An Efficient Method for the Preparation of Indole-, 7-Azaindole-, Pyrrole-containing Tertiary Alcohols

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(Received on 11th January 2016, accepted in revised form 20th December 2016)

Summary: A simple and efficient synthetic procedure for the preparation of indole-, 7-azaindole-, and pyrrol-containing tertiary alcohols from indole/azaindole/pyrrole and TEMPO-substituted 1,3-dicarbonyl compounds were developed. The mechanistic pathway for this process involves the N-O bond cleavage of TEMPO-substituted 1,3-dicarbonyl compounds to form the tricarbonyl intermediate, following Friedel-Crafts reaction of indole/aza-indole/pyrrole with this intermediate generates the tertiary alcohol product. All the processes do not need extra catalysts, dry solvents or harsh reaction conditions.

Keywords: Indole, 7-azaindole, Pyrrole, Tertiary alcohol, Synthesis.

Introduction

Indole has attracted a longstanding interest in organic, pharmaceutical and medical chemistry because of indole-based structures existing abundantly in many biologically active natural products and medicinally relevant substances [1]. In addition, the chemical modifications of indole and its derivatives have been and continue to be a research hotspot for synthetic organic chemists and medicinal chemists, especially directing 3-substituted indolyl moiety [2-5], serving as various precursors of antiviral [6], anticancer [7], antibacterial [8], anti-inflammatory [9] and cytotoxic drugs [10]. The Friedel-Crafts reaction of arene with activated ketone is an important method for the preparation of tertiary alcohol. Up to now, the Friedel-Crafts reaction of an electron rich aromatic heterocycle with activated carbonyl compounds mainly include indoles with ethyl trifluoropyruvate [11-17], 2-oxomalonate [18-21] and other α-ketoesters [22]. Although numerous methologies of indole derivation were explored, the general methods for Friedel-Crafts alkylation of heteroaromatic compounds with activated carbonyl compounds to form C-C bond reactions are still in demand. Recently, our group reported the synthesis of indole substituted tertiary alcohols through the Friedel-Crafts reaction of indoles with vicinal tricarbonyl compounds generated in situ from 1,3-dicarbonyl compounds and TEMPO [23]. During the research, we found that this reaction suffer from the diversity of substrates, especially 1,3-dicarbonyl compounds such as malonates, dibenzoylmethane, subjected to the reaction conditions, didn't give target products. We envision that the process undergo the intermediates of α-position TEMPO-substituted 1,3-dicarbonyl compounds. In order to broaden the substrate scope of tertiary alcohol synthesis and lay the foundation for the further synthesis of drug-like molecules, a series of TEMPO-substituted 1,3-dicarbonyl compounds was synthesized and further research was carried out.

Experimental

All ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ or acetone-d_6 using a Bruker ASCEND 400 spectrometer. Chemical shifts are expressed in ppm and *J* values are given in Hz. High resolutionmass spectra were recorded on Bruker micrOTOF-QIII MS (ESI and APCI). IR spectra were recorded on a Bio-Rad FTS-40 spectrometer. Columnchromatography was performed with 200-300 mesh silica gel using flash column techniques. Melting points (uncorrected) were determined on a yalixien X-4 melting point apparatus. All the solvents and reagents were used directly as obtained commercially unless otherwise noted.

*General procedure for synthesis of **2a-2k**:*

To a solution of TEMPO (5 mmol) and 1,3-dicarbonyl compounds (5 mmol) in 30 mL ethyl acetate, CAN (1 mmol) was added, the mixture was stirred at 60 °C for one and a half hours, filtered through celite, washed with ethyl acetate (3×20 mL), concentrated and purified on a silica gel chromatography to afford **2a-2k**.

*Ethyl 3-oxo-2-((2,2,6,6- tetramethylpiperidin -1-yl)oxy)butanoate **(2a)***. Colorless oil. IR (cm^{-1}) 1747, 1726, 1179; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (s, 1H), 4.25 – 4.17 (m, 2H), 2.29 (s, 3H), 1.57 – 1.31 (m, 6H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 3H),

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1.17 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1, 168.0, 93.8, 61.8, 60.4, 60.2, 40.3, 40.2, 33.2, 32.7, 26.7, 20.3, 17.1, 14.2; HRMS (ESI) calcd for $C_{15}H_{27}NO_4Na$ $(M+Na)^+$ 308.1832, found 308.1830.

Methyl 3-oxo-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)butanoate ***(2b)***. Colorless oil. IR (cm^{-1}) 1751, 1728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (s, 1H), 3.73 (s, 3H), 2.29 (s, 3H), 1.57 – 1.29 (m, 6H), 1.17 (s, 6H), 1.01 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1, 168.5, 93.6, 77.4, 60.3, 60.0, 52.6, 40.2, 40.1, 33.2, 32.6, 26.7, 20.3, 17.1. HRMS (ESI) calcd for $C_{14}H_{25}NO_4Na$ $(M+Na)^+$ 294.1676, found 294.1681.

6,6-Dimethyl-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)heptane-2,4-dione ***(2c)***. Colorless oil. IR (cm^{-1}) 1742, 1721, 1148; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (s, 1H), 2.26 (s, 3H), 1.52 – 1.33 (m, 15H), 1.18 (s, 3H), 1.14 (s, 3H), 1.08 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3, 167.0, 94.4, 82.8, 60.1, 40.3, 40.2, 33.2, 32.8, 29.8, 27.9, 26.5, 20.2, 17.1. HRMS (ESI) calcd for $C_{17}H_{31}NO_4Na$ $(M+Na)^+$ 336.2145, found 336.2146.

Benzyl 3-oxo-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)butanoate ***(2d)***. Colorless oil. IR (cm^{-1}) 1746, 1726, 1456, 1161; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 5.16 (s, 2H), 4.84 (s, 1H), 2.23 (s, 3H), 1.55 – 1.32 (m, 6H), 1.15 (s, 6H), 0.96 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.7, 167.7, 135.0, 128.6, 128.5, 128.5, 93.7, 67.3, 60.3, 60.0, 40.1, 40.0, 33.0, 32.6, 31.9, 26.5, 26.1, 20.2, 16.9. HRMS (ESI) calcd for $C_{20}H_{29}NO_4Na$ $(M+Na)^+$ 370.1989, found 370.1985.

Ethyl 3-oxo-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pentanoate ***(2e)***. Colorless oil. IR (cm^{-1}) 1746, 1722, 1180; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 1H), 4.25 – 4.08 (m, 2H), 2.86 – 2.73 (m, 1H), 2.62 – 2.50 (m, 1H), 1.53 – 1.37 (m, 5H), 1.29 – 1.22 (m, 4H), 1.17 (s, 3H), 1.16 (s, 3H), 1.07 – 1.01 (m, 6H), 0.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.6, 168.2, 93.4, 61.6, 60.3, 60.1, 40.3, 40.2, 33.1, 32.7, 32.4, 20.3, 17.1, 14.2, 7.2.

Ethyl 4-methyl-3-oxo-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pentanoate ***(2f)***. Colorless oil. IR (cm^{-1}) 1748, 1719, 1182; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.23 – 4.11 (m, 2H), 3.10 – 2.99 (m, 1H), 1.55 – 1.32 (m, 6H), 1.24 (t, J = 7.1 Hz, 3H), 1.19 – 1.13 (m, 6H), 1.09 (d, J = 7.0 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H), 1.02 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0, 168.2, 92.7, 61.6, 60.5, 60.0, 40.3, 40.2, 37.4, 33.0, 32.8, 20.3, 20.2, 19.2, 17.7, 17.0, 14.1. HRMS (ESI) calcd for $C_{17}H_{31}NO_4Na$ $(M+Na)^+$ 336.2145, found 336.2147.

Ethyl 3-oxo-3-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propanoate ***(2g)***. Colorless oil. IR (cm^{-1}) 1749, 1686, 1181; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.7 Hz, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 5.38 (s, 1H), 4.22 –4.10 (m, 2H), 1.69 – 1.33 (m, 6H), 1.32 – 1.24 (m, 3H), 1.19 – 1.13 (m, 6H), 0.98(s, 3H), 0.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.8, 168.3, 134.6, 133.8, 130.0, 128.6, 93.0, 61.8, 60.6, 60.1, 40.3, 40.1, 33.3, 32.6, 20.4, 20.3, 17.1, 14.1. HRMS (ESI) calcd for $C_{20}H_{29}NO_4Na$ $(M+Na)^+$ 370.1989, found 370.1987.

Dimethyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)malonate ***(2h)***. White soild: m.p. 86-87 ºC. IR (cm^{-1}) 1768, 1642, 1091; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (s, 1H), 3.76 (s, 6H), 1.56 – 1.29 (m, 6H), 1.16 (s, 6H), 1.02 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 86.6, 60.5, 52.7, 40.2, 32.6, 20.3, 17.1. HRMS (ESI) calcd for $C_{14}H_{25}NO_5Na$ $(M+Na)^+$ 310.1625, found 310.1623.

Diethyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)malonate ***(2i)***. White soild: m.p. 32-33 ºC. IR (cm^{-1}) 1764, 1737, 1186; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (s, 1H), 4.26 – 4.19 (m, 4H), 1.56 – 1.39 (m, 6H), 1.26 (t, *J* = 7.1 Hz, 6H), 1.17 (s, 6H), 1.05 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 86.9, 61.8, 60.4, 40.3, 32.7, 20.3, 17.1, 14.2. HRMS (ESI) calcd for $C_{16}H_{29}NO_5Na$ $(M+Na)^+$ 338.1938, found 338.1940.

3-((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)pentane-2,4-dione ***(2j)***. Light yellow soild: m.p. 54-55 ºC. IR (cm^{-1}) 1733, 1701, 1078; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (s, 1H), 2.20 (s, 6H), 1.45 – 1.36 (m, 6H), 1.17 (s, 6H), 0.95 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 101.7, 60.1, 40.2, 33.0, 27.2, 20.2, 17.0. HRMS (ESI) calcd for $C_{14}H_{25}NO_3Na$ $(M+Na)^+$ 278.1727, found 278.1732.

1,3-Diphenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propane-1,3-dione ***(2k)***. Light yellow soild: m.p. 164-165 ºC. IR (cm^{-1}) 1694, 1670, 1596, 1577, 1224; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.6 Hz, 4H), 7.53 (t, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 4H), 6.27 (s, 1H), 1.60 – 1.40 (m, 6H), 1.11 (s, 6H), 0.92 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 134.8, 133.9, 130.3, 128.6, 99.3, 60.3, 40.2,

33.1, 20.4, 17.1. HRMS (ESI) calcd for $C_{24}H_{29}NO_3Na$ $(M+Na)^+$ 402.2040, found 402.2040.

General procedure for preparation of compounds 3-37.

The solution of indole (0.5 mmol) and α-oxy-2,2,6,6-tetramethylpiperidin-1-yl dicarbonyl compounds (0.5 mmol) in CH_3CO_2H (3.0 mL) was stirred at room temperature for 3 hours. TLC indicate that the reaction is completed. The reaction solution was poured into the saturated $NaHCO_3$ solution (20 mL), the mixtures was extracted by ethyl acetate (15 mL×2). The organic phase was dried over Na_2SO_4, filtered, concentrated under reduced pressure. The residue was then purified by flash chromatography on 200~300 mesh silica gel to provide the corresponding product Ethyl 2-hydroxy-2-(1H-indol-3-yl)-3-oxobutanoate (**3-37**).

The spectra of compounds **3-5, 7-12, 14, 1620, 22-23,** 25-**28, 30-31** were analyzed in our early report[23]. Compound **34** was reported by Chakrabarty [25] and its ^1H NMR spectra was provided.

*Dimethyl 2-hydroxy-2-(4-hydroxy-1H-indol-3-yl)malonate **(6)***. Yield: 66%. White soild: m.p. 175-176 ºC; IR (cm^{-1}) 3385, 1757, 1730, 1594, 1231; ^1H NMR (400 MHz, Acetone-d_6) δ 10.37 (s, 1H), 7.37 (d, *J* = 2.7 Hz, 1H), 7.00 – 6.91 (m, 2H), 6.45 (dd, *J* = 7.5, 1.0 Hz, 1H), 3.78 (s, 6H), 3.11 – 2.81 (m, 2H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 171.1, 151.3, 140.2, 124.6, 116.6, 112.2, 106.2, 104.5, 79.5, 53.9; HRMS (ESI) calcd for $C_{13}H_{13}NO_6Na$ $(M+Na)^+$ 302.0635, found 302.0637.

*Ethyl 2-hydroxy-2-(5-hydroxy-1H-indol-3-yl)-3-oxobutanoate **(13)***. Yield: 94%. Yellow soild: m.p. 165-166 ºC; IR (cm^{-1}) 3353, 1743, 1698, 1195; ^1H NMR (400 MHz, Acetone-d_6) δ 10.16 (s, 1H), 7.70 (s, 1H), 7.46 (d, *J* = 2.6 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 1H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.71 (dd, *J* = 8.7, 2.2 Hz, 1H), 5.40 (s, 1H), 4.31 – 4.20 (m, 2H), 2.15 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 205.1, 171.5, 151.9, 132.6, 127.4, 125.8, 112.8, 112.1, 105.5, 83.5, 62.5, 25.0, 14.4; HRMS (ESI) calcd for $C_{14}H_{15}NO_5Na$ $(M+Na)^+$ 300.0842, found 300.0838.

*Ethyl 2-hydroxy-2-(5-nitro-1H-indol-3-yl)-3-oxobutanoate **(15)***. Yield: 64%. Yellow solid: m.p. 108-109 ºC; IR (cm^{-1}) 3353, 1716, 1521, 1332, 1237; ^1H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.67 (s, 1H), 8.11 (d, *J* = 9.0 Hz, 1H), 7.66 (s, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 4.83 (s, 1H), 4.48 – 4.29 (m, 2H), 2.30 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5, 170.1, 142.2, 139.5, 127.2, 124.6, 118.4, 118.1, 114.3, 111.6, 82.1, 63.4, 24.7, 14.0; HRMS(ESI) calcd for $C_{14}H_{14}N_2O_6Na$ $(M+Na)^+$ 329.0750, found 329.0753.

*Ethyl 2-(7-bromo-1H-indol-3-yl)-2-hydroxy-3-oxobutanoate **(21)***. Yield: 60%. White soild: m.p. 100-102 ºC; IR (cm^{-1}) 3356, 1715, 1094; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.56 – 7.50 (m, 2H), 7.34 (d, *J* = 7.6 Hz, 1H), 6.98 (t, *J* = 7.9 Hz, 1H), 4.76 (s, 1H), 4.41 – 4.23 (m, 1H), 2.21 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.4, 170.3, 135.3, 126.4, 125.1, 124.8, 121.7, 119.9, 113.4, 105.0, 82.3, 63.1, 24.9, 14.2 ; HRMS (ESI) calcd for $C_{14}H_{14}BrNO_4Na$ $(M+Na)^+$ 361.9998, found 362.0006 .

*Ethyl 2-hydroxy-2-(2-methyl-1H-indol-3-yl)-3-oxobutanoate **(24)***. Yield: 80%. Yellow soild: m.p. 107-108 ºC; IR (cm^{-1}) 3369, 1715, 1254; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 0.34H), 8.04 (s, 0.72H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.23 (d, *J* = 7.0 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 4.70 (s, 0.32H), 4.68 (s, 0.72H), 4.43 – 4.24 (m, 2H), 2.39 (s, 2.10H), 2.36 (s, 1.06H), 2.29 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.2, 171.4, 135.1, 134.3, 127.0, 121.7, 120.4, 119.3, 110.7, 106.8, 82.5, 62.8, 25.7, 14.2, 13.7, 13.6; HRMS (ESI) calcd for $C_{15}H_{17}NO_4Na$ $(M+Na)^+$ 298.1050, found 298.1053.

*Ethyl 2-hydroxy-2-(1H-indol-3-yl)-4-methyl-3-oxopentanoate **(29)***. Yield: 92%. Yellow soild: m.p. 114-116 ºC; IR (cm^{-1}) 3445, 3400, 1712, 1695, 1098; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 4.88 (s, 1H), 4.41 – 4.24 (m, 2H), 3.25 – 3.12 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.1, 170.4, 136.3, 125.4, 124.5, 122.4, 120.5, 120.2, 111.4, 111.3, 82.3, 62.7, 35.4, 20.4, 19.8, 14.1; HRMS (ESI) calcd for $C_{16}H_{19}NO_4Na$ $(M+Na)^+$ 312.1206, found 312.1209.

*2-Hydroxy-2-(1H-indol-3-yl)-1,3-diphenylpropane-1,3-dione **(32)***. Yield: 81%. Yellow soild: m.p. 162-164 ºC; IR (cm^{-1}) 3403, 1688, 1656, 1229; ^1H NMR (400 MHz, Acetone-d_6) δ 10.42 (s, 1H), 8.09 (d, *J* = 7.6 Hz, 4H), 7.58 – 7.48 (m, 3H), 7.46 – 7.26 (m, 6H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.33 (s, 1H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 198.8, 138.2, 134.2, 131.8, 129.4, 127.4, 126.3, 123.1,

122.2, 120.7, 115.5, 112.9, 87.2. HRMS (ESI) calcd for $C_{23}H_{17}NO_3Na$ $(M+Na)^+$ 378.1106, found 378.1109.

Dimethyl 2-hydroxy-2-(1H-indol-3-yl)malonate ***(33)***. Yield: 93%. White soild: m.p. 102-103 ºC; IR (cm^{-1}) 3331, 1732, 1239; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.39 (s, 1H), 7.31 (d, J = 6.4 Hz, 1H), 7.22 – 7.15 (m, 1H), 7.14 – 7.07 (m, 1H), 4.34 (s, 1H), 3.82 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 136.6, 125.4, 124.2, 122.6, 120.7, 120.4, 112.0, 111.6, 77.8, 53.9; HRMS (ESI) calcd for $C_{13}H_{13}NO_5Na$ $(M+Na)^+$ 286.0686, found 286.0687.

Diethyl 2-hydroxy-2-(1H-indol-3-yl)malonate ***(34)***. Yield: 98%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.72 (s, 0.45H), 7.70 (s, 0.55H), 7.40 (d, J = 2.0 Hz, 0.58H), 7.37 (d, J = 2.4 Hz, 0.47H), 7.29 (t, J = 8.1 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 4.37 – 4.23 (m, 5H), 1.27 (t, J = 7.1 Hz, 6H).

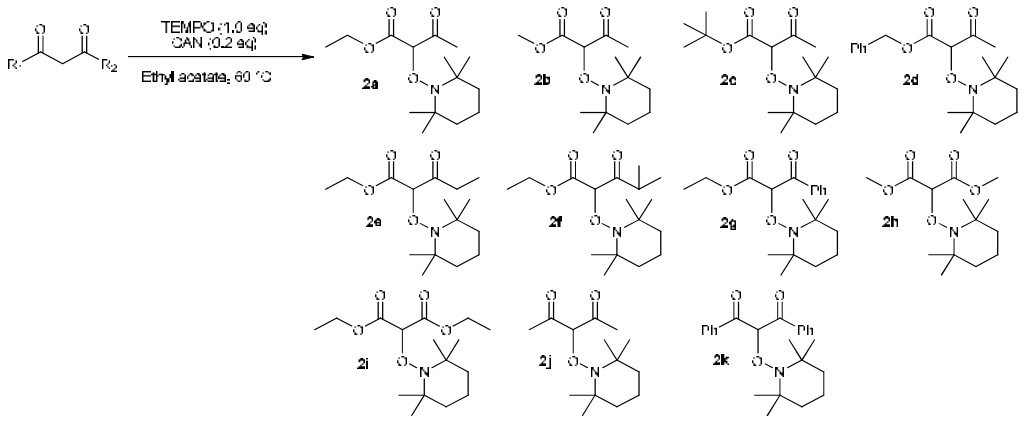
Ethyl 2-hydroxy-3-oxo-2-(1H-pyrrolo[2,3-b]pyridin-3-yl)butanoate ***(35)***. Yield: 53%. Yellow oil; IR (cm^{-1}) 3260, 1712, 1278; ^1H NMR (400 MHz, $CDCl_3$) δ 11.71 (s, 1H), 8.30 (d, *J* = 4.6 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.70 (s, 1H), 7.08 (dd, *J* = 8.0, 4.8 Hz, 1H), 5.26 (s, 1H), 4.41 – 4.24 (m, 2H), 2.23 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.4, 170.5, 149.0, 142.9, 129.9, 125.0, 118.5, 116.3, 110.3, 82.5, 63.0, 24.8, 14.2; HRMS (ESI) calcd for $C_{13}H_{14}N_2O_4Na$ $(M+Na)^+$ 285.0846, found 285.0837.

Ethyl 2-(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-hydroxy-3-oxobutanoate ***(36)***. Yield: 65%. White soild: m.p. 155-156 ºC; IR (cm^{-1}) 3262, 1742, 1715, 1249; ^1H NMR (400 MHz, $CDCl_3$) δ 10.93 (s, 1H), 8.37 (d, *J* = 2.0 Hz, 1H), 8.21 (d, *J* = 1.9 Hz, 1H), 7.72 (d, *J* = 2.3 Hz, 1H), 4.98 (s, 1H), 4.43 – 4.28 (m, 2H), 2.26 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 170.4, 147.3, 143.9, 132.4, 126.3, 120.1, 112.3, 110.3, 82.5, 63.5, 24.7, 14.2; HRMS (ESI) calcd for $C_{13}H_{13}BrN_2O_4Na$ $(M+Na)^+$ 362.9951, found 362.9957.

Dimethyl 2-hydroxy-2-(1-methyl-1H-pyrrol-3-yl)malonate ***(37)***. Yield: 61%. Colorless oil; IR (cm^{-1}) 3466, 1735; ^1H NMR (400 MHz, $CDCl_3$) δ 6.61 (t, *J* = 2.2 Hz, 1H), 6.04 – 6.02 (m, 2H), 4.06 (s, 1H), 3.88 (s, 6H), 3.57 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 126.5, 125.2, 110.0, 106.5, 53.8, 35.0; HRMS (ESI) calcd for $C_{10}H_{13}NO_5Na$ $(M+Na)^+$ 250.0686, found 250.0692.

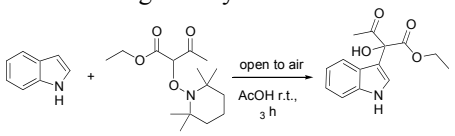
Results and Discussion

Initially, α-position TEMPO-substituted 1,3-dicarbonyl compounds (**2a-2k**) (Scheme 1) were prepared according to the method reported in the literature [24]. α-Aminoxylated ethyl acetoacetate and indole was selected as model substrates to investigate the tandem reaction. As shown in table 1, the choice of solvent influenced the reaction significantly: organic acid such as acetic acid, propionic acid, butyric acid all could promote the reaction to afford ethyl 3-methylquinoxaline-2-carboxylate **3** in high yields (Table 1, entries 1-3). Non-acidic solvents such as THF, acetonitrile, toluene, are all the poor solvent for the domino process, extended reaction time and elevated reaction temperature all didn't improve the reaction results (Table 1, entries 4-6). In presence of stoichiometric organic base or acid also didn't promote the transformation. Therefore, the optimal conditions for the tertiary alcohol forming reaction start with indole **1a** (0.5 mmol) and α-TEMPO ethyl acetoacetate **2a** (0.5 equiv) was stirred in acetic acid at room temperature for 3 hours.



Scheme 1 The synthesis of α-position TEMPO-substituted β-dicarbonyl compounds.

Table 1. The synthesis of heterocycle-containing tertiary alcohols.[a]

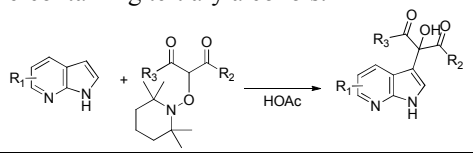


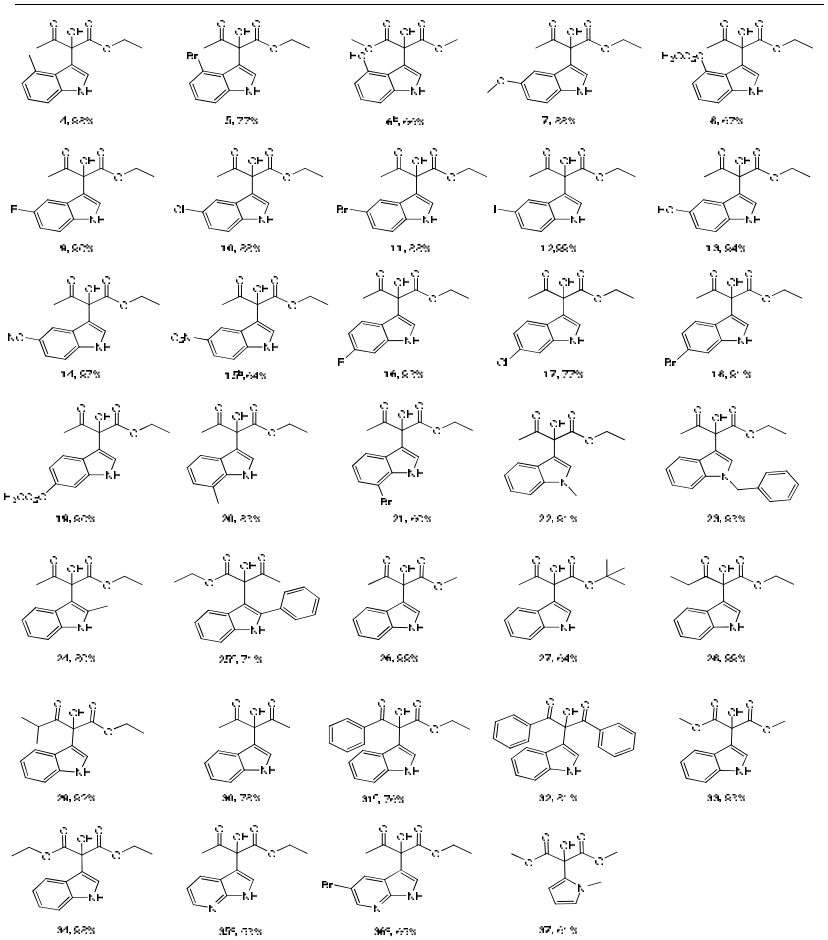
1a (0.5 mmol) **2a** (0.5 mmol) **3** (92%)

Entry	solvent	Temp/time	yields[b]
1	$MeCO_2H$	r.t./3h	92%
2	$EtCO_2H$	r.t./3h	88%
3	$PrCO_2H$	r.t./3h	85%
4	THF	Reflux/2 h	nr[c]
5	CH_3CN	Reflux/2 h	nr
6	PhMe	Reflux/2 h	nr
7[d]	THF	Reflux/2 h	nr
8[e]	THF	Reflux/2 h	nr

[a] Reaction conditions: a mixture of Indole **1a** (0.5 mmol), **2a** (0.5 mmol) in the designated solvent was stirred at the indicated temperatures for the times indicated. [b] Isolated yields. [c] No reaction. [d] In presence of 1.1 mmol TEA. [e] In presence of 1.1 mmol HOAc.

Table-2: The scope of heterocycle-containing tertiary alcohols.[a]





[a] Reaction conditions: indoles **1** (0.5 mmol) and α-oxy-2,2,6,6-tetramethylpiperidin-1-yl dicarbonyl compounds **2** (0.5 mmol) in CH_3CO_2H (3.0 mL) was stirred at room temperature for 3 h. [b] Reaction was stirred at 60 °C for 10 h. [c] Reaction was stirred at 60 °C for 4 h. [d] Reaction was stirred at 60 °C for 8 h.

The generality of this process was examined (Table 2). The results demonstrated that the domino process is applicable to a wide range of indoles and β-dicarbonyl compounds; as a result, it enables ready synthetic access to diverse indole-containing tertiary alcohol at their β-positions. Specifically, indoles possessing a variety of electronically different substituents, including halogen, alkyl, alkoxy, cyano and methoxy carbonyl groups at different positions on the bezene ring undergo reaction to produce the corresponding substituted tertiary alcohol in good to excellent yields (Table 2, compounds **4, 5, 7-12, 14, 16-21**). Group containing active protons, such as HO-substituted indole, also transformed smoothly in the process and gave the corresponding title products in good to excellent yields (compounds **6** and **13**). 5-Nitro indole affording target tertiary alcohol (**15**) in 64% yield need 10 h at 60 °C due to the strong electron-withdrawing properties of the nitro group. *N*-methyl and *N*-benzyl indoles also react with TEMPO-substituted ethyl acetoacetate to form the coupling products in excellent yields (compounds **22** and **23**). 2-Methyl- and 2-phenylindole, containing a C-2 substituent, also reacts to form the corresponding alcohol (compounds **24** and **25**) with a mixture of atropisomers, owing to the presence of the methyl and phenyl group limits free rotation about the C-C bond connecting the indole and hydroxyacetoacetate group, in good yield (see ^{1}H and ^{13}C NMR spectral data). Apart from various indoles, 7-azaindole and pyrrole also performed well in this transformation, and provided 7-azaindole- (compounds **35** and **36**) and pyrrole-containing tertiary alcohol (**37**) in acceptable yield. TEMPO-substituted β-keto esters containing sterically different substituents subjected to the tandem reaction afford the corresponding indole-containing tertiary alcohol in good to excellent yields (compounds **26~29, 31**) under optimized conditions. TEMPO-substituted β-diketone, such as acetyl acetone and dibenzoylmethane, reacted with indole also resulting in the desired tertiary alcohol in good yields (compounds **30** and **32**).TEMPO-substituted dimethyl malonate and diethyl malonate subjected to the domino process affording the target products in almost quantitative yields (**33** and **34**).

The proposed mechanism for the formation of **3** was shown in Figure 1. Initially, the α-position TEMPO-substituted ethyl acetoacetate **2a** undergoes loss of tetramethylpiperidine (TEMPH) through acidic elimination by the protonation route to form ethyl 2,3-dioxobutanoate **A**. Accordingly, in presence of acetic acid, indole adds to diketone ester **A** to form indolylcarbinols **3** through the Friedel-Crafts reaction.

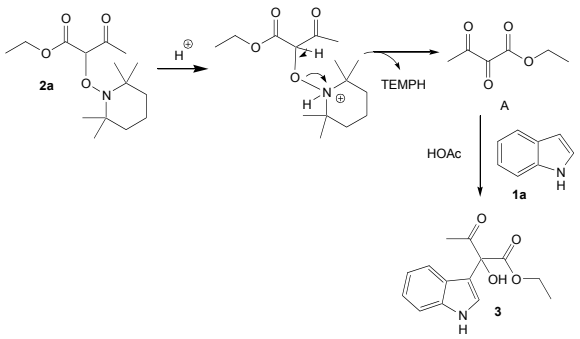


Fig. 1: Proposed mechanism.

Conclusion

In conclusion, an efficient, and operationally simple method to afford indole-, 7-azaindole-, and pyrrole-containing tertiary alcohols was developed, which is compatible with a wide range of substituents and substitute patterns. Importantly, these processes, which generate diverse tertiary alcohols, take place under mild conditions and without the need for dry solvents or harsh reaction conditions. Further investigations probing the synthesis of heterocycle derivatives and the biological properties of new substances produced are underway and will be described in due course.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 81172953).

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