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Oxidative ring-contraction of 3*H*-1-benzazepines to quinoline derivatives

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ABSTRACT

When treated with SeO_2, 2,4-diphenyl-3*H*-1-benzazepine (**1**) is oxidized equally at C3 and C5, giving either products of rearrangement or fragmentation; in both cases quinoline derivatives are the primary products. When C3 is oxidized, electrocyclization followed by ring-opening with phenyl migration gives the major product phenyl(3-phenylquinolin-2-yl)methanone (**6**), whereas C5 oxidation produces 2,4-diphenylquinoline (**2**) and 1,2-bis(2,4-diphenylquinolin-3-yl)diselane (**8**). Oxidation of C5 in **1** also results in formation of 2-(3,5-diphenylfuran-2-yl)aniline (**7**). On the other hand, 3-methyl-2,4-diphenyl-3*H*-1-benzazepine (**9**) upon treatment with SeO_2 gives primarily a product of oxidation of C3, 2,3-diphenylquinoline (**5**). Oxidation of C5 in (**9**) is a minor pathway, and gives both 3-methyl-2,4-diphenylquinoline (**10**) and (3-methyl-2-phenylquinolin-4-yl)(phenyl)methanone (**11**). CO was detected as a byproduct in both reactions. Although the ring-contraction reaction using SeO_2 has been previously noted, no mechanistic proofs have been firmly established. In this Letter, we provide evidence for the ring-contraction of benzazepines to quinolines through a fragmentation path (loss of CO and acetic acid) or through rearrangement.

We have reported[1] that treatment of 2,4-diphenyl-3*H*-1-benzazepine (**1**) with two equiv of NBS, a catalytic amount of DBP, and water gave 2,4-diphenylquinoline derivatives **2**, **3**, and **4** (Scheme 1). A mechanism was proposed that involved both free-radical and ionic intermediates. Initial free-radical bromination of C5 of benzazepine **1** led to ring-contraction and eventually, oxidative loss of C5 in the form of carbon monoxide. Bromoquinolines **3** and **4** resulted from subsequent bromination of quinoline **2**.

Reported here will be preliminary results of the oxidation of benzazepine **1** and its 3-methylated derivative with selenium dioxide. We found one precedent in the literature where selenium dioxide was used as a catalyst for the ring-contraction of cycloalkanones to cycloalkanecarboxylic acids.[2] In that study, a full mechanistic proof was lacking, as there were no intermediates detected or isolated. We anticipated that the initial oxidation would occur at the allylic C3, and would result in oxidative loss of this carbon atom, giving an isomer of **2** as product. We will show below that this is indeed the case for 3-methyl-**1**, but **1** itself gives primarily the product of an oxidative rearrangement, rather than fragmentation. It is hoped that an understanding of the mechanisms will lead to reaction conditions resulting in synthetically useful yields of the quinoline products.

Treatment of benzazepine **1** with 1.7 equiv of selenium dioxide, a small amount of KH_2PO_4, and water in dioxane solvent at 90 °C—conditions employed previously for allylic oxidation[3]—gave a mixture of five oxidation products (Scheme 2). Surprisingly, the product of oxidative loss of C3, namely 2,3-diphenylquinoline (**5**), was isolated only in small amounts (2–3%). The ^1H and ^{13}C NMR spectra of **5** were identical to those reported in the literature.[4] The major product was phenyl(3-phenylquinolin-2-yl)methanone (**6**), in which a deep-seated oxidative rearrangement had occurred. Three more products—apparently the result of initial oxidation of C5—were isolated in low yields: quinoline **2**,[1] furan **7**, and surprisingly the diselenide **8**. The presence of an additional product, carbon monoxide, was inferred by a positive test using a detector we have employed previously.[1] A brief optimization study established that 1.7 equiv of SeO_2 was the minimum amount required for complete conversion of starting material. The structures of quinoline **6**, furan **7**, and the diselenide **8** were all established by X-ray crystallography (see SI for details).

Treatment of the 3-methylated derivative of benzazepine **1** (**9**)[5] under the conditions of Scheme 2 with 3.5 equiv of SeO_2 (the amount that gave the best yield) and higher temperature

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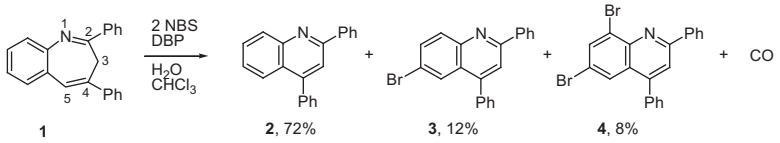
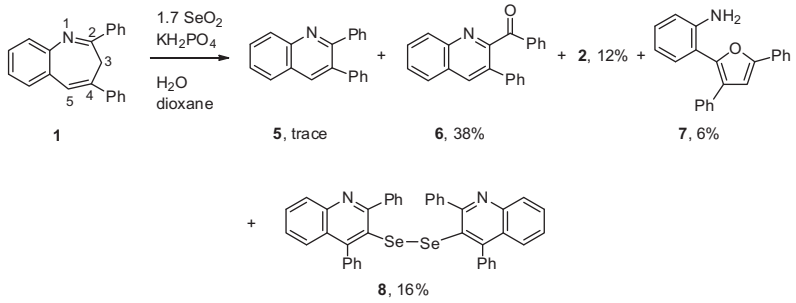


Scheme 1. Oxidative ring-contraction of a benzazepine reported previously.



Scheme 2. Oxidation of benzazepine **1** with excess SeO_2.

(110 °C) also gave initial oxidation of C3, but in this case, a fragmentation reaction resulted, giving quinoline **5** as the major product (Scheme 3). The other characterized products were the 3-methylated quinoline **10** (the analogue of quinoline **2**), compounds **11** and **6**. The ^{1}H and ^{13}C NMR spectra of **10** were identical to those reported in the literature.[6] The structure of **11** was confirmed by 1D and 2D NMR experiments. Also seen in the reaction mixture was acetic acid, which presumably carried C3 of the starting material in the form of the carbonyl carbon atom. The presence of an additional product, carbon monoxide, was inferred by a positive test using a detector we have employed previously.[1]

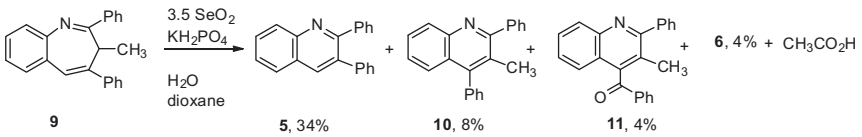
Schemes 2 and 3 show the contrast between the reactivity of benzazepines **1** and **9**. While both apparently undergo initial oxidation primarily at C3, the methyl group of **9** changes the result from rearrangement (**1** → **6**) to fragmentation (**9** → **5** + CH_3CO_2H). And, like the reaction from Scheme 1 employing NBS, both reactions from the current work give products from initial oxidation of C5 (**2**, **7**, **8**, **10**, and **11**). Scheme 4 shows possible mechanisms for formation of quinolines **5** and **6**, starting with C3 oxidation of benzazepines **1** and **9**.

Selenium dioxide is first converted to the actual oxidant, selenous acid, by initial reaction with water. Intermediate **12** is the result of the well-documented allylic oxidation procedure.[7] Electrocyclization, which is a well-known process for analogous substituted benzazepines,[1] then occurs to give cyclopropanes **13** or **14**. From here, product formation is determined by the presence of the methyl group. Unlike cyclopropane **14**, **13** has the option of forming cyclopropanone **15** by loss of elemental selenium (observed in the crude) and water. This kind of process involving loss of selenium and water has been proposed for the last step in the oxidation of ketones to 1,2-diketones.[8] Cyclopropanone **15** can either rearrange in the manner indicated by the arrows, giving ketone **6**, or it can fragment with loss of carbon monoxide,[1] giving quinoline **5**.

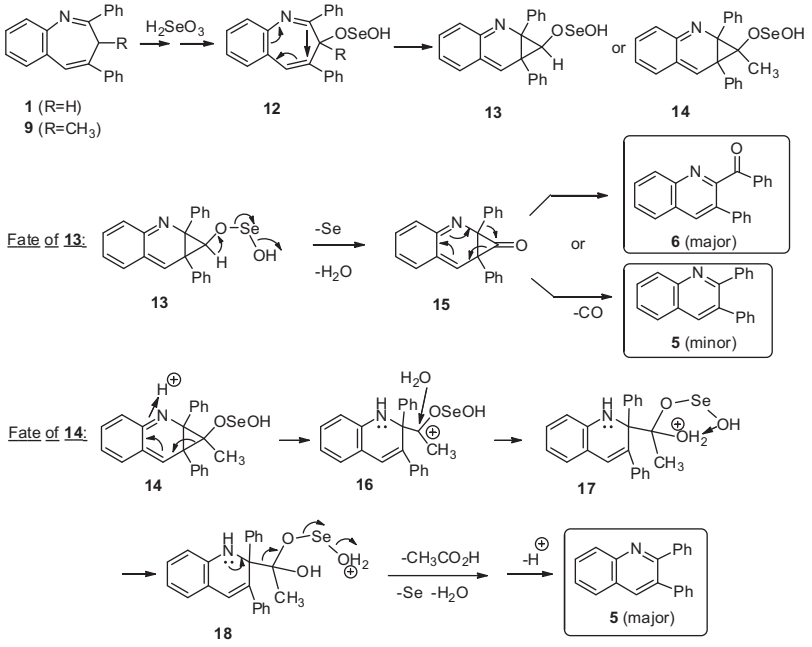
Cyclopropanes like **13** and **14** would be highly sensitive to the acidic conditions of the reaction mixture. Since **14** cannot give a ketone analogous to **13**, it is possible that the cyclopropane ring undergoes acid-catalyzed rupture instead, giving cation **16**. This could be attacked by water, giving cation **17**; a proton is then transferred, giving intermediate **18**. The driving force for aromatization then causes ejection of acetic acid—detection of which we have noted above—elemental selenium, and water. Loss of a proton then finally yields the major product from benzazepine **9**, quinoline **5**.

Formation of quinoline products **2, 10** and **11**, furan **7**, and diselenide **8** requires initial oxidation of C5 of benzazepines **1** and **9**, which seems unlikely, as C5 is not allylic. Thus, it is postulated that benzazepines **1** and **9** first partially isomerize to their 5*H* isomers **19** and **20**, respectively (Scheme 5), by an acid-catalyzed rearrangement we have documented for benzazepine **1**.[9] 5*H*-benzazepines **19** and **20** are then oxidized by selenous acid to intermediates **21** and **22**, as in Scheme 4 for **12**. Electrocyclization then gives cyclopropanes **23** and **24**. These give quinolines **2** and **10** by a process analogous to **13** → **5** in Scheme 4.

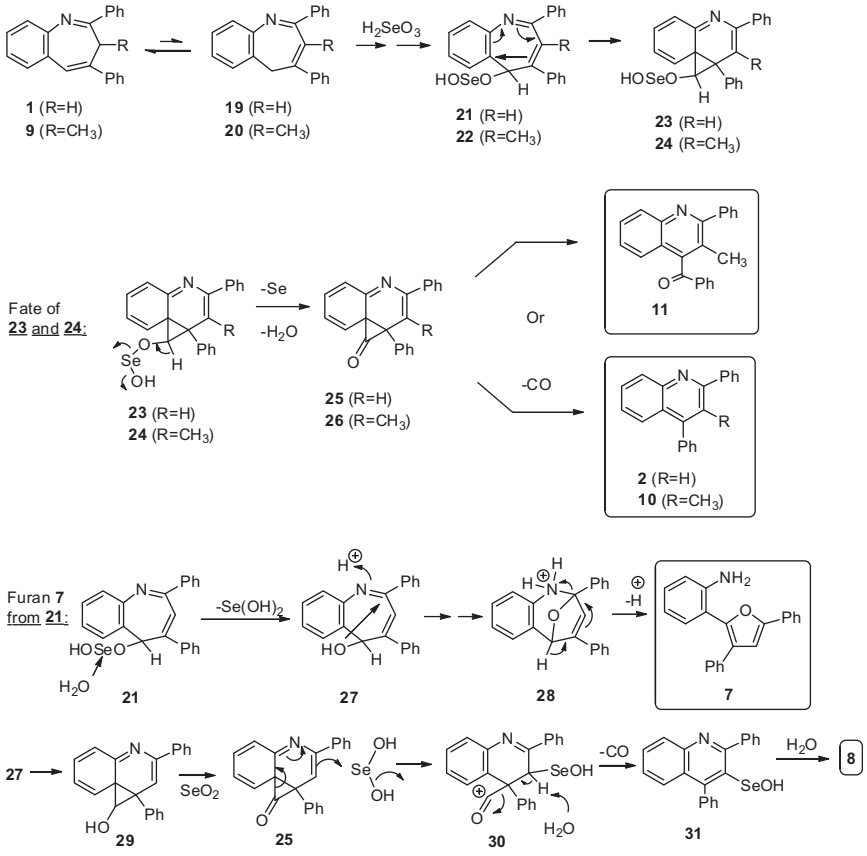
Production of **11** (4%) from **26** can be rationalized similar to that of the rearrangement of **15** to **6**. Surprisingly, we have also verified formation of **6** (4%) from the oxidation of **9**. This may involve demethylation of intermediate **14** to **15** by SeO_2 before converting to **6**. Oxidative demethylation in the presence of SeO_2 has been previously noted.[10] Formation of the diselenide **8** (16%) and furan **7** (6%) could occur from the same intermediate **27**. Before electrocyclization, attack of water on the selenium atom of **21** would result in loss of $Se(OH)_2$ and production of allylic alcohol **27**. This process is analogous to the last step of the well-known allylic oxidation procedure.[7] Protonation of the nitrogen atom of the imino group followed by intramolecular attack of the hydroxyl group would give tricycle **28**, after transfer of a proton from the oxygen atom to the nitrogen atom. Furan formation is completed by



Scheme 3. Oxidation of benzazepine **9** with excess SeO_2.



Scheme 4. Mechanisms rationalizing the formation of products from **1** and **9**, with initial oxidation of C3.



Scheme 5. Mechanisms rationalizing formation of the minor products with initial oxidation of C5.

cleavage of a C–N bond, and loss of a proton. To make **8**, intermediate **27** first undergoes electrocyclization to give **29** followed by oxidation to **25**. Further reaction with $Se(OH)_2$ gives the reactive intermediate **30** which aromatizes and loses CO to give **31**. In the presence of water, intermediate **31** undergoes disproportionation to the diselenide **8**.[11]

We have shown that SeO_2 oxidation of benzazepines **1** and **9** provides quinoline derivatives by both rearrangement and

fragmentation. Unlike our previously reported oxidation of **1** with NBS, where initial oxidation of C3 followed by fragmentation was the exclusive outcome, SeO_2 gives products of both rearrangement and fragmentation after first oxidation of either C3 or C5. The major product, 2-benzoylated quinoline **6**, is the result of C3 oxidation followed by rearrangement accompanied by phenyl migration; C3 ends up as part of a carbonyl group in the quinoline product. The presence of a methyl group at C3 in the starting material again gives primarily initial C3 oxidation, followed this time by expulsion of C3 in the form of acetic acid after ring-contraction, resulting in quinoline **5** as the major product. Minor but appreciable amounts of quinolines derived from initial oxidation of C5 in both benzazepines **1** and **9** are the result of isomerization of these 3*H* benzazepines to their less stable 5*H* forms, before oxidation occurs.

Typical experimental procedure

In a typical experiment, benzazepines **1** or **9** (1 equiv), SeO_2 (1.7 equiv for **1** and 3.5 equiv for **9**), and catalytic amount of KH_2PO_4 in water were dissolved in dioxane and heated (90–95 °C for **1**, 110 °C for **9**) for 18 h. After cooling, elemental Se was filtered and the yellow mixture was extracted with aqueous $NaHCO_3$, saturated brine, and dried over $MgSO_4$. Rotary evaporation gave a crude product which was purified by radial chromatography (silica gel, 2% EtOAc/hexane). All new compounds were confirmed by X-ray or detailed spectral data, and known compounds were compared with the spectra of authentic compounds. See SI for experimental details.

Acknowledgements

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Supplementary data

Supplementary data (X-ray crystal structure for **6** (Fig. S1), **7** (Fig. S2), **8** (Fig. S3), spectroscopic data (^{1}H NMR, ^{13}C NMR) for compounds **6**, **7**, **8** and **11**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.094.

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