Supplementary information

Three-component access to pyrroles promoted by the CAN/silver nitrate system under high-speed vibration milling. A generalization of the Hantzsch pyrrole synthesis

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General experimental information

Mechanochemical reactions were carried out in a Retsch MM200 mixer mill at a frequency of 20 Hz using a 25 mL zirconium oxide grinding jar and a single zirconium oxide ball 20 mm in diameter.

Melting points were measured with a Reichert 723 hot-stage microscope. Infrared spectra were recorded with a Perkin–Elmer Paragon 1000 FTIR spectrophotometer as thin films on NaCl disks.

NMR spectroscopic data were recorded using a Bruker Avance 250 spectrometer operating at 250 MHz for $^1$H NMR and 63 MHz for $^{13}$C NMR, respectively (CAI de Resonancia Magnética Nuclear, Universidad Complutense).

Elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 combustion microanalyzer.

All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS) were of commercial quality and were used as received.

Reactions were monitored by thin layer chromatography on aluminium plates coated with silica gel and fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC 40–63 µm).
General procedure for the preparation of pyrroles 4

The suitable ketone (1.00 mmol), N-iodosuccinimide (NIS, 225 mg, 1.00 mmol) and p-toluenesulphonic acid (18 mg, 10% mmol) were added to a ball mill vessel along with a zirconium oxide ball. The vessel was fixed to a horizontal vibratory arm and it was allowed to vibrate for 60 min at a frequency of 20 s\(^{-1}\). Then, a mixture of the corresponding amine (1.95 mmol), the suitable \(\beta\)-dicarbonyl compound (1.5 mmol) and ceric ammonium nitrate (CAN, 27 mg, 5% mmol), previously stirred at room temperature during 30 min, and silver nitrate (169 mg, 1.00 mmol) were added to the vessel. The reaction was subjected to the vibratory movement for 60 min at the same frequency. Then, the vessel was cleansed with ethyl acetate and the suspension was filtered to remove silver iodide. The organic layer was washed with water (2 mL), dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure. Purification by column chromatography on silica gel eluting with a petroleum ether-ethyl acetate mixture afforded the desired pyrroles 4.

Compounds 4l, 4m and 4p were prepared following the general procedure from the previously isolated corresponding \(\alpha\)-iodoketones (1.00 mmol) (see pages S14-S16).
Ethyl 2-methyl-5-phenyl-1-(p-tolyl)-1H-pyrrole-3-carboxylate (4a). Prepared from acetophenone (120 mg, 1.00 mmol), p-toluidine (162 mg, 1.5 mmol) and ethyl acetoacetate (195 mg, 1.5 mmol); yield: 271 mg (85%); yellowish solid; mp: 95-98 °C; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta = 1.41$ (t, $J = 7.1$ Hz, 3H), 2.41 (s, 3H), 2.43 (s, 3H), 4.36 (q, $J = 7.1$ Hz, 2H), 6.83 (s, 1H), 7.11-7.03 (m, 4H), 7.29-7.15 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta = 12.5, 14.5, 21.1, 59.5, 109.8, 112.6, 126.4, 128.0, 128.1, 129.8, 132.4, 133.5, 135.4, 138.1, 165.6$ ppm; IR (neat) $\nu = 1703.1, 1226.6$ cm$^{-1}$; elemental analysis (%) calcd. for C$_{21}$H$_{21}$NO$_2$: C 78.9, H 6.63, N 4.39; found: C 78.59, H 6.84, N 4.11.

Ethyl 1-butyl-2-methyl-5-phenyl-1H-pyrrole-3-carboxylate (4b). Prepared from acetophenone (120 mg, 1.00 mmol), butylamine (143 mg, 1.95 mmol) and ethyl acetoacetate (195 mg, 1.5 mmol); yield: 242 mg (85%); light orange solid; mp: 49-53 °C; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta = 0.82$ (t, $J = 7.2$ Hz, 3H), 1.19 (sext, $J = 7.2$ Hz, 2H), 1.38 (t, $J = 7.1$ Hz, 3H), 1.60-1.48 (m, 2H), 2.65 (s, 3H), 3.93- 3.87 (m, 2H), 4.32 (q, $J = 7.1$ Hz , 2H), 6.58 (s, 1H), 7.48-7.34 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta = 11.5, 13.5, 14.5, 19.7, 32.7, 43.8, 59.2, 109.6, 111.8, 127.4, 128.4, 129.3, 133.1, 133.4, 136.3, 165.6$ ppm; IR (neat) $\nu = 1699.4, 1243.3$ cm$^{-1}$; elemental analysis (%) calcd. for C$_{18}$H$_{23}$NO$_2$: C 75.76, H 8.12, N 4.91; found: C 75.55, H 7.85, N 4.78.
Ethyl 1-sec-butil-5-phenyl-2-methyl-1H-pyrrole-3-carboxylate (4c). Prepared from acetophenone (120 mg, 1.00 mmol), sec-butyamine (143 mg, 1.95 mmol) and ethyl acetoacetate (195 mg, 1.5 mmol); yield: 265 mg (93%); yellow viscous liquid; $^1$H NMR (CDCl$_3$, 250 MHz): δ= 0.70 (t, J = 7.4 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H), 1.51 (d, J = 7.1 Hz, 3H), 1.76-1.63 (m, 1H), 1.98-1.86 (m, 1H), 2.74 (s, 3H), 4.28-4.19 (m, 1H), 4.30 (q, J = 7.1 Hz, 2H), 6.51 (s, 1H), 7.42-7.31 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): δ=11.0, 13.0, 14.5, 20.7, 28.9, 54.5, 59.2, 109.8, 112.3, 127.5, 128.2, 130.1, 134.0, 134.7, 136.1 165.8 ppm; IR (neat) ν=1698.6, 1242.6 cm$^{-1}$; elemental analysis (%) calcd. for C$_{18}$H$_{23}$NO$_2$: C 75.76, H 8.12, N 4.91; found: C-75.08, H 7.94, N 4.80.

Ethyl 1-benzyl-5-phenyl-2-methyl-1H-pyrrole-3-carboxylate (4d). Prepared from acetophenone (120 mg, 1.00 mmol), benzyamine (161 mg, 1.5 mmol) and ethyl acetoacetate (195 mg, 1.5 mmol); yield: 230 mg (68%); yellow viscous liquid; $^1$H NMR (CDCl$_3$, 250 MHz): δ = 1.40 (t, J = 7.1 Hz, 3H), 2.49 (s, 3H), 5.17 (s, 2H), 4.33 (q, J = 7.1 Hz, 2H), 6.72 (s, 1H), 6.95 (dd, J = 6.5, 1.6 Hz, 2H), 7.34-7.28 (m, 8H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): δ = 11.6, 14.5, 41.7, 59.4, 109.8, 112.5, 125.5, 127.3, 127.5, 128.4, 128.8, 129.0, 132.5, 134.2, 137.0, 137.6, 165.7 ppm; IR (neat) ν = 1698.0, 1240.5 cm$^{-1}$; elemental analysis (%) calcd. for C$_{21}$H$_{21}$NO$_2$: C 78.97, H 6.63, N 4.39; found: C 78.65, H 6.84, N 4.15.
Ethyl 1-dimethylamino-2-methyl-5-phenyl-1H-pyrrole-3-carboxylate (4e). Prepared from acetophenone (120 mg, 1.00 mmol), N,N-dimethyl-hydrazine (90 mg, 1.5 mmol) and ethyl acetoacetate (195 mg, 1.5 mmol); yield: 191 mg (60%); reddish oil; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta$ = 1.37 (t, $J$ = 7.1 Hz, 3H), 2.71 (s, 3H), 2.95 (s, 6H), 4.30 (q, $J$ = 7.1 Hz, 2H), 6.53 (s, 1H), 7.32 - 7.43 (m, 3H), 7.52 (dd, $J$ = 8.3, 1.8 Hz, 2H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta$ = 12.1, 14.5, 45.2, 59.3, 107.4, 110.3, 127.0, 127.8, 129.0, 132.7, 137.3, 165.3 ppm; IR (neat) $\nu$ = 1695.8, 1241.8 cm$^{-1}$; elemental analysis (%) calcd. for C$_{16}$H$_{20}$N$_2$O$_2$: C 70.56, H 7.40, N 10.29; found: C 70.96, H 7.45, N 10.19

Ethyl 1-butyl-5-phenyl-2-propyl-1H-pyrrole-3-carboxylate (4f). Prepared from acetophenone (120 mg, 1.00 mmol), butylamine (143 mg, 1.95 mmol) and ethyl-3-oxohexanate (237 mg, 1.5 mmol); yield: 250 mg (80%); yellow oil; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta$ = 0.80 (t, $J$ = 7.2 Hz, 3H), 1.07 (t, $J$ = 7.3 Hz, 3H), 1.13-1.22 (m, 2H), 1.37 (t, $J$ = 7.1 Hz, 3H), 1.43 -1.57 (m, 2H), 1.65-1.78 (m, 2H), 2.96-3.02 (m, 2H), 3.87-3.94 (m, 2H), 4.34 (q, $J$ = 7.1 Hz, 2H), 6.58 (s, 1H), 7.33-7.47 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta$ = 13.5, 14.3, 14.5, 19.8, 23.6, 27.7, 33.3, 43.9, 59.2, 110.0, 111.5, 127.4, 128.4, 129.3, 133.2, 133.3, 141.1, 165.3 ppm; IR (neat) $\nu$ = 1698.8, 1242.2 cm$^{-1}$; elemental analysis (%) calcd. for C$_{20}$H$_{27}$NO$_2$: C 76.55, H 9.48, N 4.25; found: C 76.21, H 9.28, N 4.31.
Ethyl 2-ethyl-1-hexyl-5-phenyl-1H-pyrrole-3-carboxylate (4g). Prepared from acetophenone (120 mg, 1.00 mmol), hexylamine (197 mg, 1.95 mmol) and ethyl 3-oxopentanoate (216 mg, 1.5 mmol); yield: 229 mg (70%); yellow oil; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta$ = 0.81 (t, $J$ = 6.5 Hz, 3H), 1.01-1.20 (m, 6H), 1.27 (t, $J$ = 7.5 Hz, 3H), 1.35 (t, $J$ = 7.1 Hz, 3H), 1.42-1.60 (m, 2H), 3.04 (q, $J$ = 7.5 Hz, 2H), 3.84-3.90 (m, 2H), 4.29 (q, $J$ = 7.1 Hz, 2H), 6.55 (s, 1H), 7.45-7.31 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta$ = 13.9, 14.5, 19.0, 22.3, 26.2, 31.1, 31.2, 44.0, 59.2, 110.0, 111.1, 127.4, 125.3, 128.4, 133.2, 133.3, 142.3, 165.3 ppm; IR (neat) $\nu$ = 1698.8, 1241.9 cm$^{-1}$; elemental analysis (%) calcd. for C$_{21}$H$_{29}$NO$_2$: C 77.02, H 8.93, N 4.28; found: C 77.32, H 8.83, N 4.22;

Ethyl 1-butyl-2-(ethoxycarbonylmethyl)-5-phenyl-1H-pyrrole-3-carboxylate (4h). Prepared from acetophenone (120 mg, 1.00 mmol), butylamine (142 mg, 1.95 mmol) and diethyl 3-oxopentanedioate (303 mg, 1.5 mmol); yield: 218 mg (61%); white solid; mp: 55-58 ºC; $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ = 0.78 (t, $J$ = 7.2 Hz, 3H), 1.08-1.23 (m, 2H), 1.31 (t, $J$ = 7.1 Hz, 3H), 1.35 (t, $J$ = 7.1 Hz, 3H), 1.43-1.55 (m, 2H), 3.87-3.93 (m, 2H), 4.18 (s, 2H), 4.22 (q, $J$ = 7.1 Hz, 2H), 4.28 (q, $J$ = 7.1 Hz, 2H), 6.61 (s, 1H), 7.34-7.47 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz) $\delta$ = 13.4, 14.2, 14.4, 19.7, 31.6, 32.9, 44.2, 59.5, 61.1, 110.1, 113.5, 127.6, 128.4, 129.4, 131.6, 133.0, 134.3, 165.1, 170.1 ppm; IR (neat) $\nu$ = 1738.3, 1698.2, 1246.7, 1222.8 cm$^{-1}$; elemental analysis (%) calcd for C$_{21}$H$_{27}$NO$_4$: C, 70.56; H, 7.61; N, 3.92; found: C 70.28, H 7.35, N 4.06.
1-(1-Butyl-2-methyl-5-phenyl-1H-pyrrole-3-yl)ethanone (4i). Prepared from acetophenone (120 mg, 1.00 mmol), butylamine (143 mg, 1.95 mmol) and 2,5-pentanedione (150 mg, 1.5 mmol); yield: 207 mg (81%); yellow liquid; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta = 0.82$ (t, $J = 7.2$ Hz, 3H), 1.15-1.25 (m, 2H), 1.48-1.61 (m, 2H), 2.38 (s, 3H), 2.57 (s, 3H), 3.86-3.93 (m, 2H), 6.50 (s, 1H), 7.35-7.49 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta = 12.1$, 13.5, 19.7, 28.5, 32.6, 43.6, 110.9, 120.8, 127.6, 128.5, 129.4, 132.9, 133.2, 135.9, 195.1 ppm; IR (neat) $\nu = 1650.7$ cm$^{-1}$; elemental analysis (%) calcd. for C$_{17}$H$_{21}$NO: C 79.96, H 8.29, N 5.49; found: C 79.77, H 7.93, N 5.32.

1-Hexyl-2-methyl-5-phenyl-1H-pyrrole-3-carboxamide (4j). Prepared from acetophenone (120 mg, 1.00 mmol), hexylamine (197 mg, 1.95 mmol) and acetoacetamide (151 mg, 1.00 mmol); yield: 256 mg (90%); white solid; mp: 126-129 °C; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta = 0.84$ (t, $J = 7.0$ Hz, 3H), 1.15-1.25 (m, 6H), 1.51-1.58 (m, 2H), 2.66 (s, 3H), 3.83-3.90 (m, 2H); 5.71 (br s, 2H), 6.27 (s, 1H), 7.33-7.44 (m, 5H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta = 11.4$, 13.8, 22.3, 26.1, 30.5, 31.0, 43.9, 107.1, 113.6, 127.4, 128.4, 129.4, 133.0, 133.3, 134.9, 168.1 ppm; IR (neat) $\nu = 3403.4$, 3195.7, 1637.7, 1600.5 cm$^{-1}$; elemental analysis (%) calcd. for C$_{18}$H$_{24}$N$_2$O: C 76.02, H 8.51, N 9.85; found: C 75.25, H 8.19, N 9.67.
**Ethyl 1-butyl-2-methyl-5-(2-naphth-2-yl)-1H-pyrrole-3-carboxylate (4k).** Prepared from 1-naphthalen-2-yl ethane (169 mg, 1.00 mmol), butylamine (143 mg, 1.95 mmol) and ethyl acetoacetate (195 mg, 1.5 mmol); yield: 324 mg (97%); yellow viscous liquid; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta$ = 0.82 (t, $J$ = 7.2 Hz, 3H), 1.20 (sext, $J$ = 7.2 Hz, 2H), 1.41 (t, $J$ = 7.1 Hz, 3H), 1.58 (q, $J$ = 7.2 Hz, 2H), 2.70 (s, 3H), 3.95-4.01 (m, 2H), 4.35 (q, $J$ = 7.1 Hz), 6.71 (s, 1H), 7.51-7.56 (m, 3H), 7.86-7.92 (m, 4H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta$ = 11.6, 13.5, 14.5, 19.7, 32.7, 44.0, 59.3, 110.2, 112.0, 126.1, 126.3, 127.3, 127.7, 127.9, 130.5, 132.4, 133.2, 133.3, 136.6, 165.6 ppm; IR (neat) $\nu$ = 1697.9, 1232.0 cm$^{-1}$; **elemental analysis (%)** calcd. for C$_{22}$H$_{25}$NO$_2$: C 78.77, H 7.51, N 4.18; found: C 78.43, H 7.71, N 4.05.

**Ethyl 1-butyl-5-(1H-indol-3-yl)-2-methyl-1H-pyrrole-3-carboxylate (4l).** Prepared from 1-(1H-indol-3-yl)-2-iodoethane (285 mg, 1.00 mmol), butylamine (143 mg, 1.95 mmol) and ethyl acetoacetate (195 mg, 1.5 mmol); yield: 243 mg (75%); yellow solid; mp: 87-91ºC; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta$ = 0.76 (t, $J$ = 7.3 Hz, 3H), 1.15 (sext, $J$ = 7.3 Hz, 2H), 1.38 (t, $J$ = 7.1 Hz, 3H), 1.46-1.58 (m, 2H), 2.67 (s, 3H), 3.85-3.91 (m, 2H), 4.32 (q, $J$ = 7.1 Hz, 2H), 6.65 (s, 1H), 7.18 (t, $J$ = 7.1 Hz, 1H), 7.24 (d, $J$ = 2.6 Hz, 1H), 7.27 (t, $J$ = 7.1 Hz, 1H), 7.46 (d, $J$ = 8.0 Hz, 1H), 7.59 (d, $J$ = 7.8 Hz, 1H), 8.33 (br s, 1H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta$ = 11.7, 13.5, 14.6, 19.7, 32.9, 44.0, 59.2, 108.9, 110.4, 111.2, 111.7, 119.8, 120.3, 122.5, 123.7, 125.6, 127.7, 135.7, 135.9, 165.8 ppm; IR (neat) $\nu$ = 3318.6, 1672.9, 1244.9 cm$^{-1}$; **elemental analysis (%)** calcd. for C$_{20}$H$_{24}$N$_2$O$_2$: C 74.04, H 7.46, N 8.64; found: C 73.89, H 7.29, N 8.41.
Ethyl 1-butyl-2-methyl-5-(thiophen-2-yl)-1H-pyrrole-3-carboxylate (4m). Prepared from 2-iodo-1-(thiophen-2-yl)-1-ethanone (252 mg, 1.00 mmol), butylamine (143 mg, 1.95 mmol) and ethyl acetoacetate (195 mg, 1.5 mmol); yield: 282 mg (97%); yellow viscous liquid; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta$ = 0.91 (t, $J$ = 7.2 Hz, 3H), 1.23-1.38 (m, 2H), 1.37 (t, $J$ = 7.1 Hz, 3H), 1.57-1.70 (m, 2H), 2.63 (s, 3H), 3.92-3.98 (m, 2H), 4.30 (q, $J$ = 2.5 Hz, 1H), 6.70 (s, 1H), 7.04 (dd, $J$ = 3.5, 1.2 Hz, 1H), 7.10 (t, $J$ = 7.1 Hz, 1H), 7.35 (dd, $J$ = 5.1, 1.2 Hz, 1H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta$ = 11.5, 13.6, 14.5, 19.8, 32.9, 44.1, 59.3, 111.5, 111.9, 125.3, 125.6, 126.5, 127.2, 134.0, 136.9, 165.4 ppm; IR (neat) $\nu$ = 1698.3, 1241.4 cm$^{-1}$; elemental analysis (%) calcd. for C$_{16}$H$_{21}$NO$_2$S: C 65.95, H 7.26, N 4.81, S 11.00; found: C 65.74, H 7.06, N 4.69, S 10.80.

Ethyl 1-butyl-5-tert-butyl-2-methyl-1H-pyrrole-3-carboxylate (4n). Prepared from 3,3-dimethyl-butan-2-one (100 mg, 1 mmol), butylamine (143 mg, 1.95 mmol) and ethyl acetoacetate (195 mg, 1.5 mmol); yield: 167 mg (67%); yellow oil; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta$ = 1.01 (t, $J$ = 7.2 Hz, 3H), 1.35 (t, $J$ = 7.1 Hz, 3H), 1.38 (s, 9H), 1.35-1.49 (m, 2H), 1.61-1.74 (m, 2H), 2.55 (s, 3H), 3.91-3.98 (m, 2H), 4.27 (q, $J$ = 7.1 Hz, 2H), 6.31 (s, 1H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): $\delta$ = 11.4, 13.7, 14.6, 20.2, 30.8, 31.9, 32.8, 45.3, 59.1, 105.6, 110.3, 136.7, 140.1, 165.7 ppm; IR (neat) $\nu$ = 1698.7, 1230.4 cm$^{-1}$; elemental analysis (%) calcd. for C$_{16}$H$_{27}$NO$_2$: C 72.41, H 10.25, N 5.28; found: C 71.57, H 9.94, N 5.26.
Ethyl 1-butyl-2,4-dimethyl-5-phenyl-1H-pyrrole-3-carboxylate (4o). Prepared from propiophenone (134 mg, 1.00 mmol), butylamine (143 mg, 1.95 mmol) and ethyl acetoacetate (195 mg, 1.5 mmol); yield: 215 mg (72%); yellow oil; $^1\text{H NMR}$ (CDCl$_3$, 250 MHz): $\delta = 0.74$ (t, $J = 7.2$ Hz, 3H), 1.11 (sext, $J = 7.2$ Hz, 2H), 1.36 (t, $J = 7.1$ Hz, 3H), 1.36-1.46 (m, 2H), 2.11 (s, 3H), 2.57 (s, 3H), 3.68-3.75 (m, 2H), 4.30 (q, $J = 7.1$ Hz, 2H), 7.23-7.43 (m, 5H) ppm; $^{13}\text{C NMR}$ (CDCl$_3$, 63 MHz): $\delta = 11.8, 13.4, 14.5, 19.7, 32.7, 43.7, 59.0, 110.9, 117.8, 127.5, 128.2, 130.7, 131.1, 132.5, 135.3, 166.5$ ppm; IR (neat) $\nu = 1692.7, 1253.1$ cm$^{-1}$; elemental analysis (%) calcd. for $\text{C}_{19}\text{H}_{25}\text{NO}_2$: C 76.22, H 8.42, N 4.68; found: C 75.94, H 8.75, N 4.38.

Ethyl 1-butyl-2-methyl-4,5-diphenyl-1H-pyrrole-3-carboxilate (4p). Prepared from 2-ido-1,2-diphenylethanone (322 mg, 1 mmol) butylamine (143 mg, 1.95 mmol) and ethyl acetoacetate (195 mg, 1.5 mmol); yield: 231 mg (64%); yellow oil; $^1\text{H NMR}$ (CDCl$_3$, 250 MHz): $\delta = 0.80$ (t, $J = 6.5$ Hz, 3H), 1.04 (t, $J = 7.1$ Hz, 3H), 1.18 (sext, $J = 7.5$ Hz, 2H), 1.47-1.61 (m, 2H), 2.67 (s, 3H), 3.78-3.85 (m, 2H), 4.11 (q, $J = 7.1$ Hz, 2H), 7.11-7.26 (m, 7H), 7.29-7.35 (m, 3H) ppm; $^{13}\text{C NMR}$ (CDCl$_3$, 63 MHz): $\delta = 11.7, 13.4, 13.8, 19.7, 32.7, 43.9, 59.1, 111.0, 123.6, 125.4, 126.7, 127.4, 128.0, 130.6, 131.2, 131.4, 132.1, 135.0, 166.0$ ppm; IR (neat) $\nu = 1693.2, 1230.7$ cm$^{-1}$; elemental analysis (%) calcd. for $\text{C}_{24}\text{H}_{27}\text{NO}_2$: C 79.74, H 7.53, N 3.87; found: C 79.94, H 7.35, N 3.72.
Ethyl 2-methyl-5-phenyl-1H-pyrrole-3-carboxylate (4q). Prepared from acetophenone (120 mg, 1 mmol); yield: 188 mg (82%); gray solid; mp: 100-104 °C; $^1$H NMR (CDCl$_3$, 250 MHz): δ = 1.40 (t, $J = 7.1$ Hz, 3H), 2.62 (s, 3H), 4.33 (q, $J = 7.1$ Hz, 2H), 6.87 (d, $J = 2.9$ Hz, 1H), 7.33-7.47 (m, 5H), 8.54 (br s, 1H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): δ = 13.4, 14.5, 59.5, 107.3, 113.4, 123.6, 126.5, 128.9, 129.9, 131.8 136.1, 165.5 ppm; IR (neat) ν = 1669.1, 1237.8 cm$^{-1}$; elemental analysis (%) calcd. for C$_{14}$H$_{15}$NO$_2$: C 73.34, H 6.59, N 6.11; found: C 73.11, H 6.30, N 5.77.

Ethyl 5-(p-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (4r). Prepared from 1-(4-chloro-phenyl)-ethanone (154 mg, 1.00 mmol); yield: 158 mg (60%); white solid; mp: 155-157 °C; $^1$H NMR (CDCl$_3$, 250 MHz): δ = 1.39 (t, $J = 7.1$ Hz, 3H), 2.61 (s, 3H), 4.32 (q, $J = 7.1$ Hz, 2H), 6.85 (d, $J = 2.9$ Hz, 1H), 7.33-7.43 (m, 4H), 8.69 (br s, 1H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz): δ = 13.4, 14.5, 59.7, 107.8, 113.5, 124.8, 128.9, 129.1, 130.3, 132.1, 136.6, 165.5 ppm; IR (neat) ν = 3321.8, 1672.1, 1235.2 cm$^{-1}$; elemental analysis (%) calcd. for C$_{14}$H$_{14}$ClNO$_2$: C 63.76, H 5.35, N 5.31; found: C 63.39, H 5.40, N 5.30
Diethyl 5,5'-((biphenyl-4,4'-diyl)bis(1-butyl-2-methyl-1H-pyrrole-3-carboxylate) (4s). Prepared from 1-((4'-acetyl)biphenyl-4-yl)ethanone (238 mg, 1.00 mmol), butylamine (285 mg, 3.9 mmol) and ethyl acetoacetate (390 mg, 3 mmol); iodination time: 120 min; yield: 533 mg (94%); yellow solid; mp: 178-181 °C; $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$: 0.85 (t, $J$ = 7.2 Hz, 6H), 1.18-1.31 (m, 4H), 1.39 (t, $J$ = 7.1 Hz, 6H), 1.52-1.62 (m, 4H), 3.92-4.00 (m, 4H), 2.66 (s, 6H), 4.32 (q, $J$ = 7.1 Hz, 4H), 6.63 (s, 2H), 7.47 (d, $J$ = 8.4 Hz, 4H), 7.72 (d, 4H, $J$ = 8.4 Hz) ppm; IR (neat) $\nu$ = 1697.8, 1246.3 cm$^{-1}$; $^{13}$C NMR (CDCl$_3$, 63 MHz) $\delta$: 11.6, 13.5, 14.5, 19.7, 32.7, 44.0, 59.3, 110.0, 112.0, 126.9, 129.6, 132.2, 133.0, 136.6, 139.3, 165.6 ppm; elemental analysis (%) calcd. for C$_{36}$H$_{44}$N$_2$O$_4$: C 76.02, H 7.80, N 4.93; found: C 75.66, H 7.55, N 5.03.

Diethyl 1,1'-(ethane-1,2-diyl)bis(2-methyl-5-phenyl-1H-pyrrole-3-carboxylate) (4t). Prepared from acetophenone (120 mg, 1.00 mmol), ethylenediamine (51 mg, 0.85 mmol) and ethyl acetoacetate (85 mg, 130 mmol); yield: 145 mg (60%); white solid; mp: 224-226 °C; $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ = 1.36 (t, $J$ = 7.1 Hz, 6H), 1.98 (s, 6H), 3.88 (s, 4H), 4.28 (q, $J$ = 7.1 Hz, 4H), 6.48 (s, 2H), 7.15-7.20 (m, 4H), 7.36-7.42 (m, 6H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz) $\delta$: 10.2, 14.5, 43.1, 59.3, 110.3, 112.4, 128.0, 128.6, 129.7, 132.0, 133.0, 136.1, 165.3 ppm; IR (neat) $\nu$ = 1701.6, 1242.9 cm$^{-1}$; elemental analysis (%) calcd. for C$_{30}$H$_{32}$N$_2$O$_4$: C 74.36, H 6.66, N 5.78; found: C 73.81, H 6.54, N 5.83.
General procedure for the iodination of ketones 1l and 1m

To a solution of the suitable ketone (1 eq) in anhydrous methanol, iodine (1 eq) and cupper (II) oxide (1 eq) were added. The mixture was stirred at rt for 5 min and, then, refluxed until no starting material was detected by TLC. The reaction was cooled, filtered and the solvent was removed. The residue was dissolved in ethyl acetate (10 mL) and washed with a 10% solution of Na$_2$S$_2$O$_3$ (20 mL). The aqueous phase was extracted with ethyl acetate (2 x 20 mL) and the combined organic phases were dried over anhydrous sodium sulphate and the solvent was evaporated. The α-iodoketones thus obtained were used in the next reaction without further purification.

\[ \text{R} \text{CH}_3 \xrightarrow{\text{I}_2, \text{CuO}, \text{MeOH, reflux}} \text{R} \text{I} \]

1-(1H-Indol-3-yl)-2-iodoethanone. Prepared from 1-(1H-indol-2-yl)ethanone (395 mg, 2.5 mmol); reaction time: 3 h; yield: 620 mg (87%); yellowish solid; mp: 87-89 ºC; IR (neat) ν = 3222.7 (N−H), 1635.7 (C=O) cm$^{-1}$; $^1$H NMR (CD$_3$OD, 250 MHz) δ = 4.94 (s, 2H), 7.25-7.28 (m, 2H), 7.45-7.51 (m, 1H), 8.19-8.24 (m, 1H), 8.30 (s, 1H) ppm; $^{13}$C NMR (CD$_3$OD, 63 MHz) δ = 3.5, 113.3, 115.0, 123.2, 123.8, 124.9, 127.5, 136.2, 138.9, 191.8 ppm.

\[ \text{O} \text{I} \]

2-Iodo-1-(thiophen-2-yl)ethanone. Prepared from 1-(thiophen-2-yl)ethanone (315 mg, 2.5 mmol); reaction time: 1 h; yield: 559 mg (89%); yellow solid.; mp: 130-134 ºC; IR (neat) ν = 1705.6 (C=O) cm$^{-1}$; $^1$H NMR (CDCl$_3$, 250 MHz) δ = 4.32 (s, 2H), 7.17 (dd, J = 7.3, 2.4 Hz, 1H), 7.71 (dd, J = 7.3, 2.4 Hz, 1H), 7.81 (dd, J = 3.9, 1.1 Hz, 1H) ppm; $^{13}$C NMR (CDCl$_3$, 63 MHz) δ = 1.4, 128.3, 133.4, 135.1, 140.2, 186.0 ppm.
Preparation of 2-bromo-1,2-diphenylethanone

To a flask protected from light with aluminium foil were added a suspension of 1,2-diphenylethanone 1p (1.96 g, 10 mmol) in water (5 mL) and a 48% aqueous solution of HBr (0.56 mL, 5 mmol). After stirring the reaction mixture at room temperature for 5 minutes, a 33% aqueous solution of H₂O₂ (0.51 mL, 5 mmol) was added. The additions of HBr and H₂O₂ were repeated twice within intervals of 2-3 h while the mixture was stirred. After 24 h, ethyl acetate (10 mL) was added and the organic layer was washed with a 10% solution of Na₂S₂O₃ (5 mL) and dried over anhydrous sodium sulphate. Removal of the solvent under reduce pressure and purification of the residue by column chromatography on silica gel, eluting with petroleum ether-ethyl ether (99:1), gave 2.59 g (95%) of the desired product as a white solid. Mp: 44-47 °C; IR (neat) ν: 1690.8, 990.3 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ = 6.42 (s, 1H), 7.35-7.61 (m, 8H), 8.02 (dt, J = 7.1, 1.2 Hz, 2H) ppm; ¹³C NMR (CDCl₃, 63 MHz) δ = 51.0, 128.8, 129.0, 129.1, 133.7, 134.1, 135.9, 191.0 ppm.¹

¹ A. Podgoršek, S. Stavber, M. Zupan and J. Iskra, Green Chem. 2007, 9, 1212.
Preparation of 2-iodo-1,2-diphenylethanone

A solution of sodium iodide (1.50 g, 10 mmol) in anhydrous acetone (10 mL) was added to a solution of 2-bromo-1,2-diphenylethanone (2.50 g, 9 mmol) in the same solvent (20 mL). The formation of sodium bromide or chloride precipitate was observed instantly. The reaction was stirred at rt for 10 min and, then, filtered. Removal of the solvent under reduced pressure afforded 2.90 g (99%) of the expected iodoketone as a pale orange solid. No further purification was needed. Mp: 91-93 °C; IR (neat) ν: 1680.1 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ = 6.65 (s, 1H), 7.46-7.57 (m, 2H), 7.60-7.66 (m, 3H), 7.33-7.37 (m, 3H), 8.04 (dt, J = 7.1, 1.2 Hz, 2H) ppm; ¹³C NMR (CDCl₃, 63 MHz) δ = 27.8, 128.7, 128.8, 129.0, 129.5, 133.6, 137.3, 192.2 ppm.²
