Pergamon

Tetrahedron Letters, Vol. 35, No. 48, pp. 8965-8968, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02027-2

1,5-Diazacyclooctane-3,7-Derivatives as Precursors of the 3,7-Diaza[3.3.0]bicyclooctane and 3,7,10-Heterocyclic[3.3.3]propellane Ring Systems[1]

Paritosh R. Dave* and Farhad Forohar
GEO-CENTERS, INC. at ARDEC, 762 Route 15 South, Lake Hopatcong, NJ 07849

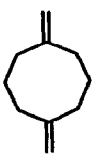
and

Theodore Axenrod, Lida Qi, Clara Watnick and Hamid Yazdekhasti
Department of Chemistry, The City College of the City University of New York, New York, NY 10031

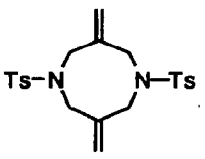
Abstract. A simple synthesis of 3,7-disubstituted-1,5-diazacyclooctanes from p-toluenesulfonamides and 3-chloro-2-chloromethylpropene has been developed. Unusual transannular reactions in these eight-membered ring intermediates provide easy access to novel 3,7-diaza[3.3.0]bicyclooctane and 3,7,10-heterocyclic[3.3.3]propellane ring systems.

Introduction

By conventional methodologies the synthesis of heteroatom-containing tricyclic compounds conjoined in a carbon-carbon single bond (propellanes) is frequently a very challenging task.[2,3] In the course of on-going investigations in these laboratories the sharp contrast in behavior between 1,5-bismethylenecyclooctane 1 and the related ditosyl derivative of 3,7-bismethylene-1,5-diazacyclooctane[4] 2 towards various reagents was noted. This report describes some unanticipated products obtained from 2, their characterization, and the synthetic advantage they offer as a means of gaining entry in the relatively inaccessible 3,7-diaza[3.3.0]bicyclooctane and 3,7,10-heterocyclic[3.3.3]propellane ring systems.[5] The latter are important as potential bifunctional mimics of transaminases.[6]



1

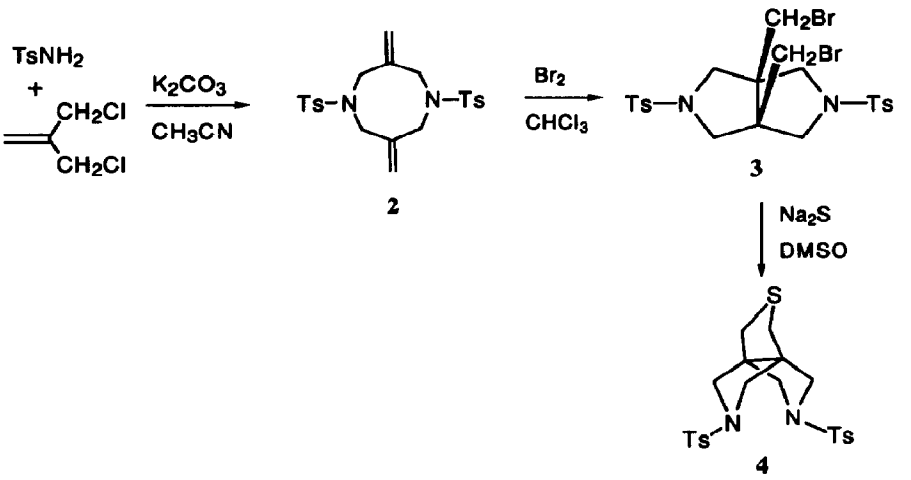


2

Results and Discussion

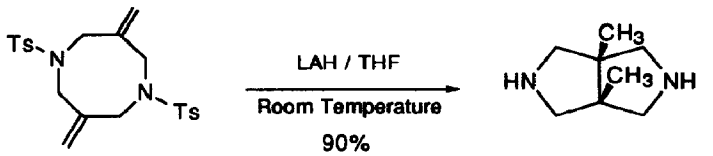
The 3,7-diaza[3.3.0]bicyclooctane ring system has scarcely been investigated and the one reported example in the literature was prepared by a lengthy multi-step synthesis.[2] Ring contractions[7] to diazepines and piperidines have previously been observed in diazocine chemistry,[8] but transannular ring closures to bicyclic systems appear to be unknown. A marked propensity to undergo transannular ring

closure is found in both **1** and **2**, but quite dissimilar products are obtained.[9] The reaction of **2** with bromine, for example, gives 1,5-dibromomethyl-3,7-diazabicyclo[3.3.0]octane **3** as the only product, whereas **1** gives bicyclo[3.3.1]nonane derivatives.[10] Further reaction of **3** with sodium sulfide in dimethylsulfoxide, for example, provided a facile route in 80% yield to the N,N'-di-p-toluenesulfonyl-3,7-diaza-10-thia[3.3.3]propellane **4**.



2 **3** **4**

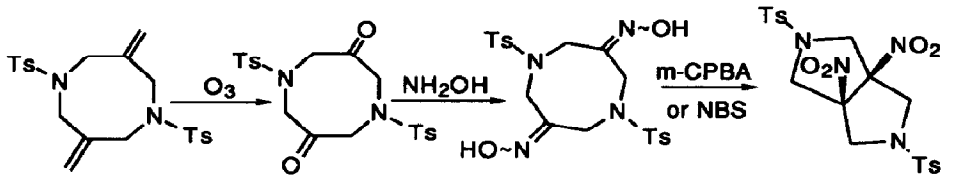
When **2** was treated with lithium aluminum hydride, in an attempted reductive detosylation to prepare the parent 3,7-bismethylene-1,5-diazacyclooctane, the strong proclivity of this system to undergo transannular ring-closure was again apparent. The reduction of the tosylamido function was accompanied, to our surprise, by the reduction of the exomethylene groups. NMR and mass spectra confirmed the structure of the product as **5**. While we are aware of no precedent,[11] the formation of this



2 **5**

bicyclic system can be rationalized, mechanistically, in terms of a hydride attack at one of the exocyclic methylene carbons followed by transannular anionic ring closure. Indeed, the product of this reduction when quenched with D_2O led to the incorporation of deuterium in one of the methyl groups. Similarly, reduction with LAD followed by H_2O quenching also led to incorporation of deuterium in one of the methyl groups, while D_2O quenching resulted in both methyls as isotopically labeled $-CH_2D$ groups.[12]

To extend the considerable synthetic potential that these cyclization reactions have in the construction of difficultly accessible structures, **2** was subjected to ozonation to afford the diketone **6**. It should be noted that 1,5-diazacyclooctane-3,7-diones can not be prepared by oxidation of the corresponding readily available 3,7-diols.[13] This ozonation was followed, in successive steps, by oxymation to **7** and oxidation to give the ring-closed vicinal dinitro derivative, 1,5-dinitro-3,7-diazabicyclo[3.3.0]octane, **8**. Similar transannular reactions of bisoximes have been described by Paquette,[14] Zajac[15] and recently by Camps, et al.[5]



2 **6** **7** **8**

In conclusion, a convenient preparation of 3,7-functionalized-N,N-di-p-toluenesulfonyl-1,5-diazacyclooctanes has been developed. These intermediates, through unusual transannular cyclizations, provide easy access to the little known 3,7-diaza[3.3.0]bicyclooctane and 3,7,10-heterocyclic-[3.3.3]propellane ring systems. The scope and utility of these reactions are under active investigation in these laboratories and will be reported in more detail in the future.

Acknowledgment. PRD and FF thank Dr. Gerald Doyle for helpful discussions and ARDEC for financial assistance under contract DAAA-21-89-C-0013.

References and Notes

1. Presented in part at the 207th National Meeting of American Chemical Society, San Diego, CA. March 13-18, 1994.
2. Altman, J.; Babad, E.; Itzchaki, J.; Ginsburg, D. *Tetrahedron, Suppl.* 8, Part I, **1966**, 279.
3. Knowles, P.; Harris, N.V. *J. Chem. Soc., Perkin Trans.* **1983**, 1,1475.
4. The synthesis of compound **2** has been achieved in 60 % yield by the reaction of p-toluenesulfonamide with 3-chloro-2-chloromethylpropene in refluxing acetonitrile (4 h) containing suspended potassium carbonate. **2** has reportedly been made in low yield as a mixture with higher oligomers, see Suzuki, M.; Lim, J-C.; Oguni, M.; Eberhardt, A.; Saegusa, T. *Polymer Journal,* **1990**, 22, 815.
5. Camps, P.; Munoz-Torrero, D. *Tetrahedron Lett.* **1994**, 35, 3187.
6. Wu, Y.; Ahlberg, P. *Acta Chemica Scand.* **1992**, 46, 60.
7. Paudler, W.W.; Zeiler, A.G.; Gapski, G.R. *J. Org. Chem.* **1969**, 34, 1001.

8. For a review see, Perlmutter, H.D. *Adv. Heterocyclic Chemistry*, **1989**, 46, 1.

9. All compounds reported have been fully characterized. The relevant data are: **2**: mp 194-197 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ2.43 (s, 6H), δ3.82 (s, 8H), δ5.19 (s, 4H), δ7.67 (d, J=8.3 Hz, 4H), δ7.31 (d, J=8.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ21.5, δ53.0, δ118.1, δ127.1, δ129.7, δ135.8, δ141.8, δ143.5; LRMS (EI) calc. for $C_{22}H_{26}N_2S_2O_4$ 446.1; found m/z, 445.9; **3** : mp 218-220 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ2.45 (s, 6H), δ3.16 (d, J=10.5 Hz, 4H), δ3.31 (d, 10.5 Hz, 4H), δ3.21 (s, 4H), δ7.33 (d, J=8.4 Hz, 4H), δ7.64 (d, J=8.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ21.6, δ34.0, δ56.0, δ57.3, δ127.7, δ130.0, δ131.9, δ144.5; LRMS (CI) calc. for $C_{22}H_{26}Br_2N_2S_2O_4$ 624 [$(M+NH_4)^+$] found m/z, 624; **4**: mp 195-196 °C; ^{1}H NMR (300 MHz, acetone-d_6, TMS) δ2.46 (s, 6H), δ2.80 (s, 4H), δ3.02 (d, J=9.7 Hz, 4H), δ3.08 (d, 9.7 Hz, 4H), δ7.47 (d, J=8.4 Hz, 4H), δ7.66 (d, J=8.4 Hz, 4H); ^{13}C NMR (75 MHz, acetone-d_6, TMS) δ21.0, δ42.3, δ57.8, δ66.1 δ128.5, δ130.2, δ132.5, δ144.8: LRMS (EI) calc. for $C_{22}H_{26}N_2S_3O_4$ 478; found 478; **5**: oil, picrate mp 258°C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ0.99 (s, 6H), δ2.71 (d, J=11.2 Hz, 4H), δ2.92 (d, J=11.2 Hz, 4H), δ2.61 (s, 2H, br); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ20.4, δ51.7, δ62.6.;LRMS (EI) calc. for $C_8H_{16}N_2$ 140.1; found m/z, 140; **6**: mp 275 °C ; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ2.45 (s, 6H), δ4.08 (s, 8H), δ7.72 (d, J=8.3Hz, δ133.9, δ145.1, δ204.3; LRMS (CI-NH_3) calc. for $C_{20}H_{22}N_2S_2O_6$ 468 [$(M+NH_4)^+$] ; found m/z, 468; **7**: anti isomer, mp 239°C(d); ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ2.41 (s, 6H), δ3.84 (s, 4H), δ4.09 (s, 4H), δ7.46 (d, J=7.9 Hz, 4H), δ7.69 (d, J=7.9 Hz, 4H), δ11.3 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, TMS) δ21.0, δ47.0, δ52.3, δ126.6, δ130.0, δ134.6, δ143.9, δ152.9; LRMS (CI-NH_3) calc. for $C_{20}H_{24}N_4S_2O_6$ 480.1; [$(M+H)^+$ and $(M+NH_4)^+$] found m/z, 481 and 498; **8**: mp 154-156 °C; ^{1}H NMR (300 MHz, DMSO-d_6, TMS) δ2.47 (s, 6H), δ3.89 (d, J=11.5 Hz, 4H), δ4.00 (d, J=11.5 Hz, 4H), δ7.40 (d, J=8.3 Hz, 4H), δ7.70 (d, J=8.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ21.7, δ55.1, δ94.0, δ127.5, δ130.4, δ131.8, δ145.5; LRMS (EI) calc. for $C_{20}H_{22}N_4S_2O_8$ 510.1; found m/z, 510.

10. Baggaley, K.H.; Evans, W.H.; Graham, S.H.; Jonas D.A.; Jones, D.H. *Tetrahedron*, **1968**, 24, 3445.

11. Only highly polarized alkenes are reduced by LAH. See Granoth, I.; Segall, Y.; Leader, H.; Alkabets, R. *J. Org. Chem.* **1976**, 41, 3682.

12. The several isotopically labeled products obtained in these reactions exhibited the expected m/z ions indicative of the incorporation of one or two deuterium atoms. In addition, an isotope shift was observed in the ^{13}C NMR spectrum confirming the presence of the deuterium only in the methyl groups. For example, the ^{13}C-{^{1}H} spectrum of $C_8H_{15}DN_2$ exhibited δ20.2 (singlet), δ20.0 (triplet, ^1J (^{13}C-^{2}H) = 19.0 Hz), δ51.5, δ62.3. DEPT experiments were in complete agreement with these conclusions.

13. Paudler, W.W.; Gapski, G.R.; Barton, J.M. *J. Org. Chem.* **1966**, 31, 277.

14. Waykole, L.M.; Shen, C.C.; Paquette, L.A. *J. Org. Chem.* **1988**, 53, 4969.

15. Zajac, W. personal communication.

(*Received in USA* 2 *September* 1994; *accepted* 11 *October* 1994)