

Efficient synthesis of some oxalacetic acid and pyruvic acid derivatives from the reactions of 2,3-furandiones with 2-phenylindole

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Abstract

Oxalacetic acid and pyruvic acid derivatives have been synthesized efficiently in high yields by the treatment of 4-ethoxycarbonyl-5-phenyl-2,3-furandione and 4-benzoyl-5-phenyl-2,3-furandione with 2-phenylindole at room temperature and converted to simple derivatives such as an ester or a hydrazone.

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Furandiones are extremely versatile synthons in heterocyclic chemistry.¹ Thermal decarbonylation of these compounds yields α -oxoketenes as intermediates, which are able to undergo cyclo- and nucleophilic addition reactions with heterodienophiles and nucleophiles, respectively.² In addition, these compounds also show typical carbonyl, lactone and α,β -unsaturated carbonyl reactions depending on the structures of the nucleophiles.³ Furandiones can be subdivided depending on the substitution pattern on C-4, 5. In particular, furandiones having a carbonyl functionality at C-4 offer specific reactivities towards nucleophiles as well as cycloaddition processes.¹ On the other hand, the indole nucleus is present in a wide variety of natural and synthetic compounds, many of which have proved to be interesting in a chemical and biological context due to their showing a wide spectrum of pharmacological action.⁴ Despite the significant work performed on the reactions of furandiones with various nucleophiles, the reactions of

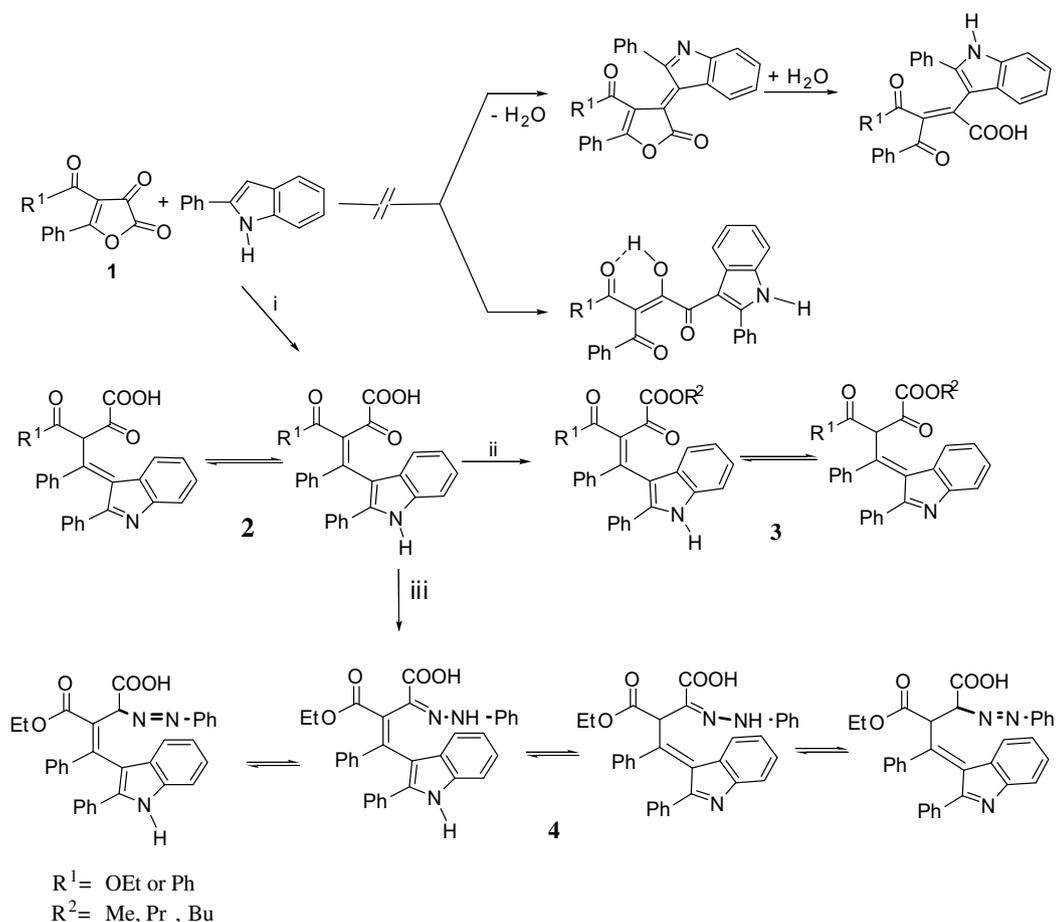
furandiones with indoles have not been reported. In an attempt to remedy this situation, we decided to extend our previous studies⁵ on the reactions of furandiones **1**, bearing carbonyl functionalities at C-4, to the reaction with 2-phenylindole.

Our approach revealed that furandiones **1** react with 2-phenylindole to yield derivatives of oxalacetic acid or pyruvic acid, both of which are important natural metabolites.⁶ The reaction conditions are mild and the experimental procedure is simple. The products were formed in high yields (85–89%).⁷ Due to the presence of three electrophilic sites with different reactivity (C-2, C-3 and C-5) in furandiones **1** that can react with nucleophiles,⁸ the reactions of **1** with 2-phenylindole may produce three isomeric indole derivatives. However, the results of TLC studies for each reaction indicated the presence of only one product, the structures of which were identified as ethyl 2-[phenyl-(2-phenyl-1*H*-indol-3-yl)-methylene]-oxalacetate and 3-benzoyl-2-oxo-4-phenyl-4-(2-phenyl-1*H*-indol-3-yl)-but-3-enoic acid **2** (Scheme 1).

The formation of only one of the three possible structures is based on an X-ray study of butyl 2-[phenyl-(2-phenyl-1*H*-indol-3-yl)-methylene]-oxalacetate thus excluding the other possible isomers (Fig. 1).

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Scheme 1. Reagents and conditions: (i) dry benzene, room temperature; (ii) corresponding alcohol, H_2SO_4 , reflux; (iii) phenylhydrazine, xylene, 0°C .

In the title compound shown in Figure 1,⁹ the bond lengths and angles are in agreement with the values reported for other organic compounds.¹⁰ The (C1–C8/N6) ring system is almost planar, with maximum deviations of $-0.027(3)$, $0.027(5)$, $-0.039(3)$ and $0.029(2)$ Å,

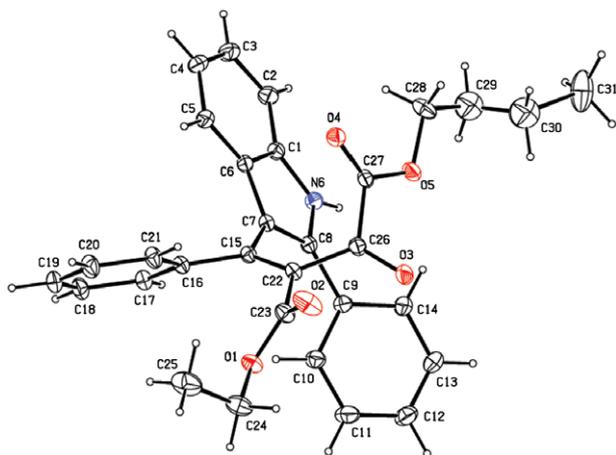
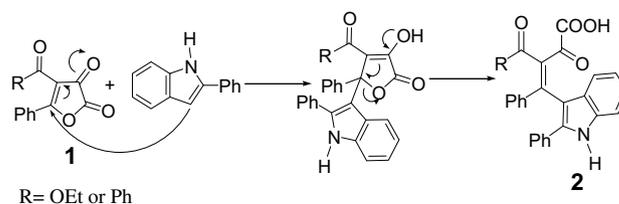


Fig. 1. An ORTEP-3 drawing of butyl 2-[phenyl-(2-phenyl-1H-indol-3-yl)-methylene]-oxalacetate **3c** with atom numbering scheme. Displacement ellipsoids are drawn at the 20% probability level. H atoms are of arbitrary size.

for atoms C1, C3, C6 and C8, respectively. This ring system adopts dihedral angles of $35.62(15)^\circ$ and $78.94(14)^\circ$, with the planes of the (C9–C14) and (C16–C21) phenyl rings, respectively. The crystal structure is stabilized by two intermolecular $\text{N-H}\cdots\text{O}$ and $\text{C-H}\cdots\text{O}$ hydrogen bonds [$\text{N6-HN6}\cdots\text{O3}^i = 144(3)^\circ$, $\text{HN6}\cdots\text{O3}^i = 2.14(4)$ Å, $\text{N6}\cdots\text{O3}^i = 2.956(4)$ Å and $\text{C31-H31B}\cdots\text{O2}^i = 145^\circ$, $\text{H31B}\cdots\text{O2}^i = 2.51$ Å, $\text{C31}\cdots\text{O2}^i = 3.342(7)$ Å. Symmetry code: (i) $1/2 - x, -1/2 + y, 3/2 - z$].

A reasonable reaction pathway from furandiones **1** to oxalacetic acid and pyruvic acid derivatives **2** is outlined briefly in Scheme 2.

The formation of compounds **2** may be initiated by Michael addition, via nucleophilic attack at C-5 of the furan ring in **1** by the CH group at C-3 of 2-phenylindole.



Scheme 2.

Rearrangement of the intermediates thus formed may lead to ring opening to give oxalacetic acid or pyruvic acid derivatives **2** (Scheme 2).

The structures of compounds **2** were confirmed by analytical and spectral data. In addition, while conversion of oxalacetic and pyruvic acids **2** into their corresponding ester derivatives **3** has been accomplished by Fischer esterification showing the presence of a free carboxyl group,¹¹ we have also succeeded in obtaining hydrazone **4** formed by the reaction of phenylhydrazine with the oxo group of oxalacetic acid.¹²

Both the ¹H NMR and ¹³C NMR spectra showed evidence for the presence of a tautomeric equilibrium between the two tautomers of the keto forms of the oxalacetic and pyruvic acid derivatives **2**, **3** and **4** in both DMSO and in CDCl₃ solutions. However, 2-oxo-3-[phenyl-(2-phenyl-indol-3-ylidene)-methyl]-succinic acid-4-ethyl ester and 3-benzoyl-2-oxo-4-phenyl-4-(2-phenyl-indol-3-ylidene)-butyric acid and their ester derivatives did not show any tendency to enolize both in DMSO and CDCl₃ although their enol forms should be stabilized by intramolecular hydrogen bridges. Similar observations have also been made with closely related dipivaloyl acetic acid, pivaloyl malonic acid, dibenzoyl acetic acid and benzoyl malonic acid derivatives.^{2c-e}

In conclusion, 2-phenylindole has been employed here for the first time as an efficient nucleophilic reagent for the regiospecific synthesis of oxalacetic acid and pyruvic acid derivatives from furandiones.

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- General procedure for the synthesis of acid derivatives **2**: A solution of 2,3-furandione **1** (1 mmol) and 2-phenylindole (1 mmol) in dry benzene was stirred at room temperature for 10 min. The precipitated product was filtered off and crystallized from toluene to give ethyl 2-[phenyl-(1*H*-indol-3-yl)-methylene]-oxalacetate **2a** (89%) as violet crystals, mp 178–179 °C (decomp) or 3-benzoyl-2-oxo-4-(2-phenyl-1*H*-indol-3-yl)-but-3-enoic acid **2b** (85%) as orange crystals, mp 172–174 °C (decomp). Data for **2a**: ¹H NMR (300.13 MHz, CDCl₃) δ 13.1 (br, 0.27H, OH, indoline form), 12.4 (br, 0.73H, OH, indole form), 11.9 (s, 0.73H, NH, indole form), 7.1–7.6 (m, 14H, ArH), 6.7 (s, 0.27H, CH, indoline form), 4.0–3.9 (m, 2H, OCH₂CH₃), 0.9–0.8 (m, 3H, OCH₂CH₃). ¹³C NMR (75 MHz, DMSO) δ 187.6 (C=O), 185.7 (C=O), 166.4 (C=O), 165.3 (C=O), 163.8 (C=O), 163.2 (C=O), 155.6, 153.8, 143.5, 140.0, 139.4, 138.8, 137.2, 136.7, 136.3, 131.1, 130.3, 129.6, 129.4, 129.3, 129.1, 128.8, 128.7, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 127.4, 125.9, 122.7, 122.2, 120.7, 120.3, 119.6, 118.9, 111.9, 111.8, 111.0, 60.5 (OCH₂CH₃), 60.4 (OCH₂CH₃), 13.5 (OCH₂CH₃), 13.3 (OCH₂CH₃). IR (KBr) ν 3420 (NH), 1775 (C=O), 1681 (C=O), 1646 (C=O). Anal. Calcd for C₂₇H₂₁N₁O₅: C, 73.73; H, 4.78; N, 3.19. Found: C, 73.67; H, 4.79; N, 3.11. Data for **2b**: ¹H NMR (300.13 MHz, CDCl₃) δ 13.6 (br, 0.29H, OH, indoline form), 12.8 (br, 0.71H, OH, indole form), 11.5 (s, 0.71H, NH, indole form), 7.0–8.1 (m, 19H, ArH), 6.6 (s, 0.29H, CH, indoline form). ¹³C NMR (75 MHz, DMSO) δ 195.2 (C=O), 194.9 (C=O), 187.8 (C=O), 185.8 (C=O), 164.6 (C=O), 161.5 (C=O), 154.5, 144.3, 142.2, 139.8, 139.1, 137.6, 137.5, 137.2, 136.8, 136.7, 135.1, 133.7, 133.5, 131.8, 131.0, 130.9, 130.7, 130.3, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 127.9, 127.8, 127.6, 125.4, 123.3, 122.9, 121.2, 120.8, 120.2, 119.9, 113.2, 112.5, 112.4, 111.8, 93.7. IR (KBr) ν 3377 (NH), 1762 (C=O), 1669 (C=O), 1610 (C=O). Anal. Calcd for C₃₁H₂₁NO₄: C, 78.90; H, 4.45; N, 2.97. Found: C, 78.80; H, 4.40; N, 2.93.
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- Crystallographic data for the title compound shown in Figure 1: C₃₁H₂₉NO₅, fw = 495.55, monoclinic, C2/c, a = 23.2939(11) Å, b = 11.8828(4) Å, c = 21.2011(11) Å, β = 115.969(4)°, V = 5275.9(4) Å³, Z = 8, 5802 independent reflections, 3864 reflections were observed (I > 2σ(I)), R₁ = 0.0776, wR₂ = 0.2545 (observed), R₁ = 0.0995, wR₂ = 0.2773 (all data). Crystallographic data (excluding structure factors) for the structure of **3c** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 652010. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 0 1223 336033 or deposit@ccdc.cam.ac.uk].

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11. Ester derivatives **3** were synthesized via Fischer esterification. 2-Oxo-3-[phenyl-(2-phenyl-1*H*-indol-3-yl)-methylene]-succinic acid 1-methyl ester 4-ethyl ester **3a** (71%) (orange crystals), mp 235 °C and 3-benzoyl-2-oxo-4-(2-phenyl-1*H*-indol-3-yl)-but-3-enoic acid butyl ester **3b** (74%) (orange crystals), mp 178 °C. Data for **3a**: ¹H NMR (300.13 MHz, CDCl₃) δ 12.2 (s, 0.82H, NH, indole form), 6.9–7.6 (m, 14H, ArH), 6.6 (s, 0.18H, CH, indole form), 4.08–3.98 (m, 2H, OCH₂CH₃), 3.67 (m, 3H, OCH₃), 0.99–0.73 (m, 3H, OCH₂CH₃). ¹³C NMR (75 MHz, DMSO) δ 185.6 (C=O), 184.1 (C=O), 166.4 (C=O), 165.8 (C=O), 162.9 (C=O), 162.6 (C=O), 157.6, 155.5, 155.4, 145.2, 141.1, 139.7, 138.7, 137.2, 136.9, 131.4, 131.1, 130.3, 130.1, 129.8, 129.5, 129.3, 129.2, 129.0, 128.9, 128.7, 128.4, 128.1, 123.7, 122.8, 121.5, 121.0, 120.1, 119.4, 112.5, 112.3, 111.1, 61.1 (OCH₂CH₃), 60.8 (OCH₂CH₃), 53.1 (OCH₃), 52.7 (OCH₃), 14.0 (OCH₂CH₃), 13.8 (OCH₂CH₃). IR (KBr) ν 3286 (NH), 1742 (C=O), 1695 (C=O), 1651 (C=O). Anal. Calcd for C₂₈H₂₃NO₅: C, 74.09; H, 5.07; N, 3.08. Found: C, 74.01; H, 5.07; N, 2.97. Data for **3b**: ¹H NMR (300.13 MHz, CDCl₃) δ 11.7 (s, 0.82H, NH, indole form), 6.9–7.9 (m, 19H, ArH), 6.6 (s, 0.18H, CH, indole form), 3.4–3.0 (m, 2H, O(CH₂)₃CH₃), 1.2–1.0 (m, 4H, O(CH₂)₃CH₃), 0.8–0.7 (m, 3H, O(CH₂)₃CH₃). ¹³C NMR (75 MHz, DMSO) δ 194.6 (C=O), 187.3 (C=O), 185.9 (C=O), 163.0 (C=O), 162.3 (C=O), 157.1, 155.4, 145.1, 142.5, 139.6, 138.6, 138.1, 137.5, 137.4, 137.2, 136.9, 136.8, 134.9, 133.8, 132.9, 131.8, 131.5, 131.2, 131.1, 130.6, 130.3, 129.4, 129.2, 129.1, 129.0, 128.9, 128.8, 128.5, 128.1, 127.8, 127.7, 126.9, 123.6, 122.9, 121.4, 120.9, 120.2, 119.8, 113.0, 112.5, 112.0, 66.0 (O(CH₂)₃CH₃), 65.9 (O(CH₂)₃CH₃), 30.1 (O(CH₂)₃CH₃), 29.9 (O(CH₂)₃CH₃), 18.9 (O(CH₂)₃CH₃), 18.8 (O(CH₂)₃CH₃), 13.9 (O(CH₂)₃CH₃), 13.8 (O(CH₂)₃CH₃). IR (KBr) ν 3329 (NH), 1725 (C=O), 1667 (C=O), 1630 (C=O). Anal. Calcd for C₃₅H₂₉NO₄: C, 79.60; H, 5.49; N, 2.65. Found: C, 79.49; H, 5.51; N, 2.58.
12. Synthesis of hydrazone derivative **4**: Phenylhydrazine (1 mmol) was added dropwise to a solution of **2a** (1 mmol) in xylene at 0 °C. The resulting mixture was stirred for 3 h and the yellow precipitate thus formed was filtered off and recrystallized from butanol to give 2-(phenyl-hydrazino)-3-[phenyl-(2-phenyl-1*H*-indol-3-yl)-methylene]-succinic acid 4-ethyl ester **4** (68%) as yellow crystals (red coloured in solution state), mp 233–235 °C (decomp). Data for **4**: ¹H NMR (300.13 MHz, CDCl₃) δ 13.3 (br, 0.56H, OH), 13.2 (br, 0.28H, OH), 11.9 (br, 0.16H, OH), 11.8 (br, 0.36H, NH), 11.7 (br, 0.20H, NH), 7.1–7.6 (m, 19H, ArH), 6.8 (s, 0.54H, N-NH), 6.5 (s, 0.44H, CH), 3.9–3.8 (m, 2H, OCH₂CH₃), 2.5 (s, 0.56H, CH), 0.9–0.8 (m, 3H, OCH₂CH₃). ¹³C NMR (75 MHz, DMSO) δ 176.1 (C=O), 169 (C=O), 167.6 (C=O), 166.5 (C=O), 166.3 (C=O), 165.9 (C=O), 165.1 (C=O), 155.7, 151.1, 149.5, 146.3, 143.3, 142.1, 141.0, 139.9, 139.6, 136.7, 136.5, 136.2, 136.0, 131.7, 131.0, 130.0, 129.8, 129.7, 129.5, 129.3, 129.2, 128.9, 128.8, 128.7, 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 127.6, 125.6, 125.1, 125.0, 124.7, 124.3, 123.9, 122.9, 122.2, 122.1, 121.7, 121.6, 120.3, 119.8, 119.3, 114.1, 112.0, 99.1, 61.1, 60.2, 59.9 (OCH₂CH₃), 59.3 (OCH₂CH₃), 14.1 (OCH₂CH₃), 13.9 (OCH₂CH₃). IR (KBr) ν 3444 (NH), 1750 (C=O), 1690 (C=O). Anal. Calcd for C₃₃H₂₇N₃O₄: C, 74.77; H, 5.09; N, 7.93. Found: C, 74.65; H, 5.00; N, 7.89.