ORGANIC LETTERS

2008
Vol. 10, No. 3
385−388

Stereoselective C9 Arylation and Vinylation of *Cinchona* Alkaloids

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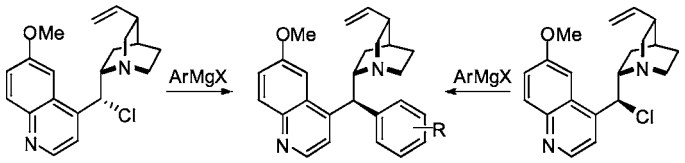
Received November 2, 2007

ABSTRACT



A simple and efficient method for the highly stereoselective C-9 arylation and vinylation of *Cinchona* alkaloids was developed. Both 9*S*- and 9*R*-chloroquinine with PhMgBr yielded 9*S*-phenylquinine (X-ray structure). The reactions with various aryl and vinyl Grignard reagents resulted in the series of 9*S*-aryl and vinyl alkaloid derivatives. The stereochemical outcome was rationalized by coordination of the magnesium atom to the quinuclidine nitrogen, thus directing the nucleophilic attack at the C-9 stereogenic center.

In the last two decades, *Cinchona* alkaloids (Figure 1) have gained much interest because of their successful applications

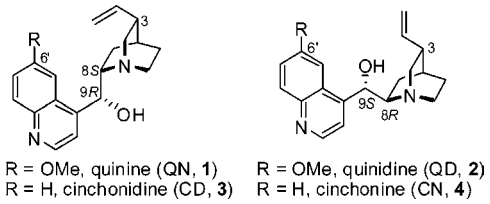


Figure 1. Major *Cinchona* alkaloids.

in asymmetric synthesis.[1] For their prominent role as chiral bases, ligands, phase-transfer catalysts, and surface modifiers, they were even considered as belonging to a *privileged catalyst* class.[2] The most often used selective synthetic modifications of *Cinchona* alkaloids were based on the replacement of C-9 hydroxy group by other functionalities, including those with nitrogen,[3] halogen,[4] and chalcogen[5] heteroatoms.

However, the stereochemistry of some of these transformations was not so obvious. The stereochemical outcome of the reaction of thionyl chloride with quinine was not a retention as believed,[6] but rather inversion of configuration, as it was proved by X-ray crystallography.[7] Another example is the acidic hydrolysis of methanesulfonyl esters derived from alkaloids of native and inversed (*epi*) configuration at

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10.1021/ol7026625 CCC: $40.75
Published on Web 01/08/2008

the C-9 stereogenic center. Both substrates gave a product of the same *epi*-configuration only. The authors suggested that a hydrogen-bound water molecule was one of the possible causes of such a course.[8]

To the best of our knowledge, there is only a single, nearly 60-year-old report on the effective building of the new C−C bond by the replacement of the C-9 hydroxy group.[9] A coupling reaction between 9-chloroquinine and phenylmagnesium bromide was described by Ochiai et al. However, the authors made no statement on the stereochemistry at position 9 of either the substrate or the product of the reaction.

In the present paper, we report an unexpected stereochemical course of this reaction and its use for the efficient synthesis of a series of new 9-aryl and 9-vinyl derivatives of *Cinchona* alkaloids.

The alkaloids and their C-9 epimers[8] were transformed to the corresponding chloro derivatives with inversion of configuration by treatment with thionyl chloride.[4b] Thus, we obtained both epimers of chloroquinine and cloroquinidine: 9*R*-Cl-QN (**6**), 9*S*-Cl-QN (**5**), 9*R*-Cl-QD (**8**), 9*S*-Cl-QD (**9**), as well as 9*S*-Cl-CD and 9*S*-Cl-CN. Additionally, 9*S*-Br-QN was obtained through the known procedure of Apel reaction.[4c]

9*S*-Chloroquinine (**5**) was reacted with the Grignard reagent obtained from bromobenzene and magnesium as described before.[9] The product was isolated by chromatography (65% yield) or, as reported,[9] by crystallization of the thiocyanate salt. A single crystal of this salt was submitted to X-ray analysis (Figure 2), and the structure of 9*S*-Ph-QN (**7**) was proved unambiguously.

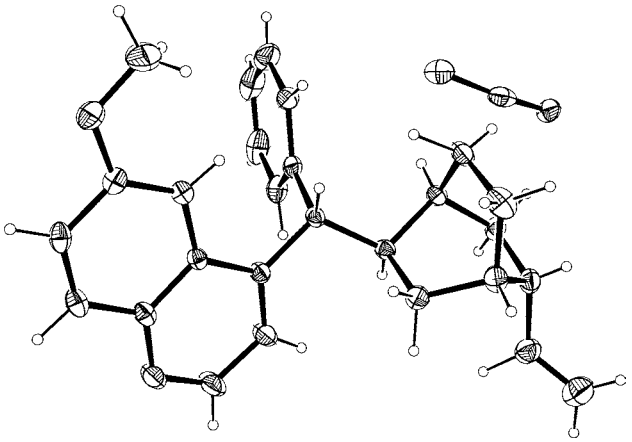
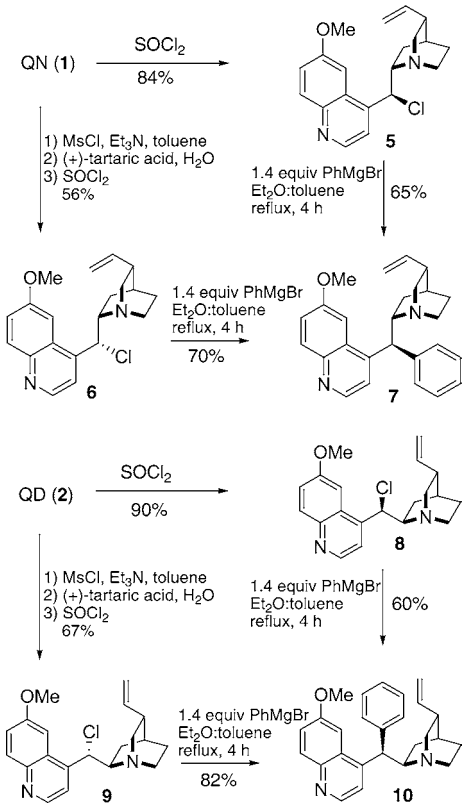


Figure 2. X-ray structure of 9*S*-Ph-QN (**7**) thiocyanate salt.

Accordingly, the configuration at the substitution center was retained. Interestingly, when a different isomer, 9*R*-Cl-QN (**6**), was used in the same reaction, the isolated product (70%) was identical to the previous one; i.e., in this case, 9*S*-Ph-QN (**7**) was obtained with the inversion of configuration (Scheme 1). The product of different configuration, 9*R*-Ph-QN, was neither isolated nor observed in the spectra.

Scheme 1. Synthesis of 9*S*-Ph-QN and 9*R*-Ph-QD



The same procedure was applied for 9-chloro derivatives of quinidine. Here again the reaction of either 9*R*-Cl-QD (**8**) and 9*S*-Cl-QD (**9**) with phenylmagnesium bromide yielded one and the same product, 9*R*-Ph-QD (**10**) (Scheme 1). Its relative configuration was confirmed by 2D ^{1}H NMR experiment (NOESY) (Figure 3).

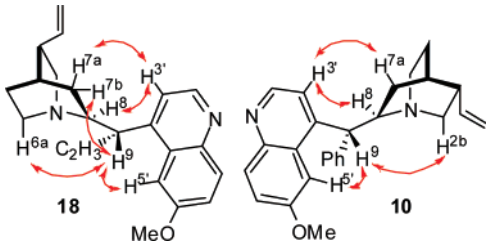


Figure 3. Selected NOE correlations for 9*S*-C_2H_3-QN (**18**) and 9*R*-Ph-QD (**10**).

Thus, when the configurations at the C-9 and C-8 stereogenic centers of chloro derivatives were the same (*like*-

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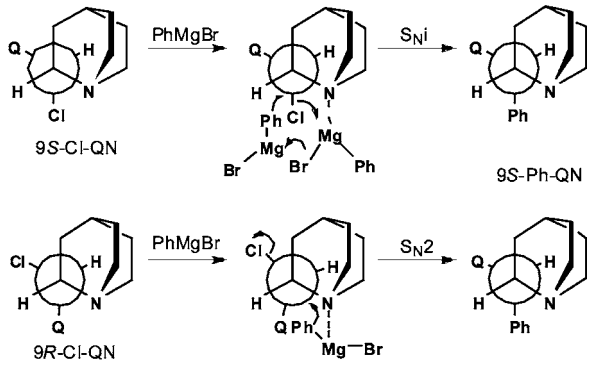
isomers) the reaction proceeded with the retention of configuration. On the other hand, the substrates with different configurations at C-9 and C-8 (*unlike*-isomers) reacted with inversion. Generally better yields were observed for chloroderivatives of *unlike*-configuration. The additional yield improvement (up to 88%) was achieved when a 2-fold excess of arylmagnesium compound was used.

It seems that binding of magnesium species by the quinuclidine nitrogen is essential to achieve such unexpected stereoselectivity (Scheme 2). A similar effect has already

Scheme 2. Suggested Mechanism of the Substitution Reaction



Q = 6-methoxyquinoline; vinyl group ommited for clarity.

been postulated in order to explain the observed diastereoselectivities of DIBALH reduction of quinidinone[10] as well as the addition of alkyl group to quinine's quinoline.[11] In our case, in the most stable conformation of *like*-isomers (9*S*-Cl-QN and 9*R*-Cl-QD) the chlorine atom is located very closely to the quinuclidine-bound magnesium atom. The reaction that follows requires the participation of the two-metal center and proceeds according to S_Ni mechanism leading to retention of configuration. In the case of *unlike*-isomers (9*R*-Cl-QN and 9*S*-Cl-QD), the chlorine atom is preferably oriented antiperiplanar to the quinuclidine nitrogen. Here, similar binding of magnesium structure is followed by the S_N2-like attack and usual inversion of configuration. This explanation is valid for both quinine and quinidine, since apart from the location and orientation of a vinyl group they can be regarded as enantiomers.

Otherwise, a common intermediate would, in the case of *Cinchona* alkaloids, require an extremely strained aziridinium ion, which is unlikely.[4c] Moreover, it would be responsible for a limited diastereoselectivity only and high content of the elimination and ring-expansion products. None of these products were formed in more than trace amounts. Also, contrary to the reported stereoselectivity of nucleophilic substitution by organomagnesium compounds attributed to anchimeric assistance,[12] in our case no difference was found between the reactions of 9*S*-Cl-QN and 9*S*-Br-QN with phenylmagnesium bromide. Additionally, when the reaction of 9*S*-Cl-QN with phenylmagnesium bromide was quenched before completion, the recovered chloro derivative was identical to the substrate used; therefore, a rapid isomerization between **5** and **6** can be ruled out under these conditions.

Attempted reactions with phenyllithium or lithium diphenylcuprate instead of the Grignard reagent gave 4% 9*S*-Ph-QN or complete substrate recovery, respectively. Cinchonine (**4**) and cinchonidine (**3**) were transformed to the corresponding 9-phenyl derivatives **12** and **11** in 23−39% yield. Because of the higher yield observed in the series of the 6′-methoxy-bearing compounds **7** and **10** vs those without this substituent **11** and **12**, we suppose that the additional complexation of one of the magnesium atoms may facilitate the substitution. Such an effect has already been observed for reactions involving Grignard reagents.[13] Moreover, an inspection of the corresponding molecular model does not exclude a similar interaction in our case.

Several other aryl derivatives were prepared in fair to good yields by reaction of 9*S*-Cl-QN with various aryl Grignard reagents. Both 2-naphthylmagnesium bromide as well as hindered 1-naphthylmagnesium bromide reacted easily, producing **13** and **14**, respectively (Figure 4).

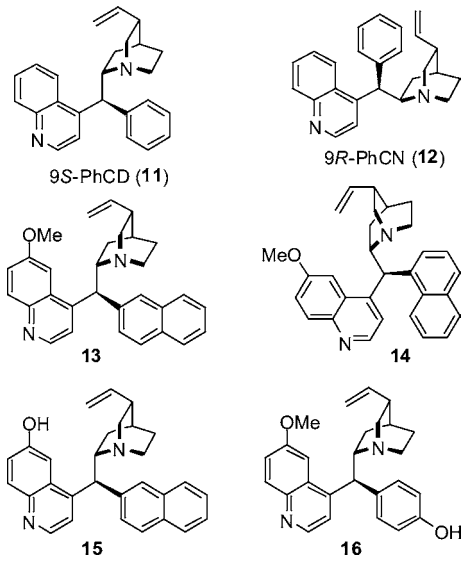


Figure 4. *Cinchona* alkaloid derivatives.

An attempted substitution of 9-chloroquinine with ethylmagnesium bromide gave a complex mixture, and we could not obtain the desired product. However, when a THF solution of either 9*S*-Cl-QN or 9*R*-Cl-QN was treated with vinylmagnesium bromide, 9*S*-vinylquinine (**18**) was formed as the only isomer. The reaction was complete within 1 h at room temperature. The NOESY experiments for **18** revealed a conformation very similar to that found in the crystal structure of **7** thiocyanate. Hydrogen H-8 shows no cross-

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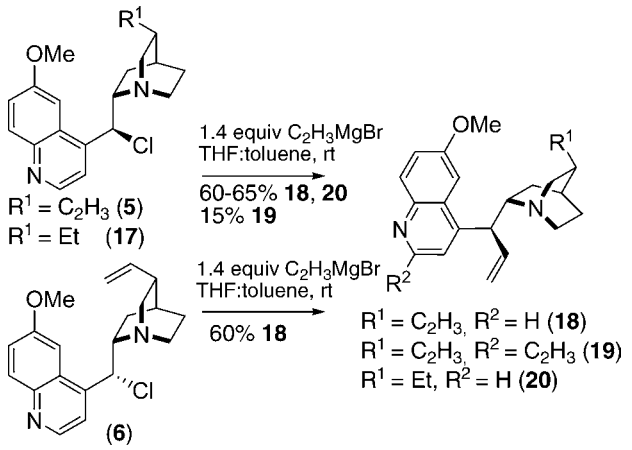
peak with hydrogen H-9, suggesting their antiperiplanar orientation. Strong correlations of H-9 with quinoline's H-5′ and H-7b were observed. Three hydrogens, H-7a, H-8, and H-3′, correlate with each other. This averaged conformation cannot be justified by 9*R*-vinylquinine, but it fits to the 9*S*-epimer (Figure 3).

When less than 1.2 equiv of vinylmagnesium bromide was added, nearly 50% of substrate was recovered, while the use of more than 1.5 equiv led to a pronounced nucleophilic substitution at the quinoline 2′-carbon atom[11,14] (Scheme 3).

Scheme 3. Synthesis of Vinyl Derivatives



We did not observe such byproducts with arylmagnesium halides, unless they were used in more than 2-fold excess.

With the intention of examining transformation of the obtained 9-arylalkaloids into the prospective organocatalysts, we prepared the products bearing free phenolic hydroxy groups as a hydrogen bond donor.[15] The methoxymethyl ether of *p*-iodophenol[16] was converted to the corresponding Grignard reagent and subsequently coupled with 9*S*-Cl-QN. The product was deprotected with 95% trifluoroacetic acid giving **16**. The phenolic group can also be uncovered by cleavage of the 6′-methyl ether inherited from the quinine structure. Sodium ethylthiolate in DMF[15b] was found to provide the most satisfactory results, giving **15** from **13** in 75% yield. In order to obtain chiral building blocks suitable for further selective transformations, compound **20** with a single vinyl group only was obtained from the corresponding dihydro derivative (**17**).

In conclusion, 9-chloro-substituted derivatives of *Cinchona* alkaloids were arylated and vinylated in a highly stereoselective manner. The outcome depended on the relative configurations at C-8 and C-9 centers. The reaction with aryl- and vinylmagnesium halides gave a series of the respective 9-aryl and 9-vinyl compounds with the retention for *like*- and inversion for *unlike*-C8,C9-configurations. The products are amenable for further conversion to the prospective catalysts, and these transformations are underway in our laboratory.

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

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