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New and efficient one-pot synthesis of functionalized γ-spirolactones mediated by vinyltriphenylphosphonium salts

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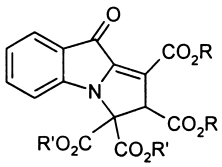
Abstract—The addition of dimethyl acetylenedicarboxylate to isatin derivatives in the presence of triphenylphosphine leading to new highly functionalized γ-spirolactones is reported.

1. Introduction

We have recently described[1] the synthesis of functionalized dihydro-pyrroloisoindole derivatives from the reaction of triphenylphosphine, dialkylphthalimidomalonates and dialkyl acetylendicarboxylate using an intramolecular Wittig reaction.[2–5] With the purpose of preparing dihydro-pyrroloindoles, e.g. **1**, dialkylisatinomalonate was treated with dialkylacetylendicarboxylat and triphenylphosphine.



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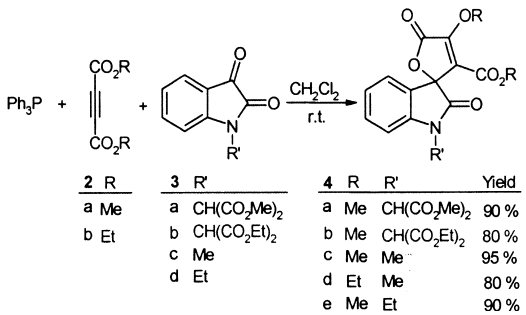
The dihydro-pyrroloindole derivatives **1** was not observed, but γ-spirolactones **4a** and **4b** were isolated in fairly high yield. We also found that *N*-alkylisatins **3c** and **3d** reacted with dialkylacetylendicarboxylates **2a** and **2b** to yield **4c**–**4e** in fairly high yield (Scheme 1). On the basis of the chemistry of trivalent phosphorus nucleophiles, it is reasonable to assume that γ-spirolactone **4** result from the initial addition of triphenylphosphine to acetylenic ester and concomitant addition to activated carbonyl to afford γ-spirolactones.[6] The γ-spirolactone formation can be rationalized as shown in Scheme 2. The structure of compounds were deduced from their elemental analyses and their IR, ^{1}H and ^{13}C NMR spectra.

The mass spectra of compounds **4a**–**4e** displayed molecular ion peaks at *m/z* 419, 447, 303, 331 and 317 respectively.



Scheme 1.

Initial fragmentations involve loss of the γ-spirolactone side chains.

The ^{1}H NMR spectrum of **4a** exhibited singlets readily recognizable as arising from the methoxy groups (3.76, 3.84, 4.00 and 4.40) protons, along with a singlet at 5.85 from the methine proton. A fairly complex multiplet was observed for the aromatic protons at 6.9–7.8. The ^{13}C NMR spectrum of **4a** displayed nineteen distinct resonances in agreement with the γ-spirolactone structure. Partial assignment of these resonances are given in Section 2. The characteristic signal due to spiro carbon was discernible at 80.58 in the ^{13}C NMR spectrum of **4a**. Two ^{13}C signals were observed at about δ 122 and 131 for **4a** which are assigned to C3′ (^{13}C=C–OMe) and C4′ (C=^{13}C–OMe) respectively and are similar to those observed for spirolactones.[6] The ^{1}H and ^{13}C NMR spectra of **4b**–**4e** are similar to those of **4a**, except for ester residue, and the absence of methine proton resonance for **4c**–**4e** (see Section 2).

In conclusion, we have found that the reaction of isatin derivatives with DMAD (dimethyl acetylene dicarboxylate) in the presence of triphenylphosphine leads to a facile synthesis of highly functionalized γ-spirolactones in fairly high yield. The one-pot nature of the present procedure

Keywords: γ-spirolactones; acetylenic esters; triphenylphosphine; isatin.

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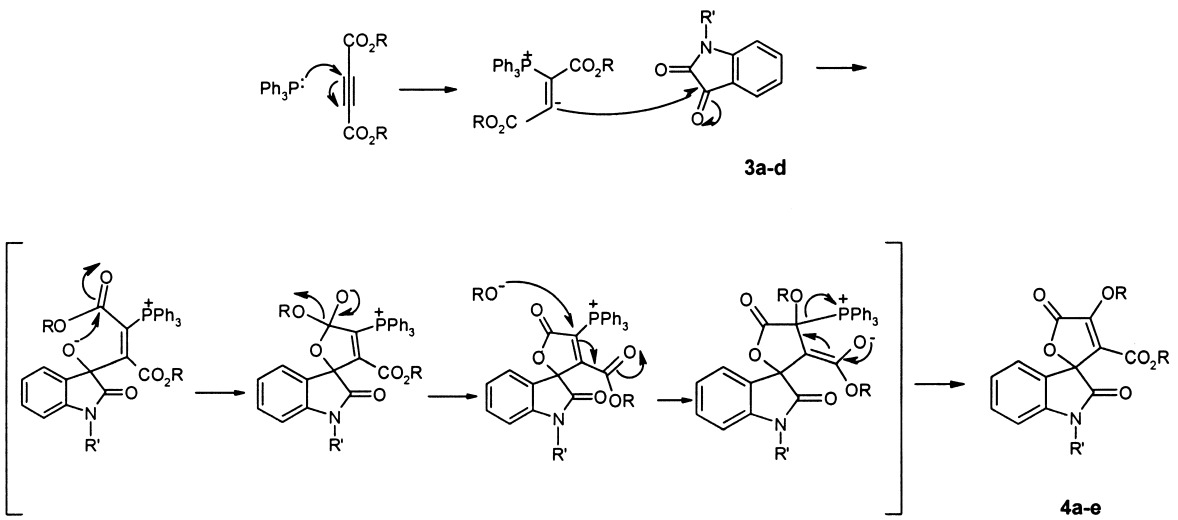

Scheme 2.

makes it an interesting alternative to multistep approaches. Further investigations of the present method will be required to establish its scope and limitations.

2. Experimental

Compounds **2a** and **2b** were obtained from Fluka (Buchs, Switzerland) and were used without further purification. 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 BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, JEOL EX-90A spectrometer at 90 and 22.6 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV.

2.1. Preparation of dialkyl indolomalonate 3a, 3b

Compounds **3a**, **3b** were prepared from dialkylbromomalonates and the potassium isatin by known methods[7] and identified as follows.

2.1.1. 1-Dimethyl-2,3-dioxoindolomalonate 3a. Yellow crystals, mp 155°C; IR (KBr) (ν_{max}, cm^{-1}): 1740, 1750 and 1760 (C=O); MS, *m/z* (%): 277 (M^+,30), 190 (M^++1−CO_2Me−CO, 50), 130 [$CH(CO_2Me)_2$, 33], 162 (M^++1−2CO_2Me, 87); Anal. Calcd for $C_{13}H_{11}NO_6$ (277.22): C, 56.32; H, 3.99; N, 5.05%. Found: C, 56.1; H, 4.1; N, 4.9%. ^{1}H NMR (90 MHz, $CDCl_3$): δ=3.9 (6H, s, $2OCH_3$), 5.9 (1H, s, NCH), 6.9–7.8 (4H, m, arom.); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ=181.16, 164.51 and 157.46 (3C=O), 148.99 (C7a), 138.08 (C6), 125.01 (C7), 124.07 (C5), 117.72 (C4), 112.39 (C3a), 55.87 (CH–N), 53.26 (2 OMe).

2.1.2. 1-Diethyl-2,3-dioxoindolomalonate 3b. Red crystals, mp 95–96°C; IR (KBr) (ν_{max}, cm^{-1}): 1735, 1750 and 1760 (C=O); MS, *m/z* (%): 305 (M^+, 25), 204 (M^++1−CO_2Et−EtOH, 50), 147 (M^++1−CH$(CO_2Et)_2$,87); Anal. Calcd for $C_{15}H_{15}NO_6$ (305.27): C, 59.01; H, 4.95; N, 4.59%. Found: C, 59.1; H, 4.9; N, 4.6%. ^{1}H NMR (90 MHz, $CDCl_3$): δ=1.2–1.4 (6H, 2t, *J*=7.2 Hz, $2CH_3$), 4.2–4.5 (4 H, 2q, *J*=7.2 Hz, $2OCH_2$), 5.9 (1H, s, N–CH), 6.85–7.8 (4H, m, arom.); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ=181.57, 164.43 and 154.83 (3C=O), 149.32 (C7a), 138.25 (C6), 25.38 (C7), 124.32 (C5), 117.93 (C4), 112.96 (C3a), 63.08 ($2OCH_2$), 56.40 (CH–N), 13.99 and 13.95 ($2CH_3$).

2.2. Preparation of *N*-alkyl isatin 3c and 3d

Compounds **3c** and **3d** were prepared from alkyl benzensulfonates and the potassium isatin by known methods[7] and identified as follows.

2.2.1. *N*-Methyl isatin 3c. Purple crystals, mp 129–130°C; IR (KBr) (ν_{max}, cm^{-1}): 1730, 1750 (C=O); *m/z* (%): 161 (M^+, 20), 147 (M^++1−Me, 18); Anal. Calcd for $C_9H_7NO_2$ (161.16): C, 67.07; H, 4.37; N, 8.69%. Found: C, 67.2; H, 4.5; N, 8.5%. ^{1}H NMR (90 MHz, $CDCl_3$): δ=3.23 (3H, s, N–CH_3), 6.82–7.8 (4H, m, arom.); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ=183.41 and 158.28 (2C=O),151.48 (C7a), 138.57 (C6), 125.14 (C7), 123.87 (C5), 117.40 (C4), 110.11 (C3a), 26.22 (CH_3–N).

2.2.2. *N*-Ethyl isatin 3d. Purple crystals mp 86–87°C; IR (KBr) (ν_{max}, cm^{-1}): 1735, 1750 (C=O); *m/z* (%): 175 (M^+, 87), 147 (M^++1−Et, 20), 118 (M^+−Et−CO, 85); Anal. Calcd for $C_{10}H_9NO_2$ (175.2): C, 68.56; H, 5.18; N, 7.99%. Found: C, 68.4; H, 5.3; N, 8.2%. ^{1}H NMR (90 MHz, $CDCl_3$): δ=1.30 (3H, t, CH_3), 3.80 (2H, q, N–CH_2), 6.85–7.80 (4H, m, arom.); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ=183.73 and 157.92 (2C=O), 150.71 (C7a), 138.37 (C6), 125.46 (C7), 123.67 (C5), 117.64 (C4), 110.07 (C3a), 34.98 (N–CH_2), 12.54 (CH_3).

2.3. General procedure for synthesis of alkyl-5′,2-dioxo-4′-alkoxy spiro[1-substituted indol-3,2′-(2′,5′-dihydrofuran)]-3′-carboxylate 4

To a magnetically stirred solution of *N*-substituted

isatin (2 mmol) and triphenylphosphine (2 mmol) in dichloromethane (3 ml) was added dropwise, dimethyl acetylenedicarboxylate (2 mmol, 0.284 g) at room temperature over 10 min. After 3 h the solvent was removed in vacuum. The residue was crystallized in commercial ethanol, and purified by recrystallization from ethanol.

2.3.1. Methyl-5′,2-dioxo-4′-methoxy spiro[1-(malonic acid dimethyl ester)indol-3,2′-(2′,5′-dihydrofuran)]-3′-carboxylate 4a. Yellow crystal, mp 152°C, yield 90%; IR (KBr) (ν_{max}, cm^{-1}): 1735, 1750, 1760 and 1780 (C=O); *m/z* (%): 420 (M^++1, 15), 419 (M^+, 60), 360 (M^++1−CO_2Me, 68), 300 (M^++1−2CO_2Me, 18), 59 (CO_2Me, 87); Anal. Calcd for $C_{19}H_{17}NO_{10}$ (419.34): C, 54.42; H, 4.08; N, 3.34%. Found: C, 54.7; H, 4.3; N, 3.3%. ^{1}H NMR (90 MHz, $CDCl_3$): δ=3.6, 3.8, 4.0 and 4.4 (12H, 4 s, 4OMe), 5.85 (1H, s, NCH), 6.8–7.6 (4 H, m, arom.); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ=169.68, 164.71, 164.32, 164.28 and 159.62 (5C=O), 149.32 (C7a), 141.83 (C6), 131.12 (C4′), 123.91 (C7), 123.50 (C5), 122.10 (C3′), 117.88 (C4), 111.04 (C3a), 80.58 (C spiro), 55.91 (CHN), 60.34, 53.10, 52.61 and 51.92 (4OMe).

2.3.2. Methyl-5′, 2-dioxo-4′-methoxy spiro[1-(malonic acid diethyl ester)indol-3,2′-(2′,5′-dihydrofuran)]-3′-carboxylate 4b. White crystal, mp 125°C, yield 80%; IR (KBr) (ν_{max}, cm^{-1}): 1700, 1745, 1760 and 1685 (4C=O); *m/z* (%): 447 (M^+, 75), 403 (M^++1−OEt, 15), 285 (M^++1−$CH(CO_2Et)_2$−CO_2Me, 53), 59 (CO_2Me, 62); Anal. Calcd for $C_{21}H_{21}NO_{10}$ (447.4): C, 56.38; H, 4.73; N, 3.13%. Found: C, 56.3; H, 4.7; N, 3.1%. ^{1}H NMR (90 MHz, $CDCl_3$): δ=1.1–1.5 (6H, 2t, $2CH_3$), 3.6 and 4.4 (6H, 2 s, 2OMe), 4.2–4.4 (4H, 2q, $2OCH_2$), 5.85 (1H, s, N–CH), 6.9–7.6 (4H, m, arom.); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ=170.21, 165.29, 164.43, 164.40 and 160.15 (5C=O), 149.81 (C7a), 142.56 (C6), 131.41 (C4′), 124.24 (C7), 123.83 (C5), 122.61 (C3'), 118.66 (C4), 111.82 (C3a), 81.16 (C-spiro), 62.87, 62.79 ($2OCH_2$), 60.76 and 52.29 (2OMe), 56.81 (CH–N), 13.98 and 13.93 ($2CH_3$).

2.3.3. Methyl-5′,2-dioxo-4′-methoxy spiro[1-methyl-indol-3,2′-(2′,5′-dihydrofuran)]-3′-carboxylate 4c. Pink crystal, mp 167°C, yield 95%; IR (KBr) (ν_{max}, cm^{-1}): 1705, 1740 and 1780 (C=O);); *m/z* (%): 303 (M^+, 25), 289 (M^++1−Me, 15), 273 (M^++1−OMe, 53), 59 (CO_2Me, 62); Anal. Calcd for $C_{15}H_{13}NO_6$ (303.27): C, 59.4; H, 4.32; N, 4.62%. Found: C, 59.5; H, 4.4; N, 4.6%. ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.26 (3H, s, N–CH_3), 3.59 and 4.36 (6H, 2 s, 2OMe), 6.91–7.44 (4H, m, arom.); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=169.98, 165.54 and 160.59 (3C=O), 149.31 (C7a), 144.97 (C6), 131.82 (C4'), 124.23 (C7), 123.39 (C5), 122.95 (C3′), 119.18 (C4), 109.12 (C3a), 81.64 (C-spiro), 60.36 and 52.31 (2OMe), 26.93 (N–Me).

2.3.4. Ethyl-5′,2-dioxo-4′-ethoxy spiro[1-methyl-indol-3,2′-(2′,5′-dihydrofuran)]-3′-carboxylate 4d. White crystals, mp 115.5°C, yield 80%; IR (KBr) (ν_{max}, cm^{-1}): 1725, 1740 and 1790 (C=O); *m/z* (%): 331 (M^+, 15), 317 (M^++1−Me, 15), 287 (M^++1−OEt, 42), 73 (CO_2Et, 58); Anal. Calcd for $C_{17}H_{17}NO_6$ (331.32): C, 61.63; H, 5.17; N, 4.23%. Found: C, 61.6; H, 5.1; N, 4.1%. ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.92 (3H, t, J=7.1 Hz, CH_3 of ester), 1.42 (3H, t, J=7.2 Hz, CH_3 of ether), 3.20 (3H, s, N–CH_3), 3.95 (2H, 2q, J=7.1 Hz, CH_2 of ester), 4.70 (2H, 2q, J=7.2 Hz, CH_2, of ether), 6.86–7.41 (4H, m, arom.); ^{13}C NMR (125.77 MHz, $CDCl_3$): δ=170.54, 166.17 and 160.28 (3C=O), 149.55 (C7a), 145.37 (C6), 132.15 (C4′), 124.65 (C7), 123.75 (C5), 123.55 (C3′), 119.48 (C4), 109.39 (C3a), 82.11 (C spiro), 69.94 and 61.59 ($2OCH_2$), 27.24 (N–CH_3), 15.71 and 13.91 ($2CH_3$).

2.3.5. Methyl-5′,2-dioxo-4′-methoxy spiro[1-ethyl-indol-3,2′-(2′,5′-dihydrofuran)]-3′-carboxylate 4e. White crystals, mp 163–164°C, yield 90%; IR (KBr) (ν_{max}, cm^{-1}): 1730, 1740, 1780 (C=O); *m/z* (%): 317 (M^+, 14), 289 (M^++1−Et, 18), 287 (M^++1−OMe, 48), 59 (CO_2Me, 46); Anal. Calcd for $C_{16}H_{15}NO_6$ (317.3): C, 60.57; H, 4.76; N, 4.41%. Found: C, 60.6; H, 4.7; N, 4.4%. ^{1}H NMR (90 MHz, $CDCl_3$): δ=1.2–1.4 (3H, t, CH_3 of N–Et), 3.6 and 3.38 (6H, 2 s, $2OCH_3$), 3.5–4.1 (2H, m, CH_2 of N–Et), 6.9–7.6 (4H, m, arom.); ^{13}C NMR (22.6 MHz, $CDCl_3$): δ=169.56, 165.57 and 160.43 (3C=O), 149.48 (C7a), 144.11 (C6), 131.77 (C4′), 124.48 (C7), 123.18 (C5), 122.90 (C3′), 119.23 (C4), 109.21 (C3a), 81.68 (C-spiro), 60.42 and 52.12 (2OMe), 35.49 (CH_2 of N–Et), 12.21 (CH_3 of N–Et).

Caution: acetylenic esters are lachrymator.

Acknowledgements

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