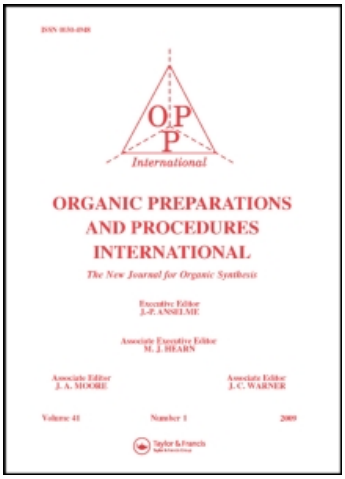

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IMPROVED SYNTHESIS OF ALKYL DIACETYLACETATES

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OPPI BRIEFS

IMPROVED SYNTHESIS OF ALKYL DIACETYLACETATES

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(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[1,2] and carminic acids,[3] for the preparation of pyridazines,[4,5] for anodic dehydrodimerisations,[6] in cycloaddition reactions of halogenated quinones,[7] for functionalised ketenimines,[8] in an asymmetric hydrogenation procedure,[9] for amindinopyrazole derivatives[10] and the preparation of other heterocycles.[11,12] The ethyl member (**2b**, R = Et) prepared first by Claisen[13] and by James[14] from sodioacetylacetone and ethyl chloroformate, by Elion[15] and by Michael[16] from acetyl chloride and ethyl sodioacetoacetate was accompanied in all cases by the O-acetyl derivative (**3**) as shown in *Eq 1*.

$$\underset{}{CH_3COCl} + \underset{\mathbf{1}}{CH_3COCH_2CO_2R} \longrightarrow \underset{\mathbf{2}}{(CH_3CO)_2CHCO_2R} + \underset{\mathbf{3}}{CH_3C(OAc)=CHCO_2R} \qquad (1)$$

The formation of the O-acetyl compound (**3**) could be supressed by the use of magnesium (1.0 m) instead of sodium with acetyl chloride (1.5 m) and ethyl acetoacetate (1.0 m),[17,18] in 50-60% (Spassow[17]) and 75% yields (Ogata[18]) respectively. Compound **2b** has also been obtained as a by-product of the decarboxylation of 3-ethoxycarbonyl-2,4-dioxopentane-1,3-dicarboxylic acid. [19] In a general synthesis of β-keto esters described by Viscontini and Merckling[20] ethyl diacetylacetate (*Eq. 2*; R = Me) was one of a number of ethyl C-acylacetoacetates which were first prepared and then hydrolyzed to the final β-keto product. The first step was performed in diethyl ether containing Mg and the final step in ethanolic NH_3. However, the 73% yield of **2b** in this case constitutes only a marginal improvement on the procedure of Spassow.

$$RCOCl + CH_3COCH_2CO_2Et \longrightarrow RCO(COCH_3)CH_2CO_2Et \longrightarrow RCOCH_2CO_2Et \qquad (2)$$

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 dichoromethane 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

$$(CH_3CO)_2O + \underset{\mathbf{1}}{CH_3COCH_2CO_2R} \longrightarrow \underset{\mathbf{2}}{(CH_3CO)_2CHCO_2R} \qquad (3)$$

a) R = Me b) R = Et c) R = Bn d) R = iPr e) R = tBu f) R = $MeOCH_2CH_2$

EXPERIMENTAL SECTION

Routine ^1H 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_4Si as internal standard. When necessary, ^{13}C and high resolution ^1H 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^{-1} were obtained on a Perkin-Elmer 1420 instrument. Routine TLC was performed on Camlab silica gel plates with fluorescent indicator (UV_{254}). 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 hydrochoric 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.*,[13] 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 cm^{-1} (C-O, ester); ^1H NMR (80 MHz, $CDCl_3$): δ 2.34 (6H, s, 2Me), 3.77 (3H, s, MeO_2C), 17.8 (1H, s, HO, D_2O exch.); m/z: 158 (M^+, 28%), 143 (25), 85 (19),43 (100).

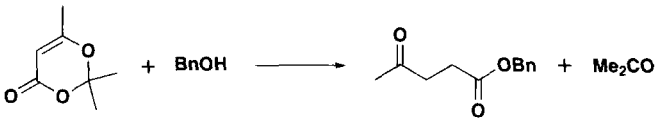
Anal. Calcd for $C_7H_{10}O_4$: C, 53.2; H, 6.4. Found: C, 53.1; H, 6.4

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.*[17] 95-97°/12 mm. IR (film): 2950 (C-H), 1690 (C=O), 1549 (C=C, conj. with ester), 1405br. (O-H), 1215, 1170 cm^{-1} (C-O, ester); ^1H NMR (80 MHz, $CDCl_3$): δ 1.30 (3H, t, *J* 9 Hz, Me, ester) 2.30 (6H, s, 2Me), 4.23 (2H, q, *J* 9 Hz, OCH_2 , ester) 17.7 (1H, s, OH, D_2O exch.); m/z: 172 (M^+, 25%), 157 (20), 127 (24), 98 (23), 85 (25) 43 (100).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.8; H, 7.0. Found: C, 55.8 ; H, 7.1

Benzyl Diacetylacetate (2c) *By Transesterification.*- A solution of benzyl alohol (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.*[21] 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 cm^{-1} (C-H, arom.); ^1H NMR (80 MHz, $CDCl_3$): δ 2.33 (6H, s, 2Me), 5.22 (2H, s, OCH_2Ph), 7.33 (5H, s, Ph), 17.8 (1H, s, OH, D_2O exch.); m/z: 234 (M^+, 7%): 127 (24), 100 (11), 91 (100) 85 (8), 43 (15).

Anal. Calcd for $C_{13}H_{14}O_4$: 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; ^1H NMR (80 MHz, $CDCl_3$): δ 1.30 (6H, d, *J* 7.5 Hz, Me_2CHO_2C), 2.30 (6H, s, 2MeCO), 5.10 (1H, sept. *J* 7.5 Hz, $OCHMe_2$) 17.65 (1H, s, OH, D_2O 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; ^1H NMR (80 MHz,

$CDCl_3$): δ 1.52 (9H, s, Me_3CO_2C), 2.30 (6H, s, 2MeCO), 17.44 (1H,s, OH, D_2O, 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; ^1H NMR (80 MHz, $CDCl_3$): δ 2.35 (6H, s, 2MeCO), 3.34 (3H, s, $CH_3OCH_2CH_2O_2C$), 3.61 (2H t, *J* 7.5 Hz, CH_2OMe), 4.31 (2H, t, *J* 7.5 Hz ,CH_2OCO), 17.79 (1H, s, OH, D_2O, exch.).

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

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

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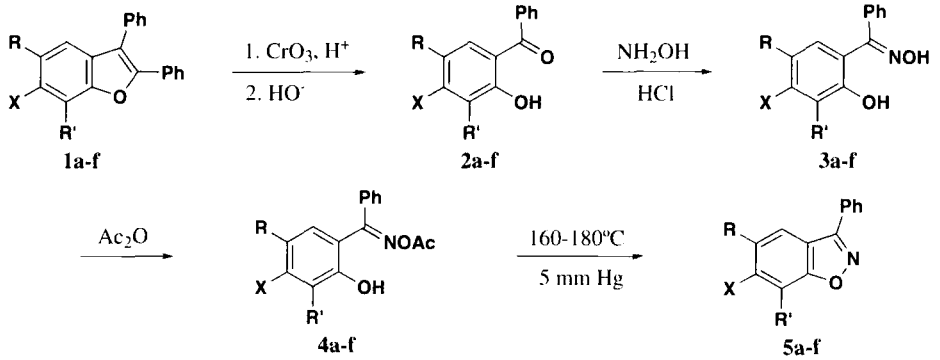
6-Substituted benzisoxazoles have been developed as potent and selective inhibitors of the enzyme acetylcholinesterase.[1] In addition, some of these 1,2-benzisoxazoles are biologically active displaying antitubercular and antifungal activity.[2] Consequently, the development of synthetic methods for 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.[3,4] 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_3, R' = H, X = Br; c) R = H, R' = CH_3, X = Br;
d) R = H, R' = H, X = I; e) R = CH_3, R' = H, X = I; f) R = H, R' = CH_3, X = I.

Scheme 1