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Tandem ring-contraction/decarbonylation of 2,4-diphenyl-3*H*-1-benzazepine to 2,4-diphenylquinoline

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ABSTRACT

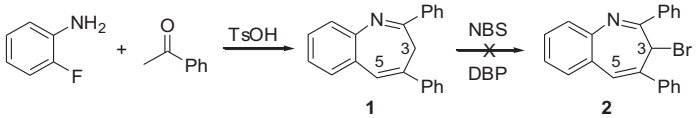
Attempted free-radical bromination of 2,4-diphenyl-3*H*-1-benzazepine (**3**) with NBS led to an unusual ring-contraction reaction, giving rise to 2,4-diphenylquinoline (**5**) in high yield. This is a convenient path for the synthesis of a quinoline in one step from the easily accessible 1-benzazepine. We have elucidated the mechanism of ring-contraction reaction using ^{13}C-labeled and deuterated benzazepines, and DFT calculations. There is strong experimental evidence that the departing carbon atom is initially part of a reactive intermediate dibromomethyl cation, which leads to methyl formate upon reaction with methanol. In the absence of methanol, water can complete the ring-contraction. In this case, the departing carbon atom is in the form of carbon monoxide.

1. Introduction

We have reported a synthesis of 2-aryl-3*H*-1-benzazepines such as **1**, in one step from 2-haloanilines and acetophenone derivatives (Scheme 1).[1] The impetus for that study was the possibility of new and efficient preparations of biologically active 1-benzazepines,[2] which have the same framework as **1**, but have a higher level of saturation. In an effort to functionalize C-3, benzazepine **1** was treated with 1 equiv of NBS and a small amount of the free-radical initiator dibenzoyl peroxide (DBP), in refluxing chloroform. Instead of the expected bromobenzazepine **2**, quinoline **4** was isolated (Scheme 2). This ring-contraction with loss of a carbon atom may be related to conversion of 3*H*-azepines to pyridines[3] and 1*H*-benzazepines to isoquinolines.[4] However, in those studies the fate of the missing carbon atom was not ascertained, thus the intimate mechanistic details were not soundly established. This paper describes the results of our investigation on the fate of the missing carbon and the theoretical calculations to support the proposed mechanistic path for the ring-contraction reaction.

2. Result and discussion

When the benzazepine **1** was treated with 2 equiv of NBS with a catalytic amount of DBP, ring-contraction proceeded very well—quinolines **4**,[5] **6**,[6] and **8** were isolated for a total of 92% yield, and the structures were confirmed by NMR spectra and HRMS. The structure of **6** was also confirmed by an X-ray crystal structure. We rationalize the formation of **6** and **8** by reaction of **4** with NBS, as



1 **2**

Scheme 1. Previously published synthesis of benzazepine **1** and attempted bromination.

bromination of quinoline derivatives with NBS is a known reaction.[7] It has also been suggested[8] that the quinoline–bromine complex is probably the source of the electrophile for ring

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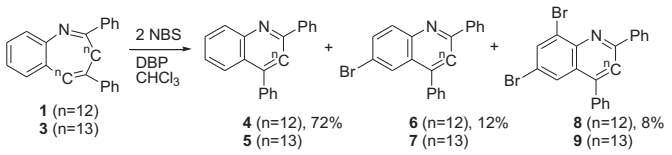


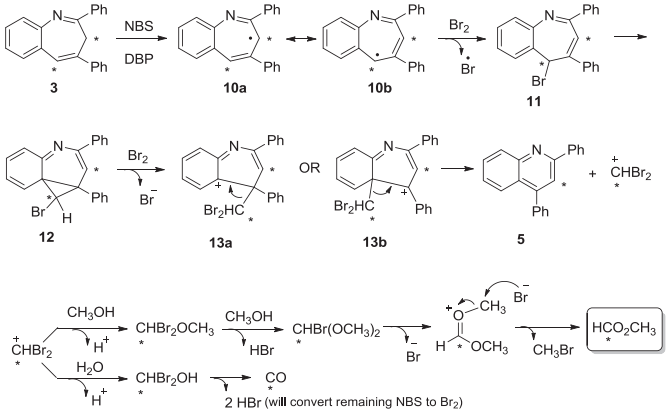
Scheme 2. Ring-contraction of unlabeled and labeled benzazepines, giving quinoline derivatives.

bromination of an uncomplexed quinoline like **4**, which leads to **6**. Similarly, dibromination leading to **8** would be facilitated by the quinoline–bromine complex of **6** with the uncomplexed quinoline **6**.

Bromination of **1** with Br_2 on the other hand, produced a complex mixture, affording quinolines **4**, **6**, and **8**, in poor yields: 10, 3.6, and 2.3%, respectively.

We then performed the important control experiment of leaving out the DBP initiator, which resulted in production of quinoline **4** in less than 10% yield. This establishes that at least part of the mechanism must be of the free-radical type. In order to find a product containing the missing carbon atom, we prepared doubly labeled benzazepine **3** from 2-fluoroaniline and acetophenone-β-^{13}C. The assumption here is that C-5 could be the carbon atom that is lost, and having it labeled would make it easier to find. Consistent with the mechanism we reported earlier,[1] the labels ended up at C-3 and C-5 in the benzazepine. Treatment of labeled benzazepine **3** with NBS led to the ejection of one of the labeled carbon atoms (presumably C-5), while the other labeled carbon atom remained to give products **5**, **7**, and **9**. We eventually found the 'missing' carbon atom to be the carbon atom in carbon monoxide. The series of experiments leading to this will be described below.

A mechanism, which fits all the data given above, and that to be given, is applied to doubly labeled benzazepine **3** in Scheme 3 (labels are indicated by asterisks). Resonance-stabilized radicals **10a** and **10b** are produced as intermediates in free-radical bromination with part of the first equivalent of NBS. Reaction of **10b** with bromine, which is produced from the conversion of NBS by HBr, and is the actual species that brominates,[9] yields monobromide **11** and the chain-carrying bromine radical.



Scheme 3. Mechanism for ring-contraction of benzazepine **3**, and the fate of the dibromomethyl cation in the presence of either MeOH or water.

We note that bromination of C-3 could actually be the first step of the mechanism. The Mulliken spin densities using the Gaussian 09 program (B3LYP method and 6-31G(d) basis set[10]) for the radical **10a**/**b** revealed the values of the spin density of 0.055, 0.980, and 0.036 at N-1, C-3, and C-5, respectively. This implies that bromination occurs mainly at C-3 to yield **2**. However, additional calculations show that the 3-bromobenzazepine **2** can isomerize to its 5-bromo isomer **11**, which ultimately results in quinoline **5** (see Scheme S1 and its accompanying discussion in Supplementary data).

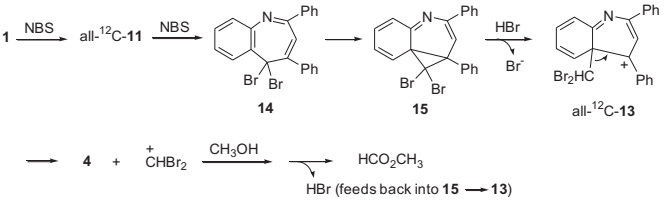
Since we find that use of 2 equiv of NBS maximizes the yield, we first considered that a second bromination at C-5 could have occurred, followed by electrocyclization. In this case, expulsion of dibromocarbene would rationalize formation of quinoline **5**. However, we observed no trapping of the putative carbene with *trans*-stilbene, and did not detect any carbene dimerization products. As an alternate method to trap the carbene, excess methanol was added to the reaction containing the labeled benzazepine **3** and NBS, under scrupulously dry conditions, with the expectation of finding the trapping product dibromomethoxymethane.[11] Surprisingly, aside from labeled quinoline **5**, we detected methyl formate, which contained the label in the carbonyl group. The presence of the labeled methyl formate was initially deduced by the ^{13}C NMR data (161.6 ppm for the C=O) of the reaction crude in an NMR tube.

Because of the difficulties associated with detection and isolation of methyl formate and methyl bromide, the putative byproduct we propose for the very last step producing methyl formate, we ran the reaction in the presence of EtOH. The result was production of ^{13}*C*-labeled ethyl formate and ethyl bromide, both of which were isolated and identified by their NMR spectra.

Although formation of the ^{13}*C*-labeled formate ester can support the presence of a carbene, the failure to trap the carbene with *trans*-stilbene makes this route implausible. Thus, we considered that the production of quinoline and methyl formate did proceed through monobromide **11**, and could have proceeded through a geminally dibrominated derivative, but not with expulsion of a carbene. Evidence to be given later will rule out the intermediacy of a geminally dibrominated benzazepine.

We rationalize the formation of methyl formate in Scheme 3. Monobromide **11** undergoes electrocyclization, giving cyclopropane **12**. Assuming that the free-radical bromination giving **11** did not finish completely at this stage, there will be some bromine available to rupture the cyclopropane ring in either way, giving cation **13a** or **13b**. Loss of dibromomethyl cation completes the ring-contraction, giving quinoline **5**. The cation is trapped by methanol, and subsequent reaction with more methanol gives bromodimethoxymethane. Loss of a bromide ion followed by nucleophilic attack on the oxonium ion provides methyl formate. A similar nucleophilic attack on an oxonium ion was also noted by Grob and Freiberg.[12]

The cation **13a** or **13b**, which produces dibromomethyl cation and 2,4-diphenylquinoline does not necessarily have to arise from bromine-induced rupture of cyclopropane **12**, as shown in Scheme 3. The data we have presented so far are also consistent with initial dibromination giving **14** and acid-catalyzed conversion of a dibrominated cyclopropane intermediate, **15** (Scheme 4). Substitution of CD_3OD for CH_3OH would allow the processes of Schemes 3 and 4 to be differentiated. If production of methyl formate were to occur as in Scheme 3, then presence of CD_3OD should not result in incorporation of deuterium at the carbon atom of the carbonyl



Scheme 4. Hypothetical ring-contraction reaction mechanism, if dibromination had first occurred.

group. On the other hand, if the dibromocyclopropane **15** was an intermediate, then presence of CD_3OD should result in a significant level of deuteration at the carbonyl group of methyl formate. This is because most of the acid would be in the form of DBr, split off in the last steps.

In the event, benzazepine **3** was treated with 2 equiv of NBS, a small amount of DBP, and excess CD_3OD, in chloroform as before. The result was production of methyl formate, which had incorporated no detectable deuterium at the carbonyl group carbon atom (Fig. 1, bottom trace). This appears to rule out dibromination of benzazepine **1** as a possibility. In order to verify this in the 'reverse' sense, we synthesized benzazepine **1**, selectively deuterated at C-3 and C-5 (65% deuteration as analyzed by ^1H NMR), by treating acetophenone-(methyl-d_3) with deuterated 2-fluoroaniline (ND_2). The ring-contraction of this deuterated benzazepine in the presence of excess CH_3OH produced DCO_2CH_3 as evidenced by the splitting of the signal due to the carbonyl carbon atom (Fig. 1, top trace). The peak marked DCO is a triplet with a coupling constant of 34.6 Hz and a 0.20 ppm upfield shift from the HCO singlet. This result, consistent with the observed ring-contraction of ^{13}C-labeled benzazepine **3** in the presence of CD_3OD, also supports formation of the monobromocyclopropane intermediate **12**. In short, the hydrogen atom attached to the carbon atom of the carbonyl group in methyl formate has to come from the intermediate itself and not from the alcohol additive.

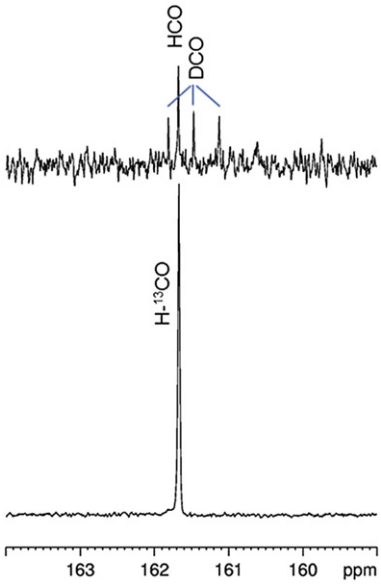


Fig. 1. ^{13}C NMR spectrum of the crude ring-contraction reaction mixture. *Top trace*: using deuterated **1** and CH_3OH. *Bottom trace*: using **3** and CD_3OD.

With the mechanism established for the process containing methanol, the question remained: how does ring-contraction occur in its absence? First, we found that the reaction does not proceed well under scrupulously anhydrous conditions in the absence of CH_3OH. The reaction was carried out in a sealed dry NMR tube in dry $CDCl_3$, and a complex mixture of products resulted, without formation of quinoline derivatives. However, if the reaction is run in glassware that has not been flame-dried, and no special pains are taken to exclude atmospheric moisture, then the reaction proceeds well. We had originally assumed that, in the absence of MeOH, if adventitious water was to complete the ring-contraction process, we would find the departing carbon atom in the carbonyl group of formic acid. Nonetheless, after the work-up, we never detected formic acid either in the organic or the aqueous layer. An alternative is the loss of a gaseous molecule carrying the missing carbon atom. It has been reported that photochemical dehalogenation of bromoform with water produces carbon monoxide and HBr via the $CHBr_2(OH)$ intermediate.[13] Since the $CHBr_2$ cation depicted in Scheme 3 may form the same intermediate by reaction with water, it is conceivable that carbon monoxide is produced during the ring-contraction. To prove this, we set up the reaction with an added CO detector tube. We observed a strong positive test (color change from yellow to gray) to indicate that indeed CO was being generated (Fig. 2). Because the ring-contraction was *not* carried out under scrupulously dry conditions, generation of CO, at first slow, was observed in the detector. As the reaction continued for several more hours, the darkening of the color in the detector tube became more visible. After 18 h of reflux, water was added through a syringe and the tube became completely dark as more CO was generated. The darkening of the detector tube (described in the vendor's manual) is a result of reduction of the palladium complex $Na_2Pd(SO_3)_2$ by CO to metallic Pd, CO_2, SO_2, and Na_2SO_3. Thus, in the absence of CH_3OH, adventitious water is required for completion of the ring-contraction and results in formation of carbon monoxide.

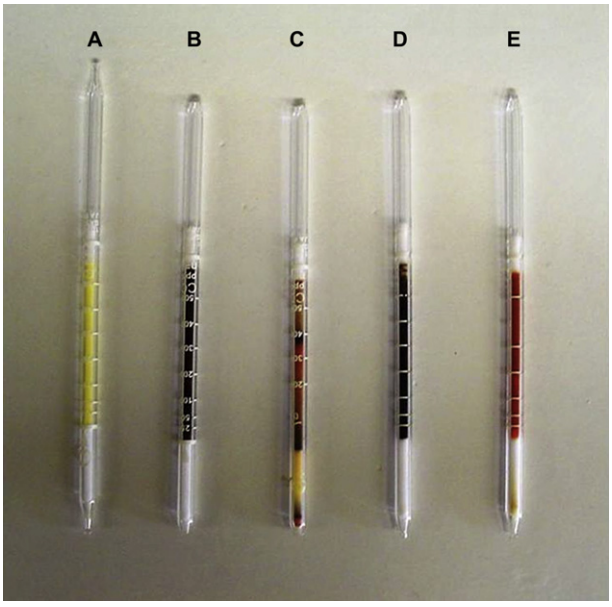


Fig. 2. The effect of released gases on the CO sensor during the ring-contraction reaction. Tubes *A* and *B* indicate reference colors for the unexposed and CO-exposed sensors. Tube *C* shows slow discoloration to gray (due to CO) after 18 h of reflux. Tube *D* shows substantial release of CO after addition of water. Tube *E* captures the effect of refluxing a mixture of HBr, NBS, benzoyl peroxide, and bromine, without benzazepine, for 3 h to rule out the possibility of a false positive (absence of a gray color). The reddening of tube E is due to Br_2.

The mechanism of Scheme 3 has two components, which utilize the bromine produced from 2 equiv of NBS in different ways. The first component is of the free-radical type, giving monobromide **11** and succinimide by-product. Before this process is complete, the bromine begins to convert cyclopropane **12** into cation **13a** or **13b**. This is the start of the second component, an ionic chain reaction. Methyl formate is eventually produced, with loss of HBr along the way. Some of this HBr will react with more NBS, giving more bromine (and more succinimide by-product), which then converts more cyclopropane **12**. Once the whole reaction is complete, there will be 2 equiv of succinimide present, which we have detected by its NMR spectrum, 1 equiv of CH_3Br, and a little less (allowing for the bromine atoms in bromoquinolines **7** and **9**) than 1 equiv of HBr. We infer the presence of HBr by a drop in the pH of the reaction mixture we observe as time passes.

3. Conclusion

In summary, reaction of benzazepine **1** with NBS gave the expected product of allylic bromination only as an intermediate in a complex series of transformations. The result was formation of 2,4-diphenylquinoline by ring-contraction with loss of one of the carbon atoms and two of the hydrogen atoms. When methanol was added to the reaction mixture, the carbon atom was found to be in the carbonyl group of methyl formate. Several possible mechanisms were ruled out by using either doubly ^{13}C-labeled or deuterated benzazepines, in the presence of either methanol-d_4 or methanol, respectively. These experiments strongly suggested the intermediacy of the dibromomethyl cation, leading eventually to methyl formate upon reaction with methanol. In the absence of methanol, adventitious water reacts with the ejected dibromomethyl cation to give carbon monoxide. This ring-contraction provides a convenient method to synthesize substituted quinolines.

4. Experimental section

4.1. General

All ^1H and ^{13}C NMR spectra were referenced to TMS and recorded on a 400 MHz spectrometer. To observe the C–D coupling, the experimental parameters are adjusted to a delay time of 10 s. Gastec Detector Tube, no. 1La Carbon Monoxide 25–500 ppm (scale range) was used to detect CO. HRMS data were obtained using ESI-TOF method.

*Collection and reduction of X-ray data for (**6**).* A crystal ($0.30\times0.07\times0.07$ mm) of $C_{21}H_{14}BrN$ (***6***) was cut from a large cluster of crystals and mounted on a glass fiber. It was transferred to a Bruker Kappa Apex II diffractometer for the collection of diffraction data. Diffraction data for (**6**) indicated: orthorhombic symmetry and systematic absences consistent with space group $Pca2_1$ and $Pbcm$. $Pca2_1$ was used for the solution and refinement of the structure based on E statistics. The Flack parameter refined to 0.003(12). The supplementary crystallographic data for this compound can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif with the access number 901542.

Computational methods. Optimizations were performed with Gaussian 09[14] using the B3LYP method and a 6-31G(d) basis set. The uB3LYP/6-31G(d) was employed to study radical **10**. This level of DFT calculation is in agreement with the experimentally observed product **4**. We also calculated harmonic vibrational frequencies to confirm whether the optimized structures were minima or transition states. The intrinsic reaction coordinate (IRC) calculations were conducted to verify the reaction pathways involving **TS-I** and **TS-II** (Scheme S1 of Supplementary data).

4.2. Synthesis of 2,4-diphenylquinoline (4), 6-bromo-2,4-diphenylquinoline (6), 6,8-dibromo-2,4-diphenylquinoline (8)

A solution of benzazepine **1** (100 mg, 0.34 mmol), NBS (120 mg, 0.67 mmol, recrystallized from $CHCl_3$), and a catalytic amount of dibenzoyl peroxide (~10 mg) in 8 mL of distilled $CHCl_3$ was heated at reflux for 18 h under N_2. After cooling, the yellow mixture was extracted with 10 mL of dilute aqueous $Na_2S_2O_3$, 10 mL of saturated NaCl, and dried over $MgSO_4$. Rotary evaporation gave a crude product (0.250 g), which was purified by radial chromatography (silica gel, hexane) to give, in order of elution, 12.0 mg (8%) of dibromide **8**, 15.2 mg (12%) of monobromide **6**,[6] and 68.8 mg (72%) of quinoline **4**.[5] Compounds **4** and **6** have very close R_f values.

*4.2.1. Compound **6**.* ^1H NMR ($CDCl_3$, 400 MHz) δ 8.11 (2H, dt, J=6.94, 1.57 Hz), 8.03 (1H, d, J=9.04 Hz), 7.96 (1H, d, J=2.18 Hz), 7.76 (1H, s), 7.72 (1H, dd, J=9.04, 2.18 Hz), 7.52–7.38 (8H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5(q), 146.7 (q), 145.7 (q), 137.5 (q), 136.0 (q), 133, 131.9, 129.6, 129.5 (2C), 128.9 (2C), 128.9 (2C), 128.7, 127.8, 127.5 (2C), 125.3 (q), 118.7 (q), 118.4. HRMS calcd for $C_{21}H_{14}NBr+H$ m/z 360.0388, found 360.0401; mp 151–153 °C.

*4.2.2. Compound **8**.* ^1H NMR ($CDCl_3$, 400 MHz) δ 8.25 (2H, dt, J=6.85, 1.58 Hz), 8.10 (1H, d, J=2.11 Hz), 7.90 (1H, d, J=2.11 Hz), 7.83 (1H, s), 7.53–7.42 (8H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.2 (q), 149.1 (q), 144.5 (q), 138.6 (q), 137.4 (q), 136.0, 130.1, 129.5 (2C), 129.0 (2C), 128.9 (2C), 127.8 (q), 127.7 (2C), 127.0 (q), 127.6 (2C), 120.3, 119.6 (q). HRMS calcd for $C_{21}H_{13}NBr_2+H$ m/z 439.9474, found 439.9475; mp 154–155 °C.

4.3. Synthesis of ^{13}C-labeled benzazepine 3, and quinolines 5, 7, and 9

^{13}C-labeled benzazepine at positions 3 and 5 (**3**) was obtained by treating methyl-^{13}C-labeled acetophenone and 2-fluoroaniline according to the reported procedure.[1] Compound **3** was converted to **5**, **7**, and **9** using the same procedure described earlier for unlabeled benzazepine **1**.

*4.3.1. Compound **3** (labeled at C-3 and C-5).* C-3 and C-5 are observed at 33.88 and 126.86 ppm, respectively. The methylene protons at C-3 are split as broad doublets centered at 3.33 ppm with J_{C-H}=132.9 Hz. The proton attached to C-5 appears as a doublet of doublets centered at 8.02 ppm. It is coupled to C3 and C5 with J_{C-H} values of 156.2 and 7.79 Hz. HRMS calcd for $C_{22}H_{17}N+H$ m/z 298.1506, found 298.1495.

*4.3.2. Compound **5**.* Labeled C-3 is observed at 119.41 ppm. The proton attached to C-3 appears as a doublet centered at 7.75 ppm with J_{C-H}=161.3 Hz. HRMS calcd for $C_{21}H_{15}N+H$ m/z 283.1316, found 283.1308.

*4.3.3. Compound **7**.* Labeled C-3 is observed at 120.07 ppm. The proton attached to C-3 appears as a doublet centered at 7.76 ppm with J_{C-H}=160.8 Hz. An important feature is the singlet at 7.97 ppm for the proton attached to C-5. The coupling pattern observed in this ring is important for assigning the compound as the 6-bromo and not the 5-bromo. The 5-bromo adduct would have made all protons in this ring appear as multiplets. HRMS calcd for $C_{21}H_{14}NBr+H$ m/z 361.0421, found 361.0412.

*4.3.4. Compound **9**.* Labeled C-3 is observed at 120.35 ppm. The proton attached to C-3 appears as a doublet centered at 7.84 ppm with J_{C-H}=162.0 Hz. An important feature is a small *meta* coupling in the proton spectrum due to protons attached to C-5 and C-7. HRMS calcd for $C_{21}H_{13}NBr_2+H$ m/z 440.9507, found 440.9514.

4.4. Preparation of deuterated benzazepine and variation of the reaction with added MeOH/CD_3OD

Deuterated 2-fluoroaniline (ND_2) was synthesized by adding D_2O to 2-fluoroaniline and heating the mixture to 60 °C for 24 h. The enrichment was at best 97% and did not increase on longer heating. Deuterated benzazepine (65% enriched at positions 3 and 5) was synthesized by treating deuterated 2-fluoroaniline (ND_2) with methyl-deuterated acetophenone. To the labeled benzazepine **3** (50 mg, 0.17 mmol) was sequentially added, a catalytic amount of dibenzoyl peroxide (~5 mg), $CDCl_3$ (3 mL), MeOH (0.4 mL), and NBS (60 mg, 0.33 mmol, recrystallized from $CHCl_3$), and the reaction mixture was heated in an NMR tube at 70 °C for 18 h under N_2. The work-up was performed as before. The reaction was

repeated by replacing **3** with deuterated benzazepine and also by replacing CH_3OH with CD_3OD.

Acknowledgements

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Supplementary data

X-ray crystal structure for **6** (Fig. S1), Mulliken atomic spin densities for **10**, chemical shifts for compounds **4**, **6**, and **8** (Table S1), spectroscopic data (^{1}H NMR, ^{13}C NMR) for compounds **3**, **5**–**9**, the CIF file for **6**, calculated energies for the ring-contraction pathway (Scheme S1) and a discussion of Scheme S1. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.10.052.

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