Synthesis of indoles and quinolones by sequential Wittig and Heck reactions

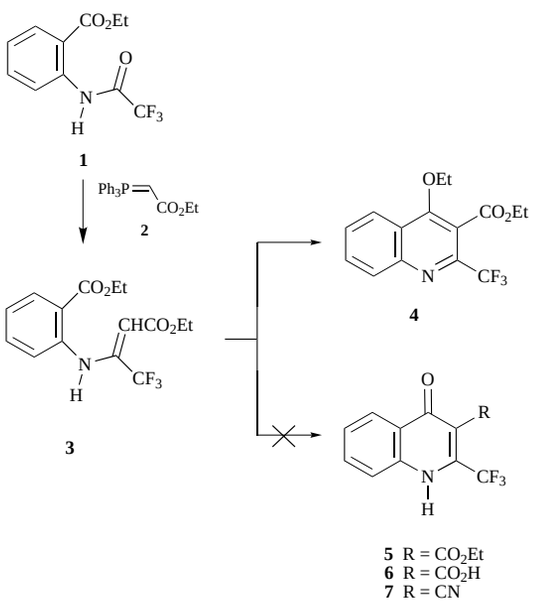
Elliot J. Latham and Stephen P. Stanforth*

Department of Chemical and Life Sciences, University of Northumbria at Newcastle, Newcastle upon Tyne, UK NE1 8ST

Trifluoroacetamido derivatives 18a–c and 19a–c react with phosphorane 2 in boiling toluene to give the corresponding enamines 12a–c and 13a–c respectively which are precursors of the trifluoromethylated indoles 14a–c and quinolones 15a–c.

Introduction

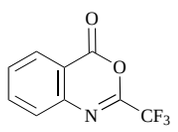
We have recently shown that the Wittig reaction of ethyl 2-trifluoroacetamidobenzoate **1** with phosphorane **2** in the melt (180 °C) gave the quinoline derivative **4** in low yield *via* a putative enamine intermediate **3** (Scheme 1).[1] Thus, the cyclisation



Scheme 1

of the enamine **3** in this reaction proceeded with loss of water giving product **4** and not by loss of ethanol yielding the quinolone **5**. We had hoped at the outset of these studies that the latter mode of cyclisation involving loss of ethanol would occur as this would provide, after hydrolysis of the ester substituent, a useful route to the carboxylic acid **6** which is structurally related to the well known quinolone antibacterial agents. Derivatives of ester **1** similarly gave products **4** when reacted with phosphorane **2**. In contrast, ethyl and methyl esters of trifluoroacetamidothiophenecarboxylic acids reacted with phosphorane **2** or its corresponding methyl ester in toluene at reflux to yield enamine derivatives which were isolated and characterised and subsequently cyclised under basic conditions giving trifluoromethylated thienopyridones.[2]

In order to circumvent the problem of the undesired mode of cyclisation of ester **1** in the Wittig reaction, we investigated an alternative strategy for the synthesis of quinolones **5**.[3] Thus, the reaction of 2-trifluoromethyl-4*H*-3,1-benzoxazin-4-one **8** with phosphorane **2** gave the phosphorane **9**. An intramolecular Wittig reaction on compound **9** was then attempted as a possible route to quinolone **5** but when phosphorane **9** was heated in the melt (180 °C) a fragmentation reaction occurred, for which we have proposed a mechanism,[3] and the only product which could be isolated was the ester **1**. Intramolecular Wittig reactions of amides have been reported on several occasions and are usually associated with relatively reactive phosphoranes which cyclise under appropriately mild conditions.[4–6]



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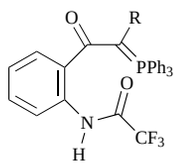
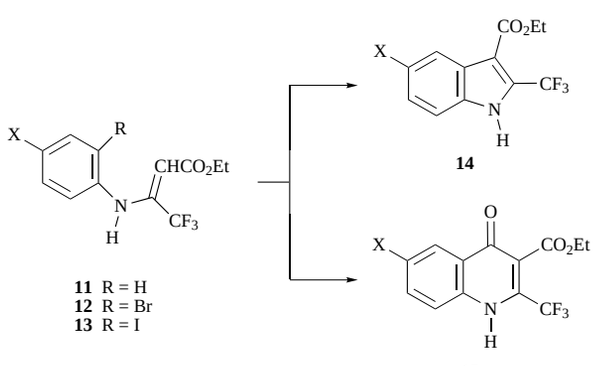


9 R = CO_2Et
10 R = CN

Results and discussion

We initially prepared the cyanophosphorane **10** from benzoxazinone **8** and cyanomethylenetriphenylphosphorane in order to attempt an intramolecular Wittig reaction as a route to quinolone **7** and therefore avoid the fragmentation problem described above for compound **9**, with the cyano group in heterocycle **7** being a suitable carboxylic acid equivalent. Phosphorane **10**, mp 249–251 °C, was readily prepared in good yield but when heated in boiling 1,2-dichlorobenzene solution for 22 h gave no characterisable products except for triphenylphosphine oxide.

We therefore developed an alternative strategy to trifluoromethylated heterocycles and the studies described below relate to the synthesis of both indoles[7–11] and quinolones[12] from common intermediates based upon our Wittig methodology (Scheme 2).[13] We anticipated that the halogen containing enam-



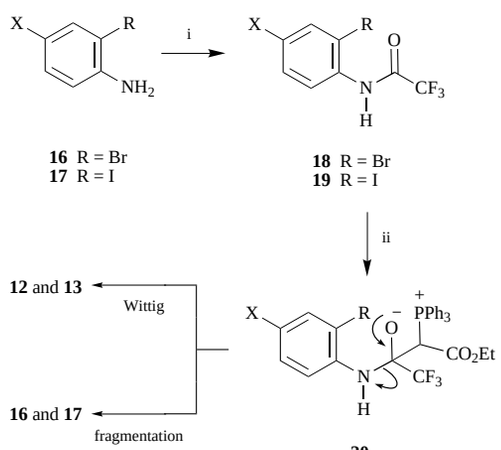
a, X = CN; **b**, X = CO_2Et; **c**, X = NO_2

Scheme 2

ines **12a–c** and **13a–c** might undergo an intramolecular Heck reaction giving indoles **14a–c** as there is literature precedence[14–17] for this method of constructing the indole ring, although it has not been used to our knowledge to synthesise 2-trifluoromethylated indoles possessing electron deficient 5-substituents. Additionally, carbonylation[18,19] of these enamines with carbon monoxide might also give the 2-trifluoromethylated quinolones **15a–c**. Thus, a range of highly substituted trifluoromethylated indoles and quinolones would be available using this methodology.

In order for the Wittig reaction of aryltrifluoroacetamido derivatives to be successful, an electron withdrawing group, capable of accommodating the nitogen lone pair by mesomerism, is required in the substrate. Thus the group X in trifluoroacetamido precursors **18a–c** and **19a–c** of enamines **12a–c** and **13a–c** respectively was chosen as the cyano, ethoxycarbonyl and nitro groups.

The trifluoroacetamido derivatives **18a–c** and **19a–c** were prepared in good yield by treatment of the aniline derivatives **16a–c** and **17a–c** respectively with trifluoroacetic anhydride (Scheme 3). When compounds **18a–c** were heated with phosphorane **2** in boiling toluene solution the enamines **12a–c** (63–95%) were formed and isolated as yellow oils after chromatography. Compounds **18a** and **18c** also gave some of the anilines **16a** and **16c** respectively which are derived from fragmentation of the betaine intermediate **20** (arrows, Scheme 3). Similarly, compounds **19a–c** reacted with phosphorane **2** giving, after chromatography, enamines **13a–c** (54–63%) respectively. Enamine **13a** was obtained as a yellow solid, mp 84–86 °C and enamines **13b** and **13c** were both isolated as yellow oils. Only enamine **13c** was accompanied by the fragmentation product, aniline derivative **17c**.



16 R = Br
17 R = I

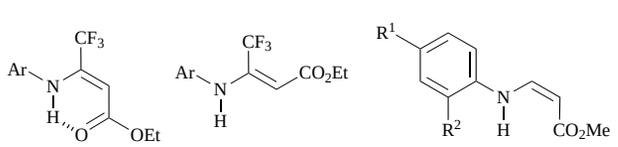
18 R = Br
19 R = I

20

a, X = CN; **b**, X = CO_2Et; **c**, X = NO_2

Scheme 3 *Reagents and conditions:* i, trifluoroacetic anhydride; ii, **2**, toluene, reflux

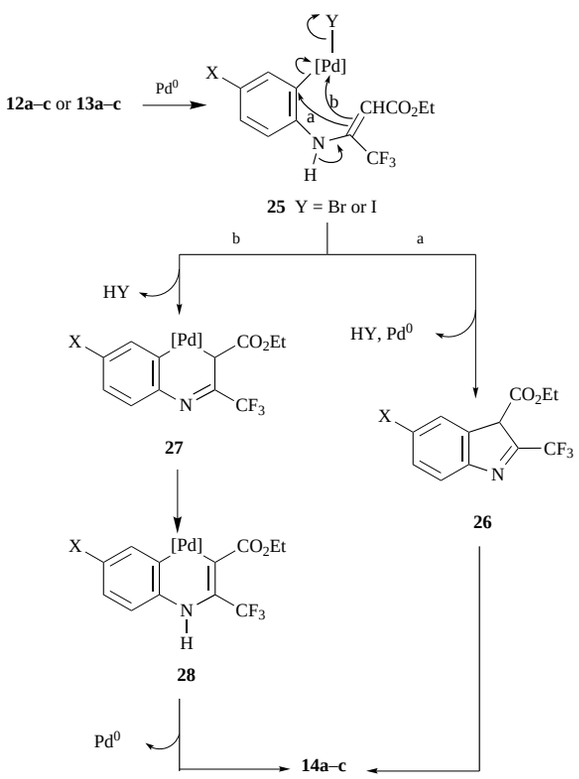
In the ^{1}H NMR spectra of enamines **12a–c** and **13a–c** only one alkenyl proton signal was observed as a singlet (δ 5.45–5.73). Of the two possible geometrical isomers **21** and **22** for the enamine products, we tentatively assign the *Z* stereochemistry **21** to the major isomer for the following reason.



21 **22** **23** R^1 = H, R^2 = Br; **24** R^1 = OMe, R^2 = NO_2

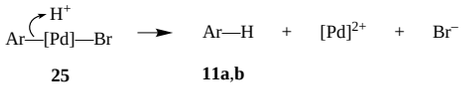
Bozell and Hegedus[20] prepared a series of enamines including compounds **23** and **24** by a palladium(II) catalysed addition of methyl methacrylate to 2-bromoaniline and 2-nitro-4-methoxyaniline respectively. The product **23** was shown by ^{1}H NMR spectroscopy to be the *Z* isomer because the alkenyl protons (δ 4.92, $CDCl_3$) showed an 8 Hz coupling constant. The *Z* isomer of compound **23** can be associated with intramolecular hydrogen bonding between the amino proton and the ester carbonyl group and intramolecular hydrogen bonding is also apparent in formula **21**. Compound **24** was similarly prepared and was shown to be a mixture of *Z* and *E* isomers; the *Z* isomer can involve hydrogen bonding between the amino proton and the ester carbonyl group whereas in the *E* isomer the amino proton can still be hydrogen bonded to the adjacent nitro group. A series of related *N*-methylated enamines were also prepared and in these compounds, which cannot form intramolecular hydrogen bonds, only the *E* isomers were formed as indicated by the 13 Hz coupling constant between the alkenyl protons in their ^{1}H NMR spectra.

When enamine **12a** was heated in DMF solution at 120 °C with a catalytic quantity of palladium acetate and triphenylphosphine with tripropylamine as the base, an intramolecular Heck reaction ensued (Scheme 4) giving indole **14a** (54%) after chromatography. Two mechanistic pathways to indole **14a** from enamine **12a** can be envisaged; one pathway involves formation of the 3*H*-indole **26** (arrows a, Scheme 4) and the alternative pathway involves formation of the palladacycles **27** and **28** (arrows b, Scheme 4) from which indole **14a** is formed by a reductive elimination of palladium(0). In addition to the indole product **14a**, the enamine **11a** (28%) was also formed in the Heck reaction. Enamine **12b** also gave a mixture of indole **14b** (50%) and byproduct **11b** (31%) in a similar Heck reaction but in contrast indole **14c** could not be successfully prepared from enamine **12c** under these conditions. Authentic samples of the byproducts **11a** and **11b** were prepared from a Wittig reaction between phosphorane **2** and 4-trifluoroacetamidobenzonitrile or ethyl 4-trifluoroacetamidobenzoate as appropriate.



Scheme 4

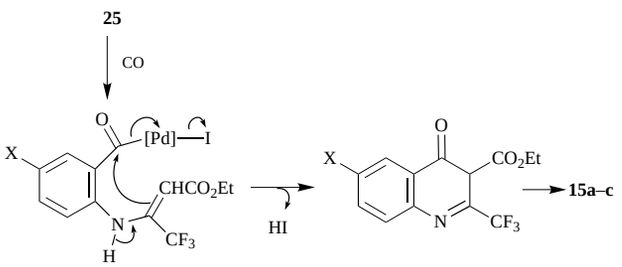
The byproducts **11a** and **11b** possibly originate from protonation of the palladium intermediate **25** by tripropylamine hydrobromide as shown in Scheme 5. Such a protonation would how-



Scheme 5

ever generate palladium(II) which would have to be reconverted to palladium(0) to continue the catalytic cycle. We reasoned that by removing the proton source by replacing tripropylamine with sodium hydrogen carbonate the formation of the byproducts would be avoided. Thus, enamine **12b** gave only indole derivative **14b** although the yield of this compound (44%) was now reduced. Although the enamine **12c** failed to yield indole **14c** in the Heck reaction, the more reactive iodo compound **13c** gave product **14c** (44%) using sodium hydrogen carbonate as the base.

Quinolones **15a–c** (54–77%) were readily prepared from enamine precursors **13a–c** respectively under similar reaction conditions to those described above except that the reactions were performed under an atmosphere of carbon monoxide at ambient pressure (Scheme 6). This overall transformation of



Scheme 6

aniline derivatives **17a–c** into 2-trifluoromethylated quinolone derivatives **15a–c** represents an expedient route to compounds which are structurally related to the quinolone antibacterial compounds.

We have demonstrated that the Wittig reaction of aryltrifluoroacetamido derivatives is a practical method for synthesising enamine derivatives and that these enamines can be readily converted into trifluoromethylated indoles and quinolones with useful substitution patterns.

Experimental

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR spectrophotometer as potassium bromide discs unless otherwise indicated. ^{1}H NMR spectra were obtained on either a JEOL 90Q (90 MHz) or a JEOL EX 270 FT (270 MHz) instrument in $CDCl_3$ solution using tetramethylsilane as an internal standard. *J* Values are given in Hz. Elemental analyses were performed by the University of Leeds or the University of Newcastle upon Tyne and high resolution mass spectra were obtained at the University of Newcastle upon Tyne. Column chromatography utilised Merck silica gel 60. Light petroleum had bp 40–60 °C. Bromoanilines **16a**–**c**[21] and iodoanilines **17a–c**[22] were prepared by treatment of the parent aniline derivatives with either *N*-bromosuccinimide or an iodine–hydrogen peroxide mixture respectively according to literature procedures. Compounds **18a–c** have been described previously in the literature.[23]

[1-(2-Trifluoroacetamidobenzoyl)]cyanomethylenetriphenylphosphorane 10

A mixture of 2-trifluoromethyl-4*H*-3,1-benzoxazin-4-one **8** (0.53 g, 2.5 mmol) and cyanomethylenetriphenylphosphorane (1.5 g, 5.0 mmol) was heated (2 h) in toluene (20 cm^3) at reflux under a nitrogen atmosphere. The mixture was allowed to cool to room temperature and then cooled in an ice-bath giving *the title compound* **10** (0.90 g, 71%) as a white solid; mp 249–251 °C (from acetonitrile) (Found: C, 67.50; H, 3.80; N, 5.55. $C_{29}H_{20}F_3N_2O_2P$ requires C, 67.43; H, 3.91; N, 5.42%); ν_{max}/cm^{-1} 3200, 3080, 2180, 1720, 1590, 1510, 1280 and 1195; δ_H 11.44 (1H, br s, NH), 8.39 (1H, dd, *J* 8 and 1.5, ArH), 8.23 (1H, dd, *J* 7.5 and 2, ArH) and 7.91–7.30 (17H, m, ArH).

Attempted preparation of quinolone 7

Phosphorane **10** (0.20 g, 0.39 mmol) was heated (22 h) at reflux in 1,2-dichlorobenzene under a nitrogen atmosphere. After cooling to room temperature, the solvent was removed by distillation under reduced pressure and the residue was purified by column chromatography (eluent, light petroleum–ethyl acetate, 1:1). The only material from the complex mixture of products which could be identified by ^{1}H NMR spectroscopy from the column fractions was triphenylphosphine oxide.

Trifluoroacetamido derivatives 19a–c

3-Iodo-4-trifluoroacetamidobenzonitrile 19a. The synthesis of compound **19a** is representative. 2-Iodo-4-cyanoaniline (8.3 g, 34 mmol) and trifluoroacetic anhydride (10.7 g, 51 mmol) were heated (3 h) in dichloromethane (40 cm^3) at reflux. After cooling to room temperature, the mixture was washed successively with saturated aqueous sodium hydrogen carbonate and then water. The organic layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure giving *the title compound* **19a** (5.36 g, 46%) as cream needles; mp 149–151 °C (from heptane) (Found: C, 32.15; H, 0.85; N, 8.05. $C_9H_4F_3IN_2O_2$ requires C, 31.79; H, 1.19; N, 8.24%); ν_{max}/cm^{-1} 3355, 3000, 2343, 2230, 1730, 1518, 1530, 1469, 1285, 1194, 908 and 718; δ_H 8.45 (1H, d, *J* 9, H-5), 8.13 (1H, d, *J* 2, H-2) and 7.85–7.62 (1H, m, H-6). The >N*H* signal was too broad to locate.

Ethyl 3-iodo-4-trifluoroacetamidobenzoate 19b. Compound **19b** (94%) was prepared in a similar method to compound **19a** as light grey needles; mp 106–108 °C (from heptane) (Found: C, 34.10; H, 2.15; N, 3.50. $C_{11}H_9F_3INO_3$ requires C, 34.13; H, 2.35; N, 3.62%); ν_{max}/cm^{-1} 3304, 3076, 2986, 1708, 1595, 1534, 1389, 1269, 1187 and 766; δ_H 8.50 (1H, d, *J* 2, H-2), 8.35 (1H, d, *J* 9, H-5), 8.07 (1H, dd, *J* 9 and 2, H-6), 4.40 (2H, q, *J* 9, CH_2) and 1.40 (3H, t, *J* 9, CH_3). The >N*H* signal was too broad to locate.

3-Iodo-4-trifluoroacetamidonitrobenzene 19c. Compound **19c** (94%) was prepared in a similar method to compound **19a** as pale yellow needles; mp 124–126.5 °C (from heptane) (Found: C, 27.00; H, 0.90; N, 7.55. $C_8H_4F_3IN_2O_2$ requires C, 26.69; H, 1.12; N, 7.78%); ν_{max}/cm^{-1} 3329, 3100, 1708, 1604, 1581, 1548, 1514, 1465, 1396, 1186 and 738; δ_H 8.72 (1H, d, *J* 2.5, H-2), 8.50 (1H, d, *J* 9, H-5) and 8.30 (1H, dd, *J* 9 and 2.5, H-6). The >N*H* signal was too broad to locate.

Synthesis of enamines 11a, 11b, 12a–c and 13a–c

Enamine 11a. The synthesis of enamine **11a** is representative. A mixture of 4-trifluoroacetamidobenzonitrile (0.40 g, 1.9 mmol) and phosphorane **2** (1.30 g, 3.7 mmol) was heated (6 h) in dry toluene (10 cm^3) at reflux under a nitrogen atmosphere. After cooling to room temperature and removal of the solvent by evaporation under reduced pressure, the residue was purified by column chromatography (eluent, light petroleum–ethyl acetate, 1:1) giving *ethyl* 3-(4-*cyanophenylamino*)-4,4,4-*trifluorobut*-2-*enoate* **11a** (0.11 g, 21%) as a yellow oil (Found: C, 54.70; H, 3.85; N, 9.25; M$^+$, 284.0776. $C_{13}H_{11}F_3N_2O_2$ requires C, 54.93; H, 3.91; N, 9.86%; *M*, 284.0773); ν_{max}(CCl_4)/cm^{-1} 3207, 2993, 2227, 1675, 1625, 1602, 1510, 1482, 1366, 1295, 1213, 928 and 804; δ_H 9.99 (1H, br s, NH), 7.65 (2H, d, *J* 8, H-3), 7.22 (2H, d, *J* 8, H-2), 5.52 (1H, s, CH), 4.21 (2H, q, *J* 8, CH_2) and 1.31 (3H, t, *J* 8, CH_3).

Enamine 11b. Using a similar procedure to that described above for the preparation of enamine **11a**, ethyl 4-trifluoroacetamidobenzoate gave *ethyl* 3-(4-*ethoxycarbonylphenylamino*)-4,4,4-*trifluorobut*-2-*enoate* **11b** (34%) as a yellow oil after

column chromatography (eluent, light petroleum–ethyl acetate, 1:1) [Found: M^+, 332.1110. $C_{15}H_{16}F_3NO_4$ (M + H) requires *M*, 332.1110]; δ_H 9.88 (1H, br s, NH), 7.99 (2H, d, *J* 8, H-3), 7.16 (2H, d, *J* 8, H-2), 5.39 (1H, s, CH), 4.48–4.00 (4H, m, 2 × CH_2) and 1.45–1.03 (6H, m, 2 × CH_3).

Enamine 12a. Using a similar procedure to that described above for the preparation of enamine **11a**, compound **18a** gave *ethyl* 3-(2-*bromo*-4-*cyanophenylamino*)-4,4,4-*trifluorobut*-2-*enoate* **12a** (69%) as a pale yellow oil after column chromatography (eluent, dichloromethane) (Found: C, 42.74; H, 2.55; N, 7.75. $C_{13}H_{10}BrF_3N_2O_2$ requires C, 42.99; H, 2.78; N, 7.95%); $\nu_{max}(CCl_4)/cm^{-1}$ 2984, 2231, 1744, 1681, 1636, 1598, 1512, 1293, 1212 and 778; δ_H 9.72 (1H, br s, NH), 7.89 (1H, d, *J* 2, H-3), 7.55 (1H, dd, *J* 8 and 2, H-5), 7.22 (1H, d, *J* 8, H-6), 5.65 (1H, s, CH), 4.22 (2H, q, *J* 8, CH_2) and 1.32 (3H, t, *J* 8, CH_3). Subsequent fractions from the column gave a small quantity of a mixture of enamine **12a** and 2-bromo-4-cyanoaniline as determined by ^{1}H NMR spectroscopy.

Enamine 12b. Using a similar procedure to that described above for the preparation of enamine **11a**, compound **18b** gave *ethyl* 3-(2-*bromo*-4-*ethoxycarbonylphenylamino*)-4,4,4-*trifluorobut*-2-*enoate* **12b** (95%) as a pale yellow oil after column chromatography (eluent, dichloromethane) (Found: C, 43.80; H, 3.75; N, 3.35. $C_{15}H_{15}BrF_3NO_4$ requires C, 43.92; H, 3.69; N, 3.42%); $\nu_{max}(CCl_4)/cm^{-1}$ 3220, 2983, 1723, 1680, 1635, 1598, 1290 and 1209; δ_H 9.79 (1H, br s, NH), 8.30 (1H, d, *J* 2, H-3), 7.99 (1H, dd, *J* 8 and 2, H-5), 7.25 (1H, d, *J* 8, H-6), 5.58 (1H, s, CH), 4.55–4.09 (4H, m, 2 × CH_2) and 1.51–1.18 (6H, m, 2 × CH_3).

Enamine 12c. Using a similar procedure to that described above for the preparation of enamine **11a**, compound **18c** gave *ethyl* 3-(2-*bromo*-4-*nitrophenylamino*-4,4,4-*trifluorobut*-2-*enoate* **12c** (63%) as a pale yellow oil after column chromatography (eluent, dichloromethane) (Found: C, 37.80; H, 2.70; N, 7.40. $C_{12}H_{10}BrF_3N_2O_4$ requires C, 37.62; H, 2.64; N, 7.31%); $\nu_{max}(CCl_4)/cm^{-1}$ 3404, 2990, 1683, 1637, 1587, 1529, 1295 and 1211; δ_H 9.76 (1H, br s, NH), 8.50 (1H, d, *J* 2, H-3), 8.17 (1H, dd, *J* 9 and 2, H-5), 7.26 (1H, d, *J* 9, H-6), 5.75 (1H, s, CH), 4.25 (2H, q, *J* 8, CH_2) and 1.30 (3H, t, *J* 8, CH_3). Subsequent fractions from the column gave a small quantity of a mixture of enamine **12c** and 2-bromo-4-nitroaniline as determined by ^{1}H NMR spectroscopy.

Enamine 13a. Using a similar procedure to that described above for the preparation of enamine **11a**, compound **19a** gave *ethyl* 3-(2-*iodo*-4-*cyanophenylamino*)-4,4,4-*trifluorobut*-2-*enoate* **13a** (63%) as a pale yellow solid; mp 84–86 °C (from heptane) after column chromatography (eluent, dichloromethane) (Found: C, 38.15; H, 2.30; N, 6.55. $C_{13}H_{10}F_3IN_2O_2$ requires C, 38.07; H, 2.46; N, 6.83%); ν_{max}/cm^{-1} 2989, 2343, 2228, 1681, 1636, 1593, 1508, 1294, 1224, 831 and 668; δ_H 9.64 (1H, br s, NH), 8.14 (1H, d, *J* 2, H-3), 7.62 (1H, dd, *J* 9 and 2, H-5), 7.28 (1H, d, *J* 9, H-6), 5.66 (1H, s, CH), 4.28 (2H, q, *J* 8, CH_2) and 1.37 (3H, t, *J* 8, CH_3).

Enamine 13b. Using a similar procedure to that described above for the preparation of enamine **11a**, compound **19b** gave *ethyl* 3-(2-*iodo*-4-*ethoxycarbonylphenylamino*)-4,4,4-*trifluorobut*-2-*enoate* **13b** (58%) as a pale yellow oil after column chromatography (eluent, dichloromethane) (Found: M^+, 456.9999. $C_{15}H_{15}F_3INO_4$ requires *M*, 457.0009); $\nu_{max}(CCl_4)/cm^{-1}$ 3375, 2983, 1721, 1679, 1633, 1592, 1291 and 1209; δ_H 9.60 (1H, br s, NH), 8.53 (1H, d, *J* 2, H-3), 8.00 (1H, dd, *J* 8 and 2, H-5), 7.25 (1H, d, *J* 8, H-6), 5.58 (1H, s, CH), 4.53–4.10 (4H, m, 2 × CH_2) and 1.52–1.20 (6H, m, 2 × CH_3).

Enamine 13c. Using a similar procedure to that described above for the preparation of enamine **11a**, compound **19c** gave *ethyl* 3-(2-*iodo*-4-*nitrophenylamino*)-4,4,4-*trifluorobut*-2-*enoate* **13c** (54%) as a pale yellow oil after column chromatography (eluent, dichloromethane) (Found: M^+, 429.9638. $C_{12}H_{10}F_3IN_2O_4$ requires *M*, 429.9637); $\nu_{max}(CCl_4)/cm^{-1}$ 3000, 1730, 1681, 1635, 1580, 1525, 1293 and 1211; δ_H 9.60 (1H, br s, NH), 8.70 (1H, d, *J* 2, H-3), 8.19 (1H, dd, *J* 8 and 2, H-5), 7.25 (1H, d, *J* 8, H-6), 5.70 (1H, s, CH), 4.22 (2H, q, *J* 8, CH_2) and 1.31 (3H, t, *J* 8, CH_3). Subsequent fractions from the column gave a small quantity of a mixture of enamine **13c** and 2-iodo-4-nitroaniline as determined by ^{1}H NMR spectroscopy.

Synthesis of indoles 14a–c

Indole 14a. A mixture of enamine **12a** (0.50 g, 1.4 mmol), triphenylphosphine (0.07 g, 0.27 mmol), palladium(II) acetate (0.03 g, 0.13 mmol) and tripropylamine (0.30 g, 2.1 mmol) was heated (6.5 h) with stirring in DMF (20 cm^3) at 120 °C (oil-bath temperature) under a nitrogen atmosphere. The mixture was allowed to cool to room temperature and water and dichloromethane were added. The organic portion was separated, washed with dilute hydrochloric acid and then with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (eluent, light petroleum–ethyl acetate, 5:2) yielding *ethyl* 5-*cyano*-2-*trifluoromethylindole*-3-*carboxylate* **14a** (0.21 g, 54%) as a pale yellow solid; mp 220–222 °C (from ethanol) (Found: C, 55.60; H, 3.05; N, 9.85. $C_{13}H_9F_3N_2O_2$ requires C, 55.32; H, 3.22; N, 9.93%); ν_{max}/cm^{-1} 3246, 3000, 2229, 1715, 1567, 1444, 1386, 1222, 1157 and 821; δ_H 9.42 (1H, br s, NH), 9.23 (1H, d, *J* 2, C-4), 8.30 (1H, dd, *J* 8 and 2, C-6), 7.60 (1H, d, *J* 8, C-7), 4.47 (2H, q, *J* 8, CH_2) and 1.45 (3H, t, *J* 8, CH_3). Enamine **11a** (0.11 g, 28%), identical with an authentic sample, was also isolated from the column.

Indole 14b. Method A: using a similar method to that described above for the synthesis of indole **14a**, enamine **12b** gave *diethyl* 2-*trifluoromethylindole*-3,5-*dicarboxylate* **14b** (50%) after column chromatography (eluent, dichloromethane) as a cream solid; mp 186.5–188.5 °C (from ethanol) (Found: C, 55.10; H, 4.35; N, 4.10. $C_{15}H_{14}F_3NO_4$ requires C, 54.71; H, 4.29; N, 4.25%); ν_{max}/cm^{-1} 3278, 2990, 1703, 1623, 1555, 1442, 1366, 1340, 1182 and 770; δ_H 9.03 (1H, d, *J* 2, H-4), 8.10 (1H, dd, *J* 9 and 2, H-6), 7.50 (1H, d, *J* 9, H-7), 4.62–4.29 (4H, m, 2 × CH_2) and 1.65–1.30 (6H, m, 2 × CH_3). The >N*H* signal was too broad to locate. Enamine **11b** (31%), identical with an authentic sample, was also isolated from the column.

Method B: using a similar method to that described in Method A except that sodium hydrogen carbonate was used as the base instead of tripropylamine, indole **14b** (44%) was produced, identical with an authentic sample.

Indole 14c. Using a similar method to that described above for the preparation of indole **14a**, except that sodium hydrogen carbonate was used instead of tripropylamine as base, enamine **13c** gave *ethyl* 5-*nitro*-2-*trifluoromethylindole*-3-*carboxylate* **14c** (44%) as a pale yellow powder after column chromatography (eluent, dichloromethane); mp 177–179 °C (from carbon tetrachloride) (Found: C, 47.70; H, 2.75; N, 8.95. $C_{12}H_9F_3N_2O_4$ requires C, 47.69; H, 3.01; N, 9.27%); ν_{max}/cm^{-1} 3319, 3010, 1686, 1564, 1533, 1481, 1457, 1375, 1343, 1181 and 751; δ_H 9.41 (1H, br s, NH), 9.26 (1H, d, *J* 2, H-4), 8.32 (1H, dd, *J* 9 and 2, H-6), 7.60 (1H, d, *J* 9, H-7), 4.49 (2H, q, *J* 8, CH_2) and 1.50 (3H, t, *J* 8, CH_3).

Synthesis of quinolones 15a–c

The synthesis of compound **15a** is representative. A mixture of enamine **13a** (0.50 g, 1.2 mmol), triphenylphosphine (0.06 g, 0.23 mmol), palladium(II) acetate (0.03 g, 0.01 mmol) and sodium hydrogen carbonate (0.31 g, 3.7 mmol) was heated (2 h) with stirring in DMF (10 cm^3) at 120 °C (oil-bath temperature) under an atmosphere of carbon monoxide at ambient pressure. The mixture was allowed to cool to room temperature, poured into water (40 cm^3) and then acidified to pH 2–3 with dilute hydrochloric acid. The mixture was extracted several times with ethyl acetate and the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure giving *ethyl* 6-*cyano*-2-*trifluoromethyl*-4-*oxo*-1,4-*hydroquinoline*-3-*carboxylate* **15a** (0.20 g, 54%) as a white solid; mp

>239 °C (decomp.) (from ethanol) (Found: C, 54.25; H, 2.75; N, 9.00; M^+, 310.0582. $C_{14}H_9F_3N_2O_3$ requires C, 54.20; H, 2.93; N, 9.03%; *M*, 310.0566); ν_{max}/cm^{-1} 3082, 2969, 2232, 1735, 1626, 1597, 1523, 1487, 1303, 1215, 1099, 1022 and 834; δ_H 13.20 (1H, br s, NH), 8.75 (1H, d, *J* 1.5, H-5), 8.21 (1H, dd, *J* 8 and 1.5, H-7), 8.02 (1H, d, *J* 8, H-8), 4.56 (2H, q, *J* 7, CH_2) and 1.48 (3H, t, *J* 7, CH_3).

Quinolone 15b. Using a similar procedure to that described for the synthesis of compound **15a**, *diethyl* 2-*trifluoromethyl*-4-*oxo*-1,4-*dihydroquinoline*-3,6-*dicarboxylate* **15b** (77%) was prepared as a pale yellow powder; mp >254 °C (decomp.) (from ethanol) (Found: C, 54.05; H, 3.71; N, 3.80; M^+, 357.0833. $C_{16}H_{14}F_3NO_5$ requires C, 53.78; H, 3.96; N, 3.92%; *M*, 357.0824); ν_{max}/cm^{-1} 3066, 2904, 1727, 1628, 1570, 1529, 1279, 1203, 1166, 1116, 1020, 853 and 769; δ_H 9.09 (1H, d, *J* 2, H-5), 8.48 (1H, dd, *J* 8 and 2, H-7), 8.15 (1H, d, *J* 8, H-8), 4.59–4.52 (2H, q, *J* 7, CH_2), 4.52–4.44 (2H, q, *J* 7, CH_2) and 1.50–1.44 (6H, m, 2 × CH_3). The >N*H* signal was too broad to be located.

Quinolone 15c. Using a similar procedure to that described for the synthesis of compound **15a**, *ethyl* 6-*nitro*-2-*trifluoromethyl*-4-*oxo*-1,4-*dihydroquinoline*-3-*carboxylate* **15c** (73%) was prepared as a pale tan solid; mp 245–248 °C (from toluene) (Found: M^+, 330.0017. $C_{13}H_9F_3N_2O_5$ requires *M*, 330.0464); ν_{max}/cm^{-1} 3082, 2947, 1733, 1600, 1519, 1476, 1347, 1303, 1215, 1069, 842 and 725; δ_H 9.28 (1H, d, *J* 2.5, H-5), 8.63 (1H, dd, *J* 9 and 2.5, H-7), 8.26 (1H, d, *J* 9, H-8), 4.57 (2H, q, *J* 7, CH_2) and 1.49 (3H, t, *J* 7, CH_3). The >N*H* signal was too broad to be located.

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