A Convenient and Efficient One-Pot Synthesis of 3-Acylisoxazoles Using Iron(III) Salts

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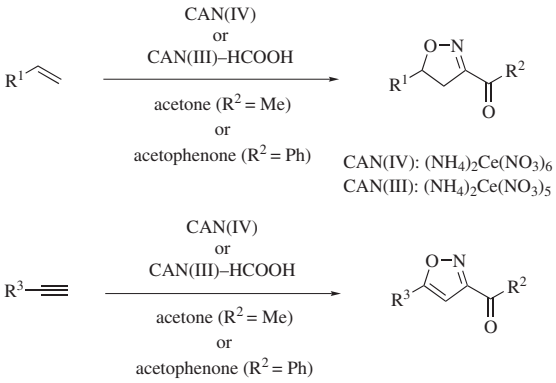
Abstract: 3-Acylisoxazoles were synthesized by the reaction of alkenes or alkynes with ketones (acetone or acetophenone), as both a reagent and the solvent, by three methods: iron(III) nitrate under reflux, iron(III) salt–nitrogen dioxide (NO_2) at room temperature, and iron(III) nitrate under microwave irradiation (MW).

Key words: alkenes, alkynes, ketones, iron(III) nitrate, 3-acylisoxazoles

Isoxazoles play an important role in biochemistry, organic chemistry, and bioorganic chemistry. The isoxazole ring is a mimic of both carboxylic acid and amide functions, isoxazoles are frequently used in agrochemicals and medicines.[1–3] In synthetic organic chemistry, 4,5-dihydroisoxazoles are versatile synthetic intermediates in the preparation of a variety of compounds with 1,3-difunctional groups such as β-hydroxy ketones,[4] γ-amino alcohols,[5] α,β-unsaturated oximes,[6] and β-hydroxy nitriles.[7] We have recently reported the novel one-pot synthesis of 3-acylisoxazoles using CAN.[8] The reaction of alkenes or alkynes with CAN(IV) [$(NH_4)_2Ce(NO_3)_6$] or CAN(III) [$(NH_4)_2Ce(NO_3)_5{\cdot}4H_2O$] and formic acid in acetone under reflux gave the 3-acetylisoxazole derivatives. In the case of acetophenone, 3-benzoylisoxazole derivatives were obtained (Scheme 1).[9] In the literature, 3-acetylisoxazole derivatives were transformed into *N*-{4-[4-isoxazolyl]-2-thiazolyl} oxamic acid derivatives, potent orally active antianaphylactic agents.[10] The 3-benzoylisoxazole derivatives have also become interesting key building blocks for drug candidates such as 3-[2-(2,5-dimethylphenoxymethyl)-α-methoxyiminobenzyl]isoxazole which possess potent fungicidal activity against crop diseases[11] and 3-(1-hydroxybenzyl)-5-dimethylaminomethylisoxazole methiodide, an antimuscarinic agents.[12]

We have investigated many novel reaction systems using cerium salts[13] for selective oxidations. Although reactions with cerium salts proceeded smoothly, a reaction using non-toxic and inexpensive metal salts is required from an economic, practical, and environmental point of view. Along this line, we selected iron(III) nitrate as a mild and safe oxidizing reagent for isoxazole formation. Iron(III) nitrate is an abundant, cheap, and non-toxic metal nitrate.



Scheme 1 One-pot synthesis of 3-acylisoxazoles using CAN[8,9]

It is known that iron(III) nitrate converts aromatic compounds into nitro compounds,[14] while clayfen [iron(III) nitrate impregnated on K-10 bentonite clay] was employed for the oxidation of alcohols,[15] the nitration of alkenes,[16] the cleavage of thioacetals to aldehydes or ketones,[17] and the conversion of hydrazines to azides.[18] In this paper, we would like to propose a convenient and efficient one-pot synthesis of 3-acylisoxazoles using iron(III) salts: iron(III) nitrate under reflux and iron(III) chloride–nitrogen dioxide (NO_2) at room temperature. In addition, to increase the reactivity and to shorten the reaction time, a microwave-assisted reaction was developed.

Synthesis of 3-Acylisoxazoles by Iron(III) Nitrate

In order to develop a new one-pot synthesis of 3-acylisoxazoles using inexpensive and non-toxic metal nitrate, the reactions of 1-octene (**1**) with several metal nitrates in acetone were carried out (Scheme 2 and Table 1). Although nitrates such as ammonium, magnesium(II), and aluminum(III) gave undesired results (Table 1, entries 1–3), the use of iron(III) or copper(II) nitrate afforded 3-acetyl-5-hexyl-4,5-dihydroisoxazole (**2**)[9] in 85% and 22% yields, respectively (Table 1, entries 4 and 5). In particular, the reaction using iron(III) nitrate gave the best yield of **2**.

Initially the effect of the amount of iron(III) nitrate was examined (Table 2, entries 1–5). The corresponding isoxazole derivative **2** was obtained in 85% yield when equimolar amounts of iron(III) nitrate and olefin were used (Table 2, entry 2). Increasing or decreasing the amount of iron(III) nitrate decreased the yield. It seems

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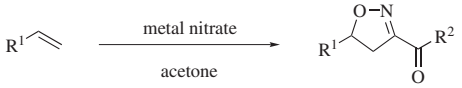


1 **2**

1 : $R^1 = n\text{-}C_6H_{13}$
2 : $R^1 = n\text{-}C_6H_{13}$, R^2 = Me

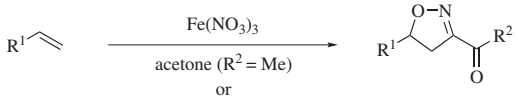
Scheme 2

Table 1 Reaction of 1-Octene (**1**) with Metal Nitrate in Acetone

Entry[a]	Metal nitrate	Time (h)	Product (%)[b]
1	NH_4NO_3	30	No reaction
2	$Mg(NO_3)_2$	25	No reaction
3	$Al(NO_3)_3$	25	No reaction
4	$Fe(NO_3)_3$	10	**2** (85)
5	$Cu(NO_3)_2$	20	**2** (22)

[a] 1-Octene (**1**; 0.5 mmol), metal nitrate (0.5 mmol), and acetone (3.0 mL) were reacted under reflux.
[b] Determined by GLC analysis using *n*-dodecane as internal hydrocarbon standard.

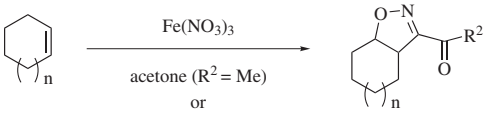
that the product or intermediate was oxidized by an excess of iron(III) nitrate. On the basis of these results, we further examined the reaction of alkenes **3**–**15** and alkynes **43**–**48** using iron(III) nitrate (0.5 mmol, 1.0 equiv) in acetone or acetophenone (Schemes 3– 5). These results are shown in Tables 2 and 3. The reaction of 1-alkenes **3**–**5**, allyl compounds **6**–**11**, and cycloalkenes **12**–**15** using iron(III) nitrate in acetone under reflux gave the corresponding 3-acetyl-4,5-dihydroisoxazoles **16**–**28** in about 39–80% yields (Table 2, entries 6–18). In the case of acetophenone, the corresponding 3-benzoyl-4,5-dihydroisoxazoles **29**–**42** were obtained in 39–88% yields (Table 2, entries 19–32). Also, the reaction of several alkynes **43**–**48** using iron(III) nitrate in acetone or acetophenone afforded the corresponding isoxazole derivatives **49**–**54** and **55**–**60** in high yields of 65–87% (Table 3). This reaction by the application of iron(III) nitrate gave the corresponding isoxazole derivatives in similar high yields, compared with the reaction using CAN(III)–formic acid.[8,9] It seems that this reaction mediated by Fe^{3+} accelerates the formation of isoxazole derivatives, while not promoting side-reactions including the nitration of alkenes. The iron salt was removed by filtration using hyflo super-cel® as a filter aid after the reaction, thus, the isoxazole derivatives were simply isolated by silica gel column chromatography, compared with the more complicated techniques required for the reaction using CAN. This reaction uses inexpensive and non-toxic iron(III) nitrate, providing a convenient and useful one-pot synthesis of the 3-acetyl- and 3-benzoylisoxazole derivatives.



1, **3**–**11** **2**, **16**–**24** **29**–**38**

2: $R^1 = n\text{-}C_6H_{13}$, R^2 = Me
16: $R^1 = n\text{-}C_5H_{11}$, R^2 = Me
17: $R^1 = n$-Bu, R^2 = Me
18: $R^1 = n$-Pr, R^2 = Me
19: $R^1 = CH_2C_6H_{11}$, R^2 = Me
20: $R^1 = CH_2Ph$, R^2 = Me
21: $R^1 = CH_2SMe$, R^2 = Me
22: $R^1 = CH_2CN$, R^2 = Me
23: $R^1 = CH_2OPh$, R^2 = Me
24: $R^1 = CH_2CO_2Me$, R^2 = Me
29: $R^1 = n\text{-}C_6H_{13}$, R^2 = Ph
30: $R^1 = n\text{-}C_5H_{11}$, R^2 = Ph
31: $R^1 = n$-Bu, R^2 = Ph
32: $R^1 = n$-Pr, R^2 = Ph
33: $R^1 = CH_2C_6H_{11}$, R^2 = Ph
34: $R^1 = CH_2Ph$, R^2 = Ph
35: $R^1 = CH_2SMe$, R^2 = Ph
36: $R^1 = CH_2CN$, R^2 = Ph
37: $R^1 = CH_2OPh$, R^2 = Ph
38: $R^1 = CH_2CO_2Me$, R^2 = Ph

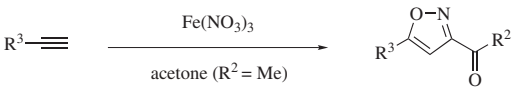
Scheme 3



12–**15** **25**–**28** **39**–**42**

25: n = 0, R^2 = Me
26: n = 1, R^2 = Me
27: n = 2, R^2 = Me
28: n = 3, R^2 = Me
39: n = 0, R^2 = Ph
40: n = 1, R^2 = Ph
41: n = 2, R^2 = Ph
42: n = 3. R^2 = Ph

Scheme 4



43–**48** **49**–**54** **55**–**60**

49: $R^3 = n\text{-}C_6H_{13}$, R^2 = Me
50: $R^3 = n\text{-}C_5H_{11}$, R^2 = Me
51: $R^3 = n$-Bu, R^2 = Me
52: $R^3 = n$-Pr, R^2 = Me
53: $R^3 = CO_2Et$, R^2 = Me
54: $R^3 = c\text{-}C_6H_{10}OH$, R^2=Me
55: $R^3 = n\text{-}C_6H_{13}$, R^2 = Ph
56: $R^3 = n\text{-}C_5H_{11}$, R^2 = Ph
57: $R^3 = n$-Bu, R^2 = Ph
58: $R^3 = n$-Pr, R^2 = Ph
59: $R^3 = CO_2Et$, R^2 = Ph
60: $R^3 = c\text{-}C_6H_{10}OH$, R^2 = Ph

Scheme 5

Structural Analysis (X-ray Analysis)

We previously reported the structures of **2**, **16**–**42**, and **49**–**60** determined by spectral methods such as ^{1}H NMR, ^{13}C NMR, IR spectroscopy, EIMS, and HRMS.[9] In this paper, the structure of ethyl 3-benzoylisoxazolecarboxylate (**59**) was confirmed by X-ray analysis and the ORTEP drawing is shown in Figure 1.

Synthesis of 3-Acylisoxazoles by Iron(III) Salts–NO_2 System

It is known that iron(III) nitrate decomposes at high temperatures, and nitrogen oxides (NO_x) including nitrogen

Table 2 Reaction of Alkenes **1**, **3**–**15** with Iron(III) Nitrate in Acetone or Acetophenone

Entry[a]	Substrate	$Fe(NO_3)_3$ (equiv)	Solvent	Time (h)	Product (%)[b]
1	**1** (R^1 = *n*-C_6H_{13})	0.5	Acetone	55	**2** (44)
2	**1**	1.0	Acetone	10	**2** (85)
3	**1**	1.5	Acetone	10	**2** (80)
4	**1**	2.0	Acetone	10	**2** (75)
5	**1**	4.0	Acetone	10	**2** (68)
6	**3** (R^1 = *n*-C_5H_{11})	1.0	Acetone	8	**16** (77)
7	**4** (R^1 = *n*-Bu)	1.0	Acetone	8	**17** (77)
8	**5** (R^1 = *n*-Pr)	1.0	Acetone	8	**18** (75)
9	**6** (R^1 = $CH_2C_6H_{11}$)	1.0	Acetone	10	**19** (79)
10	**7** (R^1 = CH_2Ph)	1.0	Acetone	10	**20** (80)
11	**8** (R^1 = CH_2SMe)	1.0	Acetone	5	**21** (49)
12	**9** (R^1 = CH_2CN)	1.0	Acetone	8	**22** (68)
13	**10** (R^1 = CH_2OPh)	1.0	Acetone	8	**23** (70)
14	**11** (R^1 = CH_2CO_2Me)	1.0	Acetone	8	**24** (58)
15	**12** (n = 0)	1.0	Acetone	8	**25** (57)
16	**13** (n = 1)	1.0	Acetone	8	**26** (39)
17	**14** (n = 2)	1.0	Acetone	12	**27** (65)
18	**15** (n = 3)	1.0	Acetone	12	**28** (83)
19	**1**	1.0	Acetophenone	15	**29** (88)
20	**3**	1.0	Acetophenone	12	**30** (86)
21	**4**	1.0	Acetophenone	12	**31** (85)
22	**5**	1.0	Acetophenone	10	**32** (82)
23	**6**	1.0	Acetophenone	14	**33** (87)
24	**7**	1.0	Acetophenone	14	**34** (88)
25	**8**	1.0	Acetophenone	12	**35** (56)
26	**9**	1.0	Acetophenone	12	**36** (79)
27	**10**	1.0	Acetophenone	12	**37** (84)
28	**11**	1.0	Acetophenone	12	**38** (88)
29	**12**	1.0	Acetophenone	12	**39** (68)
30	**13**	1.0	Acetophenone	12	**40** (69)
31	**14**	1.0	Acetophenone	15	**41** (72)
32	**15**	1.0	Acetophenone	15	**42** (82)

[a] Substrate **1**, **3**–**15** (0.5 mmol), iron(III) nitrate (0.25–2.0 mmol), and acetone (3.0 mL) were reacted under reflux. Substrate **1**, **3**–**15** (0.5 mmol), iron(III) nitrate (0.5 mmol), and acetophenone (3.0 mL) were reacted at 80 °C.
[b] Determined by GLC analysis using *n*-dodecane as the internal hydrocarbon standard.

Table 3 Reaction of Alkynes **43**–**48** with Iron(III) Nitrate in Acetone or Acetophenone

Entry[a]	Substrate	Solvent	Time (h)	Product (%)[b]
1	**43** (R^3 = *n*-C_6H_{13})	Acetone	12	**49** (79)
2	**44** (R^3 = *n*-C_5H_{11})	Acetone	12	**50** (78)
3	**45** (R^3 = *n*-Bu)	Acetone	10	**51** (71)
4	**46** (R^3 = *n*-Pr)	Acetone	10	**52** (65)
5	**47** (R^3 = CO_2Et)	Acetone	15	**53** (86)
6	**48** (R^3 = *c*-$C_6H_{10}OH$)	Acetone	15	**54** (87)
7	**43**	Acetophenone	14	**55** (85)
8	**44**	Acetophenone	14	**56** (82)
9	**45**	Acetophenone	12	**57** (74)
10	**46**	Acetophenone	12	**58** (74)
11	**47**	Acetophenone	18	**59** (79)
12	**48**	Acetophenone	18	**60** (79)

[a] Substrate **43**–**48** (0.5 mmol), iron(III) nitrate (0.5 mmol), and acetone (3.0 mL) were reacted under reflux. Substrate **43**–**48** (0.5 mmol), iron(III) nitrate (0.5 mmol), and acetophenone (3.0 mL) were reacted at 80 °C.
[b] Determined by GLC analysis using *n*-dodecane as the internal hydrocarbon standard.

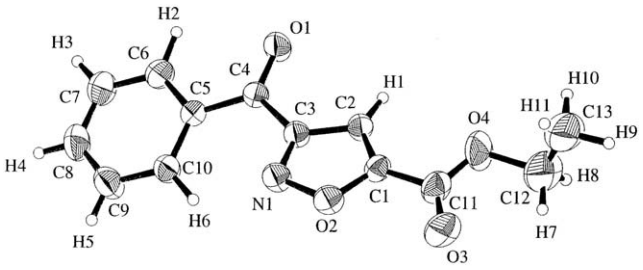
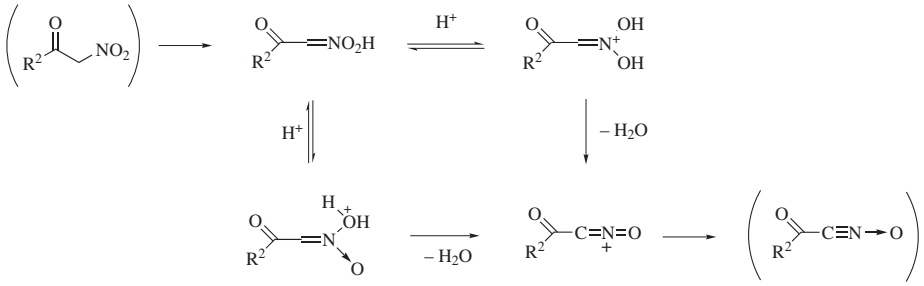


Figure 1 ORTEP drawing of ethyl 3-benzoylisoxazolecarboxylate

monoxide (NO) and nitrogen dioxide (NO_2) are generated from iron(III) nitrate. Also, we previously proposed a 1,3-dipolar cycloaddition mechanism for the reaction of dipolarophiles and nitrile oxides via the acid-catalyzed dehydration of α-nitroketones from the nitration of acetone or acetophenone (Scheme 6).[9] In the present reaction, it seems that nitrogen oxides play an important role in the nitration of ketones. In order to investigate this reaction mechanism, the reaction of 1-octene (**1**) using iron salts and nitrogen dioxide gas in acetone was carried out (Scheme 7, Table 4). Nitrogen dioxide is an inorganic compound, but it may be regarded as the nitro group itself from the standpoint of organic chemistry. Hence, nitrogen dioxide was employed as the nitrating agent for several organic compounds.[19–23] The reaction using nitrogen dioxide in the absence of iron salts did not give the corresponding isoxazole derivative, but gave 1-nitro-1-octene (**61**) and 1-nitro-2-octanol (**62**) in 23% and 22% yields, respectively (Table 4, entry 1). When nitrogen dioxide was bubbled through (ca. 45 mL/min) 1-octene (**1**; 0.5 mmol), iron(III) chloride (0.5 mmol, 1.0 equiv), and acetone (3.0 mL) at room temperature, the corresponding isoxazole derivative **2** was obtained in a moderate yield of 68% (Table 4, entry 8). The yields of the isoxazole derivative decreased as the temperature or the amount of iron(III) chloride increased (Table 4, entries 9–12). In addition, the reaction using ammonium iron(III) sulfate gave the corresponding isoxazole derivative **2** in 51% yield, however, in the case of FeO(OH) as the oxidant, only trace amounts of the isoxazole derivatives were obtained (Table 4, entries 13 and 14). On the other hand, the use of iron(II) chloride gave the isoxazole derivative **2** in low yields of 10–19% (Table 4, entries 15–20). Increasing of the amount of iron(II) chloride did not accelerate the formation of isoxazole derivative, but escalated the side reactions to nitroolefin and nitro-alcohol. Also, the reaction using iron(II) acetate and iron(II) sulfate furnished very little of the corresponding isoxazole derivative (Table 4, entries 21 and 22). From the results, it is shown that the presence of Fe^{3+} is required for the formation of isoxazole derivatives, and the application of Fe^{3+} efficiently produced the isoxazole derivatives, compared with the application of Fe^{2+}. We propose the reaction pathway shown in Scheme 8. It



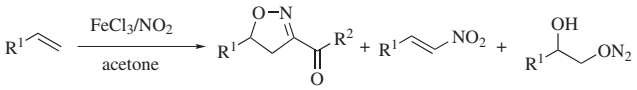
Scheme 6 Formation of nitrile oxides from ketones[9]

Table 4 Reaction of 1-Octene (**1**) with Fe Salts–NO_2 in Acetone

Entry[a]	Iron salts	Equivalents	Temperature (°C)	Time (h)	**2** (%)[b]	**61** (%)[b]	**62** (%)[b]
1	–	–	r.t.	12	–	23	22
2	$FeCl_3$	0.1	r.t.	12	trace	8	11
3	$FeCl_3$	0.5	r.t.	12	12	14	12
4	$FeCl_3$	1.0	r.t.	1	20	12	8
5	$FeCl_3$	1.0	r.t.	3	25	13	9
6	$FeCl_3$	1.0	r.t.	6	40	13	9
7	$FeCl_3$	1.0	r.t.	9	61	15	11
8	$FeCl_3$	1.0	r.t.	12	68	15	11
9	$FeCl_3$	1.0	reflux	12	29	14	10
10	$FeCl_3$	1.5	r.t.	12	54	15	14
11	$FeCl_3$	2.0	r.t.	12	44	19	14
12	$FeCl_3$	4.0	r.t.	12	29	21	18
13	$FeNH_4(SO_4)_2$	1.0	r.t.	12	51	25	21
14	FeO(OH)	1.0	r.t.	20	trace	28	27
15	$FeCl_2$	0.1	r.t.	12	trace	19	17
16	$FeCl_2$	0.5	r.t.	12	10	20	17
17	$FeCl_2$	1.0	r.t.	12	19	25	17
18	$FeCl_2$	1.5	r.t.	12	16	26	17
19	$FeCl_2$	2.0	r.t.	12	15	31	15
20	$FeCl_2$	4.0	r.t.	12	12	36	14
21	$Fe(CH_3COO)_2$	1.0	r.t.	14	trace	19	21
22	$FeSO_4$	1.0	r.t.	14	4	26	22

[a] NO_2 was bubbled (ca. 45 mL/min, 20 s) through 1-octene (**1**; 0.5 mmol), iron(III) salt (0–2.0 mmol), and acetone (3.0 mL).
[b] Determined by GLC analysis using *n*-dodecane as the internal hydrocarbon standard.

seems that this reaction can proceed by two reaction pathways: the nitration of alkenes by nitrogen dioxide (**Path A**), and the 1,3-dipolar cycloaddition of dipolarophiles and nitrile oxides in ketones (**Path B**). It seems that the role of Fe^{3+} is to promote the nitration of ketones by nitrogen dioxide. Therefore α-nitroketones are transformed into nitrile oxides through protonation and dehydration, which is generated from the oxidation and nitration of ketones by Fe^{3+} or nitrogen dioxide, followed by the formation of isoxazole derivatives (**Path B**). However, partial direct nitration of alkenes by nitrogen dioxide occurs (**Path A**), the isoxazole derivatives are obtained in only moderate yield (68%).

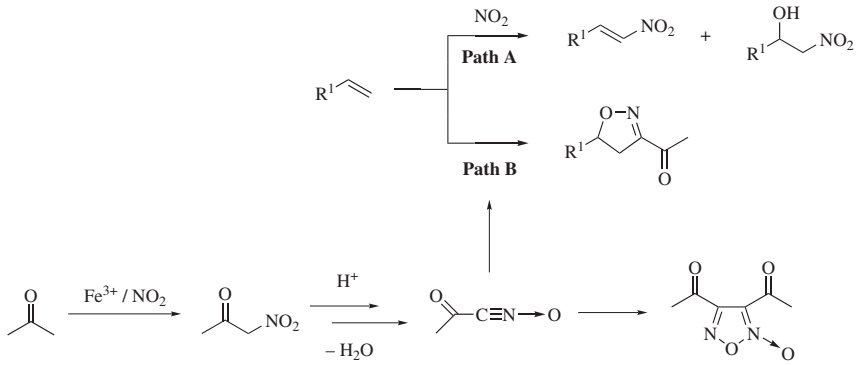


1 **2** **61** **62**

2: $R^1 = n\text{-}C_6H_{13}$, $R^2 = Me$
61, **62**: $R^1 = n\text{-}C_6H_{13}$

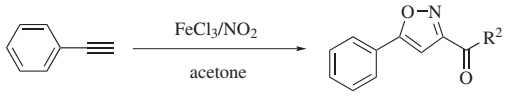
Scheme 7

In the present method, the corresponding isoxazole derivatives were obtained at room temperature using nitrogen dioxide; therefore, we applied this method to highly reactive acetylenic compounds. Although the reaction of ethynylbenzene (**63**) using iron(III) nitrate under reflux conditions gave a poor yield (15%), the corresponding isoxazole derivative **64** was obtained in 51% yield when iron(III) chloride and nitrogen dioxide were employed at room temperature (Scheme 9). Consequently, the newly



Scheme 8 Reaction pathway using $FeCl_3$–NO_2 in acetone

proposed method provides an efficient one-pot synthesis of 3-acetylisoxazole derivatives from active alkynes and shows a novel and efficient utilization of nitrogen dioxide.



63 **64**: R^2 = Me Yield: 51%

Scheme 9 NO_2 was bubbled (ca. 45 mL/min, 20 s) through substrate **63** (0.5 mmol), iron(III) chloride (0.5 mmol), and acetone (4.0 mL) were reacted at room temperature.

Effect of Microwave Irradiation on the Synthesis of 3-Acylisoxazoles by Iron(III) Nitrate

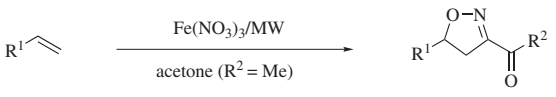
Microwave irradiation has been used to accelerate a variety of organic reactions.[24] Varma and co-workers reported that styrene derivatives were nitrated by the application of iron(III) nitrate and microwave irradiation.[16] Therefore, we attempted to apply microwave irradiation to the reaction using iron(III) nitrate (Scheme 10 and Table 5). When 1-octene (**1**; 0.5 mmol), iron(III) nitrate (0.5 mol), and acetone (3.0 mL) were reacted under microwave irradiation (120 W) for 30 minutes at 60 °C, the corresponding isoxazole derivative **2** was obtained in 79% yield (Table 5, entry 8). We also found that irradiation time influenced the yields of isoxazole derivatives (Table 5, entries 7–10). The optimum irradiation time was 30 seconds, it appears that longer irradiation times accelerated the nitration of acetone. Based on these results, this method is shown to be a new microwave-assisted one-pot synthesis of 3-acetylisoxazole derivatives, which requires a short reaction time.

In conclusion, the reaction using non-toxic and inexpensive iron(III) nitrate provides a simple, convenient and efficient one-pot synthesis of 3-acetyl- and 3-benzoylisoxazole derivatives. In addition, the method using iron(III) salts and nitrogen dioxide (NO_2) gave new isoxazole derivatives under mild conditions and represents a new and effective utilization of nitrogen dioxide. Also, because the microwave-assisted synthesis of the 3-acetylisoxazole derivatives appreciably reduces the reaction time, this reaction using microwave irradiation is a novel and efficient method for synthesizing isoxazole derivatives.

Table 5 Application of Microwave Irradiation

Entry	Watts	Time (s)	Product **2** (%)[b]
1	80	20	19
2	90	20	44
3	100	20	45
4	110	20	56
5	120	20	76
6	130	20	53
7	120	10	34
8	120	30	79
9	120	40	75
10	120	50	72

[a] 1-Octene (**1**; 0.5 mmol), $Fe(NO_3)_3$ (0.5 mmol), and acetone (3.0 mL) were employed. Microwave setting: power, 80–130 W; pressure, 15 bar; 60 °C.
[b] Determined by GLC analysis using *n*-dodecane as the internal hydrocarbon standard.



1 **2**

1 : R^1 = *n*-C_6H_{13}
2 : R^1 = *n*-C_6H_{13}, R^2 = Me

Scheme 10

Melting points were determined on a Yanaco micro melting point apparatus. 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 $CDCl_3$ with TMS as the internal standard. GLC analyses were performed using a GLC-column (DB-1, 25 m) equipped with a Shimazu GLC-17A. HRMS (EI)

analyses were performed on a JMS-GLC mate II/HP-6890 with an ionizing energy of 70 eV. All chemicals were purchased from Kanto Kagaku, Tokyo Kasei Kogyo Corporation and Wako Pure Chemical Industries, Ltd. (silica gel 60: 0.063–0.200 nm). The yields of the products were determined by GLC analysis using *n*-dodecane as the internal hydrocarbon standard. The reaction conditions are shown in Tables 1– 5. The spectral data (IR, ^{1}H NMR, ^{13}C NMR, EIMS, CI-MS, and HRMS) of 3-acetylisoxazoles **2**, **16**–**28**, and **49**–**54** and 3-benzoylisoxazoles **29**–**42**, **55**–**60** were reported in our previous paper.[9]

Reaction of 1-Octene (1) with Iron(III) Nitrate in Acetone; Typical Procedure

A mixture of 1-octene (**1**; 1.122 g, 10.0 mmol) and iron(III) nitrate nonahydrate (4.040 g, 10.0 mmol) in acetone (40 mL) was stirred under reflux for 10 h. The reaction mixture was filtered through hyflo super-cel® and the residue on the funnel was washed with acetone (2 × 10 mL). The filtrate was concentrated in vacuo, the residue was dissolved in EtOAc (100 mL) and washed with aq $NaHCO_3$ (2 × 5 mL), sat. aq NaCl (2 × 5 mL), and H_2O (2 × 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed (hexane–EtOAc, 4: 1) to give **2**[9] as a pale yellow oil (1.349 g, 68%).

Reaction of 1-Octene (1) with Iron(III) Nitrate in Acetophenone; Typical Procedure

A mixture of 1-octene (**1**; 1.122 g, 10.0 mmol) and iron(III) nitrate nonahydrate (4.040 g, 10.0 mmol) in acetophenone (40 mL) was stirred at 80 °C for 15 h. The reaction mixture was filtered through hyflo super-cel® and the residue on the funnel was washed with acetone (2 × 10 mL). The filtrate was concentrated in vacuo, the residue was dissolved in EtOAc (100 mL), washed with aq $NaHCO_3$ (2 × 5 mL), sat. aq NaCl (2 × 5 mL), and H_2O (2 × 5 mL). The combined organic phases were dried over Na_2SO_4, concentrated in vacuo, and acetophenone was removed by reduced pressure distillation. The residue was chromatographed (hexane–EtOAc, 4:1) to give **29**[9] as a pale yellow oil (1.843 g, 71%).

59; Crystal X-ray Diffraction Data[25]

Molecular formula: $C_{13}H_{11}NO_4$, F_w: 245.23, clear plate-like, size: 0.08 × 0.36 × 0.44 mm, monoclinic, space group *C*2/c, *a* = 9.887 (1) Å, *b* = 13.516 (1) Å, *c* = 18.111 (2) Å, *β* = 97.289 (4)°, V = 2400.8 (5) Å^3, θ = 4.70–51.21°, T = 298 ± 1 K, Z = 8, *F*(000) = 1024.00, D_x = 1.357 gm^{-3}, μ = 1.02 cm^{-1}. Data were collected on a Bruker SMART APEX CCD diffractometer (M_o–K_α radiation, λ = 0.71069 Å) at 298 ± 1 K; total of 9274 reflections, of which 3436 unique [$R_{(int)}$ = 0.024]. Structure solution: direct methods (SIR92); refinement: full-matrix least-squares; anomalous dispersion: all non-hydrogen atoms; observations: 1025 [I > 2σ(I)]; variables: 164, *R* = 0.063, *R*1 = 0.063, *wR*2 = 0.052. Goodness-of-fit = 0.05, max shift/error in final cycle = 0.047, max and min peak in final difference map: 0.17 and –0.14 e$^-$/Å^3.

Reaction of 1-Octene (1) with Iron(III) Chloride in Acetone; Typical Procedure

NO_2 (ca. 45 mL/min) was bubbled through a mixture of 1-octene (**1**; 0.0561 g, 0.5 mmol), iron(III) chloride hexahydrate (0.1352 g, 0.5 mmol) and acetone (3.0 mL) for 20 s, and the resulting solution was stirred at r.t. for 12 h. The reaction mixture was filtered using hyflo super-cel® and the residue on the funnel was washed with acetone (2 × 3 mL). After the filtrate was concentrated in vacuo, the residue was dissolved in EtOAc (10 mL), washed with aq $NaHCO_3$ (2 × 2 mL), sat. aq NaCl (2 × 2 mL), and H_2O (2 × 2 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed (hexane–EtOAc, 4:1) to give 3-acetyl-5-hexyl-4,5-dihydroisoxazole (**2**)[9] as a pale yellow oil (0.0546 g, 55%).

3-Acetyl-5-phenylisoxazole (64)

Colorless needles (hexane); mp 99.8–100.6 °C.

IR (KBr): 1707, 1559 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.79–7.83 (m, 2 H), 7.47–7.54 (m, 3 H), 6.89 (s, 1 H), 2.70 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 192.2, 171.7, 162.7, 130.8, 129.1, 126.0, 97.7, 27.3.

HRMS: *m*/*z* calcd for $C_{11}H_9NO_2$: 187.0633; found: 187.0634.

Microwave-Irradiated Reaction; Typical Procedure

A mixture of 1-octene (**1**; 0.0561 g, 0.5 mmol), iron(III) nitrate nonahydrate (0.2020 g, 0.5 mmol) and acetone (3.0 mL) were irradiated (120 W) at 60 °C for 30 min in a self-tuning single-mode CEM Discover™ Focused Synthesizer. The reaction mixture was filtered through hyflo super-cel® and the residue on the funnel was washed with acetone (2 × 3 mL). After the filtrate was concentrated in vacuo, the residue was dissolved in EtOAc (10 mL), washed with aq $NaHCO_3$ (2 × 2 mL), sat. aq NaCl (2 × 2 mL), and H_2O (2 × 2 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed (hexane–EtOAc, 4:1) to give **2**[9] as a pale yellow oil (0.0507 g, 51%).

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References

(1) Patra, A.; Bhaduri, A. P.; Khanna, A.; Chander, R.; Dikshit, M. *Bioorg. Med. Chem.* **2003**, *11*, 2269.
(2) Srivastava, S.; Bajpai, L. K.; Batra, S.; Bhaduri, A. P.; Maikhuri, J. P.; Gupta, G.; Dhar, J. D. *Bioorg. Med. Chem.* **1999**, *7*, 2607.
(3) Cheng, J.; Izenwasser, S.; Zhang, C.; Zhang, S.; Wade, D.; Trudell, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1775.
(4) Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123.
(5) Kozikowski, A. P.; Chen, Y. Y. *J. Org. Chem.* **1981**, *46*, 5248.
(6) Lee, S. Y.; Lee, B. S.; Lee, C.-W.; Oh, D. Y. *J. Org. Chem.* **2000**, *65*, 256.
(7) Yashiro, A.; Nishida, Y.; Kobayashi, K.; Ohno, M. *Synlett* **2000**, 361.
(8) Itoh, K.; Takahashi, S.; Ueki, T.; Sugiyama, T.; Takahashi, T. T.; Horiuchi, C. A. *Tetrahedron Lett.* **2002**, *43*, 7035.
(9) Itoh, K.; Horiuchi, C. A. *Tetrahedron* **2004**, *60*, 1671.
(10) Chiarino, D.; Grancini, G.; Frigeni, V.; Biasini, I.; Carenzi, A. *J. Med. Chem.* **1991**, *34*, 600.
(11) Kai, H.; Ichiba, T.; Miki, M.; Takase, A.; Masuko, M. *J. Pesticide Sci.* **1999**, *24*, 130.
(12) Amici, M. D.; Conti, P.; Vistoli, G.; Carrea, G.; Ottolina, G.; Micheli, C. D. *Med. Chem. Res.* **2001**, *10*, 615.
(13) (a) He, L.; Horiuchi, C. A. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2515. (b) He, L.; Horiuchi, C. A. *Appl. Organomet. Chem.* **1999**, *13*, 867. (c) Horiuchi, C. A.; Ochiai, K.; Fukushima, H. *Chem. Lett.* **1994**, 185. (d) Horiuchi, C. A.; Kiji, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 421.
(14) Coombes, R. G.; Russell, L. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1751.
(15) Cornelis, A.; Laszlo, P. *Synthesis* **1980**, 849.

(16) Varma, R. S.; Naicker, K. P.; Liesen, P. J. *Tetrahedron Lett.* **1998**, *39*, 3977.
(17) Cornelis, A.; Laszlo, P. *Synthesis* **1985**, 909.
(18) Laszlo, P.; Polla, E. *Tetrahedron Lett.* **1984**, *25*, 3701.
(19) Suzuki, H.; Takaoka, H.; Yamamoto, H.; Ogawa, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2927.
(20) Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 5663.
(21) Suzuki, H.; Murashima, T.; Kozai, I.; Mori, T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1591.
(22) Nose, M.; Suzuki, H.; Suzuki, H. *J. Org. Chem.* **2001**, *66*, 4356.
(23) Suzuki, H.; Mori, T. *J. Org. Chem.* **1997**, *62*, 6498.
(24) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
(25) The crystallographic data is deposited at the Cambridge Crystallographic Data Centre under CCDC number 262303.