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Triphenylphosphine-catalysed one-pot synthesis of γ-butyrolactone derivatives and highly substituted enones via reaction of dimethyl acetylenedicarboxylate and aryl aldehydes

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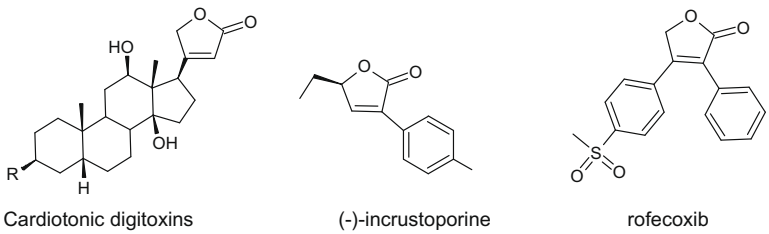
ABSTRACT

The reaction between dimethyl acetylenedicarboxylate and various aryl aldehydes in the presence of triphenylphosphine leads to unsaturated γ-butyrolactone derivatives and highly substituted enones in fairly good yields at room temperature.

Unsaturated γ-butyrolactones or butenolides are important structural units in natural products and are intermediates in organic synthesis.[1–6] There has been considerable effort on the synthesis of these compounds[7–10] due to the discovery of many naturally occurring cytotoxic or antitumour agents containing this structural unit. They are typical products of a polyketide biosynthesis pathway. Examples include the cardiotonic digitoxins from *Digitalis* sp.[11] and the antifungal agents (−)-incrustoporine[12] and rofecoxib (Scheme 1) for the treatment of rheumatoid arthritis.[13] This ring system has been the objective of synthetic projects in several laboratories.[1–6]

Multicomponent reactions (MCRs) have emerged as a highly valuable synthetic tool in the context of modern drug discovery.[14–17] In continuation of our general interest in MCRs involving zwitterionic species, we envisaged the possibility of trapping 1,3-dipoles with aryl aldehydes. In the event we did not observe the expected MCR product, instead the reaction afforded the corresponding unsaturated γ-butyrolactones and highly substituted enones with Ph_3P playing a mediator role in the formation of a carbon–carbon bond between the aldehyde and DMAD.[18,19]

The one-pot three-component reactions of aryl aldehydes **1** with dimethyl acetylenedicarboxylate in the presence of Ph_3P proceeded spontaneously at room temperature in CH_2Cl_2 and were complete within 24 h. The ^1H and ^{13}C NMR spectra of the reaction mixtures clearly indicated the presence of two products, namely, the unsaturated γ-butyrolactone **2** and highly substituted enone **3** (Scheme 2). These products were separated by column chromatography and identified as **2a–2g** and **3a–3g** based on their



Scheme 1. Examples of pharmaceutically relevant butenolides.

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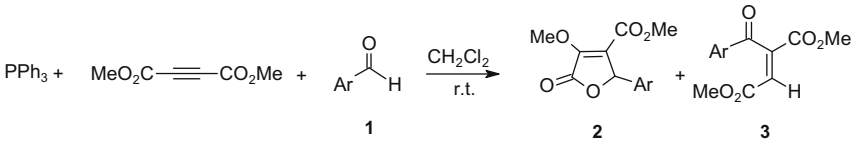


Aldehyde	Ar	Yield (%) of **2**	Yield (%) of **3**
1a	4-Nitrophenyl	48	45
1b	4-Chlorophenyl	52	40
1c	4-Bromophenyl	50	38
1d	4-Methylphenyl	70	25
1e	4-Methoxyphenyl	75	20
1f	3-Nitrophenyl	55	35
1g	2,6-Dichlorophenyl	52	40

Scheme 2.

elemental analyses and their IR, ^{1}H and ^{13}C NMR spectral data. The mass spectra of the products displayed molecular ion peaks at appropriate *m*/*z* values.

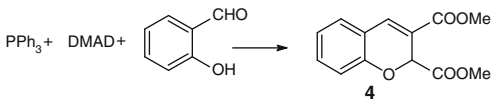
In terms of the amount of Ph_3P required for the reaction of aryl aldehydes **1** and DMAD to afford compounds **2** and **3**, the best results were obtained using a stoichiometric amount (1 mmol). In the absence of Ph_3P, no products formed, whilst in the presence of 10–20 mol % of Ph_3P, the products were obtained in low yields (<30%).

The ^{1}H NMR spectrum of **2a** exhibited two singlets identified as methoxy groups at δ 3.69 and δ 4.33 along with a sharp singlet for the methine proton at δ 6.07. The ^{13}C NMR spectrum of **2a** showed 11 distinct resonances in agreement with the structure of methyl 2-(4-nitrophenyl)-2,5-dihydro-4-methoxy-5-oxofuran-3-carboxylate.[20] The ^{1}H NMR spectrum of **3a** showed the presence of two singlets due to the methoxy groups at δ 3.66 and δ 3.79 along with a sharp singlet for the olefinic proton at δ 7.13. The ^{13}C NMR spectrum of *E*-**3a** showed 11 distinct resonances in agreement with the proposed structure. The ^{1}H and ^{13}C NMR spectra of **2b**–**2g** were similar to those of **2a**, and the spectra of **3b**–**3g** were similar to those of **3a** except for the substituted phenyl ring, which exhibited characteristic resonances with appropriate chemical shifts.

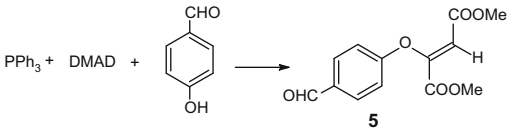
In the reaction of Ph_3P and DMAD with *o*-hydroxybenzaldehyde, the initially formed phosphorane ylide underwent addition–cyclisation as a result of an intramolecular Wittig reaction.[21] Thus 2*H*-chromene **4** was formed in excellent yield (85%) (Scheme 3).

The addition of *p*-hydroxybenzaldehyde to DMAD in the presence of Ph_3P leads to product **5** in 60% yield (Scheme 4).

In conclusion, the three-component reaction of aryl aldehydes with dimethyl acetylenedicarboxylate in the presence of Ph_3P provides a simple entry to the synthesis of unsaturated γ-butyrolactone derivatives and highly substituted enone compounds of potential synthetic interest and possible candidates for Diels–Alder reactions. The present procedure carries the advantage that not only the reaction is performed under neutral conditions but also the reagents can be mixed without any activation or modification.



Scheme 3.



Scheme 4.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.004.

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20. *Typical procedure for the preparation of methyl 2,5-dihydro-4-methoxy-2-(4-nitrophenyl)-5-oxofuran-3-carboxylate* (**2a**) *and dimethyl 2-(4-nitrobenzoyl)-butenedioate* (**3a**). To a stirred solution of 4-nitrobenzaldehyde (0.151 g, 1 mmol) and triphenylphosphine (0.262 g, 1 mmol) in CH_2Cl_2 (10 ml) was added dimethyl acetylendicarboxylate (0.142 g, 1 mmol) in CH_2Cl_2 (2 ml), at room temperature, over 10 min via a syringe. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (Merck silica gel 60, 70–230 mesh) using hexane/EtOAc (8:2) as eluent. The solvent was evaporated to afford the products **2a** and **3a**.
Methyl 2,5-dihydro-4-methoxy-2-(4-nitrophenyl)-5-oxofuran-3-carboxylate (**2a**). Yellow oil, (0.140 g, 48%). IR (KBr) (ν_{max}/cm^{-1}): 1775 and 1682 (C=O), 1637

(C=C), 1214 (C–O). ^{1}H NMR ($CDCl_3$): δ = 3.69 (3H, s, OMe), 4.33 (3H, s, CO_2Me), 6.07 (1H, s, CH), 7.50 (2H, d, $^3J_{HH}$ = 8.2 Hz, CH_{arom}), 8.23 (2H, d, $^3J_{HH}$ = 8.2 Hz, CH_{arom}). ^{13}C NMR ($CDCl_3$): δ = 52.52 and 60.35 ($2OCH_3$), 78.28 (CH), 121.62 (*C*=C–OMe), 123.97 and 128.39 ($4CH_{arom}$), 130.05 and 148.33 ($2C_{arom}$), 148.53 (C=*C*–OMe), 161.11 and 166.00 (2C=O). MS (*m*/*z*, %): 293 (M^+, 21), 278 (3), 264 (26), 234 (37), 150 (41), 143 (100), 115 (25), 83 (15), 59 (22). Anal. Calcd for $C_{13}H_{11}NO_7$ (293.23): C, 53.25; H, 3.78; N, 4.78. Found: C, 53.3; H, 3.8; N, 4.8.

Dimethyl 2-(4-nitrobenzoyl)-butenedioate (**3a**). Red oil, (0.132 g, 45%). IR (KBr) (ν_{max}/cm^{-1}): 1727 and 1682 (C=O), 1437 (C=C), 1214 (C–O). ^{1}H NMR ($CDCl_3$): δ = 3.66 and 3.79 (6H, s, 2OMe), 7.13 (1H, s, C=CH), 8.04 (2H, d, $^3J_{HH}$ = 8.0 Hz, CH_{arom}), 8.32 (2H, d, $^3J_{HH}$ = 8.0 Hz, CH_{arom}). ^{13}C NMR ($CDCl_3$): δ = 52.79 and 53.50 ($2OCH_3$), 131.39 (C=*C*H), 124.10, 129.58, 129.92, 150.63 ($6C_{arom}$), 144.42 (*C*=CH), 162.98 and 164.20 (2C=O ester), 190.79 (C=O). MS (*m*/*z*, %): 293 (M^+, 16), 278 (10), 262 (9), 150 (100), 104 (22), 92 (12), 76 (20), 59 (13). Anal. Calcd for $C_{13}H_{11}NO_7$ (293.23): C, 53.25; H, 3.78; N, 4.78. Found: C, 53.3; H, 3.7; N, 4.8.

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