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### IMPROVED SYNTHESIS OF ALKYL DIACETYLACETATES

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## OPPI BRIEFS

## IMPROVED SYNTHESIS OF ALKYL DIACETYLACETATES

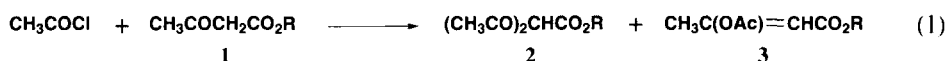
Submitted by S. J. Bingham and J. H. P. Tyman\*<sup>†</sup>  
(11/20/00)

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Alkyl diacetylacetates (**2**) are significant starting materials for the synthesis of a number of natural products, notably kermesic<sup>1,2</sup> and carminic acids,<sup>3</sup> for the preparation of pyridazines,<sup>4,5</sup> for anodic dehydrodimerisations,<sup>6</sup> in cycloaddition reactions of halogenated quinones,<sup>7</sup> for functionalised ketenimines,<sup>8</sup> in an asymmetric hydrogenation procedure,<sup>9</sup> for amidinopyrazole derivatives<sup>10</sup> and the preparation of other heterocycles.<sup>11,12</sup> The ethyl member (**2b**, R = Et) prepared first by Claisen<sup>13</sup> and by James<sup>14</sup> from sodioacetylacetone and ethyl chloroformate, by Elion<sup>15</sup> and by Michael<sup>16</sup> from acetyl chloride and ethyl sodioacetoacetate was accompanied in all cases by the O-acetyl derivative (**3**) as shown in *Eq 1*.

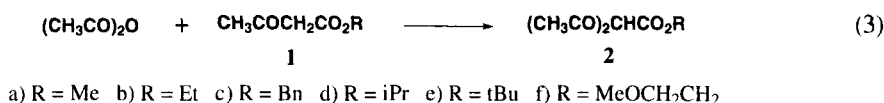


The formation of the O-acetyl compound (**3**) could be suppressed by the use of magnesium (1.0 m) instead of sodium with acetyl chloride (1.5 m) and ethyl acetoacetate (1.0 m),<sup>17,18</sup> in 50-60% (Spassow<sup>17</sup>) and 75% yields (Ogata<sup>18</sup>) respectively. Compound **2b** has also been obtained as a by-product of the decarboxylation of 3-ethoxycarbonyl-2,4-dioxopentane-1,3-dicarboxylic acid.<sup>19</sup> In a general synthesis of  $\beta$ -keto esters described by Viscontini and Merckling<sup>20</sup> ethyl diacetylacetate (*Eq. 2*; R = Me) was one of a number of ethyl C-acylacetates which were first prepared and then hydrolyzed to the final  $\beta$ -keto product. The first step was performed in diethyl ether containing Mg and the final step in ethanolic  $\text{NH}_3$ . However, the 73% yield of **2b** in this case constitutes only a marginal improvement on the procedure of Spassow.



In our initial experiments following the descriptions by Spassow and of Viscontini, we found that methyl and ethyl diacetylacetate were barely obtainable in 50-60% and 70% yields respectively. However in further development work larger quantities were required and we sought a substantially improved procedure for the starting materials in our synthetic program as well as potentially for a number of other related structures.

We now report that yields from 90-97% of alkyl diacetylacetates (**2**) can be obtained by reacting the appropriate alkyl acetoacetate (**1**) (1.0 mol) in dichloromethane containing anhydrous magnesium chloride (1.0 mol) followed by the addition of pyridine (2.0 mol) at 0° and finally of acetic anhydride (1.1 mol) as shown in *Eq. 3*. Their spectroscopic properties indicate that all the final products exist as the (100 %) hydrogen-bonded enolic structures in solution



### EXPERIMENTAL SECTION

Routine <sup>1</sup>H NMR spectra were recorded on Varian T60, CFT-20 and Jeol FX 200 instruments at 60, 80 and 200 MHz respectively in deuterated solvents with Me<sub>4</sub>Si as internal standard. When necessary, <sup>13</sup>C and high resolution <sup>1</sup>H NMR spectra were obtained at 400 MHz on a Bruker 400 WM. Mass spectra were recorded on a modified AEI MS 902 at 70eV. Infrared spectra in the range 600-4000 cm<sup>-1</sup> were obtained on a Perkin-Elmer 1420 instrument. Routine TLC was performed on Camlab silica gel plates with fluorescent indicator (UV<sub>254</sub>). GLC analyses were obtained with a Hewlett-Packard 402 instrument with FID on glass columns 25 mm id by 152 cm length packed with celite 100-120 and 5% OV17 as stationary phase under nitrogen (30 mL/min.) and an oven temperature of 150°.

Elemental analyses were performed by Butterworth Laboratories, Teddington, Middlesex, and by Medac Ltd., Brunel.

**General Method for the Preparation of Alkyl Diacetylacetates.**- With continuous magnetic stirring the respective alkyl acetoacetate (1.0 mol) was added to a suspension of anhydrous magnesium chloride (95.2 g, 1.0 mol) in dry dichloromethane (800 mL) under nitrogen. After 15 min., the mixture was cooled to 0° and dry pyridine (162 mL, 2 mol) slowly added over 5-10 min. After a further 30 min. at 0°, acetic anhydride (104 mL, 1.10 mol) was added over 5-10 min. and the reaction temperature allowed to rise to ambient. After 16 h, the suspension was cooled once more to 0° and the mixture quenched with cold 3.0 M hydrochloric acid (1000 mL) at 0° whereby solids present gradually dissolved and two layers formed. After a further hour, the liquid phases still at 0° were separated and the lower organic solvent layer dried (anhydrous sodium sulfate), filtered, the solvent removed *in vacuo* and the resultant oil distilled under reduced pressure.

**Methyl Diacetylacetate (2a).**- Methyl acetoacetate (116.12 g, 1.0 mol), treated as above afforded methyl diacetylacetate (150.2 g, 95% yield) as a clear, colorless oil, bp 63-65°/0.3 mm. Hg, *lit.*,<sup>13</sup> 101-102°/20 mm. Hg, which solidified at 4°. IR (film): 3000 (C-H, adj. to CO), 2960 (C-H), 1715 (α,β-

unsat. ester), 1560 br (C=C, conj.), 1405 br (O-H), 1215 and 1170  $\text{cm}^{-1}$  (C-O, ester);  $^1\text{H NMR}$  (80 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.34 (6H, s, 2Me), 3.77 (3H, s,  $\text{MeO}_2\text{C}$ ), 17.8 (1H, s, HO,  $\text{D}_2\text{O}$  exch.);  $m/z$ : 158 ( $\text{M}^+$ , 28%), 143 (25), 85 (19), 43 (100).

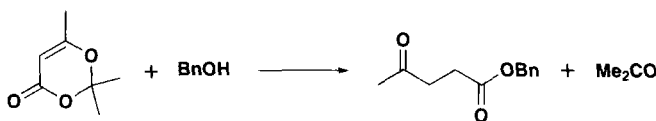
*Anal.* Calcd for  $\text{C}_7\text{H}_{10}\text{O}_4$ : C, 53.2; H, 6.4. Found: C, 53.1; H, 6.4

**Ethyl Diacetylacetate (2b).**- Ethyl acetoacetate (130.1 g, 1.0 mol), treated by the general method gave the product (180.6 g, 90%) as a clear, colorless oil, bp. 56-60°/0.6 mm. Hg, *lit.*<sup>17</sup> 95-97°/12 mm. IR (film): 2950 (C-H), 1690 (C=O), 1549 (C=C, conj. with ester), 1405br. (O-H), 1215, 1170  $\text{cm}^{-1}$  (C-O, ester);  $^1\text{H NMR}$  (80 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.30 (3H, t,  $J$  9 Hz, Me, ester) 2.30 (6H, s, 2Me), 4.23 (2H, q,  $J$  9 Hz,  $\text{OCH}_2$ , ester) 17.7 (1H, s, OH,  $\text{D}_2\text{O}$  exch.);  $m/z$ : 172 ( $\text{M}^+$ , 25%), 157 (20), 127 (24), 98 (23), 85 (25) 43 (100).

*Anal.* Calcd for  $\text{C}_8\text{H}_{12}\text{O}_4$ : C, 55.8; H, 7.0. Found: C, 55.8; H, 7.1

**Benzyl Diacetylacetate (2c) By Transesterification.**- A solution of benzyl alcohol (100 mL, 104.5 g, 0.97 mol) and methyl acetoacetate (100 mL, 107.6 g, 0.93 mol) was heated and stirred at 140° for 16 h and methanol collected. The mixture was then distilled to give benzyl acetoacetate, bp 110-112°/0.6 mm/Hg, *lit.*<sup>21</sup> bp 156-159°/10 mm/Hg, as a clear, colorless oil, (75.3 g, 49%).

*From Diketene Acetone Adduct (2,2,6-trimethyl-1,3-dioxene-4-one).*- A solution of benzyl alcohol (15.5 mL, 16.20 g, 0.15 mol) and diketene acetone adduct (20 mL, ca. 85% pure material) was heated for 2 h at 140° and the acetone liberated collected in a cold trap. The mixture was then distilled to give the product, bp 110-112°/0.6 mm Hg, as a clear, colorless oil, (17.2 g, 69%).



Benzyl diacetylacetate was prepared from benzyl acetoacetate by the general method in 96% yield as a clear, colorless oil, bp 100-110°/0.7 mm. Hg; IR (film): 3050 (C-H, arom), 2950 (C-H, aliph.), 1700 (C=O, ester), 1550 (C=C, conj.) 1420 br. (O-H), 1260, 1060 (C-O, ester), 750  $\text{cm}^{-1}$  (C-H, arom.);  $^1\text{H NMR}$  (80 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.33 (6H, s, 2Me), 5.22 (2H, s,  $\text{OCH}_2\text{Ph}$ ), 7.33 (5H, s, Ph), 17.8 (1H, s, OH,  $\text{D}_2\text{O}$  exch.);  $m/z$ : 234 ( $\text{M}^+$ , 7%): 127 (24), 100 (11), 91 (100) 85 (8), 43 (15).

*Anal.* Calcd for  $\text{C}_{13}\text{H}_{14}\text{O}_4$ : C, 66.7; H, 6.0. Found: C, 66.6; H, 6.1

The following three compounds were characterized spectroscopically and also by elemental analyses although the latter data are unfortunately no longer available.

**isoPropyl Diacetylacetate (2d):** isoPropyl acetoacetate (144.1 g, 1.0 mol) by the general method afforded the product (180.6 g, 97%) as a clear, colorless oil, bp 56-60°/0.6 mm. Hg;  $^1\text{H NMR}$  (80 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.30 (6H, d,  $J$  7.5 Hz,  $\text{Me}_2\text{CHO}_2\text{C}$ ), 2.30 (6H, s, 2MeCO), 5.10 (1H, sept.  $J$  7.5 Hz,  $\text{OCHMe}_2$ ) 17.65 (1H, s, OH,  $\text{D}_2\text{O}$  exch.).

**t-Butyl Diacetylacetate (2e):** t-Butyl acetoacetate (158.2 g, 1.0 mol), treated by the general method gave the product (192.1 g, 96%) as a clear, colorless oil, bp 60-64°/0.6 mm. Hg;  $^1\text{H NMR}$  (80 MHz,

CDCl<sub>3</sub>): δ 1.52 (9H, s, Me<sub>3</sub>CO<sub>2</sub>C), 2.30 (6H, s, 2MeCO), 17.44 (1H, s, OH, D<sub>2</sub>O, exch.).

**2-Methoxyethyl Diacetylacetate (2f):** 2-Methoxyethyl acetoacetate (160.2 g, 1.0 mol), by the general method afforded the title compound (188.0 g, 93%) bp 50-54°/0.6 mm Hg, as a clear, colorless oil; <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>): δ 2.35 (6H, s, 2MeCO), 3.34 (3H, s, CH<sub>3</sub>OCH<sub>2</sub>CH<sub>2</sub>O<sub>2</sub>C), 3.61 (2H t, J 7.5 Hz, CH<sub>2</sub>OMe), 4.31 (2H, t, J 7.5 Hz, CH<sub>2</sub>OCO), 17.79 (1H, s, OH, D<sub>2</sub>O, exch.).

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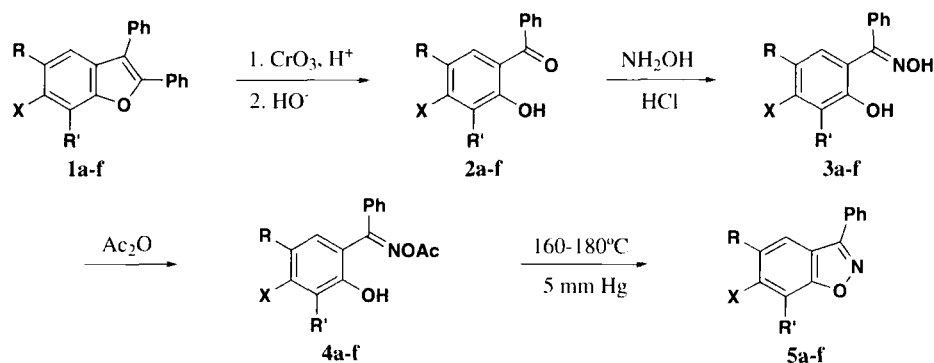
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**SYNTHESIS OF 6-HALO-1,2-BENZISOXAZOLES,  
 CHROMENO-6,7-ISOXAZOLES AND CHROMENO-6,7-OXAZOLES**

Submitted by Lenuta Cires\*, Harry Ofenberg and Cotinica Craita  
 (04/18/00)

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6-Substituted benzisoxazoles have been developed as potent and selective inhibitors of the enzyme acetylcholinesterase.<sup>1</sup> In addition, some of these 1,2-benzisoxazoles are biologically active displaying antitubercular and antifungal activity.<sup>2</sup> Consequently, the development of synthetic methods for the elaboration of suitably substituted 1,2-benzisoxazole derivatives constitutes an area of current interest. Moreover, 6-substituted-1,2-benzisoxazoles can be only obtained by cyclization, since electrophilic substitution of 1,2-benzisoxazoles affords 5- or 7-substituted derivatives.<sup>3,4</sup> The presence of a halogen at position 6 of 3-phenyl-1,2-benzisoxazole would allow access to models displaying an array of promising chemical and physical properties. We now report the preparation of 6-halo-3-phenyl-1,2-benzisoxazoles **5a-f** (Scheme 1) as well as the conversion of furocoumarin **7** to



- a) R, R' = H, X = Br; b) R = CH<sub>3</sub>, R' = H, X = Br; c) R = H, R' = CH<sub>3</sub>, X = Br;  
 d) R = H, R' = H, X = I; e) R = CH<sub>3</sub>, R' = H, X = I; f) R = H, R' = CH<sub>3</sub>, X = I.

**Scheme 1**