Novel Synthesis of 2*H*-3,1-Benzoxazine Derivatives

Jia-Rong Li *, Shu-Ling Ma, Yong-Jiang Sun, Xiao-Jie Wei and Zhi-Ming Zhou

School of Chemical Engineering and Environment, Beijing Institute of Technology, Beijing, 100081, P. R. China

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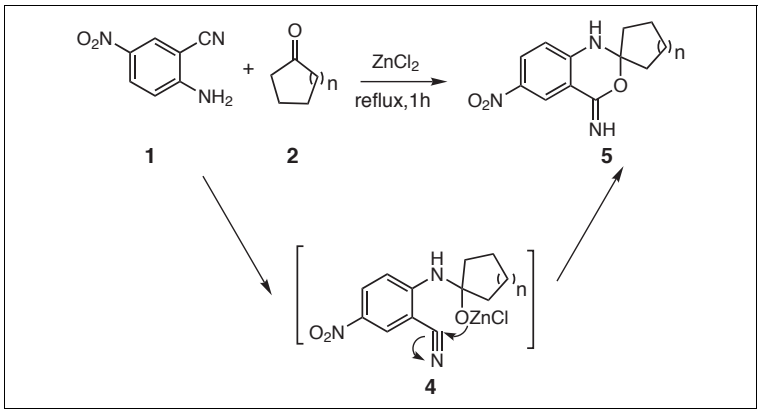

On heating of the 2-amino-5-nitrobenzonitrile **1** with cyclohexanone **2a** in the presence of catalyst, the novel compound 6-nitrospiro[3,1-benzoxazine-2,1'-cyclohexan]-4(1*H*)-imine **5a** was formed. Also, reaction of **1** with cyclopentanone **2b** or cycloheptanone **2c** afforded **5b** or **5c** respectively. All new compounds were identified by ^{1}H NMR, ^{13}C NMR, IR, MS spectra and elemental analysis. The crystal structure of product **5a** was determined by crystal X-ray diffraction. And the mechanism for these reactions is proposed.

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Introduction.

It is well known that heterocyclic compound is a very important component in organic chemistry and it has extensive applications in many fields such as biochemistry, medical industry, etc. Development of novel synthetic methods for the construction of new analogs of bioactive heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry. Comparing to other benzoxazine series, 2*H*-3,1-benzoxazine derivatives have paid to little attention duo to their rare synthetic methods. However, these compounds are a series of potent nonsteroidal progesterone receptor agonists [1-3], and have many other applications such as plant growth regulating and anti-stress activities, *etc* [4]. In addition, these compounds are the key intermediates in the synthesis of antimicrobial named carbapenems [5,6].

The reaction of 2-aminobenzonitrile with cyclohexanone **2a** in the presence of Lewis acids catalyst is a well-known reaction that leads to the formation of tacrine (9-amino-1,2,3,4-tetrahydroacridine, one of acetylcholine-esterase inhibitors for the treatment of mild to moderate Alzheimer's disease) [7-12]. Herein, we hope to report a novel cyclization of nitrile **1** with cyclic ketones to provide an efficient synthesis of 2*H*-3,1-benzoxazine derivatives.

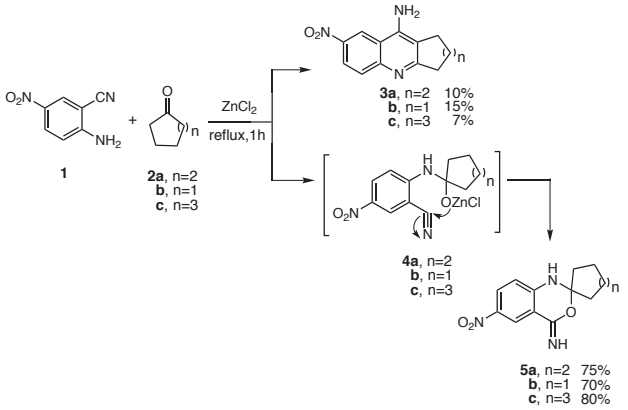
Results and Discussion.

After several trial experimentations we have found that the reaction of nitrile **1** with cyclohexanone **2a** afforded the 6-nitrospiro[3,1-benzoxazine-2,1'-cyclohexan]-4(1*H*)-imine **5a** in 75% yield and 7-nitrotacrine **3a** in 10% yield (Scheme 1). The structure assignment of product **5a** is based on spectroscopic evidences and crystal X-ray diffraction. The molecular mass of the product **5a** is 261. The IR spectrum is consistent with the assigned structure, showing absorption at 3359 cm^{-1}(NH) and 1672 cm^{-1}(C=N). In the ^{1}H NMR of **5a**, two singlet signals appeared at δ 8.44 (=NH) and 8.08 (NH), respectively. Signals assigned for the benzene ring and cyclohexanone ring were also observed in the corresponding region. The formation of product **5a** can be explained by attack of the amino group of nitrile **1** onto the carbonyl carbon atom of **2a** to give intermediate **4a** and subsequent cyclization by attack of the oxygen atom onto the nitrile group of **1** (Scheme 1). During the cyclization two new bonds were formed.

The choice of the catalyst played a crucial role: Optimal results were obtained by the use of $ZnCl_2$. The use of *p*-toluenesulfonic, CuCl and anhydrous $AlCl_3$ was much less effective. The cyclization of nitrile **1** with **2a**, catalyzed by means of 1.2 equivalent of $ZnCl_2$ (cyclohexanone, reflux), afforded **5a** in 75% yield. In contrast to the above

result we carried out the reaction of nitrile **1** with **2a** in the presence of other catalysts such as $AlCl_3$, we have not obtained the product **5a** but the 7-nitrotacrine **3a** in 80% yield. On the other hand, the reaction time is also an important parameter, and the best results were obtained when refluxed 1 hour. Due to prolong reaction time, the yield of product **5a** is reduced but the yield of byproduct **3a** increased.

Scheme 1



Crystallographic Date and Structure Determination of Compound **5a**.

A yellow crystal of the compound **5a** with dimensions of 0.32 mm x 0.30 mm x 0.20 mm was mounted on a glass fiber in random orientation. The data were collected by Rigaku Raxis RApid IP diffractometer with graphite monochromated Mo-Kα radiation (λ= 0.71073 Å) by using a ω/2θ scan mode in the range of 2.88°<θ< 27.48° at 293(2) K. A total of 4205 reflections were collected with 2178 unique ones (R_{int} = 0.0626). The intensity data were collected for *Lp* factors and semi-empirical absorption. The structure was solved by direct method and expanded by using Fourier difference techniques with SHELXS-97. All of the non-hydrogen atoms were located with successive difference Fourier synthesis. The structure was refined by full-matrix least-squares method on F^2 with anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms were added according to theoretical models. The final refinement gave R = 0.0994, wR = 0.3001. A summary of the crystallographic results is listed in Table 1. The final atomic parameters and equivalent isotropic thermal parameters for non-hydrogen atoms are listed in Table 2. The selected bond lengths and bond angles are illustrated in Table's 3 and 4 respectively. Figure 1 shows the molecular structure and Figure 2 shows the packing diagram of compound **5a**.

In compound **5a**, N (2), O (1), O (2) and benzene ring are coplanar and the atoms N (3), O (3), C (7) are nearly in the plane of benzene ring. The least-squares plane equations of N (3), O (3), C (7) and benzene is 31011 x + 11648 y + 61443 z = 915441. The dihedral angles between the plane formed by N (3), O (3) and C (6) and the above plane is 37.2°. Bond lengths indicate partial double bond character at the C (7)-N (1) bond. From the packing diagram of compound **5a** the intermolecular interactions occur at N (3)-H (3A)...O (1) (3.286 (4) Å, symmetry code: x-1,-y+1/2, z+1/2) and N (1)-H (1C)...O (3) (2.842 (4) Å, symmetry code: -x+2,-y,-z+2).

Table 1

Summary of Crystallographic Results for Compound **5a**

Formula	$C_{13}H_{15}N_3O_3$
Formula weight	261.28
Temperature	293 (2) K
Crystal system	Monoclinic
Space group	$P2_1/c$
a (Å)	6.6339 (13)
b (Å)	25.329 (5)
c (Å)	7.3756 (15)
α (°)	90
β (°)	91.85 (3)
γ (°)	90
V (Å^3)	1238.7 (4)
D_{calc} (g/cm^3)	1.401
Z	4
F(000)	552
Crystal size (mm)	0.32 x 0.30 x 0.20
Wavelength (Å)	0.71073
θ range for data collection (°)	2.88-27.48
Indices ranges	-8 ≤h ≤8, -31 ≤k ≤32, -8 ≤l ≤8
Reflections collected	4205
Independent reflections	2178
R (int)	0.0626
Data/ restraints/ parameters	2178/ 0/ 174
Final R indices [I>2$^\sigma$ (I)]	R_1 = 0.0994, wR_2 = 0.3001

Similarly, nitrile **1** reacted with **2b** or **2c** to afford 6-nitrospiro[3,1-benzoxazine-2,1'-cyclopentan]-4(1*H*)-imine **5b** in 70% yield and 7-nitrotacrine derivative **3b** in 15% yield or 6-nitrospiro[3,1-benzoxazine-2,1'-cycloheptan]-4(1*H*)-imine **5c** in 80% yield and 7-nitrotacrine derivative **3c** in 7% yield (Scheme 1).

In conclusion, this work demonstrates a very simple and efficient method for the synthesis of the 2*H*-3,1-benzoxazine derivatives under the catalyst in good yields.

EXPERIMENTAL

Melting points were determinated using XT4 microscope melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrophotometer and were run as KBr pellets. Only the most significant IR absorption bands are listed. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz on a Brucker 400 spectrometer. Chemical shifts are reported in δ (ppm) relative to internal tetramethylsilane. Mass spectra were recorded on a

Table 2

Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$)

Atom	x	y	z	U(eq)	Atom	x	y	z	U(eq)
O(1)	13419(4)	2926(1)	7971(5)	72(1)	C(5)	5495(5)	569(2)	12118(7)	63(1)
O(2)	14692(5)	2179(1)	7320(5)	76(1)	C(6)	7469(5)	872(1)	11952(6)	45(1)
O(3)	8663(4)	583(1)	10676(5)	72(1)	C(7)	10132(5)	800(1)	9759(6)	47(1)
N(1)	11338(4)	533(1)	8921(5)	51(1)	C(8)	10203(5)	1382(1)	9723(5)	42(1)
N(2)	13391(4)	2446(1)	7988(5)	53(1)	C(9)	11760(5)	1638(1)	8909(5)	43(1)
N(3)	7074(4)	1399(1)	11156(5)	48(1)	C(10)	11727(5)	2179(1)	8806(6)	44(1)
C(1)	8585(6)	920(1)	13743(7)	59(1)	C(11)	10126(5)	2469(1)	9436(6)	47(1)
C(2)	7270(9)	1155(2)	15206(9)	84(2)	C(12)	8571(5)	2221(1)	10209(6)	47(1)
C(3)	5412(12)	817(2)	15386(11)	112(3)	C(13)	8586(4)	1666(1)	10394(5)	41(1)
C(4)	4222(7)	770(2)	13579(10)	88(2)					

*U*eq is defined as one third of the trace of the orthogonalized *Uij* tensor

Table 3

Selected Bond lengths [Å]

Bond	Dist.	Bond	Dist.	Bond	Dist.
O(3)-C(7)	1.324(4)	N(3)-C(6)	1.479(4)	C(4)-C(5)	1.481(6)
O(3)-C(6)	1.448(4)	C(1)-C(6)	1.498(6)	C(5)-C(6)	1.527(5)
N(1)-C(7)	1.229(4)	C(1)-C(2)	1.530(6)	C(7)-C(8)	1.477(4)
N(2)-C(10)	1.443(4)	C(2)-C(3)	1.510(8)	C(8)-C(9)	1.373(4)
N(3)-C(13)	1.348(4)	C(3)-C(4)	1.532(10)	C(8)-C(13)	1.395(4)

Table 4

Selected Bond Angles [°]

Bond	(°)	Bond	(°)	Bond	(°)
C(7)-O(3)-C(6)	123.3(3)	O(3)-C(6)-N(3)	107.0(3)	C(9)-C(8)-C(7)	120.2(3)
O(2)-N(2)-C(10)	118.2(3)	O(3)-C(6)-C(1)	110.4(3)	C(13)-C(8)-C(7)	118.9(3)
O(1)-N(2)-C(10)	119.0(3)	N(3)-C(6)-C(1)	110.7(3)	C(9)-C(10)-C(11)	121.5(3)
C(13)-N(3)-C(6)	119.6(2)	O(3)-C(6)-C(5)	106.6(3)	C(9)-C(10)-N(2)	118.7(3)
C(6)-C(1)-C(2)	112.1(4)	N(3)-C(6)-C(5)	110.2(3)	C(11)-C(10)-N(2)	119.8(3)
C(3)-C(2)-C(1)	109.1(4)	C(1)-C(6)-C(5)	111.8(4)	N(3)-C(13)-C(8)	118.8(3)
C(2)-C(3)-C(4)	111.5(5)	N(1)-C(7)-O(3)	122.1(3)	N(3)-C(13)-C(12)	122.4(3)
C(5)-C(4)-C(3)	111.7(4)	N(1)-C(7)-C(8)	121.2(3)	C(8)-C(13)-C(12)	118.8(3)
C(4)-C(5)-C(6)	113.3(4)	O(3)-C(7)-C(8)	116.7(3)		

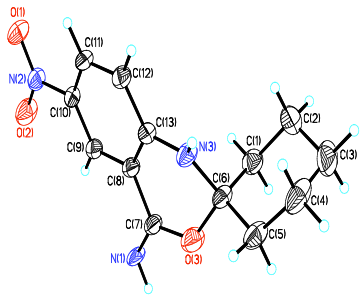


Figure 1. Crystal structure of compound **5a**

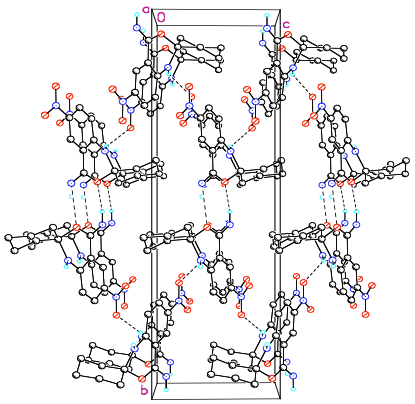


Figure 2. Packing diagram of compound **5a**

ZAB-HS mass spectrometer using ESI ionization. Elemental analyses were within ± 0.4% of theoretical values and were performed on an Elementar Vario EL.

General Procedure.

6-Nitrospiro[3,1-benzoxazine-2,1'-cyclohexan]-4(1*H*)-imine (**5a**) and 7-nitrotacrine (**3a**).

2-Amino-5-nitrobenzonitrile **1** (6.00 mmol, 1.0 g) refluxed in 10 ml of cyclohexanone **2a** under the catalyst of $ZnCl_2$ (7.00 mmol, 1.0 g) for 1.0 h. The reaction mixture was cooled and the formed precipitate was filtrated. The filtration residue was dispersed into water and titrated to pH 12-13 by 20% sodium hydroxide. After filtration, the crude product was purified by silica gel column chromatography eluting with ethyl acetate/light petroleum (1:1/v: v) to give **5a** and **3a**, respectively. Compound **5a** was obtained as yellow crystals, yield 75%; m.p. 297-299 °C; IR (KBr): 3359 and 3188 (NH), 2935 (CH_2), 1672 (C=NH), 1618(aromatic CH), 1529 and 1313 (NO_2) cm^{-1}; ^1H NMR (DMSO): δ 8.44 (s, 1H, =NH), 8.39 (d, 1H, J=2.8 Hz, ArH), 8.10 (dd, 1H, J=2.8, 7.7 Hz, ArH), 8.08 (s, 1H, R_1R_2NH), 6.94 (d, 1H, J=7.7 Hz, ArH), 1.80-1.05 (m, 10H, C_5H_{10}); ^{13}C NMR (DMSO): δ 21.13, 21.13, 24.74, 38.36, 38.36, 69.19, 112.88, 114.99, 124.57, 129.26, 137.27, 151.85, 161.66; MS: m/z 261 (M^+).

Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.78; N, 16.08. Found: C, 59.73; H, 5.79; N, 16.09.

Compound **3a** was obtained as yellow crystals, yield 10%; m.p. 171-173 °C; IR (KBr): 3443(NH_2), 2943(CH_2), 1655(aromatic CH), 1585 and 1326(NO_2) cm^{-1}; ^1H NMR (DMSO): δ 9.33 (d, 1H, J=2.4 Hz, ArH), 8.23 (dd, 1H, J=2.4, 9.2 Hz, ArH), 7.77 (d, 1H, J=9.2 Hz, ArH), 7.06 (s, 2H, RNH_2), 2.89-1.84 (m, 8H, C_4H_8); ^{13}C NMR (DMSO): δ 22.58, 22.68, 24.00, 34.04, 111.15, 115.86, 120.96, 122.02, 129.61, 142.58, 149.24, 151.18, 161.65; MS: m/z 243 (M^+).

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.88; H, 5.44; N, 17.54.

6-Nitrospiro[3,1-benzoxazine-2,1'-cyclopentan]-4(1*H*)-imine (**5b**) and 7-Nitrotacrine Derivative (**3b**).

Compound **5b** and compound **3b** were obtained in a similar method as that of **5a** and **3a** where **5b** was obtained as yellow crystals, yield 70%; m.p. 281-283 °C; IR (KBr): 3319 and 3180(NH), 2912(CH_2), 1672(C=NH), 1619(aromatic CH), 1534 and 1310 (NO_2) cm^{-1}; ^1H NMR (DMSO): δ 8.56 (s, 1H, =NH), 8.42 (d, 1H, J=2.4 Hz, ArH), 8.30 (s, 1H, NH), 8.10 (t, 1H, J=2.4, 8.0 Hz, ArH), 6.82 (d, 1H, J=2.4, 8.0 Hz, ArH), 1.88-1.67 (m, 8H, C_2H_8); ^{13}C NMR (DMSO): δ 21.90, 21.90, 40.15, 40.15, 77.32, 112.31, 114.14, 124.11, 128.62, 136.68, 151.63, 161.21; MS: m/z 247 (M^+).

Anal. Calcd. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.33; H, 5.31; N, 17.08.

Compound **3b** as yellow crystals, yield 15%; m.p. 296-298 °C; IR (KBr): 3401(NH_2), 1617(aromatic CH), 1571 and 1328(NO_2) cm^{-1}; ^1H NMR (DMSO): δ 9.25 (d, 1H, J=2.4 Hz, ArH), 8.21 (dd, 1H, J=2.4, 9.2 Hz, ArH), 7.78 (d, 1H, J=9.2 Hz, ArH), 7.09 (s, 2H, RNH_2), 2.94-2.02 (m, 6H, C_3H_6); ^{13}C NMR (DMSO): δ 22.38, 28.13, 35.29, 115.59, 116.63 120.78, 121.97, 129.81, 142.71, 148.95, 151.59, 170.76; MS: m/z 229 (M^+).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.49; H, 4.74; N, 18.12.

6-Nitrospiro[3,1-benzoxazine-2,1'-cycloheptan]-4(1*H*)-imine (**5c**) and 7-Nitrotacrine Derivative (**3c**).

Compound **5c** and compound **3c** were obtained in a similar method as that of **5a** and **3a** where **5c** is obtained as yellow crystals, yield 80%; m.p. 298-300 °C; IR (KBr): 3325 and 3195(NH), 2920(CH_2), 1669(C=NH), 1617(aromatic CH), 1537 and 1306 (NO_2) cm^{-1}; ^1H NMR (DMSO): δ 8.55 (s, 1H, =NH), 8.40 (d, 1H, J=2.8 Hz, ArH), 8.26 (s, 1H, NH), 8.09 (dd, 1H, J=2.8, 8.8 Hz, ArH), 6.82 (d, 1H, J=8.8 Hz, ArH), 1.94 (s, 4H, CH_2), 1.54 (s, 8H, CH_2); ^{13}C NMR (DMSO): δ20.77, 20.77, 29.21, 29.21, 41.85, 41.85, 72.70, 112.19, 114.27, 124.09, 128.78, 136.67, 151.17, 160.91; MS: m/z 275 (M^+).

Anal. Calcd. for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.11; H, 6.33; N, 15.18.

Compound **3c** as yellow crystals, yield 7%; m.p. 236-238 °C; IR (KBr): 3434(NH_2), 2913(CH_2), 1656(aromatic CH), 1584 and 1327(NO_2) cm^{-1}; ^1H NMR (DMSO): δ 9.28 (s, 1H, ArH), 8.21 (d, 1H, J=8.0 Hz, ArH), 7.78 (d, 1H, J=8.0 Hz, ArH), 7.01 (s, 2H, RNH_2), 3.03 (d, 2H, CH_2), 2.85 (s, 2H, CH_2), 1.82 (s, 2H, CH_2), 1.58 (d, 4H, CH_2); ^{13}C NMR (DMSO): δ 25.13, 26.29, 27.25, 31.48, 39.26, 115.67, 116.42, 120.52, 121.23, 129.69, 142.43, 149.09, 149.12, 167.96; MS: m/z 257 (M^+).

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.40; H, 5.87; N, 16.23.

Acknowledgements.

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