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Reactions of Unsymmetrical α-Diazo-β-Diketones with Imines: Syntheses of 4*H*-1,3-Oxazin-4-ones

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ABSTRACT: *Cycloaddition reactions of an unsymmetrical α-diazo-β-diketone, 2-diazo-1-phenyl-1,3-butanedione, with a series of imines having various substituents were studied. The results indicated that only cycloadducts derived from acetylphenylketene, which was generated by the thermal Wolff rearrangement of 2-diazo-1-phenyl-1,3-butanedione with phenyl migration, and imines were obtained.* © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:165–168, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10015

INTRODUCTION

α-Diazo-β-diketones, diacyldiazomethanes, are highly reactive and useful synthons for the syntheses of oxy-containing six-membered heterocyclic compounds [1–3]. They show a pronounced tendency to undergo a Wolff rearrangement by thermal, photolytic, or metal catalytic elimination of nitrogen to generate acylketenes. The acylketenes participate preferentially as the 4π component in inverse (diene LUMO controlled) Diels–Alder reactions with electron-rich and/or dipolar dieneophiles [4–9]. They are especially prone to undergo [2 + 4] cycloadditions with heterodienophiles, such as imines [4–7], nitriles [8], aldehydes and ketones [9,10], and thiones [11], as well as electron-rich alkenes or alkynes, for example, enamines [11] or enol ethers [12]. They can also react with some heterocumulenes [13], such as carbodiimides and isocyanates.

Recently, we studied the reactions of α-diazo-β-diketones with the imine moieties present in 1,5-benzodiazepines and 1,5-benzothiazepines and found that the reactive species were actually acetylphenylketene or benzoylmethylketene, generated from unsymmetrical 2-diazo-1-phenyl-1,3-butanedione, and produced, respectively, 1,3-oxazinone derivatives with methyl and phenyl groups in different positions [6,7]. In order to understand the differences in the reactions, we have now investigated the reactions of unsymmetrical 2-diazo-1-phenyl-1,3-butanedione with a series of relatively simple imines.

RESULTS AND DISCUSSION

A series of imines **1a–l** were obtained by reaction of aromatic aldehydes with aromatic amines [14,15]. Unsymmetrical 2-diazo-1-phenyl-1,3-butanedione was reacted with each of the imines **1a–l** in refluxing anhydrous toluene for 0.5–2 h to give cycloadducts, 2,3-diaryl-6-methyl-5-phenyl-2,3-dihydro-4*H*-1,3-oxazin-4-ones (**2a–j**), in yields of 26–57%. No corresponding reactions occurred with imines **2k** ($R^1 = Ph$, $R^2 = p\text{-}NO_2$) and **2l** ($R^1 = R^2 = p\text{-}NO_2$) (Scheme 1). The results indicated that the imines reacted with acetylphenylketene specifically, although 2-diazo-1-phenyl-1,3-butanedione can generate acetylphenylketene and benzoylmethylketene in a ratio of 1.3:1 [7]. Also, it was found that the

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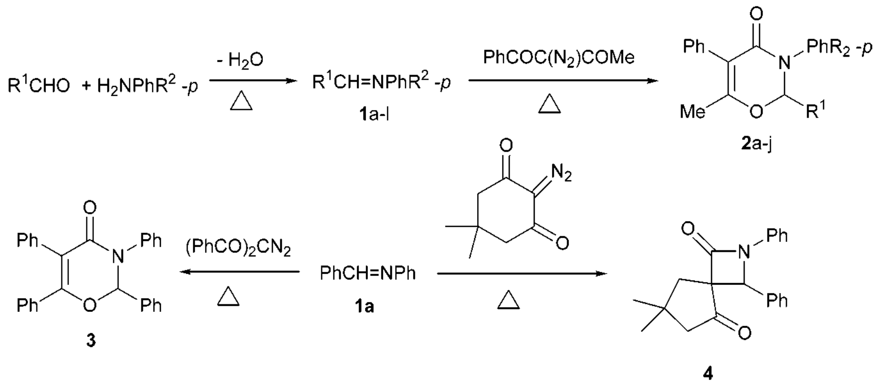


SCHEME 1 Reaction of α-diazo-β-diketones and imines.

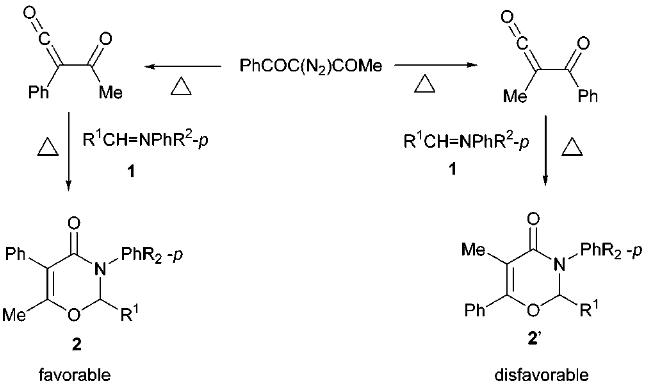
yields depend on the substituents; imines with electron-donating group(s) gave higher yields and imines with electron-withdrawing group(s) gave lower yields, or even no reaction. For example, **2k** with one electron-withdrawing p-NO$_2$ group and **2l** with two electron-withdrawing p-NO$_2$ groups gave no products. In order to verify the lack of reactivity of imines **2k** and **2l**, reactions of these two imines with the highly reactive 2-diazo-1,3-diphenyl-1,3-propanedione was also attempted, but no desired products were found. In additional studies, we found that the reaction of imine **1a** with 2-diazo-1,3-diphenyl-1,3-propanedione yielded the cycloadduct 2,3-dihydro-2,3,5,6-tetraphenyl-4*H*-1,3-oxazin-4-one (**3**). However, cyclic α-diazo-β-diketone, 2-diazo-5,5-dimethyl-1,3-cyclohexanedione, reacted with imine **1a** to give a [2 + 2] cycloadduct, a β-lactam derivative, 7,7-dimethyl-2,3-diphenyl-2-azaspiro[3.4]octane-1,5-dione (**4**).

All cycloadducts described in the present study were fully characterized by ^{1}H NMR, MS, and IR spectroscopies and by elemental analyses (Tables 1 and 2). Although product **2a** was previously prepared from imine **1a** and the acylketene that was generated by pyrolysis of the appropriate 4*H*-1,3-dioxin-4-one [16], the products described in [16] showed the methyl group in the compound **2a** to resonate at 1.93 ppm upfield, while that in the related compound **2′a,** described [16], resonated at 1.98 ppm downfield in the ^{1}H NMR spectra (Scheme 2). Furthermore, the ^{1}H NMR data of compound **2a** reported in [16] did not match with its structure. Thus, we again report here its full characteristic data. According to our previous results [6,7] the methyl group in 6-methyl-5-phenyl-1,3-oxazin-4-one derivatives (**2**) should be at $\delta = 2.01$–1.94, downfield because of the neighboring oxygen and that in 5-methyl-6-phenyl-1,3-oxazin-4-one derivatives (**2′**) should be at $\delta = 1.87$–1.82, upfield because of the neighboring carbonyl group. Furthermore, our structure was confirmed by an X-ray crystal diffraction analysis [7,17].

Based on the above results, we can conclude that the reaction of imines with unsymmetrical 2-diazo-1-phenyl-1,3-butanedione give generally [2 + 4] cycloadducts derived from the imines and acetylphenylkene, although 2-diazo-1-phenyl-1,3-butanedione can generate both acetylphenylkene and benzoylmethylkene.

EXPERIMENTAL

Melting points were obtained on a Yanaco melting point apparatus and are uncorrected. Elemental analyses were carried out on an Elementar Vario EL elemental analyzer. The ^{1}H NMR spectra were recorded in CDCl$_3$ solution on a Varian Mercury 200 spectrometer with TMS as an internal standard. The IR spectra were taken on a Brucker Vector 22 FT-IR spectrophotometer in KBr. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. TLC separations were performed on silica gel G plates with petroleum ether (30–60)/ethyl acetate (5:1) as



SCHEME 2 Reaction of unsymmetrical 2-diazo-1-phenyl-1,3-butanedione and imines.

TABLE 1 Physical and Spectral Data

Compd	*R^1*	*R^2*	*Yield (%)*	*m.p. (°C)*	*^1H NMR ($CDCl_3$/TMS) δ(ppm), J (Hz)*	*IR (cm^{-1}) C=O*	*MS/FAB (m/z) (MH^+)*
2a	Ph	H	32	130–131	7.60–7.19 (15H, m, aromatic), 6.70 (1H, s, CH), 1.94 (3H, s, Me)	1650	342
2b	*p*-MeO Ph	MeO	44	120–121	7.50–6.80 (13H, m, aromatic), 6.56 (1H, s, CH), 3.80 (3H, s, MeO), 3.77 (3H, s, MeO), 1.96 (3H, s, Me)	1660	402
2c	*p*-MeO Ph	H	43	77–78	7.50–6.90 (14H, m, aromatic), 6.65 (1H, s, CH), 3.81 (3H, s, MeO), 1.95 (3H, s, Me)	1651	372
2d	*p*-MeO Ph	NO_2	26	154–155	8.23–7.35 (13H, m, aromatic), 6.74 (1H, s, CH), 3.83 (3H, s, MeO), 1.95 (3H, s, Me)	1659	417
2e	*p*-ClPh	H	38	151–152	7.54–7.17 (14H, m, aromatic), 6.66 (1H, s, CH), 1.95 (3H, s, Me)	1652	376
2f	*p*-NO_2Ph	H	28	124–125	8.31–6.25 (14H, m, aromatic), 6.76 (1H, s, CH), 1.95 (3H, s, Me)	1658	387
2g	Ph	MeO	57	167–168	7.60–6.82 (14H, m, aromatic), 6.61 (1H, s, CH), 3.77 (3H, s, MeO), 1.95 (3H, s, Me)	1659	372
2h	Ph	Cl	43	142–143	7.55–7.18 (14H, m, aromatic), 6.50 (1H, s, CH), 1.94 (3H, s, Me)	1661	376
2i	*p*-NO_2Ph	MeO	34	156–157	8.30–6.84 (13H, m, aromatic), 6.68 (1H, s, CH), 3.78 (3H, s, MeO), 1.96 (3H, s, Me)	1649	417
2j	2-Furyl	H	51	140–141	7.56–7.10 (11H, m, aromatic), 6.66 (1H, s, CH), 6.55 (1H, d, *J* = 3 Hz, CH), 6.39 (1H, d, *J* = 3 Hz, CH), 1.98 (3H, s, Me)	1654	332
3	Ph	H	66	202–203	7.62–7.18 (20H, m, aromatic), 6.70 (1H, s, CH)	1659	404
4	Ph	H	9.4	215–216	7.41–7.20 (10H, m, aromatic), 5.05 (1H, s, CH), 2.58 (1H, d, *J* = 14 Hz, H in CH_2), 2.33 (1H, d, *J* = 14 Hz, H in CH_2), 2.11 (1H, d, *J* = 18 Hz, H in CH_2), 1.89 (1H, d, *J* = 18 Hz, H in CH_2), 1.22 (3H, s, Me), 1.15 (3H, s, Me)	1765 1740	320

TABLE 2 Elemental Analysis Data

			Calcd.			*Found*		
Compd	*Molecular Formula*	*Molecular Weight*	*C*	*H*	*N*	*C*	*H*	*N*
2a	$C_{23}H_{19}NO_2$	341.14	80.92	5.61	4.10	81.03	5.38	3.90
2b	$C_{25}H_{23}NO_4$	401.45	74.80	5.77	3.49	75.06	5.82	3.62
2c	$C_{24}H_{21}NO_3$	371.43	77.61	5.70	3.77	77.89	5.80	3.78
2d	$C_{24}H_{20}N_2O_5$	416.43	69.22	4.84	6.73	69.31	5.00	6.74
2e	$C_{23}H_{18}ClNO_2$	375.85	73.50	4.83	3.73	73.74	4.89	3.69
2f	$C_{23}H_{18}N_2O_4$	386.40	71.49	4.70	7.25	71.66	4.97	7.01
2g	$C_{24}H_{21}NO_3$	371.43	77.61	5.70	3.77	77.58	5.83	4.01
2h	$C_{23}H_{18}ClNO_2$	375.85	73.50	4.83	3.73	73.38	5.02	3.69
2i	$C_{24}H_{20}N_2O_5$	416.43	69.22	4.84	6.73	69.01	5.02	6.97
2j	$C_{21}H_{17}NO_3$	331.36	76.12	5.17	4.23	76.03	5.10	4.38
3	$C_{28}H_{21}NO_2$	403.47	83.35	5.25	3.47	83.50	5.20	3.50
4	$C_{21}H_{21}NO_2$	319.40	78.97	6.63	4.39	79.06	6.89	4.53

the eluent, and the plates were visualized with UV light.

α-Diazo-β-diketones were prepared following literature procedures [6,7] and imines were synthesized based on literature methods [14,15].

Reaction of α-Diazo-β-diketones and Imines

General Procedure. Imine **1** (1 mmol) and α-diazo-β-diketone (1.1 mmol) were dissolved in anhydrous toluene (10 ml). The resulting mixture was refluxed for 0.5–2 h, the optimum reaction time being determined by TLC monitoring (silica gel). The solvent was evaporated under reduced pressure to give a residue that was crystallized from a mixture of petroleum ether (30–60) and benzene or separated on a silica gel column with use of petroleum ether (30–60)/ethyl acetate (5:1) as the eluent to give colorless crystals **2, 3,** and **4**.

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