Tetrahedron Letters,Vol.23,No.44,pp 4545-4546,1982 0040-4039/82/444545-02$03.00/0
Printed in Great Britain

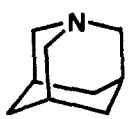
THE SYNTHESIS OF 2-CYANO-1-AZAADAMANTANE

George H. Wahl, Jr.* and Susan E. Zemyan[1a,b]

Department of Chemistry, North Carolina State University
Raleigh, N.C. 27650

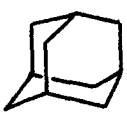
Abstract. A convenient synthesis of 2-cyano-1-azaadamantane (4) has been developed. The title compound is prepared *via* a five-step procedure from bicyclic compound 5 in an overall yield of 31%.

Quinuclidine derivatives, and more recently, adamantyl derivatives have exhibited a wide range of biological activity and have thus been the subject of considerable attention.[2] 1-Azaadamantane (1), the tricyclic counterpart to quinuclidine (2), and also a nitrogen-containing analog of adamantane (3) is therefore a potential source of new bioactivity. However, until now, few syntheses of 1 have been published and routes to specifically substituted derivatives are virtually non-existent. We now describe a practical preparation of 2-cyano-1-azaadamantane (4).

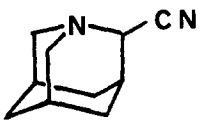


1

2

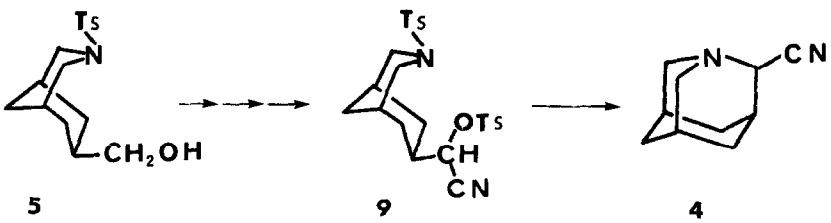


3



4

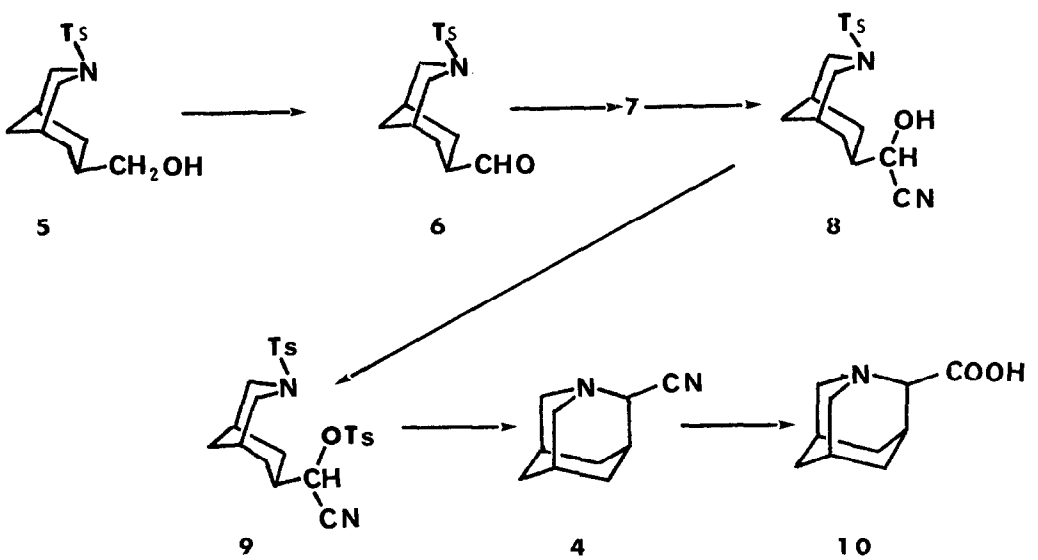
The present synthesis utilizes the *endo* bicyclic alcohol 5, first prepared by Speckamp and co-workers.[3] We envisioned elaboration of this alcohol into the α-cyano tosylate 9, which could be closed to the nitrile substituted tricyclic ring structure.[4] The nitrile, insensitive to the chosen cyclization conditions, provides a facile route to a variety of substituted azaadamantanes.



5 9 4

Oxidation of 5 to the *endo* aldehyde 6 was accomplished utilizing pyridinium chlorochromate.[5] The reaction medium was buffered with sodium acetate to suppress any unwanted *endo*→*exo* epimerization at C_7.[6] Treatment of the crude reaction product with a saturated ethanolic/aqueous solution of sodium bisulfite afforded the addition product, 7, m. 197-201°, in a 63%

yield from the alcohol. Compound 7 was then converted to the cyanohydrin *via* treatment with a methylene chloride/aqueous potassium cyanide mixture to yield 8 as a white solid, m. 162-4° in 71% yield. Tosylation of the hydroxyl group of 8 by a standard method[7] afforded the desired α-cyano toxylate 9, m. 137-9°, in 85% yield. Refluxing 9 in a 1:1 mixture of hydrochloric/acetic acid for 15 hrs. produced not the expected ring closure product (4), but rather the α-amino acid (10),[8] its hydrolysis product. That 10 did indeed arise from hydrolysis of 4 is quite likely, since treatment of 9 under the same conditions for only 1-1/2 hrs. produced an 80% yield of spectroscopically pure 2-cyano-1-azaadamantane (4). This hydrolysis probably accounts for the decreased yields of 4; therefore shorter reaction times can be used to optimize the yield of 2-cyano-1-azaadamantane. Derivatives of 4 are currently under study and will be discussed in a later publication.



References

1. (a) Taken in part from the Ph.D. thesis of SEZ, 1981; (b) Present address: Division of Environmental Chemistry, The Johns Hopkins University, Baltimore, Maryland 21211.

2. *e.g.*, Yakhontov, L.N., Mashkovs, M.D., Mikhlina, E.E., *Khim. Far. Zh.*, 14, 23 (1980); Kovalev, I.I., *ibid.*, 11, 19 (1977).

3. Speckamp, W.N.; Dijkink, J.; Dekkers, A.W.J.D.; Huisman, H.O.; *Tetrahedron*, 1971, 27, 3143.

4. Literature precedent for this transformation was found in the quinuclidine series: Augustine, R.L.; Wanat, S.F.; *Synth. Commun.*, 1971, 1, 241.

5. Corey, E.J. and Suggs, J.W., *Tetrahedron Lett.*, 1975, 2647.

6. Proof of stereochemistry of these and other 3-azabicyclo[3.3.1]nonanes will be discussed in a forthcoming publication. The *endo* configuration is required for successful ring closure.

7. Tipson, R.S.; *J. Org. Chem.*, 1944, 9, 235.

8. All new compounds had satisfactory spectral and elemental analyses.

(Received in USA 3 August 1982)