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Synthesis of regiospecifically substituted quinolines from anilines

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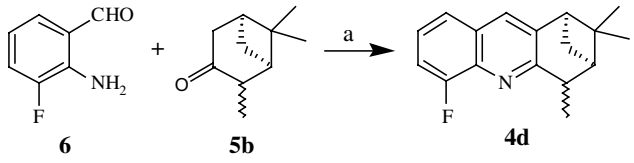
Abstract—A protocol for the synthesis of quinolines substituted on both pyridine and benzo-fused rings is reported. The method is based on the formylation of a substituted *N*-(*tert*-butoxycarbonyl)aniline followed by direct cyclisation and aromatisation of the intermediate product obtained by condensation of the formed *N*-Boc *o*-aminobenzaldehyde with an enolisable carbonyl compound. Yields up to 88% have been obtained.

During the course of our studies related to the synthesis of new chiral pyridine–phosphine ligands we required a practical procedure for accessing chiral 5-fluoro-1,2,3,4-tetrahydroacridines. Among the approaches, the Friedländer reaction which entails the condensation of an enolisable carbonyl compound with an *o*-amino aryl aldehyde, generally obtained by reduction of the corresponding *o*-nitro aryl aldehyde, appeared the most attractive.[1] However, in many cases the yield of this reaction is unsatisfactory due to the relative instability of the *o*-amino aryl aldehyde which can readily undergo self-condensation reactions. This circumstance has been observed by us when the 2-amino-3-fluorobenzaldehyde (**6**)[2] by treatment under Friedländer conditions (EtOH or carbitol, saturated KOH in MeOH, room temperature to 130 °C) with the chiral ketone 2,6,6-trimethylbicyclo[3.1.1]heptan-3-one (**5b**), gave the 5-fluorotetrahydroacridine **4d** in only 15% yield (Scheme 1).



6 **5b** **4d**

Scheme 1. Reagents and conditions: (a) KOH, EtOH, reflux.

A brilliant solution of this problem has been very recently developed by McNaughton and Miller who have been able to obtain directly substituted quinolines from ketones and *o*-nitrobenzaldehydes by a one-pot reduction–condensation sequence.[3] This method provides products in high yields, but suffers of the fact that the number of commercially available substituted *o*-nitrobenzaldehydes is exceedingly small and their preparations are in many cases difficult. For instance, the 3-fluoro-2-nitrobenzaldehyde from which **4d** would be the prepared, is an unknown compound.

In this article we wish to report a version of the Friedländer quinoline synthesis which avoids the isolation of the *o*-amino benzaldehyde intermediate and which allows the preparation of quinolines substituted on both pyridine and benzo-fused rings from several anilines and carbonyl compounds.

The method is hinged upon the direct azaannulation and aromatisation of the intermediate product obtained by condensation of an enolisable carbonyl compound with a *N*-(*tert*-butoxycarbonyl) *o*-aminobenzaldehyde. This aldehyde is produced by formylation of a substituted *N*-(*tert*-butoxycarbonyl)aniline which is in turn obtained from the corresponding aniline.[4] The global process is depicted in Scheme 2 and the results obtained using a number of substituted *o*-aminobenzaldehydes and carbonyl compounds are summarised in Table 1.

The *N*-Boc anilines **2a**–**c** were readily prepared in high yield by heating a THF solution of the corresponding

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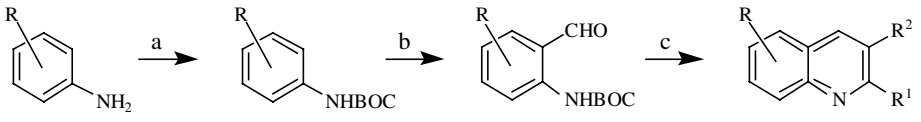
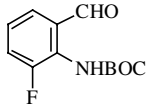
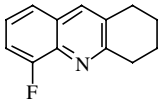
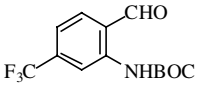
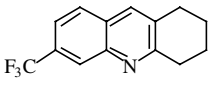
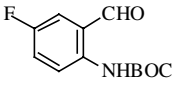
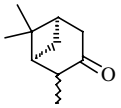
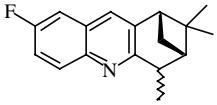
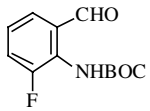
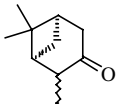
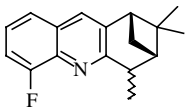
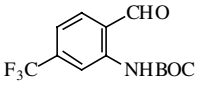
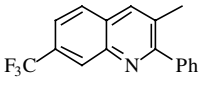
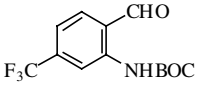
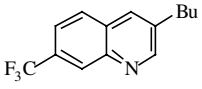
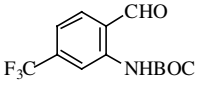
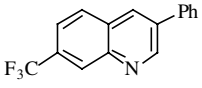
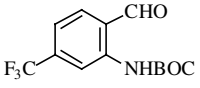
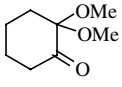
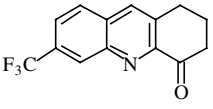


Scheme 2. Reagents and conditions: (a) $(Boc)_2O$, THF, 60 °C, 15 h; (b) *t*-BuLi, THF, −50 °C, 3 h, then DMF, −78 °C to rt; (c) **5a**–**f**, *t*-BuOK, 1,4-dioxane, rt, 1–7 h; then 3 N HCl, reflux 1–4 h.

Table 1. Synthesis of quinolines from *N*-Boc anilines (Scheme 2)[a]

Entry	Aldehyde	Carbonyl compound	Product	Yield[b] (%)
1	 **3a**	 **5a**	 **4a**	62
2	 **3b**	 **5a**	 **4b**	85
3	 **3c**	 **5b**	 **4c**	45
4	 **3a**	 **5b**	 **4d**	88
5	 **3b**	 **5c**	 **4e**	34
6	 **3b**	 **5d**	 **4f**	38
7	 **3b**	 **5e**	 **4g**	29
8	 **3b**	 **5f**	 **4h**	27

[a] Reaction conditions: carbonyl compound (24.0 mmol), *t*-BuOK (0.539 g, 48.0 mmol), *tert*-butyl *N*-(2-formylphenyl)carbamate (20.0 mmol) in dry 1,4-dioxane (15 mL) at rt, 1–7 h; then 3 N HCl reflux 1–4 h.
[b] Isolated yields.

anilines **1a**–**c** with di-*tert*-butyl dicarbonate.[5] The aldehydes **3a**–**c** were obtained by treating the dianions of **2a**–**c**, generated using 2.2 equiv of *tert*-butyllithium in THF, with *N*,*N*-dimethylformamide.[6,7] The position of the formyl group onto the benzene ring depends upon the regiospecificity of directed metallation, which has been established for many substituted aniline derivatives.[4]

The condensation and the azaannulation reactions were carried out by a one-pot method. Firstly, aldehydes **3a**–**c** and carbonyl compounds **5a**–**f** in dioxane containing potassium *tert*-butoxide were stirred at room temperature for 1–7 h and then a 3 N hydrochloric acid solution was added. Heating the resulting mixture under reflux for 1–4 h led to the quinolines **4a**–**h**.[8] The reaction times

of each step depend from the steric hindrance of the carbonyl compound.

The combination of the aldehydes **3a**–**c** with cyclohexanones **5a**,**b** afforded the corresponding 1,2,3,4-tetrahydroacidines **4a**–**d** in good yields (Table 1, entries 1–4). Most gratifyingly, the 5-fluorotetrahydroacridine **4d** (Table 1, entry 4) was obtained in high yield (88%). Modest yields were instead obtained with acyclic carbonyl compounds **5c**–**e** (Table 1, entries 5–7).

In order to obtain an easy entry into 2,3-dihydro-1*H*-acridin-4-one derivatives, which are useful intermediates in the synthesis of more complexes heterocycles,[9] the reaction of the aldehyde **3b** with 2,2-dimethoxycyclohexanone (**5f**) was examined. The acridinone **4h** was obtained in low yield (Table 1, entry 8) which was not possible to improve also when the analogue cyclic ketal 1,4-dioxaspiro[4.5]decan-6-one was used. This outcome is likely attributable to the relatively low stability of **4h** which we noted to undergo ready degradation on standing at room temperature for one week.

In conclusion, we have developed a method for the preparation of regiospecifically functionalised quinolines from substituted anilines and carbonyl compounds. This procedure, which complements existing ones, is particularly useful for the preparation of substituted 1,2,3,4-tetrahydroacridines[10] from sterically hindered cyclohexanones.[11]

Acknowledgements

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References and notes

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2. The 2-amino-3-fluorobenzaldehyde has been obtained in 55% yield by hydrolysis of the corresponding *N*-Boc derivative **3a** (1,4-dioxane, HCl (3 N), 60 °C, 3 h).
3. McNaughton, B. R.; Miller, B. L. *Org. Lett.* **2003**, *5*, 4257.
4. For a review on direct *ortho* metallation, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879; For more recent examples, see: (a) Dischino, D. D.; Gribkoff, V. K.; Hewawasam, P.; Luke, G. M.; Rinehart, J. K.; Spears, T. L.; Starret, J. E., Jr. *J. Labelled Compd. Radiopharm.* **2003**, *2*, 139; (b) Hewawasam, P.; Fan, W.; Knipe, J.; Moon, S. L.; Boissard, C. G.; Gribkoff, V. K.; Starett, J. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1779; (c) Hewawasam, P.; Meanwell, N. A. *Tetrahedron Lett.* **1994**, *35*, 7303.
5. *N*-Boc anilines **2a**–**c** were prepared by heating at 60 °C the required aniline with di-*tert*-butyl dicarbonate in a THF solution for 15 h as described: Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798.
6. *Typical procedure for the preparation of tert-butyl N-(2-formylphenyl)carbamates* **3a**–**c**: a solution of *t*-BuLi (1.5 M in pentane, 29.3 mL, 44.0 mmol) was added dropwise to a solution of *tert*-butyl *N*-phenylcarbamate (20.0 mmol) in dry THF (40 mL) cooled at −78 °C. After 15 min at −78 °C the solution was warmed at −50 °C and stirred at this temperature for 3 h. Then, the mixture was cooled at −78 °C and a solution of DMF (1.9 g, 26.0 mmol) in THF (5 mL) was added dropwise. After 15 min at −78 °C the solution was allowed to reach slowly room temperature (overnight) and then quenched with brine and extracted with Et_2O. The organic phase was dried (Na_2SO_4), the solvent was evaporated and the residue was purified by flash chromatography (petroleum ether/EtOAc) to give pure aldehyde. *tert-Butyl N-(2-formyl-6-fluorophenyl)carbamate* (**3a**): yield 3.39 g (71%); mp 186–189 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.01 (s, 1H), 7.96 (s, 1H), 7.57 (d, 1H, J = 6.9 Hz), 7.40–7.22 (m, 2H), 1.50 (s, 3H). Anal. Calcd for $C_{12}H_{14}FNO_3$: C, 60.24; H, 5.90; N, 5.85. Found: C, 60.38; H, 5.98; N, 5.79. *tert-Butyl N-(2-formyl-5-fluorophenyl)carbamate* (**3b**): yield 4.51 g (78%); oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.45 (s, 1H), 9.98 (s, 1H), 8.82 (s, 1H), 7.77 (d, 1H, J = 8.1 Hz), 7.36 (d, 1H, J = 8.1 Hz), 1.55 (s, 9H). Anal. Calcd for $C_{13}H_{14}F_3NO_3$: C, 53.98; H, 4.88; N, 4,84. Found: C, 53,85; H, 4,82; N, 4,87. *tert-Butyl N-(2-formyl-4-fluorophenyl)carbamate* (**3c**): yield 2.48 g (52%); mp 73–75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.22 (s, 1H), 9.85 (s, 1H), 8.48 (dd, 1H, J = 9.0, 4.8 Hz), 7.37–7.26 (m, 2H), 1.53 (s, 9H). Anal. Calcd for $C_{12}H_{14}FNO_3$: C, 60.24; H, 5.90; N, 5.85. Found: C, 60.34; H, 5.86; N, 5.89.
7. Compound **3b** was obtained with the nonformylated starting material **2b** in a 6:4 mixture, respectively. This mixture was used in the next step without further purification: Cordi, A. A.; Decos, P.; Ruano, E.; Al-Badri, H.; Fugier, C.; Chapman, A. G.; Meldum, B. S.; Thomas, J.-Y.; Roger, A.; Lestage, P. *Farmaco* **2002**, *57*, 787.
8. *General procedure for the preparation of quinolines* **4a**–**h**: the carbonyl compound (2.4 mmol) was added to a suspension of *t*-BuOK (0.539 g, 4.8 mmol) in dry 1,4-dioxane (15 mL). The solution was stirred for 10 min at room temperature and then *tert*-butyl *N*-(2-formylphenyl)carbamate (2.0 mmol) was added. The reaction was stirred at room temperature until the disappearance of the spot of the aldehyde on TLC (1–7 h). A 3 N solution of HCl (6 mL) was added and the resulting mixture was heated under reflux from 1 to 4 h. Most part of the solvent was evaporated under reduced pressure and the residue was taken up with a 5% NaOH solution and extracted with Et_2O. The organic phase was dried (Na_2SO_4), the solvent was evaporated and the residue was purified by flash chromatography to give pure quinoline. *5-Fluoro-1,2,3,4-tetrahydroacridine* (**4a**): chromatographic eluent: petroleum ether/EtOAc, 8:2; mp 74–76 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.47 (d, 1H, J = 8.1 Hz), 7.38–7.22 (m, 2H), 3.18 (t, 2H, J = 6.3 Hz), 7.97 (t, 2H, J = 6.3 Hz), 2.05–1.84 (m, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 159.92, 159.19, 134.56, 132.13, 125.13, 125.02, 122.48, 112.43, 112.18, 33.64, 29.25, 23.04, 22.69. Anal. Calcd for $C_{13}H_{12}FN$: C, 77.59; H, 6.01; N, 6.96. Found: C, 77.66; H, 6.13; N, 6.88. *6-Trifluoromethyl-1,2,3,4-tetrahydroacridine* (**4b**): chromatographic eluent:

petroleum ether/EtOAc, 8:2; mp 63–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.82 (s, 1H), 7.78 (d, 1H, J = 8.7 Hz), 7.58 (d, 1H, J = 8.7 Hz), 3.14 (t, 2H, J = 6.3 Hz), 2.99 (t, 2H, J = 6.3 Hz), 2.03–1.84 (m, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 161.08, 145.43, 134.57, 133.24, 128.57, 127.96, 126.22, 126.17, 121.10, 121.06, 33.51, 29.29, 22.95, 22.62. Anal. Calcd for $C_{14}H_{12}F_3N$: C, 66.93; H, 4.81; N, 5.57. Found: C, 66.77; H, 4.91; N, 5.71. *7-Fluoro-1,3-methano-2,2,4-trimethyl-1,2,3,4-tetrahydroacridine* (**4c**): this compound was obtained as a 93:7 mixture of epimers at C4; chromatographic eluent: petroleum ether/EtOAc, 8:2; mp 89–95 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (dd, 1H, J = 9.3, 5.4 Hz), 7.52 (s, 1H), 7.39–7.25 (m, 2H), 3.40–3.30 (m, 1H), 2.94 (t, 1H, J = 5.7), 2.83–2.75 (m, 1H, minor isomer), 2.69–2.60 (m, 1H, major isomer), 2.48–2.32 (m, 1H, minor isomer), 2.50 (dt, 1H, J = 6.2, 2.6, minor isomer), 2.22 (dt, 1H, J = 6.0, 2.4, major isomer), 1.61 (d, 3H, J = 7.2, minor isomer), 1.48 (d, 3H, J = 7.2, major isomer), 1.45 (s, 3H), 1.38 (d, 1H), 0.65 (s, 3H). Anal. Calcd for $C_{17}H_{18}FN$: C, 79.97; H, 7.11; N, 5.49. Found: C, 79.78; H, 7.23; N, 5.45. *5-Fluoro-1,3-methano-2,2,4-trimethyl-1,2,3,4-tetrahydroacridine* (**4d**): this compound was obtained as a 8:2 mixture of epimers at C4; chromatographic eluent: petroleum ether/EtOAc, 85:15; mp 92–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, 1H, J = 1.8 Hz), 7.48 (d, 1H, J = 8.1 Hz), 7.41–7.24 (m, 2H), 3.45 (dq, 1H, J = 6.3, 1.5 Hz), 2.96 (t, 1H, J = 5.4 Hz), 2.71–2.62 (m, 1H), 2.23 (dt, 1H, J = 6.0, 2.4 Hz), 1.64 (d, 3H, J = 7.5 Hz, minor isomer), 1.51 (d, 3H, J = 6.9 Hz, major isomer), 1.46 (s, 3H, major isomer), 1.38 (d, 1H, J = 10.2, major isomer), 0.68 (s, 3H, minor isomer), 0.66 (s, 3H, major isomer). Anal. Calcd for $C_{17}H_{18}FN$: C, 79.97; H, 7.11; N, 5.49. Found: C, 79.78; H, 7.23; N, 5.45. *6-Trifluoromethyl-3-methyl-2-phenylquinoline* (**4e**): This compound was purified by flash chromatography using petroleum ether/Et_2O 9:1; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.05 (s, 1H), 7.87 (d, 1H; J = 8.7 Hz), 7.67 (dd, 1H, J = 8.7, 1.8 Hz), 7.62–7.56 (m, 2H), 7.54–7.42 (m, 3H), 2.49 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 161.99, 145.51, 14.20, 136.50, 131.56, 128.95, 128.75, 128.55, 128.37, 127.85, 127.21, 127.15, 122.00, 121.95, 20.70. Anal. Calcd for $C_{17}H_{12}F_3N$: C, 71.07; H, 4.21; N, 4.88. Found: C, 71.25; H, 4.29; N, 4.79. *3-Butyl-6-trifluoromethylquinoline* (**4f**): chromatographic eluent: petroleum ether/Et_2O, 9:1; oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.38 (s, 1H), 7.93 (s, 1H), 7.84 (d, 1H, J = 8.4), 7.66 (d, 1H, J = 8.4 Hz), 2.81 (t, 2H, J = 7.8 Hz), 1.78–1.64 (m, 2H), 1.48–1.34 (m, 2H), 0.96 (t, 3H, J = 7.2 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 153.48, 145.61, 137.51, 133.66, 129.60, 128.38, 127.00, 126.95, 122.08, 122.03, 32.93, 32.86, 22.18, 13.71. Anal. Calcd for $C_{14}H_{14}F_3N$: C, 66,39; H, 5,57; N, 5,53. Found: C, 66.44; H, 5.65; N, 5.46. *6-Trifluoromethyl-3-phenylquinoline* (**4g**): chromatographic eluent: petroleum ether/EtOAc, 8:2; mp 136–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.27 (d, 1H, J = 2.4 Hz), 8.44 (s, 1H), 8.33 (d, 1H, J = 2.4 Hz), 7.99 (d, 1H, J = 8.4 Hz), 7.78–7.68 (m, 3H), 6.60–7.42 (m, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 151.33, 146.23, 137.10, 135.66, 132.78, 129.49, 129.30, 129.13, 129.62, 127.48, 127.14, 127.08, 122.66, 122.62. Anal. Calcd for $C_{16}H_{10}F_3N$: C, 70.33; H, 3.69; N, 5.13. Found: 70.45; H, 3.75; N, 5.12. *6-Trifluoromethyl-2,3-dihydro-1H-acridin-4-one* (**4h**): chromatographic eluent: petroleum ether/EtOAc, 8:2; oil; ^{1}H NMR(300 MHz, $CDCl_3$): δ 8.67 (s, 1H), 8.20 (s, 1H), 7.94 (d, 1H, J = 8.7 Hz), 7.77 (dd, 1H, J = 8.8, 1.5 Hz), 3.26 (t, 1H, J = 6.0 Hz), 2.97 (t, 1H, J = 6.0 Hz), 2.30 (t, 1H, J = 6.0 Hz). Anal. Calcd for $C_{14}H_{10}F_3NO$: C, 63.40; H, 3.80; N, 5.28. Found: C, 63.97; H, 4,10; N, 5,48.

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11. A very interesting one-pot procedure has been developed by for the synthesis of quinoline and 1,2,3,4-tetrahydroacridine derivatives. The method is based on the formylation of *ortho*-dilithiated *N*-pivaloylanilines followed by treatment with carbonyl compounds and KHMDS. However, the method failed when 2-methycyclohexanone was used as the carbonyl component Úbeda, J. I.; Villacampa, M.; Avendaño, C. *Synthesis* **1998**, 1176.