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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5987–5990

# Synthesis of diastereomeric 2,4-disubstituted pyrano[2,3-*b*]quinolines from 3-formyl-2-quinolones through O–C bond formation via intramolecular electrophilic cyclization

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Received 2 May 2007; revised 12 June 2007; accepted 20 June 2007
Available online 27 June 2007

**Abstract**—A number of 3-homoallyl-2-quinolones have been synthesized from 3-formyl-2-quinolones by reaction with allylindium bromide in aqueous DMF. Intramolecular electrophilic cyclization of these quinolones with iodine afforded either exclusively, or predominantly, racemic cis-diastereoisomers. Nucleophilic substitution reactions at the iodomethyl group afforded a mixture of tetracyclic products and unreacted racemic trans-diastereoisomer.


Quinolines and their annelated derivatives are important compounds due to their presence in numerous natural products along with their wide-ranging applications as drugs, pharmaceuticals and agrochemicals.[1] Pyranoquinolines are an important class of compounds that are found in a number of alkaloids such as flindersine, oricine, geibalasine and verprisine, and derivatives of these alkaloids show biological activity including anti-allergic, anti-inflammatory, psychotropic and estrogenic.[2]

Consequently, numerous syntheses have been developed for pyrano-annelated quinolines.[3] Cycloaddition and cyclization reactions are amongst the most useful routes for the synthesis of these compounds. Cycloaddition reactions, particularly Lewis acid catalyzed hetero Diels–Alder reactions, have been recently explored for the synthesis of pyrano[3,2-*c*]quinolines.[4] Bhuyan et al. have reported a one-pot synthesis of tetracyclic pyrano[2,3-*b*]quinolines via intramolecular 1,3-dipolar cycloaddition reactions using 1,3-dipoles such as nitrones, nitrile oxides and nitrile imines.[5] Examples of cyclization reactions for the synthesis of pyrano[2,3-*b*]-quinolines include the use of DDQ,[6] the Prevost reaction[7] and polyphosphoric acid.[2e] These have been less explored due to drawbacks such as difficulties in obtaining starting materials and poor yields of both starting materials and final products. Thus there is a need to develop new and efficient synthetic routes for the preparation of this class of compounds.

The 2-chloro-3-formylquinolines **1**,[8] easily accessible from simple acetanilides via a Vilsmeier–Haack approach, and their 3-cyano and 3-methoxycarbonyl derivatives have been used by us to prepare annelated carbocycles[9] and sulfur- and nitrogen-containing heterocycles[10] with diverse functionalities. In continuation of these studies, we report the stereocontrolled synthesis of racemic cis-disubstituted pyrano[2,3-*b*]quinolines from 3-formyl-2-quinolones **2**, (which are themselves easily prepared from 3-formyl-2-quinolines **1**), through O–C bond formation via intramolecular electrophilic cyclization (Scheme 2, Table 1). Reports on analogous compounds have been published via different routes from 2-chloro-3-formylquinolines.[5,11]

The starting 3-formyl-2-quinolones **2** were easily prepared in good yields (80–98%) by refluxing 2-chloro-3-formylquinolines **1** in aqueous acetic acid.[12] Allylation of **2** to give 3-homoallyl-2-quinolones **3** was achieved by reaction with in situ generated allylindium bromide in aqueous DMF at room temperature (Scheme 1) in excellent yields (89–94%). The structure of compound **3a** was ascertained from spectroscopic data.[13] Intramolecular electrophilic cyclization of compound **3a** with $I_2$ in THF in the presence of sodium bicarbonate at room

*Keywords*: Pyrano[2,3-*b*]quinolines; Diastereomers; Quinolines; Oxaiodination.
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doi:10.1016/j.tetlet.2007.06.127

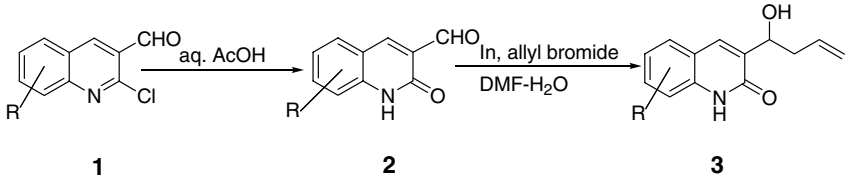
**Table 1.** Synthesis of diastereomeric *cis*/*trans*-4-hydroxy-2-iodomethylpyrano[2,3-*b*]quinolines from 3-homoallyl-2-quinolones **3**

| Entry | Substrate | R | Time (h) | Product | Ratio (cis/trans) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **3a** | H | 4.0 | **4a/5a** | 77:23 | 88 |
| 2 | **3b** | 6-Me | 2.5 | **4b/5b** | 90:10 | 81 |
| 3 | **3c** | 7-Me | 4.0 | **4c/5c** | 79:21 | 84 |
| 4 | **3d** | 7-OMe | 3.0 | **4d/5d** | 84:16 | 83 |
| 5 | **3e** | 8-Me | 3.5 | **4e/5e** | 100:0 | 85 |
| 6 | **3f** | 8-Et | 2.5 | **4f/5f** | 100:0 | 88 |

temperature gave an 88% yield of a mixture of **4a/5a**,[14] (Scheme 2) which consisted predominantly of the cis-diastereoisomer, 4-hydroxy-2-iodomethylpyrano[2,3-*b*]-quinoline **4a** (as determined from $^1$H NMR spectroscopy). The diastereoisomers **4a/5a** were chromatographically inseparable. The stereochemical assignments in *cis*-4-hydroxy-2-iodomethylpyrano[2,3-*b*]quinoline **4a** were initially determined from NMR spectral data and were supported by chemical transformations. The $^1$H NMR spectrum of *cis*-**4a** showed a downfield chemical shift for the C-5 proton ($\delta = 8.32$) in comparison to that of the corresponding *trans*-isomer **5a**, which appeared at $\delta = 8.12$.[14,15] The downfield chemical shift of the C-5 proton in the cis-isomers may result from an eclipsed arrangement of the 4-hydroxy group with the C-5 H bond, that is, the hydroxy group occupies an equatorial position in the cis-conformation. Similar observations were also made in the $^{13}$C NMR data relating to the chemical shifts of C-2 and C-4 in the cis-isomers, which appeared downfield in comparison to the trans-isomers.[14,15] The magnetically non-equivalent $CH_2I$ group protons were well resolved and showed the expected AB quartet system in cis-compounds, but were considerably less well resolved for the trans-compounds as a result of slow interconversion of the conformers by ring flipping. Dreiding molecular models further suggested that the most stable conformation of the cis-isomers have the hydroxy group at C-4 and the iodomethyl group at C-2 in equatorial positions.

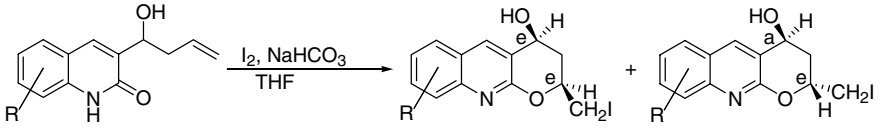
Although the cis and trans isomers in Table 1, entries 1–4 were chromatographically inseparable, nucleophilic substitution at the iodomethyl carbon in cis and trans **4a/5a** with sodium hydroxide in acetonitrile led to two separable compounds on TLC. The products were characterized as tetracyclic quinoline **6a** (63% yield), presumably formed by internal $S_N2$ attack of the 4-hydroxy group at the 2-iodomethyl group of the pyran ring, which favoured the 1,3-diaxial conformation of *cis*-isomer **4a**. Unreacted *trans*-4-hydroxy-2-iodomethylpyrano[2,3-*b*]quinoline **5a** (30% yield) was also recovered. Similar results were obtained, when the reaction was carried out with either NaOH or NaCN at reflux in aqueous acetonitrile (Scheme 3).

Finally, we explored the scope of the iodomethyl group in these pyrano-annelated quinolines by performing an elimination reaction on **4a/5a** with DBU or *t*BuOK in dry benzene at room temperature. A mixture of two products was obtained which was characterized as tetracyclic quinoline **6a** (42% yield) along with the desired elimination product **7a**[16] (38% yield). Similarly, *cis* **4e**




**1** **2** **3**

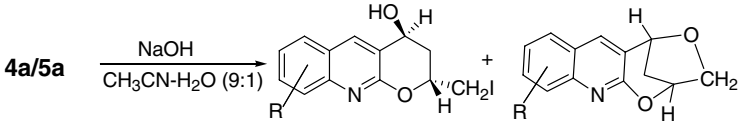
**Scheme 1.**




**3** **4** **5**

R = H, 6-Me, 7-Me, 7-OMe, 8-Me, 8-Et.

**Scheme 2.**




**5a** **6a**

**Scheme 3.**