HETEROCYCLES, Vol. 75, No. 3, 2008, pp. 577 - 582. © The Japan Institute of Heterocyclic Chemistry
Received, 10th October, 2007, Accepted, 26th November, 2007, Published online, 30th November, 2007. COM-07-11239

PYROLYTIC STUDY OF CYCLIC 2-AZIDOKETONES

Chin-Hsing Chou,* Li-Tse Chu, I-Ying Chen, and Bo-Jian Wu

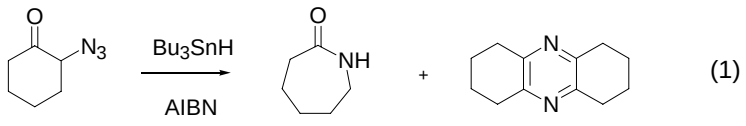
Department of Chemistry and Center for Nanoscience and Nanotechnology, National Sun Yat-Sen University, Kaohsiung, Taiwan, 804, R.O.C
ch-chou@mail.nsysu.edu.tw

Abstract – Flash vacuum pyrolysis of 2-azidocyclohexanone (**1**) gave a condensed dimer (**6**), a ring expanded product (**7**) and 2-methylpyridine (**8**). On the other hand, pyrolysis of 2-azidocyclopentanone (**4**) and 2-azido-cycloheptanone (**5**) gave ring expanded products (**12**) and (**13**), respectively, as the main products.

INTRODUCTION

The thermal decomposition of alkyl azides usually yield imino compounds, presumably via nitrene intermediates that undergo 1,2-H shift. Nitrene is a highly reactive intermediate, which is known to proceed many different reactions including dimerization,[1] addition to double bond,[2] insertion into C-H bond,[3] and rearrangements.[4]

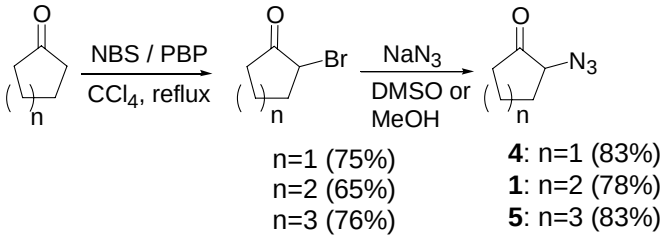
The 2-azidoketones are useful precursors in organic synthesis especially in the synthesis of heterocyclic compounds such as oxazoles,[5] imidazoles[6,7] and pyrazines.[7] For instance, Benati and co-workers reported that 2-azidocyclohexanone (**1**) reacts with tributyltin hydride to generate azepan-2-one (**2**) and tricyclic pyrazine (**3**) (eq. 1).[7] As part of our continuing effort to study the chemistry of nitrene intermediates,[8] we have carried out flash vacuum pyrolysis (FVP)[9] of **1** and its homologues, 2-azidocyclopentanone (**4**) and 2-azidocycloheptanone (**5**). We wish to report our results herein.



1 **2** (8%) **3** (55%) (1)

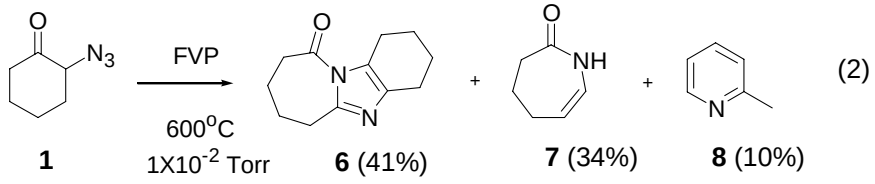
RESULTS AND DISCUSSION

The cyclic 2-azidoketones, (**1**), (**4**), and (**5**) were prepared by 2-bromination of the parent ketones, followed by treatment of the resulting bromide with sodium azide (Scheme 1).[7]

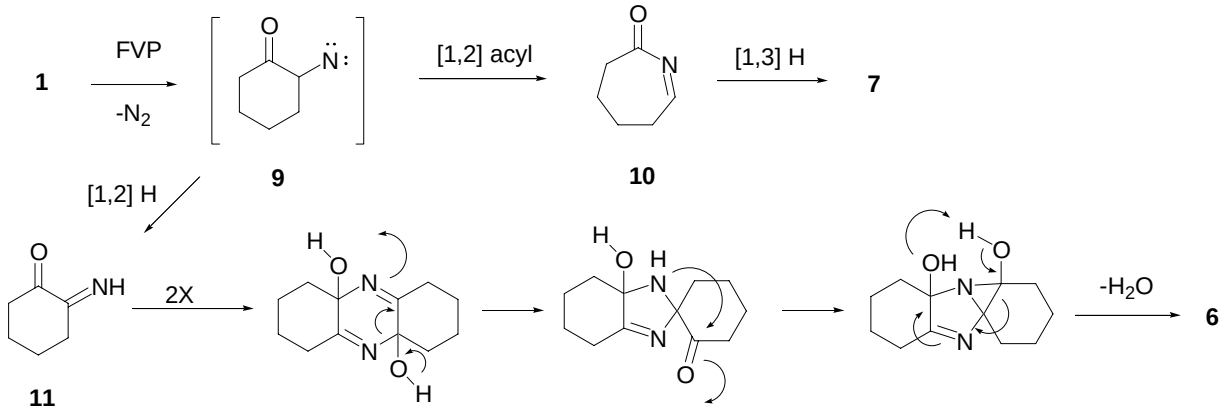


Scheme 1

FVP of **1** at 600 °C and ca. 1 x 10^{-2} Torr gave a condensed dimer, 1,2,3,4,6,7,8,9-octahydrobenzo[4,5]imidazo[1,2-a]azepin-10-one (**6**) as the major product (41%), along with a ring expanded product, 1,3,4,5-tetrahydroazepin-2-one (**7**) (34%)[10] and 2-methylpyridine (**8**) (10%)[11] (eq. 2). The pyrolysis temperature at 600 °C appeared to be the optimum reaction condition for our study. FVP of **1** at temperatures higher than 700 °C gave products that are too complicated to be identified, whereas FVP of **1** at lower than 500 °C would leave unreacted starting material.



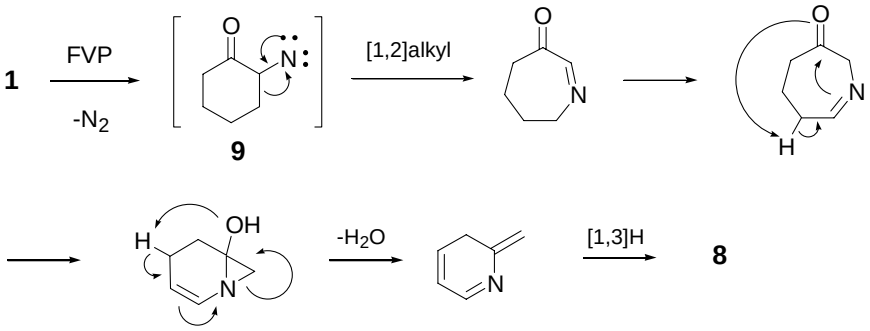
Formation of **6** and **7** from FVP of **1** can be rationalized by a set of reactions proposed as shown in Scheme 2. FVP of **1**, presumably will generate the nitrene intermediate (**9**) as the primary product, which could undergo either 1,2-acyl or 1,2-H shift[12] to give **10** or **11**, respectively. 1,3-H shift from **10** will lead to the observed **7**. The double ring-fused imidazole (**6**) is a new compound, which could be formed by dimerization of **11**, followed by elimination of a H_2O molecule.



Scheme 2

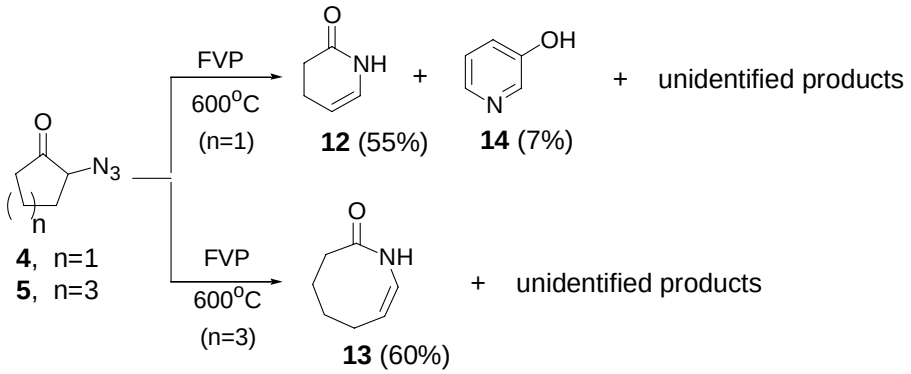
Generation of **8** from **1** was unexpected. Wentrup and co-workers have reported that FVP of phenyl azide gives 2-methylpyridine, via a rearrangement of the resulting phenylnitrene to 2-pyridylcarbene.[4] As our

best knowledge, thermal conversion of 2-azidocyclohexanone (**1**) to 2-methylpyridine (**8**) is the first observed example involving rearrangement of non-aromatic nitrene to pyridine derivative. The mechanism to account for the formation of **8** is tentatively proposed as shown in Scheme 3.

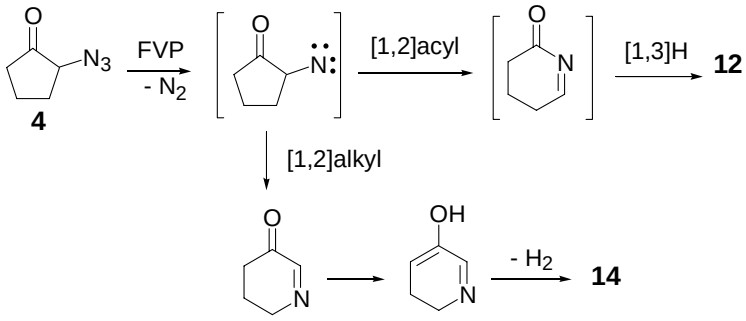


Scheme 3

In order to study the ring size effect, we have also pyrolyzed **4** and **5**. FVP of **4** and **5** at 600 ^{o}C and ca. 1 x 10^{-2} Torr gave their corresponding ring-expanded products, 3,4-dihydro-1*H*-pyridin-2-one (**12**)[13] (55%) and 3,4,5,6-tetrahydro-1*H*-azocin-2-one (**13**) (60%), respectively, as the main products (Scheme 4). In addition, FVP of **4** also gave a minor product, 3-hydroxypyridine (**14**)[14] (7%), presumably *via* a ring expansion and elimination of a H_2 molecule as shown in Scheme 5.



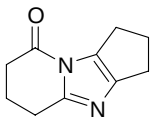
Scheme 4



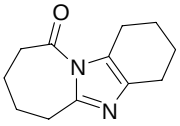
Scheme 5

Molecular mechanics calculations using Chem 3D minimization method, for **6** and the other two possible condensed dimers (**15**) and (**16**) from FVP of **4** and **5** respectively, yield the following steric energies

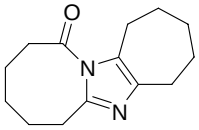
(Kcal/mole): **15** (23.2), **6** (18.5), **16** (31.4). Such results suggest that **6** is substantially lower in energy than **15** and **16** and may account for the formation of **6** rather than **15** and **16**.



15



6



16

In summary, although FVP of **1**, **4** and **5** give their corresponding ring expanded products, (**7**), (**12**) and (**13**), only **1** generates imidazole (**6**) as the major product. In addition, FVP of **1** and **4** also give pyridines (**8**) and (**14**), respectively. The thermal conversion of cyclic 2-azidoketones to pyridine derivatives are the first observed examples. We are currently extending our study to the acyclic 2-azidoketones.

EXPERIMENTAL

Infrared spectra were recorded with a FTS-175/185 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were carried out in $CDCl_3$ with Varian VXR-500 NMR spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). Mass spectra were recorded with a VG QUATTRO 5022 spectrometer. High resolution mass spectra (HRMS) were recorded with a VG70-250S spectrometer.

General pyrolysis procedure[9]

The furnace was maintained at temperatures in the range 500-700 °C. A sample (ca. 1.0 g) for pyrolysis was placed into the sample chamber and the system was evacuated to ca. 1×10^{-2} Torr. During the pyrolysis $CDCl_3$ was deposited into the cold trap through a side arm. The pyrolysis process took about 1 h to finish. After the pyrolysis was completed, nitrogen was introduced into the system, the liquid-nitrogen-cooled trap was warmed to room temperature and all the FVP products were collected. These products were analyzed by ^{1}H, ^{13}C NMR, IR and Mass. The percent yields were determined from ^{1}H NMR.

General procedure for preparation of the cyclic 2-azidoketones **1a-c**

The cyclic 2-azidoketones, (**1**), (**4**), and (**5**) were prepared in 78-83% yields from treatment of the corresponding cyclic 2-bromoketones with sodium azide (2 equiv.) in DMSO. The cyclic 2-bromoketones were prepared in 65-76% yields by bromination of the parent ketones with *N*-bromosuccinimide (NBS, 1 equiv.) and a catalytic amount of dibenzoyl peroxide (DBP) in refluxing tetrachloromethane for 8 h. The crude cyclic 2-azidoketones were purified by column chromatography on silica gel (*n*-hexane : AcOEt = 5 : 1).

Spectral data of products

1,2,3,4,6,7,8,9-Octahydrobenzo[4,5]imidazo[1,2-*a*]azepin-10-one (**6**): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.07 (t, *J* = 6.0 Hz, 2H), 2.82-2.79 (m, 2H), 2.65 (t, *J* = 6.0 Hz, 2H), 2.55 (t, *J* = 6.0 Hz, 2H), 2.08-2.03 (m, 2H), 1.98-1.93 (m, 2H), 1.90-1.85 (m, 2H), 1.83-1.80 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.01, 144.20, 139.81, 130.53, 42.87, 39.58, 25.82, 24.28, 22.92, 22.60, 21.12, 19.17; IR (neat, cm^{-1}) 2941, 2242, 1667; HRMS Calcd for $C_{12}H_{16}N_2O$: 204.1263, Found: 204.1260.

1,3,4,5-Tetrahydroazepin-2-one (**7**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (bs, 1H), 5.76-5.72 (m, 1H), 5.04-5.00 (m, 1H), 2.60-2.58 (m, 2H), 2.29-2.27 (m, 2H), 1.93-1.91 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.92, 122.07, 112.67, 36.88, 28.81, 21.43; MS *m/z* (%) 111 (M^+, 100).
[lit.[10] **7**: ^{1}H NMR ($CDCl_3$) δ 1.91 (m, 2H), 2.21 (m, 2H), 2.57 (m, 2H), 4.98 (m, 1H), 5.76 (m, 1H), and 8.15 (s, 1H); IR (neat, cm^{-1}) 3125, 1665.]

2-Methylpyridine (**8**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 3.9 Hz, 1H), 7.52 (td, *J* = 8.1, 2.1 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.04 (t, *J* = 4.8 Hz, 1H), 2.52 (s, 3H), MS *m/z* (%) 93 (M^+, 100).
[lit.[11] **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (1H), 7.55 (1H), 7.14 (1H), 7.08 (1H), 2.55 (3H).]

3,4-Dihydro-1*H*-pyridin-2-one (**12**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (bs, 1H), 6.08-6.06 (m, 1H), 5.11-5.08 (m, 1H), 2.52-2.49 (t, *J* = 8.0 Hz, 2H), 2.37-2.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.16, 124.83, 105.01, 30.46, 20.07; IR (neat, cm^{-1}) 3240, 1662; MS *m/z* (%) 97 (M^+, 100).
[lit.[13] **12**: colorless oil; IR ($CDCl_3$, cm^{-1}) 3248 (NH), 1666 (CO); ^{1}H NMR ($CDCl_3$) δ 2.31 (m, 2H), 2.50 (t, *J* = 8.02 Hz, 2H), 5.09 (m, 1H), 6.09 (m, 1H), 7.00 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 19.86, 30.24, 104.60, 124.95, 171.96; MS *m/z* (%) 97 (M^+, 100), 69 (25), 68(28), 56 (13), 54 (22), 43 (13).]

3,4,5,6-Tetrahydro-1*H*-azocin-2-one (**13**): colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 1H), 5.97 (d, *J* = 8.5 Hz, 1H), 5.54 (q, *J* = 7.5 Hz, 1H), 2.43 (t, *J* = 6.0 Hz, 2H), 2.13-2.10 (m, 2H), 1.78-1.73 (m, 2H), 1.62-1.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.06, 125.46, 123.70, 32.68, 26.02, 24.29, 23.98; IR ($CDCl_3$, cm^{-1}) 3384, 1648; HRMS Calcd for $C_7H_{11}NO$: 125.0841, Found : 125.0842.

3-Hydroxypyridine (**14**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, *J* = 2.5 Hz, 1H), 8.10 (dd, *J* = 4.5, 1.0 Hz, 1H), 7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.91, 139.48, 136.58, 125.08, 124.83; IR (neat, cm^{-1}) 3417, 1469, 1376, 1283; MS *m/z* (%) 96 (M+1, 100), 95 (M^+, 30).
[lit.[14] **14**: yellow solid; Mp 127 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (s, 1H), 8.03-8.01 (m, 1H),

7.28-7.27 (m, 2H).]

ACKNOWLEDGMENTS

We thank the National Science Council of the Republic of China for financial support.

REFERENCES

1. M. Sumitani, S. Nagakura, and K. Yoshihara, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 2995.
2. P. P. Nicholas, *J. Org. Chem*., 1975, **40**, 3396.
3. G. Smolinsky and B. I. Feuer, *J. Org. Chem*., 1966, **31**, 3882.
4. W. D. Crow and C. Wentrup, *Tetrahedron Lett.*, 1968, **24**, 6149; R. M. Moriarty and M. Rahman, *Tetrahedron*, 1965, **21**, 2877; C. Wentrup and H. W. Winter, *J. Am. Chem. Soc*., 1980, **102**, 6159.
5. P. Molina, P. M. Fresenda, and P. Almendros, *Synthesis*, 1993, 54.
6. J. H. Boyer and D. Straw, *J. Am. Chem. Soc*., 1952, **74**, 4506.
7. L. Benati, R. Leardini, M. Minozzi, D. Nanni, P. Spagnolo, S. Strazzari, G. Zanardi, and G. Calestani, *Tetrahedron*, 2002, **58**, 3485.
8. C. H. Chou, L. T. Chu, S. J. Chiu, C. F. Lee, and Y. T. She, *Tetrahedron*, 2004, **60**, 6581.
9. C. H. Chou and W. S. Trahanovsky, *J. Am. Chem. Soc*., 1986, **108**, 4138.
10. A. R. Doumaux, Jr. and D. J. Trecker, *J. Org. Chem*., 1970, **35**, 2121.
11. K. Matsumoto, M. Kannami, and M. Oda, *Tetrahedron Lett.*, 2003, **44**, 2861.
12. C. Wentrup, *Reactive Molecules*, John Wiley & Sons: New York, 1984, p. 177-214.
13. I. Ozimz, A. Korda, and W. Shay, *J. Org. Chem*., 1991, **56**, 2024.
14. K. W. Anderson, T. Ikawa, R. E. Tundel, and S. L. Buchwald, *J. Am. Chem. Soc*., 2006, **128**, 10694.