Intramolecular radical cyclisations to pyridines

David C. Harrowven,[a,*] Benjamin J. Sutton[a] and Steven Coulton[b]

[a]*Department of Chemistry, The University, Southampton S017 1BJ, UK*
[b]*GlaxoSmithKline, New Frontiers Science Park (North), Third Avenue, Harlow, Essex CM19 5AW, UK*

Abstract—Intramolecular radical additions to the α-, β- and γ-carbons of a pyridine have each been shown to be facile processes. When a *cis*-alkene conjoins an *ortho*-iodoarene and a pyridine, radical cyclisation induced by homolysis of the carbon to iodine bond favours a 6-*exo/endo*-trig course. With a two carbon alkane conjoining the *ortho*-iodoarene and the pyridine, intermolecular hydrogen atom abstraction, 6-*exo/endo*-trig cyclisation and 5-*exo*-trig cyclisation modes compete. That the spirocyclic intermediates formed in the 5-*exo*-trig cyclisation rearrange with migration of the alkyl chain is noteworthy. © 2001 Elsevier Science Ltd. All rights reserved.

In our recent total synthesis of the alkaloid toddaquinoline, an intramolecular addition of an aryl radical to the α-carbon of a pyridine featured as a key step.[1] That success led us to question whether related radical additions to the β- and γ-carbons of a pyridine would also be facile if conducted intramolecularly.[2] In this Letter we report the results of that study which has established the effectiveness of each cyclisation mode and uncovered a series of unprecedented radical rearrangement reactions.

The first cyclisation examined involved azastilbene **1**, which, on treatment with tributyltin hydride under standard radical forming conditions, was smoothly transformed into benzo[*f*]quinoline **4** in 47% yield. Notably, cyclisation to the β-carbon had been achieved and was followed by re-aromatisation of the heterocyclic ring (Scheme 1).

The related cyclisation of azastilbene **5**, in which a radical precursor was tethered by an alkene to the β-carbon of the pyridine, also underwent cyclisation on treatment with tributyltin hydride to give a 5:4 mixture of benzo[*h*]quinoline **6** and benzo[*f*]isoquinoline **7** in near quantitative yield (Scheme 2). Of interest was the poor discrimination in the cyclisation step between the α- and γ-carbons of the pyridine since, in related intermolecular additions, aryl radicals have been shown to add preferentially to the α-carbon of a pyridine.[3,4]

The final cyclisation of this series involved azastilbene **8**, with a radical precursor tethered by an alkene to the γ-carbon of the pyridine. In this case cyclisation mediated by tributyltin hydride gave benzo[*h*]isoquinoline **9** as the only identified product of the reaction in 98% yield. This pleasing result again demonstrated the facile nature of intramolecular radical additions to the β-carbon of a pyridine (Scheme 3).
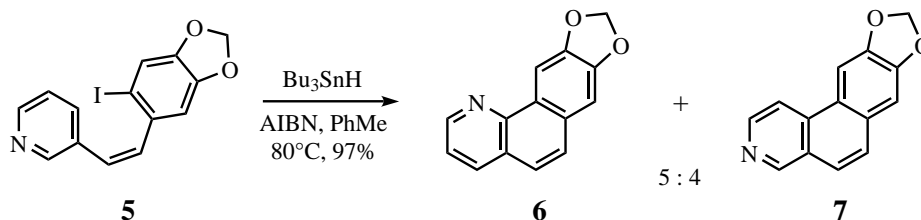
In each of the aforementioned examples we had observed the production of heteroaromatic products
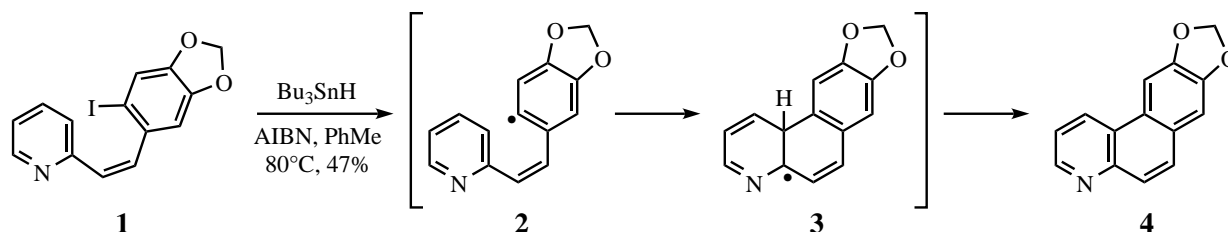
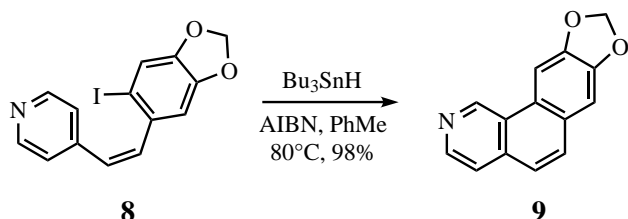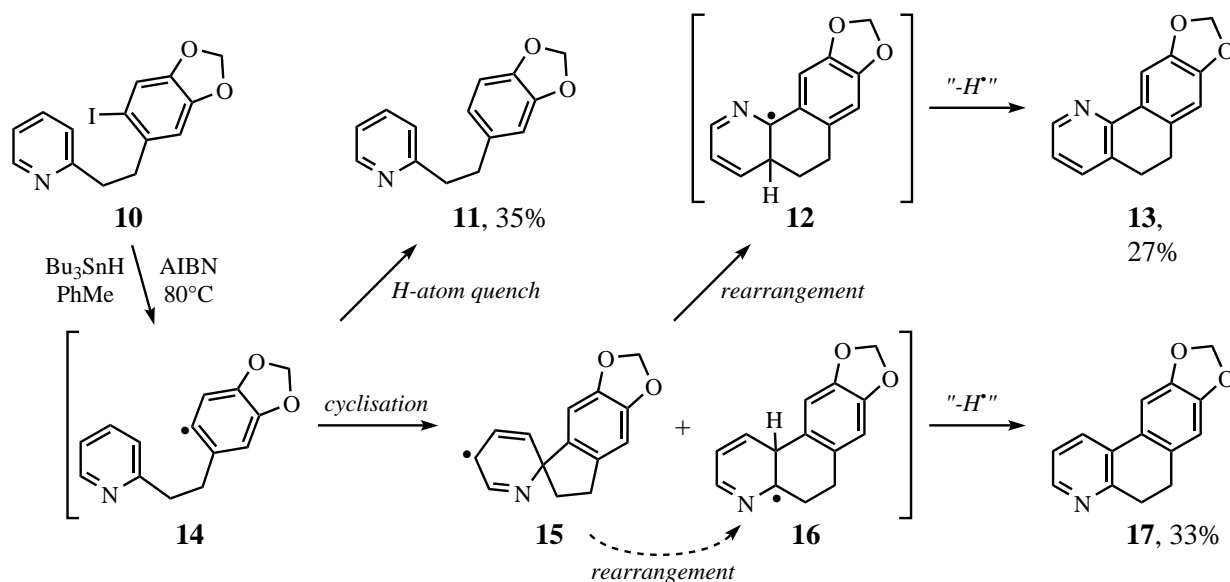**Scheme 1.**

Scheme 2.

Scheme 3.

resulting from 6-*exo*/*endo*-trig radical cyclisations. We next decided to investigate the extent to which the alkene tether was influencing the course of each reaction. Each of the azastilbenes **1**, **5** and **8** was therefore reduced to produce substrates **10**, **18** and **25**.

On exposure of **10** to tributyltin hydride under standard radical forming conditions, a complex product mixture was given comprising of reduced starting material **11** (35%), the expected dihydrobenzo[*f*]quinoline **17** (33%) and an unprecedented rearrangement product, dihydrobenzo[*h*]quinoline **13** (27%). The reaction is doubtless initiated by the homolysis of the carbon to iodine bond leading to aryl radical **14**. As this substrate has a flexible tethering chain, the 6-*exo*/*endo*-trig course is slowed significantly. Indeed, it now appears to compete with hydrogen atom abstraction, leading to **11**, and an alternative 5-*exo*-trig cyclisation mode leading

to spirocycle **15**. The two radical intermediates now follow courses leading to re-aromatisation of the pyridine moiety. For **16** this is achieved through loss of a hydrogen atom to give **17**, while for the spirocyclic intermediate **15** a skeletal rearrangement to **12** promotes aromatisation through loss of a hydrogen atom to give **13** (Scheme 4).[5]

A more complex product mixture arose when aryl iodide **18** was exposed to tributyltin hydride under radical forming conditions. Accompanying the reduction product **20** were two heterocycles, dihydrobenzo[*h*]quinoline **13** and dihydrobenzo[*f*]isoquinoline **24**, derived from direct 6-*exo*/*endo*-trig cyclisations to the α- and γ-carbons of the pyridine, respectively. Two further products, dihydrobenzo[*h*]isoquinoline **23** and dihydrobenzo[*f*]quinoline **17**, arising from rearrangement of the spirocyclic intermediate **21** were also identified (Scheme 5).

Iodoarene **25**, with the saturated tether linking the radical precursor to the γ-carbon of the pyridine, completed the series. This reaction likewise followed a complex course, though the products **26** and **23**, respectively, derived by intermolecular hydrogen atom abstraction and direct cyclisation to the β-carbon of the pyridine, accounted for most of the mass balance. The rearrangement product **23** was also observed, albeit in less than 20% yield (Scheme 6).

Scheme 4.
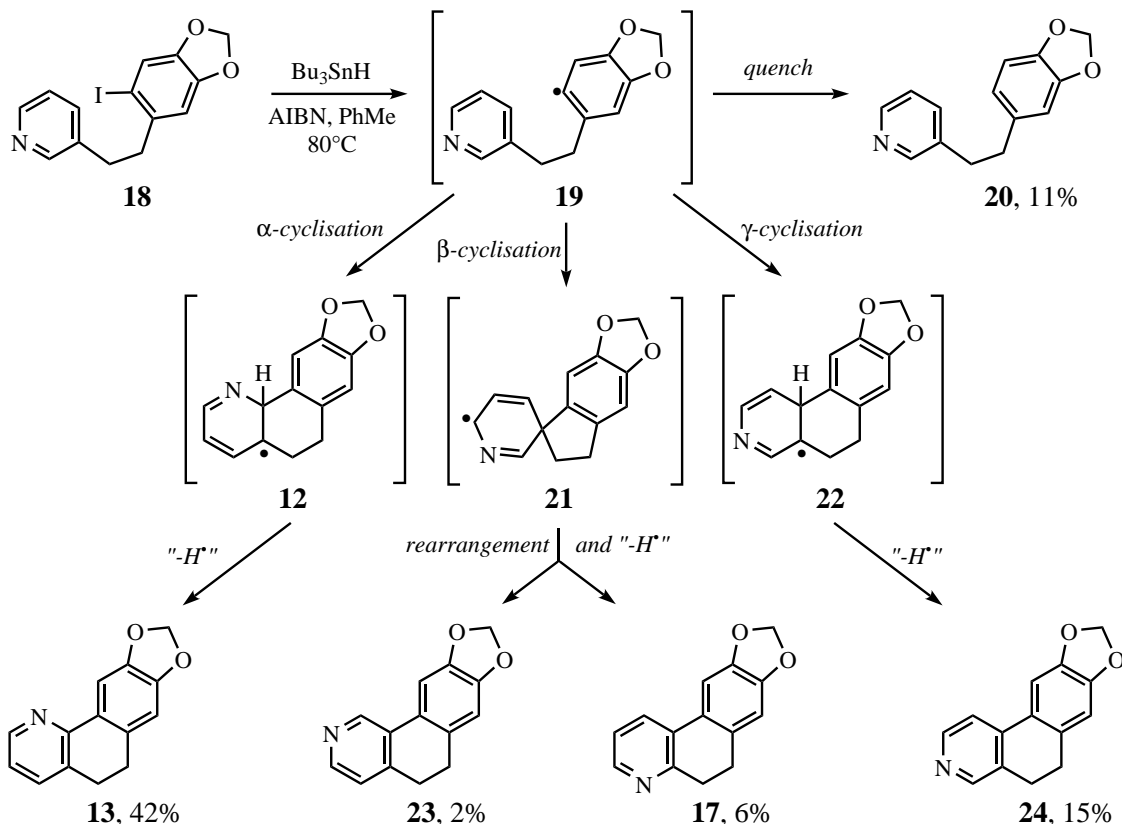
Scheme 5.
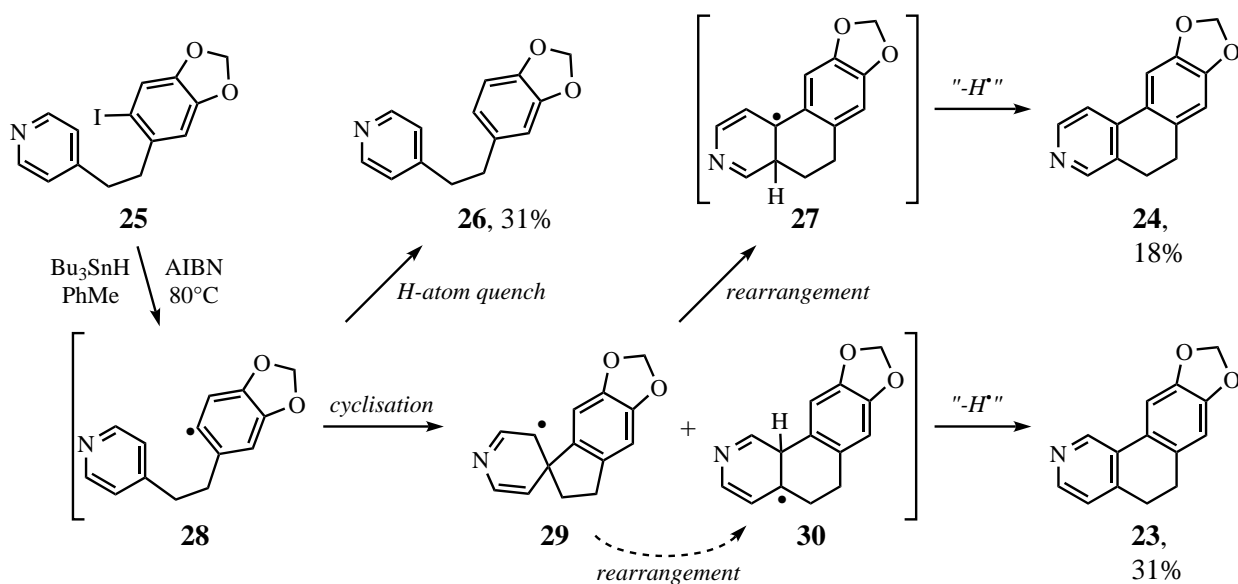
Scheme 6.

In conclusion, we have shown that intramolecular radical additions to the α-, β- and γ-carbons of a pyridine are all facile. We have also shown that the tether plays a crucial role in determining the course of the reaction. With a *cis*-alkene conjoining an *ortho*-iodoarene and a pyridine, cyclisation favours a 6-*exo*/*endo*-trig course. Using a more flexible two carbon alkane to conjoin the *ortho*-iodoarene and the pyridine, hydrogen atom abstraction and 5-*exo*-trig cyclisation modes become competitive. That the spirocyclic intermediates formed in the latter of these pathways rearrange with migration of the alkyl chain is a further noteworthy observation. We are presently examining other radical additions to aromatic and heteroaromatic ring systems in the hope of gaining a greater insight into this fascinating area of chemistry.[6]

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