Synthesis of Oxazoles by the Reaction of Ketones with Iron(III) Solvates of Nitriles

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Oxazoles having functionalized carbon substituents at the C-2 position were synthesized in one step by the oxidation of ketones with iron(III) solvates of nitriles, *i.e.*, $Fe(RCN)_6(ClO_4)_3$ (solvate A) or $Fe(RCN)_6(FeCl_4)_3$ (solvate B), in the corresponding nitriles.

Keywords oxazole; ketone; oxidation; nitrile; iron(III) nitrile solvate

Numerous methods for synthesizing the oxazole ring system have been reported to date.[1] Interest in oxazoles has been renewed recently in view of their utility in synthetic chemistry as a masked carbonyl group[2] and also their various pharmacological activities, namely, anti-inflammatory,[3] hypoglycemic,[4] and hypolipidemic activities,[5] and inhibitory activities on aldose reductase,[6] blood platelet aggregation,[7] *etc.* This paper describes a new and one-step synthesis of oxazole derivatives having functionalized carbon substituents at the C-2 position above by the reaction of ketones with iron(III) solvates of nitriles.[8]

We found that the reactions of benzyl phenyl ketone with the iron(III) solvates of nitriles, $Fe(RCN)_6(ClO_4)_3$ (solvate A) or $Fe(RCN)_6(FeCl_4)_3$ (solvate B), prepared from $Fe(ClO_4)_3 \cdot 9H_2O$ or $FeCl_3$ either by the addition of Ac_2O to remove the water ligand of ferric perchlorate in nitriles or by dissolving $FeCl_3$ in nitriles as reported previously,[8,9] gave the oxazoles in one step. The reaction of benzyl phenyl ketone with the type A solvate (R = Me) at room temperature for 1 h afforded 2-methyl-4,5-diphenyloxazole (**1a**)[10] and benzoin acetate (**2**)[11] in yields of 41.4 and 35.6%, respectively (method A-1). Alternatively, reaction of benzyl phenyl ketone with the type B solvate (R = Me) at 80 °C for 15 min gave **1a** and desyl chloride (**3**)[12] in yields of 39.0 and 32.7%, respectively, and the reaction at 80 °C for 2 h resulted in only **1a** in 93.2% yield (method B-1). The latter result suggests that the chloride **3** may be transformed to the oxazole under these conditions by the reaction with MeCN used as the solvent.[13] These results conflict with a previous report[14] in which the reaction of benzyl phenyl ketone with $FeCl_3$ (in the ratios of 1 : 2) in MeCN under aerobic condition with refluxing for 24 h gave benzil, benzaldehyde, the chloride **3**, and benzoic acid in yields of 15, 38, 14, and 20%, respectively, and the oxazole **1a** was not obtained. This difference may be due to the molar ratios of $FeCl_3$ to the ketone used, because 4 mol of $FeCl_3$ is necessary to prepare the solvate B, and 8 mol of $FeCl_3$ is

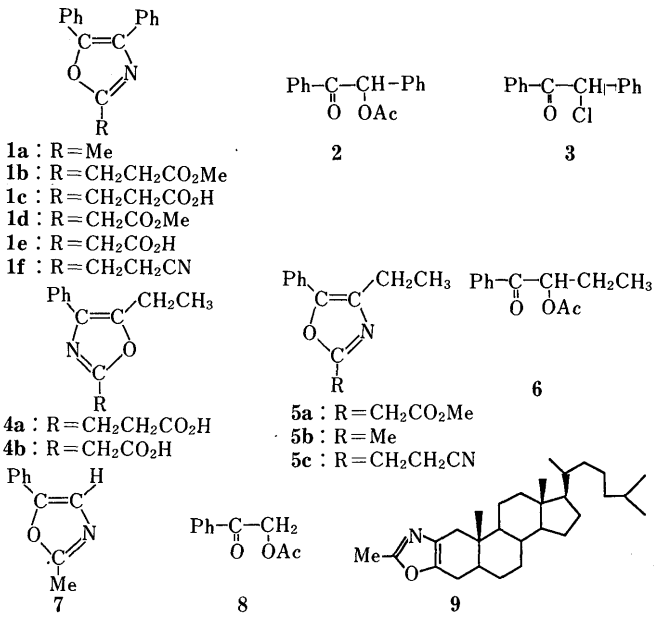

Chart 1

TABLE I. Reaction of Benzyl Phenyl Ketone with Iron(III) Solvates of Nitriles

Run	Fe(III) solvate	Solvent system	Method[a]	Reaction time	Yield of product (%)[b] 1a—f	2	3	Recov.
1	$Fe(MeCN)_6(ClO_4)_3$	AcOH–MeCN	A-1	30 min	41.4 (**a**)[2]	35.6		21.0
2	$Fe(CH_2=CHCN)_6(ClO_4)_3$	AcOH–CH_2=CHCN	A-1	30 min		56.5		14.2
3	$Fe(NCCH_2CH_2CO_2Me)_6(ClO_4)_3$	AcOH–$NCCH_2CH_2CO_2Me$–CH_2Cl_2	A-2	2 h	28.0 (**b**)	52.8		13.8
4	$Fe(NCCH_2CH_2CN)_6(ClO_4)_3$	AcOH–$NCCH_2CH_2CN$–CH_2Cl_2	A-2	2 h	41.1 (**f**)	28.7		28.0
5	$Fe(MeCN)_6(FeCl_4)_3$	MeCN	B-1	15 min	39.0 (**a**)		32.7	23.0
6	$Fe(MeCN)_6(FeCl_4)_3$	MeCN	B-1	2 h	93.2 (**a**)			
7	$Fe(NCCH_2CH_2CO_2Me)_6(FeCl_4)_3$	$NCCH_2CH_2CO_2Me$–$MeNO_2$	B-2	1 h	79.2 (**c**)[3]			
8	$Fe(NCCH_2CO_2Me)_6(FeCl_4)_3$	$NCCH_2CO_2Me$–$MeNO_2$	B-2	1 h	64.4 (**e**)			
9	$Fe(NCCH_2CH_2CN)_6(FeCl_4)_3$	$NCCH_2CH_2CN$–$MeNO_2$	B-2	1 h	67.5 (**f**)			
10	$Fe(Ac_2O)_3(ClO_4)_3$	AcOH–Ac_2O–CH_2Cl_2	C	16 h		55.0		23.0
11	$Fe(bpy)_3(ClO_4)_3$	AcOH–MeCN	D	3 h	27.0 (**a**)			37.0
12	$Fe(bpy)_3(ClO_4)_3$	AcOH–$NCCH_2CO_2Me$	D	30 min	17.0 (**d**)			57.0

a) Method A-1: reaction with $Fe(RCN)_6(ClO_4)_3$ in AcOH–RCN at room temperature; method A-2: reaction with $Fe(RCN)_6(ClO_4)_3$ in AcOH–RCN–CH_2Cl_2 at room temperature; method B-1: reaction with $Fe(RCN)_6(FeCl_4)_3$ in RCN at 60—80 °C; method B-2: reaction with $Fe(RCN)_6(FeCl_4)_3$ in RCN–$MeNO_2$ at 60—80 °C; method C: reaction with $Fe(Ac_2O)_3(ClO_4)_3$ in AcOH–Ac_2O–CH_2Cl_2 at room temperature; method D: reaction with $Fe(bpy)_3(ClO_4)_3$ in AcOH–RCN at 60—80 °C. *b*) Isolated yields.

TABLE II. Reaction of Ketones with Iron(III) Solvates of Nitriles

Run	Ketone	Nitrile RCN R=	Method[a]	Reaction time	Yield of product (%)[b]
13	$PhCH_2COCH_2CH_3$	$CH_2CH_2CO_2Me$	B-2	10 min	**4a** (51.8)
14	$PhCH_2COCH_2CH_3$	CH_2CO_2Me	B-2	5 min	**4b** (32.7)
15	$PhCOCH_2CH_2CH_3$	CH_2CO_2Me	B-2	1 h	**5a** (20.7)
16	$PhCOCH_2CH_2CH_3$	Me	A-1	1 h	**5b** (49.0)[15]; **6** (9.2)
17	$PhCOCH_2CH_2CH_3$	CH_2CH_2CN	A-2	2 h	**5c** (37.6); **6** (1.9)
18	$PhCOCH_3$	Me	A-1	1 h	**7** (34.6); **8** (7.9)
19	Cholestanone	Me	A-1	15 min	**9** (33.5)

a) Method A-1: reaction with $Fe(RCN)_6(ClO_4)_3$ in AcOH–RCN at room temperature; method A-2: reaction with $Fe(RCN)_6(ClO_4)_3$ in AcOH–RCN–CH_2Cl_2 at room temperature; method B-2: reaction with $Fe(RCN)_6(FeCl_4)_3$ in RCN–CH_2NO_2 at 60—80 °C. *b*) Isolated yields.

TABLE III. Physical Data for Oxazoles Prepared

Compd.	mp (°C) (Recrystn. solv.)	Molecular formula MS *m/z* (M^+): Calcd (Found); *Anal.*	IR (Nujol or neat) cm^{-1}	H-NMR ($CDCl_3$) δ
1a[2]	Oil	$C_{16}H_{13}NO$ 235.0998 (235.1015)	1595	2.45 (3H, s), 7.00—7.30 (6H), 7.30—7.60 (4H)
1b	58—59 (MeOH–H_2O)	$C_{19}H_{17}NO_3$ 308.1285 (308.1240)	1730 1590	3.07 (4H, m), 3.70 (3H, s), 7.25—7.50 (6H), 7.50—7.72 (4H)
1c[3]	160.5—161.5 (MeOH–H_2O)	$C_{18}H_{15}NO_3$ 293.1052 (293.1083) *Anal.* Calcd: C, 73.70; H, 5.15; N, 4.78 Found: C, 73.66; H, 5.35; N, 4.60	1718 1560	3.07 (4H, m), 7.15—7.50 (6H), 7.50—7.72 (4H), 10.70 (1H, br s)
1d	98—99 (Et_2O–hexane)	$C_{18}H_{15}NO_3$ 293.1051 (293.1091)	1722 1590	3.78 (3H, s), 3.98 (2H, s), 7.30—7.50 (6H), 7.50—7.70 (4H)
1f	119—120 (Et_2O)	$C_{18}H_{14}N_2O$ 274.1103 (274.1068) *Anal.* Calcd: C, 78.81; H, 5.14; N, 10.21 Found: C, 79.01; H, 5.08; N, 10.02	2250 1585	3.07 (4H, m), 7.20—7.50 (6H), 7.50—7.75 (4H)
4a	109.5—110 (MeOH–H_2O)	$C_{14}H_{15}NO_3$ 245.1050 (245.1047) *Anal.* Calcd: C, 68.56; H, 6.16; N, 5.71 Found: C, 68.39; H, 6.19; N, 5.74	1700 1580	1.22 (3H, t, J=8.0 Hz), 2.82 (2H, q, J=8.0 Hz), 2.90 (4H, m), 7.30—7.75 (5H), 11.50 (1H, br s)
4b	125—127 (Et_2O–hexane)	$C_{13}H_{13}NO_3$ 231.0896 (231.0953)	1705 1580	1.28 (3H, t, J=8.0 Hz), 2.90 (2H, q, J=8.0 Hz), 3.95 (2H, s), 6.68 (1H, br s), 7.20—7.72 (5H)
5a	Oil	$C_{14}H_{15}NO_3$ 245.1050 (245.1035)	1740 1580	1.30 (3H, t, J=8.0 Hz), 2.90 (2H, q, J=8.0 Hz), 3.78 (3H, s), 3.90 (2H, s), 7.25—7.75 (5H)
5b[15]	Oil	$C_{12}H_{13}NO$ 187.0998 (187.0999)	1585	1.25 (3H, t, J=7.0 Hz), 2.42 (3H, s), 2.86 (2H, q, J=7.0 Hz), 7.25—7.75 (5H)
5c	Oil	$C_{14}H_{14}N_2O$ 226.1105 (226.1150)	2200 1580	1.30 (3H, t, J=8.0 Hz), 2.88 (2H, q, J=8.0 Hz), 3.01 (4H, m), 7.25—7.75 (5H)
7	39—41 (Et_2O–hexane)	$C_{10}H_9NO$ 159.0683 (159.0728)	1585	2.52 (3H, s), 7.30—7.50 (3H), 7.63—7.80 (2H), 7.82 (1H, s)
9	128—130 (Acetone)	$C_{29}H_{47}NO$ 425.3658 (425.3660) *Anal.* Calcd: C, 81.82; H, 11.13; N, 3.29 Found: C, 81.63; H, 11.43; N, 3.53	1660 1565	0.68 (3H, s), 0.78 (3H, s), 0.86 (6H, d, J=7.0 Hz), 0.91 (3H, d, J=6.5 Hz), 0.95—2.10 (25H), 2.15 (1H, br), 2.20 (1H, d, J=15.0 Hz), 2.38 (1H, dd, J=5.0, 14.0 Hz), 2.39 (3H, s), 2.51 (1H, d, J=15.0 Hz)

required to synthesize oxazoles from ketones.

Related reactions of benzyl phenyl ketone with the solvates A or B (R=$-CH_2CH_2CO_2Me$, $-CH_2CO_2Me$, and $-CH_2CH_2CN$) in either CH_2Cl_2 (method A-2) or $MeNO_2$ (method B-2) gave the ozaxoles **1b**, **1c**, **1e** and **1f**, along with **2** as shown in Table I.[16] In run 2, the oxazole was not obtained since polymerization of acrylonitrile catalyzed by the iron(III) solvate proceeded, and only the acetate **2** was afforded. Although acetates were produced as a by-product in method A, the oxazoles could be obtained as a sole product in method B. The reaction catalyzed by the iron(III) Ac_2O solvate afforded only the acetoxylated product (run 10). Similar reactions of the solvates A and B with the ketones, namely, benzyl ethyl ketone, phenyl propyl ketone, and acetophenone, also afforded the oxazoles **4**, **5**, and **7** along with the acetates **6** and **8**[17] as shown in Table II.

Reaction of cholestanone with the solvate A (R=Me) gave the oxazole **9** (33.5%). The structure of **9** was assigned by analysis of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum ($CDCl_3$), in which signals corresponding to seven protons were observed at lower field below 2.15 ppm, namely, 2.15 (1H, br, fine coupling, C(4)-H), 2.20 (1H, d, J=15.0 Hz, C(1)-H), 2.38 (1H, dd, J=5.0 and 14.0 Hz, C(4)-H), 2.39 (3H, s, Me–C=N), and 2.51 (1H, d, J=15.0 Hz, C(1)-H).

These reactions may proceed with one-electron or double one-electron oxidation by iron(III) solvates, followed by addition of nitrile to a radical or a cation as shown in Chart 2; this is in accordance with a report on the synthesis of oxazoles from ketones and nitriles using copper(II) trifluoromethanesulfonate.[18]

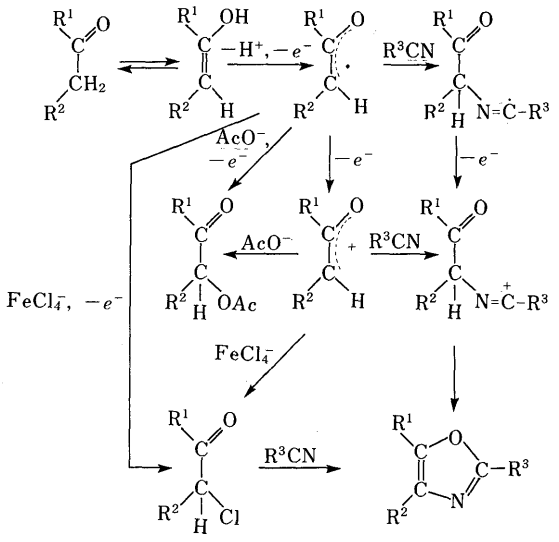

Chart 2

One-electron oxidation is a key step in this reaction mechanism. The half oxidation potentials in 0.1 M tetraethylammonium perchlorate MeCN solution ($E_{1/2}$ V *vs.* saturated calomel electrode (SCE)) of the ketones used were as follows: $PhCOCH_2Ph$, 2.25; $PhCH_2COCH_2CH_3$, 2.20; $PhCOCH_3$, 2.60; and cholestanone, 2.40; *etc.*, being higher than the formal redox potential $E^\circ = 1.73$ V *vs.* SCE of the solvate A (R = Me). Therefore, these oxidations may proceed at the enol forms. Reaction of benzyl phenyl ketone with $Fe(bpy)_3(ClO_4)_3$, $E^\circ = 1.10$ V [lower than that of the solvate A (R = Me)], in MeCN also afforded the oxazole **1a** (method D, Table I, run 11). This evidence may also suggest that the oxidation process does not involve ligand formation between the iron(III) and the enols.

The question arises, is the nitrile that attacks the radical or the cation either ligand nitrile or solvent nitrile? The following evidence suggests that nitrile consumed to form oxazoles is derived from the solvent. That is, (a) reactions of the ketones with $Fe(bpy)_3(ClO_4)_3$ afford the oxazoles (runs 11 and 12, Table I) although the ligand of this complex could not be displaced by nitriles having weak donor abilities; (b) none of the oxazoles are formed when less than 6 mol of nitrile with respect to the iron(III) salt was used in the reaction of method A-2 (Table I).

Experimental

All melting points are uncorrected. Infrared spectra (IR) were recorded with a Hitachi 260-10 spectrometer, ^{1}H-NMR spectra with a Varian T-60 or JEOL JNM-GX 270 spectrometer with tetramethylsilane as an internal standard ($CDCl_3$ solution) and mass spectra (MS) with a JEOL JMS-D 300 spectrometer. Elementary analyses were done by Ms. M. Takeda and Ms. A. Sakamoto, Kissei Pharmaceutical Company, Matsumoto, Japan. Wako Silica Gel C-200 (200 mesh) and Merck Kieselgel 60 F-254 were used for column chromatography and thin-layer chromatography (TLC), respectively. Cyclic voltammetric analyses were carried out using a Yanagimoto P8 polarograph. (Details of the measurement have been given in refs. 8 and 9.)

General Procedure for Oxidation of Ketones with $Fe(RCN)_6(ClO_4)_3$ in AcOH–RCN (Method A-1) A solution of ketone (10 mmol) in nitrile (10 ml) was added in one portion with stirring to a solution of $Fe(RCN)_6(ClO_4)_3$[8] [prepared by adding Ac_2O (23 ml) to a solution of $Fe(ClO_4)_3 \cdot 9H_2O$ (12 g, 23 mmol) in nitrile (110 ml) with stirring under ice-water cooling], and the mixture was stirred at room temperature for 10—60 min. Ice-water (200 ml) and diluted HCl (20 ml) were added, and the whole was stirred for 15 min followed by addition of saturated aqueous NaCl (200 ml) and extraction with ether-methylene chloride (3 : 1, 2 × 200 ml). The organic layer was washed with water (2 × 300 ml) and saturated $NaHCO_3$ (200 ml), dried on Na_2SO_4, and then evaporated. The product was separated by silica gel column chromatography using hexane–chloroform (1 : 1) as an eluent.

Runs 1, 2, 16, 18, and 19 (Tables I and II) were done by this method.

2-Acetoxy-1-phenyl-1-butanone (6) By-product in runs 16 and 17. Colorless oil. IR (neat) cm^{-1}: 1740, 1698, 1600, 1580. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J = 7.0 Hz), 2.00 (2H, br, fine coupling), 2.20 (3H, s), 5.85 (1H, t, J = 7.0 Hz), 7.42—7.65 (3H, m), 7.85—8.10 (2H, m).

General Procedure for Oxidation of Benzyl Phenyl Ketone with $Fe(RCN)_6(ClO_4)_3$ in AcOH–RCN–CH_2Cl_2 (Method A-2) A solution of $Fe(RCN)_6(ClO_4)_3$ in AcOH–RCN–CH_2Cl_2 was prepared by the addition of Ac_2O (2.3 ml, 23 mmol) and nitrile (23 mmol, 2.6 or 1.9 g in the case of $NCCH_2CH_2CO_2Me$ or $NCCH_2CH_2CN$) to crystals of $Fe(ClO_4)_3 \cdot 9H_2O$ (1.2 g, 2.3 mmol), and then diluting with methylene chloride (10 ml). Benzyl phenyl ketone (196 mg, 1 mmol) was added to the resulting solution in one portion. Stirring was done for 2 h at room temperature, then ice-water (20 ml), diluted HCl (10 ml), and saturated aqueous NaCl (100 ml) were added and the reaction mixture was extracted with ether (2 × 50 ml). The organic layer was washed with water (3 × 200 ml) and saturated $NaHCO_3$ (100 ml), dried on Na_2SO_4, and evaporated. The residue was subjected to silica gel column chromatography using hexane–chloroform (1 : 1) as an eluent (runs 3 and 4, Table I).

Phenyl propyl ketone was also treated by this method (run 17, Table II).

Reaction of Benzyl Phenyl Ketone with $Fe(MeCN)_6(FeCl_4)_3$ in MeCN (Method B-1) Benzyl phenyl ketone (392 mg, 2 mmol) was added to a solution of $Fe(MeCN)_6(FeCl_4)_3$[9] in MeCN prepared by dissolving anhydrous $FeCl_3$ (3.3 g, 20 mmol) in dry MeCN (30 ml), and the whole was heated at 60—80 °C for 15 min (run 5) or 2 h (run 6). The resulting mixture was cooled to room temperature and worked up in accordance with method A-2. The residue was subjected to silica gel column chromatography using chloroform as an eluent.

General Procedure for Oxidation of Ketones with $Fe(RCN)_6(FeCl_4)_3$ in RCN–$MeNO_2$ (Method B-2) A ketone (2 mmol) was added in one portion to a yellow colored solution of $Fe(RCN)_6(FeCl_4)_3$ (*ca.* 5 mmol) in RCN–$MeNO_2$ prepared by dissolving anhydrous $FeCl_3$ (3.3 g, 20 mmol) in nitrile (5 ml) and nitromethane (20 ml), and the whole was heated at 60—80 °C for 5—60 min. The resulting decolorized solution was cooled to room temperature and then worked up in accordance with method A-2. In the case of run 9, the reaction residue was purified by recrystallization from ether–hexane. In the other cases, runs 7, 8, 13, 14, and 15 (Tables I and II), the products were purified by recrystallization of the carboxylic acid derivatives of oxazoles obtained by hydrolysis of the residues with alcoholic KOH.

Reaction of Benzyl Phenyl Ketone with $Fe(Ac_2O)_3(ClO_4)_3$ in AcOH–CH_2Cl_2 (Method C) Benzyl phenyl ketone (196 mg, 1 mmol) was added in one portion to a violet solution obtained by dilution with methylene chloride (10 ml) of a solution of $Fe(Ac_2O)_3(ClO_4)_3$ prepared by careful addition of Ac_2O (3 ml) to $Fe(ClO_4)_3 \cdot 9H_2O$ (1.2 g, 2.3 mmol), and the whole was allowed to stand at room temperature over night. The reaction mixture was worked up according to method A-2 and purified by silica gel column chromatography to give 140 mg (55.0%) of benzoin acetate (2), mp 80—82 °C (ether–hexane) and 40 mg (20.4%) of recovered material.

Reaction of Benzyl Phenyl Ketone with $Fe(bpy)_3(ClO_4)_3$ in AcOH–RCN (Method D) Benzyl phenyl ketone (98 mg, 0.5 mmol) was added in one portion to a blue solution of $Fe(bpy)_3(ClO_4)_3$ in AcOH–MeCN prepared by the addition of Ac_2O (0.3 ml) to a solution of $Fe(bpy)_3(ClO_4)_3 \cdot 3H_2O$ (880 mg, 1 mmol) in RCN (6 ml), and the whole was heated at 60—80 °C for 3 h. The resulting solution was worked up according to method A-1. In the case of run 11, the residue was purified by silica gel column chromatography using hexane–chloroform (1 : 1) as an eluent. In the case of run 12, the residue was hydrolyzed and worked up according to the method B-2.

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