HETEROCYCLES, Vol. 68, No. 8, 2006, pp. 1685 - 1689. © The Japan Institute of Heterocyclic Chemistry
Received, 16th March, 2006, Accepted, 1st June, 2006, Published online, 2nd June, 2006. COM-06-10737

HETERO-DIELS-ALDER REACTION OF ETHYL 2-NITROSOACRYLATE AND CYCLOHEXADIENES, AND BROMINE INDUCED DIENE ISOMERIZATION

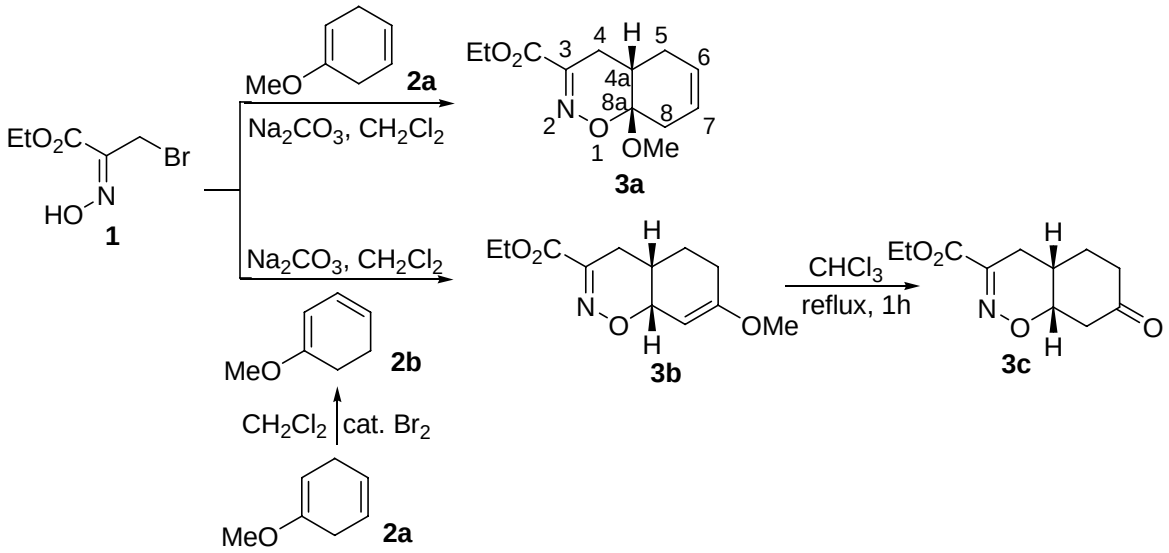
Jian Song,[a] Yongcheng Lin*[a], Yau Shan Szeto,[b] and Wing Lai Chan*[c]

[a]School of Chemistry and Chemical Engineering, Sun Yat-sen University, Guangzhou 510275, P. R. China. Tel: 86 (20) 84039623. Fax: 86 (20) 84039623. E-mail: ceslyc@zsu.edu.cn [b]Institute of Textile and Clothing, [c]Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong, P. R. China. Tel: 851-34008723. E-mail: wlchan@polyu.edu.hk

Abstract – Bicyclic 8a-methoxy-1,2-oxazine (**3a**) and bicyclic 7-methoxy-1,2-oxazine (**3b**) were prepared *via* Hetero-Diels-Alder reaction between 1-methoxy-1,4-cyclohexadiene (**2a**) and ethyl 2-nitrosoacrylate generated *in situ* from ethyl bromopyruvate oxime (**1**). The formation of **3b** was ascribed to bromine, released from **1**, which induced transformation of **2a** to 1-methoxy-1,3-cyclohexadiene (**2b**). **3b** could be easily transformed to oxazinone (**3c**) in $CHCl_3$, or other organic solvents in the presence of a trace amount of acid.

INTRODUCTION

1,2-Oxazine derivatives are important intermediates in organic synthesis. These heterocycles can be easily converted into various functionalities *via* oxidations, reductions or hydrolysis.[1] In general, they are prepared by cycloaddition reaction of olefins and transient nitrosoalkene intermediates generated by dehydrohalogenation of α-halogen oximes.[2] As a part of our study on the total synthesis of metabolites from marine microorganisms,[3] we studied the synthesis of the bicyclic 1,2-oxazine systems which could also be used as key precursors to other heterocyclic compounds. In the course of our study on the cycloaddition reaction of ethyl 2-nitrosoacrylate, generated by the treatment of ethyl bromopyruvate oxime (**1**) and sodium carbonate, to methoxycyclohexadiene (**2a**), an interesting bromine initiated double bond shift of diene (**2a**) to give **2b** was observed. Double bond shift of diene induced by bromine had never been reported before. Cycloaddition of ethyl 2-nitrosoacrylate with diene (**2a**) gave bicyclic 8a-methoxy-1,2-oxazine (**3a**), and with the double bond shifted diene gave 7-methoxy-1,2-oxazine (**3b**).



Scheme 1

RESULTS AND DISCUSSION

Freshly prepared bromo-oxime (**1**) from ethyl bromopyruvate and hydroxylamine[4] was stirred with 2.0 equiv. of cyclohexadiene (**2a)** in dry dichloromethane at room temperature for a few minutes, and then sodium carbonate was added. After stirring for 5 h, 3-ethoxycarbonyl-8a-methoxy-4,4a,5,8-tetrahydro-1,2-benzoxazine (**3a**) was obtained as the major product, together with a trace amount of 7-methoxy bicyclic 1,2-oxazine (**3b**). If freshly prepared (**1**) was not used, **3b** would be obtained as the major product. With a slight modification of the procedure by adding **2a** to a stirring mixture of oxime (**1**) and sodium carbonate, only **3a** was obtained. The reaction was performed by using different solvents (Et_2O and THF) and the results obtained were almost the same. The formation of **3b** was unexpected. Based on the structure of **3b** and the concerted mechanism analyzed, it was rationalized that 1-methoxy-1,3-cyclohexadiene (**2b**) had to be involved as the intermediate in the reaction process. We thus used **2b** to react with bromo-oxime directly under similar condition, and oxazine (**3b**) was obtained as expected. The formation of **2b** from **2a** had to be *via* a double bond shift mechanism. It was also observed that ethyl bromo-oxime (**1**) turned into light brownish color after few weeks, and we believed that it could be the result of a radical process of the oxime which generated a low concentration of molecular bromine to color the compound. In the reaction between **1** and **2a**, the bromine initiated the isomerization of **2a** into **2b**, probably in a manner similar to the iodine induced double bond shifted isomerization in alkenes.[5]

A test experiment was conducted by simply stirring **2a** in dichloromethane in the presence of a trace amount of bromine, and **2b** was produced in a high yield within minutes at room temperature. Polymerization was observed if the reaction mixture was standing for a longer period (one or two hours), and this reaction could be stopped by the addition of sodium carbonate. Double bond shift of **2a** did not

occurred in the presence of hydrogen chloride or acetic acid under the same condition. This could exclude the association of H^+ in the isomerization process. To the best of our knowledge, this is the first reported example of bromine induced double bond shift of diene; and it is experimentally facile when compared to the existing methods.[6]

The structures of **3a**,**b** were elucidated by spectroscopic methods. **3a** with the methoxy group at C-8a was clearly evidenced by the ^{13}C-NMR signal at δ 98.8, a signal which was attributed to carbon attached to two oxygen atoms. There was no other signal of oxygen-bearing carbon, except the two obvious carbon signals of the MeO- and EtO- groups. The structure of **3b** was elucidated by 1D and 2D NMR. The multiplet at δ 4.91 and δ 4.25 were assigned to C-8 and C-8a protons respectively, and the 1H-1H COSY signals also clearly indicated the correlation of the protons connected to these two carbons, and thus the location of the methoxy group was at C-7.

Oxazine (**3b**) is relatively unstable. It was easily transformed to 3-ethoxycarbonyl-4,4a,5,6,8,8a-hexahydro-7*H*-1,2-benzoxazin-7-one (**3c**) in chloroform solution at room temperature. This transformation was also achieved smoothly in other organic solvent, such as THF, in the presence of a small amount of H_2SO_4. The structure of **3c** was unambiguously assigned by single-crystal X-Ray analysis.[7] The carbonyl group (C9 in the crystal structure in Figure 1) is at C-7 in **3c**, a solid proof for the assigned conformation of **3b**.

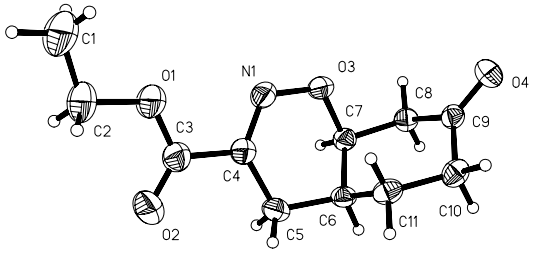


Figure 1. The view of the molecule (**3c**)

EXPERIMENTAL

Melting points were uncorrected. IR spectra were recorded on a Bruker Equinox55-FTIR spectrophotometer. NMR spectra were recorded on a Varian Inova 300 NMR spectrometer. Mass spectra were recorded on a VG ZAB-HS mass spectrometer. X-Ray data were generated on a Bruker Smart 1000CCD system diffractometer. Elemental analyses were carried out on a Vario EL elemental analyzer.

1-Methoxy-1,3-cyclohexadiene (2b)

To a stirring solution of 1-methoxycyclohex-1,4-diene (**2a**) (75 mg, 85% from Sigma-Aldrich Co.)(**2a** :anisole = 85 : 15) in CH_2Cl_2 (5 mL) was added 0.1mL of diluted Br_2 (22 mg Br_2 in 3 mL of CH_2Cl_2) at rt. The mixture was stirred for a further 10 min and then the reaction was quenched by

anhydrous Na_2CO_3. The mixture was filtered through Celite and the filtrate was evaporated to give the crude product. The ^{1}H-NMR of the crude product indicated the presence of **2b** as the major component (75%) (**2b** : **2a** : anisole = 75 : 10 : 15). The ^{1}H-NMR spectrum of the crude **2b** was identical with the spectrum of an authentic sample (65% **2b**) from Sigma-Aldrich.

3-Ethoxycarbonyl-8a-methoxy-4,4a,5,8-tetrahydro-1,2-benzoxazine (**3a**)

A solution of the ethyl bromopyruvate oxime (**1**) (0.85 g, 4 mmol) in CH_2Cl_2 (100 mL) was stirred with anhydrous Na_2CO_3 (2.33 g, 22 mmol) for 10 min at rt, and then to the suspension was added **2a** (1.30 g, 10 mmol). The mixture was stirred for a further 5 h, and the reaction mixture was filtered through Celite. The solvent was removed and the residue was purified by chromatography (SiO_2) (5-10% AcOEt-petroleum ether as eluent) to afford **3a** in 57% yield (0.509g, 2.3mmol) as a colourless oil. FT-IR (film, Si): 3415.6, 2938.5, 1717.8, 1298.2, 1129.9, 669.7cm^{-1}. ^{1}H-NMR (300MHz, $CDCl_3$, δ, Hz): 5.56 (m, 2H), 4.34 (m, 2H), 3.31 (s, 3H), 2.78 (m, 2H), 2.0-2.35 (m, 4H), 1.88 (m, *J*= 7Hz, 1H), 1.36, 1.39, 1.41(t, 3H). ^{13}C-NMR(300MHz, $CDCl_3$, δ): 163.7, 150.7, 124.8, 122.6, 98.8, 62.2, 49.3, 32.6, 30.1, 29.8, 24.8, 14.5. MS (EI) *M/Z* 240(M+1)$^+$, 222, 121, 109, 91, 69, 55. Anal. Calcd for $C_{12}H_{17}NO_4$: C 60.24, H 7.16, N 5.85. Found: C 60.36, H 7.28, N 5.94.

3-Ethoxycarbonyl-7-methoxy-4a,5,6,8a-tetrahydro-4*H*-1,2-benzoxazine (**3b)**

The solution of **1** (111 mg, 0.53 mmol), **2a** (138 mg, 1.06 mmol) and 0.3 ml of diluted Br_2 (22 mg Br_2 in 3mL of CH_2Cl_2) in CH_2Cl_2 (12.5 mL) was stirred for 5 min and then to the solution was added anhydrous Na_2CO_3 (312 mg, 2.94 mmol) at rt. After stirring for a further 5 h, the mixture was filtered through Celite. The filtrate was evaporated and the residue was purified on a silica gel column (5-10% AcOEt-petroleum ether as eluent) to give **3b** in 61% yield (72 mg, 0.33 mmol) as a colourless oil. FT-IR (film, Si): 3407.5, 2935.6, 1715.2, 1239.4, 1108.7cm^{-1}. ^{1}H-NMR (500MHz, CD_3COCD_3, δ, Hz): 4.91 (m, *J*=6Hz, 1H), 4.25 (m, 1H), 4.21 (q, *J*= 7Hz, 2H), 3.58 (s, 3H), 1.60-2.70(m, 7H), 1.26 (t, *J*= 7Hz, 3H). ^{13}C-NMR(300MHz, $CDCl_3$, δ): 169.0, 167.4, 154.0, 96.8, 77.4, 66.4, 59.5, 33.6, 33.3, 32.0, 29.0, 19.2. MS (EI) *M/Z* 240(M+1)$^+$, 222, 166, 123, 109, 81, 69, 55. Anal. Calcd for $C_{12}H_{17}NO_4$: C 60.24, H 7.16, N 5.85. Found: C 60.06, H 7.24, N 5.64.

3-Ethoxycarbonyl-4,4a,5,6,8,8a-hexahydro-7*H*-1,2-benzoxazin-7-one (3c)

A solution of **3b** in $CHCl_3$ (AR grade from Aldrich) was refluxed for 1h and then the solvent was removed, the residue obtained was purified upon preparative TLC (SiO_2 254 with 35% AcOEt-petroleum ether as eluent), yielded **3c** in an almost quantitative yield. mp 83-84°C. FT-IR (KBr): 3414.3, 2945.4, 1715.6, 1129.5, 1108.9cm^{-1}. ^{1}H-NMR (300MHz, $CDCl_3$, δ, Hz): 4.30 (q, *J*= 7Hz, 2H), 4.25 (m, 1H), 2.30-2.90(m, 6H), 1.88 (m, 2H), 1.70 (m, 1H), 1.34 (t, *J*= 7Hz, 3H). ^{13}C-NMR(300MHz, $CDCl_3$, δ): 203.5, 160.9, 146.6, 73.7, 59.8, 41.6, 37.4, 26.1, 24.8, 23.5, 11.9. MS (EI) *M/Z* 226(M+1)$^+$, 89, 57, 43. Anal. Calcd for $C_{11}H_{15}NO_4$: C 58.66, H 6.71, N 6.22. Found: C 58.45, H 6.88, N 6.10.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (20072058) and the 863 Foundation of China (2003AA624010) and the Natural Science Foundation of Guangdong Province, China (021732).

REFERENCES (AND NOTES)

1. (a) J. Angermann, K. Homann, H.-U. Reißig, and R. Zimmer, *Synlett,* 1995, **10**, 1014. (b) J. K. Gallos, V. C. Sarli, A. C. Varvogli, C. Z. Papadoyanni, S. D. Papaspyrou, and N. G. Argyropoulos, *Tetrahedron Lett.,* 2003, **44**, 3905. (c) M. Buchholz, F. Hiller, and H.-U. Reißig, *Eur. J. Org. Chem.,* 2002, **16**, 2838. (d) R. Zimmer and H.-U. Reißig, *J. Org. Chem.,* 1992, **57**, 339.
2. I. M. Lyakalo and S. L.Ioffe, *Russ. Chem. Rev.,* 1998, **67**, 467.
3. Y. C. Lin, Z. Shao, G. Jiang, S. Zhou, J. Cai, L. L. P. Vrijmoed, and E. B. G. Jones, *Teterahedron,* 2000, **56**, 9607.
4. H. C. J. Ottenhoijm, R. Plate, J. H. Noordick, and J. D. M. Herscheid, *J. Org. Chem.,* 1982, **47**, 2147.
5. S. J. Rhoads, J. K. Chattopadhyay, and E. E. Waali, *J. Org. Chem.,* 1970, **35**, 3352.
6. (a) C. C. Kanakam, N. S. Mani, H. Ramanatha and G. S. R. Subba Rao, *J. Chem. Soc., Perkin Trans. 1,* 1989, **11**, 1907. (b) R. A. Rennels and J. V. McCluusky, *Synth. Commun.,* 2004, **34**, 651. (c) T. Matsumoto, A. Ichihara, M. Yanagiya, and C. H. Eugster, *Helv. Chim. Acta*, 1985, **68**, 2324. (d) A. J. Birch and K. P. Dastur, *Tetrahedron Lett.,* 1972, **13**, 4195. f) A. J. Birch, *J. Chem. Soc.,* 1950, 1551.
7. Crystal structure determinations $C_{11}H_{15}NO_4$, MW= 225.24, Monoclinic, space group P2(1)/c, Unit cell dimensions a = 20.220(9) Å, α=90deg, b= 5.183(2) Å, β= 102.410(8) deg, c= 11.235(5) Å, γ= 90 deg. Volume= 1149.9(9)$Å^3$, *Z*=4, D_{calcd}= 1.301 $mg \cdot m^{-3}$, *m*= 0.099 mm^{-1}, F(000)= 480. All single-crystal data were collected using the hemisphere technique on a Bruker SMART 1000CD system diffractometer with graphite monochromated Mo Kα radiation λ=0.71073 at 293(2) K. The structures were solved by direct methods using SHELXTLV5.0 (Simemens Industrail Automation Inc, Madision.WI) and refined using full-matrix least-squares difference Fourier techniques. All non-hydrogen atoms were refined with anisotropic displacement parameters and all hydrogen atoms were placed in idealized positions and refined as riding atoms with the relative isotropic parameters. Absorption corrections were applied with the Siemens Area Detector ABSorption program (SADABS). The final value of R was 0.0537*,* ωR_2 = 0.1492 [I>2sigma(I)]. The CCDC number is 288270.