Reactions of α-Diazoketones with Indolinone imines: Synthesis of New 1,3,3-Triaryl-1'-methylspiro[azetidine-2,3'-indoline]-2',4-diones

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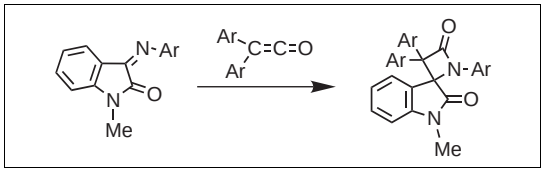

The paper describes the synthesis of new 1,3,3-triary-1'-methylspiro[azetidine-2,3'-indoline]-2',4-diones from reaction of the 2-diazo-1,2-diarylethanones with 3-arylimino-1-methyl-2-indolinones. The compounds have been characterized by satisfactory analytical and spectral (IR, ^{1}H NMR and ^{13}C NMR) data. The diarylketenes, generated *in situ* from thermal decomposition of the 2-diazo-1,2-diarylethanones, react with azomethine linkage in preference to carbonyl group leading to the formation of products.

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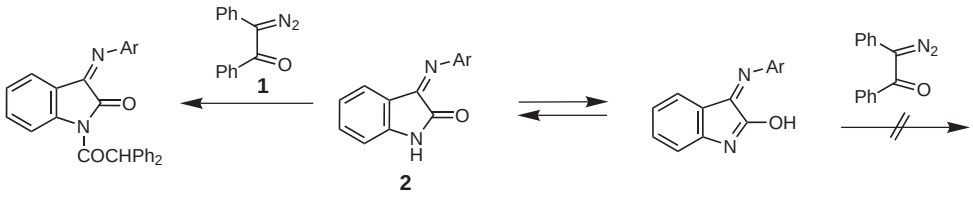
Introduction.

Diazoketones are well known precursors of the reactive intermediates such as ketenes, carbenes and carbenoids [1]. The reactions of these intermediates with compounds containing heteroatoms are useful in the synthesis of diverse types of heterocyclic compounds including many complex and biologically important natural products [2]. The Staudinger reaction involving cycloaddition of ketenes with imines leads to the formation of biologically important cyclic amides β-lactams [3]. However, the reactions of ketenes with ambident substrates often depend on the electronic and steric environment around the particular functional group. The reaction of diphenylketene with benzil monoimines occurs at C=N group in preference to the C=O group [4]. Similar reactions of ketenes with benzophenone *N*-phenyl hydrazone [5] and with fluorinone *N*-benzoyl hydrazone [6] are reported to occur at N-H bond and C=N bond, respectively, forming *N*,*N*-disubstituted hydrazones and 2-azetidinones.

The literature reveals diverse types of biological activities associated with indoline-2,3-dione isatin [7-9]. We, therefore, initiated studies on the reactions of diarylketenes with isatin derivatives. We opted for the α-diazoketones instead of the acid chloride-base [3] to generate the diarylketenes as the reactions of the former compounds appeared more versatile and simple to carry out requiring no acid, base and water work-up which might be risky to stability of the lactam ring. We used this method recently to synthesize 2-azetidinones from the imines of thiophene-2-carbaldehyde [10]. An equimolar reaction of 2-diazo-1,2-diphenylethanone **1** with 3-arylimino-2-indolinones **2** having five possible reactive sites has been observed by our group to occur exclusively at amido nitrogen forming the corresponding *N*-diphenylacyl derivatives (Scheme I) [11].

This paper reports the reaction of the 2-diazo-1,2-diarylethanones **1a,b** with 3-arylimino-1-methyl-2-indolinones **2a-e**. The diarylketenes react selectively with azomethine linkage leading to the formation of new spiro-[azetidine-indoline]diones. The 2-azetidinones are biologically important compounds [12]. It is worth mentioning that only a few stable spiroazetidinones are reported in the literature [4,8,13-15].

Scheme I



Results and Discussion.

An equimolar reaction of 2-diazo-1,2-di-*p*-tolylethanone (**1a**) with 3-phenylimino-1-methyl-2-indolinone (**2a**) in acetonitrile afforded a white crystalline compound characterized as 1-phenyl-3,3-bis(4-methylphenyl)-1'-

methylspiro[azetidine-2,3'-indoline]-2',4-dione (**3a**) on the basis of satisfactory analytical and spectral data (see experimental). The IR spectrum showed two strong absorption bands at 1735 and 1725 cm^{-1} corresponding to two lactam carbonyl groups. The ^{13}C NMR spectrum showed the two carbonyl carbons at δ 173.45 and 166.91 ppm. In the IR and ^{13}C spectra of the product **3a**, the disappearance of the band at 1610 cm^{-1} corresponding to imino linkage and imino carbon at δ 165.7 ppm, respectively confirmed the reaction at azomethine linkage of the **2a**.

Similar reactions of 2-diazo-1,2-di-*p*-tolylethanone (**1a**) with 3-arylimino-1-methyl-2-indolinones (**2b**-**e**) and of 2-diazo-1,2-phenylethanone (**1b**) with 3-arylimino-1-methyl-2-indolinones (**2c**-**e**) also afforded products **3b**-**e** and **3f**-**h**, respectively in excellent yields.

The ^1H NMR spectra of the crude reaction mixture did not show any evidence of the formation of product due to reaction at amido carbonyl establishing the high reactivity of azomethine linkage towards diarylketenes even after introducing a methyl group on the amide nitrogen.

The mechanism of formation of the product, which is similar to the one proposed earlier for such reactions [10], is shown in Scheme II. Thermal decomposition of the diazoketones leads to the formation of carbenes with extrusion of nitrogen. The carbenes undergo the Wolff-rearrangement to generate diarylketenes. The reaction of imine with ketene may lead to the formation of a *zwitterionic* intermediate, which cyclizes to give the product.

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 ^1H and ^{13}C NMR spectra were recorded in a $CDCl_3$ solution at 300 MHz and 75.4 MHz, respectively, on a Bruker™ spectrometer.

Benzil, 4,4-dimethylbenzil, 1-methylindolin-2,3-dione, amines and hydrazine hydrate were Sigma products. The acetonitrile was dried by refluxing over P_2O_5. 2-Diazo-1,2-diarylethanones **1** were prepared by oxidation of appropriate benzil monohydrazones using bis(acetylacetonato)copper(II) according to reported method [16].

Preparation of 3-*N*-Arylimino-1-methyl-2-indolinones (**2a**-**e**).

An equimolar amount (10 mmole) of an appropriate amine and 1-methylindolin-2,3-dione in ethanol was refluxed for 2-4 h. The solvent was evaporated under reduced pressure and the orange solid obtained was recrystallized from ethanol to afford the compounds **2a**-**e**.

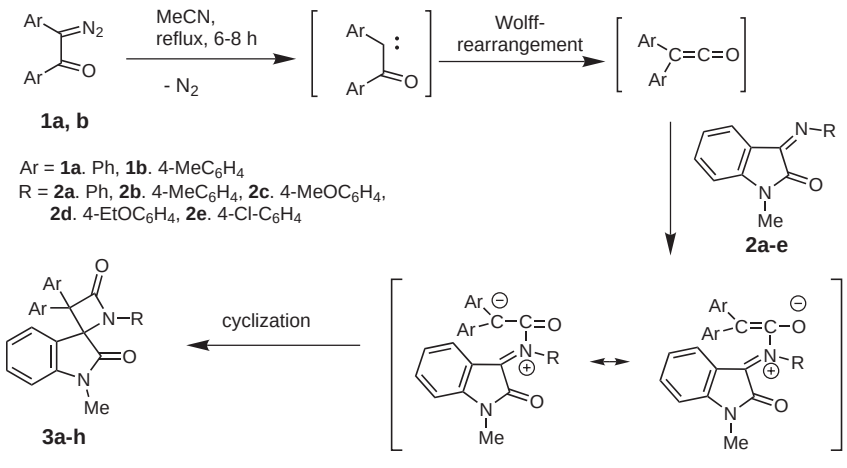
Reaction of 2-Diazo-1,2-diarylethanones with 3-*N*-Arylimino-1-methyl-2-indolinones.

An equimolar amount of 2-diazo-1,2-diarylethanones **1** and imines **2** (1 mmole of each) in 10 ml of dry acetonitrile was heated to reflux under an atmosphere of nitrogen for 6-8 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**. The analytical and spectral data are given below.

1-Phenyl-3,3-bis(4-methylphenyl)-1'-methylspiro[azetidine-2,3'-indoline]-2',4-dione (**3a**).

Yield 73 %; m. p. 194°C; IR (KBr, cm^{-1}): 1735, 1725; ^1H NMR ($CDCl_3$, δ ppm): 7.4 (dd, 3H, arom), 7.21-6.97 (m, 12H, arom), 6.72 (t, 1H, arom), 6.27 (d, 1H, arom), 3.33 (s, 3H, N-Me), 2.86 and 2.26 (two s, 6H, two C-Me); ^{13}C NMR ($CDCl_3$, δ ppm): 173.45, 166.91, 144.17, 137.67, 137.28 (two C), 135.62, 135.46, 130.85, 129.50, 129.45, 129.29, 128.37, 127.37, 126.83,

Scheme II



3a. Ar = 4-MeC_6H_4, R = Ph; **3b**. Ar = 4-MeC_6H_4, R = 4-MeC_6H_4;
3c. Ar = 4-MeC_6H_4, R = 4-$MeOC_6H_4$; **3d**. Ar = 4-MeC_6H_4, R = 4-$EtOC_6H_4$;
3e. Ar = 4-MeC_6H_4, R = 4-ClC_6H_4; **3f**. Ar = Ph, R = 4-$MeOC_6H_4$;
3g. Ar = Ph, R = 4-$EtOC_6H_4$; **3h**. Ar = Ph, R = 4-ClC_6H_4

124.93, 123.25, 122.68, 117.92, 108.90, 76.50, 71.61, 27.20, 21.52, 21.38.

Anal. Calcd. for $C_{31}H_{26}N_2O_2$: C,81.20; H, 5.72; N, 6.11. Found: C, 80.97; H, 6.02; N, 5.88.

1-(4-Methylphenyl)-3,3-bis(4-methylphenyl)-1'-methyl-spiro-[azetidine-2,3'-indoline]-2',4-dione (**3b**).

Yield 79 %; m. p. 190°C; IR (KBr, cm^{-1}): 1738, 1727; ^1H NMR ($CDCl_3$, δ ppm): 7.42 (d, 2H, arom), 7.38 (dt, 1H, arom), 7.16 (d, 2H, arom), 7.10-6.97 (m, 9H, arom), 6.72 (t, 1H, arom), 6.27 (d, 1H, arom), 3.32, (s, 1H, N-Me), 2.28, 2.26 and 2.23 (three s, 9H, three C-Me).

Anal. Calcd. for $C_{32}H_{28}N_2O_2$: C, 81.33; H, 5.97; N, 5.93. Found: C, 81.02; H, 6.15; N, 5.60.

1-(4-Methoxyphenyl)-3,3-bis(4-methylphenyl)-1'-methyl-spiro-[azetidine-2,3'-indoline]-2',4-dione (**3c**).

Yield 86 %; m. p. 204; IR (KBr, cm^{-1}): 1740, 1730; ^1H NMR ($CDCl_3$, δ ppm): 7.42 (d, 2H, arom), 7.36 (dt, 1H, arom), 7.18 (d, 2H, arom), 7.12-6.97 (m, 7H, arom), 6.74 (m, 3H, arom), 6.28 (d, 1H, arom), 3.71 (s, 3H, OMe), 3.30, (s, 1H, N-Me), 2.28 and 2.27 (two s, 6H, two C-Me); ^{13}C NMR ($CDCl_3$, δ ppm): 172.23, 165.26, 155.65, 142.86, 136.21, 135.81, 134.36, 134.23, 129.42, 129.19, 128.02, 127.87, 126.98, 125.92, 125.46, 121.97, 121.24, 118.60, 113.37, 107.47, 75.19, 70.54, 54.37, 25.77, 20.11, 19.98.

Anal. Calcd. for $C_{32}H_{28}N_2O_3$: C, 78.67; H, 5.78; N, 5.73. Found: C, 78.28; H, 5.46; N, 5.55.

1-(4-Ethoxyphenyl)-3,3-bis(4-methylphenyl)-1'-methyl-spiro-[azetidine-2,3'-indoline]-2',4-dione (**3d**).

Yield 90 %; m. p. 155°C; IR (KBr, cm^{-1}): 1740, 1730; ^1H NMR ($CDCl_3$, δ ppm): 7.42 (d, 2H, arom), 7.36 (dt, 1H, arom), 7.17 (d, 2H, arom), 7.08 (d, 4H, arom), 7.00 (d, 3H, arom), 6.76-6.68 (m, 3H, arom), 6.29 (d, 1H, arom), 3.93 (q, 2H, OCH_2), 3.30, (s, 1H, N-Me), 2.28 and 2.26 (two s, 6H, two C-Me), 1.34 (t, 3H, Me); ^{13}C NMR ($CDCl_3$, δ ppm): 173.65, 166.66, 156.46, 144.29, 137.59, 137.20, 135.79, 135.67, 130.79, 130.46, 129.41, 129.26, 128.40, 127.34, 126.89, 123.43, 122.62, 120.05, 115.40, 108.85, 76.61, 71.98, 64.01, 27.15, 21.50, 21.36, 15.13.

Anal. Calcd. for $C_{33}H_{30}N_2O_3$: C, 78.86; H, 6.02; N, 5.57. Found: C, 79.33; H, 6.05; N, 5.34.

1-(4-Chlorophenyl)-3,3-bis(4-methylphenyl)-1'-methyl-spiro-[azetidine-2,3'-indoline]-2',4-dione (**3e**).

Yield 64 %; m. p. 198; IR (KBr, cm^{-1}): 1730, 1724; ^1H NMR ($CDCl_3$, δ ppm): 7.40 (m, 3H, arom), 7.17-6.97 (m, 11H, arom), 6.74 (t, 1H, arom), 6.25 (d, 1H, arom), 3.32 (s, 3H, N-Me), 2.28 and 2.26 (two s, 6H, two Me); ^{13}C NMR ($CDCl_3$, δ ppm): 173.25, 166.90, 144.14, 137.82, 137.41, 135.82, 135.43, 135.23, 131.08, 130.11, 129.63, 129.51, 129.36, 128.28, 127.31, 126.74, 122.86, 122.81, 119.17, 109.07, 76.86, 71.70, 27.24, 21.53, 21.39.

Anal. Calcd. for $C_{31}H_{25}N_2O_2Cl$: C, 75.52; H, 5.11; N, 5.68. Found: C, 75.27; H, 5.36; N, 5.85.

1-(4-Methoxyphenyl)-3,3-diphenyl-1'-methylspiro[azetidine-2,3'-indoline]-2',4-dione (**3f**).

Yield 87 %; m. p. 218; IR (KBr, cm^{-1}): 1740, 1730; ^1H NMR ($CDCl_3$, δ ppm): 7.57 (dd, 2H, arom), 7.38-7.18 (m, 9H, arom), 7.12 (dt, 2H, arom), 7.05 (d, 1H, arom), 6.72 (dt, 3H, arom), 6.23 (d, 1H, arom), 3.71 (s, 3H, O-Me), 3.33 (s, 3H, N-Me); ^{13}C NMR ($CDCl_3$, δ ppm): 173.50, 166.33, 157.13, 144.27, 138.50, 138.40, 130.96, 130.49, 128.69, 128.64, 128.61, 128.02, 127.81, 127.24, 127.12, 123.19, 122.70, 120.03, 114.80, 108.96, 76.88, 71.93, 55.78, 27.20.

Anal. Calcd. for $C_{30}H_{24}N_2O_3$: C, 78.24; H, 5.25; N, 6.08. Found: C, 77.90; H, 5.56; N, 5.80.

1-(4-Ethoxyphenyl)-3,3-diphenyl-1'-methylspiro[azetidine-2,3'-indoline]-2',4-dione (**3g**).

Yield 90 %; m. p. 232°C; IR (KBr, cm^{-1}): 1740, 1730; ^1H NMR ($CDCl_3$, δ ppm): 7.55 (dt, 2H, arom), 7.38-7.18 (m, 9H, arom), 7.08 (dt, 2H, arom), 7.00 (d, 1H, arom), 6.71 (m, 3H, arom), 6.24 (dd, 1H, arom), 3.92 (q, 2H, O-CH_2), 3.31 (s, 3H, N-Me), 1.34 (t, 3H, C-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 173.51, 166.31, 156.51, 144.28, 138.51, 138.41, 130.93, 130.34, 128.68, 128.61 (two C), 127.99, 127.79, 127.25, 127.13, 123.23, 122.67, 120.04, 115.40, 108.93, 76.97, 71.94, 64.01, 27.20, 15.13.

Anal. Calcd. for $C_{31}H_{26}N_2O_3$: C, 78.46; H, 5.52; N, 5.90. Found: C, 78.67; H, 5.36; N, 5.71.

1-(4-Chlorophenyl)-3,3-diphenyl-1'-methylspiro[azetidine-2,3'-indoline]-2',4-dione (**3h**).

Yield 90 %; m. p. 190; IR (KBr, cm^{-1}): 1735, 1728; ^1H NMR ($CDCl_3$, δ ppm): 7.53 (dt, 2H, arom), 7.38-7.02 (m, 14H, arom), 6.72 (td, 1H, arom), 6.20 (dd, 1H, arom); ^{13}C NMR ($CDCl_3$, δ ppm): 173.26, 166.57, 144.16, 138.18, 138.00, 135.73, 131.24, 130.24, 129.66, 128.78, 128.73, 128.50, 128.18, 127.96, 127.23, 127.00, 122.85, 122.68, 119.19, 109.16, 76.98, 71.70, 27.26.

Anal. Calcd. for $C_{29}H_{21}N_2O_2Cl$: C, 74.91; H, 4.55; N, 6.03. Found: C, 74.67; H, 4.36; N, 5.85.

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