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I_2-Mediated Desulfurative Annulation of α-Oxothioamides and Aroylhydrazides: Synthesis of α-Keto-1,3,4-oxadiazoles

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Abstract

An iodine-mediated desulfurative cyclization of α-oxothioamides with aroylhydrazides has been developed for the synthesis of 2-aroyl-5-aryl-1,3,4-oxadiazoles. The reaction uses 0.5 equiv of molecular iodine in 1,2-dichloroethane (DCE) at 80 °C under ambient air, requires no transition metal, base or added oxidant, and avoids $POCl_3$ and other strong dehydrating agents. The thioamide sulfur acts as a traceless leaving group, so the oxadiazole ring is assembled in a single operation from two readily available components, with NH_3 and H_2S as the only by-products. Screening of solvent, iodine loading and temperature showed that DCE is superior to DMF, DMSO, DCM and THF and that heating is essential: the model compound phenyl(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (3a) was obtained in 90% yield in 2.5 h at 80 °C, compared with 25–30% at room temperature. Nine ketone-bearing oxadiazoles (3a–i) carrying phenyl, electron-rich and electron-poor aryl, naphthyl, biphenyl and thienyl groups on the aroyl unit were isolated in 75–90% yield. A plausible mechanism is proposed in which iodine activates the thioamide sulfur, followed by hydrazide addition, loss of ammonia, intramolecular O-cyclization and elimination of H_2S.

Keywords: 1,3,4-oxadiazole; iodine; α-oxothioamide; aroylhydrazide; desulfurative cyclization; transition-metal-free

Introduction

The 1,3,4-oxadiazole ring is a privileged five-membered heterocycle in medicinal chemistry, owing to its thermal and hydrolytic stability, its ability to act as a bioisostere of ester and amide groups, and its capacity to engage biological targets through hydrogen bonding and other non-covalent interactions. Compared with its 1,2,4-isomer, the 1,3,4-oxadiazole generally shows lower lipophilicity and better metabolic stability and aqueous solubility [1]. Derivatives of this heterocycle display a broad range of pharmacological activities, including antimicrobial, anticancer, anti-inflammatory, anticonvulsant and antidiabetic effects [2]. The clinical relevance of the scaffold is illustrated by raltegravir, an approved anti-HIV integrase inhibitor [3], and zibotentan, an endothelin A receptor antagonist that has been evaluated as an anticancer agent [4], both of which contain a 1,3,4-oxadiazole ring. Beyond medicine, 2,5-diaryl-1,3,4-oxadiazoles such as PBD are electron-

deficient, luminescent π-systems used in materials science, and further derivatives find use in agrochemistry [5].

Among the possible substitution patterns, 2,5-disubstituted derivatives are the most widely studied, because the two substituents can be varied independently to tune biological activity and physicochemical properties, and 2,5-diaryl derivatives additionally offer an extended conjugated framework [2,5]. Within this family, 2-aroyl-5-aryl-1,3,4-oxadiazoles (aryl 5-aryl-1,3,4-oxadiazol-2-yl ketones) are of particular interest: the ketone carbonyl at C-2 is an additional hydrogen-bond acceptor that is conjugated with the electron-poor ring, and it offers a handle for further transformations such as reduction, condensation or nucleophilic addition. Access to these α-keto-oxadiazoles is, however, limited. The best-known approach is a one-pot condensation of arylglyoxals with hydrazides, followed by oxidative cyclization of the in situ formed hydrazide–hydrazone with a stoichiometric 2-iodoxybenzoic acid/tetraethylammonium bromide system [6]. Complementary routes from simple, stable and readily available building blocks, which avoid pre-oxidized arylglyoxals and hypervalent iodine reagents, are therefore desirable.

The most established route to 2,5-disubstituted 1,3,4-oxadiazoles is the cyclodehydration of N,N′-diacylhydrazines, or of acid hydrazides with carboxylic acids, using strong dehydrating agents such as phosphorus oxychloride ($POCl_3$), thionyl chloride, phosphorus pentachloride, phosphorus pentoxide or perchloric and sulfuric acids [7–9]. For example, Kędzia and co-workers obtained 2-aryl-5-phenylazenyl-1,3,4-oxadiazoles by heating the corresponding carbonohydrazide precursors in excess $POCl_3$ for several hours [7]. Dornelles and co-workers coupled acyl hydrazides directly with N-protected α-amino acids in the presence of $POCl_3$ and showed that microwave irradiation shortens the reaction time from several hours to a few minutes, with moderate to good yields [8]. Łuczyński and Kudelko likewise screened PCl_5, $SOCl_2$, $HClO_4$ and P_2O_5, among other reagents, for the microwave-assisted cyclodehydration of unsymmetrical N,N′-diacylhydrazines [9]. Despite their wide use, these protocols require pre-formed diacylhydrazines, employ corrosive and moisture-sensitive reagents in excess, generate acidic waste, tolerate acid-sensitive functional groups poorly, and do not directly deliver a ketone at C-2.

Oxidative cyclization of N-acylhydrazones is an alternative that avoids strongly acidic dehydrating agents. A wide variety of oxidants has been employed for this purpose, including ceric ammonium nitrate, $KMnO_4$, $FeCl_3$, Br_2, PbO_2, chloramine-T, HgO/I_2 and hypervalent iodine reagents [10]. Transition-metal-free variants include the I_2/K_2CO_3-mediated oxidative C–O bond formation from aldehydes and hydrazides described by Yu and co-workers [11] and the DDQ-promoted one-pot synthesis from acid hydrazides and aldehydes reported by Jasiak et al. [5]. These methods, however, start from aldehyde-derived hydrazones and therefore install an aryl, alkyl or vinyl group at C-2 rather than an aroyl group, and they generally require a stoichiometric oxidant.

Growing environmental awareness has also driven the development of greener routes to oxadiazoles, including microwave irradiation, ultrasonication, grinding or milling, photocatalysis, electrochemical and solvent-free protocols, which aim to reduce hazardous reagents, waste and reaction times [12,13]. Most of these approaches, however, address the classical diaryl or aryl/alkyl substitution patterns and still rely on the same hydrazide or hydrazone precursors, which leaves room for new bond disconnections that give access to C-2 acylated oxadiazoles.

α-Oxothioamides (α-ketothioamides), readily prepared from α-oxodithioesters and ammonium chloride/sodium acetate [14], are bifunctional building blocks that combine an electrophilic ketone with a thioamide unit whose sulfur can act as a nucleophile and, after activation, as a leaving group. Mantelingu, Rangappa and co-workers have exploited them in Hantzsch-type reactions with α-bromoketones to give 2-acyl-4-(het)arylthiazoles [14] and in the electrochemical, TBAI-mediated oxidative dimerization to 3,5-bis(acyl)-1,2,4-thiadiazoles [15]; related dithioesters have been converted into 1,3,4-thiadiazoles with hydrazine hydrate [16]. The same group has shown that molecular iodine alone dimerizes α-oxothioamides to 3,5-diacyl-1,2,4-thiadiazoles [17], and that benzothiohydrazides cyclize with aldehydes under TBAI-catalysed electrochemical conditions to give 2,5-disubstituted 1,3,4-thiadiazoles [18]. In addition, α-ketothioesters react with o-phenylenediamines and o-aminophenols with loss of the thiol component to give 2-acylbenzimidazoles and 2-acylbenzoxazoles [19,20]. Singh and co-workers have likewise shown that thioamides are readily activated under photo-oxidative and hypervalent-iodine conditions to give thiadiazoles and thiazolothiadiazoles [21,22]. Taken together, these precedents show that the sulfur of a thioamide next to a carbonyl group can be activated by iodine, and that the thio-substituted carbon of α-oxo thio compounds is attacked by N-nucleophiles with expulsion of sulfur. This suggests that α-oxothioamides, reacted with aroylhydrazides, could lead directly to C-2 aroyl oxadiazoles.

Building on these precedents, we report an iodine-mediated desulfurative cyclization of α-oxothioamides **2** with aroylhydrazides **1** in 1,2-dichloroethane (DCE) at 80 °C, which furnishes 2,5-disubstituted 1,3,4-oxadiazoles **3** bearing an aroyl group at C-2 and an aryl group at C-5 (Scheme 1). In the products reported here the C-5 aryl group (Ar) is phenyl, and the aroyl group (R^1) is a substituted phenyl, naphthyl, biphenylyl or thienyl ring. The reaction is transition-metal-free, avoids $POCl_3$ and other strong dehydrating agents, does not require pre-formed diacylhydrazines or acylhydrazones, and uses the thioamide sulfur as a traceless leaving group, so that the heterocyclic ring is assembled in a single operation from two readily available components.

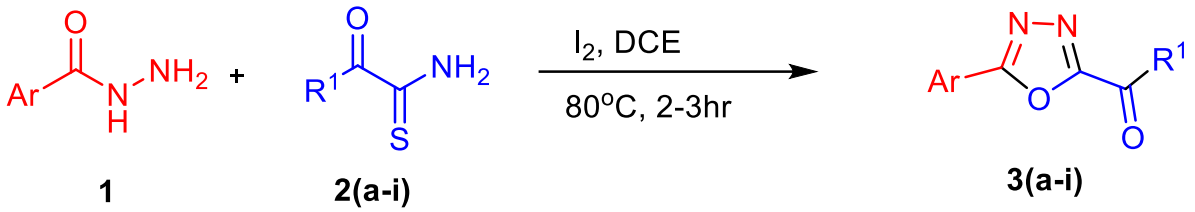
Experimental

All reagents and solvents were purchased from **Sigma-Aldrich** and used without further purification unless otherwise stated. IR spectra were recorded on a PerkinElmer Spectrum IR spectrometer. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively, in $CDCl_3$. Mass spectra were recorded by LC-MS.

General procedure for synthesis of 2-aroyl-5-aryl-1,3,4-oxadiazoles 3(a-i).

To a solution of α-oxothioamide **(2)** (1 equiv) in dichloroethane (5 mL), iodine (0.5 equiv) was added; after two minutes, benzhydrazide **(1)** (1 equiv) was added to the reaction flask at room temperature. Next, the vial was placed in a preheated metal block at 80 °C in the presence of ambient air. After the reaction was completed, the reaction mixture was cooled to room temperature and then saturated with $Na_2S_2O_3$ solution. The reaction mixture was then extracted thrice with ethyl acetate (3 × 20 mL). The organic layers were combined and dried over anhydrous Na_2SO_4, and the solvent was then removed under reduced pressure. Finally, the crude product was purified on a 200–400 mesh silica gel chromatography column using petroleum ether/ethyl acetate as an eluent to obtain the desired product **3** as a white solid.The structures 3(a-i) confirmed by spectral characterization. The recorded data given below.

To identify the optimal reaction conditions, the reaction of **1** with **2a** was carried out in different solvents, with different iodine loadings, at different temperatures and for different reaction times. The results are summarized in Table 1.



1 **2(a-i)** **3(a-i)**

a) $R^1 = C_6H_5$; **b)** R^1 = 4-OCH_3-C_6H_4; **c)** R^1 = 1-naphthyl; **d)** R^1 = 4-C_6H_5-C_6H_4; **e)** R^1 = 3-Br-C_6H_4; **f)** R^1 = 3-OCH_3-C_6H_4; g) R^1 = 3-NO_2-C_6H_4; **h)** R^1 = 2-thienyl**;** **i)** R^1 = 4-CH_3-C_6H_4; Ar = C_6H_5 for all.

Scheme 1. **Synthesis of 2-aroyl-5-aryl-1,3,4-oxadiazoles 3(a–i) from aroylhydrazides 1 and α-oxothioamides 2**

Table 1. Optimization of reaction conditions for the synthesis of **phenyl(5-phenyl-1,3,4-oxadiazol-2-yl)methanone 3a**

Entry	solvent	Equivalence of iodine	temp(^{0}C)	time(h)	% yield (3)
1	DMF	0.5	rt	4	25
2	DMF	1.0	rt	12	15
3	DMF	1.5	80	6	40
4	DCE	0.5	rt	6	25
5	DCE	1.0	rt	10	30
6	**DCE**	**0.5**	**80**	**2.5**	**90**
7	DCM	0.5	40	3	---
8	DCM	1.0	40	4	20
9	DMSO	0.5	80	6	20
10	DMSO	1.0	100	5	10
11	THF	0.5	rt	5	---
12	THF	1.0	60	8	40
13	**DCE**	0.0	**80**	8	---

Reaction conditions: benzhydrazide (**1**, 1 equiv), 2-oxo-2-phenylethanethioamide (**2a**, 1 equiv), solvent (5 mL), ambient air.(Isolated yield of **3a**).

phenyl(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (3a) yield 90%

IR (cm^{-1}): 2921**,**1689,1601**,**1561,1145,772

^{1}H NMR(400 MHz, $CDCl_3$)**:** δ 8.15-8.10(m,2H), 7.92-7.91(d,2H),7.65-7.54(m6H)

^{13}C NMR(100MHz, $CDCl_3$)**:** δ 173.49, 163.71, 159.43, 133.95, 132.98, 132.41, 130.10, 129.43, 128.64, 127.50, 122.47. LCMSm/z [M+H]$C_{15}H_{10}N_2O_2$ found to be 251.03

(4-methoxyphenyl)(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (3b) yield 89%

IR (cm^{-1}):2944**,**1698, 1650, 1555, 1097,821.

^{1}H NMR(400 MHz, $CDCl_3$)**:** δ 8.64–8.61 (*d*, 2H), 8.25–8.23 (*d*, 2H), 7.61–7.57 (*m*, 3H), 7.07–7.05 (*d*, 2H), 3.95(s,3H).

^{13}C NMR(100MHz, $CDCl_3$)**:** δ 175.88, 165.17, 161.12, 133.56, 132.73, 130.59, 129.23, 127.78, 127.41, 122.98, 114.18, 55.67

. LCMSm/z [M+H] $C_{16}H_{12}N_2O_3$ found to be 281.13

naphthalen-1-yl(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (3c) yield 82%

IR (cm^{-1}): 3060**,** 1678, 1598, 1548, 1232

^{1}H NMR(400 MHz, $CDCl_3$)**:** δ 8.78–8.76 (*d*, 1H), 8.63–8.60 (*dd*, 1H), 8.29–8.27 (*d*, 2H), 8.20–8.18 (*d*, 1H), 7.99–7.97 (*d*, 1H), 7.72–7.58 (*m*, 6H).

^{13}C NMR(100MHz, $CDCl_3$)**:** δ 170.96, 163.71, 159.43, 133.95, 132.98, 132.73, 133.41, 130.10, 129.43, 129.22, 129.00, 128.69, 128.64, 128.61, 127.50, 127.29, 122.47. LCMSm/z [M+H] $C_{19}H_{12}N_2O_2$ found to be 301.06

[1,1'-biphenyl]-4-yl(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (3d) yield 83%

IR (cm^{-1}): 3068, 1674, 1603, 1534, 1150,765

^{1}H NMR(400 MHz, $CDCl_3$)**:** *δ* 8.71–8.69 (*d*, 2H), 8.29–8.27 (*d*, 2H), 7.84–7.82 (*d*, 2H), 7.72–7.70 (*d*, 2H), 7.66–7.29 (*m*, 6H).

13C NMR: *δ* 177.13, 166.04, 161.07, 147.58, 139.55, 133.10, 132.87, 131.61, 129.29, 129.07, 128.66, 127.87, 127.44, 127.42, 122.90. LCMSm/z [M+H] $C_{21}H_{14}N_2O_2$ found to be 327,25

(3-bromophenyl)(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (3e) yield 80%

IR (cm^{-1}): 3072, 1689, 1601, 1561,1140,1032,775

^{1}H NMR(400 MHz, $CDCl_3$)**:** *δ* 8.14–8.09 (*m*, 3H), 7.85–7.83 (*d*, 1H), 7.68–7.57 (*m*, 4H), 7.43–7.39 (*t*, 1H).

^{13}C NMR (100MHz, $CDCl_3$)**:** 177.32, 163.74, 159.06, 135.77, 133.10, 133.08, 132.90, 132.16, 131.61, 131.61, 130.10, 129.50, 129.05, 128.05, 127.51, 127.25, 122.74, 122.32, LCMSm/z [M+H] $C_{15}H_9BrN_2O_2$ found to be 329.08

(3-methoxyphenyl)(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (3f) yield 85%

IR (cm^{-1}): 2932, 1692, 1614, 1546, 1132, 764

^{1}H NMR(400 MHz, $CDCl_3$)**:** *δ* 8.28–8.25 (*m*, 3H), 8.80 (*s*, 1H), 7.65–7.58 (*m*, 3H), 7.53–7.42 (*t*, 1H), 7.30 (*d*, 1H), 3.95 (*s*, 3H).

^{13}C NMR (100MHz, $CDCl_3$)*δ*166.02,160.99,159.86,135.50,132.89,129.87,129.29,127.85 123.95,122.86,122.04,114.37, 55. 59 LCMSm/z [M+H] $C_{16}H_{12}N_2O_3$ found to be 281.06

(3-nitrophenyl)(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (3g) yield 78%

IR (cm^{-1}): 2998, 1695, 1594, 1549, 1312, 1124, 784

^{1}H NMR (400 MHz, $CDCl_3$)**:** *δ* 8.43–8.40 (*d*, 1H), 8.16–8.11 (*m*, 4H), 7.68–7.59 (*m*, 4H).

^{13}C NMR(100MHz, $CDCl_3$): 176.01, 163.53, 158.93, 144.57, 134.89, 132.05, 130.26, 128.52, 127.51, 125.30, 123.90, 122.58, 119.97

LCMSm/z [M+H] $C_{15}H_9N_3O_4$ found to be 296.10

(5-phenyl-1,3,4-oxadiazol-2-yl)(thiophen-2-yl)methanone (3h) yield 75%

IR (cm^{-1}): 3121, 2987, 1667, 1564, 1315, 1182, 781

^{1} H NMR(400 MHz, $CDCl_3$): δ 8.19–8.17 (m, 3H), 7.59–7.57 (m, 5H)

^{13}C NMR(100MHz, $CDCl_3$)**:** 178.78, 163.60, 157.37, 142.28, 132.58, 131.32, 129.02, 128.05, 125.05, 125.05, 124.30

LCMSm/z [M+H] $C_{13}H_8N_2O_2S$ found to be 257.17

(5-phenyl-1,3,4-oxadiazol-2-yl)(p-tolyl)methanone (3i) yield 80%

IR (cm^{-1}): 2973, 1701,1610 ,1178,792

^{1} H NMR: (400 MHz, $CDCl_3$) δ 8.61–8.59 (d, 2H), 8.26–8.24 (d, 2H), 7.66–7.57 (m, 5H)

^{13}C NMR(100MHz, $CDCl_3$)**:** 176.93, 166.21, 166.08,142.46,132.80,131.96,131.18,129.60,129.13,127.97,123.16,22.85

LCMSm/z [M+H] $C_{16}H_{12}N_2O_2$ found to be 265.08

Results and Discussion

Optimization of reaction conditions

To establish suitable conditions for the desulfurative cyclization, the reaction of benzhydrazide (**1**) with 2-oxo-2-phenylethanethioamide (**2a**) to give phenyl(5-phenyl-1,3,4-oxadiazol-2-yl)methanone (**3a**) was chosen as the model system. Solvent, iodine loading, temperature and reaction time were varied, and the results are summarized in Table 1.

We first examined DMF as solvent. With 0.5 equiv of iodine at room temperature, **3a** was obtained in only 25% yield after 4 h (entry 1). Increasing the iodine loading to 1.0 equiv and the time to 12 h lowered the yield to 15% (entry 2), and heating to 80 °C with 1.5 equiv of iodine gave 40% after 6 h (entry 3). More iodine therefore did not help in DMF. Switching to 1,2-dichloroethane (DCE) gave a similar result at room temperature: 25% yield with 0.5 equiv of iodine after 6 h (entry 4) and 30% with 1.0 equiv after 10 h (entry 5). The small gain from doubling the iodine, obtained only with a longer reaction time, shows that iodine loading does not limit the reaction at room temperature. Temperature, by contrast, had a large effect. Heating the DCE reaction to 80 °C with 0.5 equiv of iodine raised the yield to 90% and shortened the reaction time to 2.5 h (entry 6), whereas DMF at the same temperature gave only 40% in 6 h even with 1.5 equiv of iodine (entry 3). These conditions were therefore taken as optimal.

Other solvents were less effective. In dichloromethane (DCM) at 40 °C, no product was detected with 0.5 equiv of iodine after 3 h (entry 7), and 1.0 equiv gave 20% after 4 h (entry 8). In DMSO, 20% of **3a** was obtained with 0.5 equiv of iodine at 80 °C (entry 9) and 10% with 1.0 equiv at 100 °C (entry 10), so higher temperature and more iodine did not help. In THF there was no reaction at room temperature (entry 11), and a 40% yield was reached only at 60 °C with 1.0 equiv of iodine over 8 h (entry 12).

The strong solvent dependence may be related to how strongly each solvent interacts with iodine. Lewis-basic, coordinating solvents such as DMF, DMSO and THF can bind molecular iodine and may reduce its ability to act as an electrophilic, thiophilic activator of the thioamide sulfur; in addition, DMSO can react with iodine itself. The weakly coordinating DCE gave the best result. DCM performed poorly even when compared with DCE at room temperature, so its low boiling point, which limits the reaction to about 40 °C, is probably not the only factor. These explanations are tentative and were not examined further. In DCE, heating raised the yield from 25–30% to 90% (entries 4–6).

In summary, the best result was obtained with 0.5 equiv of I_2 in DCE at 80 °C for 2.5 h under ambient air, which gave **3a** in 90% yield (Table 1, entry 6). No metal catalyst, base or added oxidant was used. These conditions were applied to the substrate scope study.

Substrate scope

With the optimized conditions in hand (0.5 equiv of I_2, DCE, 80 °C, ambient air), the generality of the desulfurative cyclization was examined by varying the aroyl group (R^1) of the α-oxothioamide **2** while keeping benzhydrazide as the coupling partner, so that Ar = C_6H_5 in every product (Scheme 1, Table 2). All nine substrates gave the desired 2-aroyl-5-phenyl-1,3,4-oxadiazoles **3a–i** in 75–90% isolated yield.

The highest yields were obtained with the unsubstituted benzoyl substrate (**3a**, 90%) and with the methoxy-substituted substrates, 4-methoxyphenyl (**3b**, 89%) and 3-methoxyphenyl (**3f**, 85%). The 4-methylphenyl derivative **3i** was obtained in 80%. The substrates bearing electron-withdrawing substituents, 3-bromophenyl (**3e**, 80%) and 3-nitrophenyl (**3g**, 78%), were also tolerated, and their yields were similar to or slightly lower than that of **3i**. The bromo and nitro groups are retained in the products, which leaves handles for further functionalization. Extended aromatic systems were compatible as well: the 1-naphthyl (**3c**, 82%) and 4-biphenylyl (**3d**, 83%) ketones were formed efficiently, showing that the reaction is not strongly affected by the size of the group next to the carbonyl. The heteroaryl substrate, 2-thienyl, gave **3h** in 75% yield, the lowest in the series.

Overall, the yields fall within a narrow window (75–90%) and show no clear dependence on the electronic nature of the aroyl substituent. Electron-donating (**3b**, **3f**, **3i**), electron-withdrawing (**3e**, **3g**), extended aromatic (**3c**, **3d**) and heteroaryl (**3h**) groups all performed similarly, with the unsubstituted benzoyl group giving the

highest yield. In this study the C-5 aryl group was kept constant as phenyl, so variation of the aroylhydrazide component remains to be explored.

The structures of all products were established by IR, ^{1}H NMR, ^{13}C NMR and LC-MS data (see Experimental).

Table 2. Substrate scope for the synthesis of 2-aroyl-5-aryl-1,3,4-oxadiazoles 3a–i.

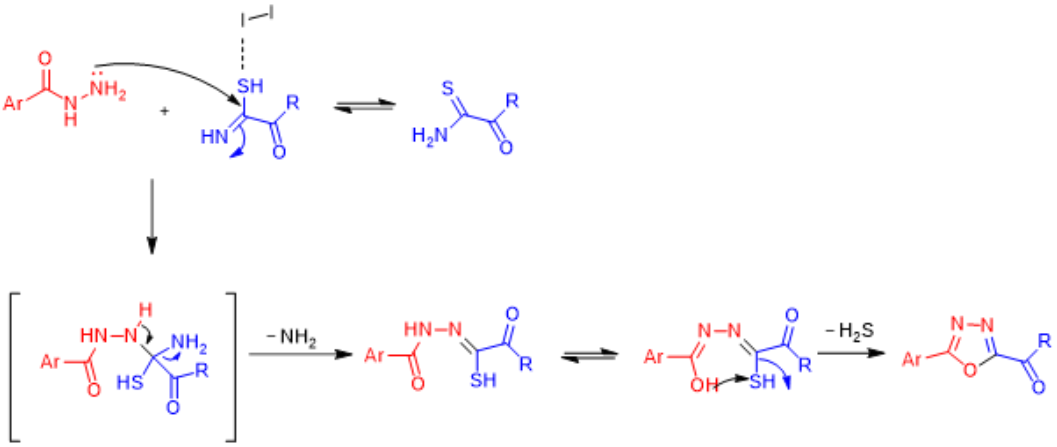
Product	R^1 (aroyl group)	Yield (%)
3a	C_6H_5	90
3b	4-OCH_3-C_6H_4	89
3c	1-Naphthyl	82
3d	4-C_6H_5-C_6H_4	83
3e	3-Br-C_6H_4	80
3f	3-OCH_3-C_6H_4	85
3g	3-NO_2-C_6H_4	78
3h	2-Thienyl	75
3i	4-CH_3-C_6H_4	80

Reaction conditions: aroylhydrazide 1 (1 equiv), α-oxothioamide 2 (1 equiv), I_2 (0.5 equiv), DCE (5 mL), 80 °C, ambient air. Ar = C_6H_5 in all products; R^1 is the aroyl substituent. Yields refer to the isolated products.

Proposed Mechanism

A plausible mechanism for the formation of oxadiazoles **3** is shown in Scheme 2. The α-oxothioamide **2** is in equilibrium with its iminothiol tautomer, whose sulfur is activated by coordination to molecular iodine [17,22]; this increases the electrophilicity of the thioamide carbon. Nucleophilic attack of the terminal NH_2 group of aroylhydrazide **1** on this carbon gives a tetrahedral intermediate bearing SH, NH_2, the N-acylhydrazinyl group and the aroyl group. Proton transfer and elimination of ammonia then deliver an N-acylhydrazone-type thio intermediate, which is in equilibrium with its thione tautomer.

Tautomerization of the amide to its iminol form places a nucleophilic oxygen next to the C–SH carbon. Intramolecular attack of this oxygen closes the five-membered ring, and subsequent elimination of H_2S results in aromatization to the 2-aroyl-5-aryl-1,3,4-oxadiazole **3**, in analogy to the loss of sulfur in the cyclocondensation of α-ketothioesters with o-aminophenols and o-phenylenediamines [19,20]. Overall, the sequence is redox-neutral (**1** + **2** → **3** + NH_3 + H_2S), so iodine is proposed to act as a thiophilic activator rather than as a stoichiometric oxidant. This mechanism is based on literature precedent and has not been tested experimentally; the role of air and the fate of the iodine (H_2S can be oxidized by iodine) remain to be examined.



Scheme 2. Proposed mechanism for the iodine-mediated formation of 2-aroyl-5-aryl-1,3,4-oxadiazoles 3.

Conclusion

In conclusion, we have developed an iodine-mediated desulfurative cyclization of α-oxothioamides with aroylhydrazides that provides 2-aroyl-5-aryl-1,3,4-oxadiazoles in a single operation. Optimization identified 0.5 equiv of I_2 in DCE at 80 °C under ambient air as the best conditions, giving the model compound **3a** in 90% yield within 2.5 h. At room temperature DCE gave only 25–30%, and DMF, DMSO, THF and DCM gave at most 40%. The method needs no transition metal, base, added oxidant or dehydrating agent such as $POCl_3$, and it does not require pre-formed diacylhydrazines, acylhydrazones or arylglyoxals.

Nine oxadiazoles bearing a C-2 aroyl group (3a–i) were obtained in 75–90% yield, and methoxy, methyl, bromo, nitro, naphthyl, biphenyl and thienyl substituents were all tolerated. A plausible mechanism is proposed in which iodine acts as a thiophilic activator of the thioamide rather than as a stoichiometric oxidant, and the thioamide sulfur is expelled as H_2S after ring closure, with NH_3 and H_2S as the only by-products. The retained ketone offers a handle for further transformations, so these oxadiazoles should serve as useful building blocks. Extension to a wider range of aroylhydrazides and experimental mechanistic studies to support the proposed pathway are natural next steps.

Declaration of competing interest.

The authors declare no conflict of interest.

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