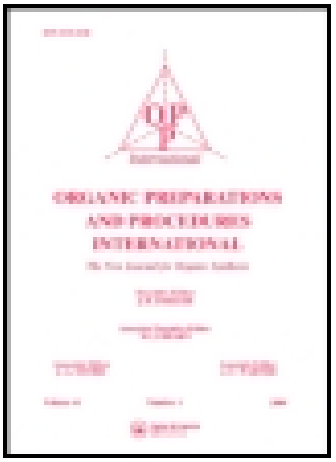

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# AN ALTERNATIVE SYNTHESIS OF ETHYL 3-(2-CHLORO-4,5-DIFLUOROPHENYL)-3-OXOPROPIONATE AND ETHYL 3-(2,6-DICHLORO-5-FLUOROPYRIDIN-3-YL)-3-OXOPROPIONATE

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# AN ALTERNATIVE SYNTHESIS OF ETHYL 3-(2-CHLORO-4,5-DIFLUOROPHENYL)-3-OXOPROPIONATE AND ETHYL 3-(2,6-DICHLORO-5-FLUOROPYRIDIN-3-YL)-3-OXOPROPIONATE

*Submitted by* (02/26/96)

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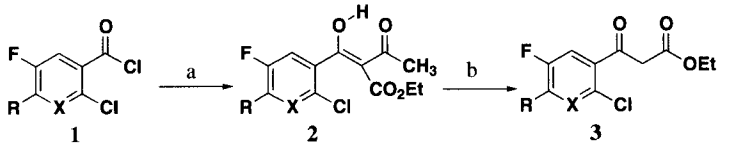
β-(Haloaryl)-β-oxopropionates are key intermediates for the preparation of quinolinone antibacterial agents.[1] There have been numerous examples of the synthesis of β-ketoesters,[2] many of which proceed *via* the acylation of various malonate derivatives.[3] For example, the synthesis of ethyl 3-(2,6-dichloro-5-fluoro-pyridin-3-yl)-3-oxopropionate (**3b**) has been described from diethyl malonate with magnesium ethoxide[4] and from ethyl malonic acid with n-butyllithium.[5] The conversion of acyl diethyl malonates to β-ketoesters is often attended by problems with the selective hydrolysis and decarboxylation of one ester group. The use of a malonate half-ester avoided this problem, but originally only pyrophoric bases such as n-butyllithium or methylmagnesium bromide were utilized for the deprotonation. After Rathke described the mild acylation of diethyl malonate with triethylamine and an acid chloride in the presence of magnesium chloride,[6] Wemple applied these conditions to potassium ethyl malonate in acetonitrile or ethyl acetate.[7] This paper describes a further advancement based on Rathke's work which uses ethyl acetoacetate instead of potassium ethyl malonate which has the advantage of the use of an inexpensive and non-hygroscopic starting material (ethyl acetoacetate). A less used route to ethyl benzoylacetate is acylation of ethyl acetoacetate followed by deacetylation.[8] Although the acylation of ethyl acetoacetate with benzoyl chloride in the presence of magnesium chloride and pyridine in methylene chloride was described, the deacetylation step was not.[6]




1 2 3

a) $CH_3COCH_2CO_2Et$, 2-methylimidazole, $MgCl_2$, tetrahydrofuran a) X = CH; R = F
b) pyridinium tosylate, ethanol b) X = N; R = Cl

For the acylation step with our desired acid chlorides, a variety of bases and solvents were screened with a view of finding a more environmentally acceptable combination. Rathke had reported that only weak bases such as pyridine gave the desired C-acylation while triethylamine lead to O-acylation. We found that 2-methylimidazole in tetrahydrofuran was preferred for both lab and large scale work. This was due both to the low level of side products generated with this combination as

well as the advantage of using a base which was a crystalline solid with little odor compared with pyridine which reduced worker exposure and the use of a non-halogenated solvent. Although the use of acylimidazoles in these acylations is well precedented,[9] an imidazole has not been used for the dual function of base and acyl transfer agent. The reactions were performed at or below room temperature and the intermediate diketoester **2a** was isolated in near quantitative yield as a low melting solid. Both the NMR spectrum of **2a** in $CDCl_3$ as well as a single crystal X-ray structure determination showed it to exist in the enol form.[10] The pyridyl diester **2b** was isolated as an oil. NMR in $CDCl_3$ indicated that two distinct enol forms of **2b** were present in a 3:1 ratio. The enol form of the acetyl group is presumably the minor form.

The deacetylation of **2a** and **2b** was attempted first under conditions described in the literature.[8] The desired deacetylation was accompanied by small amounts of decarboxylation to the methyl ketone with acetic acid/water, toluenesulfonic acid/ethanol or sodium acetate/ethanol. The use of pyridinium toluenesulfonate as a catalyst in refluxing ethanol led to a clean deacetylation with no overreaction. Both β-ketoesters **3a** and **3b** were isolated as low melting crystalline solids directly from the reaction mixture by cooling and addition of hexanes. Both the benzoyl **3a** and the pyridyl **3b** exhibited only traces of the keto form (NMR in $CDCl_3$). This procedure has been used at lab scale for both **3a** and **3b** and at multikilogram scale for **3b**.

## EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained on a Brucker WM 300 (300 MHz) spectrometer in deuteriochloroform. 2-Chloro-4,5-difluorobenzoic acid was available from Aldrich Chemical Company. Anhydrous tetrahydrofuran from Aldrich Chemical Company was used as is from Sure/Seal™ bottles. 2-Chloro-4,5-difluorobenzoylchloride (**1a**) and 2,6-dichloro-5-fluoro-3-pyridinecarbonyl chloride (**1b**) were prepared from the carboxylic acid with thionyl chloride in toluene. A procedure for the pyridyl derivative (**1b**) is given below.

**2,6-Dichloro-5-fluoro-3-pyridinecarbonyl Chloride (1b).**- A slurry of 2,6-dichloro-5-fluoro-3-pyridinecarboxylic acid (20g, 0.095 mole)[4] in toluene (100 mL) with a few drops of dimethylformamide was stirred at 24° as thionyl chloride (10 mL, 16.3g, 0.137 mole) was added over a 2 minute period. The reaction was heated slowly to reflux over 45 min. during which time a solution resulted. The reaction was held at reflux for 3 hrs, cooled to 40° and concentrated at reduced pressure. The resulting oil was diluted twice with 50 mL toluene and reconcentrated. The acid chloride was an oil containing residual toluene and was suitable for use in the next step. $^1H$ NMR ($CDCl_3$): δ 8.22 (d,1), 2.33 (s, toluene, 10%).

**Ethyl 2-(2,6-Dichloro-5-fluoropyridine-3-carbonyl)-3-oxobutyrate (2b).**- A slurry of magnesium chloride (7.98g, 0.084 mole, Aldrich anhydrous) in dry tetrahydrofuran (90 mL) was stirred at 22° as ethyl acetoacetate (10.92g, 0.084 mole) was added over a 1 min. period. After the slurry was stirred for 20 min., it was cooled to 5° in an ice water bath and 2-methylimidazole (13.77g, 0.168 mole) was added in portions over 3 min.. The reaction slurry was stirred at 10° for 20 min. followed by the drop-

wise addition of the acid chloride (21.42g, 0.084 mole, 10% toluene) in dry tetrahydrofuran (35 mL) over 15 min., while the internal temperature was kept < 15°. Then, the reaction was allowed to warm to room temperature and stirred for 18 hrs.

The reaction was cooled to 10° and 4N HCl (90 mL) was added in one portion. This was stirred for 5 min. and toluene (135 mL) was added and stirred for 15 min.. The organic phase was separated and washed with 4N HCl (90 mL) and water (90 mL). Water was added and the two phase system was adjusted with saturated sodium bicarbonate to pH 6.8.[11] The organic phase was dried over magnesium sulfate and evaporated to afford 26.58g, (99%) of an oil. IR (neat): 1717, 1648, 1591, 15657, 1477 $cm^{-1}$. $^1H$ NMR ($CDCl_3$) [major form (75%)]: δ 14.58 (s, 1), 7.49 (d, 1), 4.05 (q, 2), 2.58 (s, 3), 1.00 (t, 3), and [minor form (25%)]: δ 14.55 (s,1), 7.60 (d, 1), 4.09 (q, 2), 2.42 (s, 3), 0.91 (t, 3). Mass spectrum: *m/z* 322/324 (M), 276/278 (M – EtOH).

*Anal.* Calcd. for $C_{12}H_{10}Cl_2FNO_4$: C, 44.75; H, 3.13; N, 4.35. Found: C, 44.61; H, 3.06; N, 4.10

**2-(2-Chloro-4,5-difluorobenzoyl)-3-oxobutyric Acid Ethyl Ester (2a)**.- 2-(2-Chloro-4,5-difluorobenzoyl)-3-oxobutyric acid ethyl ester (**2a**), mp. 43-46°, was prepared in 98% yield in a similar manner. IR (KBr): 1714, 1673, 1599, 1563, 1499 $cm^{-1}$. $^1H$ NMR ($CDCl_3$ ): δ 14.57 (s, 1), 7.27 (dd, 1), 7.20 (dd, 1), 4.00 (q, 2), 2.54 (s, 3), 0.98 (t, 3). Mass spectrum: *m/z* 305/307 (M), 259/261 (M – EtOH).

*Anal.* Calcd. for $C_{13}H_{11}ClF_2O_4$: C, 51.25; H, 3.64. Found: C, 51.12; H, 3.62

**Ethyl 3-(2,6-Dichloro-5-fluoropyridin-3-yl)-3-oxopropionate (3b)**.- Diketoester **2b** from above was dissolved in anhydrous ethanol (46 g, 1 mole) with pyridinium tosylate (0.552g, 2.2 mmoles) and gently refluxed for 18 hrs. Upon cooling to 35°, the product began to crystallize. Hexanes (50 mL) were added and the slurry stirred at -10° for 30 min. The product was collected and washed with hexanes to give 13.25g, 57% of colorless solid, mp. 76-79°. The filtrate was evaporated, slurried with cold hexanes and a second crop of β-ketoester was isolated (3.26g, 14%), mp. 69-74°. The total yield was 16.5g (70%). IR (KBr): 1711, 1647, 1627, 1592, 1553 $cm^{-1}$. $^1H$ NMR ($CDCl_3$ ): δ 12.58 (s, 1), 7.83 (d, 1), 5.84 (s, 1), 4.20 (q, 2), 1.35 (t, 3).

*Anal.* Calcd. for $C_{10}H_8Cl_2FNO_3$: C, 42.88; H, 2.88; N, 5.00. Found: C, 42.99; H, 2.73; N, 5.19

**3-(2-Chloro-4,5-difluorophenyl)-3-oxopropionic Acid Ethyl Ester (3a)**.– 3-(2-Chloro-4,5-difluorophenyl)-3-oxopropionic acid ethyl ester (**3a**), mp. 60–63° was prepared in 76% yield according to the same procedure. IR (KBr): 1776 1716, 1658, 1612, 1594, 1506 $cm^{-1}$. $^1H$ NMR: δ 12.52 (s, 1), 7.50 (dd, 1), 7.29 (dd, 1), 5.60 (s, 1), 4.28 (q, 2), 1.35 (t, 3). Mass spectrum: *m/z* 263/265 (M).

*Anal.* Calcd. for $C_{11}H_9ClF_2O_3$: C, 50.31; H, 3.45. Found: C, 50.30; H, 3.33

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10. The X-ray data for **2a** have been submitted to the Cambridge Crystallographic Centre. We thank Dr. Jon Bordner, Pfizer Central Research, Groton, CT for the single crystal X-ray analysis of **2a**.

11. The pH adjustment from 3 to 6.8-7 removed residual acid from the reaction. At higher pH's, the sodium salt of the β-ketoester can be extracted into water.



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## AN IMPROVED SYNTHESIS OF *bis*(*p*-PHENYLENE)-32-CROWN-4

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*bis*(*p*-Phenylene)-32-crown-4 (**6**), a hydrophobic macrocycle containing two decamethylene spacers, is a potentially important cyclic component of polyrotaxanes.[1-3] Herein we report an improved, four-step synthesis of **6**, relative to the previous one-step method[4] (5 to 7% yield).

1,10-*bis*(*p*-Formylphenoxy)decane (**3**) was prepared in 94% yield by alkylation of *p*-hydroxybenzaldehyde (**1**) with 1,10-dibromodecane (**2**).[5] Baeyer-Villiger oxidation[6] of **3** with *m*-chloroperbenzoic acid gave a 97% yield of 1,10-*bis*(*p*-formyloxyphenoxy)decane (**4**). Hydrolysis of **4** with aqueous NaOH in EtOH gave (88%) 1,10-*bis*(*p*-hydroxyphenoxy)decane (**5**). (**5** can also be obtained directly from hydroquinone and **2**.[7,8]) Cyclization of *bis*phenol **5** with **2** was carried out in the