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Thermal Cycloaddition Reaction of Symmetrical and Unsymmetrical α-Diazo-β-diketones with 4-Aryl-2-methyl-2,3-dihydro-1,5-benzothia/diazepines

Jiaxi Xu and Sheng Jin

College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China

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ABSTRACT: *Symmetrical and unsymmetrical α-diazo-β-diketones undergo thermal Wolff rearrangements to generate α-carbonylketenes to participate as dienes in Diels–Alder reactions with 4-aryl-2-methyl-2,3-dihydro-1,5-benzothia/diazepines to give, where applicable, regiospecific cycloadducts, 4a,5,6,12-tetrahydro-1H/1H,7H-1,3-oxazino[3,2-d][1,5]benzothia/diazepin-1-ones. A mechanism of formation of the regiospecific cycloadducts is suggested.* © 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 35–40, 1999

INTRODUCTION

Numerous reports have appeared in the literature describing preparations of benzothiazepines and benzodiazepines, and their fused heterocyclic derivatives, due to their pharmaceutical activities [1–5]. 1,3-Oxazinobenzodiazepin-1-ones, benzodiazepines fused with 1,3-oxazinone, have received attention owing to their potential anxiolytic and hypnotic activities [6]. The present work deals with the syntheses of some novel 4a,5,6,12-tetrahydro-1*H*/1*H*,7*H*-1,3-oxazino[3,2-*d*][1,5]benzothia/diazepin-1-one derivatives by the cycloadditions of 4-aryl-2-methyl-2,3-dihydro-1,5-benzothia/diazepines with symmetrical and unsymmetrical α-diazo-β-diketones, 2-diazo-1,3-diphenyl-1,3-propanedione **3**, and 2-diazo-1-phenyl-1,3-butanedione **4**.

Correspondence to: Jiaxi Xu.
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RESULTS AND DISCUSSION

4a,5,6,12-Tetrahydro-1*H*/1*H*,7*H*-1,3-oxazino[3,2-*d*]-[1,5]benzothia/diazepin-1-one derivatives have been synthesized by Diels–Alder reactions of 2,3-dihydro-1,5-benzothia/diazepines, **1**, **2**, with both symmetrical and unsymmetrical α-diazo-β-diketones. α-Diazo-β-diketones can undergo thermal Wolff rearrangement to generate α-carbonylketenes, then they can give rise to dienes to participate in Diels–Alder reactions [7,8]. When an unsymmetrical α-diazo-β-diketone, 2-diazo-1-phenyl-1,3-butanedione, was used as a potential diene source, it could undergo two different thermal Wolff rearrangements to generate two α-carbonylketenes, acetyl phenyl ketene and benzoyl methyl ketene, by phenyl group or methyl group migration, respectively. Unexpectedly, in these reactions, the cycloadducts were found to be formed in a regiospecific manner. Only 2,6-dimethyl-3,4a-diphenyl-4a,5,6,12-tetrahydro-1*H*-1,3-oxazino[3,2-*d*][1,5]benzothiazepin-1-one **6** was formed in the reaction of **1** with **4**, and 4a-aryl-7-benzoyl-2,6-dimethyl-3-phenyl-4a,5,6,12-tetrahydro-1*H*,7*H*-1,3-oxazino[3,2-*d*][1,5]benzodiazepin-1-ones **8** were formed in the reactions of **2a,b** with **4**. The physical constants and spectral and elemental analysis data are summarized in Tables 1 and 2. Up to now, the thermal cycloadduction reaction of an

TABLE 1 Physical and Spectral Data

Compd	*Yield %*	*m.p. °C*	*^{1}H NMR, ^{13}C NMR ($CDCl_3$/TMS) δ (ppm), J(Hz)*	*IR(KBr) $\nu(cm^{-1})$*	*MS/FAB m/z $(M + 1)^+$*
5	59	163–164	1.30 (3H, d, J = 7.2), 2.33 (3H, s, ArMe), 1.70 (1H, dd, J = 4.0, 16.0), 2.63 (1H, dd, J = 12.0, 16.0), 3.62 (1H, ddq, J = 4.0, 7.2, 12.0), 6.80–8.00 (18H, m, aromatic)	1660	490
6	18	186–187	1.23 (3H, d, J = 7.2), 1.82 (3H, s, Me), 1.57 (1H, dd, J = 4.0, 16.0), 2.32 (3H, s, ArMe), 2.48 (1H, dd, J = 12.0, 16.0), 3.56 (1H, ddq, J = 4.0, 7.2, 12.0), 7.03–7.85 (13H, m, aromatic)	1655	428
7a	52	163–164	1.15 (3H, d, J = 5.6), 2.27 (3H, s, ArMe), 1.83 (1H, dd, J = 12.0, 16.0), 2.76 (1H, dd, J = 4.8, 16.0), 4.03 (1H, dd, J = 4.8, 12.0), 6.50–7.95 (21H, m, aromatic)	1650	577
7b	63	154–155	1.31 (3H, d, J = 6.4), 2.33 (1H, dd, J = 12.0, 16.0), 2.65 (1H, dd, J = 4.8, 16.0), 5.78 (1H, ddq, J = 4.8, 6.4, 12.0), 6.60–7.98 (26H, m, aromatic) 18.2, 45.5, 47.1, 92.6, 114.3, 125.5, 127.3, 127.7, 127.9, 128.3, 128.6, 128.7, 128.9, 129.8, 130.1, 130.3, 130.6, 131.4, 132.7, 133.6, 135.3, 135.7, 135.8, 143.2, 158.8, 162.4	1650	563
8a	20	196–197	1.09 (3H, d, J = 5.6, Me), 1.85 (3H, s, Me), 2.25 (3H, s, ArMe), 2.23 (1H, dd, J = 12.8, 14.4), 2.66 (1H, dd, J = 5.6, 14.4), 4.12 (1H, ddq, J = 5.6, 5.6, 12.8), 6.47–8.00 (16H, m, aromatic)	1660	515
8b	38	196–197	1.08 (3H, d, J = 6.4, Me), 1.82 (3H, s, Me), 2.24 (1H, dd, J = 10.8, 14.8), 2.66 (1H, dd, J = 4.8, 14.8), 4.06 (1H, dd, J = 4.8, 10.8), 6.30–8.71 (21H, m, aromatic)	1650	501

TABLE 2 Elemental Analysis Data

			Cald.			*Found*		
Compd	*Molecular Formula*	*Molecular Weight*	*C*	*H*	*N*	*C*	*H*	*N*
5	$C_{32}H_{27}NO_2S$	489.63	78.50	5.56	2.86	78.58	5.39	2.94
6	$C_{27}H_{25}NO_2S$	427.56	75.85	5.89	3.28	75.88	5.78	3.37
7a	$C_{39}H_{32}N_2O_3$	576.69	81.23	5.59	4.86	81.16	5.38	4.92
7b	$C_{38}H_{30}N_2O_3$	562.67	81.12	5.37	4.98	80.97	5.46	5.03
8a	$C_{34}H_{30}N_2O_3$	514.62	79.35	5.88	5.44	79.11	5.97	5.20
8b	$C_{33}H_{28}N_2O_3$	500.60	79.18	5.64	5.60	79.33	5.72	5.88

unsymmetrical α-diazo-β-diketone with a C=N double bond has not been reported.

In order to elucidate the structures of the thermal cycloadducts of unsymmetrical 2-diazo-1-phenyl-1,3-butanedione with benzothia/diazepines, a typical product was subjected to X-ray diffraction analysis. The colorless crystal of 7-benzoyl-2,6-dimethyl-4a-(4-methylphenyl)-3-phenyl-4a,5,6,12-tetrahydro-1*H*,7*H*-1,3-oxazino[3,2-*d*][1,5]benzodiazepin-1-one, $C_{34}H_{30}N_2O_3$, **8b**, prepared by reaction of **2b** with **4**, was obtained by evaporation from its saturated ethyl acetate solution. A crystal with approximate dimensions of 0.08 × 0.30 × 0.40 mm was examined on an Enraf-Nonius CAD-4 four-circle diffractometer with MoK_α (λ = 0.71073 Å) radiation. The compound **8b** crystallized in the monoclinic space group P2$_1$/*n* with cell dimensions a = 11.560 (1) Å, b = 19.058 (3) Å, c = 13.207 (2) Å, β = 106.82 (1)°, V = 2785.2 (7) Å^3, Z = 4, and D_c = 1.230 g/cm^3. The structure was solved by the direct method and refined by the full-matrix least-squares method, and the final crystallographic discrepancy factor is 0.046 for 2278 observed reflections (see Tables 3–5).

The molecular backbone is a tricyclic system, which is formed from a benzene ring, a seven-membered heteronucleus, and a 1,3-oxazinone ring. The

TABLE 3 Atomic Fractional Coordinates and Thermal Parameters

	x	*y*	*z*	*Biso*		*x*	*y*	*z*	*Biso*
N1	0.3284(3)	0.1421(2)	0.8952(3)	3.3(1)	C16	0.0718(5)	0.0773(3)	1.1569(4)	4.1(3)
N2	0.1964(3)	0.2607(2)	0.9237(3)	3.3(1)	C17	0.0346(5)	0.0930(3)	1.0499(4)	4.1(3)
O1	0.2636(3)	0.3040(1)	1.0979(2)	3.3(1)	C18	0.0900(4)	0.1468(3)	1.0082(4)	3.6(2)
O2	0.0204(3)	0.3032(2)	0.8146(2)	5.3(2)	C19	0.5273(5)	0.1250(3)	1.0294(4)	5.8(3)
O3	0.3079(4)	0.0248(1)	0.9033(3)	5.6(2)	C20	0.2922(4)	0.0787(3)	0.8502(4)	3.7(2)
C1	0.2549(4)	0.2410(2)	1.0336(3)	3.2(2)	C21	0.2296(5)	0.0752(3)	0.7340(4)	4.0(3)
C2	0.3839(4)	0.2173(3)	1.0532(4)	3.4(2)	C22	0.2648(6)	0.0247(3)	0.6763(5)	6.0(4)
C3	0.3955(4)	0.1445(3)	1.0090(4)	3.8(2)	C23	0.2115(7)	0.0176(4)	0.5693(5)	8.4(5)
C4	0.3301(4)	0.2043(2)	0.8338(4)	3.2(2)	C24	0.1151(8)	0.0588(4)	0.5201(5)	9.8(5)
C5	0.4007(5)	0.2072(3)	0.7647(4)	4.2(3)	C25	0.0744(7)	0.1069(4)	0.5786(5)	9.2(5)
C6	0.4009(5)	0.2675(3)	0.7058(4)	5.1(3)	C26	0.1312(6)	0.1166(3)	0.6840(5)	6.2(3)
C7	0.3322(5)	0.3247(3)	0.7185(4)	5.3(3)	C27	−0.0657(5)	0.3524(3)	0.9810(4)	4.6(3)
C8	0.2664(5)	0.3229(3)	0.7903(4)	4.3(3)	C28	0.1586(5)	0.3823(3)	1.1762(4)	3.8(2)
C9	0.2641(4)	0.2624(3)	0.8483(3)	3.1(2)	C29	0.1041(5)	0.4480(3)	1.1622(4)	5.1(3)
C10	0.0876(4)	0.2957(3)	0.9040(4)	3.8(2)	C30	0.1098(6)	0.4904(3)	1.2507(5)	6.3(4)
C11	0.0620(4)	0.3270(3)	0.9968(4)	3.5(2)	C31	0.1673(6)	0.4656(3)	1.3494(5)	6.4(4)
C12	0.1550(4)	0.3367(2)	1.0844(4)	3.2(2)	C32	0.2228(5)	0.4017(3)	1.3644(4)	5.7(3)
C13	0.1818(4)	0.1862(2)	1.0742(3)	3.1(2)	C33	0.2199(5)	0.3596(3)	1.2771(4)	4.6(3)
C14	0.2178(4)	0.1710(3)	1.1817(4)	3.5(2)	C34	0.0153(5)	0.0172(3)	1.2010(5)	5.4(3)
C15	0.1682(5)	0.1177(3)	1.2223(4)	4.1(3)					

TABLE 4 Selected Bond Lengths (Å)

N1-C3	1.479(6)	N1-C4	1.439(6)
N2-C1	1.462(6)	N2-C9	1.433(6)
N2-C10	1.380(6)	O1-C1	1.457(5)
O1-C12	1.366(6)	O2-C10	1.219(6)
C1-C2	1.508(7)	C2-C3	1.525(7)
C10-C11	1.468(7)	C11-C12	1.344(7)

TABLE 5 Selected Bond Angles (°)

C3-N1-C4	117.3(4)	C3-N1-C20	118.4(4)
C4-N1-C20	122.6(4)	C1-N2-C9	120.5(4)
C1-N2-C10	116.5(4)	C9-N2-C10	120.6(4)
C1-O1-C12	113.2(3)	N2-C1-O1	107.6(4)
N2-C1-C2	113.4(4)	N2-C1-C13	112.2(4)
O1-C1-C2	104.5(4)	O1-C1-C13	108.0(3)
C2-C1-C13	110.6(4)	C1-C2-C3	113.6(4)
N1-C3-C2	109.8(4)	N1-C3-C19	112.2(4)
C2-C3-C19	110.5(4)	N1-C4-C9	118.8(4)
N2-C9-C4	120.7(4)	N2-C10-O2	122.1(4)
N2-C10-C11	115.5(4)	O2-C10-C11	122.3(4)
C10-C11-C12	118.1(4)	C10-C11-C27	116.1(4)
C12-C11-C27	125.5(4)	O1-C12-C11	121.7(4)
O1-C12-C28	110.6(4)	C11-C12-C28	127.7(4)

central seven-membered heteronucleus has a distorted boatlike conformation, and it is *cis*-fused to the 1,3-oxazinone ring at N2 and C1, while the latter moiety is also in a slightly twisted boat conformation. The *p*-methylphenyl group on C1 and the methyl group on C3 are equatorial with respect to the central ring (Figure 1).

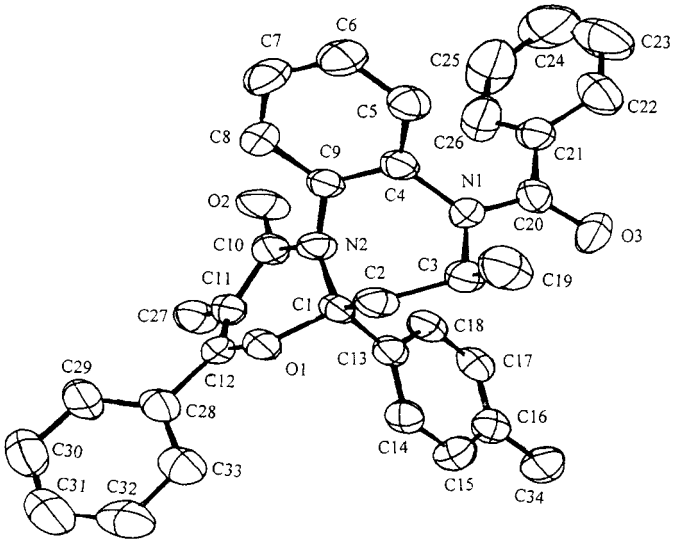


FIGURE 1 ORTEP stereoview of compound **8b**.

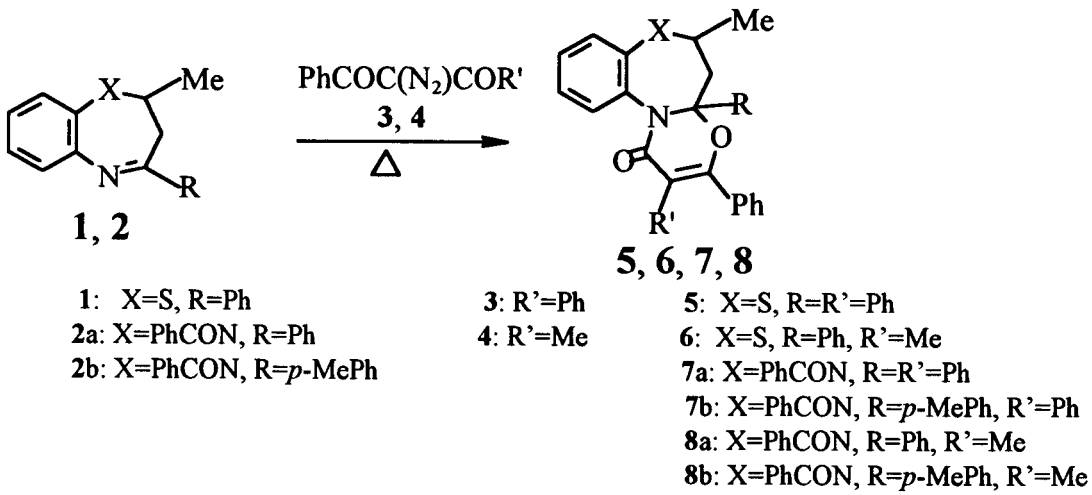
In order to obtain additional information related to the mechanism, we carried out experiments designed to capture key intermediates. Methanol was added to a xylene solution of 2-diazo-1-phenyl-1,3-butanedione **4**, and the mixture was stirred for 15 minutes at 100°C. After the solvent had been removed in vacuo, the composition of the residue was analyzed by GC and by ^{1}HNMR spectroscopy, using authenic samples of compounds **9** and **10** for calibrations. The ratios of compounds **9** and **10** obtained by both methods were generally in good agreement. The results indicated that the ratio of acetyl phenyl

ketene to benzoyl methyl ketene formed is 1.3:1 under these conditions. Our result is very similar to the result, thermolysis of 2-diazo-1-phenyl-1,3-butanedione **4** in methanol, reported by Tomioka et al. [9]. The net result indicates that phenyl migration takes place slightly more rapidly than methyl migration.

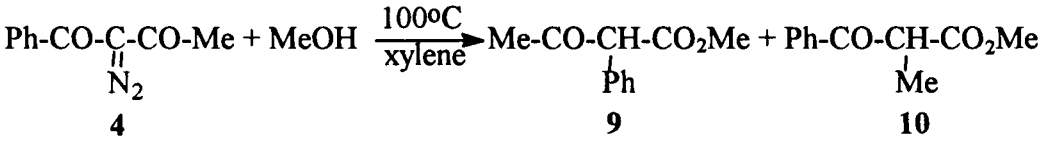
The regiospecific reactions of the unsymmetrical 2-diazo-1-phenyl-1,3-butanedione can be rationalized as follows. 2-Diazo-1-phenyl-1,3-butanedione can assume two favorable anticonformations. In one of these, a phenyl group is transoid to the diazo group **A** and, in the other, **B**, the methyl group is transoid to the diazo group [9,10]. In the thermal Wolff rearrangement, the conformer **A** presents a favorable situation for Ph migration to occur to produce the ketene **C**. On the other hand, in the **B** conformer, Me migration following loss of N_2 would be expected to occur. The main pathway from this conformer is dissociation of N_2 to generate a singlet carbene in which Me migration then occurs to produce carbene **D**. Because of the donation of the more labile π-electron cloud to the diazo carbon and the stabilization of the transition state (or short-lived intermediate) through bridging delocalization, a concerted process with Ph migration and loss of N_2 would be favored [11]. Since such stabilization is not attained in Me migration, dissociation of N_2 occurs before the Me group shifts to the diazo carbon, a less favorable pathway. Thus, the thermal Wolff rearrangement of 2-diazo-1-phenyl-1,3-butanedione **4** affords mainly acetyl phenyl ketene **C** (shown in Scheme 3). The ketene that is favored for the additions to the C=N bonds of the 1,5-benzothia/diazepines will probably be based on the frontier molecular orbital energies of the 1,5-benzothia/diazepines. According to the frontier orbital theory, the ketene, of which the frontier molecular orbital energy is close to that of the C=N bond in 1,5-benzothia/diazepine, is favored to react preferentially with the 1,5-benzothia/diazepine.

Semiempirical calculations of the energies of the frontier molecular orbitals of these two ketenes and substrate **1** have now been carried out. The initial structures of these three compounds were established by the Alchemy molecular modeling software and preoptimized by MM. The semiempirical molecular orbital computation with PM3 in the program of MOPAC Version 6.3 was carried out on a Pentium-II Microcomputer. Full geometric structure optimization was performed with each structure in order to examine their relative stabilities. The results show that the energy difference (8.392 eV) between the LUMO (−0.443 eV) of benzoyl methyl ketene **D** and the HOMO (−8.835 eV) of substrate **1** is smaller than that (8.519 eV) between the LUMO (−0.316 eV) of acetyl phenyl ketene **C** and the HOMO (−8.835 eV) of substrate **1**. This rationalizes the preferred formation of **6** from the reaction of **1** with **4** and of **8a,b** from **2a,b** with **4**.

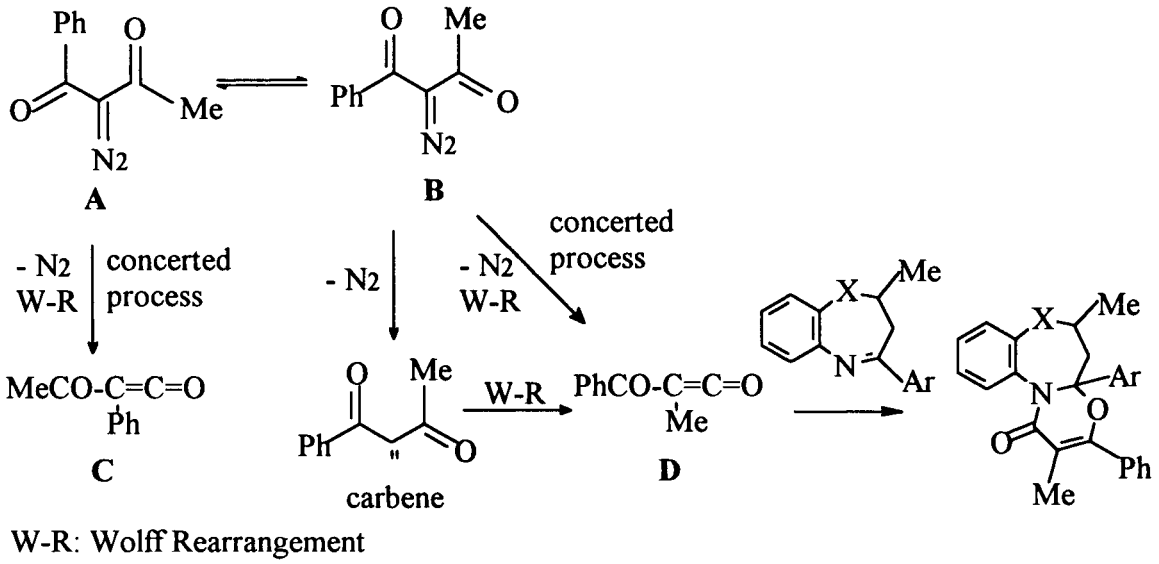
In summary, 4-aryl-2-methyl-2,3-dihydro-1,5-benzothia/diazepines underwent thermal cycloadduction reactions with symmetrical 2-diazo-1,3-diphenyl-1,3-propanedione to yield the expected 4a-aryl-6-methyl-2,3-diphenyl-1*H*/1*H*,7*H*-1,3-oxazino[3,2-*d*][1,5]benzothia/diazepin-1-one, and with the unsymmetrical 2-diazo-1-phenyl-1,3-butanedione to generate in a regiospecific manner the respective 4a-aryl-2,6-dimethyl-3-phenyl-1*H*/1*H*,7*H*-1,3-oxazino[3,2-*d*][1,5]benzothia/diazepines. The structure and stereochemistry of the cycloadducts



SCHEME 1 Cycloadduction reactions of benzothia/diazepines and α-diazo-β-diketones.



SCHEME 2 Thermolysis of 2-diazo-1-phenyl-1,3-butanedione **4** with methanol in xylene.



SCHEME 3 Mechanism of thermal cycloadduction of asymmetric 2-diazo-1-phenyl-1,3-butanedione with benzothia/diazepines.

have been confirmed by single-crystal X-ray analysis on a sample compound **8b**. A mechanism of reaction has been proposed.

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}H NMR spectra were recorded on a Varian FT-80A spectrometer, and ^{13}C NMR spectra were recorded on a 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. 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 iodine vapor.

The product ratios of the caption experiments were determined by use of a Brucker ARX400 NMR spectrometer and an HP5890II-5971 GC-MSD instrument.

The authenic compound **9** was prepared by the condensation of ethyl acetate with benzyl cyanide [12], followed by methanolysis [13]. The authenic compound **10** was synthesized by the reaction of methyl propionate with methyl benzoate [14].

4-Aryl-2-methyl-2,3-dihydro-1,5-benzothia/diazepine: General Procedure

The α,β-unsaturated ketone (0.144 mole) and *o*-aminothiophenol or *o*-phenylenediamine (0.144 mole) were dissolved in 150 mL of boiling methanol or ethanol. Heating was terminated, and piperidine (3.5 mL) was added. After the mixture had cooled to room temperature, an additional 150 mL of methanol or ethanol was added and the slurry heated until all the material dissolved. Glacial acetic acid (60 mL) was then added, and the mixture was refluxed for 1–2 hours and then allowed to stand overnight at room temperature. Yellow crystals separated that amounted to yields of 48–95%. This material was repeatedly recrystallized from methanol or ethanol. Strong infrared absorption occurred at about 1610 cm^{-1} (C=N) with no other appreciable absorption from 1620 to 2940 cm^{-1}.

α-Diazo-β-diketone: General Procedure

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

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

Melting point was 108–109°C (Ref. [11] mp 107°C, yield 70%).

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

Melting point was 62–63°C (Ref. [11] mp 63–64°C, yield 69%).

2,3-Disubstituted-4a-aryl-6-methyl-4a,5,6,12-tetrahydro-1H/1H,7H-1,3-oxazino[3,2-d][1,5]benzothia/diazepin-1-ones: General Procedure

The 1,5-benzothia/diazepine derivative (4 mmole) and the α-diazo-diketone (4.4 mmole) were dissolved in xylene (10 mL). The mixture was then stirred for 10–15 minutes at 100°C. The reaction time was determined by TLC monitoring (silica-gel G). Xylene was then evaporated at reduced pressure to give a brown oil. This material was recrystallized from benzene or separated on a silica-gel column to yield white crystals.

Thermolysis of 2-Diazo-1-phenyl-1,3-butanedione with Methanol in Xylene

2-Diazo-1-phenyl-1,3-butanedione 0.75 g (4 mmole) and methanol (1 mL) were dissolved in xylene (10 mL). The mixture was then stirred for 15 minutes at 100°C. After the solvent had been removed in vacuum, the residue was dissolved in CF_3CO_2D to prevent the enolization and to be analyzed by NMR spectroscopy and also dissolved in $CHCl_3$ to be analyzed by GC.

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