One-Pot Synthesis of 3-Benzoyl- and 3-Acetyl-1,2,4-Oxadiazole Derivatives Using Iron(III) Nitrate

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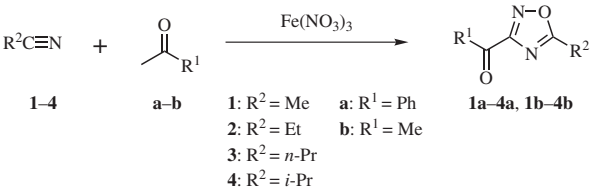
Abstract: The reaction of nitriles and acetophenone with iron(III) nitrate at 80 °C gave the corresponding 3-benzoyl-1,2,4-oxadiazole derivatives. Moreover, in this reaction using acetone, the 3-acetyl-1,2,4-oxadiazole derivatives were obtained.

Key words: ketones, nitriles, heterocycles, iron(III) nitrate, 1,2,4-oxadiazole derivatives

1,2,4-Oxadiazole derivatives have been described as important bioisosteres for esters and amides to improve the pharmacokinetics of drug candidates. In the literature, the 1,2,4-oxadiazole derivatives participate in antikinetoplastid activity,[1] β_3 adrenergic receptor agonists,[2] antiinflammatory properties,[3] muscarinic agonists[4] and serotoninergic antagonists.[5] The 1,2,4-oxadiazole derivatives have been prepared by the cycloaddition of nitrile oxides to amidoximes,[6] treatment of acylated amidoximes with bases such as NaH, NaOEt or pyridine,[7] and the O-acylation of amidoximes by an activated carboxylic acid derivative such as esters[5] or acid chlorides, followed by cyclodehydration.[8]

Recently, we reported the one-pot synthesis of 3-acetyl- and 3-benzoylisoxazole derivatives using ammonium cerium nitrate (CAN).[9] The reaction of alkenes and alkynes with CAN(IV) or CAN(III)–formic acid in acetone gave the corresponding 3-acetylisoxazole derivatives, and the same reactions in acetophenone yielded the 3-benzoylisoxazole derivatives. We have proposed the reaction mechanisms based on the formation of the nitrile oxides mediated by Ce^{3+} or Ce^{4+} from ketones.[10] Furthermore, the reaction using non-toxic iron(III) nitrate afforded similar isoxazole derivatives. We attempted to adapt the new synthesis of 1,2,4-oxadizole derivatives using these reaction systems.[11,12] Now in this paper, we report a novel and efficient one-pot synthesis of 3-benzyl- and 3-acetyl-1,2,4-oxadiazole derivatives using iron(III) nitrate.

The reaction of acetonitrile (**1**) and acetophenone with iron(III) nitrate at 80 °C afforded 3-benzoyl-5-methyl-1,2,4-oxadiazole (**1a**) (Scheme 1). Compound **1a** showed absorptions at 1713, 1681 and 1581 cm^{-1} in its IR spectrum. The ^1H NMR spectrum showed a singlet at δ = 2.71 (3 H, CH_3). The ^{13}C NMR spectra exhibited signals at δ = 182.5, 177.3 and 165.4 ppm, which were assigned to the commonly known carbonyl carbon and carbons of the 1,2,4-oxadiazole ring, respectively. Therefore, compound **1a** was identified to be 3-benzoyl-5-methyl-1,2,4-oxadiazole. These reaction conditions are summarized in Table 1. In this reaction, acetonitrile (**1**) was employed as the solvent because of its low reactivity in the 1,3-dipolar cycloaddition (Table 1, entries 1–5). And the yields of the products were based on amount of iron(III) nitrate since this reaction required excess ketones and nitriles for iron(III) nitrate. When acetophenone (5.0 mmol), acetonitrile (**1**; 4.5 mL) and $Fe(NO_3)_3$ (1.0 mmol) were employed, the corresponding 1,2,4-oxadiazole derivative **1a** in good yield of 95% (Table 1, entry 9).



Scheme 1

On the basis of these reaction conditions, the reactions using several nitriles **2–4** were carried out (Scheme 1, Table 2, entries 1–3). The corresponding 3-benzoyl-1,2,4-oxadiazole derivatives **2a–4a** were obtained in 44–95% yields. Moreover, the reaction using acetone produced 3-acetyl-5-methyl-1,2,4-oxadiazole (**1b**). The IR spectrum of **1b** showed absorptions at 1731, 1699 and 1601 cm^{-1}. The ^1H NMR spectra exhibited a singlet at δ = 2.70 (3 H, CH_3). The ^{13}C NMR spectra exhibited signals at δ = 188.8, 178.5 and 165.8 ppm, which were assigned to the commonly known carbonyl carbon and carbons of the 1,2,4-oxadiazole ring, respectively. The reaction of acetone (5.0 mmol) and acetonitrile (**1**; 4.5 mL) with $Fe(NO_3)_3$ (1.0 mmol) under reflux gave the corresponding 1,2,4-oxadiazole derivatives **1b** in 61% yield (Table 2, entry 5). Also, under the these reaction conditions, the similar 3-acetyl-1,2,4-oxadiazoles **2b–4b** from nitrile **2–4** were obtained in 25–62% yields (Table 2, entries 8–10). It seems that the formation of the 3-benzoyl-1,2,4-oxadiazole derivatives **1a–4a** from nitriles and acetophenone proceeds more smoothly, compared with the formation of the 3-acetyl-1,2,4-oxadiazole derivatives **1b–4b**.

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Table 1 Reaction Conditions

Entry[a]	Acetophenone (mmol)	Acetonitrile (**1**) (mmol)	$Fe(NO_3)_3$ (mmol)	Time (h)	Product, Yield (%)[b]
1	4.5 mL	1.0	1.0	20	**1a** (traces)
2	4.5 mL	10.0	1.0	20	**1a** (16)
3	4.5 mL	20.0	1.0	18	**1a** (27)
4	4.5 mL	40.0	1.0	18	**1a** (55)
5	4.5 mL	50.0	1.0	18	**1a** (49)
6	1.0	4.5 mL	1.0	22	**1a** (4)
7	2.0	4.5 mL	1.0	20	**1a** (27)
8	4.0	4.5 mL	1.0	18	**1a** (72)
9	5.0	4.5 mL	1.0	18	**1a** (95)
10	5.0	4.5 mL	2.0	20	**1a** (69)
11	5.0	4.5 mL	3.0	22	**1a** (48)
12	5.0	4.5 mL	4.0	22	**1a** (25)
13	7.5	4.5 mL	1.0	18	**1a** (94)
14	10.0	4.5 mL	1.0	18	**1a** (80)

[a] Reaction conditions: Acetophenone, acetonitrile (**1**) and iron(III) nitrate were employed at 80 °C.
[b] Determined by GLC analysis using *n*-dodecane as internal hydrocarbon standard. Yields based on amount of iron(III) nitrate used.

Table 2 Reaction of Ketones and Nitriles with Iron(III) Nitrate

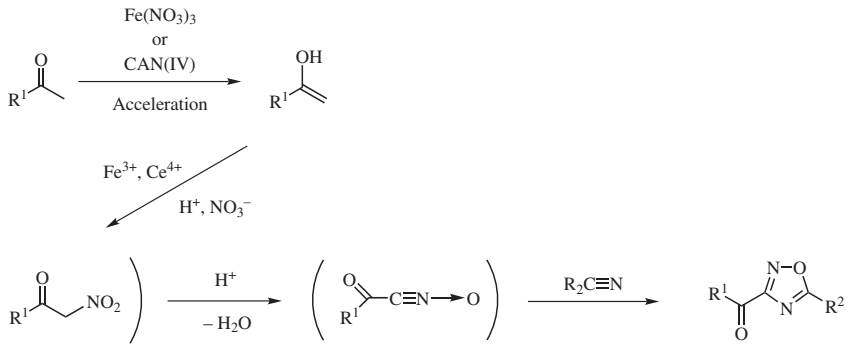
Entry[a]	Nitriles	Ketones	Mol equiv	Time (h)	Product, Yield (%)[b]
1	**2**	Acetophenone	5.0	20	**2a** (95)
2	**3**	Acetophenone	5.0	20	**3a** (95)
3	**4**	Acetophenone	5.0	22	**4a** (44)
4	**1**	Acetone	2.5	18	**1b** (47)
5	**1**	Acetone	5.0	16	**1b** (61)
6	**1**	Acetone	7.5	16	**1b** (50)
7	**1**	Acetone	10.0	14	**1b** (44)
8	**2**	Acetone	5.0	16	**2b** (62)
9	**3**	Acetone	5.0	16	**3b** (61)
10	**4**	Acetone	5.0	18	**4b** (25)

[a] Reaction conditions: Acetophenone (5.0 mmol), nitriles **2**–**4** (4.5 mL) and iron(III) nitrate (1.0 mmol) were employed at 80 °C. Acetone (2.5–10.0 mmol), nitriles **1**–**4** (4.5 mL) and iron(III) nitrate (1.0 mmol) were employed under reflux.
[b] Determined by GLC analysis using *n*-dodecane as internal hydrocarbon standard. Yields based on amount of iron(III) nitrate used.

In order to investigate the reaction mechanism, the reactions of acetophenone and acetonitrile (**1**) with several metal nitrates were carried out (Table 3). When CAN(IV) was employed, the corresponding 1,2,4-oxadiazoles **1a** was obtained in 78% yield (Table 3, entry 1). However, the reaction using $NaNO_3$, $Mg(NO_3)_2$ and NH_4NO_3 did not proceed (Table 3, entries 2–4). Previously, we have reported that CAN(IV) accelerates the enolization of ketones.[13] From these results, we proposed the reaction mechanism in Scheme 2. In this reaction mechanism, the enolization of ketones was accelerated by $Fe(NO_3)_3$ or CAN(IV), followed by the nitration of ketones. The formation of nitrile oxides proceeds via the acid-catalyzed dehydration of α-nitroketones,[10] and the 3-benzoyl- and 3-acetyl-1,2,4-oxadiazole derivatives were obtained by the 1,3-dipolar cycloaddition to nitriles. Therefore, the yields of the products were dependent on the stabilities of the nitrile oxides and the reactivity of nitriles in 1,3-dipolar cycloaddition.

In conclusion, this method using non-toxic and inexpensive iron(III) nitrate is simple, efficient and clean for producing 3-benzoyl- and 3-acetyl-1,2,4-oxadiazole derivatives.

The IR spectra were recorded using a Jasco FT-IR 230 spectrometer. The ^1H and ^{13}C NMR spectra were measured using a JEOL GSX 400 model spectrometer in $CDCl_3$ solutions with TMS used as the internal standard. Gas chromatographic analyses were performed using a GC-column (DB-1, 25 m) attached to a Shimazu GC-14A instrument. The HRMS were recorded at 75 eV using a JEOL JMS-01SG-2 instrument.



Scheme 2 Reaction mechanisms

Table 3 Application of Some Metal Nitrates

Entry[a]	Metal nitrate	Time (h)	Product (%)[b]
1	CAN(IV)	18	**1a** (78)
3	$NaNO_3$	30	No reaction
4	$Mg(NO_3)_2$	30	No reaction
5	NH_4NO_3	30	No reaction

[a] Reaction conditions: Acetophenone (5.0 mmol), acetonitrile (**1**; 4.5 mL) and metal nitrate (1.0 mmol) were employed at 80 °C.
[b] Determined by GLC analysis using *n*-dodecane as internal hydrocarbon standard. Yields based on amount of metal nitrate used.

Reaction of Acetonitrile (1) and Acetophenone with Iron(III) Nitrate; Typical Procedure

A mixture of acetonitrile (**1**; 4.5 mL), acetophenone (0.6008 g, 5.0 mmol) and iron(III) nitrate (0.4040 g, 1.0 mmol) was stirred at 80 °C for 18 h. The reaction mixture was filtered, extracted with EtOAc (50 mL) and washed with aq $NaHCO_3$ solution (2 × 2.0 mL), sat. aq NaCl (2 × 2.0 mL) and H_2O (2 × 2.0 mL). This solution was dried over Na_2SO_4 and concentrated in a vacuum, followed by acetophenone removal by reduced pressure distillation. The resulting oil was chromatographed on silica gel. Elution with hexane–EtOAc (4:1) gave 3-benzoyl-5-methyl-1,2,4-oxadiazole (**1a**) as a yellow oil (0.1504 g).

3-Benzoyl-5-methyl-1,2,4-oxadiazole (1a)
Yellow oil.

IR (NaCl): 1713, 1681, 1581 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.25–8.27 (m, 2 H), 7.50–7.68 (m, 3 H), 2.71 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 182.5, 177.3, 165.4, 134.7, 134.3, 130.3, 128.4, 12.0.

HRMS: *m*/*z* [M] calcd for $C_{10}H_8N_2O_2$: 188.0586; found $[M]^+$: 188.0583

3-Benzoyl-5-ethyl-1,2,4-oxadiazole (2a)
Yellow oil.

IR (NaCl): 1711, 1679, 1577 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.25–8.30 (m, 2 H), 7.46–7.61 (m, 3 H), 3.06 (q, *J* = 7.68 Hz, 2 H), 1.49 (t, *J* = 7.68 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 183.0, 165.6, 154.3, 135.3, 134.6, 130.6, 128.7, 20.3, 10.7.

HRMS: *m*/*z* [M] calcd for $C_{11}H_{10}N_2O_2$: 202.0742; found $[M]^+$: 202.0749.

3-Benzoyl-5-propyl-1,2,4-oxadiazole (3a)
Yellow oil.

IR (NaCl): 1712, 1679, 1580 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.28–8.33 (m, 2 H), 7.46–7.62 (m, 3 H), 3.01 (t, *J* = 7.56 Hz, 2 H), 1.90–1.99 (m, 2 H), 1.07 (t, *J* = 7.56 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 183.0, 171.3, 165.6, 135.1, 134.6, 130.6, 128.7, 28.4, 20.1, 13.6.

HRMS: *m*/*z* [M] calcd for $C_{12}H_{12}N_2O_2$: 216.0899; found $[M]^+$: 216.0898.

3-Benzoyl-5-isopropyl-1,2,4-oxadiazole (4a)
Yellow oil.

IR (NaCl): 1711, 1677, 1569 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.27–8.30 (m, 2 H), 7.46–7.61 (m, 3 H), 3.34–3.41 (m, 1 H), 1.50 (d, *J* = 6.83 Hz, 6 H).

^{13}C NMR ($CDCl_3$): δ = 183.1, 171.1, 165.5, 135.2, 134.5, 130.6, 128.7, 27.6, 20.1.

HRMS: *m*/*z* [M] calcd for $C_{12}H_{12}N_2O_2$: 216.0899; found $[M]^+$: 216.0892.

Reaction of Acetonitrile (1) and Acetone with Iron(III) Nitrate; Typical Procedure

A mixture of acetonitrile (**1**; 4.5 mL), acetone (0.2904 g, 5.0 mmol) and iron(III) nitrate (0.4040 g, 1.0 mmol) was stirred under reflux for 16 h. The reaction mixture was filtered, extracted with EtOAc (50 mL) and washed with aq $NaHCO_3$ solution (2 × 2.0 mL), sat. aq NaCl (2 × 2.0 mL) and H_2O (2 × 2.0 mL). This solution was dried over Na_2SO_4 and concentrated in a vacuum. The resulting oil was chromatographed on silica gel. Elution with hexane–EtOAc (4:1) gave 3-acetyl-5-methyl-1,2,4-oxadiazole (**1b**) as a yellow oil (0.0504 g).

3-Acetyl-5-methyl-1,2,4-oxadiazole (1b)
Yellow oil.

IR (NaCl): 1731, 1699, 1601 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.70 (s, 6 H).

^{13}C NMR ($CDCl_3$): δ = 188.8, 178.5, 165.8, 27.8, 12.4.

HRMS: *m*/*z* [M] calcd for $C_5H_6N_2O_2$: 126.0429; found $[M]^+$: 126.0433.

3-Acetyl-5-ethyl-1,2,4-oxadiazole (2b)
Yellow oil.

IR (NaCl): 1738, 1688, 1599 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.02 (q, *J* = 7.56 Hz, 2 H), 2.70 (s, 3 H), 1.45 (t, *J* = 7.56 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 189.1, 182.7, 165.7, 27.8, 20.3, 10.6.

HRMS: *m*/*z* [M] calcd for $C_6H_8N_2O_2$: 140.0586; found $[M]^+$: 140.0587.

3-Acetyl-5-propyl-1,2,4-oxadiazole (3b)
Yellow oil.

IR (NaCl): 1733, 1691, 1589 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.96 (t, *J* = 7.44 Hz, 2 H), 2.70 (s, 3 H), 1.86–1.95 (m, 2 H), 1.04 (t, *J* = 7.44 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 189.0, 181.7, 165.8, 28.4, 27.9, 20.1, 13.6.

HRMS: *m*/*z* [M] calcd for $C_7H_{10}N_2O_2$: 154.0742: found $[M]^+$: 154.0733.

3-Acetyl-5-isopropyl-1,2,4-oxadiazole (4b)
Yellow oil.

IR (NaCl): 1732, 1694, 1593 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.28–3.35 (m, 1 H), 2.70 (s, 3 H), 1.45 (d, *J* = 6.83 Hz, 6 H).

^{13}C NMR ($CDCl_3$): δ = 189.1, 185.7, 165.8, 27.9, 27.6, 20.1.

HRMS: *m*/*z* [M] calcd for $C_7H_{10}N_2O_2$: 154.0742; found $[M]^+$: 154.0733.

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References

(1) Cottrel, D. M.; Carpers, J.; Salem, M. M.; DeLuca-Fradly, K.; Croft, S.; Werbovetz, K. A. *Bioorg. Med. Chem.* **2004**, *12*, 2815.
(2) Feng, D. D.; Biftu, T.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F. Jr.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, E.; Miller, R. R.; Stearns, R. A.; Strader, C. D.; Tota, L.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1427.
(3) Srivastava, R. M.; Lima, A. A.; Viana, O. S.; Silva, M. J. C.; Catanho, M. T. J. A.; Morais, J. O. F. *Bioorg. Med. Chem.* **2003**, *11*, 1821.
(4) Orlek, B. S.; Blaney, F. E.; Brown, F.; Clark, M. S. G.; Hadley, M. S.; Hatcher, J.; Riley, G. J.; Rosenberg, H. E.; Wadsorth, H. J.; Wyman, P. *J. Med. Chem.* **1991**, *34*, 2726.
(5) Swain, C. J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E. M.; Stevenson, G.; Beer, M.; Stanton, J. *J. Med. Chem.* **1991**, *34*, 140.
(6) Quardrelli, P.; Invernizzi, A. G.; Falzoni, M.; Caramella, P. *Tetrahedron* **1997**, *53*, 1787.
(7) Korbonits, D.; Horvath, K. *Heterocycles* **1994**, *37*, 2051.
(8) Mathvink, R. J.; Barrtta, A. M.; Candelore, M. R.; Cascieri, M. A.; Deng, L.; Tota, L.; Strader, C. D.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1869.
(9) Itoh, K.; Takahashi, S.; Ueki, T.; Sugiyama, T.; Takahashi, T. T.; Horiuchi, C. A. *Tetrahedron Lett.* **2002**, *43*, 7035.
(10) Itoh, K.; Horiuchi, C. A. *Tetrahedron* **2004**, *60*, 1671.
(11) Tegeler, J. T.; Diamond, C. J. *J. Heterocycl. Chem.* **1987**, *24*, 697.
(12) Diaz-Ortiz, A.; Diez-Barra, E.; Hoz, A. D. L.; Moreno, A.; Gomez-Escalonilla, M. J.; Loupy, A. *Heterocycles* **1996**, *43*, 1021.
(13) Horiuchi, C. A.; Kiji, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 421.