Notes

New Synthesis of 5,7-Dihydroxy-4-methylphthalide, a Key Intermediate in the Synthesis of Mycophenolic Acid

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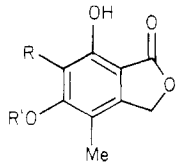
Mycophenolic acid (**1a**), isolated from *Penicillium brevi-compactum*,[1] has been the object of synthetic and biosynthetic studies by several groups of workers. The interest in the compound derives from its antibiotic and antiviral activities and the complexity of its biosynthetic scheme.[2]



1a, R = $H_2CCH{=}C(CH_3)CH_2CH_2C(O)OH$; R' = Me
b, R = H; R' = Me
c, R = R' = H

The first synthesis of the phthalidic skeleton was realized by Logan and Newbold,[3] who used orsellinic acid as starting material. Subsequently Birch[4] and Canonica[5] published total syntheses of mycophenolic acid; both groups used as synthetic intermediates hydroxyphthalide derivatives, compounds **1b** and **1c** respectively, obtained by synthetic routes. Compound **1c** is a natural product isolated from *Aspergillus flavus*.[6]

We have recently reported the synthesis of some isoxazole esters, their hydrogenation to β-enamino keto esters, and their cyclization, in acidic media, to hydroxyphthalide derivatives.[7] In this work we report a synthesis of 5,7-dihydroxy-4-methylphthalide (**1c**), obtained by cyclization of a linear chain generated from isoxazole compounds. (5-Ethoxy-4-methyl-3-isoxazolyl)methyl acetoacetate (**9**) was hydrogenated and transformed into 3-(ethoxycarbonyl)-2-oxobutyl acetoacetate (**11**); the reaction of this last product with bases (sodium ethylate followed by butyllithium) gave compound **1c**. In comparison to the known synthetic pathways[4,5] the advantages of our method are a fewer number of synthetic steps and higher total yield.

Results and Discussion

The synthesis of isoxazolic ester **9** can be effected through different pathways: following Scheme I, path A, diethyl 2-methyl-3-oxosuccinate (**2**) treated with hydroxylamine gave the isoxazol-5-one[8] **3**, which, with diazomethane, yielded two methyl derivatives, **7a** and **4**, in the ratio 1:1. Following Scheme I, path B, the chloroxime **5**, readily obtained from glycine ester[9] reacted with methylketene diethyl acetal[10] (**6**) to give, after treatment with dilute aqueous acid, the ester **7b** in 70% yield. Scheme I, path B, was more convenient for our purposes.

Alcohol **8** was readily produced by Capal-70[11] reduction of the corresponding ester **7b**, in quantitative yield at room temperature. The same reduction carried out with lithium aluminum hydride at −30 °C gave compound **8** in 80% yield; under more vigorous reactions, i.e., at room temperature, ring reduction was also obtained. 3-(Hydroxymethyl)-5-ethoxy-4-methylisoxazole (**8**) reacted with diketene at room temperature in the presence of a catalytic amount of sodium acetate to give an 81% yield of isoxazole **9**. Hydrogenation of compound **9** with 10% Pd/C in dioxane at room temperature, followed by acid treatment, gave ethyl 2-methylacetoacetate (**10**); with Raney Nickel isoxazolic alcohol **8** was obtained. When the hydrogenation was carried out in dioxane at 50 °C with hydrogen at 30 atm in the presence of palladium–Lindlar catalyst, a 95% yield of 3-(carboxyethyl)-2-oxobutyl acetoacetate (**11**) was obtained after treatment with acid.

Treatment of compound **11** with sodium ethylate at low temperature gave only 3-acetyl-4-(1-(ethoxycarbonyl)-ethyl]-2,5-dihydrofuran-2-one (**12b**) in 92% yield. Further treatment of **12b** with butyllithium at −70 °C gave 5,7-dihydroxymethylphthalide (**1c**) in 25% yield.

Experimental Section

IR spectra were recorded on a Perkin-Elmer 177 spectrophotometer. NMR spectra were registered on Varian A90 and XL100 instruments with Me_4Si as an internal standard. Mass spectra were registered on a Hitachi Perkin-Elmer RMU6D instrument. Melting points are uncorrected.

3-(Ethoxycarbonyl)-5-alkoxy-4-methylisoxazoles (7a,b). (A) Diethyl 2-methyl-3-oxosuccinate with hydroxylamine by the usual method[8] gave 3-(ethoxycarbonyl)-4-methylisoxazol-5-one (**3**). This compound with diazomethane in diethyl etther gave N- and O-methylated compounds **4** and **7a** in the ratio 1:1. The mixture was chromatographed over silica gel (70:30 hexane–Et_2O), and the products were separated to give 3-(ethoxycarbonyl)-5-methoxy-4-methylisoxazole (**7a**: mp 8 °C, 33% yield; IR (Nujol) ν_{max} 1735, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.42 (q, 2 H), 4.20 (s, 3 H), 1.93 (s, 3 H), 1.41 (t, 3 H)) and 3-(ethoxycarbonyl)-2,4-dimethylisoxazol-5-one (**4**: mp 32 °C; 35% yield; IR ν_{max} 1760, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.44 (q, 2 H), 3.42 (s, 3 H), 1.99 (s, 3 H), 1.42 (t, 3 H)).

(B) Ethyl chloro(hydroxyimino)acetate (**5**, 30.3 g, 0.2 mol) dissolved in ethyl ether (60 cm^3) was slowly added under stirring to methylketene diethyl acetal (26 g, 0.2 mol) dissolved in 50 cm^3 of triethylamine, dropwise at room temperature. After the mixture was shaken with dilute hydrochloric acid and extracted with diethyl ether, the organic layer was dried and filtered, and the solvent was removed. Distillation gave 3-(ethoxycarbonyl)-5-ethoxy-4-methylisoxazole (**7b**, 28 g, 70.3% yield): bp 103–108 °C (0.5 mmHg); mp 35 °C; IR (Nujol) ν_{max} 1735, 1640 cm^{-1}; NMR

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(11) Capal-70 (ANIC): $Ca(AlH_2(O\text{-}i\text{-}Pr)_2]_2 \cdot THF$, 70% solution in toluene.

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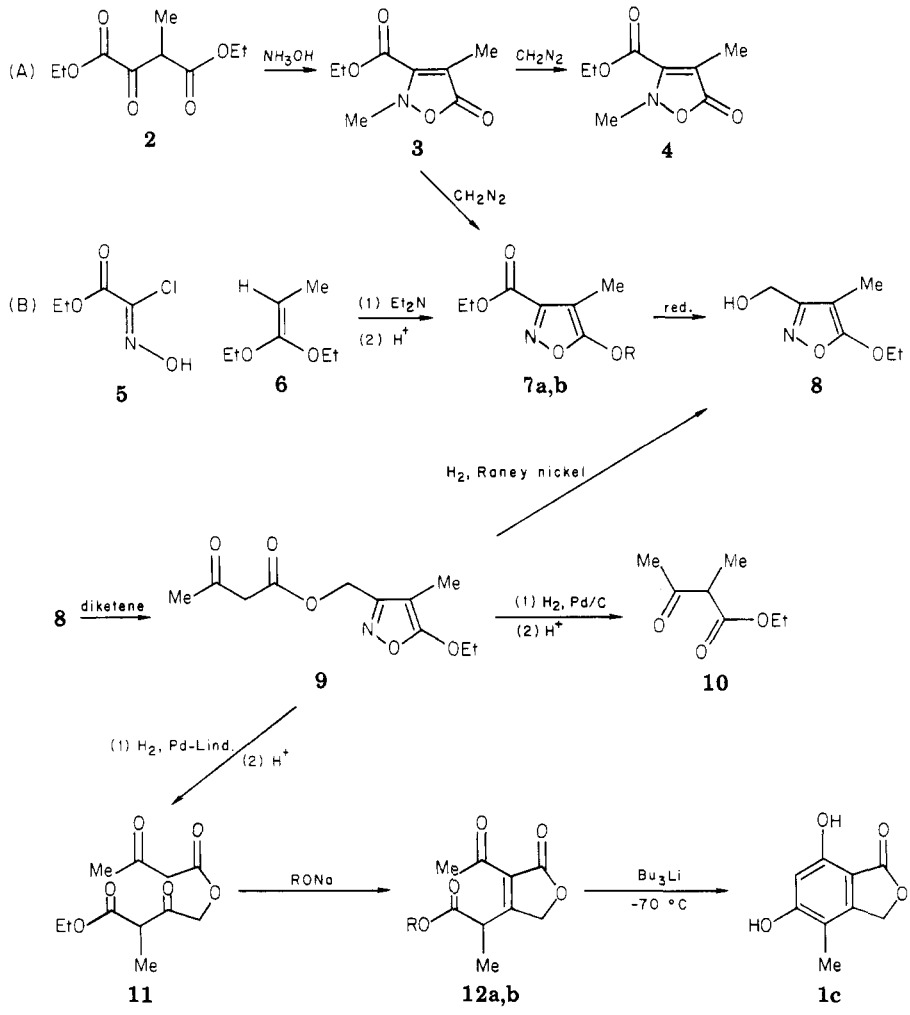
Scheme I[a]



[a] Key: a, R = Me; b, R = Et.

($CDCl_3$) δ 4.46 (q, 2 H), 4.42 (q, 2 H), 1.95 (s, 3 H), 1.43 (t, 3 H), 1.41 (t, 3 H).

Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.60; H, 6.53; N, 7.01.

3-(Hydroxymethyl)-5-ethoxy-4-methylisoxazole (8). Capal-70[1] (50 cm^3) was added with stirring at room temperature to 25 g of 3-(ethoxycarbonyl)-5-ethoxy-4-methylisoxazole (**7b**) dissolved in toluene (25 cm^3). After 4 h the mixture was shaken with dilute hydrochloric acid and extracted with diethyl ether. The organic layer was dried and filtered, and the solvent was removed. Alcohol **8**, oil, was the only product present as shown by GC analysis and the mass spectrum (19.5 g, 99% yield); the boiling point was not determined (decomposed); IR ν_{max} 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.56 (s, 2 H), 4.37 (q, 2 H), 1.82 (s, 3 H), 1.40 (t, 3 H).

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.61; H, 6.98; N, 8.89.

(5-Ethoxy-4-methyl-3-isoxazolyl)methyl Acetoacetate (9). Diketene (8.4 g, 0.1 mol) was added dropwise to a mixture of 3-(hydroxymethyl)-5-ethoxy-4-methylisoxazole (15.7 g, 0.1 mol) and sodium acetate (catalytic amount) with stirring at 20–30 °C. The mixture was directly chromatographed over silica gel, eluting with 7:3 hexane–diethyl ether. The major product was **9** (19.5 g; 81% yield) which was isolated as a viscous oil (decomposed when heating): IR ν_{max} 1750, 1720, 1650 cm^{-1}; ^1H NMR δ 5.08 (s, 2 H), 4.40 (q, 2 H), 3.52 (s, 2 H), 2.24 (s, 3 H), 1.82 (s, 3 H), 1.41 (t, 3 H); MS, *m/e* 241 (M^+, 11), 168 (76), 153 (40), 129 (52), 101 (100), 84 (88).

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.76; H, 6.27; N, 5.81. Found: C, 54.88; H, 6.21; N, 5.79.

3-(Ethoxycarbonyl)-2-oxobutyl Acetoacetate (11). A catalytic amount of Lindlar palladium (0.2 g) was added to a solution of (5-ethoxy-4-methyl-3-isoxazolyl)methyl acetoacetate (**9**, 6 g dissolved in 300 cm^3 of dioxane) and was stirred under hydrogen (30 atm) for 72 h at 50 °C. The solution was filtered, ether was added, and the mixture was shaken with dilute hydrochloric acid. The organic layer was washed with water, dried, and filtered, and the solvent was removed. The crude oil was purified by chromatography (silica gel, 70:30 hexane–Et_2O); compound **11** was the major product present (93% yield): IR ν_{max} 1770, 1740, 1720, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.88 (s, 2 H), 4.20 (q, 2 H), 3.68 (q, 1 H), 3.58 (s, 2 H), 2.30 (s, 3 H), 1.38 (d, 3 H), 1.24 (t, 3 H).

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.29; H, 6.54.

3-Acetyl-4-(1-(alkoxycarbonyl)ethyl)-2,5-dihydrofuran-2-one (12a,b). A solution of sodium ethylate (0.025 mol) in ethanol (20 cm^3) was added to an ice-cooled solution of 3-(ethoxycarbonyl)-2-oxobutyl acetoacetate (**11**, 4.9 g, 0.02 mol) in ethanol (50 cm^3). After 48 h at room temperature the mixture was neutralized with dilute hydrochloric acid and extracted with diethyl ether. The organic layer was dried and filtered, and the solvent was removed. 3-Acetyl-4-(1-(ethoxycarbonyl)ethyl)-2,5-dihydrofuran-2-one (**12b**) was isolated as an oil and was purified by chromatography (silica gel, 70:30 hexane–Et_2O; 4.2 g, 92% yield); IR ν_{max} 1760, 1730, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.00 (s, 2 H), 4.60 (q, 1 H), 4.22 (q, 2 H), 2.56 (s, 3 H), 1.50 (d, 3 H), 1.22 (t, 3 H).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.22; H, 6.09.

When the same reaction was carried out with sodium methylate in methanol, the product obtained was 3-acetyl-4-(1-(methoxycarbonyl)ethyl)-2,5-dihydrofuran-2-one (**12a**): oil; IR ν_{max} 1760, 1730, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.01 (s, 2 H), 4.58 (q, 1 H), 3.70 (s, 3 H), 2.50 (s, 3 H), 1.48 (d, 3 H; MS, *m/e* 212 (M^+, 1.3),

194 (12), 180 (58.5), 165 (22.1), 152 (29.8), 43 (100).

5,7-Dihydroxy-4-methylphthalide (1c). A solution of butyllithium (20 cm^3, 1.5 M in hexane) was added under stirring to a solution of 3-acetyl-4-(1-(methoxyccarbonyl)ethyl]-2,5-dihydrofuran-2-one (2.1 g, 0.01 mol) in 50 cm^3 of dry THF at −70 °C. The mixture was left to stand at this temperature for 3 h and then was allowed to reach ambient temperature. The mixture was shaken with dilute hydrochloric acid and extracted with diethyl ether. The organic extract was evaporated to dryness. The residue was chromatographed over silica gel (70:30 hexane–Et_2O) to give 0.45 g of 5,7-dihydroxy-4-methylphthalide (**1c**, 25% yield). Compound **1c** was identical with an authentic sample of 5,7-dihydroxy-4-methylphthalide:[12] mp 240 °C; IR (Njuol) ν_{max} 3420, 3340, 1720, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.4 (s, 1 H), 5.2 (s, 2 H), 2.05 (s, 3 H); MS, *m/e* 180 (49), 151 (100), 122 (33).

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Registry No. **1a**, 24280-93-1; **1c**, 27979-57-3; **3**, 84280-59-1; **4**, 63285-91-6; **5**, 14337-43-0; **7a**, 84280-60-4; **7b**, 84280-61-5; **8**, 84280-62-6; **9**, 84280-63-7; **11**, 84280-64-8; **12a**, 84280-65-9; **12b**, 84280-66-0; methylketene diethyl acetal, 21504-43-8; diketene, 674-82-8.

(12) We thank Prof. C. Scolastico for a sample of 5,7-dihydroxy-4-methylphthalide.

Nucleophilic Aromatic Substitution Reactions under Phase-Transfer Conditions. Synthesis of Alkyl Aryl Sulfides from Isomeric Dichlorobenzenes and Thiolates

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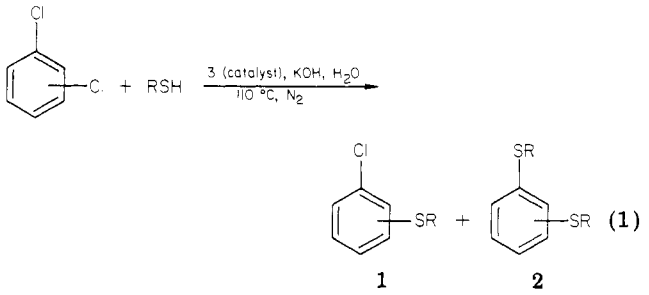
Nucleophilic aromatic substitutions (S_NAr) of slightly activated aryl halides promoted by anions require drastic conditions,[1] even with dipolar aprotic solvents.[2] It is well-known that the conditions of phase-transfer catalysis (PTC) strongly accelerate anionic substitution reactions.[3] However, most of the reported examples deal with aliphatic displacements,[3] while only a few cases are described of S_NAr reactions on activated substrates.[3c,4,5] The synthesis of 2- and 3-chlorophenyl methyl ethers from slightly activated 1,2- and 1,3-dichlorobenzene in the presence of 18-crown-6 in a PTC solid–liquid system has been also reported.[6]

We have found that S_NAr reactions of dichlorobenzenes with powerful nucleophiles such as thiolates can be much more easily performed under the conditions of liquid–liquid PTC. Reactions were carried out, according to eq 1, by stirring at 110 °C under nitrogen a heterogeneous



mixture of the substrate, dicyclohexano-18-crown-6 (**3**) as a catalyst, and the solution of the thiol in aqueous concentrated KOH. The reaction rate increases with the increase of the amount of KOH in the aqueous phase (Table I). This is likely related to the fact that, in the presence of highly concentrated alkaline solutions (60% KOH or 50% NaOH, w/w), anionic nucleophiles are transferred as nonhydrated species from the aqueous to the organic phase.[7]

The reactivity of the first chlorine atom follows the order 1,2- > 1,3- > 1,4-dichlorobenzene in agreement with the prevalent influence of the −I activating effect of chlorine atoms. As expected, thiolates react according to the order primary alkyl > secondary alkyl > tertiary alkyl ≫ aryl. No cine-substitution product was observed, neither by NMR nor by GC analyses. As shown in Table I, the product distribution depends on the nature of both substrates and thiols. In particular, with secondary and tertiary thiolates, 1,2-dichlorobenzene gives only monosubstitution derivatives **1**, while with primary thiolates, **1** together with minor amounts of the disubstituted **2** are formed. Similar **1** to **2** ratios are obtained from 1,3-dichlorobenzene, independent of the thiolate.

In the case of 1,4-dichlorobenzene the selectivity of the reaction is noticeably reduced compared to that of the isomeric dichlorobenzenes. Moreover, the selectivity decreases in passing from primary to tertiary thiolates (Table I). Thiophenol is much less reactive than alkyl mercaptans, only a 21% conversion being reached after 75 h (Table I).

Experimental Section

General Methods. NMR spectra were recorded on a Varian EM-390 90-MHz spectrometer in $CDCl_3$ solutions with Me_4Si as an internal standard; IR spectra were measured as films or Nujol mulls on a Perkin-Elmer 377 grating spectrophotometer by using NaCl cells; GC data were obtained on a Varian 3700 gas chromatograph equipped with a 3% Carbowax 20M on Chromosorb W column and were evaluated with a Varian Model 401 data system by the internal standard method. Boiling points are uncorrected.

Materials. Thiols, dichlorobenzenes, **3**, and KOH were commercially available reagent grade products. The aqueous KOH–

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