Triphenylphosphine promoted addition of acetylenic esters to benzofuran-2,3-dione: one-pot synthesis of Novel γ-Spirolactones

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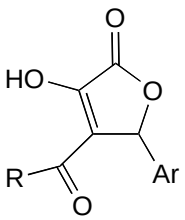
Abstract

The reaction of the zwitterionic intermediates generated from dialkyl acetylene dicarboxylates and triphenylphosphine with benzofuran-2,3-diones provides a one-pot route to new highly functionalized γ-spirolactones in good yield.

Keywords: γ-Spirolactones, benzofuran-2,3-diones, acetylenic esters, triphenylphosphine

Introduction

The 2,5-dihydrofuran-2-one moiety is an integral part of many natural and unnatural products. Recently, it has been reported that derivatives of 2,5-dihydrofuran-2-one show biological activity.[1–4] For example 2,5-dihydrofuran-2-one derivatives **1** and **2** have antimicrobial activities.[5]



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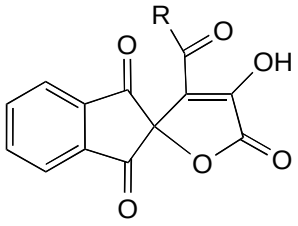
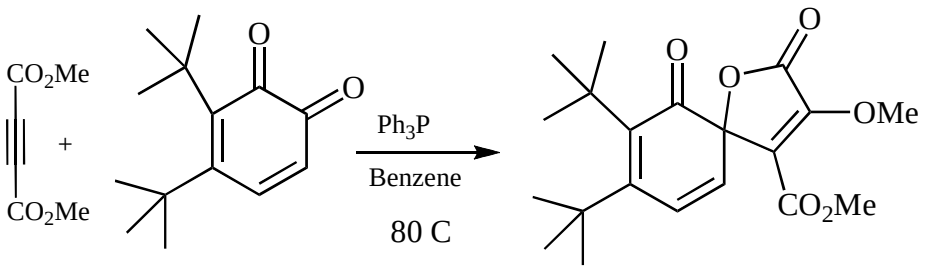


2

Recently Chatani and co-workers reported that the reaction of benzofuran-2,3-dione derivatives with CO and alkynes via a ruthenium-catalyzed carbonylative [2+2+1] cycloaddition provides a general route to γ–spiro-lactones.[6]

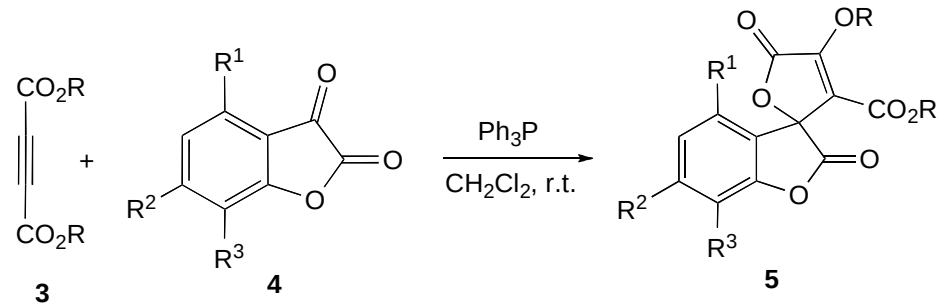
Multi-Component reactions (MCRs), in which several different starting materials can be combined in one reaction to give a highly complex product, are finding increasing use in modern organic chemistry.[7-9] They offer significant advantages over conventional linear syntheses by reducing time and by saving money, energy, and raw materials, thus providing both economic and environmental benefits. At the same time, diversity can be achieved from building up libraries by simply varying each component.[10-15]



Scheme 1

The early work of Nair and coworkers showed that the zwitterionic intermediates formed between dialkyl acetylenedicarboxylates and Ph_3P react with activated dicarbonyl compounds to afford highly functionalized γ-butyrolactones (Scheme 1).[16-18] We have also demonstrated that the activated carbonyl of phenyl glyoxalate and isatin derivatives can take part in such reactions successfully, thus constituting a ready synthesis of heterocyclic compounds.[19-20]

We now wish to report a simple one-pot three-component reaction between dialkyl acetylenedicarboxylates, Ph_3P, and benzofuran-2,3-dione derivatives leading to methyl 4'-methoxy-spiro[benzofuran-3,2'-furan]-2,5'-dione-3'-carboxylate derivatives as γ-spirolactone systems (Scheme 2 and Table 1).



Scheme 2

Table 1. The reaction of benzofuran-2,3-dione **4** with dialkyl acetylenedicarboxylate **3** in the presence of Ph_3P

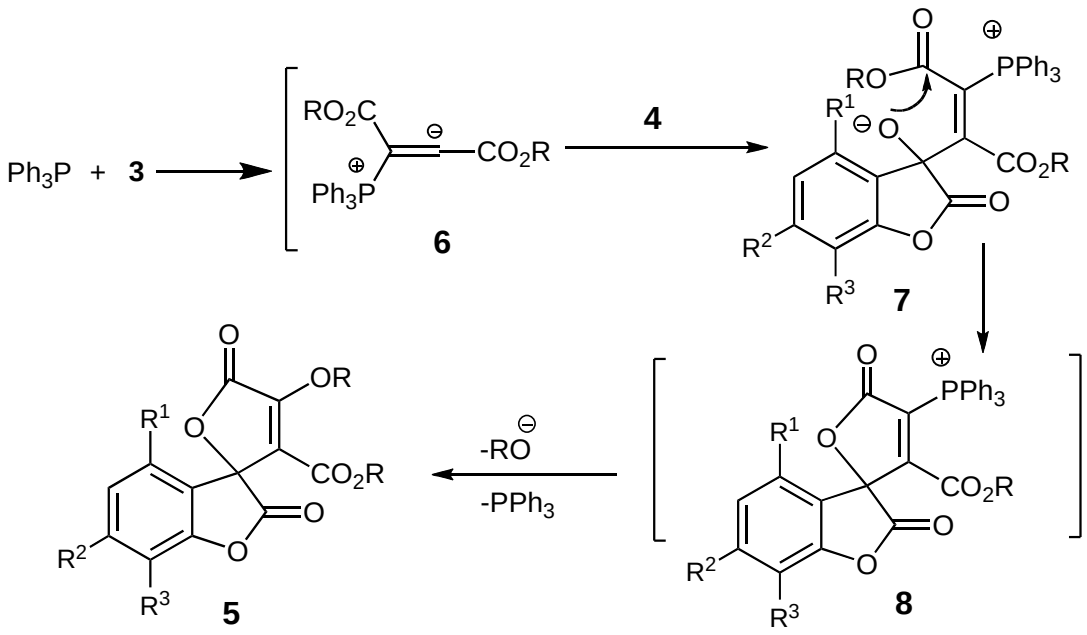
Product	R^1	R^2	R^3	R	%Yield of **5**
5a	Me	H	Me	Me	50
5b	Me	H	Me	Et	55
5c	Me	Me	H	Me	60
5d	Me	Me	H	Et	75
5e	Me	Me	H	$CHMe_2$	85
5f	Me	Me	Me	Et	44

Results and Discussion

In this type of two-component reaction catalyzed by nucleophiles, triphenylphosphine (Ph_3P) has been the most often studied nucleophilic species. As early as 1961, Tebby observed that the addition of Ph_3P to various activated alkynes like DMAD, dicyanoacetylene, and dibenzoylacetylene generates zwitterionic intermediates.[21,22]

The reactions were initiated by the addition of a solution of dimethyl acetylenedicarboxylate (**3**) (1.1 equiv in 3 ml CH_2Cl_2) to a solution of benzofuran-2,3-dione derivatives **4** (1 equiv.) and Ph_3P in CH_2Cl_2 (5 ml) at –10 °C. The mixture was stirred for 1 h. Distillation of the solvent in vacuum followed by addition of cold Et_2O or EtOH led to a crystalline product **5** in 45-85% yield (Scheme 2).

The products **5a-f** were characterized on the basis of their analytical and spectroscopic data. For example, the IR spectrum of **5a** displayed characteristic ester C=O absorptions at 1760, 1750 and 1720 cm^{-1} respectively. In the ^1H NMR spectrum, the two aromatic Me groups appeared as sharp singlets at δ 2.37 and δ 2.65 and the MeO groups resonated at δ 3.89 and δ 4.27. The ^{13}C NMR spectrum of **5a** displayed sixteen distinct signals in agreement with the proposed structure. Partial assignment of these resonances is given in the Experimental Section. The characteristic signal of the spiro carbon atom was discernable at 89.36. Finally, the γ-spirolactone formation can be rationalized as shown in Scheme 3.



Scheme 3

Conclusions

In summary, we have succeeded in synthesizing γ-spirolactones of potential synthetic interest via a one-pot reaction between dialkyl acetylenedicarboxylates and benzofuran-2,3-dione in the presence of triphenylphosphine. High yields of the products, relatively short reaction times, and use of simple starting materials are the main advantages of this method. The reactions were performed under neutral and mild conditions, and the starting materials and reagents can be reacted without any activation or modification.

Experimental Section

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were measured on a Perkin-Elmer 783 Infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz. Mass spectra were recorded on a SHIMADZU GCMS-QP5050 mass spectrometer operating at an ionization potential of 70 eV. Triphenylphosphine, and acetylenic esters **3** were obtained from Fluka (Buchs, Switzerland) and were used without purification.

General procedure for the preparation of alkyl-4'-alkoxy-spiro[benzofuran-3,2'-furan]-2,5'dione-3'-carboxylate derivatives 5

To a stirred solution of 3,5-dimethyl benzofuran-2,3-dione derivatives **4** (0.220 g, 1.0 mmol) and triphenylphosphine (0.262 g, 1 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise a solution of dimethyl acetylenedicarboxylate **3** (0.141g, 1 mmol) in dry CH_2Cl_2 (2 ml) at –10 °C over 10 min via a syringe, and the reaction mixture was then allowed to warm up to room temperature and stirred for about 20 min. On completion of the reaction, solvent was removed under vacuum and to the residues, cold diethyl ether (5 ml) for **5a** and cold ethanol (5 ml) for **5b-5f**, were added to produce pure solid products. Then, the resulting products were filtered off to afford the spirolactone **5**.

Methyl-4,7-dimethyl-4'-methoxy-spiro[benzofuran-3,2'-furan]-2,5'dione-3'-carboxylate (5a). Yield: 0.159 g (50 %), mp 202-204 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37, 2.65 (6H, 2 s, 2 CH_3), 3.89, 4.27 (6H, 2 s, 2 OMe), 6.93 (1H, d, $^3J_{HH}$ = 7.6 Hz, H5), 7.13 (1H, d, $^3J_{HH}$ = 7.6 Hz, H6), ^{13}C NMR (75.46 MHz, $CDCl_3$); δ = 15.7 and 20.6 (2 CH_3), 51.8 (OMe), 59.2 (OMe), 89.4 (C_{Spiro}), 108.9 (C3a), 110.2 (C7), 123.8 (C5), 125.9 (C6), 130.1 (C4), 131.0 (C7a), 150.3 (C4'), 151.0 (C3'), 155.2, 161.7, 163.1 (3 C=O); MS, *m/z* (%): 302 (M^+-1-Me, 100), 287 (M^+-OMe, 97), 259 (M^+-CO_2Me, 13), 227 (M^++1-CO_2Me-OMe, 33), 199 (M^++1-2CO_2Me, 27), 159 ($C_{10}H_{10}O_2^+$, 4), 172 (M^+-OMe-CO_2Me-2Me-CO, 12), 91 ($C_7H_8^+$,18), 59 (CO_2Me^+, 11); IR (KBr) (ν_{max}, cm^{-1}): 3010 (C-H_{St}), 1760, 1750, 1720 (3 C=O), 1580, 1480 (C=C) (arom); Anal. calc. for $C_{16}H_{14}O_7$ (318.28): C 60.38, H 4.43% found: C 60.0, H 4.3 %.

Ethyl-4,7-dimethyl-4'-ethoxy-spiro[benzofuran-3,2'-furan]-2,5'dione-3'-carboxylate (5b). Yield: 0.191 g (55 %), mp 119-120 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (3H, t, $^3J_{HH}$ = 7.1Hz, CH_3, of ester), 1.52 (3H, t, $^3J_{HH}$ = 7.1Hz, CH_3, of ether), 2.37, 2.62 (6H, 2 s, 2 Me), 4.34 (2H, q, $^3J_{HH}$ = 7.1 Hz, CH_2, of ester), 4.57 (2H, q, $^3J_{HH}$ = 7.1 Hz, CH_2, of ether), 6.92 (1H, d, $^3J_{HH}$ = 7.6 Hz, H5), 7.12 (1H, d, $^3J_{HH}$ = 7.6 Hz, H6); ^{13}C NMR (125.75 MHz, $CDCl_3$); δ = 14.2 and 15.0 (2 CH_3), 15.8 and 20.7 (2 CH_3), 60.8, 69. 6 (2 OCH_2), 91.9 (C_{Spiro}), 109.0 (C3a) 110.5 (C6) 124.0 (C7), 125.9 (C4), 130.2 (C5), 131.0 (C7a), 150.5 (C4'), 151.3(C3'), 155.4, 161.5, 162.7 (3 C=O); MS, *m/z* (%): 330 (M^+-1-Me, 20), 301 (M^+-OCH_2CH_3, 9), 256 (M^+-1-OCH_2CH_3-CH_2CH_3-CH_3, 100), 201 (M^+-OCH_2CH_3-CH_2CH_3-CH_3-C-CO_2, 11), 91 ($C_7H_8^+$,15); IR (KBr) (ν_{max}, cm^{-1}): 3008 (C-H_{St}), 1750, 1745, 1700 (3 C=O), 1550, 1435 (C=C) (arom); Anal. calc. for $C_{18}H_{18}O_7$ (346.34): C 62.42, H 5.24% found: C 62.6, H 5.1 %.

Methyl-4,6-dimethyl-4'-methoxy-spiro[benzofuran-3,2'-furan]-2,5'dione-3'-carboxylate (5c). Yied: 0.191 g (60 %), mp 198-199 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.27, 2.52 (6H, 2 s, 2 CH_3), 3.81, 4.19 (6H, 2 s, 2 OMe), 6.75 (1H, s, H5), 6.79 (1H, s, H7), ^{13}C NMR (125.75 MHz, $CDCl_3$); δ = 20.6 and 21.4 (2 CH_3), 51.8 (OMe), 59.2 (OMe), 89.3 (C_{Spiro}), 107.9 (C3a), 108.1 (C6), 114.7 (C7), 127.7 (C5), 132.42 (C4), 140.7 (C7a), 150.2 (C4'), 152.9 (C3'), 155.4, 161.6, 162.9 (3 C=O); MS, *m/z* (%): 302 (M^+-1-Me, 73), 287 (M^+-OMe, 100), 227 (M^++1-CO_2Me-OMe, 48), 199 (M^++1-2CO_2Me, 36), 172 (M^+-OMe-

CO_2Me-2Me-CO, 13), 91 ($C_7H_8^+$,54), 59(CO_2Me^+, 38); IR (KBr) (ν_{max}, cm^{-1}): 3010 (C-H_{St}), 1748, 1735, 1710 (3 C=O), 1550, 1430 (C=C) (arom); Anal. calc. for $C_{16}H_{14}O_7$ (318.28): C 60.38, H 4.43 % found: C 60.5, H 4.5 %.

Ethyl-4,6-dimethyl-4'-ethoxy-spiro[benzofuran-3,2'-furan]-2,5'dione-3'-carboxylate (5d). Yield: 0.259 g (75 %), mp 113-114 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3, of ester), 1.51 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3, of ether), 2.35, 2.64 (6H, 2 s, 2 Me), 4.35 (2H, q, $^3J_{HH}$ = 7.1 Hz, CH_2, of ester), 4.56 (2H, q, $^3J_{HH}$ = 7.0 Hz, CH_2, of ether), 6.87 (1H, s, H5), 7.00 (1H, s, H7); ^{13}C NMR (125.75 MHz, $CDCl_3$); δ = 14.2 and 14.9 (2 CH_3), 20.7 and 21.5 (2 CH_3), 60.80, 69.7 (2 OCH_2), 91.0 (C_{Spiro}), 108.3 (C3a), 108.4 (C6), 127.7 (C7), 131.8 (C4), 131.9 (C5), 132.1 (C7a), 150.3 (C3'), 150.6 (C4'), 155.7, 161.5, 169.6 (3 C=O); MS, *m/z* (%): 330 (M^+-1-Me, 10), 301 (M^+-OCH_2CH_3, 6), 256 (M^+-1-OCH_2CH_3-CH_2CH_3-CH_3, 52), 201 (M^+-OCH_2CH_3-CH_2CH_3-CH_3-C-CO_2, 28), 91 ($C_7H_8^+$,14), 59 (CO_2Me^+, 6); IR (KBr) (ν_{max}, cm^{-1}): 3020 (C-HST), 1760, 1745, 1705 (3 C=O), 1595, 1440 (C=C) (arom); Anal. calc. for $C_{18}H_{18}O_7$ (346.34): C 62.42, H 5.24% found: C 62.2, H 5.3 %.

Isopropyl-4,6-dimethyl-4'-isopropoxy-spiro[benzofuran-3,2'-furan]-2,5'dione-3'-carboxylate (5e). Yield: 0.318 g (85 %), mp 196-198 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (6H, d, $^3J_{HH}$ = 6.3 Hz, CH_3, of ester), 1.43 (6H, d, $^3J_{HH}$ = 6.2 Hz, CH_3, of ether) 2.27, 2.54 (6H, 2 s, 2 CH_3), 4.93 (1H, m, $^3J_{HH}$ = 6.2 Hz CH of ester), 5.17 (1H, m, $^3J_{HH}$ = 6.3 Hz CH of ether) 6.77 (1H, s, H5), 6.79 (1H, s, H7); ^{13}C NMR (125.75 MHz, $CDCl_3$); δ = 20.70 and 21.5 (2 CH_3), 21.9 and 22.4 (CH_3, of ester and ether), 68.3 (OCH ester), 79.2 (OCH ether) 93.2 (C_{Spiro}), 108.1 (C3a), 108.2 (C6), 114.8 (C7), 127.5 (C5), 132.4 (C4), 140.6 (C7a), 150.7 (C4'), 153.1 (C3'), 155.6, 160.9, 161.1 (3 C=O); MS, *m/z* (%): 358 (M^+-1-Me, 4), 316 (M^++1-O*i*-Pr, 8), 274 (M^+- C-CO_2*i*-Pr, 10), 256 (M^+-1-CO_2*i*-Pr-2Me, 100), 201 (M^++1-CO_2*i*-pPr-O*i*-Pr-CO, 5), 91 ($C_7H_8^+$,18.5); IR (KBr) (ν_{max}, cm-1): 3003 (C-H_{St}), 1755, 1745, 1710 (3 C=O), 1590, 1470 (C=C) (arom); Anal. calc. for $C_{16}H_{14}O_7$ (374.39): C 64.16, H 5.92% found: C 64.5, H 6.0%.

Ethyl-4,6,7-trimethyl-4'-ethoxy-spiro[benzofuran-3,2'-furan]-2,5'dione-3'-carboxylate (5f). Yield: 0.158 g (44%), mp 161-162 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3, of ester), 1.51 (3H, t, $^3J_{HH}$ = 7.1 Hz, CH_3, of ether), 2.26, 2.26 (6H, 2 s, 2 CH_3), 2.56 (3H, s, CH_3), 4.33 (2H, q, $^3J_{HH}$ = 7.1 Hz, CH_2, of ester), 4.56 (2H, q, $^3J_{HH}$ = 7.0 Hz, CH_2, of ether), 6.81 (1H, s, H5); ^{13}C NMR (125.75 MHz, $CDCl_3$); δ = 11. 7, 14.19 15.0, (3 CH_3), 20.1, 20.5, (2 Me), 60.8, 69.5 (2 OCH_2), 90.7 (C_{Spiro}), 107.9 (C3a), 108.2 (C7), 122.2 (C6), 128.0 (C5), 129.1 (C4), 139.2 (C7a), 150.9 (C4'), 151.2 (C3'), 155.6, 161.6, 162.6 (3 C=O); MS, *m/z* (%): 344 (M^+-1 -Me, 22), 315 (M^+-OCH_2CH_3, 16), 299 (M^+- OCH_2CH_3-CH_3, 4), 270 (M^++1-OCH_2CH_3 -CH_2CH_3 -CH_3, 100), 243 (M^++1-$CO_2CH_2CH_3$-3Me, 12), 215 (M^++1- $CO_2CH_2CH_3$-3Me-CO, 11), 91 ($C_7H_8^+$, 18.5); IR (KBr) (ν_{max} , cm^{-1}): 3010 (C-H_{St}), 1752, 1740, 1705 (3 C=O), 1585, 1485 (C=C) (arom); Anal. calc. for $C_{19}H_{20}O_7$ (360.36): C 63.33, H 5.59% found: C 64.5, H 5.6%.

Acknowledgements

We gratefully acknowledge financial support from the Research Council of the University of Birjand

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