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Synthesis of substituted 8-aminoquinolines and phenanthrolines through a Povarov approach†‡

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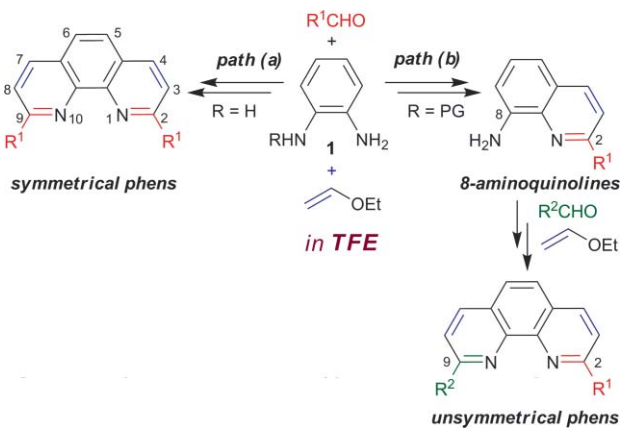
The synthesis of 8-aminoquinolines and 1,10-phenanthrolines with substituents in α of the nitrogen has been performed through an inverse-demanding aza-Diels–Alder (Povarov reaction) in the fluoroalcohols TFE or HFIP. This path involves simple starting materials: 1,2-phenylenediamines, enol ethers and aldehydes.

1,10-Phenanthrolines (phens) exhibit strong ability to chelate metals, and constitute thus a prominent family of ligands.[1] Indeed, metal complexes of phens have been widely used in catalysis for several synthetic transformations,[2,3] but they have also found biological applications through the stabilisation of the human telomerase quadruplex DNA, for example.[1b,4] The structure of phens-metal adducts is strongly related to the presence of substituents on the heterocycle.[5] Notably, the positions in α of the nitrogen atoms (positions 2 and 9) have been shown to be very critical. For example, replacing the simple phen by 2,9-dimethylated analogues, such as neocuproine or bathocuproine, as ligand in a metal-catalysed reaction has a great impact on its outcome.¶,[3a,e,g,h]

According to the literature, introducing substituents in positions 2 and/or 9 of the phen scaffold can be performed from phenanthroline itself *via* the addition of organolithium reagents, followed by an oxidation (28–73% yield); this route depends thus on the availability of the reactants.[6] Alternatively, by analogy with the quinoline synthesis an historical pathway for preparing 2,9-disubstituted phens goes through the Friedländer[7] or Doebner-von Miller reaction,[8] under strong acidic conditions (*ca.* 50% yield).[9] This procedure requires to start from 2-substituted 8-aminoquinolines, whose access is severely restricted. To our knowledge, the only substituent reported in the position 2 is a methyl group: the synthesis of 2-methyl-8-aminoquinoline results from the reaction between 2-methoxy- or 2-nitroanisole and crotonaldehyde, under harsh conditions.[10]

An attractive improvement would consist in building decorated phens directly from simple chemicals in a minimum number of steps. In this line, the Povarov reaction between *N*-aryl imines, as dienes, and electron-rich dienophiles offers a direct entry to tetrahydroquinolines, and hence to quinolines through oxidation.[11,12] While this transformation is generally catalysed by a Brønsted or Lewis acid, we reported that using fluoroalcohol solvents (trifluoroethanol, TFE or hexafluoroisopropanol, HFIP),[13–15] allowed the cycloaddition to proceed in a more attractive three-component fashion, starting directly from anilines, aldehydes and enol ethers.[16] In this context, we envisioned that starting from 1,2-phenylenediamines **1** instead of anilines could offer an interesting way to 2,9-disubstituted phenanthrolines. Two strategies have been thus envisioned. The first approach consists in reacting **1** with an excess of aldehyde and enol ether to afford, after oxidation, symmetrical phens (Scheme 1, path a). The other approach proceeds through the synthesis of an intermediate 8-aminoquinoline: interestingly, these poorly available compounds also exhibit biological activity as metalloenzyme inhibitors through Zn- or Mn-chelation.[17] In this synthetic pathway, a monoprotected *o*-phenylenediamine would undergo a Povarov reaction to afford, after oxidation, an 8-aminoquinoline. Then, by reacting this latter with another aldehyde, unsymmetrical phens would be afforded (Scheme 1, path b).



Scheme 1 Strategies for the synthesis of 2,9-disubstituted phenanthrolines.

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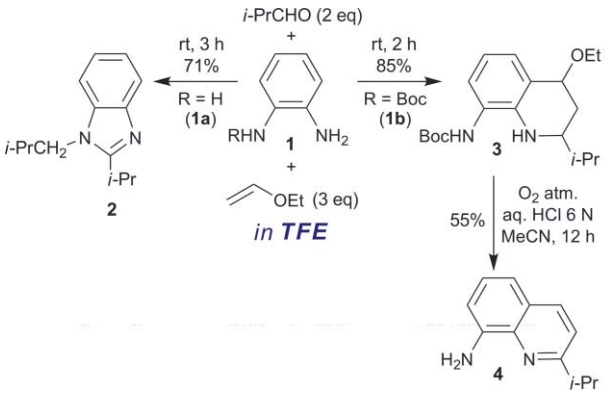
§ Part of these results has been presented at the 9th RSC Fluorine Meeting (Southampton) with the kind support of the RSC to KD.

As a preliminary investigation, 1,2-phenylenediamine **1a** was mixed with ethyl vinyl ether (EVE, 3 eq) and *iso*-butyraldehyde (2 eq) in TFE at room temperature. Unfortunately, no cycloaddition product was obtained after 3 h under these conditions, but a clean benzimidazole compound **2** was afforded in good yield (71%, Scheme 2). The formation of the product **2** resulted from the intramolecular reaction of the formed monoimine with the second amino group, this transformation being faster than the intermolecular Povarov reaction with EVE.[18] A second equivalent of *iso*-butyraldehyde then reacted to afford the *N*-*i*-butyl benzimidazole **2**. On a mechanistic standpoint, the Povarov reaction being an inverse electron-demanding cycloaddition, the presence of the donating NH_2 group might disfavor this path in the competition with the benzimidazole formation.



Scheme 2 Synthesis of benzimidazole **2** and 8-aminoquinoline **4**.

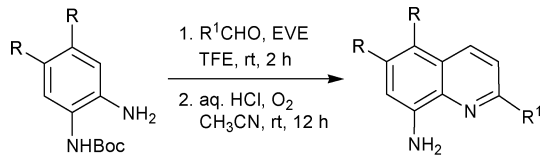
Then, the second strategy initially depicted in Scheme 1 (path b) was used. The Boc monoprotected *o*-phenylenediamine **1b** was used as substrate and reacted under the same conditions as for **1a** (with *i*-PrCHO and EVE in TFE). In this case, the Povarov reaction underwent smoothly to afford exclusively the cycloaddition product **3** in a very good 85% yield with a *cis*/*trans* ratio of 2 : 1 (Scheme 2). Hence, under acidic conditions and oxygen atmosphere, **3** underwent Boc deprotection and oxidation in the same pot to provide the 8-aminoquinoline **4** in 55% yield (Scheme 2).

Following these preliminary results, the process was repeated without isolating the tetrahydroquinoline intermediate, and then extended to other aldehydes (Table 1).

With *iso*-butyraldehyde and *n*-hexanal, the Povarov reaction took place nicely, and then TFE was evaporated and the crude mixture was treated with aq. HCl in MeCN, under oxygen atmosphere to give the aminoquinolines **4** and **5** in 46% and 59% yields, respectively, from **1b** (entries 1 and 2). In the same way, introducing a methyl substituent would normally require the use of acetaldehyde as partner. However, we previously disclosed that in HFIP, EVE could act as an acetaldehyde equivalent: in presence of an excess of EVE in HFIP, aniline was converted into the imine, which further reacted with EVE to afford the corresponding tetrahydroquinoline (Scheme 3).[19]

Pleasingly, when these conditions were applied to substrate **1b** the domino reaction took place, and the resulting Povarov adduct was then immediately converted into **6** (50% yield, entry 6). Unfortunately, with benzaldehyde as substrate, the cycloaddition reaction did not behave well in fluoro-alcohols and a slurry mixture was obtained. However, when the reaction was performed in acetonitrile in the presence of $Yb(OTf)_3$, followed by the previous oxidation procedure, the corresponding quinoline **7** was obtained in 51% yield (entry 4). Finally, the synthesis of 2,5,6-trisubstituted 8-aminoquinolines was also performed starting from the disubstituted phenylenediamine **1c**: methyl and isopropyl derivatives were prepared as from **1b**, yielding products **8** and **9** (54%, entry 5; and 50%, entry 6, respectively). With a global 46–59% yield over four steps (imine formation, cycloaddition, Boc deprotection and aromatisation), this process offers a convenient and competitive entry to novel aminoquinolines with a substituent in position 2.

Table 1 Synthesis of 2-substituted 8-aminoquinolines **4–9**[a]

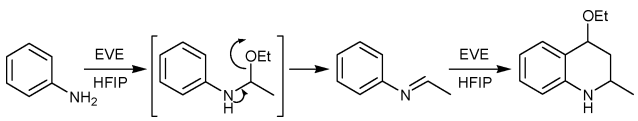


1b (R = H)
1c (R = Me)

4-9

Entry	R	R^1	Product	Yield (%)
1	H	*i*-Pr	**4**	46
2	H	*n*-C_5H_{11}	**5**	59
3[b]	H	Me	**6**	50
4[c]	H	Ph	**7**	51
5	Me	*i*-Pr	**8**	54
6[c]	Me	Me	**9**	50

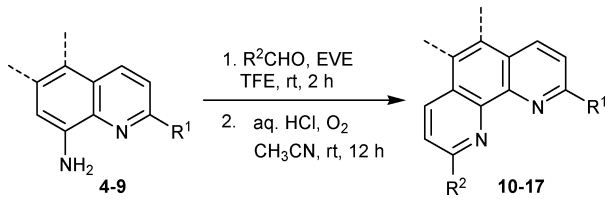
[a] Reaction conditions: Povarov reaction: **1b–c** (2.0 mmol), aldehyde (2.2 mmol), EVE (6 mmol) in TFE (4 mL), then oxidation: aq. HCl 6 N (0.8 mL) under O_2 atm. in MeCN (2 mL). [b] No aldehyde was used (see text), EVE (20 mmol) in HFIP (4 mL) then oxidation. [c] With $Yb(OTf)_3$ (0.1 mmol) in MeCN (2 mL) then oxidation.

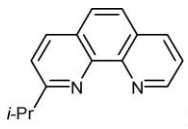
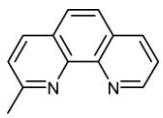
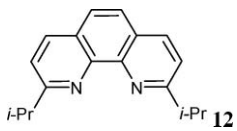
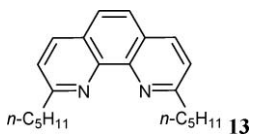
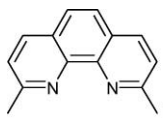
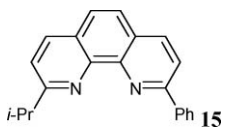
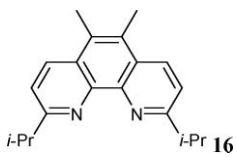
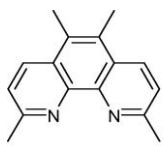


Scheme 3 Direct synthesis of tetrahydroquinoline from aniline and EVE.

Then, having in hand a good protocol for the conversion of aromatic amines into quinolines, the same Povarov/oxidation sequence was applied for the conversion of 8-aminoquinolines into phenanthrolines (Table 2). For this purpose, first experiments were assessed with the commercially available simple 8-aminoquinoline as substrate. Thus, by using *i*-PrCHO the corresponding phenanthroline **10** was obtained in 49% yield (entry 1). Following this, 2-methylphenanthroline **11** was prepared with an excess of EVE in HFIP (43% yield, entry 2). Then, 2-substituted 8-aminoquinolines **4–9** reported in Table 1 were assessed (entries 3–8). Their reactivity was close to that of the unsubstituted 8-aminoquinoline. Symmetrical phenanthrolines with *i*-Pr, *n*-pentyl and Me groups in α position of the nitrogen atoms were thus afforded in 33–50% yield over the two steps (entries 3–5). An unsymmetrical 2-phenyl-9-methylphenanthroline was also obtained from **7** and isobutyraldehyde in 50% yield (entry 6). Finally, 2,5,6,9-tetrasubstituted phens were yielded from **8** and **9** as substrates (44% and 40%, entries 7 and 8 respectively).

Table 2 Synthesis of phenanthrolines **10–17**[a]



Entry	Substrate	Product	Yield (%)
1	8-Aminoquinoline	 **10**	49
2[b]	8-Aminoquinoline	 **11**	43
3	**4**	 **12**	40
4	**5**	 **13**	33
5	**6**	 **14**	42
6	**7**	 **15**	50
7	**8**	 **16**	44
8[b]	**9**	 **17**	40

[a] Reaction conditions: Povarov reaction: 8-aminoquinoline (0.5 mmol), aldehyde (0.55 mmol), EVE (1.5 mmol) in TFE (1 mL), then oxidation: aq. HCl 6 N (0.2 mL) under O_2 atm. in MeCN (0.5 mL). [b] No aldehyde was used, EVE (5 mmol) in HFIP (1 mL) then oxidation.

In conclusion, we have developed an original methodology to access to the metal ligands 8-aminoquinolines and phenanthrolines with substituent(s) in α of the nitrogen atom(s). This route lies on a Povarov/oxidation sequence from simple chemicals (1,2-phenylenediamines, aldehydes and ethyl vinyl ether), in TFE or HFIP as promoting medium. As a perspective, this method could be used with functionalised and/or enantiopure aldehydes to obtain chiral phenanthrolines.

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Notes and references

¶ Some phen derivatives have specific names and acronyms. 4,7-Diphenyl-1,10-phenanthroline: bathophenanthroline (bp); 2,9-dimethyl-1,10-phenanthroline: neocuproine (neo); 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline: bathocuproine (bc).

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