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A radical approach to araliopsine and related quinoline alkaloids using manganese(III) acetate

Gregory Bar, Andrew F. Parsons* and C. Barry Thomas

Department of Chemistry, University of York, Heslington, York YO10 5DD, UK

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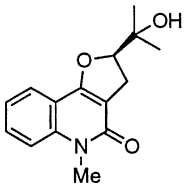
Abstract

Reaction of 4-hydroxy-1-methyl-2(1*H*)-quinolone **3** with electron-rich alkenes and manganese(III) acetate produces tricyclic quinoline alkaloids, including araliopsine **1**, in one-pot reactions. This combined intermolecular addition–cyclisation reaction produces angular and/or linear tricycles and the regioselectivity of the cyclisation is shown to depend on whether alkyl or aryl substituents are attached to the alkene.

Keywords: alkaloids; manganese and compounds; quinolines; radicals and radical reactions.

More than 200 naturally occurring quinoline alkaloids (including araliopsine **1** and *N*-methylschinifoline **2**) have been isolated from the Rutaceae family of plants, and these compounds have been shown to exhibit a wide range of important medicinal properties.[1] These include antiparasitic, anthelmintic and cytotoxic activities. As a consequence, the synthesis of these types of compound is of considerable interest and one potentially straightforward and flexible approach involves the introduction of a C-5 unit on to (commercially available) quinoline **3** by deprotonation and alkylation with prenyl bromide. The resultant alkene **4** could then be converted to a range of natural products using standard transformations (e.g. epoxidation, dihydroxylation etc.). Unfortunately, the desired alkene **4** is isolated in a very low yield (ca. 4%) from this reaction because of competitive di-alkylation and *O*-alkylation reactions.[2] With a view to developing a new, more efficient approach to these types of alkaloid, we now report the novel alkylation of quinoline **3** using a manganese(III)-promoted radical addition reaction.



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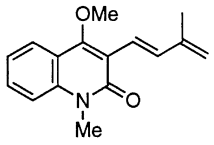

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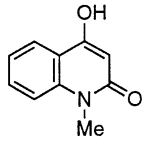

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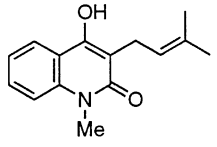

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* Corresponding author. Tel: +44-1904-432608; fax: +44-1904-432516; e-mail: afp2@york.ac.uk

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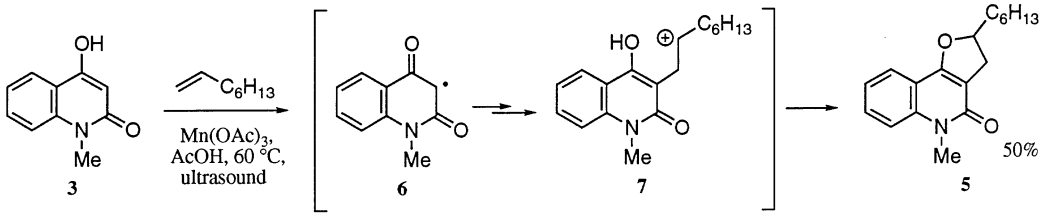
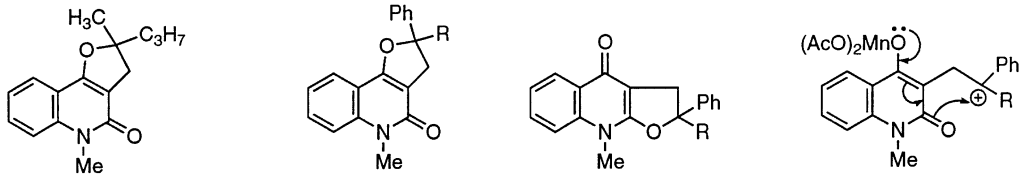
Our initial experiments involved the reaction of quinoline **3** with 1-octene and manganese(III) acetate under a variety of conditions (Scheme 1). For example, when **3** (0.57 mmol, 1 equiv.) was added to 1-octene (1 equiv.) and manganese(III) acetate (2 equiv.) in acetic acid (50 cm^3) and the solution stirred in an ultrasonic bath (300 W, 30–40 kHz) at 60°C (under an atmosphere of nitrogen) the tricycle **5** was formed in 28% yield.[3] In the absence of ultrasound no reaction took place presumably because of the low solubility of **3** in acetic acid.[4] The yield of **5** could be improved to 50% when the (ultrasound) reaction was repeated using 10 (rather than 1) equivalents of 1-octene. This reaction could also be mediated using less than 2 equivalents of manganese(III) acetate when the oxidant, potassium permanganate, was added slowly to the reaction. Hence, reaction of **3** with 1-octene (10 equiv.), manganese(III) acetate (0.3 equiv.) and potassium permanganate (0.6 equiv., added portionwise over 3 h) produced **5** in 58% yield. Potassium permanganate can therefore be used to oxidise manganese(II), which is produced as a reaction by-product, back to manganese(III).



Scheme 1.

The formation of **5** is expected to involve initial oxidation of **3** to form radical **6**. There are several potential routes by which **6** might be formed but the involvement of an intermediate manganese(III) enolate in this type of reaction is generally favoured.[5] Radical **6**, which is electrophilic, is then expected to add regioselectively (on electronic and steric grounds) to the electron-rich double bond[6] of 1-octene to form a secondary radical. Oxidation of this radical, by reaction with a second equivalent of manganese(III), will generate the corresponding secondary cation **7**, and nucleophilic attack by the enol hydroxyl group is expected to form the five-membered ring in **5**.[7] This mechanism can also explain the formation of tricycle **8** (in 64% yield) from reaction of **3** with manganese(III) acetate and 2-methyl-1-pentene. In this case, the cyclisation is expected to involve attack of the enol hydroxyl group on an intermediate tertiary carbocation.

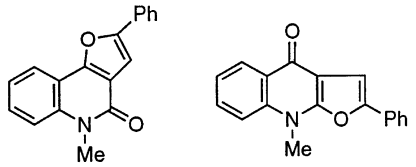


a; R = H. **b**; R = Me. **c**; R = Ph.

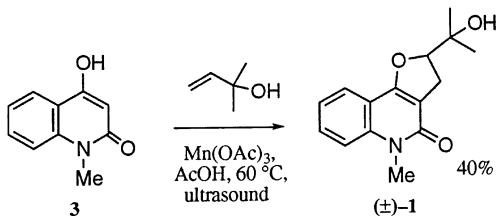
Interestingly, when styrene was used in place of 1-octene, reaction with **3** gave an approximately equal (1.1:1) mixture of the two regioisomers, **9a** and **10a**, in a combined 53% yield. The intermediate carbocation (of type **7**) therefore reacts with either of the two possible enol tautomers (of the ketone or amide) to give the two tricyclic isomers. This was also observed with other alkenes bearing an aromatic substituent(s). Reaction of **3** with α-methylstyrene gave the

angular isomer **9b** in 34% yield and the linear isomer **10b** in 52% yield, while reaction with 1,1-diphenylethylene gave a 1:1 mixture of **9c** and **10c** in a combined yield of 76%. The reason for the unexpected formation of linear isomers **10a–c** using phenyl substituted alkenes is unclear. Molecular orbital calculations (AM1 or PM3) suggest that the linear isomers are thermodynamically less stable than the angular isomers and this was supported by the slow isomerisation of **10c** to **9c** on heating in acetic acid.[8] One possible explanation could stem from the different rates of cyclisation. As the enol is expected to react more slowly with a more stable benzylic (rather than an alkyl) cation this could allow time for the formation of a second manganese(III) enolate of type **11**. Steric interactions between the benzene ring(s) and the bulky manganese(III) substituent could result in cyclisation to give the linear, rather than angular, isomer.

A similar result was observed on reaction of **3** with phenylacetylene to give the angular and linear furoquinolines, **12** and **13**, in 20 and 43% yields, respectively. In this case, addition of radical **6** to the less substituted end of the alkyne triple bond is expected to generate an intermediate α-styryl radical of the type $PhC^{\bullet}=CR_2$. Although manganese(III) does not usually oxidise vinyl radicals to vinyl cations,[9] the α-styryl radical has been shown to be a π-radical (rather than a σ-radical), with extensive delocalisation over the benzene ring.[10] As a consequence, it is likely that the manganese(III) can oxidise this (benzylic rather than vinylic-type) radical to a cation, which then reacts with either of the two possible enol tautomers to form **12** and **13**. Reaction of **3** with alternative terminal alkynes, bearing an alkyl rather than an aryl substituent, gave further support to the importance of the benzene ring. In these cases, the reactions gave a number of products in low yield, presumably because the manganese(III) cannot efficiently oxidise the intermediate vinyl radicals.

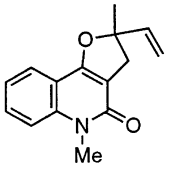


This method of radical addition/cyclisation was then applied to the synthesis of (±)-araliopsine **1**[11] by reacting quinoline **3** with manganese(III) acetate (2 equiv.) and 2-methyl-3-buten-2-ol (10 equiv.) as shown in Scheme 2. After purification by column chromatography (±)-araliopsine **1** was isolated in 40% yield. Like the related 1-octene reaction (Scheme 1), none of the corresponding linear quinoline isomer was isolated. When the same reaction was carried out using 0.3 equiv. of manganese(III) acetate in the presence of potassium permanganate (0.7 equiv.), **1** was isolated in a similar yield (35%). Reaction of **3** with the related 2-methyl-1,3-butadiene (isoprene) was also investigated, but this gave rise to a number of products in low yield including **14** in 18% yield.



Scheme 2.

It is of interest to contrast the manganese(III)-mediated reactions of **3** with those of the related α-chloro-quinoline **15**. This was formed from reaction of **3** with *N*-chlorosuccinimide (in 82% yield) and subsequent reaction with manganese(III) acetate and 2-methyl-3-buten-2-ol (under the same conditions as for the reaction with **3**), gave only a low yield of quinoline dimers (≤10% yield). The fact that no products derived from addition to the alkene double bond were isolated could reflect the stability of the first-formed tertiary radical **16**. The introduction of a chlorine atom is expected to reduce the reactivity of the radical due to electronic and steric factors. Addition of **16** to the alkene double bond could also be reversible and this is supported by the reaction of **15** with allyl *tert*-butyl sulfide (^{t}BuSCH$_2$CH=CH$_2$). This reaction produced the allyl derivative **17** in 40% yield, which was derived from intermolecular radical addition to the alkene double bond followed by β-fragmentation to expel the ^{t}BuS$^\bullet$ radical.



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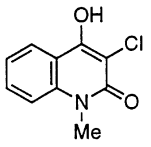

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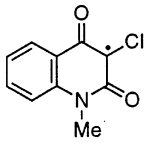

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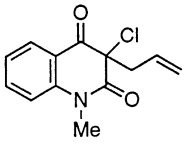

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Biologically important quinoline alkaloids, including araliopsine **1**, can therefore be prepared from reaction of quinoline **3** with electron-rich alkenes or phenylacetylene in the presence of manganese(III) acetate. This one-pot reaction gives rise to linear and/or angular tricyclic alkaloids; the regioselectivity of the cyclisation is determined by the substituents on the alkene double bond. These combined intermolecular addition–cyclisation reactions offer a quick, economical and flexible approach to quinoline alkaloids. It should also be noted that the use of manganese(III) acetate compares favourably with the use of cerium(IV) ammonium nitrate (CAN) in these alkylation reactions. Thus, reaction of **3** (1 equiv.) with 2-methyl-3-buten-2-ol (2–20 equiv.) in the presence of CAN only gave rise to dimeric products derived from homo-coupling of quinoline radical **6**.[12] The reasons for this difference are currently under investigation.

Acknowledgements

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