A facile route to the synthesis of 1,3,4-oxadiazoline derivatives

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N-Acyl araldehyde hydrazones when treated with Ac_2O/pyridine were acetylated and cyclised to 5-substituted 2-aryl-3-acetyl-1,3,4-oxadiazolines in good yield.

Keywords: *N*-acyl araldehyde hydrazones, acetic anhydride/pyridine, acetylation/cyclisation, 2-aryl-3-acetyl-1,3,4-oxadiazolines

The synthesis of 1,3,4-oxadiazoline derivatives is a well-known reaction and, although there is a lot of information on this topic, in recent years, the number of publications has increased due to the great potential of these heterocyclic compounds as chemotherapeutic agents.[1,2] Nonetheless, some aspects of heterocyclisation reaction are not so well known. Sahu *et al*. [2] used a procedure first described by Martins Alho *et al*.[3] in which they synthesised a series of functionalised 1,3,4-oxadiazoline derivatives from carbohydrate-derived benzoylhydrazones using acetic anhydride in the presence of pyridine. In this study, we have also used the procedure of Martins Alho and co-workers[3] to synthesise another class of functionalised 1,3,4-oxadiazoline derivatives starting from *N*-acyl araldehyde hydrazones.

Results and discussion

The *N*-acyl araldehyde hydrazones **1** were synthesised using a literature method.[4] Compounds **1a** and **1e** are known compounds,[4] but **1b**–**d**,**f** are novel and were characterised by their spectra and elemental analysis. Reaction at reflux between *N*-Acyl araldehyde hydrazones **1a**–**f** and acetic anhydride **2** in solvent pyridine led to 5-substituted 2-aryl-3-acetyl-1,3,4-oxadiazoline derivatives **3a**–**f** (Scheme 1) in good yields (Table 1).

Compounds **3a**–**f** were characterised by their IR, ^{1}H and ^{13}C NMR, and MS spectra and their elemental analyses.

The ^{1}H NMR spectrum of **3a** was simple and exhibited two sharp singlets, for the protons of the two methyl groups at δ 2.01, 2.27 ppm and another for the methine proton at δ 6.12 ppm. The aromatic protons appeared as multiplets at δ 7.23–8.13 ppm. The ^{13}C NMR spectrum of **3a** showed nine distinct resonances in agreement with the proposed structure. The IR spectrum showed an absorption bond at 1668 cm^{-1} for the carbonyl group. The mass spectrum of **3a** displayed the molecular ion peak at m/z = 204. The mechanism of the reaction is probably similar to that published by Martins Alho *et al*.[3,5]

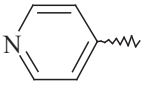
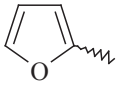
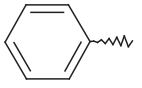
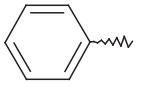
In summary, *N*-acyl araldehyde hydrazones when treated with Ac_2O/pyridine were acetylated and cyclised to 5-substituted 2-aryl-3-acetyl-1,3,4-oxadiazolines in good yield.

The present procedure carries the advantage that, not only is the reaction performed under neutral conditions, but also the starting materials and reagents can be mixed without any activation or modification.

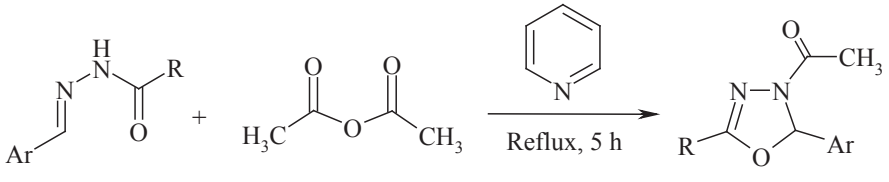
Experimental

All melting points are uncorrected. NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer (^{1}H NMR at 500 Hz, ^{13}C NMR at 125.8 Hz) in $CDCl_3$ using TMS as internal standard. Chemical shifts (δ) are given in ppm. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification. Compounds **1a**–**f** were prepared as previously described in the literature.[4]

Table 1 Acetylation/cyclisation of *N*-Acyl araldehyde hydrazones **1** to 5-substituted 2-aryl-3-acetyl-1,3,4-oxadiazolines **3** with acetic anhydride **2** and pyridine at reflux (Scheme 1)

Entry	Product	AR	R	Yield/%[a]
1	**3a**	C_6H_5	Me	89
2	**3b**	C_6H_5		90
3	**3c**	C_6H_5		87
4	**3d**	C_6H_5		93
5	**3e**	4-ClC_6H_4	Me	94
6	**3f**	4-ClC_6H_4		92

[a]Isolated yield.



1 **2** **3**

Scheme 1

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Isonicotinic acid benzylidenehydrazide (**1b**): White powder, yield 80%; m.p. 145–147 °C (EtOH); IR (KBr) (ν_{max}, cm^{-1}): 1678 (C=O); ^1H NMR: δ 6.73 (1H, broad s, NH), 7.23–8.67 (9H, m, aromatic), 8.24 (1H, s, N=CH) ppm; ^{13}C NMR: δ 121.9, 127.1, 128.7, 129.4, 133.3, 141.5 and 151.5 (aromatic), 157.5 (C=N), 168.1 (C=O) ppm; MS (*m/z*,%): 225 (M^+, 4). Anal calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65; found: C, 67.52; H, 4.85; N, 18.74%.

Furan-2-carboxylic acid benzylidenehydrazide (**1c**): White powder, yield 77%; m.p. 112–114 °C (EtOH);, IR (KBr) (ν_{max}, cm^{-1}): 1672 (C=O); ^1H NMR: δ 6.47 (1H, m, CH furan), 6.61 (1H, broad s, NH), 7.45 (1H, s, CH furan), 7.60 (1H, d, $^3J_{HH}$=2 Hz, CH furan), 7.23–8.17 (5H, m, aromatic), 8.34 (1H, s, N=CH) ppm; ^{13}C NMR: δ 111.5, 120.5, 143.7 and 145.5 (4C Furan), 126.7, 128.6, 129.2, 132.8, (aromatic), 157.7 (C=N), 167.5 (C=O) ppm; MS (*m/z*,%): 214 (M^+, 7). Anal calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08; found: C, 67.40; H, 4.65; N, 13.22%.

Benzoic acid benzylidenehydrazide (**1d**): White powder, yield 82%; m.p. 125–127 °C (EtOH); IR (KBr) (ν_{max}, cm^{-1}): 1667 (C=O); ^1H NMR: δ 6.55 (1H, broad s, NH), 7.27–8.27 (10H, m, aromatic), 8.30 (1H, s, N=CH) ppm; ^{13}C NMR: δ 126.6, 127.1, 128.6, 128.9, 129.1, 129.2, 132.4 and 132.6 (aromatic), 157.3 (C=N), 167.5 (C=O) ppm; MS (*m/z*,%): 225 (M^+, 3). Anal calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49; found: C, 75.15; H, 5.50; N, 12.35%.

Benzoic acid (4-chlorobenzylidene)hydrazide (**1f**): White powder, yield 85%; m.p. 103–107 °C (EtOH); IR (KBr) (ν_{max}, cm^{-1}): 1672 (C=O); ^1H NMR: δ 6.48 (1H, broad s, NH), 7.23–8.22 (5H, m, aromatic), 7.40 (2H, d, $^3J_{HH}$=7 Hz, aromatic), 7.75 (2H, d, $^3J_{HH}$=7 Hz, aromatic), 8.41 (1H, s, N=CH) ppm; ^{13}C NMR: δ 126.8, 128.7, 128.6, 129.0, 129.3, 132.5, 133.1 and 135.7 (aromatic), 156.5 (C=N), 167.5 (C=O) ppm; MS (*m/z*,%): 258 (M^+, 5). Anal calcd for $C_{14}H_{11}ClN_2O$: C, 65.00; H, 4.29; N, 10.83; found: C, 65.13; H, 4.20; N, 10.90%.

General procedure:

Compound **1** (1 mmol) was dissolved in a mixture of pyridine (2.5 mL) and acetic anhydride (2.5 mL), refluxed for 5 h, and then left to reach room temperature. Once cold, some ethanol was added and evaporation at reduced pressure gave a glassy residue which was subjected to silica gel column chromatography using hexane/ethyl acetate as the eluent. The product was recrystallised from EtOH.

1-(5-Methyl-2-phenyl-[1,3,4]oxadiazol-3-yl)ethanone (**3a**): White powder, yield 89%; m.p. 154–156 °C (EtOH); IR (ν_{max}, cm^{-1}): 1668 (C=O); ^1H NMR: δ 2.01 (3H, s, CH_3), 2.27 (3H, s, $NCOCH_3$), 6.12 (1H, s, CH), 7.23–8.13 (5H, m, aromatic) ppm; ^{13}C NMR: δ 11.1 (CH_3), 21.2 (CH_3), 90.3 (CH), 126.7, 128.8, 129.1 and 132.5 (aromatic), 156.7 (C=N), 167.4 (C=O) ppm; MS (*m/z*,%): 204 (M^+, 5). Anal calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72; found: C, 64.50; H, 5.83; N, 13.60%.

1-(2-Phenyl-5-pyridin-4-yl-[1,3,4]oxadiazol-3-yl)ethanone (**3b**): White powder, yield 90%), m.p. 132–135 °C (EtOH); IR (KBr) (ν_{max}, cm^{-1}): 1666 (C=O); ^1H NMR: δ 2.20 (3H, s, $NCOCH_3$), 6.17 (1H, s, CH), 7.28–8.58 (9H, m, aromatic) ppm; ^{13}C NMR: δ 21.3 (CH_3), 90.4 (CH), 122.3, 127.1, 128.8, 129.2, 133.1, 141.7 and 151.6 (aromatic), 157.3 (C=N), 167.5 (C=O) ppm; MS (*m/z*,%): 267 (M^+, 7). Anal calcd for $C_{15}H_{13}N_3O_2$: C, 67.41; H, 4.90; N, 15.72; found: C, 67.55; H, 5.02; N, 15.63%.

1-(5-Furan-2-yl-2-phenyl-[1,3,4]oxadiazol-3-yl)ethanone (**3c**): White powder, yield 87%; m.p. 124–126 °C (EtOH);, IR (KBr) (ν_{max}, cm^{-1}): 1671 (C=O); ^1H NMR: δ 2.26 (3H, s, $NCOCH_3$), 6.19 (1H, s, CH), 6.52 (1H, m, CH furan), 7.40 (1H, s, CH furan), 7.63 (1H, d, $^3J_{HH}$=2 Hz, CH furan), 7.23–8.07 (5H, m, aromatic) ppm; ^{13}C NMR: δ 21.4 (CH_3), 90.6 (CH), 111.7, 120.6, 143.5 and 145.6 (4C Furan), 126.9, 128.8, 129.1, 132.9, (aromatic), 157.5 (C=N), 167.7 (C=O) ppm; MS (*m/z*,%): 256 (M^+, 3). Anal calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93; found: C, 65.78; H, 4.90; N, 10.85%.

1-(2,5-Diphenyl-[1,3,4]oxadiazol-3-yl)ethanone (**3d**): White powder, yield 93%; m.p. 111–113 °C (EtOH); IR (KBr) (ν_{max}, cm^{-1}): 1667 (C=O); ^1H NMR: δ 2.14 (3H, s, $NCOCH_3$), 6.10 (1H, s, CH), 7.23–8.16 (10H, m, aromatic) ppm; ^{13}C NMR: δ 21.2 (CH_3), 90.2 (CH), 126.7, 127.00, 128.7, 128.8, 129.1, 129.1, 132.4 and 132.5 (aromatic), 157.2 (C=N), 167.4 (C=O) ppm; MS (*m/z*,%): 266 (M^+, 5). Anal calcd for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52; found: C, 72.30; H, 5.41; N, 10.60%.

1-[2-(4-Chlorophenyl)-5-methyl-[1,3,4]oxadiazol-3-yl]ethanone (**3e**): White powder, yield 94%; m.p. 148–150 °C (EtOH); IR (KBr) (ν_{max}, cm^{-1}): 1675 (C=O); ^1H NMR: δ 2.04 (3H, s, CH_3), 2.28 (3H, s, $NCOCH_3$), 6.15 (1H, s, CH), 7.36 (2H, d, $^3J_{HH}$=7 Hz, aromatic), 7.65 (2H, d, $^3J_{HH}$=7 Hz, aromatic) ppm; ^{13}C NMR: δ 11.1 (CH_3), 21.4 (CH_3), 90.3 (CH), 128.8, 129.1, 133.1 and 135.8 (aromatic), 156.8 (C=N), 167.6 (C=O) ppm; MS (*m/z*,%): 238 (M^+, 6). Anal calcd for $C_{11}H_{11}ClN_2O_2$: C, 55.36; H, 4.65; N, 11.74; found: C, 55.28; H, 4.50; N, 11.87%.

1-[2-(4-Chlorophenyl)-5-phenyl-[1,3,4]oxadiazol-3-yl]ethanone (**3f**): White powder, yield 92%; m.p. 120–122 °C (EtOH); IR (KBr) (ν_{max}, cm^{-1}): 1670 (C=O); ^1H NMR: δ 2.10 (3H, s, $NCOCH_3$), 6.11 (1H, s, CH), 7.23–8.12 (5H, m, aromatic), 7.34 (2H, d, $^3J_{HH}$=7 Hz, aromatic), 7.68 (2H, d, $^3J_{HH}$=7 Hz, aromatic) ppm; ^{13}C NMR: δ 21.2 (CH_3), 90.3 (CH), 126.7, 128.7, 128.8, 129.1, 129.2, 132.4, 133.1 and 135.8 (aromatic), 156.7 (C=N), 167.6 (C=O) ppm; MS (*m/z*,%): 300 (M^+, 7). Anal calcd for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.31; found: C, 63.72; H, 4.52; N, 9.20%.

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