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A SIMPLE SYNTHETIC ROUTE TO 2-SUBSTITUTED BICYCLO[1.1.1]PENTANES[1]

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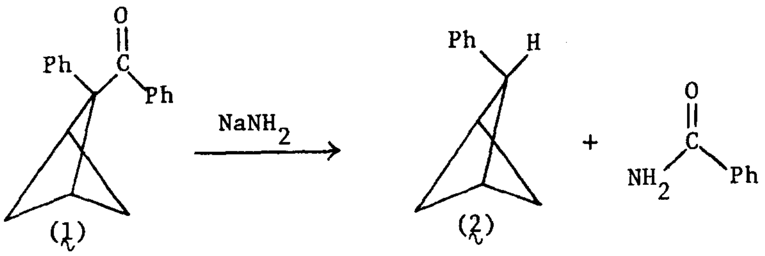
Derivatives of bicyclo[1.1.1]pentane have been synthesized via free radical substitution on the parent hydrocarbon.[2] While this method has represented the best available route to simple mono-substituted bicyclo[1.1.1]pentanes, it suffers in its overall synthetic utility because bicyclo[1.1.1] pentane, itself, is obtainable in only very low yield.[2,3] Moreover, because bridgehead free radical substitution is favored in bicyclo[1.1.1]pentanes over methylene substitution, the method is limited primarily to the preparation of 1-substituted derivatives.

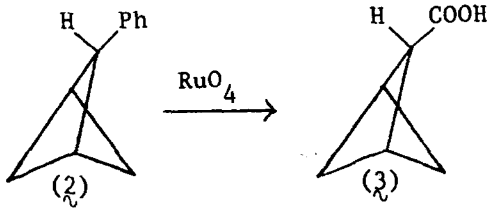
We wish to describe a synthetic route to mono-substituted 2-bicyclo[1.1.1]pentanes which utilizes the Haller-Bauer cleavage[4] of 2-benzoyl-2-phenylbicyclo[1.1.1]pentane (1). The method is simple and convenient, and affords product in high yield. Ketone (1)[31] is easily prepared from 2-hydroxy-2-phenylbicyclo[1.1.1]pentane[3g,j] which is readily available.

When 2-benzoyl-2-phenylbicyclo[1.1.1]pentane (1) is treated with 2 equiv of sodium amide in refluxing benzene, it undergoes cleavage to 2-phenyl-bicyclo[1.1.1]pentane (2) and benzamide. The reaction is facile; vpc analysis shows it to be complete after 5 hr.



The hydrocarbon (2) was isolated in quantitative yield as a colorless, volatile oil. The NMR spectrum (CCl$_4$) of (2) shows the benzyl hydrogen as a doublet at δ3.35, (J=7.0 Hz), and the methylene hydrogens as a doublet of doublets, δ2.10 (J=3.0 Hz, 10.0 Hz, 1H), multiplet δ1.77 (2H), and a doublet of doublets δ1.73 (J=3.0 Hz, 10.0 Hz, 1H). The bridgehead hydrogens appear as a singlet at δ2.68. The IR (CCl$_4$) shows absorptions at 3.35, 7.87, 9.09 and 9.91μ. The mass spectrum gave ($\frac{m}{e}$) 144 M$^+$, 129, 117, 66, 51, and 39 (base peak). The yield of (2) is exceptionally high, in light of the fact that the principal cleavage products from Haller-Bauer reaction of alkyl phenyl ketones are usually alkyl amides. The efficient formation of (2) must reflect a high degree of stability for the 2-phenylbicyclo[1.1.1]pentyl carbanion which is produced.

The phenylbicyclo[1.1.1]pentane (2) was conveniently oxidized with ruthenium dioxide and sodium periodate in methylene chloride-water to bicyclo[1.1.1]pentane-2-carboxylic acid (3) in > 85% yield.



The carboxylic acid (**3**) was obtained as a yellow oil. Its structure is consistent with its spectral characteristics: IR (chloroform) 2.95, 3.41, 5.80μ; NMR ($CDCl_3$) methine δ2.94 (doublet J=7.1 Hz (1H)), methylene δ2.49 (doublet of doublets, J=3.0 Hz, 10.0 Hz, (1H), 1.90 (doublet of doublets, J=3.0 Hz, 7.1 Hz (1H)), δ1.76 (multiplet, (2H)), bridgehead δ2.78 (singlet (2H)); ($\frac{m}{e}$) 97, 96, 95, 67 (base peak), 41, 39).

The carboxyl group is considered a very useful "synthetic handle" because it can be efficiently transformed into a wide variety of functionality.[6] Thus far, we have converted (**4**) to 2-bicyclo[1.1.1]pentylamine[7] by reaction with hydrazoic acid. We have also synthesized bicyclo[1.1.1]pentane,[7] itself, from (**4**) in 35% yield via thermal decomposition of the t-butyl hydroperoxide ester.

Acknowledgment

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References

1. This work was reported in part at the First International Symposium, Chemistry of Strained Rings, Binghamton, New York, May, 1977.
2. K. B. Wiberg and V. Z. Williams, Jr., *J. Org. Chem.*, **35**, 369 (1970).
3. For other reported syntheses of bicyclo[1.1.1]pentane and its derivatives see:
   (a) K. B. Wiberg, D. S. Connor, and G. M. Lampman, *Tet. Lett.*, **531** (1964).
   (b) K. B. Wiberg, G. M. Lampman, R. P. Ciula, D. S. Connor, P. Schertler, and J. Lavanish, *Tetrahedron*, **21**, 2749 (1965).
   (c) S. Masamune, *Tet. Lett.*, **945** (1965).
   (d) K. B. Wiberg and D. S. Connor, *J. Am. Chem. Soc.*, **88**, 4437 (1966).
   (e) J. Meinwald, W. Szkrybalo, and D. R. Dimmel, *Tet. Lett.*, **731** (1967).
   (f) R. Srinivasan and K. H. Carlough, *J. Am. Chem. Soc.*, **89**, 4932 (1967).
   (g) A. Padwa and E. Alexander, *J. Am. Chem. Soc.*, **89**, 6376 (1967).
   (h) H. K. Hall, Jr., C. D. Smith, E. P. Blanchard, Jr., S. C. Cherkofsky, and J. B. Sieja, *J. Am. Chem. Soc.*, **93**, 121 (1971).
   (i) T. W. Gibson, *J. Org. Chem.*, **39**, 845 (1974).
   (j) E. C. Alexander and J. A. Uliana, *J. Am. Chem. Soc.*, 96, 5644 (1974).
   (k) F. T. Bond and C. Y. Ho, *J. Org. Chem.*, **41**, 1421 (1976).
   (l) E. C. Alexander and J. Uliana, *J. Am. Chem. Soc.*, **98**, 4324 (1976).
   (m) E. C. Alexander and J. Uliana, *Tet. Lett.*, **1551** (1977).
   (n) D. E. Applequist and J. W. Wheeler, *Tet. Lett.*, **3411** (1977).
4. (a) For a review see K. E. Hamlin and A. W. Weston, *Org. Reactions*, **9**, 1 (1957).
   (b) P. G. Gassman, J. T. Lumb, and F. V. Zalar, *J. Am. Chem. Soc.*, **89**, 946 (1967).
5. (a) J. A. Caputo and R. Fuchs, *Tet. Lett.*, **47**, 4729 (1967).
   (b) D. G. Lee and M. Van den Engh in "Oxidation in Organic Chemistry", Part B, W. S. Trahanovsky, ed., Academic Press, New York, N.Y., 1973, pp. 177-228.
6. For examples see "Compendium of Organic Synthetic Methods", I. T. Harrison and S. Harrison; John Wiley and Sons, New York, N.Y., 1971.
7. Spectral characteristics are consistent with the assigned structure and will be reported in a full paper.