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**ARTICLE** *in* TETRAHEDRON LETTERS · APRIL 2008

Impact Factor: 2.38 · DOI: 10.1016/j.tetlet.2008.02.118



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Tetrahedron Letters

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

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Received 27 December 2007; revised 1 February 2008; accepted 21 February 2008
Available online 4 March 2008

**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.


*Keywords:* 2,3-Furandiones; Pyruvic acid; Oxalacetic acid; Heterocyclic compounds; 2-Phenylindole; X-ray

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 studies[5] 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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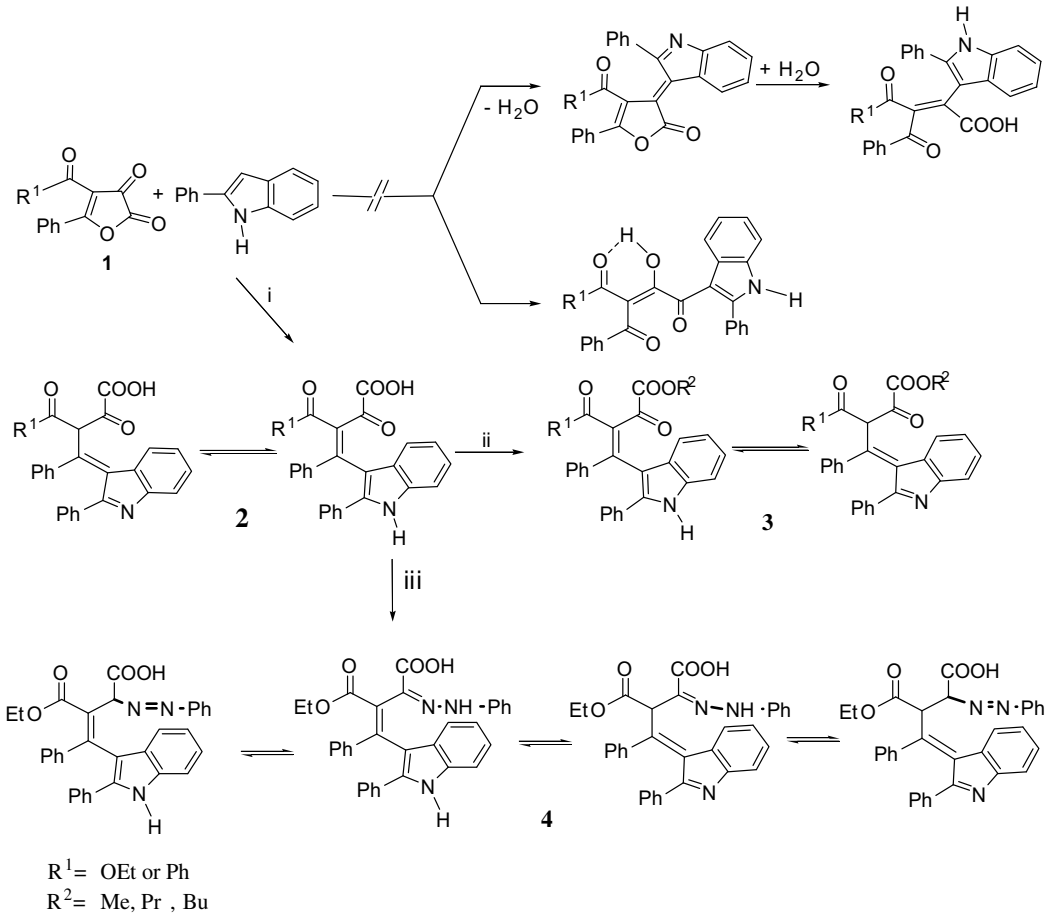
doi:10.1016/j.tetlet.2008.02.118




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

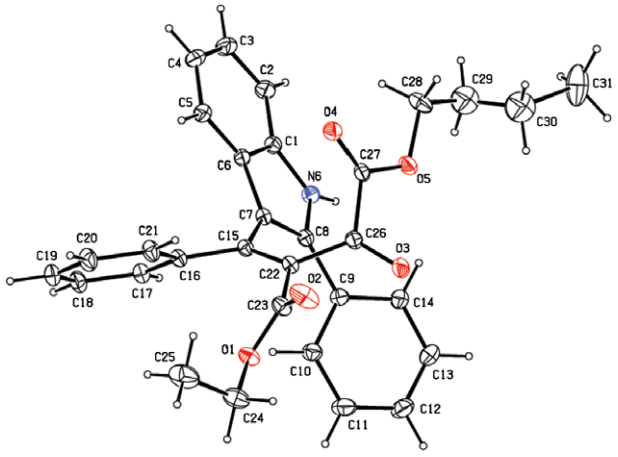
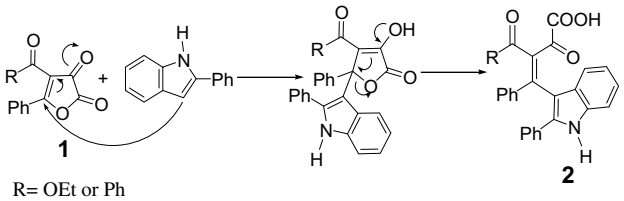



Fig. 1. An ORTEP-3 drawing of butyl 2-[phenyl-(2-phenyl-1*H*-indol-3-yl)-methylene]-oxalacetate **3c** with atom numbering scheme. Displacement ellipsoids are drawn at the 20% probability level. H atoms are of arbitrary size.

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 $^{1}H$ NMR and $^{13}C$ 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 $CDCl_3$ 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 $CDCl_3$ 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.

## Acknowledgement

The authors wish to express their appreciation and gratitude to the Scientific Research Projects Chairmanship of Yüzüncü Yil University for financial support of this study (Grant No. 2006-FBE-075).

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7. 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**: $^{1}H$ NMR (300.13 MHz, $CDCl_3$) $\delta$ 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, O*CH*$_2$CH$_3$), 0.9–0.8 (m, 3H, OCH$_2$*CH*$_3$). $^{13}C$ NMR (75 MHz, DMSO) $\delta$ 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 (O*CH*$_2$CH$_3$), 60.4 (O*CH*$_2$CH$_3$), 13.5 (OCH$_2$*CH*$_3$), 13.3 (OCH$_2$*CH*$_3$). IR (KBr) $\nu$ 3420 (NH), 1775 (C=O), 1681 (C=O), 1646 (C=O). Anal. Calcd for $C_{27}H_{21}N_1O_5$: C, 73.73; H, 4.78; N, 3.19. Found: C, 73.67; H, 4,79; N, 3.11. Data for **2b**: $^{1}H$ NMR (300.13 MHz, $CDCl_3$) $\delta$ 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). $^{13}C$ NMR (75 MHz, DMSO) $\delta$ 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) $\nu$ 3377 (NH), 1762 (C=O), 1669 (C=O), 1610 (C=O). Anal. Calcd for $C_{31}H_{21}NO_4$: C, 78.90; H, 4.45; N, 2.97. Found: C, 78.80; H, 4.40, N, 2.93.
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9. Crystallographic data for the title compound shown in Figure 1: $C_{31}H_{29}NO_5$, fw = 495.55, monoclinic, *C*2/*c*, $a = 23.2939(11)$ Å, $b = 11.8828(4)$ Å, $c = 21.2011(11)$ Å, $\beta = 115.969(4)°$, $V = 5275.9(4)$ Å$^3$, $Z = 8$, 5802 independent reflections, 3864 reflections were observed ($I > 2\sigma(I)$), $R_1 = 0.0776$, $wR_2 = 0.2545$ (observed), $R_1 = 0.0995$, $wR_2 = 0.2773$ (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-3yl)-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-3yl)-but-3-enoic acid butyl ester **3b** (74%) (orange crystals), mp 178 °C. Data for **3a**: $^{1}$H NMR (300.13 MHz, $CDCl_3$) $\delta$ 12.2 (s, 0.82H, NH, indole form), 6.9–7.6 (m, 14H, ArH), 6.6 (s, 0.18H, CH, indoline form), 4.08–3.98 (m, 2H, $OCH_2CH_3$), 3.67 (m, 3H, $OCH_3$), 0.99–0.73 (m, 3H, $OCH_2CH_3$). $^{13}$C NMR (75 MHz, DMSO) $\delta$ 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 ($OCH_2CH_3$), 60.8 ($OCH_2CH_3$), 53.1 ($OCH_3$), 52.7 ($OCH_3$), 14.0 ($OCH_2CH_3$), 13.8 ($OCH_2CH_3$). IR (KBr) $\nu$ 3286 (NH), 1742 (C═O), 1695 (C═O), 1651 (C═O). Anal. Calcd for $C_{28}H_{23}NO_5$: C, 74.09; H, 5.07; N, 3.08. Found: C, 74.01; H, 5.07; N, 2.97. Data for **3b**: $^{1}$H NMR (300.13 MHz, $CDCl_3$) $\delta$ 11.7 (s, 0.82H, NH, indole form), 6.9–7.9 (m, 19H, ArH), 6.6 (s, 0.18H, CH, indoline form), 3.4–3.0 (m, 2H, $O(CH_2)_3CH_3$), 1.2–1.0 (m, 4H, $O(CH_2)_3CH_3$), 0.8–0.7 (m, 3H, $O(CH_2)_3CH_3$). $^{13}$C NMR (75 MHz, DMSO) $\delta$ 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 ($O(CH_2)_3CH_3$), 65.9 ($O(CH_2)_3CH_3$), 30.1 ($O(CH_2)_3CH_3$), 29.9 ($O(CH_2)_3CH_3$), 18.9 ($O(CH_2)_3CH_3$), 18.8 ($O(CH_2)_3CH_3$), 13.9 ($O(CH_2)_3CH_3$), 13.8 ($O(CH_2)_3CH_3$). IR (KBr) $\nu$ 3329 (NH), 1725 (C═O),1667 (C═O), 1630 (C═O). Anal. Calcd for $C_{35}H_{29}NO_4$: 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**: $^{1}$H NMR (300.13 MHz, $CDCl_3$) $\delta$ 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, $OCH_2CH_3$), 2.5 (s, 0.56H, CH), 0.9–0.8 (m, 3H, $OCH_2CH_3$). $^{13}$C NMR (75 MHz, DMSO) $\delta$ 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 ($OCH_2CH_3$), 59.3 ($OCH_2CH_3$), 14.1 ($OCH_2CH_3$), 13.9 ($OCH_2CH3$). IR (KBr) $\nu$ 3444 (NH), 1750 (C═O), 1690 (C═O). Anal. Calcd for $C_{33}H_{27}N_3O_4$: C, 74.77; H, 5.09; N, 7.93. Found: C, 74.65; H, 5.00; N, 7.89.