Tetrahedron 72 (2016) 2643–2648

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Simple approach to modular chiral scaffolds: binding functional sulfur nucleophiles to *Cinchona* alkaloids

Mariola Zielińska-Błajet, Przemysław J. Boratyński, Łukasz Sidorowicz, Jacek Skarżewski *

Department of Organic Chemistry, Faculty Chemistry, Wrocław University of Technology, 50-370 Wrocław, Poland

ARTICLE INFO

Article history:
Received 7 January 2015
Received in revised form 29 April 2015
Accepted 11 May 2015
Available online 15 May 2015

Keywords:
Cinchona alkaloids
Sulfur nucleophiles
Epoxide ring opening
Carbon–sulfur bond formation

ABSTRACT

A series of functional modules were regio- and stereoselectively attached to the *Cinchona* alkaloid scaffolds. The S_N2 reactions of thiolates with alkaloid mesylate and epoxide introduced metal-complexing moieties, including the heterocyclic systems of pyridine and 1,10-phenanthroline. The respective H-bond donating thiourea and salane motifs were formed in an additional step. The modified *Cinchona* alkaloids were tested in the metal-catalyzed Henry and Tsuji-Trost reactions.

1. Introduction

Over the last decades many studies have been devoted to the search of chiral ligands for the metal-catalyzed enantioselective reactions. Among them, some molecular motifs have been identified as successful in different reactions (*privileged catalysts*).[1] Additionally, the application of purely organic bifunctional chiral catalysts resulted in many remarkable achievements.[2] However, often encountered catalyst-substrate specificity causes serious limitations in their application to a particular asymmetric transformation. Thus, there is still need for development of new ligands and organocatalysts. For practical reasons, it is desirable to prepare ligands from readily available materials. Recently, an introduction of new complexing or catalytically active functionalities to the already successful chiral motifs of *privileged catalysts* has attracted much interest.[3] Such modular catalysts demonstrated their usefulness and this approach is considered as an effective method for broadening the application scope of parent chiral scaffolds. Reactions applied for the attachment of functional modules should proceed smoothly and often 'click chemistry' was chosen for this purpose. However, an introduction of extended linker separates the catalytically active or complexing parts from the chiral core. In order to avoid such obstacle we decided to explore the use of reactive sulfur nucleophiles for binding catalytic groups to chiral frameworks. This approach has already been used for the synthesis of sulfur-donating ligands,[4] and now we want to extend it for a more general aim.

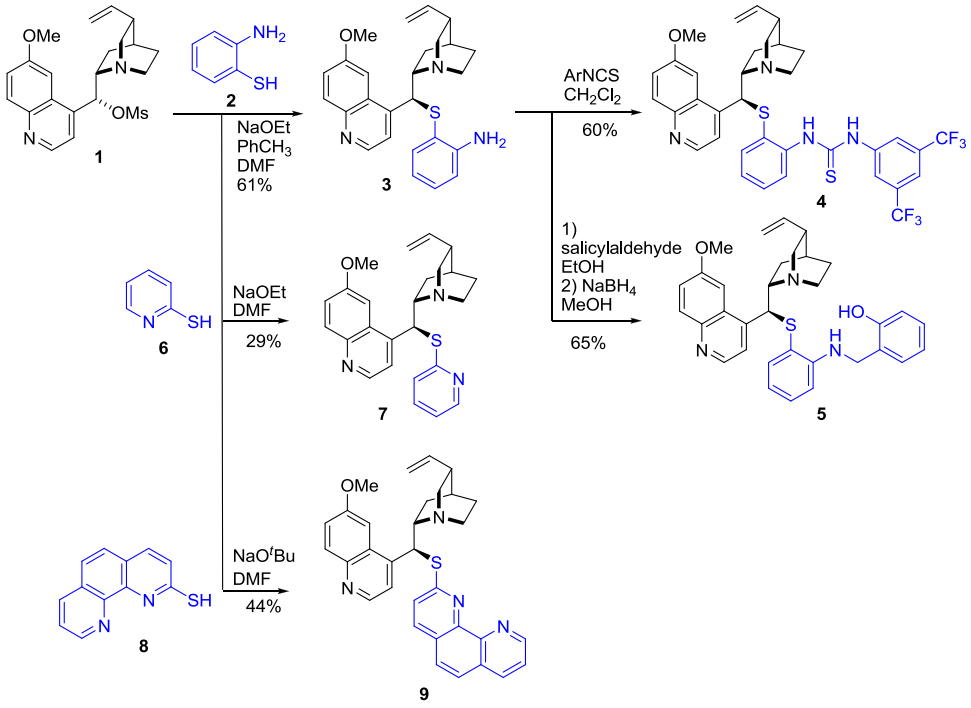
2. Results and discussion

In our previous works on *Cinchona* alkaloid scaffolds, we have demonstrated that a carbon–sulfur bond could be formed using thiophenol as a nucleophile.[5,6] The syntheses required electrophilic derivative of an alkaloid, such as the corresponding methanesulfonate or epoxide. However, in the reported reactions mostly simple phenylsulfanyl group was incorporated.[5,6] Thus, it was interesting to investigate, whether these procedures could be adopted to introduce additional functionalities, such as hydrogen-bond donating or metal-binding sites. Indeed, the reaction of quinine mesylate (**1**) and 2-aminothiophenol (**2**) delivered the corresponding amino derivative **3** with inversion of configuration at C-9. The free amino group in the product could then undergo further transformations. The derivative **4** with hydrogen-bond donating thiourea motif was obtained in the reaction of **3** with 3,5-bis(trifluoromethyl)phenyl isothiocyanate. Alternatively, **3** was transformed into the salane derivative **5** using salicylaldehyde under reductive amination conditions (Scheme 1).

Incorporation of a nitrogen atom within the aromatic ring of the thiol, such as in pyridine derivative **6**, complicates the course of the nucleophilic attack, because of tautomeric[7] and self-association equilibria.[8] Also, rather few substitutions of methanosulfonates

* Corresponding author. E-mail address: jacek.skarzewski@pwr.wroc.pl (J. Skarżewski).

http://dx.doi.org/10.1016/j.tet.2015.05.035
0040-4020/



Scheme 1. Transformations of 9-quinine mesylate.

with 2-mercaptopyridine were reported.[9] Nevertheless, we obtained the corresponding *Cinchona* alkaloid thioether **7** in moderate yield (Scheme 1). As expected, the reaction proceeded with complete inversion of configuration at C-9. The results of the reaction connecting pyridine to the *Cinchona* alkaloid scaffold were encouraging, so we decided to introduce a potent chelating moiety of 1,10-phenanthroline.[10] Consequently, we applied the phenanthroline-derived thiol **8** in the reaction with mesylate **1** and obtained **9** in fair yield. This product turned out to have large optical rotatory power ($[\alpha]_D$ of +810), exceeding nearly four times the respective value for its oxygen analogue.[3i] Such value is indicative of a highly helical structure. Also, circular dichroism revealed pronounced positive bands at 300–365 nm ($\Delta\varepsilon$=27) and 238 nm ($\Delta\varepsilon$=48). The DFT study suggested that the transitions between orbitals of phenanthroline and quinoline units can be ascribed to the CD low energy band (for the details, see: the Supplementary data).

Previously, oxygen and nitrogen-linked analogues of **3**, **7** and **9** were obtained in aromatic nucleophilic substitution using activated aryl and heteroaryl halides.[3i,11]

In an alternative approach, aimed at conserving the 9-hydroxyl group of *Cinchona* alkaloids, we intended to exploit the reactivity of corresponding epoxides. However, we have found that under ambient conditions the epoxide **10** hardly reacted with oxygen, nitrogen, and carbon nucleophiles. Nonetheless, **10** readily underwent ring opening with thiophenol as well as 2-aminothiophenol (**2**) furnishing the corresponding thioethers (**11**, Scheme 2).[6] Here, we report conversion of **11** to thiourea **12** (an analogue of **4**) in the reaction with the corresponding isothiocyanate (Scheme 2).

The ring opening of epoxides with 2-mercaptopyridine (pyridine-2-thione; **6**) was rarely applied, and only a few precedents were reported.[12] In a test experiment, we examined the reaction of **6** with styrene oxide and obtained a mixture of both regioisomeric products **15a** and **15b** in 1:1 ratio (Scheme 3).

In contrast, the reaction of **6** with cinchonine epoxide **10** led to **13** as the only product. Similarly, application of 2-mercaptophenanthroline (**8**) in the reaction with epoxide **10** gave single product **14** in nearly quantitative yield (Scheme 2). The compounds **13** and **14** were identified as tertiary 9-alcohols based on ^{13}C NMR chemical shifts of δ 81.4 and 82.5 ppm for C-9, consistent with chemical shifts (δ 79–83 ppm) observed for the previously described analogous derivatives.[6,13] Thus, the cinchonine epoxide ring opening with the heterocyclic thiolates selectively took place by the S_N2 mechanism. To the best of our knowledge, there are only few reported reactions of 2-mercapto-1,10-phenanthroline,[14] and none of them involved an epoxide ring opening.

Overall, higher yields were recorded for the transformations of epoxide **10** (75–93%) than mesylate **1** (29–61%). This was caused by **1** being prone to elimination under the required basic conditions. The sulfur nucleophiles demonstrated remarkably higher reactivity towards mesylates[9f] and epoxides[12g,15] compared to their oxygen or nitrogen analogues. Also in our hands, the reaction of 2-aminopyridine with the epoxide **10** resulted in poor conversion and only the product **16** substituted at the endocyclic nitrogen atom, not at the 2-amino group was formed (Scheme 4).

The ^{1}H NMR spectra revealed differences in the dynamics of the pyridine- and phenanthroline-based molecules. While the pyridine derivatives showed broadened signals, mostly coalescing by 318 K, the phenanthroline derivatives showed two well resolved sets of signals in roughly 1:10 ratio, corresponding to *anti* and *syn* rotamers. The observed conformations and broadening are most likely attributable to the hindered rotation of the quinoline ring that is significantly impeded by the bulky phenanthroline substituent. The energy differences between the *syn* and *anti* rotamers for **9** and **14** calculated at the DFT/B3LYP/6-31G(d,p) or CC-pVDZ level of theory were −1.8 and +1.0 kcal/mol, respectively (for details, see the Supplementary data). Such differences are in good agreement with the experimental data.

In order to examine the utility of the modified *Cinchona* alkaloids we tested their catalytic performance in two metal-mediated enantioselective reactions. The asymmetric copper-catalyzed Henry reaction of benzaldehyde with nitromethane favored the product of *S* configuration for all the quinine derivatives, except for **9**. Also the oxygen analogue of **9** (phenanthroline 9-*O*-ether) gave predominantly *R* nitroaldol.[3i] Such stereochemical outcome can be