DIARYL-α-HETEROARYLMALONATES FROM CERIUM(IV)-PROMOTED REACTIONS OF DIALKYL MALONATES WITH HETEROCYCLIC COMPOUNDS

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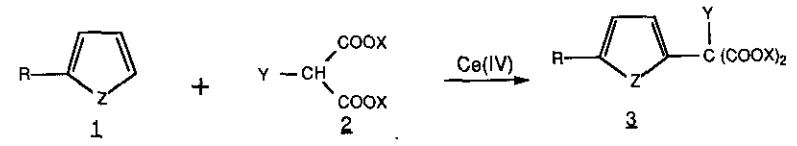
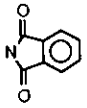
Abstract - Thiophenes, furans and their benzo analogs undergo facile malonylation in the 2-position on reaction with dialkyl malonate radicals generated with cerium(IV) reagent.

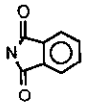
Arylmalonic acid esters are key intermediates in the synthesis of important medicinal agents such as nonsteroidal anti-inflammatory agents, barbituates and β-lactam antibiotics[1]. In response to the very limited utility of the syntheses using malonate carbanions and aromatic electrophiles some workers recently have designed syntheses which exploit the wide availability of aromatic nucleophiles. For example, the condensation of arenes or aryl anions with diethyl oxomalonate produces α-hydroxy esters which are acetylated and reduced with lithium in liquid ammonia to arylmalonate anions[2]. A more direct approach has been reported[3] which employs the reaction of a benzene derivative with the malonyl radical, $\cdot CH(COOMe)_2$. We now report the direct regiospecific malonylation of some electron rich heterocyclic systems by reaction with oxidatively - generated electrophilic malonyl radicals. The reaction is another example of the "umpolung" of the malonate anion reactivity.[4]

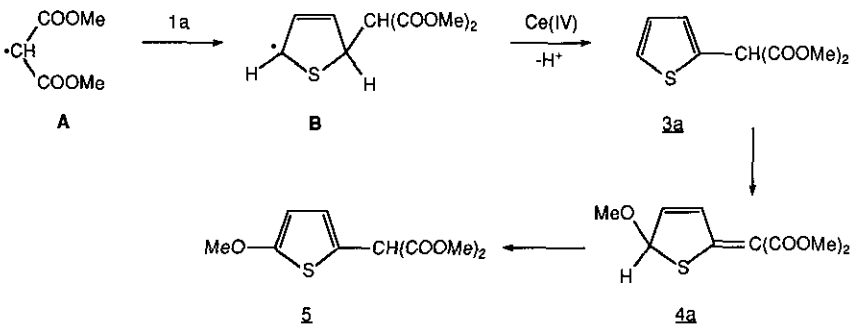
When thiophene (1a) is treated with cerium(IV) sulphate and an excess of dimethyl malonate (2) in methanol at room temperature 3a is formed in 85% yield together with a small amount of byproduct. On the basis of its nmr and mass spectrum the byproduct was identified as 4a. Based on previously reported results[5], these transformations can be interpreted in terms of an initially formed electrophilic radical species (A, Scheme I) which, not being further oxidizable by the metal salt, adds to the 2-position of thiophene. The resultant nucleo-



	R	Z
a.	H	S
b.	H	O
c.	Me	S
d	Me	O

	Y	X
a.	H	Me
b.	CH_2Ph	Et
c.	COOEt	Et
d.		Et

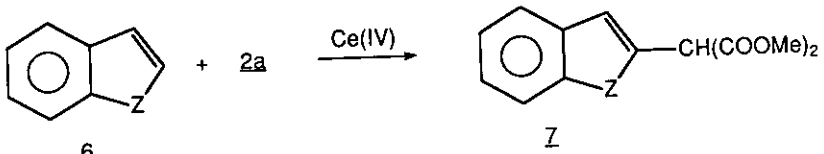
	R	Y	X	Z
a.	H	H	Me	S
b.	H	H	Me	O
c.	Me	H	Me	S
d.	Me	H	Me	O
e.	H	CH_2Ph	Et	S
f.	H	COOEt	Et	S
g	H		Et	S



SCHEME I

philic radical (B) is readily oxidized by Ce(IV) followed by proton loss to produce 3a. Since further oxidation of 3a to 4a is preferred to oxidation of dimethyl malonate (2a), an excess of 2a is required to obtain maximum yields of 3a. With an excess of oxidizing agent 4a is produced as the major product. Compound 4a could be isolated and purified by chromatography or analyzed by hplc without conversion to the aromatic form. Treatment with a small amount of diisopropylethylamine, however, results in the rapid conversion of 4a to the aromatic methoxythiophene analog 5. Furan enters an analogous substitution reaction producing 3b in 75% yield when an excess of dimethyl malonate is used and 4b in 35% yield with excess Ce(IV). Unlike 4a, however, the furan tautomer 4b fails to aromatize on treatment with base.

The 2-methyl derivatives of thiophene and furan both react in the 5-position with the malonyl radical, forming 3c and 3d in 28% and 50% yields, respectively. Benzofuran (6b) and benzothiophene (6a) were similarly malonylated to 7b and 7a in 48% and 41% yields.



6 a. Z=S b. Z=O

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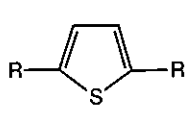

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a. R= —C(COOEt)$_2$ | CH_2Ph

b. R= —C(COOEt)$_3$

Monosubstituted malonates 2b-d enter analogous radical substitution reactions, producing the aryl malonates 3e-g. Since overoxidation of 3e-f to products analogous to 4 is not possible, use of an excess of the oxidizing agent leads instead to the bis-substitution products 8a and 8b. The phthalimidomalonate 2d forms a radical which readily dimerizes in preference to electrophilic attack.

EXPERIMENTAL

^{1}H and ^{13}C-Nmr were obtained in $CDCl_3$ on a Bruker AM300 or WM250 and Varian XL-100 Nmr spectrometers and are referred to TMS. Mass spectra were obtained on a Finnegan 450 mass spectrometer. We thank Dr. A.W. Douglas and Messrs. G. McManemin and R.A. Reamer for assistance in spectroscopic studies. Melting points are uncorrected.

Typical procedure for the preparation of 2-heteroaryl substituted malonates:

Dimethyl(2-thienyl)propanedioate (3a).

A solution of thiophene (2 ml, 25 mmoles) and dimethyl malonate (5 ml, 45 mmoles) in 90% methanol/water (50 ml) was treated with ceric sulfate (4.04 g, 10 mmoles). The heterogeneous mixture was stirred at ambient temperature under nitrogen until a negative starch-iodide test was obtained (4 hours). The solids were then filtered from the reaction mixture and rinsed with methanol (25 ml). The combined

filtrate and rinse was concentrated to 10 ml at reduced pressure and then partitioned between dichloromethane/water (50 ml each). The organic layer was washed with water (50 ml), then with saturated brine (50 ml). After drying over sodium sulfate, the solvent was removed in vacuo. The excess dimethyl malonate was distilled off at 60°C (0.5 mm Hg). Column chromatography of the residue on silica gel (50 g, 70-230 mesh, E. Merck) using dichloromethane as the eluent gave 1.82 g (85%) of 3a as a colorless oil. ^{1}H-Nmr ($CDCl_3$) δ 3.79(s, 6H), 4.96(s, 1H), 7.00(dd, 1H, J=3.4, 5.1 Hz), 7.11(dd, 1H, J=1.4, 3.4 Hz), 7.32(dd, 1H, J=1.4, 5.1 Hz). Anal. Calcd for $C_9H_{10}O_4S$: C, 50.45; H, 4.71; S, 14.96. Found: C, 50.33; H, 4.81; S, 15.09.

Dimethyl(2-furyl)propanedioate (3b).

This compound was prepared exactly as described for 3a and obtained in 75% yield. ^{1}H-Nmr ($CDCl_3$) δ 3.77(s, 6H), 4.82(s, 1H), 6.38(dd, 1H, J=2.0, 3.5 Hz), 6.44(d, 1H, J=3.5 Hz), 7.41(m, 1H). Anal. Calcd for $C_9H_{10}O_5$: C, 54.54; H, 5.09. Found: C, 55.08; H, 5.16.

The following compounds were prepared by the procedure described for 3a except that a Ce(IV)/heterocycle/malonate mole ratio of 1/1/4.5 was used:

Dimethyl(5-methyl-2-thienyl)propanedioate (3c).

A 28.5% yield of an oil was obtained. ^{1}H-Nmr ($CDCl_3$) δ 2.46(s, 3H), 3.78(s, 6H), 4.86(s, 1H), 6.63(m, 1H), 6.86(d, 1H, J=3.5 Hz). Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30; S, 14.05. Found: C, 52.71; H, 5.29; S, 13.81.

Dimethyl(5-methyl-2-furyl)propanedioate (3d).

A 50% yield of an oil was obtained. ^{1}H-Nmr ($CDCl_3$) δ 2.28(s, 3H), 3.78(s, 6H), 4.75(s, 1H), 5.95(m, 1H), 6.29(m, 1H). Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.18; H, 5.70.

Dimethyl(2-benzo[b]thienyl)propanedioate (7a).

A 41% yield of a solid, mp 81-84°C, was obtained. ^{1}H-Nmr ($CDCl_3$) δ 3.88(s, 6H), 5.00(s, 1H), 7.37(m, 3H), 7.80(m, 2H). Anal. Calcd for $C_{13}H_{12}O_4S$: C, 59.07; H, 4.58; S, 12.13. Found: C, 58.76; H, 4.75; S, 12.31.

Dimethyl(2-benzo[b]furyl)propanedioate (7b).

A 48% yield of an oil was obtained. ^{1}H-Nmr ($CDCl_3$) δ 3.76(s, 6H), 4.88(s, 1H), 6.78(s, 1H), 7.20(m, 2H), 7.41(m, 1H), 7.50(m, 1H). Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found C, 62.81; H, 4.98.

Compounds 3e-g were prepared from the substituted diethyl malonates 2b-d. The reactions were run in ethanol via the following procedure:

Diethyl(2-thienyl)benzylmalonate (3e).

A solution of thiophene (1.6 ml, 20 mmoles) and diethyl benzylmalonate (5.0 g, 10 mmoles) in absolute ethanol (50 ml) was treated with CAN (10.96 g, 20 mmoles). The solution was stirred at ambient temperature under nitrogen, until a negative starch-iodide test was obtained (5 hours). After the usual extractive work-up, the product was isolated by short path distillation. A total of 1.06 g (32%) of 3e was collected at a bath temperature of 200-240°C at 0.2 mm Hg. ^{1}H-Nmr ($CDCl_3$) δ 1.25(t, 6H, J=7 Hz), 3.7(s, 2H), 4.25(q, 4H, J=7 Hz), 6.85(m, 2H), 7.00(m, 1H), 7.14(m, 4H), 7.26(m, 1H). Anal. Calcd for $C_{18}H_{20}O_4S$: C, 65.03; H, 6.07; S, 9.65. Found: C, 64.59; H, 6.18; S, 9.28. A second fraction was collected at a bath temperature of 250-280°C at 0.2 mm Hg. This fraction contained 0.58 g (10%) of the bis-addition product 8a, ^{1}H-nmr 1.2(t, 12H, J=7 Hz), 3.6(s, 4H), 4.2(q, 8H, J=7 Hz), 6.9(m, 4H), 7.0(s, 2H), 7.15(m, 6H). Anal. Calcd for $C_{32}H_{36}O_8S$: C, 66.19; H, 6.25; S, 5.52. Found: C, 66.00; H, 6.24; S, 5.66.

Triethyl 1-(2-thienyl)methanetricarboxylate (3f).

This compound was prepared by the described procedure utilizing a mole ratio of thiophene/2c/CAN of 5/1/2. Short path distillation (bath temperature 150°C, 0.1 mm Hg) gave 1.38 g (44%) of 3f. ^{1}H-Nmr ($CDCl_3$) δ 1.3(t, 9H, J=7 Hz), 4.3(q, 6H, J=7 Hz), 6.98(m, 1H), 7.15(m, 1H), 7.33(m, 1H). Anal. Calcd for $C_{14}H_{18}O_6S$: C, 53.49; H, 5.77; S, 10.20. Found: C, 53.44; H, 5.93; S, 9.95. A second fraction, consisting of 0.55 g (10%) of 8b was obtained when the bath temperature was raised to 250-280°C (0.1 mm Hg). ^{1}H-Nmr ($CDCl_3$) δ 1.3(t, 18H, J=7 Hz), 4.3 (q, 12H), 7.05(s, 2H). Anal. Calcd for $C_{24}H_{32}O_{12}S$: C, 52.94, H, 5.92. Found: C, 53.04; H, 6.28. Mass Spec. m/z: 544.

Diethyl(2-thienyl)phthalimidomalonate (3g).

A mole ratio of thiophene/2d/Ce(IV) of 5/1/2 was used. Chromatography on silica gel with 20% ethyl acetate/dichloromethane gave 815 mg (21%) of 3g as a tan solid, mp. 79-81°C. Anal. Calcd for $C_{19}H_{17}NO_6S$: C, 58.91; H, 4.42; N, 3.62; S, 8.28. Found: C, 58.77; H, 4.49; N, 3.77; S, 8.19. The chromatography also yielded 2.0 g (66%) of a white solid which was shown to be the dimer of 2d (m/z 608).

Dimethyl[5-methoxy-2(5H)-dihydrothien-2-ylidene]propanedioate (4a).

A solution of thiophene (2 ml, 25 mmoles) and dimethyl malonate (661 mg, 5 mmol) in methanol (50 ml) was treated with ceric ammonium nitrate (10.86 g, 20 mmol). The solution was stirred under nitrogen at ambient temperature until a negative starch-iodide test was obtained (30 min). The solution was then concentrated

in vacuo to 20 ml and then partitioned between dichloromethane/water (50 ml each). The aqueous layer was washed with dichloromethane (15 ml). The organic layers were combined and washed with water (50 ml) and saturated brine (50 ml). After drying over sodium sulfate the solvent was removed in vacuo to give 760 mg of a yellow oil which crystallized on standing. Recrystallization from cyclohexane (Darco G-60) afforded 500 mg (42%) of 4a as light yellow crystals, mp 75-77°C, ^{1}H-Nmr ($CDCl_3$) δ 3.37(s, 3H), 3.82(s, 3H), 3.83(s, 3H), 6.17(dd, 1H, J=1.1, 2.6 Hz), 6.64(dd, 1H, J=2.6, 6.3 Hz), 6.98(dd, 1H, J=1.1, 6.3 Hz). ^{13}C-Nmr: see table below. Anal. Calcd for $C_{10}H_{12}O_5S$: C, 49.17; H, 4.95; S, 13.13. Found: C, 48.93; H, 4.84; S. 13.25.

Compounds 4b-d were prepared in the manner described for 3a using Ce(IV)/ heterocycle/malonate mole ratios listed:

Dimethyl [5-methoxy-2(5H)-dihydrofuran-2-ylidene]propanedioate (4b).

Mole ratio 4/5/1; 35% yield as an oil. ^{1}H-Nmr ($CDCl_3$) δ 3.46(s, 3H); 3.74(s, 3H), 3.81(s, 3H), 6.09(m, 1H), 6.61(m, 1H), 7.41(m, 1H). Anal. Calcd for $C_{10}H_{12}O_6$: C, 52.63; H, 5.30. Found: C, 52.73; H, 5.36. ^{13}C-Nmr ($CDCl_3$) δ 51.7, 53.2, [$\underline{C}(C00CH_3)_2$] and [$C(C00\underline{C}H_3)_2$], 109.5, 110.8, (C_3,C_4), 142.9, 145.6, (C_2C_5), 160.7 [$C(\underline{C}00CH_3)_2$].

Dimethyl [5-methoxy-5-methyl-2(5H)-dihydrothienylidene]propanedioate (4c).

Mole ratio 2/4/1, 50% yield as an oil. ^{1}H-Nmr ($CDCl_3$) δ 1.84(s, 3H), 3.26 (s, 3H), 3.83(s, 3H), 3.85(s, 3H), 6.41(d, 1H, J=6.0 Hz), 6.87(d, 1H, J=6.0 Hz).

Dimethyl 5-methoxy-5-methyl-2(5H)-dihydrofuranylidene]propanedioate (4d).

Mole ratio 2/4/1, 20% yield as an oil. ^{1}H-Nmr ($CDCl_3$) δ 1.62(s, 3H), 3.16(s, 3H), 3.76(s, 3H), 3.82(s, 3H), 6.55(d, 1H, J=6.0 Hz), 7.38(d, 1H, J=6.0 Hz). Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.43; H, 6.02. ^{13}C-Nmr ($CDCl_3$) δ 23.9, (5-CH_3), 51.3, 51.9, [$C(C00\underline{C}H_3)_2$] 52.4, (5-$0\underline{C}H_3$), 116.2, (C_5), 127.0 (C_4), 143.4 (C_3), 165.3 (C_2), 169.1 ($\underline{C}$-$0CH_3$).

Equilibration of 4a in the Presence of Base

Carbon-13 nmr was used to follow in situ the conversion of the methoxy—thiophenilidene diester, 4a to 5, catalyzed by diisopropylethylamine. Fifty mg of 4a was dissolved in 3 ml $CDCl_3$, the ^{13}C nmr spectrum recorded, and 10 µl diisopropylethylamine was added at room temperature. After about 20 min, about half of the initial 4a was converted to 5. After overnight aging, 4a was no

longer detectable. Carbon-13 chemical shifts, relative to the deuterochloroform solvent taken as δ_C = 77.0 ppm, are tabulated below.

Carbon Pos.	4a	5
C_2	164.5	118.9
C_3	132.1	125.7
C_4	143.1	102.9
C_5	93.8	167.2
C	115.0	53.0
Ester C=O's	165.4	167.7
Ester OMe's	52.2, 52.3	52.9
5-OMe	54.9	60.0

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