Improved Synthesis of Quinacridine Derivatives

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Abstract: An efficient synthetic pathway toward various substituted quinacridines **1** and **2** has been developed. Compared to the previous method, higher yields and easier workup were obtained.

Key words: heterocyclic synthesis, palladium coupling, aromatization, selenium oxidation, quinacridine

Quinacridine is a pentacyclic diaza aromatic motif that adopts a crescent shape when the junction between the benzo and phenanthroline rings features a [*b*,*j*] type (Figure 1). According to positions of the two endocyclic nitrogen atoms, three isomeric series of quinacridines are distinguished: *ortho*- *meta*- and *para*-quinacridine, two of which are represented in Figure 1.

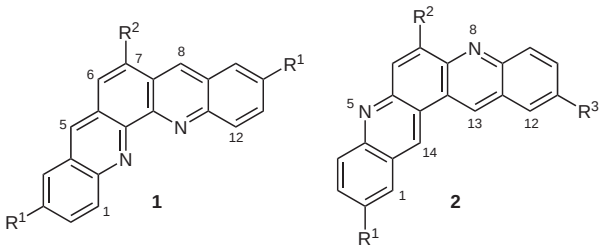
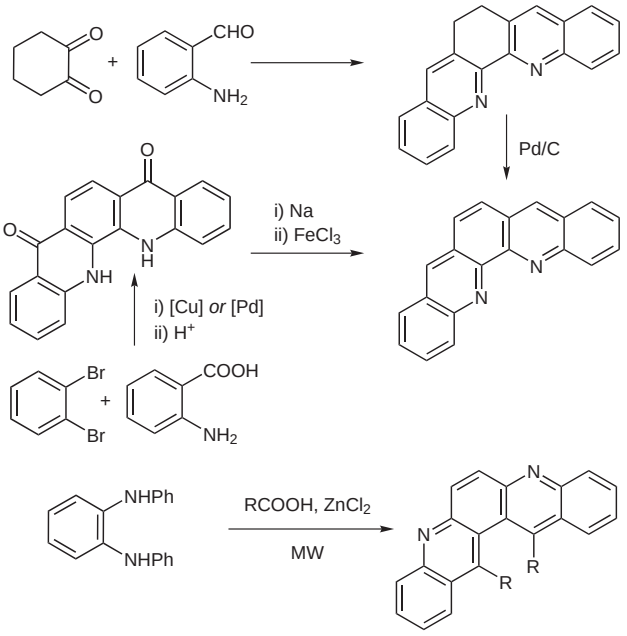


Figure 1 Structures and nomenclature of substituted *o*-quinacridine (**1**) and *p*-quinacridine (**2**). R^1, R^2, R^3 = H, CH_3, CHO.

The numerous applications of quinacridines in material science and bioorganic chemistry are directly related to their electronic properties and their structural features (substituents). For example, *o*-quinacridine, which is structurally related to the 2,2′-bipyridine bisimine ligand, has been used to chelate Ru,[1] Cu,[2] and Pd.[3] Also, sterically crowded 13,14-disubstituted *p*-quinacridines display helical chirality,[4] due to the strong distortion of the aromatic core from the planarity. Interestingly, the size of the quinacridine unit is particularly well-suited for overlapping large aromatic areas of nucleobase associations, resulting in strong and selective interactions of amino quinacridines with triplex DNA[5] and quadruplex DNA.[5c,6] In addition, quinacridines have been shown to oxidize guanines upon photoactivation, making them promising candidates for studying photoinduced charge injection into DNA.[5b] Finally, the linear quinacridones, i.e. the oxidized derivatives of quinacridines, are well-known organic pigments and have been extensively studied for their self-assembling,[7] photoconductive, doping dye emitter[8] and fluorescent[9] properties in numerous devices stemmed from materials chemistry.

For further developments and a broadened use in organic chemistry, this class of compounds deserves an improved synthetic access. Until now, angular quinacridines could be obtained by three major approaches:[10] Friedländer,[11] Bernthsen[4b] and Ulmann–Goldberg methods[5b] (see Scheme 1); each of which exhibit major drawbacks. The Friedländer approach relies on a double condensation between cyclohexanedione and amino benzaldehyde, leading to dihydroquinacridine,[12] followed by oxidation. However, its use is limited by instability of starting material, poor reproducibility of both reactions and lack of access to asymmetric quinacridines. The microwave-assisted Bernthsen reaction between *N*,*N*′-diphenylphenylenediamine and low-chain aliphatic carboxylic acid[13] although representing an attractive one-pot process, is limited to *p*-quinacridines bearing alkyl groups in positions 13 and 14.



Scheme 1 Synthetic pathways towards quinacridine by the Friedländer method (upper part), Ullmann–Goldberg method (central part) and Bernthsen-modified method (lower part).

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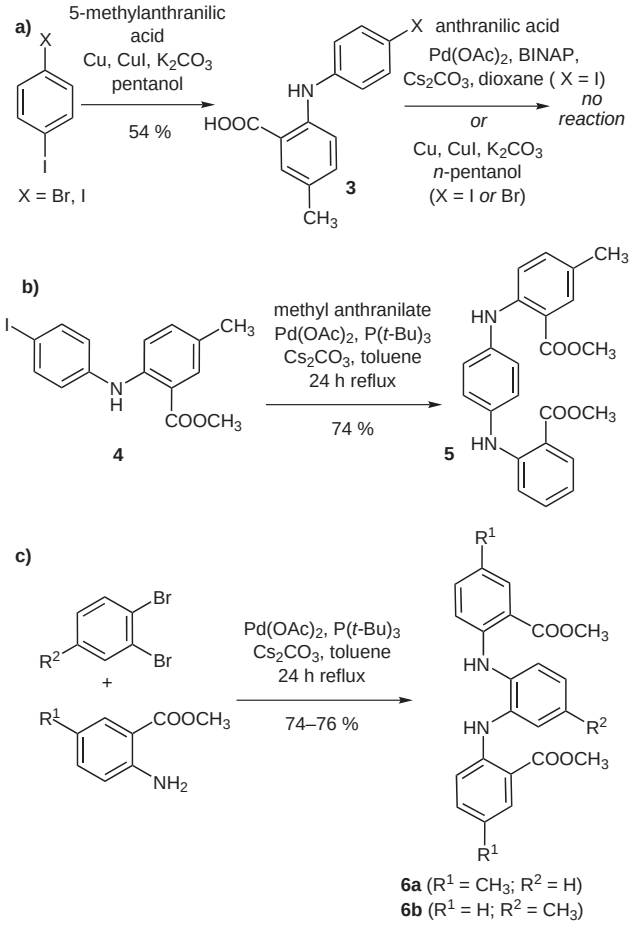
Finally, a third approach is based on copper- or palladium-catalyzed coupling followed by cyclization leading to quinacridone, which is then converted into quinacridine. Since cross-coupling allows the use of a large variety of commercially available starting materials, this pathway provides, in principle, an access to the three isomeric series with a broad range of substitution pattern. However, poor yields and extensive workup considerably diminishes its synthetic usefulness especially in the *ortho* series. Here we describe several synthetic improvements that significantly increase the overall efficiency of the initial reactional scheme.

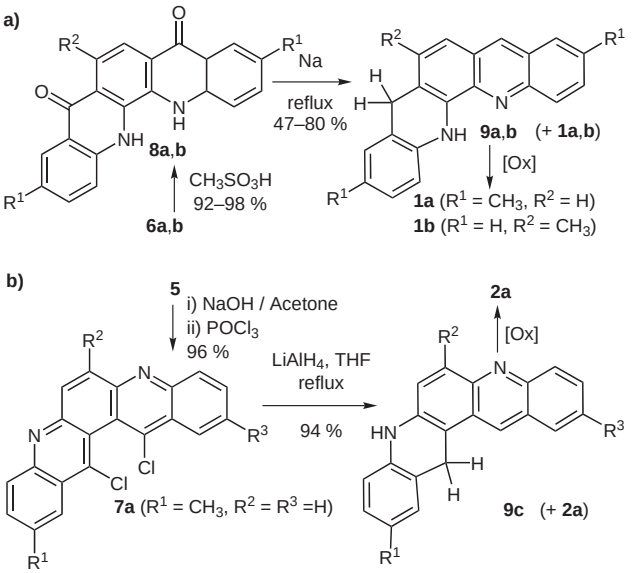
Initially, double coupling between dihalobenzene and anthranilic acid was performed under either Ullmann–Goldberg (Cu, CuI, K_2CO_3, *n*-pentanol) or Buchwald–Hartwig conditions [$Pd(OAc)_2$, BINAP, Cs_2CO_3, dioxane]. These reactions appeared highly substrate-sensitive, especially in the *ortho* series where palladium catalysis led exclusively to carbazole formation,[14,15] and copper catalysis revealed rather capricious (0–40% yields).[14] For instance, in our search of laterally monofunctionalized quinacridine **2a** ($R^1 = CH_3$, $R^2 = R^3 = H$), intermediate **3** was obtained in moderate yield (54%) under copper catalysis, whereas further amination failed whatever the catalyst (Scheme 2).



Scheme 2

Use of corresponding methyl ester **4** enabled us to carry out palladium-catalyzed coupling with good yield and made the purification steps easier.[16] Hence, precursor **5** was obtained in 74% yield by use of the $Pd(OAc)_2$–Cs_2CO_3–$P(t\text{-}Bu)_3$ catalytic system (Scheme 2, b).[17] Most remarkably, these conditions led to a dramatic improvement of the double N-arylation of *ortho* bis-bromo derivatives. Thus, **6a** and **6b** were obtained in good yield (74–76%) without carbazole formation (Scheme 2, c).

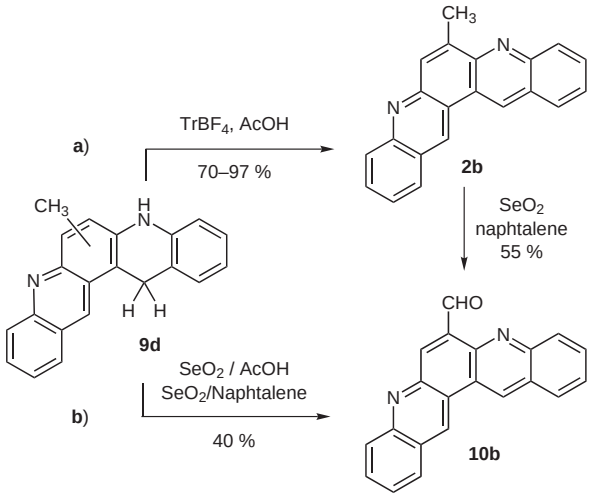
Ester **5** can be quantitatively saponified[16] and converted into dichloroquinacridines **7a** with $POCl_3$ (Scheme 3, b),[5b] but this standard treatment failed in the *ortho* series.[18] Alternatively, the methyl esters **6a**, **6b** are directly cyclized into quinacridones **8a**,**b** by hot CH_3SO_3H (Scheme 3, a).[19]



Scheme 3

Quinacridones are classically reduced by sodium in refluxing pentanol, whereas dichloroquinacridines are reduced by $LiAlH_4$ in refluxing THF (Scheme 3). Those treatments, when applied to **8a**,**b** and **7a**, respectively, afforded complex mixtures of expected product (**1a**,**b**, **2a**) and over-reduced derivative (respectively **9a**–**c**) in variable amount. Thus, the mixture has to be fully reoxidized to quinacridine, which is achieved by over-stoichiometric $FeCl_3$ treatment. However, this resulted in a dark and thick suspension and, work up was notably tedious. Use of a 5% amount of $Fe(ClO_4)_3$ in acetic acid[20] led only to a partial increase in expected product content.[21] In contrast, triphenylcarbenium tetrafluoroborate ($TrBF_4$) was found to be an efficient alternative reagent for reoxidation (Scheme 4, a).[22] Actually, *o*- (**1a**,**b**) and *p*-quinacridine (**2a**,**b**: $R^2 = CH_3$, $R^1 = R^3 = H$) were obtained with 70–97% yields from their corresponding over-reduced mixture (respectively **9a**–**d**) in milder and easier conditions as described above.[23]

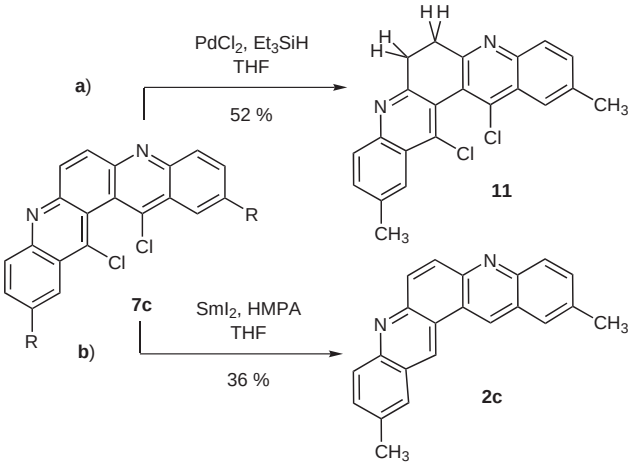
Recently, it has been shown that selenium dioxide (SeO_2) is able to oxidize 1,4-dihydropyridine into pyridine.[24] We quantitatively oxidized hydrogenated quinacridines **9d** into the quinacridine **2b** (Scheme 4).[25] Quinacridinecarboxaldehydes (such as **10b**) are key precursors to functionalized quinacridines and they are classically obtained by oxidation of aromatic methyl groups by SeO_2 in refluxing naphthalene in 55–90% yield.[5b] Thus, it was tempting to perform direct treatment of **9b** in the aim to combine the two oxidation steps (rearomatization and methyl oxidation). After rapid optimization,[26] a 92:8 mixture of **10b**–**2b** was obtained from **9d** as judged by NMR analysis. Further purifications afforded **10b** in a 40% yield.



Scheme 4

Since direct conversion of dichloroquinacridines to quinacridines is an attractive process, several reduction reagents have been tested in the hope to circumvent the over-reduction observed with $LiAlH_4$. Several assays using Pd/C–N_2H_4[27] or PEG/KOH[28] to reduce **7c** revealed unsuccessful. Finally, triethylsilane (Et_3SiH) and palladium chloride ($PdCl_2$) that has been reported to be an efficient reagent for dehydrogenation of chloroarenes[29] was assayed. Interestingly, instead of the expected compound **2c**, we obtained exclusively the 6,7-dihydrogenated product **11**[30] (52%, Scheme 5, a) which highlights the phenanthroline-like reactivity of the quinacridine system. With regards to the helical properties of **7c**[31] and **11**, our results reported herein could constitute a useful access towards novel helicenes.

Samarium diiodide (SmI_2) was then subsequently attempted in this step.[32] It has been reported that such reactions are greatly enhanced by presence of HMPA[32,33] or water[34] as a co-solvent. However, since over-reduction of 4-chloropyridine into piperidine has been described in water-containing medium,[35] we focused on the HMPA/SmI_2 system (Scheme 5, b). In such conditions,[36] complete consumption of starting material **7c** was observed but NMR analysis revealed the presence of unidentified by-products along with the desired compound **2c**. After extensive purifications, **2c** was obtained in a 36% yield.



Scheme 5

Last, worth pointing out is the extremely low reactivity of lateral methyl group independently of its position on the external benzene ring. Its conversion into aldehydic groups failed using DDQ in acetic acid,[37] silver(II) peroxodisulfate (AgS_2O_8)[38] or IBX in DMSO–fluorobenzene.[39] Similarly, oxidation into carboxylic acid derivative by warm potassium dichromate in sulfuric acid failed, as did oxidation of methylated quinacridine **2a** using hot nitric acid.

In summary, significant improvement of each step composing the synthetic pathway leading to quinacridines has been carried out. Consequently, quinacridine derivatives can now be obtained in four easy-to-perform steps from commercially available materials. The overall chemical yield ranging from 44–63%. Along with this gain in overall efficiency and practical convenience, the versatility of the synthesis has been definitively broadened. Moreover, quinacridines are structural related to acridines, thereby both series should display similar chemical behavior and the application of our study to acridine chemistry is currently investigated.

Acknowledgment

We would like to thank Dr. David Monchaud and Clémence Jacquelin for valuable discussions.

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(17) **General Procedure.**
In freshly distilled and degassed toluene (20 mL) was placed $Pd(OAc)_2$ (5% molar) under an inert atmosphere. Then tri-*tert*-butylphosphine was added (15%) and the solution was allowed to stir 10 min. Dibromobenzene derivative (5 mmol), methyl anthranilate derivative (12 mmol) and Cs_2CO_3 (15 mmol) were successively added. After overnight reflux, crude mixture was allowed to cool and was then quenched by 50 mL NH_4Cl (1 M) solution. About 100 mL CH_2Cl_2 were added and the biphasic mixture separated. The aqueous phase was extracted twice by CH_2Cl_2. Organic phases were dried on Na_2SO_4 and evaporated to dryness. The resulting brown oil was purified by column chromatography, using an CH_2Cl_2–*n*-hexane (1:1) mixture as eluant, affording a yellow powder.
Spectroscopic data for selected compounds.
Compound **5**: yellow solid; mp 85–88 °C; R_f = 0.35 (CH_2Cl_2–*n*-hexane, 1:1). ^{1}H NMR (DMSO-d_6): δ = 9.47 (s, 1 H), 9.33 (s, 1 H), 7.89 (dd, *J* = 1.8, 8.1 Hz, 1 H), 7.71 (s, 1 H), 7.41 (s, 1 H), 7.26 (s, 4 H), 7.13–7.23 (m, 3 H), 6.75–6.80 (m, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 2.23 (s, 3 H). ^{13}C NMR (DMSO-d_6): δ = 168.6, 148.0, 145.2, 137.2, 135.8, 134.8, 131.8, 131.3, 126.7, 124.2, 123.1, 117.6, 115.0, 114.0, 112.3, 111.8, 52.4, 20.1. DCI-MS: *m/z* (%) = 391 (100), 392 (26), 393 (5).
Coumpound **6b**: yellow solid; mp 97–98 °C; R_f = 0.37 (CH_2Cl_2–*n*-hexane, 1:1). ^{1}H NMR (DMSO-d_6): δ = 9.26 (s, 1 H), 9.18 (s, 1 H), 7.95 (d, *J* = 1.5 Hz, 1 H), 7.92 (d, *J* = 1.5 Hz, 1 H), 7.25–7.36 (m, 4 H), 7.13 (dd, *J* = 8.4, 1.5 Hz, 1 H), 6.99 (m, 2 H), 6.74 (m, 2 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 2.39 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ = 168.7, 168.5, 150.8, 148.5, 135.3, 134.9, 134.1, 134.0, 133.9, 131.7, 131.5, 131.4, 125.1, 124.3, 117.2, 116.8, 114.6, 114.2, 112.7, 112.1, 51.7, 51.6, 21.1. DCI-MS: *m/z* (%) = 391 (100) [M^+], 392 (26), 393 (4).

(18) In the *ortho* series, reaction with $POCl_3$ leads to intractable mixture. Nevertheless, dichloroquinacridines are preferred over quinacridones since they are more soluble and less hygroscopic.

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(21) In our hands, a 29:71 molar ratio of quinacridine **2b** (R^2 = CH_3, R^1 = R^3 = H) and dihydroquinacridine(**9b**) mixture was brought up only to 73:27 (**2b**:**9b**). Increasing the catalytic load to 7% and the reaction time from 45 min to 16 h led to a similar result.

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(23) **General Procedure.**
The amount of hydrogenated quinacridines in the mixture was estimated my NMR, based on the relative peak intensities. Characteristic peaks of hydrogenated quinacridines were located at δ = 4.5 ppm (methylene group), whereas those of quinacridine are the more downfield-shifted at δ = 9.4 ppm (*para*) or δ = 8.6 ppm (*ortho*). Lateral methyl groups are also of relevant importance and are situated in the 2.3–3.1 ppm zone, those borne by hydrogenated products being shifted more upfield. Such a mixture (300 μmol in hydrogenated compounds) was dissolved in AcOH (10 mL), $TrBF_4$ (330 μmol) was added and the mixture was heated to reflux. Crude mixture was poured in cold H_2O ca. 10 min later. The pH value was adjusted to neutrality and the brown suspension was filtered and dried. The mixture was purified by column chromatography using a gradient of MeOH in CH_2Cl_2 (1–3% v/v).

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(25) After 80 min and at r.t., a 90% conversion is observed after 30 min as judged by NMR. Due to formation of red colloidal selenium, use of $TrBF_4$ seems to be of greater synthetic use for conversion of dihydrogenated quinacridines into quinacridines.

(26) Adding SeO_2 twice in the same flask seems to be preferable than an unique initial load. Selenium dioxide was firstly reacted in a flask containing both substrate **9d** and AcOH. Then, 80 min later, AcOH was evaporated, naphthalene added, SeO_2 newly added and mixture heated to 230 °C. When both loads of SeO_2 were initially mixed with substrate and acid, a 72:28 ratio was obtained.

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(30) Compound **11**: white solid; mp 236–238 °C; R_f = 0.37 (CH_2Cl_2–MeOH, 9:1). ^{1}H NMR ($CDCl_3$): δ = 8.18 (s, 2 H), 8.02 (d, 2 H, *J* = 8.4 Hz), 7.67 (dd, 2 H, *J* = 8.7. 1.8 Hz), 3.32 (m, 4 H), 2.66 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ = 160.6, 145.9, 141.1, 137.3, 133.0, 128.6, 126.1, 124.2, 124.0, 34.1, 21.9. DCI-MS: *m/z* (%) = 379 (100) [M^+], 380 (26), 381 (67), 382 (16), 383 (12).
(31) (a) X-ray structure of intermediate **7c** (R = CH_3) showed that the molecule exhibits a dihedral angle of 35.9° (Cesario, M.; Baudoin, O.; Teulade-Fichou, M.-P. *unpublished results*). (b) Baudoin, O. *PhD Thesis*; Université Pierre and Marie Curie: Paris, **1998**.
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(36) Compound **7c** was reacted with 5 equiv of SmI_2 for 1 h at r.t. in a THF/HMPA mixture. Increasing the reaction time to 2 h or 24 h, as well as using 6 equiv of SmI_2, did not modify the reaction course.
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