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Intramolecular radical additions to quinolines

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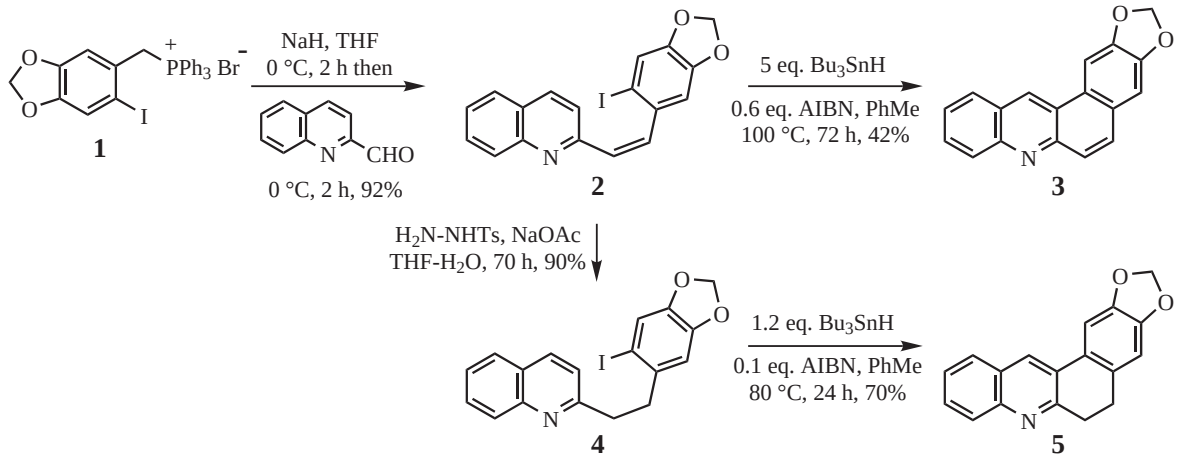
Abstract—This paper is concerned with intramolecular radical additions to quinolines. Radical additions to C-2, C-3 and C-4 of a quinoline have all been shown to proceed under neutral conditions. In each case formation of heteroaromatic products, rather than dihydroquinolines, was observed (implicating the so called oxidative tin hydride pathway).

We recently completed a total synthesis of the alkaloid toddaquinoline in which an intramolecular addition of an aryl radical to a pyridine featured as the key step.[1] This success prompted us to consider various extensions of that method. In particular we were keen to determine whether radical additions to quinolines were equally facile when conducted intramolecularly at neutral pH as this could be used to synthesise a host of interesting condensed heteroaromatics.[2–4] In this Letter we present our preliminary observations which show that intramolecular radical additions to C-2, C-3 and C-4 of a quinoline are all facile under standard tin mediated radical cyclisation conditions and result in the formation of heteroaromatic products (via the so called oxidative tin hydride pathway)[5] rather than dihydroquinolines.

Our first objective was to see if radical cyclisations to C-3 of a quinoline could be effected. To that end quinolines **2** and **4** were prepared and treated with tributyltin hydride under standard radical forming conditions.[6] Notably, alkene **2** required more forcing conditions to induce cyclisation than alkane **4**. In both cases a benzo[*a*]acridine derivative was provided, showing that these reactions follow the 'oxidative tin hydride' pathway (Scheme 1).



Scheme 1.

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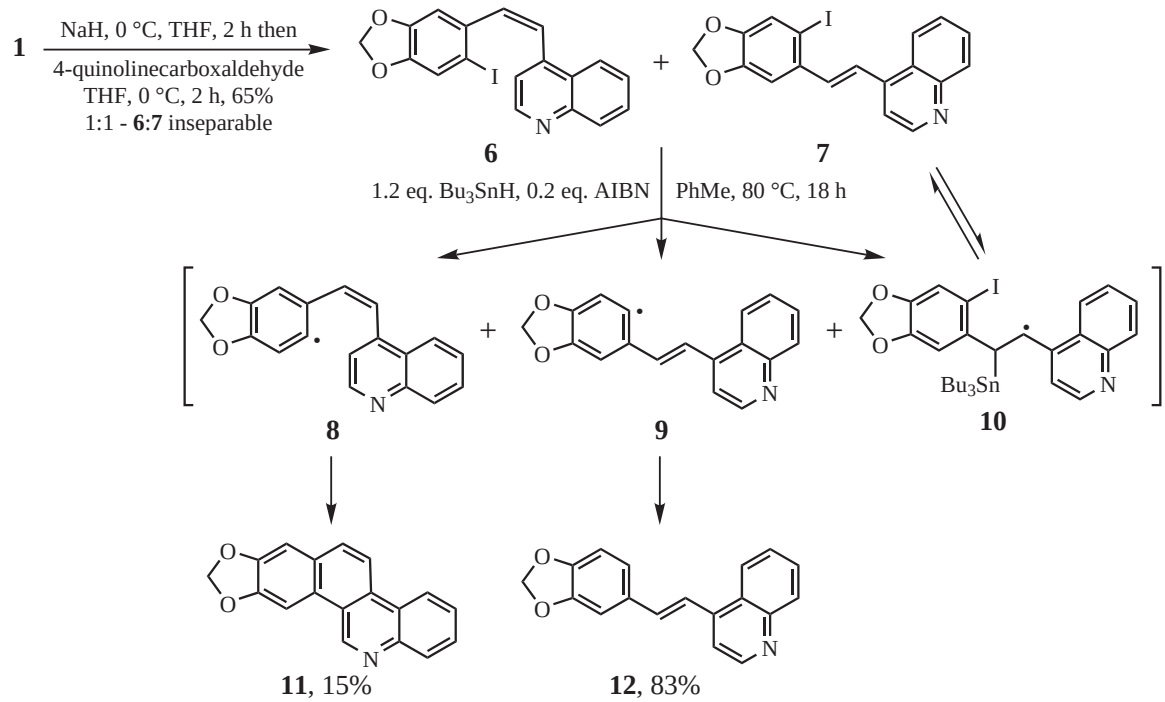
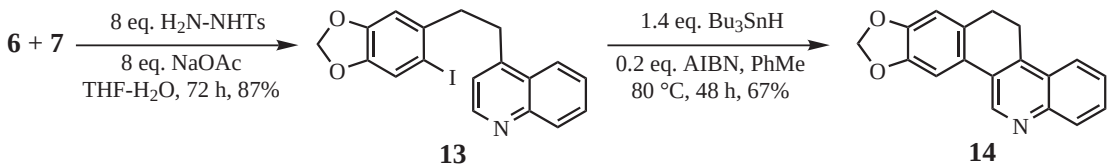
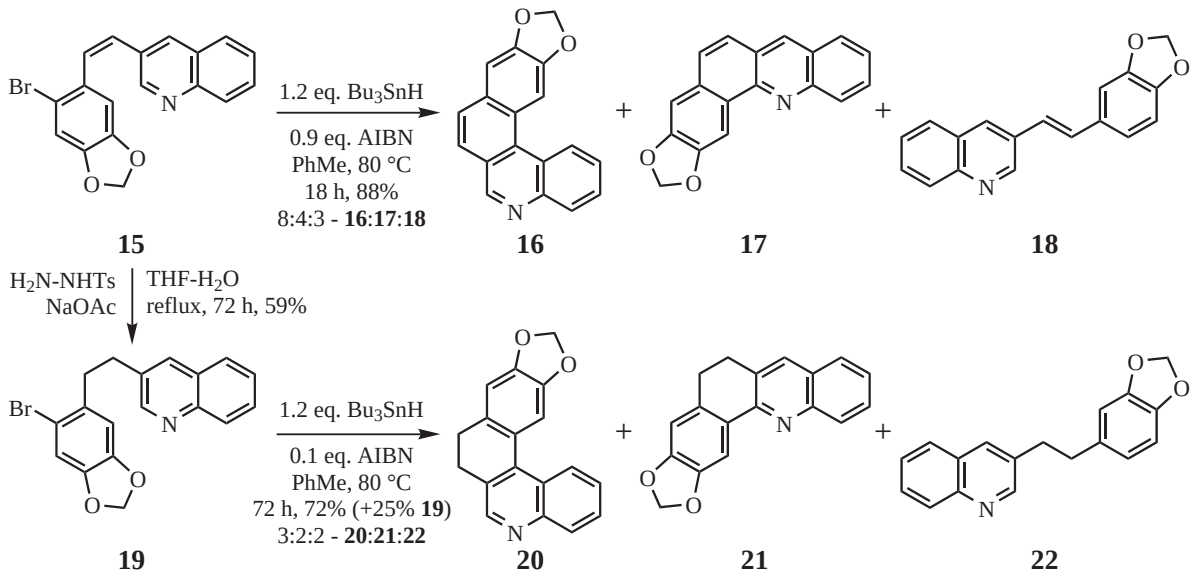
Cyclisations to C-3 of the quinoline could also be envisioned when a radical precursor is tethered at C-4 of the quinoline. To probe that reaction course the alkenes **6** and **7** were synthesised from 4-quinolinecarboxaldehyde. Attempts to separate these diastereoisomers proved intractable so the mixture was treated with tributyltin hydride under standard radical forming conditions. One major component, *trans*-alkene **12**, was given in 83% yield together with traces (15%) of the desired cyclised product **11**. This suggests that addition



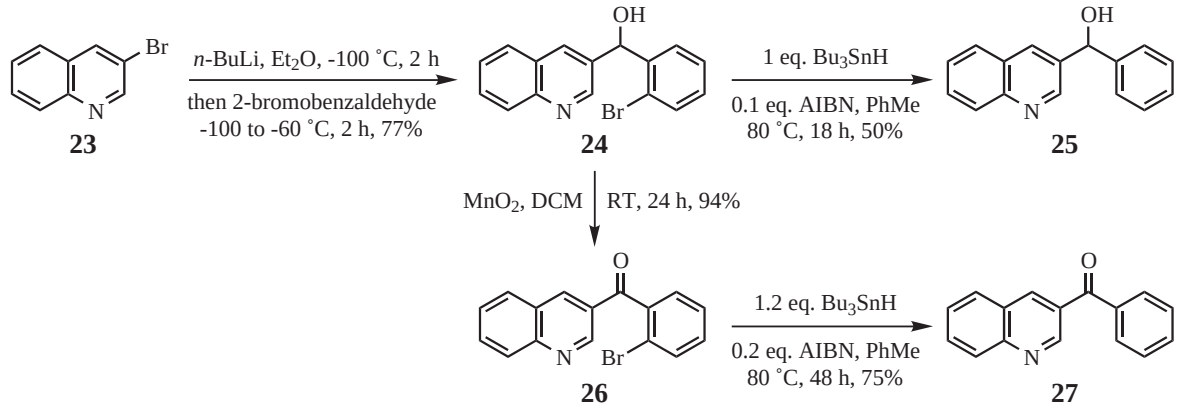
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

of tributyltin radical to the alkene **6** outpaces homolysis of the carbon to iodine bond in this case (Scheme 2).

Pleasingly, cyclisation of the corresponding alkane **13** proceeded smoothly to give dihydrobenzo[*i*]phenanthridine **14** in 67% yield (Scheme 3).

Our next objective was to tether a radical precursor at C-3 of a quinoline to see if such substrates gave rise to products derived from *ipso*-attack or cyclisation to C-2/C-4. To that end alkene **15** was synthesised and treated with tributyltin hydride under the aforementioned conditions.[6] Though cyclisation to benzo[*k*]phenanthridine **16** and benzo[*c*]acridine **17** was achieved, considerable quantities of recovered starting material accompanied these products. Indeed, only when the reaction was conducted with a near stoichiometric quantity of AIBN was all the starting material consumed! Importantly, and in contrast to radical additions to pyridines, cyclisation to C-4 of the quinoline was favoured over cyclisation to C-2.[1] This regiochemical preference was mirrored with alkane **19**: treatment with tributyltin hydride giving a complex mixture of products including dihydrobenzo[*k*]phenanthridine **20**, dihydrobenzo[*c*]acridine **21** and quinoline **22** (Scheme 4).

Finally, it is worth noting that all our attempts to effect a radical cyclisation leading to the creation of a five membered ring met with failure. For example, bromides **24** and **26** were each reduced to the corresponding arene on exposure to tributyltin hydride—suggesting that the cyclisation pathway is more akin to a 5-*endo*-trig than a 5-*exo*-trig process in such cases (Scheme 5).

In conclusion, we have shown that intramolecular radical additions to quinolines are facile processes that can be used to effect the synthesis of various condensed heterocycles. Radical additions to C-2, C-3 and C-4 of a quinoline have all been demonstrated and in each case formation of a heteroaromatic product, rather than dihydroquinoline, was observed. A rapid, stannyl radical mediated *cis* to *trans* isomerisation of a C-4 tethered styrene has also been uncovered.

Acknowledgements

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2. For an overview of radical additions to heteroaromatic bases, see: (a) Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* **1989**, *28*, 489. For recent examples, see: (b) Russell, G. A.; Rajaratnam, R.; Wang, L. J.; Shi, B. Z.; Kim, B. H.; Yao, C. F. *J. Am. Chem. Soc*. **1993**, *115*, 10596; (c) Russell, G. A.; Wang, L. J.; Yao, C. F. *J. Org. Chem*. **1995**, *60*, 5390.
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4. For related work from our group, see: (a) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron Lett*. **1999**, *40*, 4443; (b) Harrowven, D. C.; Hannam, J. C. *Tetrahedron* **1999**, *55*, 9341; (c) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron Lett*. **1999**, *40*, 1187; (d) Harrowven, D. C.; Browne, R. *Tetrahedron Lett*. **1995**, *36*, 2861; (e) Harrowven, D. C. *Tetrahedron Lett*. **1993**, *34*, 5653.
5. 'Oxidative tin hydride reaction' is a term used to describe reactions mediated by a trialkyltin hydride in which a radical cyclisation step is followed by an oxidation step in the absence of an added oxidising agent. For examples, see: (a) Bowman, W. R.; Mann, E.; Parr, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2991; (b) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119; (c)

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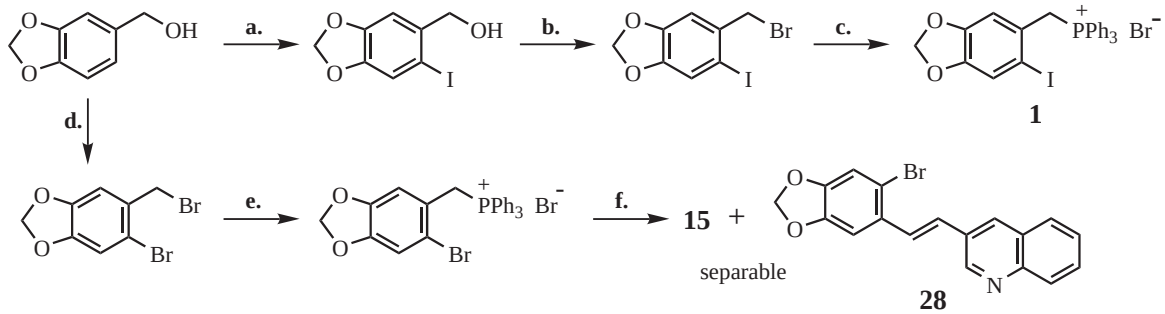
6. All new compounds gave satisfactory spectral and analytical characteristics. The Wittig reagent **1** and bromoarene **15** were synthesised according to the following sequences (Scheme 6).



Scheme 6. *Reagents and conditions*: (a) I_2, $AgOCOCF_3$, $CHCl_3$, 5 min, 83%;[7] (b) PBr_3, Et_3N, 0°C, DCM–THF, then 40°C, 30 min, 83%;[7] (c) PPh_3, xylene, 100°C, 24 h, 95%; (d) Br_2, AcOH, 0°C, 2 h, 67%;[8] (e) PPh_3, xylene, 80°C, 5 h, 100%; (f) NaH, THF, 0°C, 2 h, then 3-quinolinecarboxaldehyde, 84%, 3:1 - **15**:**28**.

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