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Synthesis of Polysubstituted, Functionalized Quinolines through a Metal-Free Domino Process Involving a C_4-C_3 Functional Group Rearrangement

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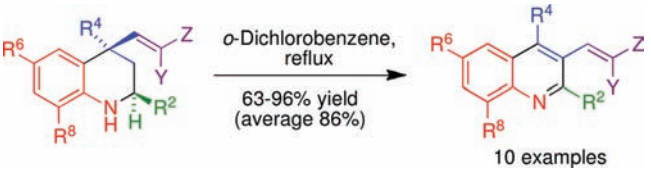
ABSTRACT



4-Alkyl-1,2,3,4-tetrahydroquinolines bearing a 4-vinyl unit ending in an electron-withdrawing group were efficiently transformed into polysubstituted, C_3-functionalized quinolines upon heating in refluxing *o*-dichlorobenzene, in a domino reaction involving an unusual C_4-C_3 functional group rearrangement.

Quinoline is one of the most important nitrogen heterocycles, being widespread in nature and present as a key structural unit in a large number of families of bioactive compounds.[1] Although quinoline synthesis has been studied for more than a century,[2,3] there is still a clear need for versatile methods that give access to highly substituted quinoline systems under environmentally benign conditions. We report here a concise route that affords polysubstituted, functionalized quinolines from simple, readily available starting materials, having as the key step a new rearrangement of 4,4-disubstituted 1,2,3,4-tetrahydroquinoline derivatives that transfers one of the C-4 substituents to the C-3-position and thus allows aromatization to take place. This rearrangement was planned to be initiated by an intramolecular Michael reaction of an *in situ* generated enamine onto Michael acceptor groups present at C-4.

The starting materials for our study came from the $InCl_3$-catalyzed Povarov-like[4] imino Diels–Alder reaction between aromatic imines and α,β-unsaturated dimethylhydrazones, acting as the dienophiles.[5] This reaction allowed the diastereoselective synthesis of 1,2,3,4-tetrahydroquinolines[6] **1** bearing a dimethylhydrazono group at the quaternary C-4 stereocenter, which were transformed into the corresponding aldehydes **2** by hydrolysis.[7] These aldehydes were then used as starting materials for the preparation of compounds **3a**–**l**, containing a C_4-vinyl unit ending in an electron-withdrawing group *via* a variety of olefination methods including Wadsworth–Emmons, Henry, and Knoevenagel reactions (Scheme 1 and Table 1).

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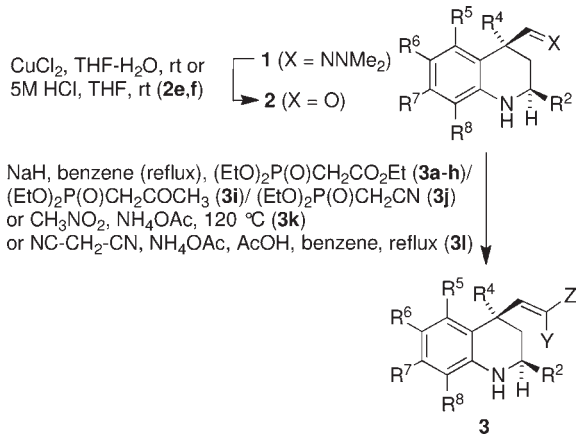
Table 1. Results Obtained in the Synthesis of Starting Materials **3**

entry	compd	R^2	Y	Z	R^4	R^5	R^6	R^7	R^8	yield **2**(%)	yield **3** (%)
1	**a**	C_6H_5	H	CO_2Et	Me	H	OMe	H	H	87	80
2	**b**	4-MeC_6H_4	H	CO_2Et	Me	H	OMe	H	H	89	86
3	**c**	4-$MeOC_6H_4$	H	CO_2Et	Me	H	Me	H	H	87	81
4	**d**	4-ClC_6H_4	H	CO_2Et	Me	H	OMe	H	H	93	72
5	**e**	C_6H_5	H	CO_2Et	Me	Me	H	Me	H	84	70
6	**f**	4-MeC_6H_4	H	CO_2Et	Me	OMe	H	OMe	H	96	86
7	**g**	C_6H_5	H	CO_2Et	Me	H	Me	H	Me	82	85
8	**h**	C_6H_5	H	CO_2Et	Et	H	OMe	H	H	85	83
9	**i**	C_6H_5	H	$COCH_3$	Me	H	OMe	H	H	[a]	80
10	**j**	C_6H_5	H	CN	Me	H	OMe	H	H	[a]	85
11	**k**	C_6H_5	H	NO_2	Me	H	OMe	H	H	[a]	96
12	**l**	C_6H_5	CN	CN	Me	H	OMe	H	H	[a]	83

[a] Compounds **3i**–**l** come from aldehyde **2a**.

Scheme 1. Synthesis of Starting Materials **3**



We next undertook the generation of an enamine function by dehydrogenation of the tetrahydroquinoline ring in compounds **3**, in order to examine its intramolecular addition onto the C-4 vinyl chain. After some experimentation, we discovered that both processes could be carried out in a single operation by simply heating compounds **3** in refluxing *o*-dichlorobenzene. This reaction afforded quinolines **4** in one step *via* an unprecedented C_4 to C_3 functional group rearrangement.[8] As shown in Figure 1, this route gives access to a broad range of polysubstituted quinolines bearing a functional group at C-3 and substituents at their C-2, C-4, C-6, and C-8 positions. The yields of the rearrangement step were normally good to excellent, but the reaction failed to afford C-5 substituted quinolines (reactions starting from **3e** and **3f**), probably for steric reasons as will be discussed below.

(8) Typical experimental procedure: A solution of the suitable compound **3** (0.7–0.8 mmol) was refluxed in *o*-dichlorobenzene (5 mL) until no starting material was detected by TLC. The reaction mixture was allowed to reach room temperature and then evaporated to dryness. The oily residue was purified by column chromatography eluting with mixtures of petroleum ether–AcOEt to give compounds **4**.

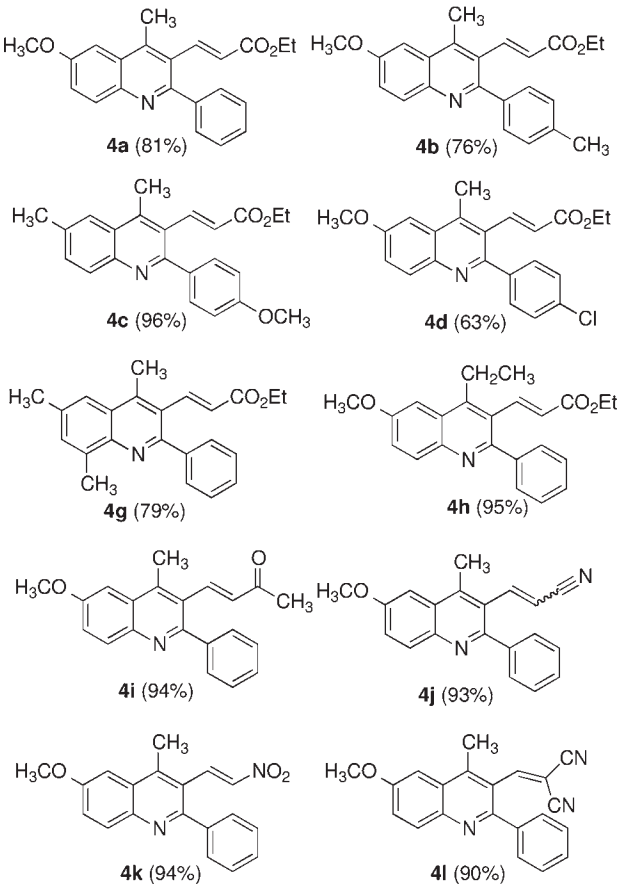
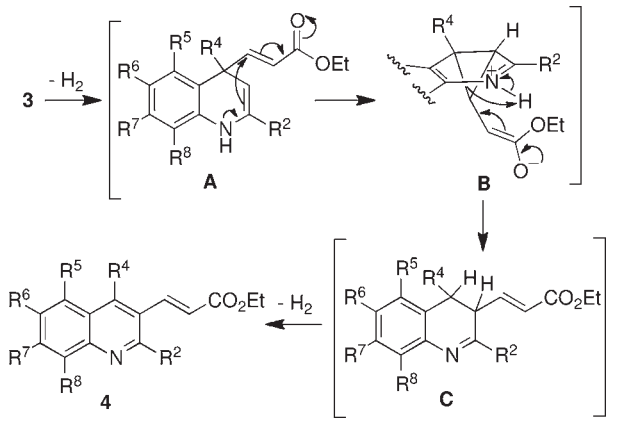


Figure 1. Scope of the quinoline synthesis. Conditions: *o*-Dichlorobenzene, reflux. Compound **4j** was obtained as a 60/40 mixture of the corresponding *E* and *Z* diastereomers.

In order to rationalize these results, we propose the domino mechanism summarized in Scheme 2, where the starting material is first dehydrogenated by air under the reaction conditions, affording intermediate **A**. An intramolecular addition of the enamine unit of **A** onto its Michael acceptor portion (exemplified here by an α,β-unsaturated ester) leads to the migration of this fragment

Scheme 2. Rationalization of the Formation of Compounds **4**



of the molecule from C-4 to C-3 *via* the generation and subsequent opening of an unstable cyclopropane intermediate **B**, leading to **C**. Finally, a second dehydrogenation reaction of **C** furnishes the aromatic quinoline derivatives **4**. Steric compression between R^5 and the substituents at C-4 in intermediate **B** explains the failure of the reactions starting from compounds **3e** and **3f**.

In conclusion, we have developed a unique route to highly substituted, functionalized quinolines based on an unprecedented domino sequence from tetrahydroquinolines involving transfer of a three-carbon unit from C-4 to C-3, thus leading to a further increase in the structural diversity of accessible substituted quinolines.

This protocol has the additional advantage of requiring only very simple starting materials and reagents and not involving the use of metal catalysts.

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Supporting Information Available. Experimental data and spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.