Reaction of 2-Diazo-1,2-diarylethanones with Benzophenone *N*-(diaryl)acyl hydrazones: Formation of 1,3,4-Oxadiazolines [1]

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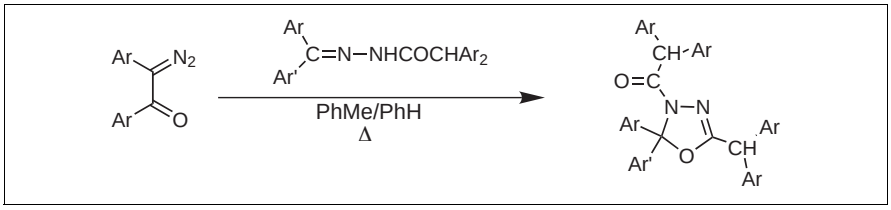

The reaction of 2-diazo-1,2-diarylethanones with benzophenone *N*-(diaryl)acyl hydrazones leads to the formation of 1,3,4-oxadiazolines. The products have been characterized on the basis of satisfactory analytical and spectral (IR, ^{1}H and ^{13}C NMR, and Mass) data. The mechanism for the formation of products through the reaction of diarylketenes, generated *in situ* from thermal decomposition of the 2-diazo-1,2-diarylethanones, with imino nitrogen and intramolecular [2 + 3] dipolar cycloaddition is suggested.

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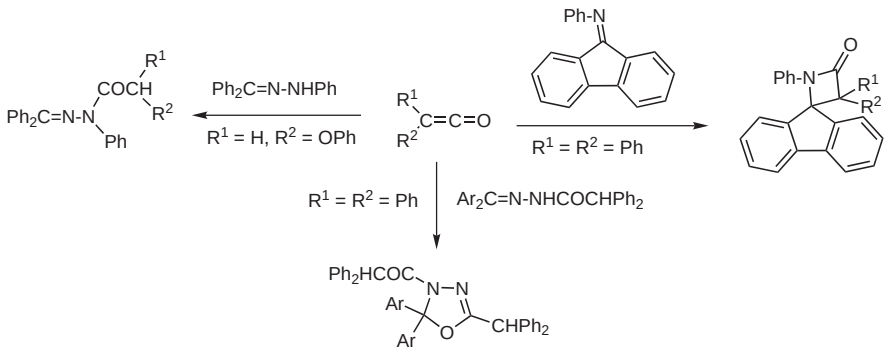
Introduction.

1,3,4-Oxadiazolines constitute a well-known class of heterocyclic compounds associated with different types of biological activity [2-4]. The common methods for the synthesis of 1,3,4-oxadiazolines involve cyclization of acyl hydrazones and their silver salts under acylating conditions [5-7]. Various research groups have been investigating the reactions of ketenes with organic compounds having nitrogen atom in different structural environments, with an objective to develop new methodologies for the synthesis of heterocyclic compounds [8]. I have been using diazocarbonyls as precursors of reactive intermediates such as diarylketenes and carbenoids [9-10]. The reactions of diazocarbonyls are simple to carry out and versatile. However, these reactions often depend on the structural (both electronic and steric) environment of the nitrogen atom in the molecule (Scheme 1). For example, Sharma and coworkers have reported the formation of *N,N*-disubstituted hydrazones in the reaction of phenoxyketene with benzophenone *N*-phenyl hydrazone [11]. Fahr and coworkers have reported the formation of 2-azetidinone in the reaction of diphenylketene with fluorenone *N*-benzoyl hydrazone [12]. We reported for the first time the formation of 1,3,4-oxadiazoline derivatives in the reaction of diphenylketene, generated from 2-diazo-1,2-diphenylethanone, with *N*-diphenylacyl hydrazones of benzophenone, 4,4-dimethoxybenzophenone and 4-chlorobenzophenone (Scheme 1) [13].

It was considered pertinent to study the scope and limitations of this method for the preparation of other 1,3,4-oxadiazolines by extending the reaction to di-*p*-tolylketene and benzophenone hydrazones substituted with different acyl groups. Accordingly, the present paper reports the reactions of 2-diazo-1,2-diphenylethanone (**1a**) with benzophenone *N*-(di-*p*-tolyl)acyl hydrazones (**2a,b**) and of 2-diazo-1,2-di-*p*-tolylethanone (**1b**) with benzophenone *N*-(di-*p*-tolyl)acyl hydrazones (**2a,b**) and benzophenone *N*-(diphenyl)acyl hydrazones (**2c,d**), which

Scheme 1



led to the formation of new 1,3,4-oxadiazoline derivatives in fair to good yields.

Results and Discussion.

An equimolar reaction of 2-diazo-1,2-diphenylethanone (**1a**) and *N*-(di-*p*-tolyl)]acyl benzophenone hydrazone (**2a**) in dry benzene afforded a white crystalline compound characterized as 1,3,4-oxadiazoline (**3a**) on the basis of satisfactory analytical and spectral data (see experimental section). The significant features of the spectral data are described in the next paragraph.

The IR spectrum of the compound **3a** showed absorption bands at 1672 and 1605 cm^{-1}, which have been assigned to amido carbonyl and imino groups, respectively. The ^1H NMR spectrum of **3a** displayed two singlet signals at δ 5.75 and 5.05 ppm, which have been attributed to methine protons adjacent to carbonyl and azomethine groups, respectively. The ^{13}C NMR spectrum of **3a** showed two downfield signals at δ 169.06 (d, $^2J_{C\text{-}H}$ = 7.35 Hz) and 157.40 ppm (d, $^2J_{C\text{-}H}$ = 9.15 Hz), which have been assigned to carbonyl and azomethine carbons, respectively. The signal at δ 103.85 ppm accounts for C-5 of the ring.

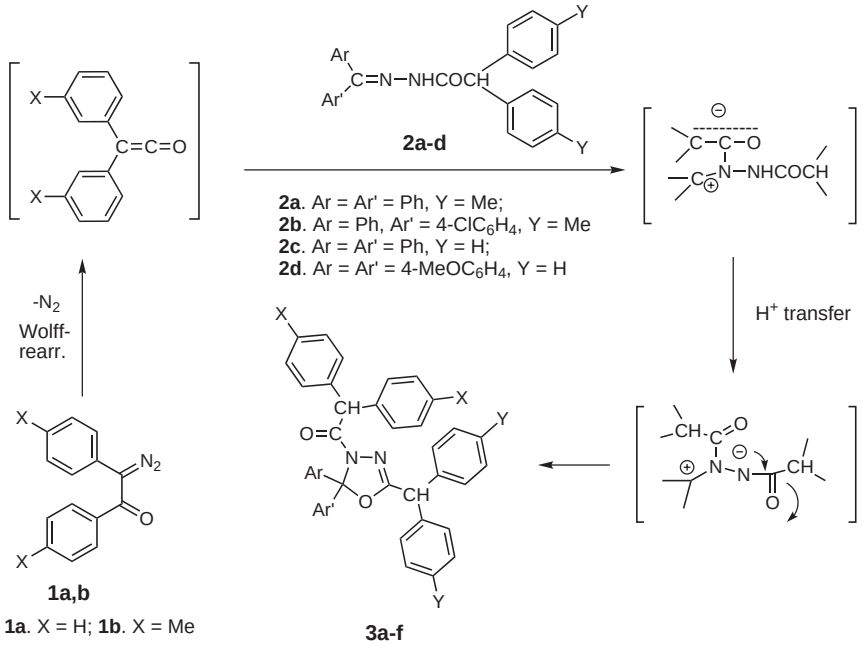
Similar reaction of the 2-diazo-1,2-diphenylethanone (**1a**) with *N*-(di-*p*-tolyl)]acyl 4-chlorobenzophenone hydrazone (**2b**) also afforded an 1,3,4-oxadiazoline (**3b**), which was characterized on the basis of satisfactory analytical data and similar nature of the IR and ^1H NMR spectra as observed in case of the product **3a**.

The reaction of 2-diazo-1,2-di-*p*-tolylethanone (**1b**) [14] with hydrazones (**2a-d**) afforded the corresponding 1,3,4-oxadiazolines (**3c-f**). However, *N*-[di-*p*-tolyl)acyl hydrazones (**2a,b**) appeared less reactive in comparison to diphenylacyl hydrazones (**2c-d**). Similarly 2-diazo-1,2-di-*p*-tolyl-2-ethanone (**1b**) afforded comparatively lower yields of the products than the 2-diazo-1,2-diphenyl-ethanone (**1a**). In both of these cases, the ^1H NMR spectra of the crude product mixtures showed the presence of the starting hydrazones even after refluxing in toluene for 16-20 h. Both **1a** and **1b** failed to react with the *N*-(*p*-tolyl)]-acyl hydrazones of 4,4'-dimethylbenzophenone.

The plausible mechanism of formation of these products is shown in Scheme 2. Diarylketenes, generated *in situ* from thermal decomposition of the diazoketones **1**, may react with imino nitrogen of the hydrazones **2** leading to a *zwitterionic* intermediate as proposed by various researchers in ketene-imine cycloaddition. A proton transfer in this *zwitterion* leading to the generation of a 1,3-dipole and subsequent [2+3] dipolar cycloaddition onto the C=O group may lead to the formation of 1,3,4-oxadiazolines **3**.

In conclusion, the paper reports the synthesis of some new 1,3,4-oxadiazolines, which might be of biological interest. This methodology of synthesis of 1,3,4-oxadiazolines using diaryketenes, generated from thermal decomposition of the 2-diazoketones, showed limited application in reactions with (diaryl)acyl hydrazones of

Scheme 2



3a. Ar = Ar' = Ph, X = H, Y = Me; **3b**. Ar = Ph, Ar, = 4-ClC_6H_4, X = H, Y = Me;
3c. Ar = Ar' = Ph, X = Y = Me; **3d**. Ar = Ph, Ar, = 4-ClC_6H_4, X = Y = Me;
3e. Ar = Ar' = Ph, X = Me, Y = H; **3f**. Ar = Ar' = 4-$MeOC_6H_4$, X = Me, Y = H

benzophenones. Further study of the reaction in order to broaden its scope is in progress and will be communicated in due course.

EXPERIMENTAL

Melting points have been recorded on a Stuart Scientific melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer-781 IR spectrophotometer using KBr disc of the sample. The ^{1}H and ^{13}C NMR spectra were recorded in a $CDCl_3$ solution at 300 MHz and 75.4 MHz, respectively, on a Bruker™ spectrometer. The mass spectra were recorded on a Mat SSQ 7000 spectrometer using dichloromethane as a solvent.

All the ketones, benzils and hydrazine hydrate were Sigma products. 2-Diazo-1,2-diarylethanones (**1**) were prepared by oxidation of appropriate benzil monohydrazones using bis–(acetylacetonato)copper(II) according to reported method [15]. *N*-(Diaryl)acyl hydrazones (**2**) were prepared by an equimolar reaction of the benzophenone hydrazones with 2-diazo-1,2-diarylethanones [16]. The solvents were dried by refluxing over sodium hydride.

General Procedure for the Reaction of 2-Diazo-1,2-diaryl-ethanones with Hydrazones.

An equimolar amount of 2-diazo-1,2-diarylethanones (**1**) and hydrazones (**2**) (1 mmole of each) in 10 ml of dry benzene or toluene (thiophene-free) was heated to reflux under an atmosphere of nitrogen for 12 h. The solvent was evaporated under reduced pressure using a rotary evaporator. The residue was triturated with ethanol to afford the white crystalline products (**3**) [17]. The analytical and spectral data of these products are given below:

5,5-Diphenyl-4-(diphenyl)acyl-2-(di-*p*-tolyl)methyl-1,3,4-oxa-diazoline (**3a**).

Yield 53 %, m. p. 159ºC, IR, 1672, 1605; δ H, 7.31-7.08 (m, 28H, arom), 5.82 (s, 1H), 5.06 (s, 1H), 2.37 (s, 6H, Me); δ C, 169.06 (d, $^{2}J_{C\text{-}H}$ = 7.35 Hz), 157.40 (d, $^{2}J_{C\text{-}H}$ = 9.15 Hz), 138.34, 138.19, 136.61, 129.74, 129.51, 129.39, 129.35, 129.08, 128.92, 128.39, 128.11, 127.85, 103.85 (C-5), 55.37, 49.25, 21.52; MS, m/z (relative intensity), 612 (M^+, 5), 418 (100, M^+ - $Ph_2C{=}C{=}O$), 390 (8, M^+ -$(MeC_6H_4)_2C{=}C{=}O$), 194 (5), 166 (7).

Anal. Calcd. for $C_{43}H_{36}N_2O_2$: C, 84.31; H, 5.88: N, 4.57. Found: C, 83.87; H, 6.06: N, 4.38.

5-*p*-Chlorophenyl-5-phenyl-4-(diphenyl)acyl-2-(di-*p*-tolyl)methyl-1,3,4-oxadiazoline (**3b**).

Yield 57 %, m. p. 142ºC, IR, 1670, 1600; δ H, 7.33-7.03 (m, 27H, arom), 5.82 (s, 1H), 5.07, 2.37 (s, 3H, Me), 2.36 (s, 3H, Me); MS, m/z (relative intensity), 647 (M^+, 12), 453 (48), 231 (40), 222 (35), 194 (100).

Anal. Calcd. for $C_{43}H_{35}N_2O_2Cl$: C, 79.75; H, 5.40: N, 4.32. Found: C, 79.47; H, 5.62: N, 4.17.

5,5-Diphenyl-4-(di-*p*-tolyl)acyl-2-(di-*p*-tolyl)methyl-1,3,4-oxa-diazoline (**3c**).

Yield 46 %, IR, 1676, 1608, δ H, 7.55-6.98 (m, 26H, arom), 5.72 (s, 1H), 4.96 (s, 1H), 2.36 (s, 6H, Me), 2.34 (s, 6H, Me); δ C 169.02, 157.70, 138.25, 136.88, 136.85, 131.98, 130.17, 129.99, 129.36, 128.89, 128.56, 128.17, 128.06, 127.85, 103.73, 55.30, 48.53, 21.45; MS, m/z (relative intensity), 640 (M^+, 55), 418 (100), 222 (5), 194 (15).

Anal. Calcd. for $C_{45}H_{40}N_2O_2$: C, 84.37; H, 6.25: N, 4.37. Found: C, 84.12; H, 6.45: N, 4.15.

5-*p*-Chlorophenyl-5-phenyl-4-(di-*p*-tolyl)acyl-2-(di-*p*-tolyl)methyl-1,3,4-oxadiazoline (**3d**).

Yield 52 %, IR, 1670, 1600; δ H, 7.77-7.10 (m, 25H, arom), 5.79 (s, 1H), 5.00 (s, 1H), 2.36 (s, 6H, Me), 2.34 (s, 6H, Me); δ C 168.45, 157.10, 138.80, 137.75, 137.25, 137.23, 136.24, 135.00, 129.45, 129.27, 128.60, 128.55, 128.35, 128.27, 127.96, 127.78, 127.54, 126.88, 102.50, 55.60, 48.80, 21.45 MS (m/z, relative intensity): 675 (M^+, 8), 453 (35), 222 (100), 217 (5), 194 (8).

Anal. Calcd. for $C_{45}H_{39}N_2O_2Cl$: C, 80.00; H, 5.77: N, 4.14. Found: C, 79.55; H, 6.02; N, 3.95.

5,5-Diphenyl-4-(di-*p*-tolyl)acyl-2-(diphenyl)methyl-1,3,4-oxa-diazoline (**3e**).

Yield 61 %, m. p. 170ºC, IR, 1675, 1600, δ H, 7.54-7.07 (m, 28H, arom), 5.73 (s, 1H), 5.06 (s, 1H), 2.36 (s, 6H, Me); δ C, 169.05 (d, $^{2}J_{C\text{-}H}$ = 7.35 Hz), 157.40 (d, $^{2}J_{C\text{-}H}$ = 9.15 Hz), 139.64, 136.60, 129.58, 129.51, 129.35, 129.08, 128.93, 128.74, 128.39, 128.11, 127.87, 127.42, 103.84, 55.37, 49.25, 21.53; MS, m/z (relative intensity), 612 (M^+, 75), 430 (15), 418 (25), 390 (100), 194 (13), 179 (14).

Anal. Calcd. for $C_{43}H_{36}N_2O_2$: C, 84.31; H, 5.88: N, 4.57. Found: C, 83.95; H, 6.19: N, 4.33.

5,5-Di-*p*-anisyl-4-(di-*p*-tolyl)acyl-2-(diphenyl)methyl-1,3,4-oxa-diazoline (**3f**).

Yield 69 %, m. p. 138ºC, IR, 1668, 1605, δ H, 7.36-7.00 (m, 22 H, arom), 6.76 (dd, 4 H), 5.80 (s, 1H), 5.03 (s, 1H), 3.85 (s, 6H, OMe), 2.35 (s, 6H, Me); δ C, 168.10 (d, $^{2}J_{C\text{-}H}$ = 7.35 Hz), 158.91 (t, MeOC),157.15 (d, $^{2}J_{C\text{-}H}$ = 9.15 Hz), 138.09, 137.03, 135.31, 135.14, 128.38, 128.11, 128.05, 127.67, 127.47, 127.22, 111.97, 102.00, 55.60, 54.26, 47.87, 20.05; MS, m/z (relative intensity), 672 (M^+, 5).

Anal. Calcd. for $C_{45}H_{40}N_2O_4$: C, 80.35; H, 5.95: N, 4.16. Found: C, 79.97; H, 6.16: N, 3.88.

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REFERENCES AND NOTES

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