https://chemclassjournal.com/
ChemClass Journal Vol. 9 Issue 2 (2025); 310-321
e-ISSN:3092-8214 p-ISSN:3092-8206
DOI: https://doi.org/10.33003/chemclas-2025-0901/160

Chalcones as Nature's Blueprint for Synthetic Innovation

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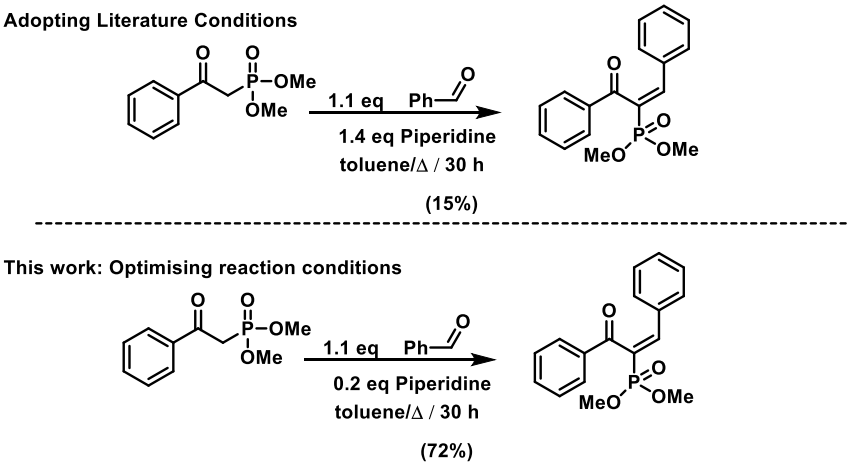
Abstract

Chalcones (1,3-diaryl-2-propen-1-ones) are classical examples of α,β-unsaturated ketones, which are depicted by their simple yet highly versatile structures. They provide a crucial link between natural product inspiration and synthetic innovation. Owing to their ease of synthesis, broad functionalization potential, and well-established biological relevance, chalcones serve as valuable scaffolds for direct applications and the construction of more complex molecular architectures. In this study, twelve (12) phosphonate chalcones were synthesised in high yields *via* the Knoevenagel condensation reaction, nine (9) of which are novel derivatives. This offers exciting opportunities for further functionalisation into higher molecular frameworks or compounds with potential biological activity.

Keywords: α,β-unsaturated ketones**,** Chalcones, Knoevenagel, Phosphonates, Scaffolds.



Scheme 1: Synthesis of model phosphonate chalcone via Knoevenagel condensation

Introduction

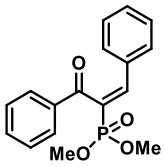
Chalcones are a class of compounds known for their wide range of biological activities, including antimicrobial, anti-inflammatory, and anticancer properties [1]. Incorporating phosphonate groups into these molecules yields β-ketophosphonate chalcones, which are a unique class of organophosphonates that serve as versatile intermediates for constructing more complex and biologically active structures [2][3]. The key structural feature enabling these applications is the phosphorus–carbon (P–C) bond, which facilitates the formation of phosphonates ($P(O)(OR)_2$), where R can be identical or different substituents.

Organophosphonates play significant roles across various domains, including medicine, pharmaceuticals, agrochemicals [4] additives, and flame retardants [5]. The Knoevenagel condensation [6], is a key strategy in synthesising β-ketophosphonate chalcones and has proven instrumental in producing pharmacologically relevant compounds, underscoring its central role in synthetic organic chemistry. Common protocols involved in their synthesis include Arbuzov, Wittig, Horner-Wadsworth-Emmons (HWE), and cross-coupling reactions. These methods are often limited by harsh conditions, lack of stereoselectivity, cumbersome multi-step procedures, and, most notably, low product yields. Knoevenagel reaction presents milder reaction conditions and high product yield.

Materials and Methods

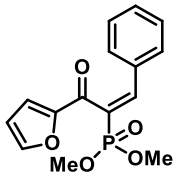
General procedure A for Representative compound

Phosphonic acid, *P*-[(*1E*)-1-benzoyl-2-phenylethyl] dimethyl ester 2a [7]



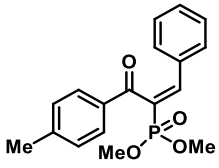
Benzaldehyde (0.20 mL, 2.40 mmol) was added to a stirred solution of β-ketophosphonate **1a** (0.50 g, 2.19 mmol) in dry toluene (30 mL). Piperidine (~0.05mL, 0.44 mmol) was added, and the resulting solution was heated for 30 hours under Dean-Stark conditions. The reaction mixture was cooled and concentrated to yield the crude product which was purified by flash column chromatography on silica gel eluting with petroleum-ether/EtOAc = 1:2 (R_f = 0.30) to afford the title compound as a yellow liquid (0.50 g, 72%); ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.81 (6H, d, *J* 11.2, 2 × OC*H*$_3$), 7.18-7.26 (3H, m, 3 × ArC*H*), 7.29 -7.34 (2H, m, ArC*H*), 7.36- 7.41 (2H, m, ArC*H*) 7.50 - 7.55 (1H, m, ArC*H*), 7.86 (1H, d, J_{PH} 26.0, PC=C*H*), 7.93-7.97 (2H, m, 2 × ArC*H*); ^{13}C NMR (100MHz; $CDCl_3$) δ_C 53.20 (2 × O*C*H$_3$, d J_{CP} 5.8), 128.7 (4 × Ar*CH*), 129.6 (2 × Ar*C*H), 129.9 (2 × Ar*C*H), 130.3 (Ar*C*H), 130.5 (Ar*C*), 133.4 (d, J_{CP} 21.4, P*C*=CH), 134.0 (Ar*C*H), 135.4 (d, J_{cp} 2.7, Ar*C*), 147.2 (H*C*=CP, d, J_{cp} 5.9), 195.5 (Ar*C*=O, d, J_{CP} 8.3); ^{31}P NMR ($CDCl_3$, 162 MHz); δ 17.06. All Data were in accordance with literature. [7]

_P_-[(_1E_)-1-Furanoyl-2-phenylethyl] phosphonic acid dimethyl ester 3b



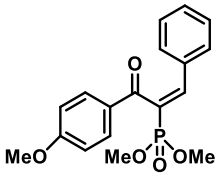
Prepared according to the general procedure **A** using benzaldehyde (0.30 mL, 2.52mmol), a solution of β-ketophosphonate **1** (0.50 g, 2.29 mmol) in dry toluene (20 mL) and piperidine (0.05 mL, 0.46 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.32), to afford the title compound (0.42 g, 60%) as deep yellow crystals. Mpt 59 – 61 ^{o}C; ν $_{max}$ (ATR / cm^{-1}); 3076, 3004, 1640, 1460, 1251; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.84 (6*H*, d, *J* 11.3, 2 × OC*H*$_3$), 6.42 (1H, dd, *J* 3.6, 1.7, ArC*H*), 7.08 (1H, d, *J* 3.4 ArC*H*), 7.24 -7.38 (5H, m, 5 × ArC*H*), 7.56 (1H, d, J_{Hp} 1.6, ArC*H*), 7.85 (1H, d, J_{Hp}25.3, C*H*=CH); ^{13}C NMR (100MHz; $CDCl_3$) δ_C 53.2 (O*C*H$_3$, d J_{CP} 5.7), 112.6 (Ar*CH*), 121.3 (Ar*C*H), 127.9 (Ar*C*), 128.8 (2 × Ar*C*H), 129.7 (2 × Ar*C*H), 130.4 (Ar*C*H), 133.5 (d, J_{CP} 21.1, P*C*=CH , 148.0 (Ar*C*H), 148.5 (PC=*C*H, d J_{cp} 6.3), 151.7 (Ar*C*, d, J_{CP}4.1),182.0 (Ar*C*O, d J_{CP} 9.5); ^{31}P NMR ($CDCl_3$, 162 MHz) δ_P 16.76; *m/z* (ESI$^+$) 307.0738 (100%, MH$^+$. $C_{15}H_{16}O_5P$ requires 307.0730), 239 (10), 121 (5).

_P_ - [_1E_)-1-_p_-tolyl-2-phenylethyl] phosphonic acid dimethyl ester 4b



Prepared according to the general procedure **A** using benzaldehyde (0.10 mL, 0.91 mmol), a solution of β-ketophosphonate **2** (0.20 g, 0.83 mmol) in dry toluene (30 mL), and piperidine (0.02 mL 0.17 mmol. The residue was purified by flash column chromatography on silica gel eluting petroleum ether/ EtOAc = 1:2 (R_f = 0.30) to afford the title compound (0.23 g, 84%) as yellow crystals; ν $_{max}$ (ATR / cm^{-1}); 2928, 2859, 1661, 1259, 1029 ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 2.36 (3H, s, ArC*H*$_3$), 3.80 (6H, d, *J* 11.3, 2 × OC*H*$_3$), 7.15 -7.27 (5H, m, 5 × ArC*H*), 7.32 (2H, d, *J* 7.5, 2 × ArC*H*), 7.79 (1H, d, J_{HP} (19.6), C=C*H*), 7.85 (2H, d, *J* 7.5, 2 × Ar*C*H); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 21.8 (*C*H$_3$, s), 53.2 (d, J_{CP} 5.8, 2 × O*C*H$_3$), 128.7 (2 × Ar*C*H), 129.5 (2 × ArCH), 129.8 (2 × Ar*C*H), 129.9 (2 × ArCH), 130.2 (ArCH), 130.6 (Ar*C*), 133.0 (d, J_{CP} 2.6 Ar*C*), 133.5 (d, J_{CP} 21.8, P*C*=CH), 145.1 (Ar*C*), 146.8 (d, J_{CP} 5.8, PC=*C*H), 195.1 (d, J_{CP} 8.1, Ar*C*O); ^{31}P NMR ($CDCl_3$, 162 MHz); δ 17.23*; m/z* (ESI$^+$) 353, 331.1098 (100%, MH$^+$. $C_{18}H_{20}O_4P$ requires 331.1094), 214 (8), 121 (10).

Phosphonic acid, *P*-[*(1E)*-1-*p*-anisyl-2-phenylethyl] dimethyl ester 5b

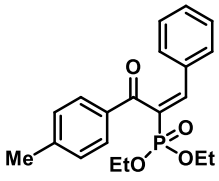


Prepared according to the general procedure **A** using benzaldehyde (0.20 mL, 1.70 mmol), a solution of β-ketophosphonate **3** (0.40 g, 1.55 mmol) in dry toluene (30 mL) and piperidine (0.05 mL, 0.60 mmol). The residue was purified by flash column chromatography on silica gel eluting with petroleum ether/EtOAc = 1:4 (R_f = 0.24), to afford the title compound as yellow crystals (0.41g, 81% yield); Mpt. 105.3 -107 ^{o}C; ν $_{max}$ (ATR / cm^{-1}); 2947, 1645, 1595, 1573, 1572; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.81 (6H, d, J_{HP} 11.3, OCH_3), 3.84 (3H, s, OCH_3), 6.86 (2H, d, *J* 9.0, 2 x ArC*H*), 7.20-7.36 (5H, m, 5 x ArC*H*), 7.81 (1H, d, J_{PH} 26.0, PC=C*H*), 7.94 (2H, d, *J* 9.0, 2 x ArC*H*]; ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 53.2 (O*C*H$_3$, d, J_{CP} 5.7), 55.5 (O*C*H$_3$), 114.0 (Ar*C*H), 128.6 (d, Ar*C*, J_{CP} 2.4), 128.7 (Ar*C*H), 128.9 (Ar*C*), 129.9 (2 x Ar*C*H), 130.2 (2 x Ar*C*H), 130.6 (Ar*C*), 132.1 (2 x Ar*C*H), 133.5 (d, J_{CP} 21.9, P*C*=CH), 146.6 (Ar*C*H, d, J_{CP} 6.0, PC=*C*H), 164.3 (Ar*C*), 193.8 (Ar*C*O, d, J_{CP} 8.3); ^{31}P NMR (162 MHz; $CDCl_3$) δ_P 17.36; *m/z* (ESI$^+$) 347.1052 (100%, MH$^+$. $C_{18}H_{20}O_5P$ requires 347.1043).

Phosphonic acid, *P*-[*(1E)*-1-O-anisyl-2-phenylethyl]dimethyl ester 6b

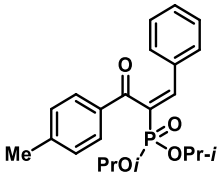
Prepared according to the general procedure **A** using benzaldehyde (0.40 mL, 3.41 mmol), a solution of β-ketophosphonate **4** (0.80 g, 3.10 mmol) in dry toluene (60 mL) and piperidine (0.10 mL, 0.62 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.33) to afford the title compound (0.52 g, 51 %) as a yellow semi-solid ν_{max} (ATR /cm^{-1}) 3007, 1661, 1596,1243, 1027; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.80 (6H, d, J_{HP} 11.3, 2 × OCH_3), 3.82 (3H, s, OCH_3), 6.86 (1H, d, *J* 8.3, ArC*H*), 6.90-6.94 (1H, m, ArC*H*), 7.18-7.25 (3H, m, 3 × ArC*H*), 7.31 -7.35 (2H, m, 2 × ArC*H*), 7.40 - 7.45 (1H, m, ArC*H*), 7.72 (1H, d, J_{HP} 25.7, PC=C*H*), 7.78 (1H, dd, *J* 7.8, 1.8, ArC*H*). ^{13}C NMR (100MHz; $CDCl_3$) δ_C 53.1 (2 × *C*H$_3$, d, J_{CP} 5.7), 55.7 (O*C*H$_3$), 111.8 (Ar*C*H), 120.3 (Ar*C*H), 126.5 (d, J_{CP} 3.1, Ar*C*), 128.3 (2 × Ar*C*H), 129.6 (2 × Ar*C*H), 129.8(Ar*C*H), 132.0 (Ar*C*H), 132.0 (Ar*C*H), 133.9 (HC=*C*P, d J_{cp} 21.8), 134.8 (Ar*C*H), 146.1 (H*C*=CP, d J_{cp} 6.3), 159.6 (2 × ArC), 191.3 (Ar*C*O, d, J_{cp} 8.3); ^{31}P NMR ($CDCl_3$, 162 MHz); δ 17.45; *m/z* (ESI$^+$) 347.1043 (100%, M+H$^+$. $C_{18}H_{20}O_5P$ requires 347.1045).

Phosphonic acid, *P* - [*1E*)-1-*p*-tolyl-2-phenylethyl] diethyl ester 7b [7]



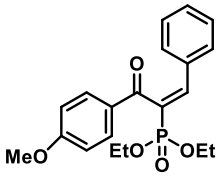
Prepared according to the general procedure **A** using benzaldehyde (0.20 mL, 2.04 mmol), a solution of β-ketophosphonate **5** (0.50 g, 1.85 mmol) in dry toluene (30 mL) and piperidine (0.05 mL, 0.37 mmol). The residue was purified by flash column chromatography on silica gel eluting with petroleum-ether/ EtOAc = 1:2 (R_f = 0.30), to afford the title compound (0.57 g, 83 %) as a yellow liquid. ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.28 (6H, t, *J* 7.0, 2 × OCH_2CH_3), 2.37 (3H, s, ArCH_3), 4.16 (4H, quint, J_{HP} 7.3, 2 × CH_2), 7.18 (2H, d, *J* 8.1, 2 × ArC*H*), 7.22 -7.26 (3H, m, 3 × ArC*H*) 7.30 -7.35 (2H, m, 2 × ArC*H*), 7.79 (1H, d, J_{HP} 26.0, ArC=C*H*), 7.86 (2H, d, *J* 8.1, 2 × ArC*H*); ^{13}C NMR (100MHz; $CDCl_3$) δ_C 16.1 (d, J_{CP} 6.7, 2 × *C*H_3), 21.8 (O*C*H_3), 62.8 (d, J_{CP} 5.7, 2 × O*C*H_2), 128.7 (2 × Ar*C*H), 129.0 (Ar*C*H), 129.2 (Ar*C*H), 129.3 (2 × Ar*C*H), 129.8 (d, *J* 4.8, 2 × Ar*C*H), 130.1 (Ar*C*H), 130.3 (Ar*C*), 133.2 (d, J_{CP} 2.3, HC=*C*P), 133.8 (Ar*C*), 144.9 (Ar*C*), 145.9 (d, J_{CP} 5.9, H*C*=CP), 195.3 (d, J_{CP} 8.1, Ar*C*O); ^{31}P NMR ($CDCl_3$, 162 MHz) δ 14.05. All data were in accordance with literature. [7]

Phosphonic acid, *P* - [*1E*)-1-*p*-tolyl-2-phenylethyl] diisopropyl ester 8b



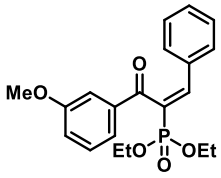
Prepared according to the general procedure **A** using benzaldehyde (0.10 mL, 1.11 mmol), a solution of β-ketophosphonate **6** (0.30 g, 1.01 mmol) in dry toluene (30 mL), and piperidine (0.03 mL, 0.30 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.45) to afford the title compound (0.35 g, 90%) as a yellow liquid; ν_{max} (ATR/cm^{-1}) 2979, 1661, 1605, 1374, 1247; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.27 (12H, dd, J_{PH} 6.0, 2.3, 2 × O(CH_3)$_2$, 2.34 (3H, s, CH_3), 4.67-4.79 (2H, m, 2 × C*H*), 7.14 (2H, d, *J* 8.1, 2 × ArC*H*), 7.16 - 7.22 (3H, m, 3 × ArC*H*), 7.28 - 7.33 (2H, m, 2 × ArC*H*), 7.75 (1H, d, J_{HP} 26.0, PC=C*H*), 7.85 (2H, d, *J* 8.1, 2 × ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 21.7 (*C*H$_3$, s), 23.8 (dd, J_{CP} 20.8, 4.6, C*C*H$_3$, 4 × *C*H$_3$), 71.7 (d, J_{CP} *6.1*, 2 × O*C*H), 128.6 (2 × Ar*C*H), 129.2 (4 × Ar*C*H), 129.8 (3 × Ar*C*H), 131.7 (ArC), 133.4 (d, J_{CP} 3.1 Ar*C*), 133.8 (ArC), 144.6 (Ar*C*), 145.0 (d, J_{CP} 6.1 H*C*=CP), 195.4 (d, J_{CP} 8.3, Ar*C*O); ^{31}P NMR (162 MHz; $CDCl_3$) δ_P 11.5**;** *m/z* (ESI$^+$) 599.2 (35%), 303.1 (18%), 345.1 (15%), 387.172 (90, MH$^+$. $C_{22}H_{27}O_4P$ requires 387.1732), 191.5 (5%).

Phosphonic acid, *P*-[(1*E*)-1-*p*-anisyl-2-phenylethyl] diethyl ester 9b [7]



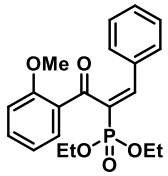
Prepared according to the general procedure **A** using benzaldehyde (0.20 mL 1.92 mmol), a solution of β-ketophosphonate **7** (0.50 g, 1.75 mmol) in dry toluene (30 mL) and piperidine (0.03 mL, 0.35 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.43) to afford the title compound as a yellow liquid (0.53 g, 81% yield); ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.27 (6H, t, *J* 7.1, 2 x OCH_2CH_3), 3.82 (3H, s, OCH_3), 4.10 - 4.20 (4H, m, 2 x CH_2), 6.84 (2H, d, *J* 9.0, 2 x ArC*H*), 7.17 -7.26 (3H, m, 3 x ArC*H*), 7.30 – 7.35 (2H, m, 2 x ArC*H*), 7.76 (1H, d, J_{PH} 26.1, C=C*H*), 7.93 (2H, d, *J* 9.0, 2 x ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 16.2 (d, J_{CP} 6.7, 2 x O*C*H$_3$,), 55.5 (O*C*H$_3$), 62.8 (d, *J* 5.7, 2 x *C*H$_2$), 113.8 (Ar*C*H), 128.7 (2 x Ar*C*H), 128.8 (Ar*C*), 129.8 (Ar*C*H), 130.1 (Ar*C*H), 132.1 (2 x Ar*CH*), 130.6 (Ar*C*), 132.1 (2 x Ar*C*H), 133.7 (d, J_{CP} 22.0 C=*C*P), 133.6 (Ar*C*), 145.7 (C=*C*H, d, J_{CP} 5.9), 164.2 (Ar*C*O); ^{31}P NMR (162 MHz; $CDCl_3$) δ_P 14.17. All data were in accordance with literature. [7]

Phosphonic acid, *P*-[(1*E*)-1-*m*-anisyl-2-phenylethyl] diethyl ester 10b



Prepared according to the general procedure **A** using benzaldehyde (0.20 mL, 1.92 mmol), a solution of β-ketophosphonate **8** (0.50 g, 1.75 mmol) in dry toluene (30 mL) and piperidine (0.03 mL, 0.35 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.45), to afford the title compound as a deep yellow viscous oil (0.55 g, 85% yield); ν_{max} (ATR / cm^{-1}) 2982, 1699, 1664, 1582, 1257; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.25 - 1.31 (6H, m, 2 x CH_3), 3.82 (3H, s, OCH_3), 4.11 - 4.21 (4H, m, 2 x OCH_2), 7.07 (1H, ddd *J* 6.7, 2.5, 1.2, ArC*H*), 7.20 – 7.27 (4H, m, ArC*H*), 7.29 – 7.34 (2H, m, 2 x ArC*H*), 7.51 – 7.54 (2H, m, 2 x ArC*H*), 7.82 (1H, d, J_{PH} 25.9, C=C*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 16.1 (d, J_{CP} 6.8, 2 x O*C*H$_3$,), 55.4 (O*C*H$_3$), 62.8 (d, *J* 5.7, 2 x *C*H$_2$), 112.9 (Ar*C*H), 120.9 (Ar*C*H), 122.8 (Ar*C*H), 128.7 (2 × Ar*C*H), 129.6 (Ar*C*H), 129.8 (2 × Ar*C*H), 130.2 (Ar*C*H), 131.8 (Ar*C*), 133.6 (d, J_{CP} 21.7, C=*C*P), 136.9 (d, Ar*C* , J_{CP} *2.5*), 146.3 (d, J_{CP} 5.8, H*C*=CP), 159.8 (Ar*C*), 195.5 (d, J_{CP} 8.8, Ar*C*O); ^{31}P NMR (162 MHz; $CDCl_3$) δ_P 14.17; *m/z* (ESI^+) 376 (8%), 375.1356 (95, $M+H^+$. $C_{20}H_{23}O_5P$ requires 375.1368).

Phosphonic acid, *P*-[(1*E*)-1-*o*-anisyl-2-phenylethyl] diethyl ester 11b

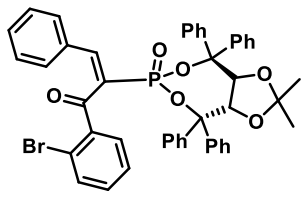


Prepared according to the general procedure **A** using benzaldehyde (0.20 mL, 1.92 mmol), a solution of β-ketophosphonate **9** (0.50 g, 1.75 mmol) in dry toluene (30 mL) and piperidine (0.03 mL, 0.35 mmol). The material obtained was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.41) to afford the title compound as a yellow liquid (0.56 g, 86% yield); ν_{max} (ATR / cm^{-1}) 3462, 2983, 1665, 1593, 1019; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.26 (6H, t, *J* 7.1, 2 x C*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 4.10 - 4.19 (4H, m, 2 x OCH_2), 6.84 – 6.92 (2H, m, 2 x ArC*H*), 7.18 -7.23 (3H, m, 3 x ArC*H*), 7.32 – 7.34 (2H, m, 2 x ArC*H*), 7.39 - 7.43 (1H, m, ArC*H*), 7.67 (1H, d, J_{PH} 25.6, C=C*H*), 7.74 – 7.78 (1H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 16.1 (d, J_{CP} 6.8, 2 x *C*H_3), 55.6 (O*C*H_3), 62.5 (d, *J* 5.6, 2 x O*C*H_2), 111.7 (Ar*C*H), 120.2 (Ar*C*H), 126.8 (d, J_{CP} 2.5, ArC), 128.3 (3 x Ar*C*H), 129.7 (Ar*C*H), 129.8 (Ar*C*H), 132.0 (Ar*C*H), 134.0 (d, J_{CP} 21.5, C=*C*P), 134.6 (Ar*C*H), 134.7 (Ar*C*), 145.5 (C=*C*H, d, J_{CP} 6.3), 159.5 (Ar*C*), 194.4 (d, *J* 9.3, Ar*C*O); ^{31}P NMR (162 MHz; $CDCl_3$) δ_P 14.40; *m/z* (ESI^+) 459 (5%), 397.1 (95, M - $2H^+$), 375.1356 (50, M+H^+. $C_{20}H_{24}O_5P$ requires 375. 1367), 227.6 (30).

(*E*)-Dimethyl (3-(2-bromophenyl)-3-oxo-1-phenylprop-1-en-1-yl) phosphonate 12b

Prepared according to the general procedure **A** using benzaldehyde (0.70 mL, 6.40 mmol), a solution of **10** (1.80 g, 5.80 mmol) in dry toluene (100 mL) and piperidine (0.11 mL, 1.20 mmol). The residue was purified by flash column chromatography on silica gel eluting with EtOAc (R_f = 0.29) to afford the title compound as a yellow liquid (0.86 g, 38 %); ν_{max} (ATR /cm^{-1}) 2953, 2851, 1668, 1601, 1574; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 3.86 (6H, d, J_{HP} 11.3, 2 × OC*H*$_3$), 7.18 -7.20 (2H, m, 2 × ArC*H*), 7.24 -7.26 (3H, m, 3 × ArC*H*), 7.32 -7.34 (2H, m, 2 × ArC*H*), 7.56 - 7.58 (1H, m, ArC*H*), 7.65 -7.67 (1H, m, ArC*H*), 7.97 (1H, d, J_{HP} 24.9, PC=C*H*). ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 53.4 (2 × *C*H_3, d, J_{CP} 5.9), 122.1 (Ar*C*H), 127.0 (Ar*C*H), 128.5 (2 × Ar*C*H), 129.7 (2 × Ar*C*H), 130.1 (Ar*C*H), 130.5 (Ar*C*), 131.3 (Ar*C*), 132.0 (Ar*C*H), 133.4 (HC=*C*P, d J_{cp} 21.0), 134.8 (Ar*C*H), 136.8 (d, J_{CP} 3.1, ArC), 149.9 (H*C*=CP, d J_{cp} 6.5), 194.0 (Ar*C*O, d, J_{cp} 8.7); ^{31}P NMR ($CDCl_3$, 162 MHz); δ 16.9; *m/z* (ESI^+) 813 (95%), 481 (2), 419 (75%), 397.0024 (80, M+H^+. $C_{17}H_{17}{}^{81}BrO_4P$ requires 397.0032), 239 (30).

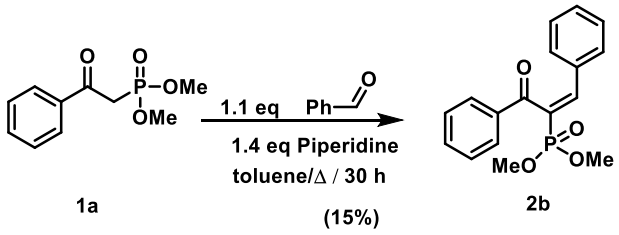
(*E*)-2'-(3a*R*,8a*R*)-2,2-Dimethyl-6-oxido-4,4,8,8-tetraphenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-[3-(2-bromophenyl)-3-oxo-1-phenylprop-1-ene-1-yl) phosphonate 14b



Prepared according to the upgraded (Table 2, entry 3) general procedure **A** using benzaldehyde (0.20 mL, 2.32 mmol), a solution of β-ketophosphonate **13** (1.50 g, 2.11 mmol) in dry toluene (100 mL) and piperidine (0.04 mL, 0.42 mmol). The residue was purified by flash column chromatography on silica gel first eluting with hexane/EtOAc (4:1), followed by EtOAc (100%) (R_f = 0.25) to give the title compound as a yellow solid (2.01 g, 95% yield) mp 165.7 °C - 167.5 °C; $[\alpha]_D^{25}$ -16 (c 1 in $CHCl_3$); ν_{max} (ATR)/cm^{-1}: 3061, 2991, 1669, 1602, 1448; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.49 (3H, s, C*H*$_3$), 0.90 (3H, s, C*H*$_3$), 5.28 (1H, d, *J* 8.0, C*H*-O), 5.61 (1H, d, *J* 8.0, C*H*-O), 7.00 - 7.07 (1H, m, ArC*H*), 7.10 - 7.25 (9H, m, 9 × ArC*H*), 7.26- 7.40 (12H, m, 12 × ArC*H*), 7.44 - 7.51 (2H, m, 2 × ArC*H*), 7.31 - 7.35 (5H, m, 5 × ArC*H*), 8.00 (1H, d, J_{HP} 27.4, PC=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 26.2 (s, *C*H$_3$), 27.1 (s, *C*H$_3$), 79.2 (d, J_{CP} 2.7, *C*H-O), 79.5 (d, J_{CP} 2.7, *C*H-O), 90.6 (d, J_{CP} 5.4, *C*-O-P), 91.3 (d, J_{CP} 7.3, C-O-P), 113.6 [*C*(CH$_3$)$_2$], 126.5 (Ar*C*H), 126.8 (d, *J* 3.6, 2 × Ar*C*H), 127.2 (2 × Ar*C*H), 127.3 (2 × Ar*C*H), 127.4 (2 × Ar*C*H), 127.5 (Ar*C*H), 127.7 (4 × Ar*C*H), 128.1 (d, *J* 8.7, Ar*C*H), 128.4 (2 × Ar*C*H), 128.8 (Ar*C*H), 129.0 (2 × Ar*C*H), 129.8 (3 × Ar*C*H), 130.0 (2 × Ar*C*H), 130.4 (Ar*C*H), 132.5 (Ar*C*H), 132.8 (Ar*C*H), 133.5 (HC=*C*P, d, J_{cp} 21.8), 134.6 (Ar*C*H), 137.0 (d, J_{CP} 4.1, Ar*C*), 139.7 (Ar*C*), 143.6 (d, J_{CP} 7.6, Ar*C*), 150.0 (d, J_{cp} 7.9, (H*C*=CP), 143.7 (Ar*C*), 144 (Ar*C*), 149 (Ar*C*), 150 (Ar*C*), 193.1 (d, J_{CP} 8.4, *C*=O); ^{31}P NMR (162 MHz, $CDCl_3$) δ 8.00; *m/z* (TOF MS ES$^+$) 838 (5), 822 (7, ^{81}Br) 819.1467 (100%, M+Na$^+$. $C_{46}H_{38}O_6Na\,^{79}BrP$ requires 819.1487), 802 (32), 789 (10).

Results and Discussions

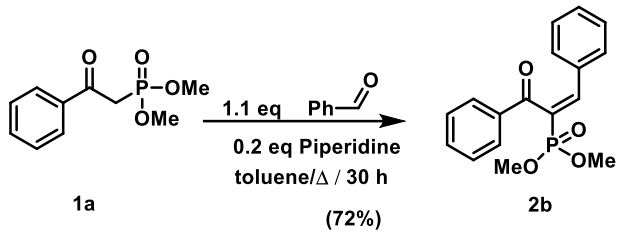
Synthesis of the model chalcone



Scheme 2: Synthesis of chalcones [8].

Following a standard literature protocol [8], the *β*-ketophosphonate chalcone **2b** was prepared under Dean-Stark conditions from a mixture of benzaldehyde, piperidine and previously synthesised **1a** [9]. The product **2b** was isolated in 15% yield after flash column chromatography (Scheme 2). Altering reaction conditions in subsequent reactions provided better results and were used as a benchmark. A seven-fold catalyst loading reduction from 1.4 to 0.2 equivalents proved to be the best reaction condition that

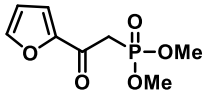
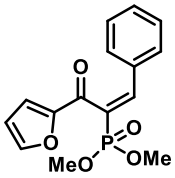
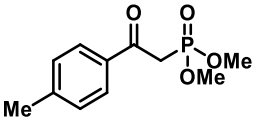
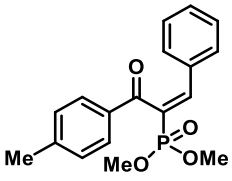
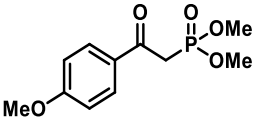
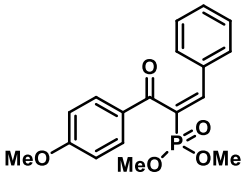
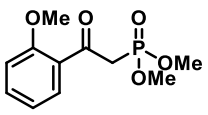
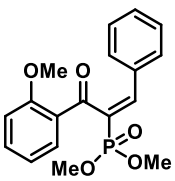
eventually led to a product yield of 72% of **2b** after purification (Scheme 3).

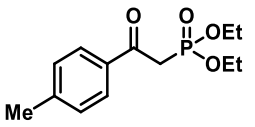
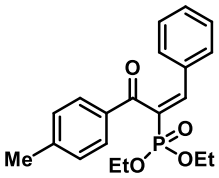
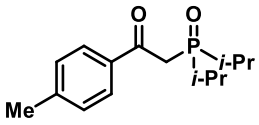
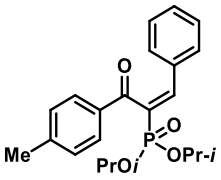
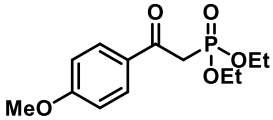
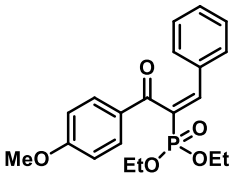
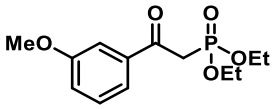
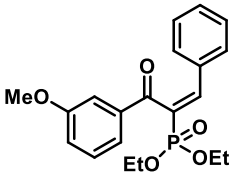
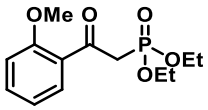
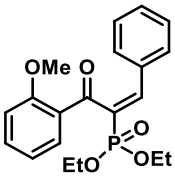
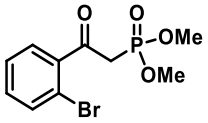
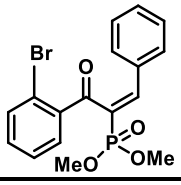


Scheme 3: Optimisation of the Knoevenagel synthesis of phosphonate chalcones

This was a remarkable breakthrough after a series of trials. [9]. Hence, this new set of Dean-Stark conditions with 0.2 equivalents of the base catalyst and 1.1 equivalents of benzaldehyde, in toluene, was regarded as optimal. To test the efficacy and scope of the amended conditions, a variety of *β*-keto phosphonates were examined under the new set of optimum conditions, which led to the synthesis of an array of phosphonate chalcones with better yields up to 90% (Table 1, entries 1-10).

Table 1: Knoevenagel condensation of β-keto phosphonates 1-10

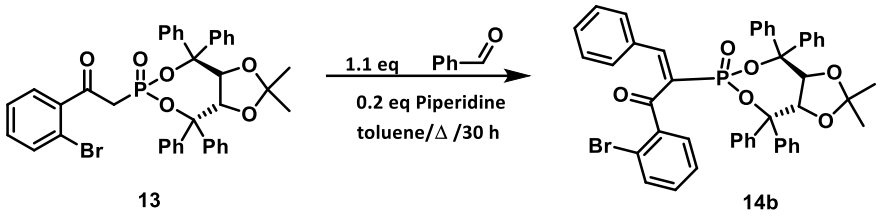
Entry	Substrate	Product	Yield (%)	Product #
1			**55**	**3b**
2			**89**	**4b**
3			**81**	**5b**
4			**51**	**6b**

5			**83**	**7b**
6			**90**	**8b**
7 8			**81**	**9b**
9			**85**	**10b**
			**86**	**11b**
10			**81**	**12b**

Conditions: 1.1 eq of benzaldehyde, and 0.2eq of piperidine were added to 1.0 eq of corresponding β-ketophosphonate in dry toluene under N_2 atmosphere and heated under Dean-Stark conditions for 30 h.

The identity of **2b** [9] with a doublet at δ 7.86 and an integral of a single proton typical of a proton β to phosphonate and $^3J_{HP}$ = 26.0 Hz was assigned an *E* configuration [9] after due comparisons with the stereochemistry of similar compounds [7] based on ^{1}H NMR analysis and interpretations. Expanding on the scope of the reaction following success with various achiral substrates of differing electronic

properties, the procedure was further explored using a previously prepared enantioenriched β-keto phosphonate **13**[9] (Scheme 4).



Scheme 4. Synthesis of TADDOL-derived bromo chalcone

However, when subjected to the established optimal conditions, initial attempts yielded only 12% product after 30 hours, with 65% of the starting material recovered, indicating the need for a longer reaction time. Extending the reaction to 48 hours improved the yield to 20%, with 50% unreacted starting material remaining. A third trial over five days led to complete consumption of the starting material and an excellent 95% yield of the *E* isomer after purification (Table 2, entry 3).

Table 2. Optimisation of TADDOL-derived bromo chalcone

Entry	Time (hrs)	% yield	SM (%)
1	30	12	65
2	48	20	50
3	120	95	-

Conditions: 1.1 eq of benzaldehyde, 0.2eq of piperidine was added to 1.0 eq of corresponding β-ketophosphonate in dry toluene under N_2 atmosphere and heated under Dean-Stark conditions for the stipulated time.

Conclusion

This study employed the Knoevenagel condensation reaction due to its efficiency in synthesising β-keto phosphonate chalcones, operational simplicity, and good yields. Optimised reaction conditions led to improved product yields of up to 95% and the synthesis of twelve (12) phosphonate-based chalcones, nine (9) of which are novel. These compounds serve as valuable intermediates for further synthetic elaboration or as templates for novel drug leads, effectively bridging the gap between natural product inspiration and synthetic innovation.

Acknowledgment

The Federal Government of Nigeria generously funded a significant portion of this research through the Tertiary Education Trust Fund (TETFund).

Declaration of Competing Interest

The author declares no competing interest but wishes to attest that this manuscript is part of a dissertation [9] work carried out in the Department of Chemistry, University of Sheffield, UK between January 2017 and November 2022. It is original except where acknowledged by reference.

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