. Structural assignments were made on the basis of elemental analyses and the spectroscopic data detailed in the Experimental section.

A similar reaction of the bromo-ester (1) with potassium cyanide in methanol did not give the corresponding 4-substituted ester, ethyl 4-cyanoacetoacetate, but methyl 3-cyano-4-hydroxycrotonate (8). The formation of the crotonate (8) can be explained as follows; addition of cyanide to the carbonyl carbon of the bromo-ester (1) gives the cyanohydrin intermediate (A). Elimination of bromide from (A) produces the oxiran derivative (B), which, on ring-opening accompanied by ester exchange, is transformed into the crotonate (8).

Treatment of compound (6) with dilute hydrochloric acid gave rise to tetronic acid (9)[4] in 60% yield. Similar treatment with hydrogen chloride in absolute ethanol afforded ethyl tetronate (10)[5] in 77% yield. Since the synthetic methods previously reported for such tetronic acid derivatives are not always satisfactory, our method provides a more convenient route to compounds (9) and (10).

Reaction of compound (7) with dilute hydrochloric acid gave 2-hydroxy-4-methylthiazole (11).

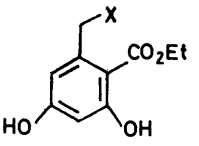
We next investigated the reaction of the 4-substituted esters (1)—(7) with diketen. Using a procedure reported previously,[3] compound (3) was allowed to react with



Scheme 2

diketen in tetrahydrofuran (THF) in the presence of sodium hydride to give ethyl 2,4-dihydroxy-6-phenoxymethylbenzoate (15) in 33% yield. When the reaction

was carried out in hexamethylphosphoramide (HMPA) instead of THF, 3-ethoxycarbonyl-6-methyl-2-phenoxymethyl-4-pyrone (12) was obtained in 28% yield. Formation of compounds (12) and (15) can be explained as shown in Scheme 2.



(13) X = Br
(14) X = OEt
(15) X = OPh
(16) X = OCH_2Ph
(17) X = SPh
(18) X = OAc

In order to obtain compounds (13)—(18), the reaction of the 4-substituted esters (1)—(6) with diketen in THF was carried out. Results are summarized in the Table.

Physical and spectroscopic properties of compounds (13)—(18)

Compound	Yield (%)	M.p. (°C)	Formula	Analysis Required (%) C	Required (%) H	Found (%) C	Found (%) H	δ(CDCl3) CH_2	δ(CDCl3) 3-H	δ(CDCl3) 5-H	$\nu_{max.}$(CHCl3)/cm^{-1} OH	$\nu_{max.}$(CHCl3)/cm^{-1} CO
(13)	8	130 (decomp.)	$C_{10}H_{11}BrO_4$	43.65	4.05	43.55	4.3	4.75	6.55 [a]		3 580, 3 280	1 655
(14)	19	88—89	$C_{12}H_{16}O_5$	60.0	6.7	59.75	6.6	4.80	6.38	6.80	3 620, 3 280	1 650
(15)	33	140—141	$C_{16}H_{16}O_5$	66.65	5.6	66.4	5.6	5.33	6.44	6.78	3 660, 3 300	1 665
(16)	16	108—109	$C_{17}H_{18}O_5$	67.55	6.0	67.7	6.0	4.84	6.39	6.85	3 600, 3 260	1 656
(17)	13	112—113	$C_{10}H_{16}O_4S$	63.15	5.3	63.25	5.4	4.35	6.16	6.38	3 640, 3 300	1 655
(18)	21	192—193	$C_{12}H_{14}O_6$	56.7	5.55	56.9	5.4	5.56	6.69	6.81 [b]	3 230, 1 700	1 643 [c]

[a] $CDCl_3$ + 5% CF_3CO_2H. [b] CF_3CO_2H. [c] KBr.

Reaction of compound (7) with diketen under the same conditions resulted in the formation of a resinous product.

EXPERIMENTAL

M.p.s and b.p.s are uncorrected. I.r. spectra were taken with a JASCO model IR-S spectrometer. N.m.r. spectra were taken on a Hitachi R-20 instrument with tetramethylsilane as internal standard.

Ethyl 4-Ethoxyacetoacetate (2).—To a solution of sodium ethoxide, prepared from sodium (2.5 g, 0.11 g atom) and absolute ethanol (100 ml), was added dropwise a solution of ethyl 4-bromoacetoacetate (1) (10.5 g, 0.05 mol) in absolute ethanol (20 ml) over 40 min, during which time the mixture was refluxed with stirring. After an additional 10 min, the mixture was cooled, neutralized with 10% hydrochloric acid, and evaporated *in vacuo* to give a residue to which water (50 ml) was added. The mixture was extracted with ether. The ether solution was condensed, and the oily residue was distilled to give *compound* (2) (4.3 g, 47%), b.p. 105—110 °C at 17 mmHg (Found: C, 54.7; H, 8.3. $C_8H_{14}O_4$ requires C, 55.15; H, 8.1%), $\nu_{max.}$(CHCl3) 1 738 and 1 720 cm^{-1}, δ($CDCl_3$) 1.22 (3 H, t, *J* 7 Hz, CH_3CH_2O), 1.28 (3 H, t, *J* 7 Hz, CH_3CH_2O), 3.50 (2 H, s, $COCH_2CO$), 3.55 (2 H, q, *J* 7 Hz, CH_3CH_2O), 4.09 (2 H, s, OCH_2), and 4.17 (2 H, q, *J* 7 Hz, CH_3CH_2O).

Ethyl 4-Phenoxyacetoacetate (3).—To a suspension of sodium hydride (50%, 4.8 g, 0.1 mol) in THF (100 ml) was added phenol (9.4 g, 0.1 mol) with continuous stirring. The mixture was heated at 50—60 °C. A solution of compound (1) (10.5 g, 0.05 mol) in THF (10 ml) was added dropwise over 25 min. After an additional 10 min, the mixture was neutralized with 10% hydrochloric acid and evaporated *in vacuo* to give a residue, to which water (50 ml) was added. The mixture was extracted with ether. The ether solution was evaporated, and the oily residue was distilled under reduced pressure to give *product* (3) (6.45 g, 58%), b.p. 105—110 °C at 0.1 mmHg (Found: C, 64.55; H, 6.45. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%), $\nu_{max.}$(CHCl3) 1 740, 1 722, and 1 600 cm^{-1}, δ(CCl_4) 1.23 (3 H, t, *J* 7 Hz, CH_3CH_2O), 3.52 (2 H, s, $COCH_2CO$), 4.12 (2 H, q, *J* 7 Hz, CH_3CH_2O), 4.51 (2 H, s, OCH_2), and 6.68—7.40 (5 H, m, ArH).

Ethyl 4-Benzyloxyacetoacetate (4).—To a suspension of sodium hydride (50%, 2.9 g, 0.06 mol) in THF (40 ml) was added benzyl alcohol (6.5 g, 0.06 mol) with continuous stirring at room temperature. To this mixture was added dropwise a solution of compound (1) (6.3 g, 0.03 mol) in THF (20 ml) over 1 h. After an additional 1 h, the mixture was neutralized with 10% hydrochloric acid. The solution was condensed *in vacuo* to give a residue, to which water (30 ml) was added. The mixture was extracted with ether. The ether solution was condensed, and the oily residue was distilled giving *product* (4) (4.3 g, 61%), b.p. 113—115 °C at 0.05 mmHg (Found: C, 66.5; H, 6.65. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%), $\nu_{max.}$(CHCl3) 1 740 and 1 723 cm^{-1}, δ(CCl_4) 1.21 (3 H, t, *J* 7 Hz, CH_3CH_2O), 3.40 (2 H, s, $COCH_2CO$), 3.98 (2 H, s, OCH_2), 4.07 (2 H, q, *J* 7 Hz, CH_3CH_2O), 4.49 (2 H, s, OCH_2), and 7.25 (5 H, s, ArH).

Ethyl 4-Thiophenoxyacetoacetate (5).—To a suspension of sodium hydride (50%, 0.96 g, 0.02 mol) in THF (50 ml) was added thiophenol (2.2 g, 0.02 mol) under nitrogen with stirring at room temperature. The mixture was warmed at 40 °C on a water-bath, and a solution of compound (1) (4.2 g, 0.02 mol) in THF (10 ml) was added dropwise over 10 min. After 2 h, the mixture was neutralized with 10% hydrochloric acid, and condensed. To the resulting residue was added water (20 ml). The mixture was extracted with ether. The ether solution was evaporated, and the oily product was distilled *in vacuo* to give compound (5) as an oil (3.32 g, 70%), b.p. 114—116 °C at 0.005 mmHg (Found: C, 60.95; H, 5.85. $C_{12}H_{14}O_3S$ requires C, 60.5; H, 5.9%), $\nu_{max.}$(CHCl3) 1 720 and 1 710 cm^{-1}, δ($CDCl_3$) 1.23 (3 H, t, *J* 7 Hz, CH_3CH_2O), 3.59 (2 H, s, $COCH_2CO$), 3.77 (2 H, s, SCH_2), 4.14 (2 H, q, *J* 7 Hz, CH_3CH_2O), and 7.26 (5 H, m, Ar-H).

Ethyl 4-Acetoxyacetoacetate (6).—To a solution of sodium acetate (5 g, 0.06 mol) in 95% ethanol (100 ml) was added dropwise a solution of compound (1) (10.5 g, 0.05 mol) in

95% ethanol (20 ml) over 30 min, during which time the solution was refluxed with stirring. After addition was complete, the mixture was refluxed for an additional 10 min and then neutralized with 10% hydrochloric acid. The solution was evaporated to give a residue, to which water (50 ml) was added. The mixture was extracted with ether. The ether solution was condensed and the crystals which precipitated were collected by suction. Recrystallization from benzene gave pale yellow prisms (0.4 g, 6%), m.p. 126—127 °C, undepressed on admixture with an authentic sample of 1,4-bisethoxycarbonylcyclohexane-2,5-dione prepared from compound (1).[6] The filtrate was condensed and the oily residue was distilled under reduced pressure to give compound (6) (4.1 g, 44%), b.p. 88—90 °C at 2 mmHg (lit.,[7] 70 °C at 0.1 mmHg), $\nu_{max.}$($CHCl_3$) 1 738 cm^{-1}, δ(CCl_4) 1.28 (3 H, t, *J* 7 Hz, CH_3CH_2O), 2.09 (3 H, s, CH_3CO), 3.36 (2 H, s, $COCH_2CO$), 4.13 (2 H, q, *J* 7 Hz, CH_3CH_2O), and 4.61 (2 H, s, OCH_2).

Ethyl 4-Thiocyanoacetoacetate (7).—To a solution of potassium thiocyanate (5.8 g, 0.06 mol) in methanol (100 ml), was added dropwise a solution of compound (1) (6.3 g, 0.03 mol) in methanol (10 ml) over 10 min at room temperature. After 1 h, the mixture was filtered and the filtrate was condensed to dryness. The residue was extracted with ether. The ether solution was condensed and subjected to silica gel column chromatography. Elution with chloroform gave *compound* (7) as a pale yellow oil (4.2 g, 75%). Purification by vacuum distillation was unsuccessful (Found: C, 44.95; H, 4.8; N, 7.4. $C_7H_9NO_3S$ requires C, 44.9; H, 4.85; N, 7.5%), $\nu_{max.}$($CHCl_3$) 2 170, 1 740sh, and 1 720 cm^{-1}, δ($CDCl_3$) 1.29 (3 H, t, *J* 7 Hz, CH_3CH_2O), 3.61 (2 H, s, $COCH_2$), 4.17 (2 H, s, SCH_2), and 4.20 (2 H, q, *J* 7 Hz, CH_3CH_2O).

Methyl 3-Cyano-4-hydroxycrotonate (8).—To a solution of potassium cyanide (2.6 g, 0.04 mol) in methanol (80 ml) was added dropwise a solution of compound (1) (4.2 g, 0.02 mol) in methanol (10 ml) with stirring over 10 min, during which time the mixture was warmed at 40—45 °C. After 1 h, the mixture was evaporated *in vacuo*. The residue was diluted with water (20 ml) and the solution was extracted with ether. The ether solution was evaporated and the residue was submitted to silica gel column chromatography using chloroform and ether as eluants. Ether elution gave an oily product, which was solidified by scrubbing with a glass rod. Recrystallization from benzene–cyclohexane gave *compound* (8) as prisms (0.35 g, 12%), m.p. 48—49 °C (Found: C, 50.75; H, 5.15; N, 9.95. $C_6H_7NO_3$ requires C, 51.05; H, 5.0; N, 9.95%), $\nu_{max.}$($CHCl_3$) 3 660, 3 500, 2 240, 1 730, and 1 645 cm^{-1}, δ($CDCl_3$) 2.55br (1 H, OH), 3.82 (3 H, s, CH_3O), 4.38 (2 H, d, *J* 2 Hz, CH_2O), and 6.67 (1 H, t, *J* 2 Hz, CH=).

Tetronic Acid (9).—A solution of the ester (6) (0.19 g) in 5% hydrochloric acid (10 ml) was stirred at room temperature for 18 h. The reaction mixture was condensed *in vacuo*, and the crystalline residue was recrystallized from ethyl acetate to give tetronic acid as prisms (60 mg, 60%), m.p. 139—140 °C (lit.,[4] 141 °C).

Ethyl Tetronate (10).—Compound (6) (1 g) was dissolved in a saturated solution of hydrogen chloride in absolute ethanol (30 ml). The mixture was stirred at room temperature for 20 h, and condensed. The residue was distilled to give ethyl tetronate (10) as an oil (0.52 g, 77%), b.p. 120—125 °C at 11 mmHg (lit.,[5] 65—66 °C at 0.008 mmHg).

2-Hydroxy-4-methylthiazole (11).—A solution of the ester (7) (1.87 g) in 5% hydrochloric acid (40 ml) was heated at 85—90 °C on a water-bath for 1 h. After cooling, the solution was saturated with salt and extracted with ether. The ether solution was condensed and the residue was recrystallized from cyclohexane to give compound (11) as needles (0.32 g, 28%), m.p. 98—99 °C (lit.,[8] 102 °C).

6-Substituted Ethyl 2,4-Dihydroxybenzoate (13)—(17).—To a solution of a β-keto ester (1)—(5) (0.01 mol) in THF (40 ml) was added sodium hydride (50%, 0.48 g, 0.01 mol) with continuous stirring and cooling. To the mixture was added dropwise a solution of diketen (0.84 g, 0.01 mol) in THF (10 ml) while the temperature was kept below −10 °C. The mixture was stirred for 30 min at the same temperature, and stirring was continued for an additional 3 h at room temperature. After being neutralized with 10% hydrochloric acid, the mixture was evaporated *in vacuo*. The residue was extracted with ether, and the ether solution was condensed. The residue was subjected to silica gel column chromatography using benzene and benzene–ethyl acetate (4 : 1) as eluant. Elution with benzene–ethyl acetate gave a crystalline substance, which was recrystallized from cyclohexane to give an ester (13)—(17). The Table summarizes yields, m.p., elemental analyses, and spectroscopic data for these products.

Ethyl 6-Acetoxymethyl-2,4-dihydroxybenzoate (18).—Employing the procedure described above, compound (6) (1.9 g, 0.01 mol) was allowed to react with diketen (0.84 g, 0.01 mol). After being neutralized with 10% hydrochloric acid, the mixture was condensed *in vacuo* and the residue was dissolved in water (50 ml) and washed with ether (20 ml). The aqueous solution was condensed to 10 ml, and the crystals which precipitated were collected by suction. Recrystallization from ethyl acetate gave compound (18) (Table).

3-Ethoxycarbonyl-6-methyl-2-phenoxymethyl-4-pyrone (12).—To a solution of compound (3) (0.67 g, 3 mmol) in HMPA (40 ml) was added sodium hydride (50%, 0.15 g, 3 mmol) with continuous stirring. A solution of diketen (0.26 g, 3 mmol) in HMPA (5 ml) was then added to the mixture. After stirring for 1 h, the mixture was poured into water (100 ml). The solution was neutralized with 10% hydrochloric acid. The mixture was extracted with benzene. The benzene solution was condensed and the residue was purified by silica gel column chromatography. Elution with chloroform gave the *pyrone* (12) (0.24 g, 28%), m.p. 67—68 °C (from cyclohexane) (Found: C, 66.9; H, 5.45. $C_{16}H_{16}O_5$ requires C, 66.65; H, 5.6%), $\nu_{max.}$($CHCl_3$) 1 740, 1 670, and 1 630 cm^{-1}, δ($CDCl_3$) 1.27 (3 H, t, *J* 7 Hz, CH_3CH_2O), 2.21 (3 H, s, CH_3), 4.24 (2 H, q, *J* 7 Hz, CH_3CH_2O), 6.01 (1 H, s, CH=), and 6.73—7.40 (5 H, m, Ar-H).

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