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New methodology for acridine synthesis using a rhodium-catalyzed benzannulation

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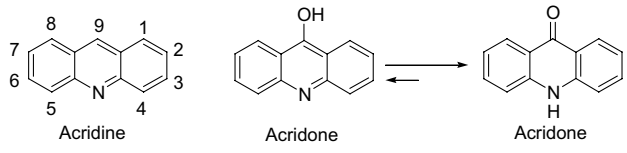
This paper is dedicated to Professor J. Lhomme

Abstract—A new methodology for the synthesis of acridine derivatives is disclosed. The starting materials are commercially available quinolines, which can be converted, via five high efficient steps, in a key quinoline intermediate substituted with a TBS-protected-enol–ether and an internal alkyne. The key and last step is a rhodium-catalyzed benzannulation of the quinoline intermediate yielding the desired poly-substituted acridines derivatives.

Acridine derivatives (Scheme 1) have been known since the 19th century where they were first used as pigments and dyes.[1] Their antiseptic activity has been discovered in the early 1900s and some derivatives were extensively used during World War I for their antibacterial and antimalarial properties.[1] In the 1920s, their potential in the fight against cancer was first noted. Since then, a large number of acridines drugs, natural alkaloids or synthetic molecules, have been tested as antitumour agents, a recent target being their telomerase and topoisomerase inhibition activity.[2] Acridines are much sought after targets since a range of these compounds continue to be used today for the treatment of acute leukaemia (amsacrine),[3] as anticancer agents (ledakrin),[4] for their antibacterial properties (acriflavine and ethacridine),[2] for action against parasites in the treatment of malaria, trypanosomiasis and leishmaniasis (quinacrine, acranil)[2] and last but not least for treatment of Alzheimer's disease (tacrine).[2,5] Acridine and acridone (Scheme 1) can be interconverted relatively easily and several synthetic routes have been designed for this matter.[2,6,7]



Scheme 1. Acridine and acridone structures and numbering.

Most routes to acridines and their derivatives proceed through the corresponding acridone (Scheme 1). This is largely due to the ease of formation of diphenylamine-2-carboxylic acids (via the Ullman reaction), which under strong acids can cyclize to the corresponding acridones.[8] Although discovered in the early 1900s, these reaction are still in use today.[9] The transformation from acridone to acridine requires harsh reductive (sodium amalgam,[1] aluminium and mercury amalgam[10]) and oxidative (chromic acid, iron(III)chloride/HCl,[1] nitric acid[9]) conditions. Among the methods for forming acridines, which do not proceed through an acridone intermediate, the best known is probably the Bernthsen reaction,[11] which involves heating a diphenylamine and an organic acid with zinc chloride for up to 40 h. Yields are not high and the temperature required for best results is between 200 and 270 °C.[11] The cyclization of diphenylamine-2-carboxaldehyde is also widely used for acridine synthesis. Again strong acid conditions (trifluoroacetic acid, sulfuric acid) and/or high temperatures are required.[12] The Pfitzinger quinoline synthesis has been adapted successfully to access acridines but requires reflux for several hours in sodium hydroxide solution.[13] Due to the harsh conditions needed in all these routes, they appear unsuitable for the synthesis of functionalized acridines

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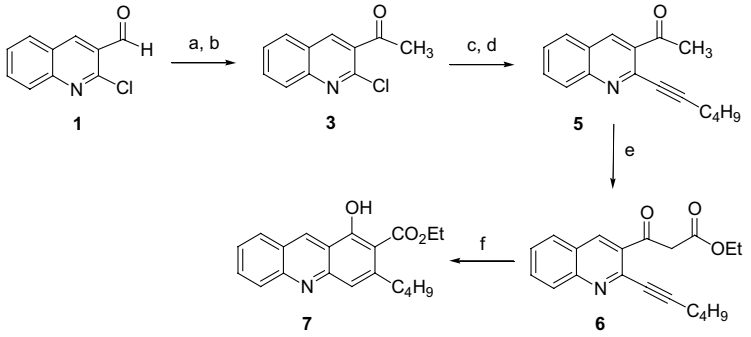


Scheme 2. Reagents and conditions: (a) 3 equiv MeMgBr, THF, 40 °C, 98%; (b) 10 equiv MnO_2, toluene, 80 °C, 80%; (c) NaI, CH_3CN, 0.5 equiv HCl 4 N, reflux, 80%; (d) 1-hexyne, 0.07 equiv $PdCl_2(PPh_3)_2$, 0.3 equiv CuI, 1.5 equiv Et_3N, toluene, rt, 65%; (e) LDA, NC(CO)OEt, 27%; (f) 1 equiv CSA, $CHCl_3$, reflux, 15%.

incorporating sensitive functional groups. This observation led us to look for alternative routes.

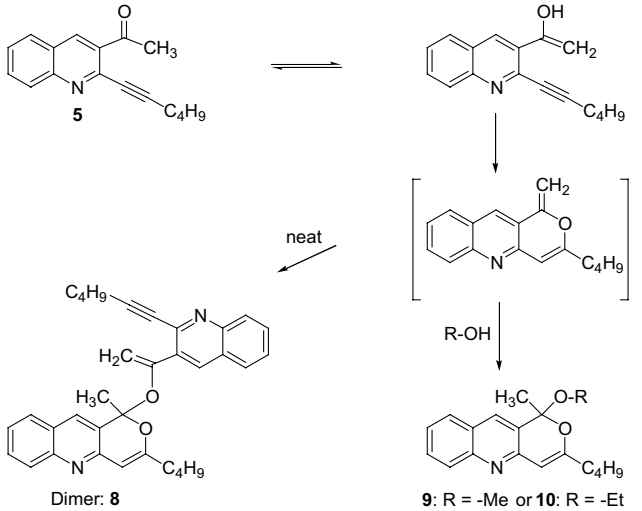
Two routes have been investigated. In the first route (Scheme 2), we attempted to adapt a benzannulation reaction described for the synthesis of naphthalene ring.[14]

Thus, we observed that intermediate **6** undergoes an acid-catalyzed benzannulation to yield **7**. Compound **6** was obtained in five steps from commercially available chloro-quinoline **1** beginning with the addition of MeMgBr (98%) and oxidation to the corresponding methyl-ketone **3** with MnO_2 (80%). Finkelstein reaction[15] on compound **3** yielded the iodo derivative **4** (80%)[16] which undergoes Sonogashira reaction[17] with 1-hexyne (65%) to give **5**. Mander reaction[18] with ethyl-cyanoformate (27%) produced the desired β-ketoester quinoline **6**. The low yield in the Mander reaction is explained by the reactivity of precursor **5**. This substance tends to dimerize, in the neat state, leading to compound **8** (detected by mass spectrometry, Scheme 3). In solution, it produces a presumed *exo*-methylene intermediate, which is unreactive in the desired transformation, but that can give rise, upon quenching in the presence of an alcohol (methanol or ethanol), to the corresponding adduct **9** or **10** via an O-cyclization-alkylation process.[19] These structures are very interesting due to their structural features, recalling Pentalongin and Dehydroherbarin derivatives, which possess a broad range of biological activities.[20]

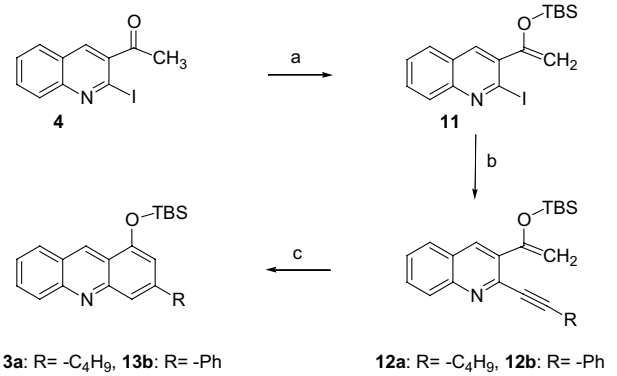
Additionally (Scheme 2), the acid-catalyzed benzannulation (CSA, $HCCl_3$, reflux), of quinoline derivative **6**, led only to 15% of the desired acridine **7**, which was accompanied by several other products. No characterization was possible due to the difficulties of separation. All attempts to obtain cleanly a predominant C-alkylative product from **6** failed.

We then chose a different route in which the reactive methyl-ketone derivative **4** was protected (Scheme 4) in order to prevent the O-alkylation reaction to occur.

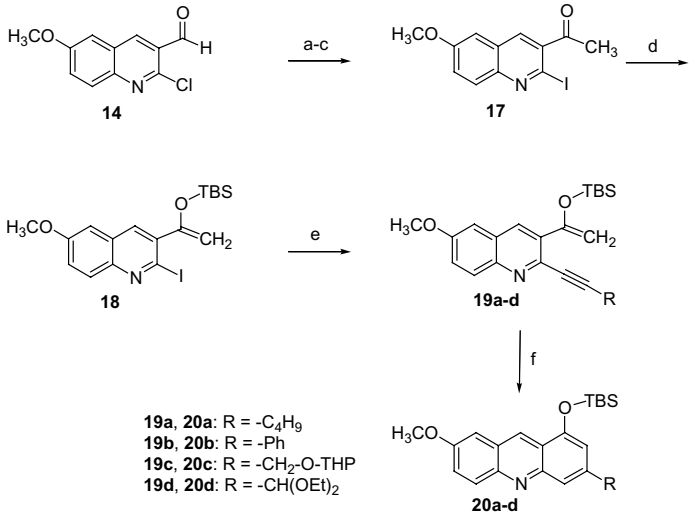
Based on work published on naphthalene derivatives,[21] we transformed **4** (from the previous route) to the O-TBS protected derivative **11** with TBSOTf and 2,6-lutidine (80%).



Scheme 3.



Scheme 4. Reagents and conditions: (a) 3 equiv TBSOTf, 3 equiv 2,6-lutidine, CH_2Cl_2, 80%; (b) 1-hexyne or phenylacetylene, 0.07 equiv $PdCl_2(PPh_3)_2$, 0.3 equiv CuI, 1.5 equiv Et_3N, toluene, rt, 80–90%; (c) 4 mol% $[Rh(CO)_2Cl]_2$, toluene, 120 °C, 60–70%.



Scheme 5. Reagents and conditions: (a) 3 equiv MeMgBr, THF, 40 °C, 98%; (b) 10 equiv MnO_2, toluene, 80 °C, quant.; (c) NaI, CH_3CN, 0.5 equiv HCl 4 N, reflux, 80–98%; (d) 2.2 equiv TBSOTf, 3 equiv Et_3N, CH_2Cl_2, 77%; (e) 1-alkyne, 0.07 equiv $PdCl_2(PPh_3)_2$, 0.3 equiv CuI, 1.5 equiv Et_3N, toluene, rt; (f) 10 mol% $[Rh(CO)_2Cl]_2$, toluene, 2–4 h, 120 °C.

After an efficient Sonogashira reaction with 1-hexyne (**12a**, 90%), metal-catalyzed cylization to the corresponding acridine **13a**, was possible with 4 mol%[22] of the Rh(I) complex $[Rh(CO)_2Cl]_2$ in 70% yield.[23] Sonogashira reaction with phenylacetylene on derivative **11** gave the intermediate **12b**, which smoothly underwent the rhodium-catalyzed annulation in 60% yield. This methodology provides 1,3-disubstituted acridines.

The same synthetic pathway was conducted also on 2-chloro-6-methoxy-quinoline-carboxaldehyde **14** (Scheme 5).

The iodo-methylketone derivative **17** was synthesized using the previous route. Action of TBSOTf with Et_3N on **17** gave the O-TBS protected derivative **18** (77%), which underwent efficient Sonogashira reaction with several alkynes: 1-hexyne (**19a**, 70%), phenylacetylene (**19b**, 60%), tetrahydro-2-(2-propynyloxy)-2*H*-pyran (**19c**, 70%),[24] 3,3-diethoxy-1-propyne (**19d**, 72%). The Rh(I)-catalyzed cyclization produced the corresponding 1,3,7-tri-substituted acridines **20a** (60%), **20b** (50%), **20c** (60%),[25] **20d** (40%).[26] We were able to use alkynes **19c** and **19d**, bearing sensitive protecting groups, in this transformation. In addition, experiments were performed under thermal conditions without catalyst. Heating derivative **19c** for 5 h at 120 °C in toluene, led to the formation of 10–15% of the desired acridine as shown by the analysis of the proton NMR spectrum.[27] Some work is still performed to improve the cyclization efficiency and to analyze more carefully the free-metal temperature-based cyclization.

In summary, we have developed a new and efficient strategy to access 1,3-disubstituted and 1,3,7-tri-substituted acridines, in a six steps pathway from commercially available quinolines. Extension of this methodology to other heterocyclic structures is underway and will be published in due course.

Acknowledgements

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22. Raising the Rh(I) complex equivalent to 0.2 or 1 equiv led apparently to complexation with the quinoline aromatic nitrogen (since NMR shifting was observed), thus limiting the yield to 30% and causing deprotection of the starting material TBS-protected enol–ether group.
23. Several other metallic complexes have been used with lower or no success: $PtCl_2$ and $PdCl_2(CH_3CN)_2$ were unefficient, $PdCl_2$ led to low starting material transformation.
24. A typical experiment for the Sonogashira reaction: 0.150 g (0.34 mmol) of **18**, 70 μL (0.51 mmol, 1.5 equiv) of the 1-alkyne tetrahydro-2-(2-propynyloxy)-2*H*-pyran and 70 μL (0.51 mmol, 1.5 equiv) of Et_3N are put in 5 mL of THF. This mixture is sonicated for 5 min with Ar bubbling. Then, CuI (20 mg, 0.3 equiv) is added and the mixture is sonicated for 5 min. Finally, $PdCl_2(PPh_3)_2$ (17 mg, 0.07 equiv) is added and the mixture is sonicated for 10 min. The reaction is left overnight at rt, then diluted with AcOEt and washed three times with NH_4Cl and brine. After evaporation, the residue was submitted to purification on silica preparative TLC. We obtained 106 mg (70%) of the desired quinoline **19c**. R_f: 0.32 (cyclohexane/AcOEt, 8/2). NMR ^1H (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.95 (d, $J = 9.2$ Hz, 1H), 7.32 (dd, $J = 2.6$, 9.2 Hz, 1H), 7.00 (s, 1H), 5.18 (s, 1H), 4.94 (m, 1H), 4.77 (s, 1H), 4.55 (s, 2H), 3.91 (s, 3H) overlapped with 3.91–3.83 (m, 1H), 3.56–3.52 (m, 1H), 1.82–1.53 (m, 6H), 0.95 (s, 9H), 0.17 (s, 6H). MS (EI): 453 ($M^{+\cdot}$). HREIMS: 453.2335 calcd for $C_{26}H_{35}NO_4Si$ ($M^{+\cdot}$), found 453.2340.
25. A typical experiment for the Rh(I)-catalyzed cyclization reaction: To a toluene (1.5 mL) solution of the Sonogashira product **19c** (0.05 g, 0.110 mmol) was added 10 mol% $[Rh(CO)_2Cl]_2$ (0.004 g, 0.011 mmol) under Ar atmosphere. The resulting mixture was heated at 120 °C for 3 h. The mixture was then diluted with AcOEt and washed three times with NH_4Cl and brine. After evaporation of the volatile, purification on a silica preparative TLC (cyclohexane/AcOEt, 8/2) we obtained 30 mg (60%) of the acridine derivative **20c** as a light yellow oil. R_f: 0.18 (cyclohexane/AcOEt, 8/2). NMR ^1H (300 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.09 (d, $J = 9.6$ Hz, 1 H), 7.80 (s, 1H), 7.46 (dd, $J = 2.6$, 9.4 Hz, 1H), 7.17 (d, $J = 2.8$ Hz, 1H), 6.87 (s, 1H), 4.95 (d, $J = 13.0$ Hz, 1H), 4.80 (t, $J = 3.4$ Hz, 1H), 4.70 (d, $J = 13.0$ Hz, 1H), 3.99 (s, 3H) overlapped with 3.99–3.93 (m, 1H), 3.60–3.55 (m, 1H), 1.79–1.54 (m, 6H), 1.14 (s, 9H), 0.35 (s, 6H). MS (EI): 453 ($M^{+\cdot}$). HREIMS: 453.2335 calcd for $C_{26}H_{35}NO_4Si$ ($M^{+\cdot}$), found 453.2335.
26. In this case, starting material was recovered.
27. Further heating led to decomposition and did not improve the yield.