ORGANIC LETTERS

2003
Vol. 5, No. 16
2773−2776

Fused Triazoles via Tandem Reactions of Activated *Cinchona* Alkaloids with Azide Ion. Second *Cinchona* Rearrangement Exemplified

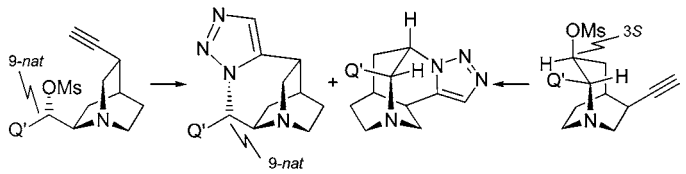
S. Röper,[†] M. H. Franz,[†] R. Wartchow,[‡] and H. M. R. Hoffmann*,[†]

Department of Organic Chemistry, University of Hannover, Schneiderberg 1B, 30167 Hannover, Germany, and Department of Inorganic Chemistry, University of Hannover, Callinstrasse 9 D-30167 Hannover, Germany

hoffmann@mbox.oci.uni-hannover.de

Received April 30, 2003

ABSTRACT



Q' = 4'-quinolyl

Intramolecular 1,3-dipolar cycloadditions of cinchona azides to the C10–C11 alkyne and C10–C11 olefin unit of the alkaloid have been designed via tandem strategy. A variety of fused triazoles and triazolines with a bis-azahomotwistane skeleton have been prepared. In trifluoroethanol, *O*-mesylcinchonidine 7-OMs and NaN_3 furnish triazole 8 as well as cage-expanded 1,5-diazatricyclo[4.4.1.0^{3,8}]undecane derivative 10. Both fused triazoles 8 and 10 are formed with retention of configuration at C9 and C3, respectively. 1-Azabicyclo[3.2.2]cage expansion is shown to be reversible.

According to an NIH work group, there is a critical need for the development of broad spectrum, nontoxic fungicidal drugs. A recent report has targeted triazoles as antifungal agents of the next generation, although tight competition from peptide antifungals is expected to remain.[1]

We report the preparation of novel fused triazoles from modified *Cinchona* alkaloids. 1,3-Dipolar addition of organic azides to alkynes is one of the most important and efficient routes to triazoles.[2,3] Accordingly, a 1,3-dipole and acetylenic acceptor had to be generated and placed into a position suitable for intramolecular cycloaddition.[4]

Starting with quinidine **1-OH** bromination followed by twofold dehydrobromination provided the 10,11-didehydro alkaloid **2-OH**.[5] Stereocenter C9 was inverted in two steps giving *epi*-configured alkaloid ***epi*-2-OH**.[6] The derived mesylate ***epi*-2-OMs** was heated with NaN_3 in absolute DMF. Workup and chromatography provided triazole **3**,[7] the structure of which was determined by spectroscopic techniques and corroborated by single-crystal X-ray diffraction (Figure 1).

[†] Department of Organic Chemistry.
[‡] Department of Inorganic Chemistry.

(1) Goldhill, J. *Pharma Report Alert: New Targets and Drug Discovery Platforms in Antifungal R&D*, Nov. 25, 2002. This report can be obtained by sending an e-mail request to the following address: leaddisc@leaddiscovery.co.uk.

(2) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604−637; 742−754. Katritzky, A. R., Rees, C. W., Eds. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, 1984. Applications: Wolf, M. E., Ed. In *Burger's Medical Chemistry and Drug Discovery*; Wiley: New York, 1997.

(3) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

(4) Review: Padwa, A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 123.

(5) Braje, W. M.; Frackenpohl, J.; Schrake, O.; Wartchow, R.; Beil, W.; Hoffmann, H. M. R. *Helv. Chim. Acta* **2000**, *83*, 777. Frackenpohl, J.; Braje, W.; Hoffmann, H. M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 47.

(6) See Braje, W.; Holzgrefe, J.; Wartchow, R.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2085.

(7) Cycloadducts **3** and **5** have a bis-azahomotwistane skeleton. For oxazahomotwistane analogues, see: von Riesen, C.; Hoffmann, H. M. R. *Chem. Eur. J.* **1996**, *2*, 680. Braje, W.; Frackenpohl, J.; Langer, P.; Hoffmann, H. M. R. *Tetrahedron* **1998**, *54*, 3495.

10.1021/ol034719y CCC: $25.00
Published on Web 07/09/2003

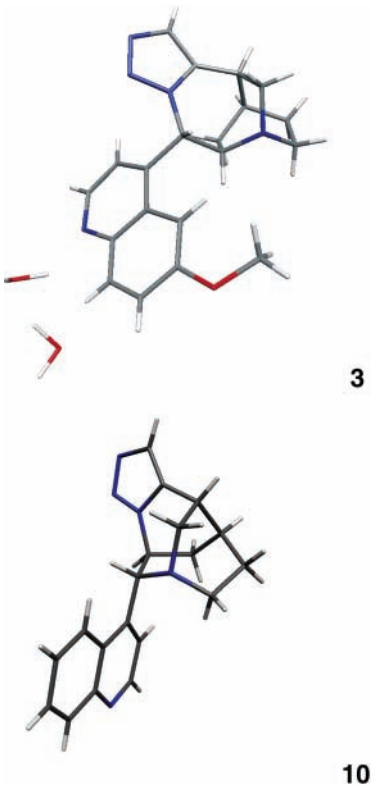
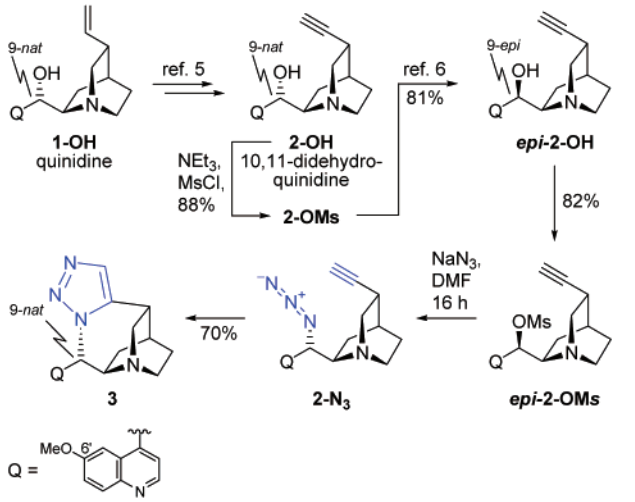


Figure 1. X-ray crystal structure of triazoles **3** and **10**.

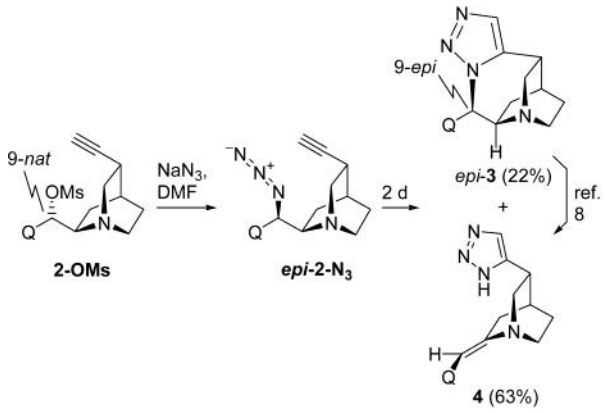
When the reaction of ***epi*-2-OMs** was stopped after 4 h, organic azide **2-N$_3$** with a C9-*nat* configuration could be isolated en route to cycloadduct **3** (Scheme 1).

Scheme 1. Intramolecular Cycloaddition of Organic Azide



By comparison, the reaction of 9-*nat*-configured **2-OMs** with NaN_3 in DMF was more sluggish (2 days; see also ref 8) and provided cycloadduct *epi*-**3** (minor) and orthogonally twisted enamino triazole **4** (major) (Scheme 2). Azide ***epi*-2-N$_3$** with nonnatural C9 stereochemistry was identified en route to ***epi*-3**.[8]

Scheme 2. Formation of Cycloadduct *epi*-**3** with Nonnatural Stereochemistry at C9

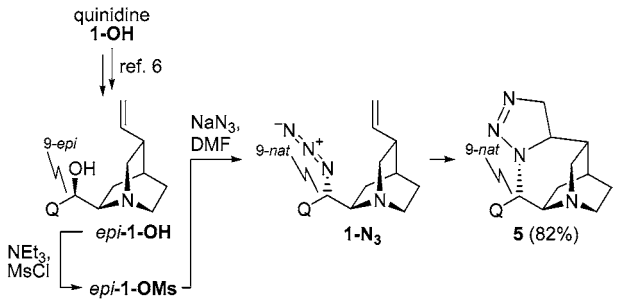


Simple unstrained olefins are often reluctant to cycloadd to organic azides. However, after conversion of 9-*epi*-quinidine into its mesylate ***epi*-1-OMs** and heating with NaN_3 in absolute DMF, triazoline **5** was prepared. Inverted organic azide **1-N$_3$** was identified as an intermediate. The formation of triazoline **5** via **1-N$_3$** demonstrates the favorable effect of intramolecularity on reactivity.

Study of Modified Cinch Bases and Change of Mechanism. Until now, nucleophilic displacement by azide ion has entailed complete inversion of configuration at C9. Changing over from quinidine **1-OH** (6′-R = OMe) to cinchonine **6-OH** (6′-R = H) may at first sight seem unimportant and inconsequential.

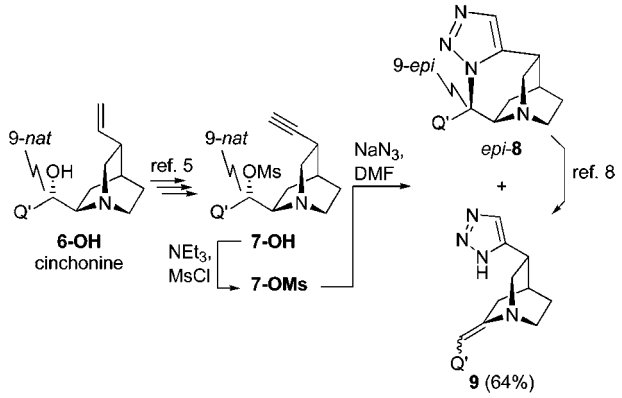
However, our previous experience suggested that the 6′-OMe group is capable of serving as a donor in S_N1-like reactions at C9 and of counteracting σ-bridging.[9,10] Starting from **6-OH**, we prepared 10,11-didehydrocinchonine **7-OH** and then **7-OMs**, which was exposed to NaN_3 in solvent DMF. Cycloadduct ***epi*-8** and consecutive triazole **9** were isolated (Scheme 4).[8] Thus, the result is similar to that with O-mesylated 10,11-didehydroquinidine **2-OMs** (Scheme 2).

Scheme 3. Fused Triazoline **5** from *epi*-Quinidine ***epi*-1-OH**



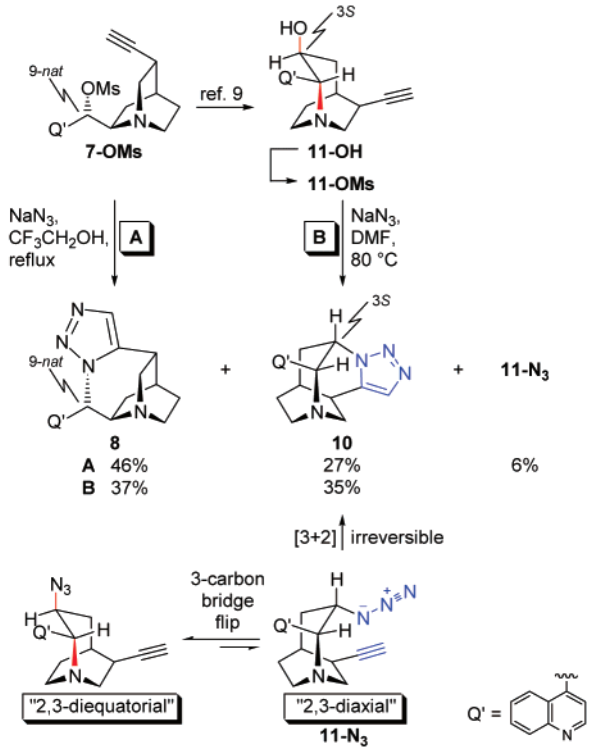
However, in weakly nucleophilic but strongly ionizing trifluoroethanol,[11] a deep-seated mechanistic change occurred

Scheme 4



with **7-OMs**: C9-*nat*-configured triazole **8** was formed with complete *retention* of configuration at C9 (Scheme 5, route

Scheme 5. Cascade Reactions of **7-OMs** and **11-OMs** with NaN_3/CF_3CH_2OH and NaN_3/DMF, Respectively



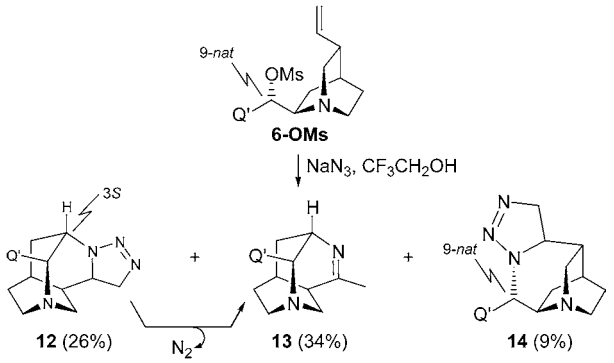
A).[12] Moreover, cage-expanded isomeric triazole **10**, which has a novel tetracyclic skeleton, was isolated. The structure of annulated 1,5-diazatricyclo[4.4.1.$0^{3,8}$]undecane **10** was confirmed by X-ray crystallography (Figure 1).

To shed further light on these puzzling rearrangements, we prepared 10,11-didehydrocinchonine isomer **11-OH**[9] and then mesylate **11-OMs**, which has a relatively hindered secondary center at C3 with a quasiequatorial leaving group. Remarkably, substitution of mesylate by azide ion furnished not only triazole **10**, with *retention* at C3, but also isomeric ring-contracted adduct **8**, even in DMF (route B).

A rational precursor of triazole **10** is organic azide **11-N_3**, which must arise from **11-OMs** with *overall retention* of configuration under S_N1-like conditions. In fact, **11-N_3** was detected (6%) in route A before complete cyclization. A three-carbon bridge flip into the less favorable quasidiaxial conformation is required to place the reacting π-components into spatial proximity (Scheme 5).

In a control experiment, we investigated the tandem reaction of *O*-mesyl cinchonine **6-OMs** in solvent trifluoroethanol. We isolated cage-expanded **12** and **13**, as well as triazoline **14** (Scheme 6; see also Scheme 3). The configuration at C9 was retained.

Scheme 6. Intermediate Organic Azide from *O*-Mesyl Cinchonine Cycloadds to Internal Olefinic Double Bond[13]



As an intermediate we suggest σ-bridged 9-*Cinchona* cation ***i***, which is capable of sustaining both cage expansion and cage contraction (Scheme 7).[10] Control of stereochemistry, which may otherwise be problematic in S_N1-like reactions, is complete.

As a further test of this theory, ring-expanded cinchonine **15-OMs** was subjected to reaction with azide ion in solvent DMF (cf. also Scheme 5). Organic azides **6-N_3** and **15-N_3** were generated side by side, independent of precursor **6-OMs** or cage-expanded **15-OMs**.

Ring contraction of β-amino mesylate **11-OMs** (giving **8**, Scheme 5) and of **15-OMs** is stereoelectronically favorable

(8) Heating ***epi*-3** in DMF at 80 °C provides triazole **4** as a consecutive product. As a rule, we have found that a variety of *Cinchona* alkaloids with 9-*epi*-configured leaving groups (OMs, OTs, Br, OP^+R_3) are prone to enamine formation. Proton H8 is antiperiplanar to the C9 leaving group and more exposed to base in the *epi* series but more screened by the quinolyl group in the 9-*nat* series. For the possibility of Winstein-Parker E2C reactions, see: Beltrame, P.; Biale, G.; Lloyd, D. J.; Parker, A. J.; Ruane, M.; Winstein, S. *J. Am. Chem. Soc.* **1972**, *94*, 2240. See also Scheme 4. In the case at hand, azide ion might attack H8 as a base and C9 as a nucleophile within a cyclic six-membered transition state.

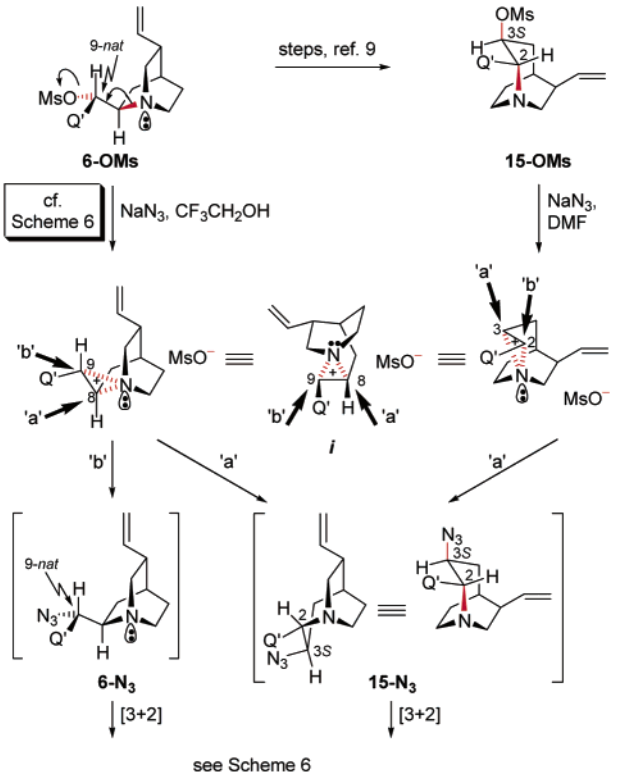
(9) Röper, S.; Franz, M. H.; Wartchow, R.; Hoffmann, H. M. R. *J. Org. Chem.* **2003**, *68*, 4944.

(10) Generation of closed σ-bridged ion ***i*** is considered to be favored for cinch bases with a C9 leaving group. An open classical C9 cation is more favorable in quinine and quinidine due to oxonium resonance via a 6′-OMe donor. See ref 9. The four nearest neighbors of the bridging nitrogen in cation ***i*** are not bonded in classical tetrahedral fashion. Instead, these four coordinating atoms are constrained in one hemisphere; the nitrogen lone pair is in the other hemisphere.

(11) McClelland, R. A. *Tetrahedron* **1996**, *52*, 6823. Mayr, H.; Minegishi, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 4493 and references therein.

(12) Preparation of **8** from 9-*nat*-configured **7-OMs** requires two steps fewer than preparation from an *epi*-configured substrate (cf. Scheme 1).

Scheme 7. Nucleophilic Displacements of **6-OMs** and **15-OMs** in the Presence of NaN_3[a]



[a] Trajectory of nucleophilic attack is indicated by "a" and "b".

because the quasiequatorial leaving group in **11-OMs** and **15-OMs** is antiperiplanar to the migrating carbon−nitrogen bond (Schemes 5 and 7).

In conclusion, while the "first *Cinchona* rearrangement" is driven by irreversible formation of a bridgehead iminium ion,[14] the "second *Cinchona* rearrangement" is more finely balanced and potentially reversible. The two rearrangements are fundamental transformations that will widen the outlook in the *Cinchona* alkaloid area for years to come.

The new triazoles and triazolines contain a number of useful pharmacophoric groups. Apart from the five-membered heterocycle a quinoline, a 1,4-diazacycloheptane[15] and a quinuclidine moiety are present.

Acknowledgment. We thank Buchler GmbH Braunschweig for *Cinchona* alkaloids, Dr. E. Hofer for spectroscopic advice, and Ulrike Eggert and Dr. Lars Ole Haustedt for their help.

Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Centre.[16]

OL034719Y

(13) Triazolines **12** and **14** are single isomers, suggesting that the fused five-membered heterocycles arise in a concerted cycloaddition.

(14) Braje, W.; Holzgrefe, J.; Wartchow, R.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2085. Röper, S.; Frackenpohl, J.; Schrake, O.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2000**, *2*, 1661. Röper, S.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2002**, *4*, 3179.

(15) For applications as tranquilizers, see: *Ullmann's Encyclopedia of Industrial Chemistry*; 6th Completely Revised Edition; Wiley-VCH: Weinheim, Germany, 2003.

(16) Supplementary publications nos. CCDC-208992 (**3**) and CCDC-208993 (**10**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).