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An Efficient Synthesis of New 2-Aryl-5-phenylazenyl-1,3,4-oxadiazole Derivatives from *N*,*N*′-Diarylcarbonohydrazides

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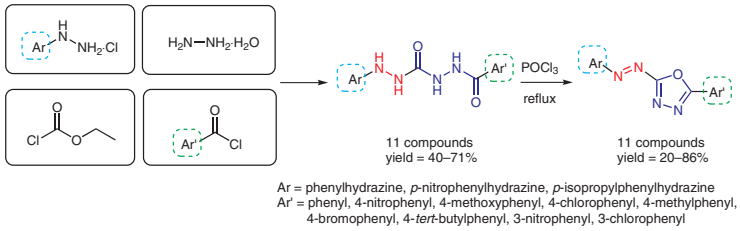

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Abstract A series of new 1,3,4-oxadiazoles conjugated to aromatic substituents by an azo linker was synthesized in a four-step reaction sequence, involving cyclodehydration of a *N*,*N*′-diacylhydrazine fragment and dehydrogenation of the neighboring hydrazine fragment of the intermediate *N*,*N*′-diarylcarbonohydrazide.

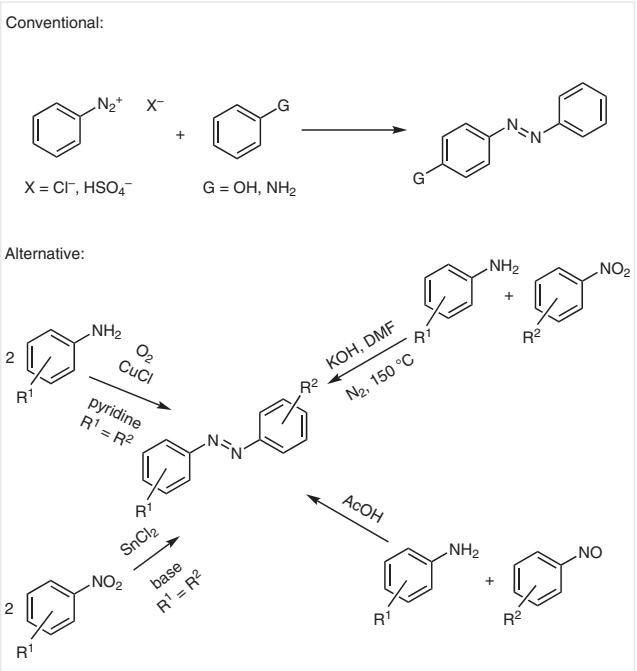
Key words 1,3,4-oxadiazoles, azo compounds, heterocycles, cyclodehydration, dehydrogenation

Oxadiazoles are five-membered heterocyclic organic compounds, containing one oxygen and two nitrogen atoms. Depending on the location of these heteroatoms, one can distinguish four oxadiazole isomers. Among them, the best known are 1,2,4-oxadiazole and 1,3,4-oxadiazole, which is due to their stability, wide range of biological activities, and possibility of their application in a range of fields.[1] For instance, 1,3,4-oxadiazole derivatives display anticancer,[2] anti-inflammatory,[3] antibacterial,[4] antifungal,[5] anticonvulsant,[6] and anti-HIV[7] activities. These heterocyclic molecules do not adversely affect the human body, and numerous studies have shown that they counteract many diseases. Therefore, they have been utilized extensively in medicine and pharmacy. Examples of medicines that contain the 1,3,4-oxadiazole scaffold are Raltegravir® (antiretroviral), Zibotentan® (anticancer), Fenadiazole® (hypnotic), Nesapidil® (antihypertensive), and Furamizole® (antibiotic).[8,9] They are also used in agriculture as herbicides, fungicides, or insecticides.[10,11] In the materials area, these heterocycles are applied in the production of heat-resistant polymers, blowing agents, optical brighteners, and anticorrosion agents.[12–15] In addition, 2,5-disubstituted-1,3,4-oxadiazoles exhibit both thermal and chemical stability, good film-forming capabilities, and interesting optoelectronic properties. The last feature is related to their electron-deficient nature and high photoluminescence quantum yield. All the above-mentioned properties enable the application of these compounds as photosensitive materials, laser dyes, or fluorescent emitters for organic light-emitting diodes (OLED). A pre-eminent example of the latter is 2-(4-*tert*-butylphenyl)-5-(4-biphenylyl)-1,3,4-oxadiazole (PBD), used as an electron-transport material (ETM) in organic light-emitting diodes.[16]

The wide range of applications of 1,3,4-oxadiazole derivatives has resulted in the development of many synthetic routes for their preparation. The most popular methods to synthesize these heterocyclic compounds involve cyclodehydration of *N*,*N*′-diacylhydrazines[17–20] and oxidative cyclization of *N*-acylhydrazones.[21–27] 1,3,4-Oxadiazole derivatives may also be prepared by cyclocondensation of acid hydrazides with triethyl orthoesters,[28] photoisomerization[29,30] of 1,2,4-oxadiazoles, and acylation and subsequent ring opening/closing of tetrazoles.[31]

In a continuation of our studies on 1,3,4-oxadiazole derivatives, we herein describe the synthesis of new 1,3,4-oxadiazoles conjugated to aromatic substituents by an azo linker. The characteristic feature of these title compounds, the azo linker, is particularly important in the area of dyestuffs and in materials science because of the possibility of reversible *cis*–*trans* photoisomerization, which is useful in the construction of polymeric materials showing various photochromic properties, such as azobenzenes.[32,33] It is generally known that the most common method for introducing such a linker is the conjugation of diazonium salts with phenols and aromatic amines. However, this methodology often requires very specific reaction conditions, including low temperatures, narrow pH range (adjusted by combination of acids or buffers), and prolonged reaction times.[34–36] In the literature, several other methods for the preparation of simple azo compounds are described, includ-

ing oxidative coupling of aromatic amines in the presence of oxygen with CuCl as a catalyst,[37] reduction of nitro compounds using $SnCl_2$,[38] condensation of both nitro and amino derivatives under basic conditions,[39] or reaction of nitroso substrates with amines in glacial acetic acid (Scheme 1).[40]

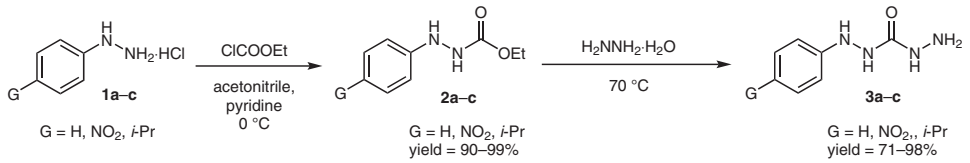


Scheme 1 Strategies of the synthesis of azo compounds

Considering the importance of this group of heterocyclic compounds to different branches of chemistry, including medicine, agriculture, dyestuffs, and materials science, we report herein an efficient pathway to obtain a series of 1,3,4-oxadiazoles that are conjugated by an azo linker to aromatic substituents. To the best of our knowledge, the preparation of the title compounds has not been reported previously.

The target 1,3,4-oxadiazole derivatives containing an azo group (**6a–k**) were obtained in a four-step reaction sequence.[41] In a typical synthetic procedure, the starting commercially available phenylhydrazine hydrochlorides (**1a–c**) were treated with ethyl chloroformate in acetonitrile at 0 °C to give the ethyl 2-phenylhydrazinecarboxylate (**2a–c)** derivatives in high yields. The resulting intermediates (**2a–c**) were heated with hydrazine hydrate to obtain *N*-phenylcarbonohydrazides (**3a–c**), also in good yields (Scheme 2). These acyclic compounds were purified by dissolving them in hot isopropanol and precipitation with hexane. The yields for individual derivatives are summarized in Table 1.

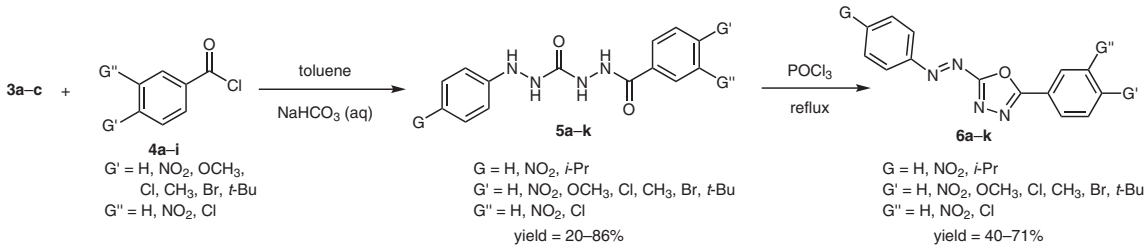
The next step required the use of commercially available benzoyl chloride (**4a**) or synthesized acid chlorides (**4b–i**) that were added dropwise to the mixture of *N*-phenylcarbonohydrazide (**3a–c**) and sodium bicarbonate in water. The substitution occurred at room temperature over 24 hours. The products (**5a–k**) so obtained were purified by recrystallization from a mixture of ethanol and acetic acid. The last step involved both the cyclization of the *N*,*N*′-diacylhydrazine fragment and dehydrogenation of the neighboring hydrazine fragment of the intermediate *N*,*N*′-diarylcarbonohydrazides (**5a–k**), which resulted in the formation of both the oxadiazole ring and the azo function (Scheme 3). To achieve this, the *N*,*N*′-diarylcarbonohydrazides (**5a–k**) were heated with phosphorus oxychloride for several hours, providing 2-aryl-5-phenylazenyl-1,3,4-oxadiazoles in satisfactory yields (40–71%, Table 2). The resulting products were purified by column chromatography with use of chloroform/ethyl acetate as the eluent. The title compounds possess lower melting points than those of the corresponding *N*,*N*′-diacylhydrazine intermediates (except **6j**) and intense colors ranging from yellow to red. As shown in



Scheme 2 Synthesis of the precursors of the title compounds

Table 1 The Resulting Ethyl 2-Phenylhydrazinecarboxylate Derivatives (**2a–c**) and *N*-Phenylcarbonohydrazide Derivatives (**3a–c**)

Entry	Substituents	Product **2**		Product **3**		
		Mp (°C)	Yield (%)	Reaction time (h)	Mp (°C)	Yield (%)
a	G = H	70–71	90	6	138–139	71
b	G = NO_2	194–195	99	4,5	–	98
c	G = *i*-Pr	73–76	99	8	167–170	72



Scheme 3 Synthesis of the title azo compounds

Table 2, this methodology displayed excellent compatibility with a variety of substituents on the benzoyl chloride. However, *N*,*N*′-diarylcarbonohydrazides bearing an electron-withdrawing group, such as nitro or bromo at the *para* position, gave higher yields of the desired product. This observation can be ascribed to the fact that electron-withdrawing substituents decrease the electron density on the carbonyl carbon, which facilitates the reaction. However, both nitro and bromo precursors required longer reaction times. To explore the scope and versatility of the method, we also decided to introduce additional substituents onto the phenylhydrazine. As a representative of an electron-withdrawing substituent we chose the nitro group (**1b**) and, in order to evaluate the result of the electron-donor effect, we introduced the isopropyl group (**1c**). In both cases we carried out the four-step reaction sequence and in both of these sequences the product yields were similar and satisfactory for both precursors.

In conclusion, we have developed a facile and efficient methodology to synthesize conjugated 2-aryl-5-phenylazenyl-1,3,4-oxadiazoles. The protocol presented herein appears to be versatile in terms of location and nature of the aromatic substituents. A number of new azo compounds, derived from 1,3,4-oxadiazole, as well as many new intermediate *N*,*N*′-diarylcarbonohydrazides were synthesized. The structures of all the intermediates and final compounds were confirmed by conventional spectroscopic analyses.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610105.

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Table 2 The Resulting *N*,*N*′-Diarylcarbonohydrazides (**5a–k**) and 1,3,4-Oxadiazole Derivatives (**6a–k**)

Entry	Substituents			Product **5**		Product **6**		
				Mp (°C)	Yield (%)	Reaction time (h)	Mp (°C)	Yield (%)
a	G = H	G' = H	G'' = H	204–206	55	3	139–140	56
b	G = H	G' = NO_2	G'' = H	216–217	86	6	160–161	71
c	G = H	G' = OCH_3	G'' = H	182–183	20	3	130–131	44
d	G = H	G' = Cl	G'' = H	213–214	62	3,5	139–140	66
e	G = H	G' = CH_3	G'' = H	199–200	41	4	129–130	64
f	G = H	G' = Br	G'' = H	212–213	61	9	182–183	63
g	G = H	G' = *t*-Bu	G'' = H	140–141	30	5	–	40
h	G = H	G' = H	G'' = NO_2	190–191	46	7	153–154	43
i	G = H	G' = H	G'' = Cl	197–198	49	4	135–136	68
j	G = NO_2	G' = H	G'' = H	212–215	34	6	226–227	63
k	G = *i*-Pr	G' = H	G'' = H	198–200	31	4	80–81	59

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(41) **Representative Procedures**
***N'*-[(2-Phenylhydrazinyl)carbonyl]benzohydrazide (5a)**
Sodium hydrogen carbonate (2.1 g, 0.03 mol) was dissolved in water (60 mL) and *N*-phenylcarbonohydrazide (**3**, 4 g, 0.02 mol) was added with vigorous stirring. Then, benzoyl chloride (**4a**, 2.9 ml 0.03 mol) dissolved in toluene (14 mL) was added dropwise to the resultant slurry and the precipitate was stirred at room temperature for 24 h. The viscous mass was cooled in an ice bath and filtered. The product was treated with diethyl ether, triturated, and dried. The solid was crystallized from a mixture of ethanol and acetic acid (3:1 v/v) to give pure *N'*-[(2-phenylhydrazinyl)carbonyl]benzohydrazide.
White solid (2.97 g, 55% yield). Mp 204–206 °C. IR (ATR): ν = 3325, 3219, 3057, 2162, 1683, 1632, 1601, 1576, 1521, 1485, 1442, 1418, 1333, 1315, 1304, 1257, 1217, 1175, 1152, 1090, 1074, 1026, 974, 899, 812, 750, 687 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ = 6.72 (t, *J* = 7.2 Hz, 1 H), 6.81 (d, *J* = 8.0 Hz, 2 H), 7.16 (t, *J* = 8.2 Hz, 2 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.55 (t, *J* = 7.2 Hz, 1 H), 7.61 (s, 1 H), 7.90 (d, *J* = 6.8 Hz, 2 H), 8.36 (s, 2 H), 10.13 (s, 1 H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 112.5, 118.6, 127.5, 128.2, 128.5, 131.5, 132.8, 149.6, 158.8, 166.1 ppm. UV-VIS: λ_{max} (MeOH) 275.5 nm (ε·10^{-3} 4.76 $cm^{-1}M^{-1}$), λ_{max} (MeOH) 231.0 nm (ε·10^{-3} 27.35 $cm^{-1}M^{-1}$), λ_{max} (MeOH) 202.0 nm (ε·10^{-3} 46.43 $cm^{-1}M^{-1}$). Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.22; H, 5.20; N, 20.75. HRMS calcd for ($C_{14}H_{14}N_4O_2$ + H^+): 271.1190; found: 271.1188.
2-Phenyl-5-phenyldiazenyl-1,3,4-oxadiazole (6a)
N'-[(2-Phenylhydrazinyl)carbonyl]benzohydrazide (**5a**, 0.01 mol) was heated with phosphorus oxychloride (19 mL) for 3 h, the course of the reaction being monitored by TLC. The resulting dark brown mixture was concentrated with a rotary evaporator. Then, distilled water (100 mL) was poured into the flask, ice cubes were added and the mixture stirred, resulting in a dark precipitate. The mixture was left over night in a refrigerator and then filtered. The resulting solid was purified by column chromatography with chloroform/ethyl acetate (5:1 v/v) as the eluent to give pure 2-phenyl-5-phenylazenyl-1,3,4-oxadiazole.
Red solid (1.4 g, 56% yield). Mp 139–140 °C. IR (ATR): ν = 2921, 2161, 1968, 1694, 1603, 1585, 1540, 1509, 1478, 1461, 1449, 1422, 1330, 1318, 1307, 1245, 1220, 1203, 1151, 1096, 1071, 1017, 975, 959, 928, 773, 721, 702, 688, 679 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.64 (m, 6 H), 8.11 (dd, J_1 =7.6 Hz, J_2 = 0.8 Hz, 2 H), 8.22 (dd, J_1 =8.4 Hz, J_2 =1.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.2, 124.4, 127.6, 128.8, 129.0, 129.2, 129.6, 132.7, 134.4, 152.8, 164.5 ppm. UV-VIS: λ_{max} (MeOH) 348.0 nm (ε·10^{-3} 5.97 $cm^{-1}M^{-1}$), λ_{max} (MeOH) 261.5 nm (ε·10^{-3} 8.33 $cm^{-1}M^{-1}$), λ_{max} (MeOH) 202.0 nm (ε·10^{-3} 18.16 $cm^{-1}M^{-1}$). Anal. Calcd for $C_{14}H_{10}N_4O$: C, 67.19; H, 4.03; N, 22.39. Found: C, 67.15; H, 4.01; N, 22.37. HRMS calcd for ($C_{14}H_{10}N_4O$ + H^+): 250.0927; found: 250.0923.