Synthesis of dialkyl {(aryl)[2,2-dimethyl-4-oxo-6-(piperidin-1-yl)-4*H*-[1,3]dioxin-5-yl]methyl}phosphonate by reaction of Meldrum's acid, aryl aldehydes and trialkyl phosphites in the presence of piperidine

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A four-component reaction between Meldrum's acid, aryl aldehydes with trialkyl phosphites in the presence of piperidine has been developed. The reaction affords dialkyl {(aryl)[2,2-dimethyl-4-oxo-6-(piperidin-1-yl)-4*H*-[1,3]dioxin-5-yl]methyl}phosphonate in moderate to good yields in a one-pot process.

Keywords: four-component reaction, Meldrum's acid, trialkyl phosphites, aryl aldehydes, piperidine

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis.[1] Due to its high acidity (pK_a 7.5)[2] and tendency to regenerate ketones or aldehydes, Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione),[3,4] appears to be an attractive reagent in organic synthesis. However, synthesis applications of this compound have received little attention except as an alternative for cyclic malonic esters.[5,6] Useful applications of alkylidene derivatives of Meldrum's acid as dienophiles in Diels–Alder reactions[7] and Michael acceptors have been reported, showing advantages of these systems over their acyclic analogues.[8,9] Alkylidene Meldrum's acids are readily accessible from Meldrum's acid and carbonyl compounds (ketones and aldehydes) on a relatively large scale.[10]

There have been many studies on the reactions between trivalent phosphorus nucleophiles and unsaturated carbonyl compounds in the presence of a proton source such as an alcohol.[11] There are other recent reports on the reaction between phosphites and acetylenic esters in the presence of an acidic organic compound, all of which proceed to products through a phosphite ylide intermediate.[12–14] However, this intermediate has not been isolated nor characterised in any of these reports and is usually hydrolysed or rearranged to the corresponding phosphonates. In the context of our recent studies[15–19] on the reactivity of isopropylidene Meldrum's acid, we studied the reaction between Meldrum's acid, aryl aldehydes with trialkyl phosphites in the presence of piperidine.

Results and discussion

The reaction of Meldrum's acid **1** and aryl aldehydes **2** with trialkyl phosphites **3** in the presence of piperidine **4** leds to dialkyl {(aryl)[2,2-dimethyl-4-oxo-6-(piperidin-1-yl)-4*H*-[1,3]-dioxin-5-yl]methyl}phosphonate **5** in good yields (Scheme 1).

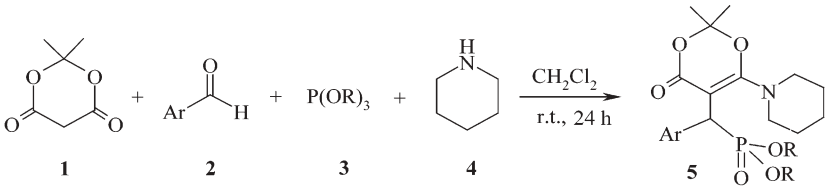
The structure of compounds **5a–e** were deduced from their elemental analyses and their IR, ^{1}H, ^{13}C, and ^{31}P NMR spectra.

A reasonable mechanism for the formation of compound **5** is presented in Scheme 2. Trialkyl phosphite attacks to the condensation product of meldrum's acid **1** and aryl aldehyde **6** leds to a diionic intermediate **7**. Cyclisation of this zwitterionic intermediate to produce the oxaphosphorane **8**. The attack of the piperidine on **8** is initiated by conjugate addition to the double bond and cleavage of the phosphorus–oxygen bond by nucleophile produced **5**.

In summary, we report the four-component reaction between Meldrum's acid, aryl aldehydes with trialkyl phosphites in the presence of piperidine to afford dialkyl {(aryl)[2,2-dimethyl-4-oxo-6-(piperidin-1-yl)-4*H*-[1,3]dioxin-5-yl]methyl}phosphonate in good yields. This method has the advantage that the reaction is performed in neutral conditions and the starting materials can be mixed without any activation nor modification.

Experimental

Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyser. Mass spectra were recorded on a Finnigan-Mat 8430 mass spectrometer operating at an ionisation potential of 70 eV.



1 **2** **3** **4** **5**

5	Ar	R	Yield%*
a	C_6H_5	Me	88
b	C_6H_5	Et	90
c	4-Cl-C_6H_4	Me	92
d	4-NO_2-C_6H_4	Me	92
e	4-NO_2-C_6H_4	Et	87

* Isolated yields

Scheme 1 Four-component reaction between Meldrum's acid and aryl aldehydes with trialkyl phosphites in the presence of piperidine.

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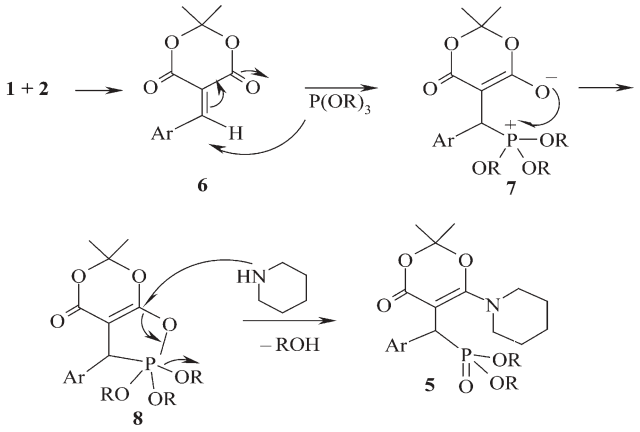

Scheme 2 Suggested mechanism for formation of compound **5**.

IR spectra were recorded on a Shimadzu IR-470 spectrometer.^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker DRX-400 Avance spectrometer in $CDCl_3$ using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Compound **1** was prepared as previously described in the literature.[10]

Synthesis of compounds **5a–e***; general procedure*

A mixture of trialkyl phosphite (2 mmol) at room temperature over 2 min was added dropwise to a magnetically stirred solution of Meldrum's acid (2 mmol) and aryl aldehydes (2 mmol) in dichloromethane (15 mL). The reaction mixture was then stirred for 1 minute. Piperidine (2 mmol) was added and the reaction mixture was stirred for another 24h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (60, 230–400 mesh) using ethyl acetate–hexane (3:1) mixture as eluent.

Dimethyl {(phenyl)-(2,2-dimethyl-4-oxo-6-piperidin-1-yl-4H-[1,3]-dioxin-5-yl)methyl}phosphonate (**5a**): Yield: 88%; Yellow oil. IR (KBr) (ν_{max}, cm^{-1}): 1675 (C=O). Anal. Calcd for $C_{20}H_{28}NO_6P$: C, 58.67; H, 6.89; N, 3.42. Found: C, 58.55; H, 6.97; N, 3.50%. MS (*m/z*, %): 409 (M^+, 8). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59–1.77 (6H, m, $3CH_2$), 1.67 (6H, s, $2CH_3$), 2.94–2.97 (4H, m, $2CH_2$), 3.71 (3H, d, $^{3}J_{PH}$ = 11 Hz, $POCH_3$), 3.74 (3H, d, $^{3}J_{PH}$ = 11 Hz, $POCH_3$), 4.98 (1H, d, $^{2}J_{HP}$ = 28 Hz, CH), 7.16–7.53 (5H, m, 5CH aromatic).^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.05 (CH_2), 25.57 ($2CH_3$), 38.98 (d, $^{1}J_{cp}$ = 140.8 Hz, P-CH), 44.09 ($2CH_2$), 52.43 and 53.00 (2d, $^{2}J_{CP}$ = 8 Hz, $P(OCH_3)_2$), 53.62 ($2CH_2$), 72.21 (CMe_2), 101.27 (d, $^{2}J_{CP}$ = 36 Hz, C=C), 127.69, 128.92, 129.28, and 130.68 (aromatic), 138.32 (=CON), 166.96 (d, $^{3}J_{CP}$ = 6.0 Hz, C=O), ^{31}P NMR (162 MHz, $CDCl_3$): δ 33.08.

Diethyl {(phenyl)-(2,2-dimethyl-4-oxo-6-piperidin-1-yl-4H-[1,3]-dioxin-5-yl)methyl}phosphonate (**5b**): Yield: 90%; Yellow oil. IR (KBr) (ν_{max}, cm^{-1}): 1680 (C=O). Anal. Calcd for $C_{22}H_{32}NO_6P$: C, 60.40; H, 7.37; N, 3.20. Found: C, 60.48; H, 7.25; N, 3.26%. MS (*m/z*, %): 437 (M^+, 3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 and 1.18 (6H, 2t, $^{3}J_{HH}$ = 7 Hz, $2CH_3$), 1.58 (6H, s, $2CH_3$), 1.25–1.82 (6H, m, $3CH_2$), 3.84–3.98 (4H, m, $2CH_2$), 4.05–4.14 (4H, m, $2POCH_2$), 5.01(1H, d, $^{2}J_{HP}$ = 28 Hz, CH), 7.04–7.43 (5H, m, 5CH aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.33 and 17.47 ($2CH_3$), 23.34 (CH_2), 26.97 ($2CH_3$), 40.29 (d, $^{1}J_{cp}$ = 140.8 Hz, P-CH), 45.37 ($2CH_2$), 62.83 and 63.61 (2d, $^{2}J_{cp}$ = 7 Hz, $2POCH_2$), 54.64 ($2CH_2$), 73.48 (CMe_2), 102.56 (d, $^{2}J_{CP}$ = 36 Hz, C=C), 127.14, 129.02, 130.29, and 130.68 (aromatic), 139.65 (=CON), 168.03 (d, $^{3}J_{CP}$ = 6.0 Hz, C=O), ^{31}P NMR (162 MHz, $CDCl_3$): δ 30.84.

Dimethyl {(4-chlorophenyl)-(2,2-dimethyl-4-oxo-6-piperidin-1-yl-4H-[1,3]dioxin-5-yl)methyl}phosphonate (**5c**): Yield: 92%; Yellow oil. IR (KBr)(ν_{max}, cm^{-1}): 1673 (C=O). Anal. Calcd for $C_{20}H_{27}ClNO_6P$: C, 54.12; H, 6.13; N, 3.16. Found: C, 54.20; H, 6.24; N, 3.04%. MS (*m/z*, %): 443 (M^+, 10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10–1.73 (6H, m, $3CH_2$), 1.52 (6H, s, $2CH_3$), 3.08–3.80 (4H, m, $2CH_2$), 3.54 (3H, d, $^{3}J_{PH}$ = 11 Hz, $POCH_3$), 3.76 (3H, d, $^{3}J_{PH}$ = 11 Hz, $POCH_3$), 4.77 (1H, d, $^{2}J_{HP}$ = 28 Hz, CH), 7.13 (2H, d, $^{3}J_{HH}$ = 7 Hz, 2CH aromatic), 7.52 (2H, d, $^{3}J_{HH}$ = 7 Hz, 2CH aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.33 (CH_2), 25.89 ($2CH_3$), 44.33 ($2CH_2$), 38.16 (d, $^{1}J_{cp}$ = 140.8 Hz, P-CH), 50.51 and 52.80 (2d, $^{2}J_{CP}$ = 8 Hz, $P(OCH_3)_2$), 53.46 ($2CH_2$), 72.24 (CMe_2), 101.52 (d, $^{2}J_{CP}$ = 36 Hz, C=C), 128.05, 130.74, 132.05, and 137.04 (aromatic), 137.04 (=CON), 167.01 (d, $^{3}J_{CP}$ = 6.0 Hz, C=O), ^{31}P NMR (162 MHz, $CDCl_3$): δ 33.14.

Dimethyl {(4-nitrophenyl)-(2,2-dimethyl-4-oxo-6-piperidin-1-yl-4H-[1,3]dioxin-5-yl)methyl}phosphonate (**5d**): Yield: 92%; Yellow oil. IR (KBr)(ν_{max}, cm^{-1}): 1672 (C=O). Anal. Calcd for $C_{20}H_{27}N_2O_8P$: C, 52.86; H, 5.99; N, 6.16. Found: C, 52.80; H, 5.85; N, 6.10%. MS (*m/z*, %): 454 (M^+, 7). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24–1.72 (6H, m, $3CH_2$), 1.58 (6H, s, $2CH_3$), 2.95–2.98 (4H, m, $2CH_2$), 3.65 (3H, d, $^{3}J_{PH}$ = 11 Hz, $POCH_3$), 3.74 (3H, d, $^{3}J_{PH}$ = 11 Hz, $POCH_3$), 4.86 (1H, d, $^{2}J_{HP}$ = 28 Hz, CH), 7.70 (2H, d, $^{3}J_{HH}$ = 7 Hz, 2CH aromatic), 7.99 (2H, d, $^{3}J_{HH}$ = 7 Hz, 2CH aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.48 (CH_2), 25.69 ($2CH_3$), 38.23 (d, $^{1}J_{cp}$ = 140.8 Hz, P-CH), 44.59 ($2CH_2$), 55.07 ($2CH_2$), 52.94 and 54.05 (2d, $^{2}J_{CP}$ = 8 Hz, $P(OCH_3)_2$), 71.95 (CMe_2), 101.93 (d, $^{2}J_{CP}$ = 36 Hz, C=C), 123.14, 129.82, 130.36, and 146.34 (aromatic), 138.25 (=CON), 167.27 (d, $^{3}J_{CP}$ = 6.0 Hz, C=O), ^{31}P NMR (162 MHz, $CDCl_3$): δ 33.25.

Diethyl {(4-nitrophenyl)-(2,2-dimethyl-4-oxo-6-piperidin-1-yl-4H-[1,3]dioxin-5-yl)methyl}phosphonate (**5e**): Yield: 87%; Yellow oil. IR (KBr)(ν_{max}, cm^{-1}): 1670 (C=O). Anal. Calcd for $C_{22}H_{31}N_2O_8P$: C, 54.77; H, 6.48; N, 5.81. Found: C, 55.90; H, 6.57; N, 5.80%. MS (*m/z*, %): 482 (M^+, 5). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 and 1.33 (6H, 2t, $^{3}J_{HH}$ = 7 Hz, $2CH_3$), 1.44–1.60 (6H, m, $3CH_2$), 1.62 (6H, s, $2CH_3$), 2.93–3.04 (4H, m, $2CH_2$), 4.07–4.15 (4H, m, $2POCH_2$), 5.17 (1H, d, $^{2}J_{HP}$ = 28 Hz, CH), 7.50 (2H, d, $^{3}J_{HH}$ = 7 Hz, 2CH aromatic), 8.16 (2H, d, $^{3}J_{HH}$ = 7 Hz, 2CH aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 16.85 and 17.08 ($2CH_3$), 22.41 (CH_2), 25.63 ($2CH_3$), 38.35 (d, $^{1}J_{cp}$ = 140.8 Hz, P-CH), 44.46 ($2CH_2$), 55.02 ($2CH_2$), 62.80 and 63.52 (2d, $^{2}J_{cp}$ = 7 Hz, $2POCH_2$), 72.13 (CMe_2), 102.24 (d, $^{2}J_{CP}$ = 36 Hz, C=C), 123.47, 129.94, 130.45, and 146.32 (aromatic), 137.82 (=CON), 167.34 (d, $^{2}J_{CP}$ = 6.0 Hz, C=O), ^{31}P NMR (162 MHz, $CDCl_3$): δ 33.20.

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