Facile Ring Opening of Tertiary Aminocyclopropanes by Photooxidation

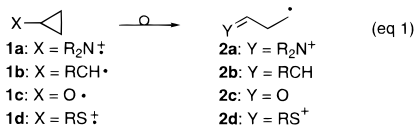
Jinhwa Lee, Jong Sun U, Silas C. Blackstock, and Jin Kun Cha*

Department of Chemistry, University of Alabama Tuscaloosa, Alabama 35487

Received June 26, 1997

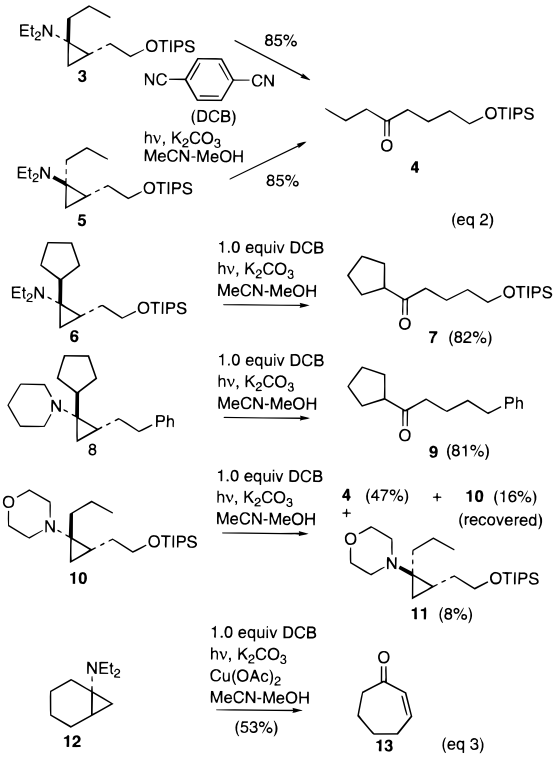
Tertiary aminocyclopropanes, which were prepared in good yield by the Simmons−Smith cyclopropanation of enamines, have been shown to resist ring cleavage by acids, bases, or electrophiles. Accordingly, ring opening was reported to require high-temperature (150−170 °C) thermolysis.[1] A new, efficient synthesis of tertiary aminocyclopropanes,[2,3] as well as other electron-donor substituted cyclopropanes,[4] prompted us to search for a facile ring cleavage under neutral conditions. Herein we report a convenient solution by employing the photosenzitized oxidative ring opening of tertiary aminocyclopropanes.

Our choice of a cyclopropylamine cation radical (**1a**)-based approach was initially made by analogy to the well-known, rapid rearrangement of cyclopropylcarbinyl radical **1b** to homoallyl radical **2b** (eq 1).[5] An isoelectronic cyclopropoxy radical **1c**,



which is conveniently generated by one-electron oxidation (with oxidants such as Fe^{+3}, Mn^{+3}, or Cu^{+2}) of cyclopropanol, is also known to readily afford the ring-opened, carbon-centered radical **2c**.[6] In addition, related ring cleavage of cyclopropyl sulfide cation radical **1d** has been reported.[7] Furthermore, analogous ring opening of the cyclopropylamine radical cation **1a** has been implicated in the inactivation by cyclopropylamines of cytochrome P-450 and monoamine oxidase[8] and was subsequently generated by radiolysis of the parent aminocyclopropane.[9,10] Despite the well-established synthetic potential of aminium radicals,[11] little work appeared on ring cleavage initiated by nonenzymic oxidation at nitrogen of aminocyclopropanes.[12]

As a result of their low ionization and oxidation potentials, tertiary amines have been widely utilized as efficient electron donors in electron transfer processes with excited states of various organic substrates. The photoinduced one-electron oxidation thus allows a convenient method for generating an amine radical cation. In a typical experiment, the 1,4-dicyanobenzene (DCB) photosensitized oxidation of the cyclopropylamine **3**[3] was performed in a deaerated solution in MeCN or 10:1 MeCN/MeOH containing K_2CO_3 by irradiation (254 or 300 nm), and ketone **4** was isolated in 85% yield as the sole product after aqueous workup (eq 2).[13,14] Similarly, the diastereomeric cyclopropylamine **5** also afforded the ketone **4** under identical conditions, but the reaction rate was considerably slower. As can be seen from additional examples in eq 3, ring



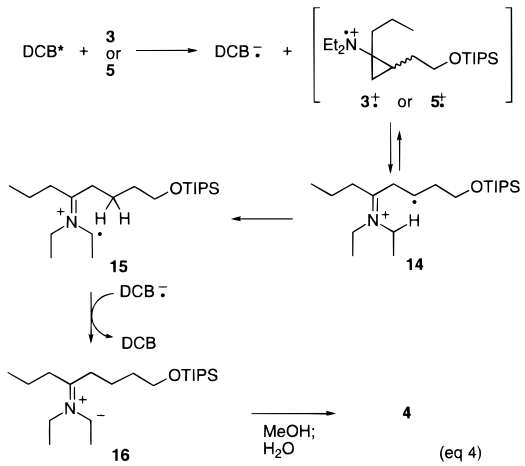
opening of the tertiary aminocyclopropanes initiated by the photosensitized oxidation appears to be general. However, identical application to dialkylamino[4.1.0]bicycloheptanes was unsuccessful. For example, most of **12** was recovered unchanged under the same conditions. Although the addition of $Cu(OAc)_2$ provides a ring-opened product, 2-cycloheptenone (**13**), at present this reaction suffers from low conversion [53% yield based on the recovered (68%) starting material], and an improvement in yield requires additional studies.

Mechanistically, the overall transformation can best be rationalized by initial formation of the tertiary aminium radical

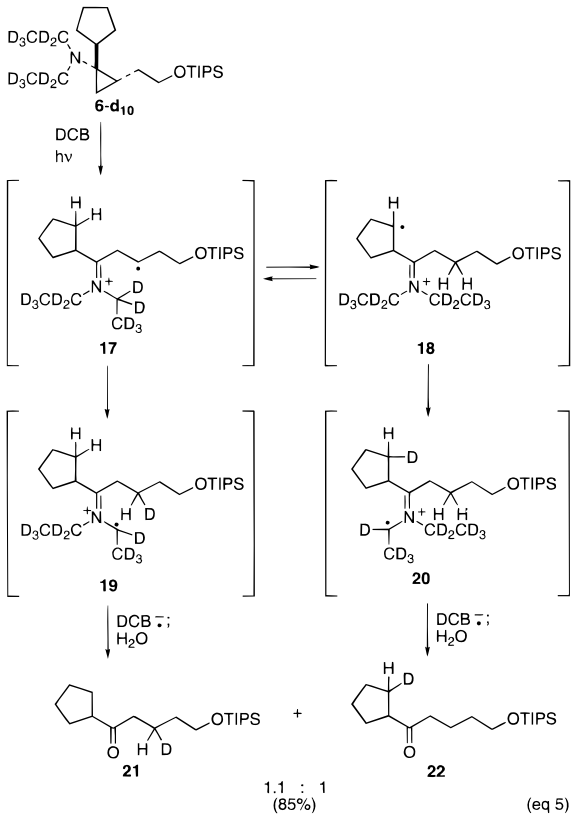
(1) Kuehne, M. E.; King, J. C. *J. Org. Chem*. **1973**, *38*, 304.
(2) Chaplinski, V.; de Meijere, A. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 413.
(3) Lee, J.; Cha, J. K. *J. Org. Chem*. **1997**, *62*, 1584.
(4) (a) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc*. **1996**, *118*, 291. (b) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc*. **1996**, *118*, 4198. (c) Lee, J.; Kim, Y. G.; Bae, J.; Cha, J. K. *J. Org. Chem*. **1996**, *61*, 4878 and references cited therein. See also: (d) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc*. **1995**, *117*, 9919. (e) Lee, J.; Cha, J. K. *Tetrahedron Lett*. **1996**, *37*, 3663. (f) U, J. S.; Lee, J.; Cha, J. K. *Tetrahedron Lett*. **1997**, *38*, 5233.
(5) (a) Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc*. **1976**, *98*, 7024. (b) Kochi, J. K.; Krusic, P. J.; Eaton, D. R. *J. Am. Chem. Soc*. **1969**, *91*, 1877.
(6) (a) For a general review of cyclopropanol, see: Gibson, D. H.; DePuy, C. H. *Chem. Rev*. **1974**, *74*, 605. See also: (b) Schaafsma, S. E.; Molenaar, E. J. F.; Steinberg, H.; de Boer, Th. J. *Recl. Trav. Chim*. **1967**, *86*, 1301. (c) Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem*. **1976**, *41*, 2073.
(7) Takemoto, Y.; Ohra, T.; Koike, H.; Furuse, S.; Iwata, C.; Ohishi, H. *J. Org. Chem*. **1994**, *59*, 4727.
(8) See, inter alia: (a) Bondon, A.; Macdonald, T. L.; Harris, T. M.; Guengerich, F. P. *J. Biol. Chem*. **1989**, *264*, 1988. (b) Hanzlik, R. P.; Tullman, R. H. *J. Am. Chem. Soc*. **1982**, *104*, 2048. (c) Silverman, R. B. *J. Biol. Chem*. **1983**, *258*, 14766. (d) Pirrung, M. C. *J. Am. Chem. Soc*. **1983**, *105*, 7207.
(9) Qin, X.-Z.; Williams, F. *J. Am. Chem. Soc*. **1987**, *109*, 595.
(10) Cyclopropylaminyl radical is also shown to undergo rapid ring opening: Maeda, Y.; Ingold, K. U. *J. Am. Chem.Soc*. **1980**, *102*, 328. See also: Sutcliffe, R.; Ingold, K. U. *J. Am. Chem.Soc*. **1982**, *104*, 6071.
(11) (a) Nelsen, S. F. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 2, Chapter 21. (b) Chow, Y. L.; Danen, W. C.; Nelsen, S. F.; Rosenblatt, D. H. *Chem. Rev*. **1978**, *78*, 243. (c) Stella, L. *Angew. Chem., Int. Ed. Engl*. **1983**, *22*, 337. (d) Newcomb, M.; Deeb, T. M. *J. Am. Chem. Soc*. **1987**, *109*, 3163. (e) Zhang, X.; Yeh, S.-R.; Hong, S.; Freccero, M.; Albini, A.; Falvey, D. E.; Mariano, P. S. *J. Am. Chem. Soc*. **1994**, *116*, 4211 and references cited therein.
(12) To the best of our knowledge, to date only a single report has appeared on oxidation of cyclopropylamines ($CuCl_2$-catalyzed, with O_2) in modest yields: Itoh, T.; Kaneda, K.; Teranishi, S. *Tetrahedron Lett*. **1975**, 2801.
(13) Aryl-substituted and strained cyclopropanes have been shown to undergo similar photosensitized ring opening reactions via the corresponding cyclopropane radical cations: (a) Rao, V. R.; Hixson, S. S. *J. Am. Chem. Soc*. **1979**, *101*, 6458. (b) Dinnocenzo, J. P.; Simpson, T. R.; Zuilhof, H.; Todd, W. P.; Heinrich, T. *J. Am. Chem. So*c. **1997**, *119*, 987 and references cited therein. (c) Gassman, P. G.; Olson, K. D.; Walter, L.; Yamaguchi, R. *J. Am. Chem. Soc*. **1981**, *103*, 4977.
(14) While the presence of K_2CO_3 was unnecessary, it was added to scavenge any adventitious acidic impurities.

S0002-7863(97)02115-X CCC: $14.00

($\mathbf{3}^{\bullet+}$ or $\mathbf{5}^{\bullet+}$) and $DCB^{\bullet-}$ by photoinduced electron transfer from **3** or **5** to DCB (eq 4). The amine radical cation undergoes either



decay by back electron transfer or ring opening to generate the β-iminium carbon radical **14**. Apparently, ring opening of the cyclopropane in $\mathbf{3}^{\bullet+}$ or $\mathbf{5}^{\bullet+}$ takes place faster than α-CH deprotonation, a well-documented alternate reaction pathway for tertiary aminium radicals.[11] Subsequent hydrogen atom abstraction, followed by aqueous workup, would furnish the observed ring-opened ketone **4**. To probe the source of the H-atom, experiments with **6** were undertaken in the presence of deuterated solvent(s), i.e., CD_3OD and/or CD_3CN: no deuterium incorporation was found in the product **7**. This result indicated that an intramolecular hydrogen transfer occurred to produce a new iminium carbon radical, such as **15**, which would readily undergo reduction by $DCB^{\bullet-}$ to afford the dipole **16** and DCB. Direct evidence for a 1,5-hydrogen transfer was obtained from the isotopically labeled **6** (**6**-d_{10}) (eq 5). Thus,



photolysis under the identical conditions resulted in a ~1.1:1 mixture of **21** and **22**, monodeuterated products of **7**: the ^{13}C NMR spectrum of the products contains triplets at δ 28.6 (J = 19.9 Hz) and 20.0 ppm (J = 19.8 Hz); the ^2H NMR spectrum shows two peaks at 1.72 and 1.66 ppm [reference $CDCl_3$ (7.26 ppm)]; satisfactory nominal [m/z 284 for $C_{16}H_{30}DO_2Si$ ($M^+ -$ *i*-Pr)] and high-resolution mass spectra (calcd for $C_{16}H_{30}DO_2Si$ 284.2156, found 284.2135) were also obtained. Formation of these two products can easily be explained by initial production of **17**, which undergoes the 1,5-hydrogen transfer to afford **18**.[15,16] Subsequent 1,5-deuterium shift would take place readily in these radical intermediates due to the greater stability of the resulting α-iminium radicals **19** and **20**. Finally, reduction by $DCB^{\bullet-}$ (see also **15** → **16**) accounts for another experimental finding that the sensitizer operates catalytically and can be recovered in excellent yield.

With regard to the reaction of the bicyclic cyclopropane **12**, it would be more susceptible than monocyclic compounds (e.g., **3**, **5**, **6**, **8**, and **10**) to ring opening, since this process should be facilitated by relief of the additional ring strain. The surprising lack of the ring-opened product can best be attributed to fast re-closure (see, for example, **14** → $\mathbf{3}^{\bullet+}$ or $\mathbf{5}^{\bullet+}$), where the 1,5-hydrogen transfer is inoperative, rather than potential poor overlap between the amine radical cation and the C−C bond of the cyclopropane ring. Similarly, a low level of conversion in the presence of $Cu(OAc)_2$ is likely due to inefficient trapping of the β-iminium carbon radical by Cu(II), compared to fast ring closure.[17] The reversible nature of $\mathbf{3}^{\bullet+}$ or $\mathbf{5}^{\bullet+}$ ⇄ **14** is confirmed by the oxidation experiment of **10**, where isomerization took place concomitantly.

In summary, cyclopropylamine cation radicals, which are readily prepared by photooxidation of tertiary aminocyclopropanes, undergo facile ring opening, followed by 1,5-hydrogen shift(s), to afford the ring-opened ketones after hydrolysis. This overall transformation allows utilization of aminocyclopropanes as synthetic equivalents of homologous enamines. Moreover, the present work might suggest a significant difference in inhibition of cytochrome P-450 and monoamine oxidase by primary and tertiary aminocyclopropanes, because internal hydrogen transfer would accompany ring opening of the radical cations derived from the latter compounds, but not from the former. Search for a more efficient method for opening tertiary amino[*n*.1.0]bicycloalkanes is currently under way,[17b] along with applications to natural product synthesis.

Acknowledgment. This work is dedicated to Professor Frederick Greene on the occasion of his 70th birthday. We are grateful to the National Institutes of Health (GM35956) for generous financial support and an NIH Research Career Development Award (GM00575 to J.K.C.). We thank Professor Drury S. Caine III for allowing us to use the photolysis apparatus.

Supporting Information Available: A representative photoinduced ring-opening procedure and characterization/spectral data (20 pages). See any current masthead page for ordering and Internet access instructions.

JA972115H

(15) Weaker bond strength of the C−H bond α to the iminium function notwithstanding, **17** → **18** is thought to occur faster than **17** → **19** due to a large primary isotope (k_H/k_D) effect.

(16) For recent examples of intramolecular hydrogen atom transfer, see inter alia: (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in the Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, p 161. (b) Baldwin, J. E.; Adlington, R. M.; Robertson, J. *Tetrahedron* **1989**, *45*, 909. (c) Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc*. **1990**, *112*, 896.

(17) (a) Attempts to trap the β-iminium carbon radical by an external H-atom donor or a halogen source have been uniformly unsuccessful. (b) Subsequently we discovered that the ring-opened, β-iminium carbon radical can be trapped effectively by a tethered olefin by means of 5-exo cyclization, affording an efficient bicyclic annulation: Lee, J.; Cha, J. K. Unpublished results.