JOC The Journal of Organic Chemistry

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The Reductive Cyclization of o-Nitroarylated-#,#-Unsaturated Aldehydes and Ketones with TiCl3/HCl or Fe/HCl Leading to 1,2,3,9-Tetrahydro-4H-carbazol-4-ones and Related Heterocycles

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b01940 • Publication Date (Web): 05 Sep 2018

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The Reductive Cyclization of *o*-Nitroarylated-α,β-Unsaturated Aldehydes and Ketones with $TiCl_3$/HCl or Fe/HCl Leading to 1,2,3,9-Tetrahydro-4*H*-carbazol-4-ones and Related Heterocycles

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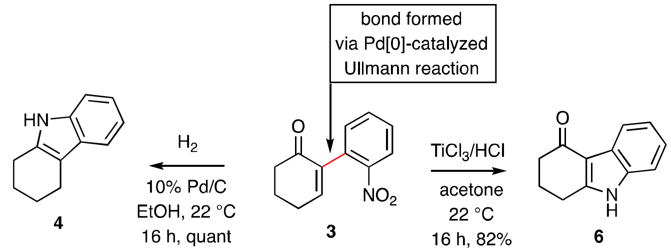
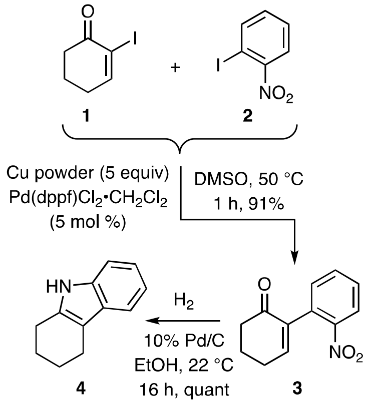
Compounds such as **3**, the product of a palladium[0]-catalyzed Ullmann cross-coupling of *o*-iodonitrobenzene and 2-iodocyclohex-2-en-1-one, undergo complementary modes of reductive cyclization depending upon the conditions employed. Thus, on treatment with hydrogen in the presence of palladium on carbon the tetrahydrocarbazole **4** is formed while reaction of the same substrate (**3**) with $TiCl_3$ in acetone affords the 1,2,3,9-tetrahydro-4*H*-carbazol-4-one **6**.



Introduction

Sometime ago[1] we reported that □-iodocyclohex-2-en-1-one (**1**) (Scheme 1) could be efficiently cross-coupled with *o*-iodonitrobenzene (**2**) in the presence of copper bronze and catalytic quantities of palladium[0] at 50 °C. Catalytic hydrogenation of the resulting *o*-nitroarylated cyclohexenone **3** then afforded the tetrahydrocarbazole **4**. We have since extended this two-step and related reaction sequences in a variety of settings, including ones that have led to a range of alkaloids as well as medicinally relevant heterocycles.[2]

Scheme 1: The palladium-catalyzed Ullmann cross-coupling/reductive cyclization sequence leading to tetrahydrocarbazole **4**

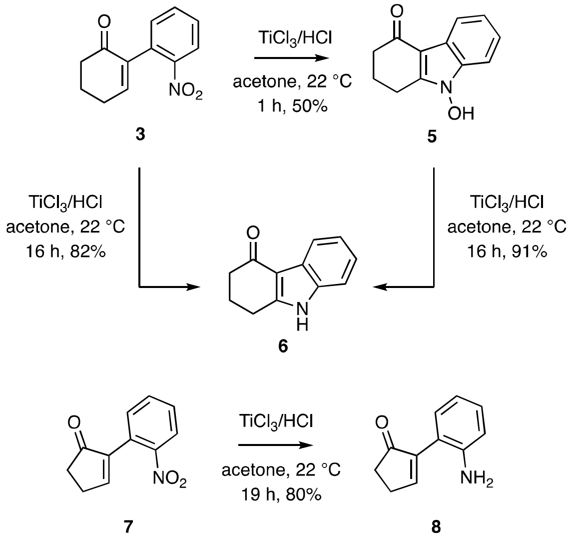


We now report that by treating cross-coupling products such as **3** with titanium trichloride[3]/HCl or iron/HCl[4] then quite distinct reductive cyclization processes takes place to give heterocyclic systems of biological interest.

Results and Discussion

As shown in Scheme 2, when compound **3** is treated with either titanium trichloride/HCl or iron/HCl at ambient temperatures for brief periods then the primary product of reaction is the *N*-hydroxytetrahydro-4*H*-carbazol-4-one **5**, the structure of which was confirmed by single-crystal X-ray analysis [see the Information (SI) for details]. Furthermore, when compound **3** or **5** was exposed to the same reagents for extended periods of time then the previously reported[5] tetrahydro-4*H*-carbazol-4-one **6** was obtained. Under optimal conditions ($TiCl_3$/HCl is generally the preferred reducing agent), the latter product could be obtained, as the exclusive one, from precursor **3** in 82% yield. Fe/HCl was much less effective in these conversions (see Experimental Section and SI for details). While the precise mode of formation of product **5** from substrate **3** remains to be established, it is clear that the former compound is a precursor to tetrahydrocarbazol-4-one **6**. The formation of compound **6** by the means just described is closely related to a protocol recently reported by Zhu and co-workers as a key step in their elegant total synthesis of aspidospermidine.[3f]

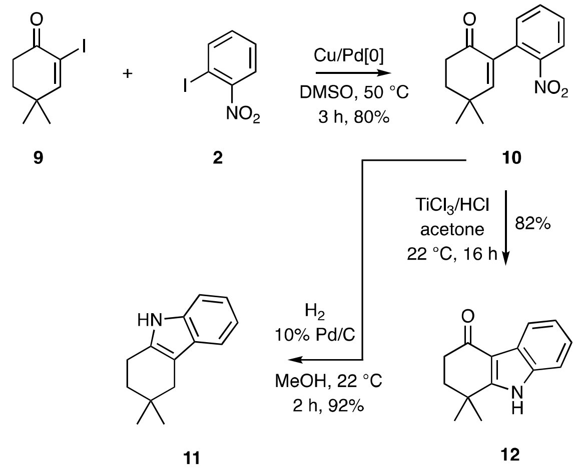
Scheme 2: The reductive cyclization of compound **3**, via *N*-hydroxyindole **5**, to 1,2,3,9-tetrahydro-4*H*-carbazol-4-one **6** and the direct reduction of nitroarene **7** to aniline **8**



The cyclization process appears to be sensitive to stereoelectronic effects as evidenced by the conversion of the cyclopentenone-appended nitroarene **7** into the corresponding aniline **8** (80%) rather than the lower homologue of heterocycle **6**. Interestingly, analogous treatment of the cycloheptenone-appended nitroarene (*viz*. the higher homologue of compound **3**) only led to complex mixtures of products.

The complementary nature of the original mode of reductive cyclization of the palladium-catalyzed Ullmann cross-coupling products and the one that can normally be best effected using $TiCl_3$/HCl is emphasized through the example shown in Scheme 3.

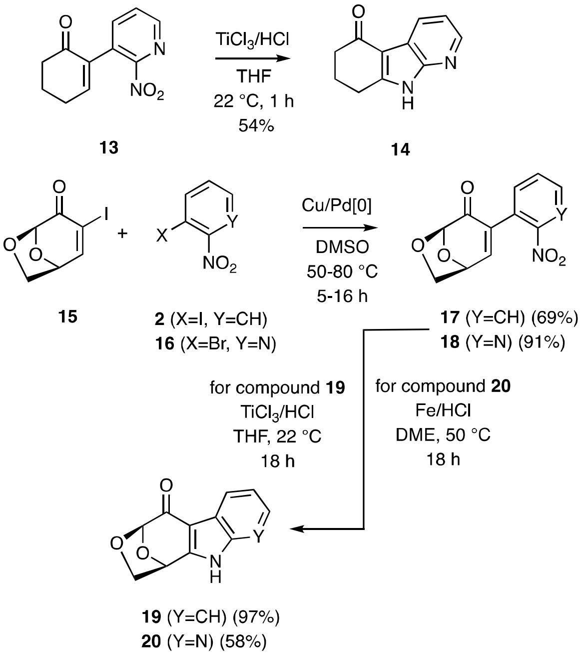
Scheme 3: The complementary behaviors of the cross-coupling product **10** under two distinct reductive cyclization conditions



Thus, cross-coupling of electrophiles **9**[6] and **2** using copper in the presence of catalytic Pd[0] afforded product **10** (80%) and on treatment of this with hydrogen in the presence of 10% palladium on carbon then the previously reported[7] *gem*-dimethylated tetrahydrocarbazole **11** is obtained in 92% yield. In contrast, on treating the same substrate with $TiCl_3$/HCl in acetone at ambient temperatures then compound **12**, an established precursor to demethoxycarazomycin B,[8] is obtained in 82% yield.

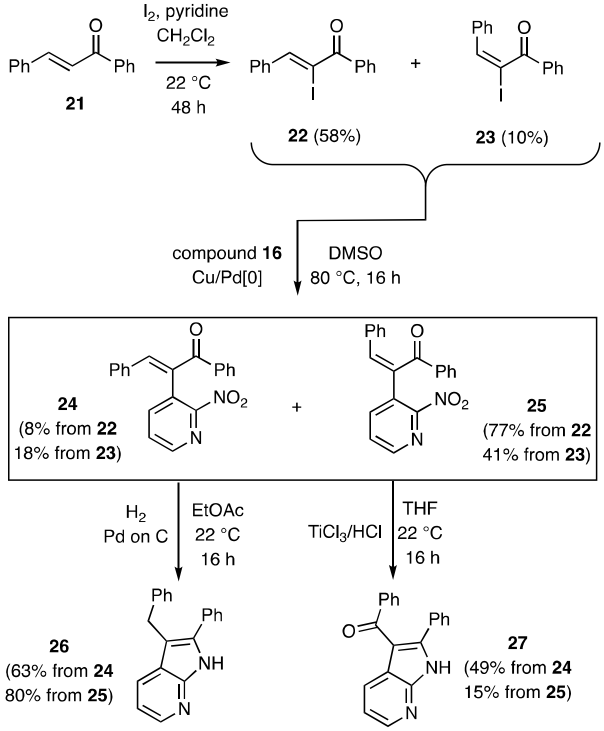
The utility of the "new" mode of reductive cyclization in establishing multi-heteroatom-containing ring systems is revealed through the examples shown in Scheme 4. Thus, exposure of the previously reported[9] coupling product **13** with $TiCl_3$/HCl gives the 7-azaindole **14** (54%) while the products derived from the cross-coupling of the homochiral iodide **15**[10] with aryl iodides **2** and **16**,[9] namely compounds **17** (69%) and **18** (91%), respectively, react with $TiCl_3$/HCl (in the former case) or Fe/HCl (in the latter case) to afford the tetracyclic products **19** (97% from **17**) and **20** (58% from **18**). The spectral data derived from these products were in complete accord with the assigned structures and a single-crystal X-ray analysis of compound **19** was obtained.

Scheme 4: The reductive cyclization reactions of substrates **13**, **17** and **18**



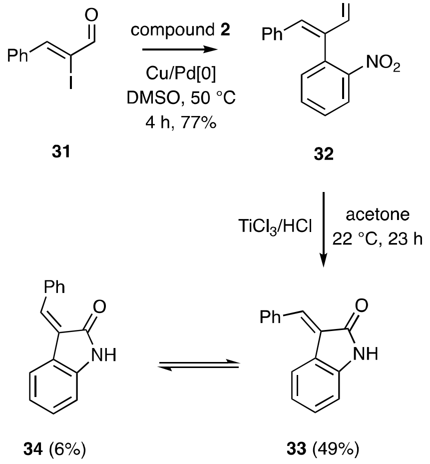
Acyclic ketones behave similarly as shown in Scheme 5. So, the Johnson α-iodination[11] of chalcone (**21**) afforded a chromatographically separable mixture of compounds **22**[12] (58%) and **23**[12] (10%) that upon palladium-catalyzed Ullmann cross-coupling with compound **16** afforded the anticipated products **24** and **25** (59-85% combined yield). The structure of the former product (**24**) was confirmed by single-crystal X-ray analysis. Since the cross-couplings of the geometrically pure *E*- and *Z*-isomeric forms of **22** and **23** are each accompanied by some double-bond isomerization it was most convenient to carry the mixture of iodinated products through the illustrated reaction sequence rather than separating these. Subjection of these cross-coupling products, either separately or as a mixture, to reductive cyclization with hydrogen in the presence of 10% palladium on carbon afforded the 3-benzyl-7-azaindole **26**[13] (63-80%) while treatment of the same substrates with $TiCl_3$ gave the 3-benzoyl-7-azaindole **27** in 15-49% yield. The structure of product **26** was confirmed by single-crystal X-ray analysis.

Scheme 5: The formation of the mixture of cross-coupling products **24** and **25** and their divergent reductive cyclizations to give 7-azaindoles **26** and **27**



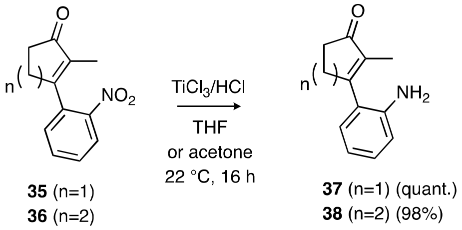
In contrast to the outcomes detailed immediately above, when the readily obtained α-iodinated cinnamaldehyde **31**[1] (Scheme 6) was subjected to palladium-catalyzed Ullmann cross-coupling with compound **2** and the ensuing product, **32**[1] (77%), treated with $TiCl_3$ then a slowly interconverting mixture of the partially chromatographically separable and isomeric cyclization products **33**[14] and **34**[14] was obtained (55% combined yield). The structure of oxindole **33**, a known antiproliferative agent,[15] was confirmed by single-crystal X-ray analysis.

Scheme 6: The formation of cinnamaldehyde **32** and its reductive cyclization



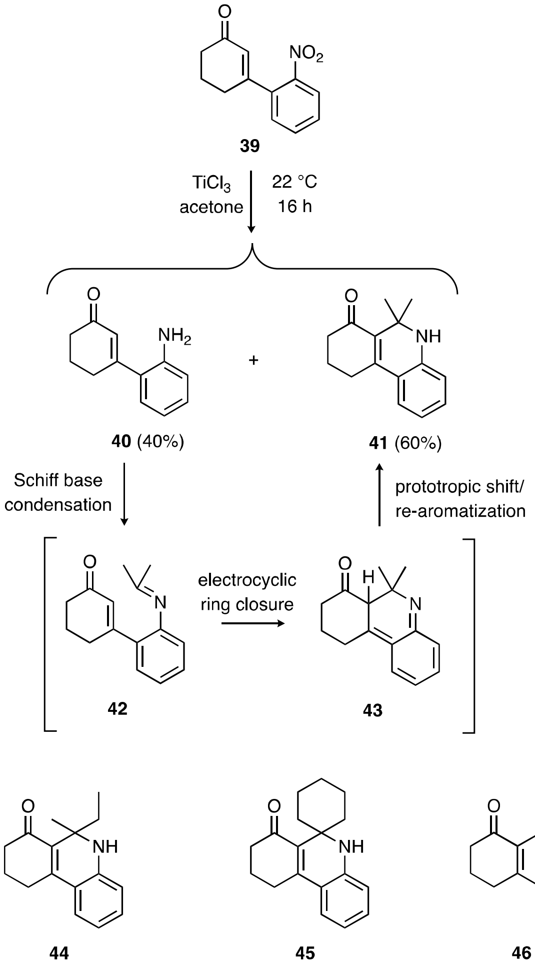
Very recently, we detailed[16] the cross-coupling of various β-iodoeneones and related compounds with *o*-iodonitrobenzene (**2**) to afford products such as compound **35** (Scheme 7). Accordingly, we sought to establish how this nitroarene and its homologue **36** would behave on exposure to $TiCl_3$/HCl. In the event, when treated under our now standard conditions each produced the corresponding aniline, viz. compounds **37** (quant.) and **38** (98%), respectively, with the structure of the latter being confirmed by single-crystal X-ray analysis.

Scheme 7: The reduction of nitroarenes **35** and **36** to the corresponding anilines



A more intriguing outcome was observed when an acetone solution of the non-methylated cross-coupling product **39**[16] (Scheme 8) was treated with $TiCl_3$ at ambient temperatures. Under these conditions the chromatographically separable products **40**[17] (40%) and **41** (60%) were obtained and their structures established by single-crystal X-ray analysis. Compound **40** is undoubtedly the primary product of reaction and the precursor to the other through its Schiff-base condensation with acetone to give imine **42** and electrocyclic ring closure of this to give compound **43** that engages in a prototropic shift with accompanying rearomatization to deliver the secondary product **41**. Consistent with this proposal, when THF solutions of compound **40** are treated, at 22 °C, with methyl ethyl ketone, cyclohexanone or benzaldehyde then the cycloadducts **44** (73%) **45** (64%), and **46** (quant.), respectively, are obtained. The structures of products **44** and **45** were confirmed by single-crystal X-ray analysis (see SI for details).

Scheme 8: The formation of the dihydroquinolines **41** and **44-46**



Conclusions

The reductive cyclization processes detailed above considerably enhance the utility of the various products available through the palladium-catalyzed Ullmann cross-coupling of *o*-halonitroarenes with either α- or β-iodinated-α,β-unsaturated enones and related systems.[2] The resulting, and in some instances previously unreported, heterocyclic ring systems should serve as useful scaffolds in a range of settings.

Experimental Section

General Experimental Procedures

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. IR spectra were recorded, using neat samples, on an attenuated total reflectance (ATR) infra-red spectrometer. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g: 5 mL : 300 mL). column chromatographic separations were carried out following protocols defined by Still et al.[18] with silica gel 60 (40– 63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents and drying agents as well as other inorganic salts were generally available from commercial sources and used as supplied. Tetrahydrofuran (THF), diethyl ether, methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.[19] Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations

Compound 5. *Method i*: A magnetically stirred mixture of compound **3**[1] (217 mg, 1.00 mmol) in acetone (5 mL) maintained at 22 °C was treated with titanium(III) chloride (5.0 mL of a 12% w/v solution in hydrochloric acid, 4.79 mmol). After 1 h the reaction mixture was diluted with ethyl acetate (20 mL) and washed with water (3 x 10 mL) then dried (Na_2SO_4), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.2$), compound **5** (100 mg, 50%) as a white, crystalline solid, no m.p., decomposition 147 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.70 (s, 1H), 7.99 (dd, *J* = 7.4 and 1.2 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.25–7.19 (complex m, 2H), 2.98 (t, *J* = 6.2 Hz, 2H), 2.44 (m, 2H), 2.20–2.08 (complex m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.0, 148.4, 134.0, 122.7, 122.2, 120.5, 120.2, 108.8, 106.5, 37.6, 22.9, 20.3; IR (ATR) ν_{max} 3062, 2946, 1710, 1575, 1462, 1311, 1256, 1182, 1096, 966, 741 cm^{-1}; MS (ESI, +ve) *m/z* 224 [(M+Na)$^+$, 100%], 202 [(M+H)$^+$, 10]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{12}H_{12}NO_2$ 202.0863; Found 202.0860.

Method ii: A magnetically stirred solution of compound **3**[1] (100 mg, 1.00 mmol) and hydrochloric acid (3 mL of a 2 M aqueous solution) in THF (5 mL) maintained at 22 °C was treated with iron powder (168 mg, 3.00 g.atom). After 18 h the reaction mixture was diluted with ethyl acetate (20 mL) then filtered through a plug of TLC-grade silica topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (1 x 10 mL) and the combined filtrates were washed with water (2 x 20 mL) then brine (1 x 20 mL) before being dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40−60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **5** (14 mg, 14%) as a white, crystalline solid. This material was identical, in all respects, with that obtained by Method i.

Compound 6. *Method i*: A magnetically stirred mixture of compound **5** (50 mg, 0.25 mmol) in acetone (1.3 mL) maintained at 22 °C was treated with titanium(III) chloride (1.3 mL of a 12% w/v solution in hydrochloric acid, 1.24 mmol). After 16 h the reaction mixture was quenched with sodium carbonate (5 mL of a saturated aqueous solution) and the resulting heterogeneous mixture filtered through diatomaceous earth. The solids so retained were washed with ethyl acetate (10 mL), the combined filtrates separated and the aqueous phase extracted with ethyl acetate (2 × 5 mL). The combined organic phases were washed with brine (20 mL) then dried (Na_2SO_4), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **6**[5] (42 mg, 91%) as a white, crystalline solid, m.p. = 174 °C (lit.[5b] m.p. = 225-228 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 7.95 (m, 1H), 7.39 (dd, *J* = 8.0 and 1.4 Hz, 1H), 7.15 (m, 2H), 2.96 (t, *J* = 6.2 Hz, 2H), 2.42 (t, *J* = 6.2 Hz, 2H), 2.10 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 192.9, 152.3, 135.8, 124.5, 122.4, 121.5, 120.2, 111.7, 111.5, 37.8, 23.4, 22.7; IR (ATR) ν_{max} 3056, 2954, 1604, 1576, 1462, 1445, 1411, 1251, 1177, 1145, 1016, 753 cm^{-1}; MS (ESI, +ve) *m/z* 208 [(M+Na)$^+$, 73%], 186 [(M+H)$^+$, 100]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{12}H_{12}NO$ 186.0913; Found 186.0912.

Method ii: A magnetically stirred solution of compound **5** (100 mg, 0.46 mmol) in hydrochloric acid (5 mL of a 3 M aqueous solution) maintained at *ca*. 100 °C was treated with iron powder (154 mg, 2.76 mmol). After 3 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (20 mL) then filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (1 × 10 mL). The combined filtrates were washed with water (2 × 20 mL) and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, ethyl acetate elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.1), compound **6** (10 mg, 12%) as a white, crystalline solid. This material was identical, in all respects, with that obtained by Method i.

Compound 8. A magnetically stirred solution of compound **7**[1] (108 mg, 0.53 mmol) in acetone (5 mL) maintained at 22 °C was treated with titanium(III) chloride (3.3 mL of a 12% w/v solution in hydrochloric acid, 3.18 mmol). After 19 h the reaction mixture was quenched with sodium carbonate (10 mL of a saturated aqueous solution) and the resulting mixture filtered through a pad of diatomaceous earth contained in a sintered glass funnel. The solids thus retained were washed with ethyl acetate (20 mL). The separated aqueous phase associated with the combined filtrates was extracted with ethyl acetate (2 x 10 mL) and the combined organic phases washed with brine (1 × 50 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 4:6 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **8** (74 mg, 80%) as a clear, red oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76 (t, *J* = 2.9 Hz, 1H), 7.15-7.10 (complex m, 2H), 6.77 (m, 1H), 6.72 (m, 1H), 4.04 (broad s, 2H), 2.80 (m, 2H), 2.60 (m, 2H); s^{13}C NMR (100 MHz, CDCl$_3$) δ 208.7, 162.7, 145.4, 144.8, 130.1, 129.6, 118.8, 118.7, 117.0, 35.2, 27.2; IR (ATR) ν_{max} 3422, 3357, 2921, 1688, 1622, 1492, 1453, 1299, 1137, 935, 751 cm^{-1}; MS (ESI, +ve) *m/z* 196 [(M+Na)$^+$, 100%], 174 [(M+H)$^+$, 5]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{11}H_{12}NO$ 174.0913; Found 174.0910.

Compound 9. A magnetically stirred mixture 4,4-dimethyl-2-cyclohexan-1-one (640 mg, 5.2 mmol) in THF/water (24 mL of a 1:1 v/v mixture) maintained at 0 °C was treated with K_2CO_3 (860 mg, 6.2 mmol), DMAP (127 mg, 1.0 mmol) and, in portions, powdered molecular iodine (1.97 g, 7.8 mmol). The ensuing mixture was warmed to 22 °C and after 3 h the reaction mixture was diluted with ethyl acetate (20 mL) before being quenched with sodium sulfite (50 ml of a saturated aqueous solution) then stirred vigorously until two clear layers were formed. The separated aqueous phase was extracted with ethyl acetate (2 × 20 mL) and the combined organic phases washed with sodium sulfite (1 × 50 mL of a saturated aqueous solution), hydrochloric acid (1 × 50 mL of a 0.5 M aqueous solution) and brine (1 × 50 mL) before being dried (Na_2SO_4) then filtered through a plug of TLC-grade silica. The filtrate was concentrated under reduced pressure and the residue so obtained subjected to flash column chromatography (silica, 1:7 v/v ethyl acetate/40-60 petroleum ether elution). Concentration of the appropriate fractions ($R_f = 0.2$) then gave compound **9**[6] (1.29 g, 91%) as a clear, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (broad s, 1H), 2.67 (t, J = 6.9 Hz, 2H), 1.92 (t, J = 6.9 Hz, 2H), 1.18 (broadened s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 168.0, 101.8, 38.0, 36.0, 33.3, 27.4; IR (ATR) ν_{max} 2959, 2926, 2864, 1687, 1583, 1317, 1142, 991, 957, 801, 724, 693 cm^{-1}; MS (ESI, +ve) m/z 273 [(M+Na)$^+$, 100%], 251 [(M+H)$^+$, 50]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_8H_{12}IO$ 250.9927; Found 250.9925.

Compound 10. A magnetically stirred suspension of compound **9** (1.17 g, 4.7 mmol), *o*-iodonitrobenzene (**2**) (2.33 g, 9.4 mmol) and copper powder (1.50 g, 23.5 mmol) in dry DMSO (10 mL) maintained at 50 °C was treated with $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (220 mg, 0.24 mmol). After 3 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (10 mL) before being filtered through a plug of TLC-grade silica topped with diatomaceous earth. The solids thus retained were washed with ethyl acetate (1 × 30 mL) and the combined filtrates were washed with ammonia (2 × 50 mL of a 5% v/v aqueous solution), water (2 x 50 mL) and brine (1 × 50 mL) before being dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:5 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **10** (920 mg, 80%) as a pale-yellow, crystalline solid, m.p. = 112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, J = 8.2 and 1.2 Hz, 1H), 7.59 (m, 1H), 7.46 (m, 1H), 7.24 (dd, J = 7.6 and 1.4 Hz, 1H), 6.65 (s, 1H), 2.61 (t, J = 6.8 Hz, 2H), 2.00 (m, 2H), 1.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 155.5, 148.6, 136.6, 133.2, 132.1, 131.7, 128.7, 124.2, 35.8, 34.7, 33.4, 27.7; IR (ATR) ν_{max} 2960, 1682, 1524, 1351, 1145, 859, 787, 725 cm^{-1}; MS (ESI, +ve) *m/z* 268 [(M+Na)$^+$, 100%], 246 [(M+H)$^+$, 56]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{14}H_{15}NO_3$ 246.1125; Found 246.1126.

Compound 11. A magnetically stirred mixture of compound **10** (50 mg, 0.20 mmol) and 10% palladium on carbon (10 mg) in dry methanol (5 mL) maintained at 22 °C was placed under a hydrogen atmosphere. After 2 h the reaction mixture was filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 5:95 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.4 in 1:10 v/v ethyl acetate/40-60 petroleum ether elution), compound **11**[7] (37 mg, 92%) as a white, crystalline solid, m.p. = 99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (broad s, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.29 (m, 1H), 7.10–7.02 (complex m, 2H), 2.73 (t, *J* = 6.5 Hz, 2H), 2.52 (s, 2H), 1.68 (t, *J* = 6.5 Hz, 2H), 1.10 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 132.8, 128.1, 120.9, 119.0, 117.6, 110.3, 109.7, 36.1, 34.9, 30.2, 28.2, 20.7; IR (ATR) ν_{max} 3406, 2950, 1468, 1357, 1327, 1236, 1187, 1008, 740, 635 cm^{-1}; MS (ESI, –ve) *m/z* 198 [(M–H)$^-$, 100%]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{14}H_{18}N$ 200.1434; Found 200.1433.

Compound 12. A magnetically stirred solution of compound **10** (50 mg, 0.20 mmol) in acetone (3 mL) maintained at 50 °C was treated with titanium(III) chloride (1.25 mL of a 12% w/v solution in hydrochloric acid, 1.20 mmol). After 16 h the reaction mixture was cooled to 22 °C then quenched with Na_2CO_3 (10 mL of a saturated aqueous solution) and the resulting heterogeneous mixture filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (20 mL) and the aqueous phase associated with the combined filtrates extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine (1 × 50 mL) then dried (Na_2SO_4) and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:8 v/v ethyl acetate/dichloromethane elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **12**[8] (35 mg, 82%) as white, crystalline solid, m.p. = 258 °C (lit.[8] m.p. = 270-274 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (broad s, 1H), 8.26 (m, 1H), 7.38 (m, 1H), 7.24 (m, 2H), 2.68 (dd, *J* = 7.0 and 6.0 Hz, 2H), 2.10 (dd, *J* = 7.0 and 6.0 Hz, 2H), 1.48 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 158.3, 135.6, 124.9, 123.4, 122.7, 121.7, 111.4, 111.0, 38.6, 35.4, 32.1, 27.4; IR (ATR) ν_{max} 3186, 2962, 1625, 1615, 1582, 1474, 1453, 1415, 1201, 881, 756 cm^{-1}; MS (ESI, +ve) *m/z* 449 [(2M+Na)$^+$, 58%], 236 [(M+Na)$^+$, 85] 214 [(M+H)$^+$, 100]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{14}H_{16}NO$ 214.1227; Found 214.1226.

Compound 14. A magnetically stirred solution of compound **13**[9] (109 mg, 0.50 mmol) in acetone (2.5 mL) maintained at 22 °C was treated with titanium(III) chloride (2.5 mL of a 12% w/v solution in hydrochloric acid, 2.39 mmol). After 16 h the reaction mixture was quenched with sodium carbonate (10 mL of a saturated aqueous solution) and the resulting heterogeneous mixture filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 20 mL) and the aqueous phase associated with the combined filtrates extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine (1 × 10 mL) then dried (Na_2SO_4) and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, ethyl acetate elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.2$), compound **14** (50 mg, 54%) as white, crystalline solid, m.p. = 179 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.01 (broad s, 1H), 8.55 (dd, J = 7.7 and 1.4 Hz, 1H), 8.31 (d, J = 4.9 Hz, 1H), 7.29 (m, 1H), 3.13 (t, J = 6.2 Hz, 2H), 2.65 (t, J = 6.4 Hz, 2H), 2.40–2.26 (complex m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 152.5, 148.8, 141.8, 130.5, 118.5, 118.2, 111.7, 37.9, 23.5, 23.4; IR (ATR) ν_{max} 3047, 2950, 2842, 1640, 1589, 1472, 1414, 1281, 1178, 1010, 776 cm^{-1}; MS (ESI, +ve) *m/z* 209 [(M+H)$^+$, 100%], 187 [(M+H)$^+$, 60]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{11}H_{11}N_2O$ 187.0866; Found 187.0865.

Compound 15. A magnetically stirred solution of levoglucosenone (1.50 g, 11.9 mmol) in dry dichloromethane (15 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (4.53 g, 17.8 mmol) then pyridine (1.05 mL, 13.1 mmol). After 48 h the reaction mixture was quenched with sodium sulfite (30 ml of a saturated aqueous solution) then stirred vigorously until two clear layers were formed. The separated aqueous phase was extracted with dichloromethane (2 × 20 mL) and the combined organic phases washed with sodium sulfite (1 × 60 mL of a saturated aqueous solution), hydrochloric acid (1 × 100 mL of a 0.5 M aqueous solution) and brine (1 × 100 mL) before being dried (Na_2SO_4) then filtered through a plug of TLC-grade silica. The filtrate was concentrated under reduced pressure and the residue so obtained subjected to flash column chromatography (silica, 1:1 v/v diethyl ether/40-60 petroleum ether elution). Concentration of the appropriate fractions ($R_f = 0.3$) then gave compound **15**[10] (2.24 g, 75%) as a pale-yellow, crystalline solid, m.p. = 64 °C (lit.[10] m.p. = 85-90 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 5.0 Hz, 1H), 5.57 (s, 1H), 4.93 (m, 1H), 3.89–3.78 (complex m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 155.5, 100.9, 99.8, 74.3, 66.5; IR (ATR) ν_{max} 3063, 2973, 2899, 1699, 1575, 1329, 1175, 1104, 978, 916, 881 cm^{-1}; MS (ESI, +ve) *m/z* 307 [(M+Na+MeOH)$^+$, 100%], 275 [(M+Na)$^+$, 55]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_6H_6IO_3$ 252.9356; Found 252.9361.

Compound 17. A magnetically stirred suspension of compound **15** (297 mg, 1.2 mmol), *o*-iodonitrobenzene (**2**) (200 mg, 0.79 mmol) and copper powder (250 g, 4.0 mmol) in dry DMSO (6 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$ (72 mg, 0.08 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) then filtered through a plug of TLC-grade silica topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (1 x 10 mL) and the combined filtrates washed with ammonia (2 × 15 mL of a 5% v/v aqueous solution), water (2 × 15 mL) and then brine (1 × 15 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, 2:8 to 1:1 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.3 in 4:6 v/v ethyl acetate/40-60 petroleum ether), compound **17** (135 mg, 69%) as a white, crystalline solid, m.p. = 137 °C. ^1H NMR (400 MHz, acetone-d_6) δ 7.92 (m, 1H), 7.53 (m, 1H), 7.27–7.18 (complex m, 2H), 5.88 (d, *J* = 4.5 Hz, 1H), 5.38 (s, 1H), 4.03 (dd, *J* = 7.1 and 4.5 Hz, 1H), 3.84 (d, *J* = 7.1 Hz, 1H) (resonance due to one proton not observed); ^{13}C NMR (100 MHz, acetone-d_6) δ 186.8, 151.6, 137.1, 125.1, 124.4, 123.3, 121.5, 113.4, 108.3, 103.2, 72.2, 68.0; IR (ATR) ν_{max} 2967, 2899, 1703, 1523, 1354, 1108, 984, 895, 794 cm^{-1}; MS (ESI, +ve) *m/z* 270 [$(M+Na)^+$, 100%]; HRMS (ESI, +ve) $[M+H]^+$ Calcd for $C_{12}H_{10}NO_5$ 248.0553; Found 248.0553.

Compound 18. A magnetically stirred suspension of compound **15** (2.77 g, 11.0 mmol), 3-bromo-2-nitropyridine (**16**)[8] (1.0 g, 5.0 mmol), copper(I) iodide (1.43 g, 7.5 mmol) and copper powder (250 g, 4.0 mmol) in dry DMSO (50 mL) maintained at 50 °C was treated with $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (204 mg, 0.25 mmol). After 5 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (20 mL) then filtered through a plug of TLC-grade silica topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 40 mL) and the combined filtrates washed with ammonia (2 × 25 mL of a 5% v/v aqueous solution), water (2 × 25 mL) then brine (1 × 25 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **18** (135 mg, 69%) as a yellow, crystalline solid, m.p. = 170 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 4.7 and 1.7 Hz, 1H), 7.79 (dd, *J* = 7.6 and 1.7 Hz, 1H), 7.65 (dd, *J* = 7.6 and 4.7 Hz, 1H), 7.32 (d, *J* = 4.8 Hz, 1H), 5.51 (s, 1H), 5.20 (t, *J* = 4.6 Hz, 1H), 4.05–3.96 (complex m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.4, 156.8, 148.8, 144.4, 141.6, 134.7, 128.1, 123.5, 101.3, 72.3, 66.9; IR (ATR) ν_{max} 2971, 2888, 1702, 1541, 1407, 1364, 1101, 984, 930, 890, 819, 647 cm^{-1}; MS (ESI, +ve) *m/z* 271 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{11}H_9N_2O_5$ 249.0506; Found 249.0509.

Compound 19. A magnetically stirred solution of compound **18** (40 mg, 0.16 mmol) in THF (1.7 mL) maintained at 22 °C was treated with titanium(III) chloride (0.85 mL of a 12% w/v solution in hydrochloric acid, 0.81 mmol). After 18 h the reaction mixture was quenched with sodium carbonate (5 mL of a saturated aqueous solution) and the resulting heterogeneous mixture filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 10 mL), the combined filtrates were separated and the aqueous phase extracted with ethyl acetate (2 × 5 mL). The combined organic phases were washed with brine (1 × 30 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 4:6 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.4), compound **19** (34 mg, 97%) as a white, crystalline solid, m.p. >250 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.1 Hz, 1H), 7.65 (m, 1H), 7.56 (m, 1H), 7.28–7.24 (complex m, 2H), 5.51 (s, 1H), 5.19 (t, *J* = 4.6 Hz, 1H), 4.06–3.95 (complex m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.7, 148.5, 142.7, 137.3, 133.5, 131.5, 129.8, 128.8, 124.6, 101.3, 72.1, 66.8; IR (ATR) ν_{max} 3278, 2924, 1651, 1479, 1452, 1076, 869 cm^{-1}; MS (ESI, +ve) *m/z* 238 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{12}H_{10}NO_3$ 216.0655; Found 216.0858.

Compound 20. A magnetically stirred solution of compound **18** (52 mg, 0.21 mmol) and hydrochloric acid (9 mL of a 1 M aqueous solution) in 1,2-dimethoxyethane (5 mL) maintained at 50 °C was treated with iron powder (59 mg, 1.10 g.atom). After 18 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (10 mL) then filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (1 x 10 mL). The combined filtrates were washed with water (2 x 20 mL) and brine (1 x 20 mL) before being dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 2:1 v/v ethyl acetate/40−60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound **20** (26 mg, 58%) as a white, crystalline solid, m.p. = 275 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.37 (m, 1H), 8.25 (dd, *J* = 7.8 and 1.6 Hz, 1H), 7.29 (dd, *J* = 7.8 and 4.8 Hz, 1H), 5.95 (d, *J* = 4.6 Hz, 1H), 5.44 (s, 1H), 4.11 (dd, *J* = 7.2 and 4.6 Hz, 1H), 3.96 (d, *J* = 7.2 Hz, 1H) (signal due to N-H group proton not observed); ^{13}C NMR (100 MHz, acetone-d_6) δ 186.5, 152.2, 149.8, 145.6, 129.6, 119.4, 117.4, 107.1, 103.1, 72.1, 68.0; IR (ATR) ν_{max} 2981, 2888, 1679, 1592, 1480, 1426, 1109, 1075, 889, 805 cm^{-1}; MS (ESI, +ve) *m/z* 239 [(M+Na)$^+$, 100%], 217 [(M+H)$^+$, 10]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{11}H_9N_2O_3$ 217.0608; Found 217.0609.

Compounds 22 and 23. A magnetically stirred solution of *trans*-chalcone (**21**) (475 mg, 2.28 mmol) in dry dichloromethane (7 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (2.00 g, 7.98 mmol) then pyridine (7 mL). After 0.5 h the reaction mixture was quenched with sodium sulfite (30 ml of a saturated aqueous solution) and vigorous stirring continued until two clear layers had formed. The separated aqueous phase was extracted with dichloromethane (2 × 10 mL) and the combined organic phases washed with sodium sulfite (1 × 60 mL of a saturated aqueous solution), hydrochloric acid (1 x 500 mL of a 0.5 M aqueous solution) and brine (1 × 50 mL) before being dried (Na_2SO_4) then filtered through a plug of TLC-grade silica. The filtrate was concentrated under reduced pressure and the residue so obtained subjected to flash column chromatography (silica, 5:95 to 1:9 v/v diethyl ether/40-60 petroleum ether gradient elution). Two fractions, A and B, were thus obtained.

Concentration of fraction A (R_f = 0.5 in 1:9 diethyl ether/40-60 petroleum ether) gave compound **22**[12] (439 mg, 58%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.92 (complex m, 2H), 7.58–7.40 (complex m, 6H), 7.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 148.5, 135.5, 135.3, 132.7, 130.2, 130.0, 129.4, 128.5, 128.4, 103.5; IR (ATR) ν_{max} 3057, 3024, 2923, 1657, 1595, 1446, 1238, 1176, 1059, 748, 689 cm^{-1}; MS (ESI, +ve) *m/z* 357 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{15}H_{12}IO$ 334.9927; Found 334.9916.

Concentration of fraction B (R_f = 0.6 in 1:9 diethyl ether/40-60 petroleum ether) gave compound **23**[12] (79 mg, 10%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.53 (m, 2H), 7.40 (m, 2H), 7.16 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 143.4, 136.0, 134.0, 132.5, 129.9, 128.8, 128.7, 128.5, 128.1, 92.7; IR (ATR) ν_{max} 3058, 3024, 2924, 1659, 1596, 1447, 1221, 1173, 1012, 750, 685 cm^{-1}; MS (ESI, +ve) *m/z* 357 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{15}H_{12}IO$ 334.9927; Found 334.9916.

Compounds 24 and 25. *Method i*: A magnetically stirred mixture of compound **22** (160 mg, 0.48 mmol), 3-bromo-2-nitropyridine (**16**) (155 mg, 0.76 mmol) and copper powder (182 mg, 4.0 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$ (43 mg, 0.05 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (10 mL) then filtered through a plug of TLC-grade silica topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 5 mL) and the combined filtrates washed with ammonia (2 × 10 mL of a 5% v/v aqueous solution), water (2 × 10 mL) and brine

(1 × 10 mL) before being dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 3:7 to 1:1 v/v diethyl ether/40-60 petroleum ether gradient elution) and so affording two fractions, A and B.

Concentration of fraction A (*R*f = 0.3 in 3:7 ethyl acetate/40-60 petroleum ether) gave compound **24** (122 mg, 77%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 4.6 and 1.8 Hz, 1H), 8.16 (dd, *J* = 7.8 and 1.8 Hz, 1H), 7.90 (m, 2H), 7.62 (dd, *J* = 7.8 and 4.6 Hz, 1H), 7.40 (m, 1H), 7.29–7.22 (complex m, 3H), 7.17–7.08 (complex m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 156.4, 147.8, 141.9, 138.3, 135.9, 134.3, 133.7, 133.4, 130.0, 129.4, 129.1, 128.3, 128.2(1), 128.9(9), 127.3; IR (ATR) v_{max} 3060, 2982, 1734, 1646, 1540, 1447, 1359, 1245, 694 cm^{-1}; MS (ESI, +ve) *m/z* 353 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{20}H_{15}N_2O_3$ 331.1077; Found 331.1080.

Concentration of fraction B (*R*f = 0.4 in 3:7 ethyl acetate /40-60 petroleum ether) gave compound **25** (12 mg, 8%) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, *J* = 4.6 and 1.9 Hz, 1H), 7.92 (m, 2H), 7.73 (m, 1H), 7.60 (m, 2H), 7.53 (m, 2H), 7.48 (s, 1H), 7.29 (m, 1H), 7.23 (m, 2H), 7.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 156.4, 148.3, 143.8, 143.5, 137.4, 135.9, 133.3, 132.4, 130.1, 129.9, 129.8, 128.7, 128.4, 128.3, 127.9; IR (ATR) v_{max} 3060, 2981, 1647, 1541, 1447, 1365, 1231, 695 cm^{-1}; MS (ESI, +ve) *m/z* 353 [(M+Na)$^+$, 100%]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{20}H_{15}N_2O_3$ 331.1077; Found 331.1079.

Method ii: Compound **23** was subjected to cross-coupling with bromopyridine **16** in the same manner as described immediately above in Method i. Subjection of the product mixture obtained on workup to flash column chromatography (silica, 3:7 to 1:1 v/v diethyl ether/40-60 petroleum ether gradient elution) afforded two fractions, A and B.

Concentration of fraction A (*R*f = 0.3 in v/v 3:7 ethyl acetate/40-60 petroleum ether) gave compound **24** (18%) as a light-yellow oil. This material was identical, in all respects, with that obtained by Method i.

Concentration of fraction B (*R*f = 0.4 in 3:7 v/v ethyl acetate/40-60 petroleum ether) gave compound **25** (41%) as a light-yellow oil. This material was identical, in all respects, with that obtained by Method i.

Compound 26. *Method i*: A magnetically stirred mixture of compound **24** (23 mg, 0.07 mmol) and 10% palladium on carbon (10 mg) in ethyl acetate (5 mL) maintained at 22 °C was placed under a hydrogen atmosphere. After 16 h the reaction mixture was flushed with nitrogen then filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3:7 to 1:1 v/v ethyl acetate/40-60 petroleum ether gradient elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.4 in 3:7 v/v ethyl acetate/40-60 petroleum ether), compound **26**[13] (13 mg, 63%) as a white, crystalline solid, no m.p., decomposition above 120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.77 (broad s, 1H), 8.18 (m, 1H), 7.69 (m, 3H), 7.50 (m, 2H), 7.42 (m, 1H), 7.32–7.15 (complex m, 5H), 6.99 (m, 1H), 4.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 140.9, 136.9, 132.3, 130.1, 129.6, 128.9, 128.6, 128.5, 128.3(1), 128.2(9), 128.2, 126.0, 115.5, 109.1, 30.5; IR (ATR) ν_{max} 3026, 2920, 2849, 1739, 1579, 1600, 1490, 1461, 1411, 765, 699 cm^{-1}; MS (ESI, +ve) *m/z* 285 [(M+H)$^+$, 100%]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{20}H_{17}N_2$ 285.1386; Found 285.1388.

Method ii: Compound **25** was subjected to reductive cyclisation in the same manner as described immediately above in Method i. Subjection of the product mixture obtained on workup to flash column chromatography (silica, 3:7 to 1:1 v/v diethyl ether/40-60 petroleum ether gradient elution) afforded, after concentration of the appropriate fractions (R_f = 0.4 in 3:7 to 1:1 v/v ethyl acetate/40-60 petroleum ether), compound **26** (80%) as a white, crystalline solid. This material was identical, in all respects, with that obtained by Method i.

Compound 27. A magnetically stirred mixture of compound **24** (45 mg, 0.14 mmol) in THF (5 mL) maintained at 22 °C was treated with titanium(III) chloride (0.9 mL of a 12% w/v solution in hydrochloric acid, 0.86 mmol). After 16 h the reaction mixture was quenched with sodium carbonate (10 mL of a saturated aqueous solution) and the resulting heterogeneous mixture filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 20 mL), the combined filtrates separated and the aqueous phase extracted with ethyl acetate (4 × 10 mL). The combined organic phases were washed with brine (1 × 50 mL) then dried (Na_2SO_4) and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 2:8 to 1:1 v/v ethyl acetate/40-60 petroleum ether gradient elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2 in 3:7 v/v ethyl acetate/40-60 petroleum ether), compound **27** (20 mg, 49%) as yellow, crystalline solid, m.p. = 159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.9 Hz, 1H), 8.15 (broad s, 1H), 7.64 (m, 2H), 7.52 (m, 2H), 7.34 (m, 4H), 7.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 148.1, 145.4, 142.5, 139.3, 131.7, 131.5, 131.1, 129.8, 129.6, 129.3, 128.4, 127.8, 117.9, 111.6 (one signal obscured or overlapping); IR (ATR) ν_{max} 2917, 2849, 1615, 1459, 1435, 1292, 936, 896, 766, 730, 698 cm^{-1}; MS (ESI, +ve) *m/z* 321 [(M+Na)$^+$, 100%], 299 [(M+H)$^+$, 70%]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{20}H_{15}N_2O$ 299.1179; Found 299.1181.

Method ii: Compound **25** was subjected to reductive cyclisation in the same manner as described immediately above in Method i. Subjection of the product mixture obtained on workup to flash column chromatography (silica, 2:8 to 1:1 v/v ethyl acetate/40-60 petroleum ether gradient elution) afforded, after concentration of the appropriate fractions (R_f = 0.2 in 3:7 v/v ethyl acetate/40-60 petroleum ether), compound **27** (15%) as a yellow, crystalline solid. This material was identical, in all respects, with that obtained by Method i.

Compound 32. A magnetically stirred mixture of compound **31**[1] (516 mg, 2.00 mmol), *o*-iodonitrobenzene (**2**) (996 mg, 4.00 mmol) and copper powder (636 mg, 10.0 mmol) in dry DMSO (10 mL) maintained at 50 °C was treated with Pd(dppf)Cl_2•CH_2Cl_2 (82 mg, 0.10 mmol). After 4 h the reaction mixture was cooled to 22 °C then diluted with ethyl acetate (10 mL) before being filtered through a plug of TLC-grade silica topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 30 mL) and the combined filtrates were washed with ammonia (2 × 40 mL of a 5% v/v aqueous solution), water (2 × 40 mL) and brine (1 × 40 mL) before being dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, toluene elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.3), compound **32**[1] (390 mg, 77%) as a clear, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.23 (m, 1H), 7.63–7.56 (complex m, 2H), 7.54 (s, 1H), 7.37–7.22 (complex m, 3H), 7.17 (complex m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 148.9, 139.7, 133.9, 133.3, 132.0, 130.5, 130.4, 129.6(1), 129.5(9), 128.7, 125.0 (one signal obscured or overlapping); IR (ATR) ν_{max} 3348, 3062, 2830, 1682, 1627, 1521, 1346, 1110, 1062, 856, 713 cm^{-1}; MS (ESI, +ve) *m/z* 276 [(M+Na)$^+$, 100%], 254 [(M+H)$^+$, 8]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{15}H_{12}NO_3$ 254.0182; Found 254.0182.

Compounds 33 and 34. A magnetically stirred solution of compound **32** (134 mg, 0.53 mmol) in acetone (5 mL) maintained at 22 °C was treated with titanium(III) chloride (3.3 mL of a 12% w/v solution in hydrochloric acid, 3.18 mmol). After 23 h the reaction mixture was quenched with sodium carbonate (10 mL of a saturated aqueous solution) and the resulting heterogeneous mixture filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 20 mL), the combined filtrates separated and the aqueous phase extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL) then dried (Na_2SO_4) and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/dichloromethane elution) and thus affording a partially separable, *ca*. 5-3:1 and slowly interconverting mixture of compounds **33**[14] and **34**[14] (64 mg, 55%) as an oily solid, R_f = 0.2 and 0.4, respectively. ^{1}H NMR (400 MHz, $CDCl_3$) δ (for compound **33**) 8.20 (broad s, 1H), 7.85 (s, 1H), 7.70–7.60 (complex m 3H), 7.52–7.41 (complex m, 3H), 7.22 (m, 1H), 6.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (for compound **33**) 170.1, 141.6, 137.7, 135.0, 130.0, 129.8, 129.5, 128.8, 127.6, 123.2, 122.0, 121.9, 110.2; ^{13}C NMR (100 MHz, $CDCl_3$) δ (for a ca. 3:1 mixture of compounds **33** and **34**) 170.0, 167.7, 141.4, 139.6, 137.6(1), 137.5(9), 134.8, 133.7, 131.9, 130.6, 139.9, 129.7, 129.3, 128.9, 128.6, 128.3, 127.4, 126.2, 125.3, 123.0, 121.8(1). 121.7(9), 121.7, 119.3, 110.1, 109.5; IR (ATR) ν_{max} (for a mixture) 3222, 3062, 1704, 1613, 1463, 1329, 1202, 781, 747, 722, 696 cm^{-1}; MS (ESI, +ve) *m/z* (for a mixture) 465 [(2M+Na)$^+$, 60%], 244 [(M+Na)$^+$, 100], 222 [(M+H)$^+$, 13]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{15}H_{12}NO$ 222.0913; Found 222.0906.

Crystals of compound **33** suitable for X-ray analysis was grown from diethyl ether (m.p. = 169 °C).

Compound 36. A magnetically stirred mixture of 3-iodo-2-methylcyclohex-2-enone[16] (213 mg, 0.90 mmol), *o*-iodonitrobenzene (**2**) (449 mg, 1.80 mmol) and copper powder (286 mg, 4.5 mmol) in dry DMSO (10 mL) maintained at 80 °C was treated with $Pd_2(dba)_3$ (77 mg, 0.08 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (10 mL) before being filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (1 x 10 mL). The combined filtrates were washed with ammonia (2 x 40 mL of a 5% v/v aqueous solution), water (2 x 40 mL) and brine (1 x 40 mL) before being dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:4 to 1:1 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.3 in 2:3 v/v diethyl ether/40-60 petroleum ether elution), compound **36** (120 mg, 61%) as a clear, light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 8.3 and 1.3 Hz, 1H), 7.71 (m, 1H), 7.55 (m, 1H), 7.24 (dd, *J* = 7.6 and 1.6 Hz, 1H), 2.65 (m, 2H), 2.59–2.46 (m, 2H), 2.27 (m, 1H), 2.15 (m, 1H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 153.9, 146.3, 136.7, 134.0, 131.8, 129.1, 128.8, 124.9, 37.8, 32.5, 23.0, 12.5; IR (ATR) ν_{max} 2947, 2870, 1665, 1523, 1344, 1111, 908, 727 cm^{-1}; MS (ESI, +ve) *m/z* 254 [(M+Na)$^+$, 100%], 232 [(M+H)$^+$, 15]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{13}H_{14}NO_3$ 232.0968; Found 232.0966.

Compound 37. A magnetically stirred solution of compound **35**[16] (150 mg, 0.69 mmol) in acetone (7 mL) maintained at 22 °C was treated with titanium(III) chloride (3.6 mL of a 12% w/v solution in hydrochloric acid, 3.45 mmol). After 16 h the reaction mixture was quenched with sodium carbonate (15 mL of a saturated aqueous solution) and the resulting heterogeneous mixture filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 20 mL) and the aqueous phase associated with combined filtrates extracted with ethyl acetate (4 × 10 mL). The combined organic phases were washed with brine (1 × 50 mL) then dried (Na_2SO_4) and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 2:3 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.3$), compound **37** (130 mg, quant.) as yellow, crystalline solid, m.p. = 108 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 1H), 7.06 (dd, *J* = 7.6 and 1.7 Hz, 1H), 6.82 (m, 1H), 6.77 (m, 1H), 3.64 (broad s, 2H), 2.84 (m, 2H), 2.51 (m, 2H), 1.73 (t, *J* = 2.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 167.7, 142.5, 138.6, 129.7, 127.4, 122.2, 118.1, 115.7, 34.4, 30.8, 9.5; IR (ATR) ν_{max} 3453, 3357, 2917, 1689, 1686, 1622, 1494, 1451, 1342, 1222, 1094, 1061, 747 cm^{-1}; MS (ESI, +ve) *m/z* 210 [$(M+Na)^+$, 100%], 188 [$(M+H)^+$, 17]; HRMS (ESI, +ve) $[M+H]^+$ Calcd for $C_{12}H_{14}NO$ 188.1070; Found 188.1069.

Compound 38. *Method i*: A magnetically stirred solution of compound **36**[16] (45 mg, 0.19 mmol) in THF (2 mL) maintained at 22 °C was treated with titanium(III) chloride (1.0 mL of a 12% w/v solution in hydrochloric acid, 0.96 mmol). After 16 h the reaction mixture was quenched with sodium carbonate (5 mL of a saturated aqueous solution) and the resulting heterogeneous mixture filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 10 mL), the phases associated with the combined filtrates separated and the aqueous one extracted with ethyl acetate (4 × 10 mL). The combined organic phases were washed with brine (1 × 50 mL) then dried (Na_2SO_4) and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.6$), compound **38** (40 mg, 98%) as light-yellow crystals, m.p. = 73 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (m, 1H), 6.92 (dd, *J* = 7.6 and 1.7 Hz, 1H), 6.79 (m, 1H), 6.74 (dd, *J* = 7.9 and 1.1 Hz, 1H), 3.57 (broad s, 2H), 2.55 (m, 4H), 2.10 (m, 2H), 1.65 (t, *J* = 2.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 154.9, 141.5, 133.6, 128.8, 127.1, 126.6, 118.4, 115.5, 37.9, 31.9, 22.9, 12.3; IR (ATR) ν_{max} 3459, 3362, 2945, 2923, 1660, 1618, 1494, 1452, 1354, 1106, 750 cm^{-1}; MS (ESI, +ve) *m/z* 224 [$(M+Na)^+$, 100%], 202 [$(M+H)^+$, 28]; HRMS (ESI, +ve) $[M+H]^+$ Calcd for $C_{13}H_{16}NO$ 202.1226; Found 202.1219.

Method ii: Reduction of compound **36** with $TiCl_3$/HCl in the same manner as detailed above but using acetone instead of THF as solvent gave, after workup and flash chromatography, compound **38** (80%) as light-yellow crystals. This material was identical, in all respects, with that obtained by Method i.

Compounds 40 and 41. A magnetically stirred mixture of compound **39**[16] (200 mg, 0.92 mmol) in acetone (10 mL) maintained at 22 °C was treated with titanium(III) chloride (5.0 mL of a 12% w/v solution in hydrochloric acid, 4.79 mmol). After 16 h the reaction mixture was quenched with sodium carbonate (20 mL of a saturated aqueous solution) and the resulting heterogeneous mixture filtered through diatomaceous earth. The solids so retained were washed with ethyl acetate (40 mL), the combined filtrates separated and the aqueous phase extracted with ethyl acetate (4 × 10 mL). The combined organic phases were washed with brine (1 × 100 mL) then dried (Na_2SO_4), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 to 4:6 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, two fractions, A and B.

Concentration of fraction A (R_f = 0.4 in 1:1 v/v ethyl acetate/40-60 petroleum ether elution) gave compound **40**[17] (80 mg, 40%) as orange-colored crystals, m.p. = 90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 1H), 7.07 (dd, J = 7.8 and 1.7 Hz, 1H), 6.78 (m, 1H), 6.73 (dd, J = 8.1 and 1.2 Hz, 1H), 6.26 (t, J = 1.6 Hz, 1H), 3.84 (broad s, 2H), 2.67 (m, 2H), 2.51 (m, 2H), 2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 161.2, 142.8, 129.7, 127.9, 127.7, 125.5, 118.3, 116.2, 37.3, 30.2, 23.1; IR (ATR) ν_{max} 3443, 3354, 2925, 1655, 1608, 1490, 1449, 1244, 1188, 747 cm^{-1}; MS (ESI, +ve) *m/z* 210 [$(M+Na)^+$, 100%], 188 [$(M+H)^+$, 9]; HRMS (ESI, +ve) $[M+H]^+$ Calcd for $C_{12}H_{14}NO$ 188.1070; Found 188.1072.

Concentration of fraction B (R_f = 0.5 in 1:1 v/v ethyl acetate/40-60 petroleum ether elution) gave compound **41** (135 mg, 60%) as red-colored crystals, m.p. = 113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, J = 7.9 and 1.5 Hz, 1H), 7.11 (m, 1H), 6.65 (m, 1H), 6.45 (dd, J = 8.0 and 1.2 Hz, 1H), 3.64 (broad s, 1H), 2.69 (t, J = 6.1 Hz, 2H), 2.43 (dd, J = 7.4 and 6.1 Hz, 2H), 2.03 (m, 2H), 1.52 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 148.2, 145.2, 133.8, 131.7, 125.2, 120.2, 117.5, 113.8, 53.8, 38.7, 29.0, 25.9, 21.6; IR (ATR) ν_{max} 3336, 2952, 2925, 1637, 1607, 1380, 1269, 743 cm^{-1}; MS (ESI, +ve) *m/z* 250 [$(M+Na)^+$, 100%], 228 [$(M+H)^+$, 70%]; HRMS (ESI, +ve) $[M+H]^+$ Calcd for $C_{15}H_{18}NO$ 228.1383; Found 228.1384.

Compound 44. A magnetically stirred solution of compound **40** (35 mg, 0.19 mmol, 1.0 eq.) in butanone (5 mL) was treated with HCl (100 μl of a 12 M aqueous solution) and the ensuing mixture was maintained at 22 °C for 16 h. The resulting mixture was quenched with sodium carbonate (5 ml of a saturated aqueous solution) and the separated aqueous layer extracted with ethyl acetate (3 × 5 mL). The combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 5:35 v/v diethyl ether/40-60 petroleum ether elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 3:7 v/v diethyl ether/40-60 petroleum ether elution), compound **44** (33 mg, 73%) as a red, crystalline solid, m.p. = 118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 7.9 and 1.3 Hz, 1H), 7.07 (m, 1H), 6.59 (m, 1H), 6.41 (dd, *J* = 8.0 and 1.1 Hz, 1H), 3.54 (broad s, 1H), 2.70 (m, 2H), 2.45 (m, 3H), 2.04 (m, 2H), 1.49 (s, 3H), 1.34 (m, 1H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 149.2, 145.8, 131.9(1), 131.8(9), 125.3, 119.5, 116.9, 113.3, 57.3, 38.8, 33.8, 28.5, 26.1, 21.7, 9.3; IR (ATR) ν_{max} 3349, 2957, 2932, 2871, 1638, 1609, 1566, 1455, 1378, 1262, 1152 cm^{-1}; MS (ESI, +ve) *m/z* 264 [$(M+Na)^+$, 100%], 242 [$(M+H)^+$, 37]; HRMS (ESI, +ve) $[M+H]^+$ Calcd for $C_{16}H_{20}NO$ 242.1545; Found 242.1547.

Compound 45. A magnetically stirred solution of compound **40** (65 mg, 0.35 mmol, 1.0 eq.) and cyclohexanone (136 mg, 1.39 mmol, 4.0 mole eq.) in THF (5 ml) was treated with HCl (100 µl of a 12 M aqueous solution) and the ensuing mixture stirred at 22 °C for 16 h. The resulting mixture was quenched with sodium carbonate (5 mL of a saturated aqueous solution) and the separated aqueous layer extracted with ethyl acetate (3 × 5 mL). The combined organic layers were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was dissolved in methanol/CH_2Cl_2 (5 mL of a 1:1 v/v mixture), the resulting solution cooled to –78 °C and $NaBH_4$ (58 mg, 1.55 mmol, 5.0 mole eq.) then added. The reaction mixture was stirred at –78 °C for 1 h then treated with acetone (5 mL) and warmed to 22 °C before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 3:7 v/v diethyl ether/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions (R_f = 0.6), compound **45** as orange crystals (59 mg, 64%), m.p. = 136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 7.8 Hz, 1H), 7.11 (m, 1H), 6.66 (m, 1H), 6.52 (dd, *J* = 8.0 and 1.1 Hz, 1H), 4.57 (broad s, 1H), 2.68 (t, *J* = 6.1 Hz, 2H), 2.51–2.34 (complex m, 4H), 2.01 (m, 2H), 1.79 (dm, *J* = 13.2 Hz, 2H), 1.70–1.56 (complex m, 3H), 1.47–1.31 (complex m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 149.1, 144.8, 134.1, 131.6, 125.3, 121.1, 117.7, 114.2, 55.4, 39.1, 32.7, 26.3, 24.7, 21.5, 21.0; IR (ATR) ν_{max} 3382, 2920, 2854, 1637, 1605, 1374, 1311, 1198 cm^{-1}; MS (ESI, +ve) *m/z* 290 [$(M+Na)^+$, 100%], 268 [$(M+H)^+$, 9]; HRMS (ESI, +ve) $[M+H]^+$ Calcd for $C_{18}H_{22}NO$ 268.1701; Found 268.1697.

Compound 46. A magnetically stirred solution of compound **40** (35 mg, 0.19 mmol, 1.0 eq.) and benzaldehyde (1.0 mL, 9.72 mmol, 52 mole eq.) in THF (3 mL) was maintained at 22 °C for 16 h then concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, 1:4 to 1:1 v/v diethyl ether/40-60 petroleum ether gradient solution) and so affording, after concentration of the appropriate fractions (R_f = 0.5 in 2:3 v/v diethyl ether/40-60 petroleum ether), compound **46** (51 mg, quant.) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.87 (dd, J = 7.5 and 2.1 Hz, 2H), 7.56–7.44 (complex m, 3H), 7.40 (m, 1H), 7.33–7.24 (complex m, 2H), 7.04 (dd, J = 7.8 and 1.1 Hz, 1H), 6.13 (broad s, 1H), 2.80 (m, 2H), 2.47 (m, 2H), 2.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 163.2, 160.4, 149.5, 136.0, 134.8, 131.6, 129.9, 129.0, 128.8(1), 128.7(9), 128.1, 125.9, 118.7, 37.5, 30.7, 23.3; IR (ATR) ν_{max} 3060, 2943, 1661, 1625, 1578, 1451, 1188, 888, 764, 754, 691 cm^{-1}; MS (ESI, +ve) m/z 298 [(M+Na)$^+$, 100%], 276 [(M+H)$^+$, 15]; HRMS (ESI, +ve) [M+H]$^+$ Calcd for $C_{19}H_{18}NO$ 276.1383; Found 276.1382.

X-ray Crystallographic Studies

Crystallographic Data

*Crystallographic Data for Compound **5**.*

$C_{12}H_{11}NO_2$, M = 201.22, T = 150 K, monoclinic, space group $P2_1/c$, Z = 8, a = 8.6966(2), b = 12.4116(4), c = 21.1857(7) Å; β = 96.602(3)°; V = 2271.59(12) Å^3, D_x = 1.177 g cm^{-3}, 4391 unique data ($2\theta_{max}$ = 144.0°), R = 0.057 [for 3120 reflections with $I > 2.0\sigma(I)$]; Rw = 0.164 (all data), S = 1.03.

*Crystallographic Data for Compound **19**.*

$C_{12}H_9NO_3$, M = 215.20, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 6.7281(1), b = 9.5441(2), c = 15.1689(4) Å; V = 974.08 Å^3, D_x = 1.467 g cm^{-3}, 1951 unique data ($2\theta_{max}$ = 147.4°), R = 0.038 [for 1890 reflections with $I > 2.0\sigma(I)$]; Rw = 0.101 (all data), S = 1.05.

*Crystallographic Data for Compound **24**.*

$C_{20}H_{14}N_2O_3$, M = 330.33, T = 150 K, monoclinic, space group $P2_1/c$, Z = 4, a = 12.5226(3), b =12.7446(3), c = 10.8100 Å; β = 107.865(2)°; V = 1642.04 Å^3, D_x = 1.336 g cm^{-3}, 3297 unique data ($2\theta_{max}$ = 147.6°), R = 0.046 [for 3062 reflections with $I > 2.0\sigma(I)$]; Rw = 0.129 (all data), S = 1.03.

*Crystallographic Data for Compound **26**.*

$C_{20}H_{16}N_2$, M = 284.35, T = 150 K, triclinic, space group $P\bar{1}$, Z = 4, a = 10.2371(7), b = 12.0551(8), c = 12.5051(9) Å; α = 93.572(6)°, β = 105.062(6)°, γ = 99.112(6) °; V = 1462.73 (18) Å^3, D_x = 1.291 g cm^{-3}, 5940 unique data ($2\theta_{max}$ = 52.8°), R = 0.046 [for 4420 reflections with $I > 2.0\sigma(I)$]; Rw = 0.120 (all data), S = 1.04.

*Crystallographic Data for Compound **33**.*

$C_{15}H_{11}NO$, $M = 221.25$, $T = 150$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 4.0072(1)$, $b = 22.2268(5)$, $c = 12.2592(3)$ Å; $\beta = 95.112(2)°$; $V = 1087.55(5)$ Å^3, $D_x = 1.351$ g cm^{-3}, 2147 unique data ($2\theta_{\max} = 148.4°$), $R = 0.052$ [for 2026 reflections with $I > 2.0\sigma(I)$]; $Rw = 0.144$ (all data), $S = 1.04$.

*Crystallographic Data for Compound **38**.*

$C_{13}H_{15}NO$, $M = 201.26$, $T = 150$ K, monoclinic, space group $P2_1/c$, $Z = 12$, $a = 13.9326(3)$, $b = 31.3218(6)$, $c = 7.6013(1)$ Å; $\beta = 98.270(2)°$; $V = 3282.67(11)$ Å^3, $D_x = 1.222$ g cm^{-3}, 6363 unique data ($2\theta_{\max} = 144.2°$), $R = 0.058$ [for 5008 reflections with $I > 2.0\sigma(I)$]; $Rw = 0.163$ (all data), $S = 1.07$.

*Crystallographic Data for Compound **40**.*

$C_{12}H_{13}NO$, $M = 187.23$, $T = 150$ K, monoclinic, space group $P2_1$, $Z = 2$, $a = 7.0538(7)$, $b = 8.4543(7)$, $c = 8.3005(10)$ Å; $\beta = 99.725(10)°$; $V = 487.89(9)$ Å^3, $D_x = 1.275$ g cm^{-3}, 1859 unique data ($2\theta_{\max} = 52.8°$), $R = 0.038$ [for 1663 reflections with $I > 2.0\sigma(I)$]; $Rw = 0.081$ (all data), $S = 1.09$.

*Crystallographic Data for Compound **41**.*

$C_{15}H_{17}NO$, $M = 227.29$, $T = 150$ K, monoclinic, space group $P2_1/n$, $Z = 4$, $a = 8.8038(8)$, $b = 12.8773(9)$, $c = 11.2318(10)$ Å; $\beta = 109.578(10)°$; $V = 1199.72(19)$ Å^3, $D_x = 1.258$ g cm^{-3}, 2446 unique data ($2\theta_{\max} = 52.8°$), $R = 0.039$ [for 2055 reflections with $I > 2.0\sigma(I)$]; $Rw = 0.107$ (all data), $S = 1.04$.

*Crystallographic Data for Compound **44**.*

$C_{16}H_{17}NO$, $M = 239.30$, $T = 150$ K, monoclinic, space group $P2_1/n$, $Z = 4$, $a = 9.3856(3)$, $b = 12.2110(3)$, $c = 12.1822(4)$ Å; $\beta = 108.645(4)°$; $V = 1322.90(7)$ Å^3, $D_x = 1.202$ g cm^{-3}, 2640 unique data ($2\theta_{\max} = 147.2°$), $R = 0.082$ [for 2373 reflections with $I > 2.0\sigma(I)$]; $Rw = 0.244$ (all data), $S = 1.06$.

*Crystallographic Data for Compound **45**.*

$C_{18}H_{21}NO$, $M = 267.36$, $T = 150$ K, monoclinic, space group $P2_1/n$, $Z = 4$, $a = 11.0667(3)$, $b = 10.0284(2)$, $c = 14.0170(3)$ Å; $\beta = 112.696(3)°$; $V = 1435.16(6)$ Å^3, $D_x = 1.237$ g cm^{-3}, 2883 unique data ($2\theta_{\max} = 148.0°$), $R = 0.047$ [for 2635 reflections with $I > 2.0\sigma(I)$]; $Rw = 0.132$ (all data), $S = 1.06$.

Structure Determinations

The images for compounds **5**, **19**, **24**, **26**, **33**, **38**, **40**, **41**, **44** and **45** were measured on either a SuperNova (Cu Kα, mirror monochromator, λ = 1.54184 Å) or Xcalibur (Mo Kα, mirror monochromator, λ = 0.71073 Å) diffractometer fitted with an area detector and the data extracted using the CrysAlis package. The structures of these compounds were solved with ShelXT[20] and refined using ShelXL[21] in OLEX2.[22] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 1852687–1852695 and 1855327). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Associated Content

Supporting Information

The Supporting Information is available free-of-charge on the ACS Publications website at DOI: 10.1021/acs.joc.XXXXXX.

X-ray derived plots for compounds **5**, **19**, **24**, **26**, **33**, **38**, **40**, **41**, **44** and **45** and copies of the NMR spectra of compounds **5**, **6**, **8-12**, **14, 15, 17-20**, **22-27**, **32-34**, **36-38**, **40**, **41** and **44-46** (PDF).

Accession Code

CCDC 1852687-1852695 and 1855327 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

Acknowledgements

We thank the Australian Research Council, the Institute of Advanced Studies, Jinan University, the Pearl River Scholar Program of Guangdong Province and the Famous Foreign Supervisor Program (Grant 2018-HWMS001) of the Ministry of Education, People's Republic of China for financial support.

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