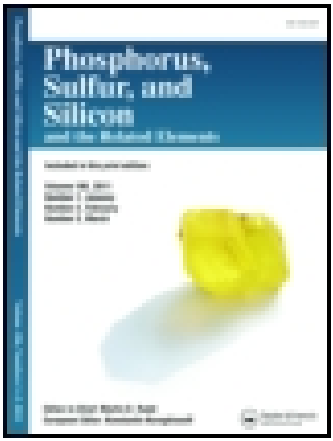

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CYCLOADDITION REACTION OF BENZOHETEROAZEPINE: SYNTHESIS OF 4a,5,6,12-TETRAHYDRO-1H-1,3-OXAZINO[3,2 -d[[1,5] BENZOTHIAZEPIN-1-ONES AND 1H,7H-1,3-OXAZINO[3,2-d][1,5] BENZODIAZEPIN-1-ONES

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CYCLOADDITION REACTION OF BENZOHETEROAZEPINE: SYNTHESIS OF 4a,5,6,12-TETRAHYDRO-1*H*-1,3-OXAZINO[3,2-*d*][1,5] BENZOTHIAZEPIN-1-ONES AND 1*H*,7*H*-1,3-OXAZINO[3,2-*d*][1,5] BENZODIAZEPIN-1-ONES

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2,3-Dihydro-1,5-benzothiazepines and 2,3-dihydro-1*H*-1,5-benzodiazepines reacted with α-carbonylketenes, generated from 2-diazo-1,3-diphenyl-1,3-propanedione and 2-diazo-1-phenyl-1,3-butandione by heating, to give [2+4] cycloadducts 4a,5,6,12-tetrahydro-1*H*-1,3-oxazino[3,2-*d*] [1,5]-benzothiazepin-1-ones and 4a,5,6,12-tetrahydro-1*H*,7*H*-1,3-oxazino [3,2-*d*][1,5]-benzodiazepin-1-ones. The cycloaddition reactions showed different regioselectivities when different 1,5-benzoheteroazepines reacted with asymmetric 2-diazo-1-phenyl-1,3-butandione. The conformations of cycloadducts and cycloaddition reaction mechanism were described.

Keywords: Benzoheteroazepines; Oxazino-benzothiazepin-1-ones; Oxazino-benzodiazepin-1-ones; Cycloaddition reaction

In recent years, biological and pharmacological activities have been well known for numerous heterocyclic aromatic tricycles[1,2]. Much attention has been paid for the synthesis of the heterocyclic compounds with new ring systems[3]. In our previous papers[4,5], an interesting phenomenon was found that the conjugation system of Ar-N=C-Ar of 1,5-benzothiazepine and 1,5-benzodiazepine is nonplanar and the C=N bond in this system is more rigid than that in other systems. We are interested in the reactivity of the C=N bond in this system, especially in the cycloaddition reaction of the C=N bond of 1,5-benzothiazepines and 1,5-benzodiazepines with α

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-carbonylketenes and two new seven-membered heterocyclic rings, 4a,5,6,12-tetrahydro-1*H*-1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one and 4a,5,6,12-tetrahydro-1*H*,7*H*-1,3-oxazino[3,2-*d*]-1,5-benzodiazepin-1-one were obtained. They are known to be potential pharmacological agents.

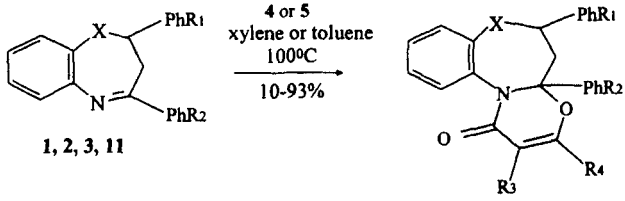
2,3-Dihydro-1,5-benzothiazepines **1** were prepared by the standard method from α, β -unsaturated ketones and *o*-aminothiophenol in excellent yields[6,7]. Among them 2-(2-bromophenyl)-4-phenyl-2,3-dihydro-1,5- benzothiazepine **1e** was further reduced to 2-(2-bromophenyl)-4-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepine with $NaBH_4$ in methanol-tetrahydrofuran at room temperature[8,9]. Both the thiazepine **1e** and its tetrahydro derivative are unknown compounds. 2,3-Dihydro-1*H*-1,5-benzodiazepines **2** were synthesized via α,β -unsaturated ketones and *o*-phenylenediamine in good yields[10].

We have tested the C=N bond of 1,5-benzothiazepine systems as a dienophile in 1,4-cycloadditions of α -carbonylketenes, generated from α -diazodiketones by heating[11,12]. The reactions of 1,5-benzothiazepines **1** with 2-diazo-1,3-diphenyl-1,3-propanedione **4** in xylene afforded 4a,6-diaryl-2,3-diphenyl-4a,5,6,12-tetrahydro-1*H*-1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-ones **6** in high yields. However, the reactions of 1,5-benzothiazepines with 2-diazo-1-phenyl-1,3-butanedione **5** under the same conditions, depending on the different 1,5-benzothiazepines, afforded 2,4a,6-triaryl-3-methyl-4a,5,6,12-tetrahydro-1*H*-1,3-oxazino [3,2-*d*][1,5]benzothiazepin-1-ones **7** with **1**a, **1**d-g or 3,4a,6-triaryl-2-methyl-4a,5,6,12-tetrahydro-1*H*-1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-ones **8** with **1**h-l in low yields. From compounds **1**b and **1**c both **7**b, **7**c and **8**b, **8**c were obtained at the same time.

We have also tested the C=N bond of 1,5-benzodiazepines as a dienophile in 1,4-cycloadditions of α - carbonylketenes above[11,12]. In order to avoid addition reactions of N-H bond in benzodiazepine with α - carbonylketene, 1-benzoyl-2,3-dihydro-1*H*-1,5-benzodiazepines **3**, instead of 2,3-dihydro-1*H*-1,5-benzodiazepines **2**, was allowed to react with **4** to afford 4a,6-diaryl-7-benzoyl-2,3-diphenyl-4a,5,6,12-tetrahydro-1*H*,7*H*-1,3-oxazino [3,2-*d*][1,5]benzodiazepin-1-ones **9**, and with **5** to afford specially 4a,6–diaryl-7-benzoyl-2-methyl-3-phenyl-4a,5,6,12-tetrahydro-1*H*,7*H*, 1,3-oxazino[3,2-*d*][1,5]benzodiazepin-1-ones **10** which was purified by column chromatography[11,12].

When an equimolar amount of 1,5-benzodiazepine **2** was used as a dienophile in 1,4-cycloaddition of α -carbonylketene, the reaction of

2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine with **4** in toluene took place, at first, addition of N-H bond to generate 1-(2-benzoyl-phenylacetyl)-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine **11**, and then followed the cycloaddition reaction of C=N bond to generate 7-(2-benzoylphenylacetyl)-2,3,4a,6-tetraphenyl-4a,5,6,12-tetrahydro-1*H*,7*H*-1,3-oxazino[3,2-*d*][1,5]benzodiazepin-1-one **12**. Two products **11**and **12** were obtained, while a sole cycloaddition reaction of C=N bond to give 2,3,4a,6-tetraphenyl-4a,5,6,12-tetrahydro-1*H*,7*H*-1,3-oxazino[3,2-*d*][1,5] benzodiazepin-1-one was not observed. The result indicated that the addition of α -carbonylketene to N-H bond is preferred to that to C=N bond in this reaction. When α -diazo-β -diketone is increased to more than two equivalents of 2,3-dihydro-1*H*-1,5-benzodiazepine, compound **12** is the sole product.



1, 2, 3, 11

6, 7, 8, 9, 10, 12

4: PhCOC(N2)COPh, **5**: PhCOC(N2)COMe
1, 6, 7, 8: X=S; **2**: X=NH; **3, 9, 10**: X=NCOPh
11, 12: X=NCOCHPhCOPh
6, 9, 12: R3=R4=Ph; **7**: R3=Ph, R4=Me; **8, 10**: R3=Me, R4=Ph

	a	b	c	d	e	f	g	h	i	j	k	l	m
R1:	H,	o-Cl,	m-Cl,	p-Cl,	o-Br,	m-Br,	p-Br,	o-MeO,	p-MeO,	m-NO2,	H,	H,	H
R2:	H,	H,	H,	H,	H,	H,	H,	H,	H,	H,	p-Cl,	p-MeO,	m-NO2

SCHEME 1

To our knowledge, these cycloadducts have previously not been reported. The structures of these products were determined by IR, MS/FAB, ^{1}H NMR spectrometries and elemental analyses. Compounds **7**d, **9**a and **12**a, each of every type compounds, also were determined by ^{13}C NMR(Table I and II).

In order to study the conformation of cycloadducts and cycloaddition mechanism, compound **7d** was subjected to X-ray diffraction analysis. The colorless crystal of **7d** obtained by evaporation of its saturated ethyl acetate solution was used for the measurement with the dimensions (mm^3) of

$0.10 \times 0.18 \times 0.30$. Accurate cell dimensions were determined on Rigaku AFC7R four circle diffractometer using graphite monochromatized MoKα (λ =0.71073Å) radiation. A summary of some crystal data are as follows: formula $C_{31}H_{24}ClNO_2S$, crystal system monoclinic, space group $P2_1/C$, a=12.672(3)Å, b=15.430(3)Å, c=14.731(3)Å, β =114.77(3)°, V=2615.4(13)Å^3, Z=4 molecules/unit cell, $d$calcd=1.29g/cm^3, the total numbers of independently observed reflections of compound **7d** with $F>6\sigma$ (F) are 1983. The final discrepancy factors after refinement of positional and anisotropic thermal parameters for nonhydrogen atoms and positional parameters for hydrogens are R=5.53%(Rw=6.92%).

TABLE I Physical and Spectral Data

Compd	*Yield %*	*m.p. % °C*	*^{1}HNMR (CDCl$_3$/TMS), ^{13}CNMR (CDCl$_3$/TMS) δ (ppm), J(Hz)*	*IR(KBr) ν (cm^{-1})*	*MS/FAB m/z (M+1)*
6a	93	191–2	2.39(1H,dd,*J*=4.8, 16.0), 2.87(1H, dd, *J*=12.0, 16.0), 4.75(1H, dd, *J*=4.8, 12.0), 6.85–7.98(24H, m, Aromatic)	1600	538
6b	92	145–6	2.22(1H, dd, *J*=4.0, 16.0), 2.87(1H, dd, *J*=12.0, 16.0), 5.42(1H, dd, *J*=4.0, 12.0), 6.85–7.98(23H, m, Aromatic)	1600	572
6c	88	186–7	2.27(1H, dd, *J*=4.0, 16.0), 2.83(1H, dd, *J*=12.0, 16.0), 4.69(1H, dd, *J*=4.0, 12.0), 6.85–7.93(23H, m, Aromatic)	1600	572
6d	88	185–6	2.28(1H, dd, *J*=4.8, 16.0), 2.84(1H, dd, *J*=12.0, 16.0), 4.72(1H, dd, *J*=4.8, 12.0), 6.85–7.95(23H, m, Aromatic)	1665	572
6e	89	160–1	2.18(1H, dd, *J*=4.0, 16.0), 2.91(1H, dd, *J*=12.0, 16.0), 5.42(1H, dd, *J*=4.0, 12.0), 6.88–7.97(23H, m, Aromatic)	1670	616
6f	87	169–170	2.28(1H, dd, *J*=4.0, 16.0), 2.83(1H, dd, *J*=12.0, 16.0), 4.70(1H, dd, *J*=4.0, 12.0), 6.85–7.95(23H, m, Aromatic)	1660	616
6g	91	162–3	2.28(1H, dd, *J*=4.8, 16.0), 2.83(1H, dd, *J*=12.0, 16.0), 4.68(1H, dd, *J*=4.8, 12.0), 6.85–7.95(23H, m, Aromatic)	1660	616
6h	44	189–190	3.82(3H, s, OMe), 2.38(1H, dd, *J*=4.0, 16.0), 2.83(1H, dd, *J*=12.0, 16.0), 5.35(1H, dd, *J*=4.0, 12.0), 6.78–7.92(23H, m, Aromatic)	1660	568
6i	37	185–6	3.74(3H, s, OMe), 2.30(1H, dd, *J*=4.0, 16.0), 2.83(1H, dd, *J*=12.0, 16.0), 4.70(1H, dd, *J*=4.0, 12.0), 6.85–7.90(23H, m, Aromatic)	1660	568

Compd	*Yield %*	*m.p. % °C*	*^{1}HNMR ($CDCl_3$/TMS), ^{13}CNMR ($CDCl_3$/TMS) δ (ppm), J(Hz)*	*IR(KBr) ν (cm^{-1})*	*MS/FAB m/z (M+1)*
6j	49	146–7	2.33(1H, dd, *J*=4.0, 16.0), 2.90(1H, dd, *J*=12.0, 16.0), 4.83(1H, dd, *J*=4.0, 12.0), 6.85–8.15(23H, m, Aromatic)	1660	583
6k	52	136–7	2.30(1H, dd, *J*=4.0, 16.0), 2.80(1H, dd, *J*=12.0, 16.0), 4.70(1H, dd, *J*=4.0, 12.0), 6.85–7.90(23H, m, Aromatic)	1660	572
6l	62	125–6	3.77(3H, s, OMe), 2.30(1H, dd, *J*=4.0, 16.0), 2.82(1H, dd, *J*=12.0, 16.0), 4.72(1H, dd, *J*=4.0, 12.0), 6.80–7.90(23H, m, Aromatic)	1660	568
7a	32	193–4	2.01(3H, s, Me), 2.23(1H,dd,*J*=4.0, 16.0), 2.65(1H, dd, *J*=11.6, 16.0), 4.68(1H, dd, *J*=4.0, 11.6), 6.75–7.95(19H, m, Aromatic)	1660	476
7b	11	180–1	2.00(3H, s, Me), 2.58(1H, dd, *J*=4.8, 14.8), 2.98(1H, dd, *J*=12.4, 14.8), 3.96(1H, dd, *J*=4.8, 12.4), 6.90–8.30(18H, m, Aromatic)	1650	510
7c	39	182–3	2.00(3H, s, Me), 2.18(1H, dd, *J*=4.8, 16.0), 2.62(1H, dd, *J*=11.4, 16.0), 4.66(1H, dd, *J*=4.8, 11.4), 6.83–7.97(18H, m, Aromatic)	1660	510
7d	25	182–3	2.00(3H, s, Me), 2.18(1H, dd, *J*=4.0, 16.0), 2.62(1H, dd, *J*=11.4, 16.0), 4.66(1H, dd, *J*=4.0, 11.4), 6.83–7.97(18H, m, Aromatic) 18.2, 41.6, 45.5, 92.1, 114.9, 125.4, 127.3, 127.8, 128.1, 128.5, 128.6, 128.9, 129.3, 130.8, 131.2, 133.1, 133.3, 135.3, 141.6, 143.6, 144.1, 160.9	1660	510
7e	54	173–4	2.01(3H, s, Me), 2.12(1H, dd, *J*=4.0, 16.0), 2.68(1H, dd, *J*=12.0, 16.0), 5.33(1H, dd, *J*=4.0, 12.0), 6.82–7.98(18H, m, Aromatic)	1660	554
7f	21	146–7	2.00(3H, s, Me), 2.18(1H, dd, *J*=4.8, 16.0), 2.66(1H, dd, *J*=12.0, 16.0), 4.65(1H, dd, *J*=4.8, 12.0), 6.77–8.02(18H, m, Aromatic)	1660	554
7g	23	186–7	1.99(3H, s, Me), 2.17(1H, dd, *J*=4.0, 16.0), 2.62(1H, dd, *J*=12.0, 16.0), 4.65(1H, dd, *J*=4.0, 12.0), 6.70–7.95(18H, m, Aromatic)	1665	554
8b	33	184–5	1.83(3H, s, Me), 2.59(1H, dd, *J*=4.8, 14.8), 2.98(1H, dd, *J*=12.4, 14.8), 3.96(1H, dd, *J*=4.8, 12.4), 6.90–8.30(18H, m, Aromatic)	1660	510
8c	10	191–2	1.86(3H, s, Me), 2.17(1H, dd, *J*=4.8, 16.0), 2.62(1H, dd, *J*=11.4, 16), 4.63(1H, dd, *J*=4.8, 11.4), 6.80–8.00(18H, m, Aromatic)	1660	510
8h	20	181–2	1.87(3H, s, Me), 3.78(3H, s, OMe), 2.28(1H, dd, *J*=4.0, 16.0), 2.68(1H, dd, *J*=12.0, 16.0), 5.16(1H, dd, *J*=4.0, 12.0), 6.65- 7.95(18H, m, Aromatic)	1660	506

Compd	*Yield %*	*m.p. % °C*	*^{1}HNMR ($CDCl_3$/TMS), ^{13}CNMR ($CDCl_3$/TMS) δ (ppm), J(Hz)*	*IR(KBr) ν (cm^{-1})*	*MS/FAB m/z (M+1)*
8i	10	144–5	1.85(3H, s, Me), 3.73(3H, s, OMe), 2.18(1H, dd, *J*=4.0, 16.0), 2.69(1H, dd, *J*=12.0, 16.0), 4.61(1H, dd, *J*=4.0, 12.0), 6.67-7.95(18H, m, Aromatic)	1660	506
8j	38	180–1	1.85(3H, s, Me), 2.18(1H, dd, *J*=4.0, 16.0), 2.63(1H, dd, *J*=12.0, 16.0), 4.73(1H, dd, *J*=4.0, 12.0), 7.10–8.10(18H, m, Aromatic)	1660	521
8k	39	140–1	1.84(3H, s, Me), 2.80(1H, dd, *J*=4.0, 16.0), 3.35(1H, dd, *J*=12.0, 16.0), 4.55(1H, dd, *J*=4.0, 12.0), 6.77–8.25(18H, m, Aromatic)	1660	510
8l	40	168–9	1.84(3H, s, Me), 3.79(3H, s, OMe), 2.18(1H, dd, *J*=4.0, 16.0), 2.63(1H, dd, *J*=12.0, 16.0), 4.65(1H, dd, *J*=4.0, 12.0), 6.77-8.18(18H, m, Aromatic)	1660	506
9a	74	201–2	3.01(1H,dd,*J*=0.2, 0.8), 5.17(1H, dd, *J*=0.2, 8.4), 6.42(1H, dd, *J*=0.8, 8.4), 6.75–7.90(29H, m, Aromatic) 42.4, 56.2, 95.2, 116.9, 124.3, 126.3, 127.5, 127.9, 128.1, 128.4, 128.6, 129.1, 129.4, 130.1, 130.4, 131.5, 132.0, 132.7, 133.4, 133.8, 134.9, 137.5, 139.2, 140.1, 160.1, 165.5, 168.7	1660	625
9b	34	165–6	3.00(1H, dd, *J*=1.6, 8.8), 5.13(1H, dd, *J*=8.0, 8.8), 6.39(1H, dd, *J*=1.6, 8.0), 6.70–8.25(28H, m, Aromatic)	1660	659
9c	76	198–9	2.99(1H, dd, *J*=1.6, 8.0), 5.11(1H, dd, *J*=8.0, 8.8), 6.46(1H, dd, *J*=1.6, 8.8), 6.77–7.87(28H, m, Aromatic)	1660	659
9d	38	173–4	2.98(1H, dd, *J*=1.6, 8.0), 5.12(1H, dd, *J*=8.0, 8.0), 6.39(1H, dd, *J*=1.6, 8.0), 6.72–7.93(28H, m, Aromatic)	1660	659
9e	36	212–3	2.21(1H, dd, *J*=12.8, 16.0), 2.96(1H, dd, *J*=3.2, 16.0), 6.10(1H, dd, *J*=3.2, 12.8), 6.85–8.05(28H, m, Aromatic)	1660	703
9f	64	197–8	3.00(1H, dd, *J*=0.8, 10.4), 5.10(1H, dd, *J*=8.0, 10.4), 6.46(1H, dd, *J*=0.8, 8.0), 6.77–7.94(28H, m, Aromatic)	1660	703
9j	64	199–200	3.04(1H, dd, *J*=1.6, 8.0), 5.21(1H, dd, *J*=8.0, 8.8), 6.45(1H, dd, *J*=1.6, 8.8), 6.76–8.18(28H, m, Aromatic)	1660	670
9k	39	241–2	3.00(1H, dd, *J*=1.6, 11.2), 5.18(1H, dd, *J*=8.0, 11.2), 6.43(1H, dd, *J*=1.6, 8.0), 6.75–7.90(28H, m, Aromatic)	1660	659
9m	67	140–1	3.10(1H, dd, *J*=1.6, 11.2), 5.18(1H, dd, *J*=8.0, 11.2), 6.41(1H, dd, *J*=1.6, 8.0), 6.73–8.83(28H, m, Aromatic)	1660	670

Compd	*Yield %*	*m.p. % °C*	*^{1}HNMR ($CDCl_3$/TMS), ^{13}CNMR ($CDCl_3$/TMS) δ (ppm), J(Hz)*	*IR(KBr) ν (cm^{-1})*	*MS/FAB m/z (M+1)*
10a	18	203–4	1.86(3H, s, Me), 2.92(1H,dd,*J*=1.6, 10.4), 5.06(1H, dd, *J*=8.0, 10.4), 6.40(1H, dd, *J*=1.6, 8.0), 6.72–7.96(24H, m, Aromatic)	1660	563
10b	29	192–3	1.85(3H, s, Me), 2.80(1H, dd, *J*=3.2, 6.0), 5.26(1H, dd, *J*=6.0, 12.0), 6.55(1H, dd, *J*=3.2, 12.0), 6.74–8.05(23H, m, Aromatic)	1660	597
10c	46	183–4	1.85(3H, s, Me), 2.88(1H, dd, *J*=1.6, 10.4), 4.99(1H, dd, *J*=8.0, 10.4), 6.41(1H, dd, *J*=1.6, 8.0), 6.73–7.85(23H, m, Aromatic)	1660	597
10d	34	187–8	1.86(3H, s, Me), 2.88(1H, dd, *J*=1.6, 10.4), 5.02(1H, dd, *J*=8.0, 10.4), 6.35(1H, dd, *J*=1.6, 8.0), 6.78–7.85(23H, m, Aromatic)	1660	597
10e	20	215–6	1.94(3H, s, Me), 2.10 (1H, dd, *J*=6.0, 12.0), 2.82(1H, dd, *J*=4.0, 6.0), 6.50(1H, dd, *J*=4.0, 12.0), 6.88–8.06(23H, m, Aromatic)	1655	641
10f	24	179–180	1.85(3H, s, Me), 2.88(1H, dd, *J*=1.6, 8.8), 4.91(1H, dd, *J*=8.0, 8.8), 4.65(1H, dd, *J*=1.6, 8.0), 6.77–8.02(23H, m, Aromatic)	1660	641
10j	50	200–1	1.86(3H, s, Me), 2.94(1H, dd, *J*=1.6, 8.8), 5.10(1H, dd, *J*=8.0, 8.8), 6.40(1H, dd, *J*=1.6, 8.0), 6.72–8.17(23H, m, Aromatic)	1660	608
10k	25	218–9	1.87(3H, s, Me), 2.82(3H, s, OMe), 2.88(1H, dd, *J*=1.6, 11.2), 5.08(1H, dd, *J*=7.2, 11.2), 6.42(1H, dd, *J*=1.6, 7.2), 6.63-7.33(23H, m, Aromatic)	1660	597
10m	45	180–1	1.85(3H, s, Me), 3.01(1H, dd, *J*=1.6, 11.2), 5.08(1H, dd, *J*=8.8, 11.2), 6.39(1H, dd, *J*=1.6, 8.8), 6.80–8.22(23H, m, Aromatic)	1660	608
11a	24	204–5	2.96(1H, dd, *J*=8.0, 12.8), 3.25(1H, dd, *J*=6.4, 12.8), 5.22(1H, s, PhCH), 6.31(1H, dd, *J*=6.4, 8.0), 6.80–8.15(24H, m, Aromatic)	1660 1710	521
12a	10	137–8	2.62(1H, dd, *J*=8.0, 15.2), 5.20(1H, dd, *J*=6.4, 15.2), 5.52(1H, s, PhCH), 6.31(1H, dd, *J*=6.4, 8.0), 6.55–7.88(34H, m, Aromatic) 29.7, 41.0, 54.5, 60.4, 95.5, 116.4, 124.0, 126.6, 127.36, 127.45, 127.7, 127.9, 128.0, 128.4, 128.5, 128.7, 129.1, 129.5, 130.1, 130.5, 130.9, 131.5, 132.5, 133.0, 133.4, 133.5, 135.2, 138.0, 138.4, 139.0, 160.1, 165.5, 194.3	1665 1675	743

TABLE II Elemental Analysis Data

Compd	*Molecular Formula*	*Molecular Weight*	*Cald.*			*Found*		
			C	*H*	*N*	*C*	*H*	*N*
6a	$C_{36}H_{27}NO_2S$	537.68	80.42	5.06	2.61	80.40	4.94	2.61
6b	$C_{36}H_{26}NClO_2S$	572.12	75.58	4.58	2.45	75.68	4.47	2.59
6c	$C_{36}H_{26}NClO_2S$	572.12	75.58	4.58	2.45	75.46	4.61	2.66
6d	$C_{36}H_{26}NClO_2S$	572.12	75.58	4.58	2.45	75.58	4.41	2.62
6e	$C_{36}H_{26}NBrO_2S$	616.57	70.13	4.25	2.27	70.38	4.44	2.02
6f	$C_{36}H_{26}NBrO_2S$	616.57	70.13	4.25	2.27	70.06	4.18	2.39
6g	$C_{36}H_{26}NBrO_2S$	616.57	70.13	4.25	2.27	70.22	4.21	2.19
6h	$C_{37}H_{29}NO_3S$	567.70	78.28	5.15	2.47	78.50	5.28	2.67
6i	$C_{37}H_{29}NO_3S$	567.70	78.28	5.15	2.47	78.09	5.29	2.71
6j	$C_{36}H_{26}N_2O_4S$	582.67	74.21	4.50	4.81	74.42	4.31	4.67
6k	$C_{36}H_{26}NClO_2S$	572.12	75.58	4.58	2.45	75.77	4.46	2.26
6l	$C_{37}H_{29}NO_3S$	567.70	78.28	5.15	2.47	78.18	5.23	2.58
7a	$C_{31}H_{25}NO_2S$	475.61	78.29	5.30	2.95	78.01	5.32	3.21
7b	$C_{31}H_{24}NClO_2S$	510.05	73.00	4.74	2.75	72.88	4.83	2.79
7c	$C_{31}H_{24}NClO_2S$	510.05	73.00	4.74	2.75	73.26	4.79	2.54
7d	$C_{31}H_{24}NClO_2S$	510.05	73.00	4.74	2.75	73.19	4.86	2.47
7e	$C_{31}H_{24}NBrO_2S$	554.50	67.15	4.36	2.53	67.29	4.62	2.24
7f	$C_{31}H_{24}NBrO_2S$	554.50	67.15	4.36	2.53	67.18	4.45	2.33
7g	$C_{31}H_{24}NBrO_2S$	554.50	67.15	4.36	2.53	67.35	4.28	2.59
8b	$C_{31}H_{24}NClO_2S$	510.05	73.00	4.74	2.75	73.28	4.63	2.98
8c	$C_{31}H_{24}NClO_2S$	510.05	73.00	4.74	2.75	73.19	4.48	2.82
8h	$C_{32}H_{27}NO_3S$	505.63	76.01	5.38	2.77	76.23	5.51	2.90
8i	$C_{32}H_{27}NO_3S$	505.63	76.01	5.38	2.77	75.88	5.47	2.84
8j	$C_{31}H_{24}N_2O_4S$	520.60	71.52	4.65	5.38	71.27	4.92	5.56
8k	$C_{31}H_{24}NClO_2S$	510.05	73.00	4.74	2.75	72.81	4.80	2.93
8l	$C_{32}H_{27}NO_3S$	505.63	76.01	5.38	2.77	76.17	5.21	2.96
9a	$C_{43}H_{32}N_2O_3$	624.74	82.67	5.16	4.48	82.41	4.94	4.67
9b	$C_{43}H_{31}N_2ClO_3$	659.18	78.35	4.74	4.25	78.07	4.47	4.51
9c	$C_{43}H_{31}N_2ClO_3$	659.18	78.35	4.74	4.25	78.46	4.60	4.26
9d	$C_{43}H_{31}N_2ClO_3$	659.18	78.35	4.74	4.25	78.56	4.49	4.32
9e	$C_{43}H_{31}N_2BrO_3$	703.63	73.40	4.44	3.98	73.28	4.42	4.02

Compd	Molecular Formula	Molecular Weight	Cald.			Found		
			C	H	N	C	H	N
9f	$C_{43}H_{31}N_2BrO_3$	703.63	73.40	4.44	3.98	73.12	4.56	4.10
9j	$C_{43}H_{31}N_3O_5$	669.74	77.12	4.67	6.27	77.31	4.53	6.49
9k	$C_{43}H_{31}N_2ClO_3$	659.18	78.35	4.74	4.25	78.56	4.54	4.26
9m	$C_{43}H_{31}N_3O_5$	669.74	77.12	4.67	6.27	77.29	4.41	6.36
10a	$C_{38}H_{30}N_2O_3$	562.67	81.12	5.37	4.98	81.07	5.32	5.21
10b	$C_{38}H_{29}N_2ClO_3$	597.11	76.44	4.90	4.69	76.71	4.80	4.78
10c	$C_{38}H_{29}N_2ClO_3$	597.11	76.44	4.90	4.69	76.23	4.76	4.51
10d	$C_{38}H_{29}N_2ClO_3$	597.11	76.44	4.90	4.69	76.28	4.83	4.47
10e	$C_{38}H_{29}N_2BrO_3$	641.56	71.14	4.56	4.37	71.28	4.67	4.25
10f	$C_{38}H_{29}N_2BrO_3$	641.56	71.14	4.56	4.37	71.02	4.69	4.59
10j	$C_{38}H_{29}N_3O_5$	607.67	75.11	4.81	6.92	75.29	4.94	7.09
10k	$C_{38}H_{29}N_2ClO_3$	527.11	76.44	4.90	4.69	76.68	4.82	4.44
10m	$C_{38}H_{29}N_3O_5$	607.67	75.11	4.56	6.92	74.97	4.63	7.06
11a	$C_{36}H_{28}N_2O_2$	520.63	83.05	5.42	5.38	83.30	5.24	5.62
12a	$C_{51}H_{38}N_2O_4$	742.87	82.46	5.16	3.77	82.40	4.99	3.91

The molecular skeleton is a tricyclic system containing a benzene ring, a seven-membered heterocyclic ring and a six-membered oxazine ring. The central thiazepine ring is slightly distorted with a boat-like conformation, and is cis-fused to the 1,3-oxazinone ring at N1 and C9, while the latter moiety is in a half-chair conformation. The phenyl group on C9 and the p-chlorophenyl group on C7 are equatorial in the central ring. That is, the 4a-phenyl and 6-(4-chlorophenyl) in compound **7d** are in "down" thiazepine configuration, the 1,3-oxazinone ring in **7d** is in "up" thiazepine configuration (shown in Figure 1). In other word, the cycloaddition reaction is a cis addition reaction and proceeds rapidly. Apparently, these cycloaddition reactions involved a Diels-Alder reaction with the formation of a oxazine ring.

The interesting feature of the molecule is that the central ring adopts slightly twisted boat-like conformation which is energically not so favorable, but this conformation is probably stabilized by the presence of the heteroatoms, especially the larger sulphur atom in the ring and by the influence of the exocyclic bulky phenyl substituents attached to C7 and C9.

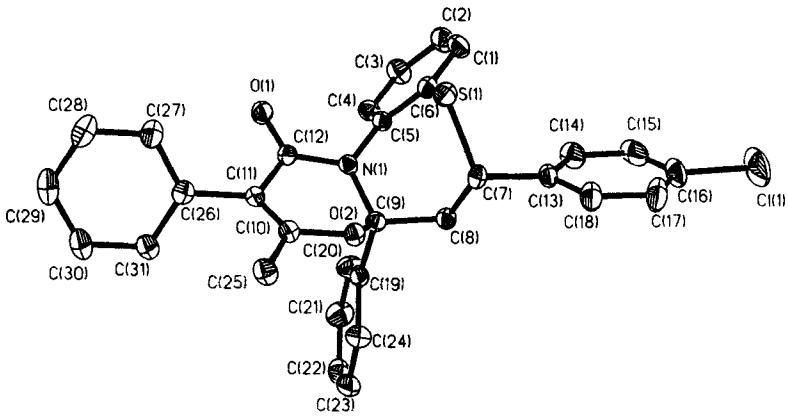
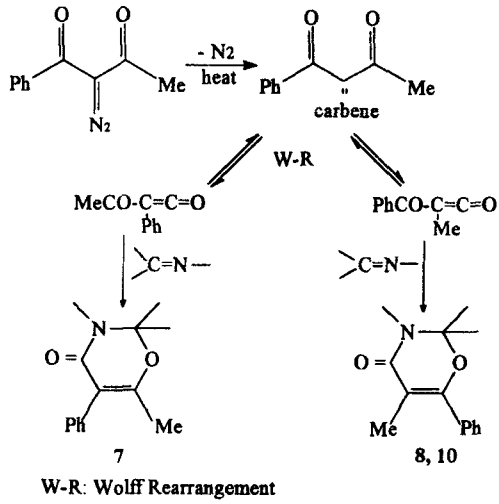


FIGURE 1 *ORTEP* stereoview of 6-(4-chlorophenyl)-2,4a-diphenyl-3-methyl-4a,5,6,12-tetrahydro-1*H*-1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one **7d**

By using asymmetric α-diazo-β-diketone **5** for this cycloaddition reaction, it was found that regioselective cycloadducts of types **7**, **8** and **10** were the main products. The reactions are explained as follows. 2-Diazo-1-phenyl-1,3-butanedione **5**, at first, released N_2 to generate quickly diacylcarbene under heating in a non-polar solvent xylene or toluene, and followed by a thermal Wolff rerrangement to give acetyl phenyl ketene and benzoyl methyl ketene, which added to the C=N double bonds of 1,5-benzoheteroazepines. The ketene which was chosen for the addition to the C=N bonds of 1,5-benzoheteroazepines will be based on the frontier orbital energies of 1,5-benzoheteroazepines. According to the frontier orbital theory, the ketene, of which the frontier orbital energy is close to that of C=N bond in 1,5-benzoheteroazepine, was favorable to react with the 1,5-benzoheteroazepine. Consequently, 1,5-benzoheteroazepines reacted with **5** to obtain two kinds of regioselective cycloadducts **7** or **8**, **10**, respectively, because of the different substituted groups and heteroatoms in the seven-membered rings. But compounds **1b** and **1c** could afford both of these two kinds of cycloadducts **7b**, **7c** and **8b**, **8c** at the same time with different regioselectivities, 1:3 (**7:8**) for **1b** and 4:1 (**7:8**) for **1c**, respectively. It was assumed those the frontier orbital energies of their C=N double bonds maybe located between those of the two ketenes mentioned above. Otherwise, different regioselectivities of their cycloadducts depended on the different frontier orbital energies of their C=N

bonds, which was near to that of different ketene. The low yields in cycloadditions with **5** were due to reversibility of Diels-Alder reaction and the formation of the expected ketene is not always favorable.



SCHEME 2

In conclusion, the cycloadditions of 1,5-benzothiazepines with 2-diazo-1,3-diphenyl-1,3-propanedione gave high yields, while those with 2-diazo-1-phenyl-1,3-butanedione gave low yields. Different regioselectivities are depending on different 1,5-benzothiazepine derivatives. However, in the case of 1,5-benzodiazepines with two compounds above only low yields and the same regioselectivity were obtained. All seven-membered rings in these heterocyclic compounds take the slightly distorted boat-like conformation and cis-fused 1,3-oxazinone rings take the half-chair conformation.

EXPERIMENTAL

Melting points were obtained on a Yanaco melting point apparatus and are uncorrected. Elemental analyses were carried out on a Perkin-Elmer 240C

analyzer. The ^{1}HNMR spectra were recorded on Varian FT-80A spectrometer with TMS as an internal standard in $CDCl_3$.[13] CNMR spectra were recorded on Brucker AR250 spectrometer with TMS as an internal standard in $CDCl_3$. The IR spectra were taken on a Nicolet 5MX-S spectrophotometer in KBr. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. The TLC were performed on silica gel G plates with petroleum ether (30–60°C) /ethyl acetate (5:1), and the plates were visualized with UV light and/or iodine vapor.

2,4-Diaryl-2,3-dihydro-1,5-benzothiazepine 1; General procedure

α, β -Unsaturated ketone (0.144mol) and o-aminothiophenol (0.144mol) were dissolved in 150mL of boiling methanol or ethanol. The heat was removed and piperidine (3.5mL) was added. After the mixture had cooled to room temperature, an additional 150 mL methanol or ethanol was added and the slurry was heated until all material dissolved. Glacial acetic acid (60mL) then was added and the mixture was refluxed for 1–2 h, allowed to stand overnight at room temperature. Yellow crystalline separated which amounted to yield 80–95%. This material was repeatedly recrystallized from methanol or ethanol, **1e** from ethyl acetate. Strong infrared absorption occurred at about 1610cm^{-1} (C=N) with no other appreciable absorption from 1620–2940cm^{-1}.

2-(2-Bromophenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine 1e

This compound was obtained as yellow needles (ethanol), mp 163–4°C,yield 91%; IR(KBr) ν (cm^{-1}): 1610; MS (m/z): 395(M+2), 393(M), 314, 211, 108; ^{1}H NMR($CDCl_3$/TMS) δ [ppm, J(Hz)]: 2.84(1H, dd, *J*=12.4, 12.4), 3.38(1H, dd, *J*=4.4, 12.4), 5.54(1H, dd, *J*=4.4, 12.4), 6.90–8.25(13H, m, Aromatic).

Anal. Cald. for $C_{21}H_{16}NBrS$ (394.25) **1e**: C, 63.96; H, 4.09; N, 3.55.

Found: C, 63.90; H, 4.11; N, 3.58.

2-(2-Bromophenyl)-4-phenyl-2,3,4,5-tetrahydro-1,5-benzothiazepine

Compound **1e** 0.79g (2mmol) was dissolved in a mixture of methanol (100 mL) and tetrahydrofuran (50 mL) at room temperature. Sodium borohy-

dride (3.0g) was added over 1.5 h, and then stirred at room temperature overnight. Solution was then evaporated at reduced pressure, and the residue is chromatographed at silica gel column, benzene/ethyl acetate (5:1) as eluent, to afford the product, and recrystallized from ethanol to yield product 0.65g (83%), mp 125–126°C; IR (KBr) ν (cm^{-1}): 3400, 1600, 1470, no 1610; MS (m/z): 397(M+2), 395(M), 362, 271, 212, 192, 136, 109; ^1H NMR ($CDCl_3$/TMS) δ [ppm, J(Hz)]: 2.47(2H, m), 3.40(1H, broad), 5.5(1H, d, *J*=4.8), 5.63(1H, dd, *J*=2.4, 5.6), 6.35–7.55(13H, m, Aromatic).

Anal. Cald. for $C_{21}H_{18}NBrS$ (396.27) : C, 63.95; H, 4.05; N, 3.56.

Found: C, 63.90; H, 4.08; N, 3.79.

α -Diazo-diketone; General procedure

1,3-Diketone (20mmol) and triethylamine 2.7g (20.5mmol) were dissolved in dichloromethane 150mL at about 0°C (ice-water bath). Tosyl azide 4.2g (21mmol) was dropwise added slowly and stirred for 4 h at 0 °C, and then stirred for 14 h at room temperature, washed five times with water (100 mL) containing potassium hydroxide (3g) and also twice with water (50 mL), Dichloromethane was then evaporated at reduced pressure, and the residue is recrystallized from methanol to yield yellow crystalline α -diazo-diketone in 83% yield. Strong infrared absorption occurred at about 1640, 1660 (C=O) and 2120cm^{-1}(C=N_2).

2-Diazo-1,3-diphenyl-1,3-propanedione 4

mp108–9°C, (lit.[15] mp 107°C, yield 70%).

2-Diazo-1-phenyl-1,3-butanedione 5:

mp 62–3°C (lit.[16] mp 63–4°C, yield 69%).

2,3-Disubstituted-4a,6-diaryl-4a,5,6,12-tetrahydro-1*H*-1,3-oxazino [3,2-*d*][1,5]benzothiazepin-1-ones 6, 7 and 8; General procedure

The 1,5-benzothiazepine derivative **1** (4mmol) and the α -diazodiketone (4.4mmol) were dissolved in xylene (10mL). The mixture was then stirred for 10–15 min at 100°C. The reaction time was determined by TLC moni-

toring (silica gel G). Xylene was then evaporated at reduced pressure to obtain brown oil. This material was recrystallized from benzene to yield white crystalline **6, 7** or **8**.

2,3-Disubstituted-4a,6-diaryl-7-benzoyl-4a,5,6,12-tetrahydro-1*H*,7*H*-1,3-oxazino[3,2-*d*][1,5]benzodiazepin-1-ones 9, 10 and 12; General procedure

The 1,5-benzodiazepine derivative (4mmol) and the α -diazodiketone (4.4mmol) were dissolved in toluene(10mL). The mixture was then stirred for 30–45 min at 100°C. The reaction time was determined by TLC monitoring (silica gel G). The toluene was then evaporated at reduced pressure to obtain brown oil. This material was separated by silica gel chromatographic column and then recrystallized from ethyl acetate or benzene to yield colorless or white crystalline products **9, 10** or **12**.

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