APPLIED ORGANOMETALLIC CHEMISTRY, VOL. 9, 399–411 (1995)

Cerium in Organic Reactions: Construction of 2-Isoxazoline Ring Mediated by Ammonium Cerium Nitrate

Takashi Sugiyama
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

Direct construction of the 2-isoxazoline ring directly from an alkene, or from an alkene and primary nitroalkane, was achieved in the presence of ammonium cerium nitrates. It has been found that (1) a carboxylic acid such as formic acid is required to promote the reaction, (2) an appropriate additive is required, when ammonium cerium(IV) nitrate is employed, but the additive is not necessary when ammonium cerium(III) nitrate is employed, (3) both ammonium cerium nitrates are converted into cerium(III) formate before the reaction takes place, and, (4) the cerium ion acts as a carrier of NO_x as well as the activator of the nitro compound, and nitrate anion is the source of the NO_x as well as the promoter of the reaction. A plausible reaction scheme has been proposed.

Keywords: 2-isoxazoline; ammonium cerium nitrate; nitrile oxide; 1,3-dipolar cycloaddition

INTRODUCTION

A number of 2-isoxazolines and 2-isoxazoles have interesting medicinal or agricultural activity.[1] For example, acivicin has potent anticancer activity.[2] In addition, 2-isoxazolines and 2-isoxazoles are highly functionalized heterocycles; they are transformed into β-hydroxy ketones, α,β-unsaturated ketones, γ-amino alcohols, and β-diketones and other natural products, due to their ability to undergo reductive ring opening.[3] Thus, construction of the 2-isoxazoline ring is still a challenging goal.

Many synthetic methods have been developed to obtain 2-isoxazolines.[4] Two major methods of preparation are the cycloaddition of nitrile oxides to alkenes and the reaction of α,β-unsaturated ketones with hydroxylamines. Additional methods include the reaction of a β-halo ketone with a hydroxylamine, the reaction of an ylide with a nitrile oxide, and the reaction of a nitroalkane with an alkene. There are also some other miscellaneous synthetic methods.

However, each method is restricted by its own scope and limitations, and an approporiate method should be selected depending upon the individual chemical requirements.

The author has been interested in finding novel transformations in organic functional groups mediated by rare-earth metal compounds, especially cerium compounds, and has reported the development of some novel reaction systems.[5] Among several characteristics, two unique properties of rare-earth metals, namely oxophilicity and high coordination number, are noteworthy.

Since the 2-isoxazoline ring can be constructed by 1,3-dipolar cycloaddition of a nitrile oxide with an alkene as described above, it is reasonable to expect the direct preparation of isoxazoline from ammonium cerium(IV) nitrate and an alkene. That is, if an aliphatic nitro compound is formed by the reaction of an alkene with a cerium compound, it might be converted into the corresponding nitrile oxide in the presence of the cerium compound. The nitrile oxide reacts, in turn, with another molecule of alkene to give an isoxazoline derivative.

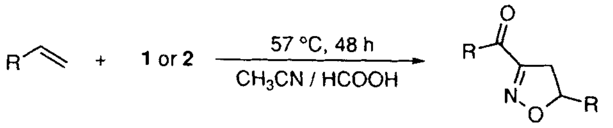
In the present paper, the author reports the results for a one-step synthesis of isoxazoline derivatives by the reaction of alkenes with ammonium cerium nitrate (Eqns [1] and [2]).

RESULTS AND DISCUSSION

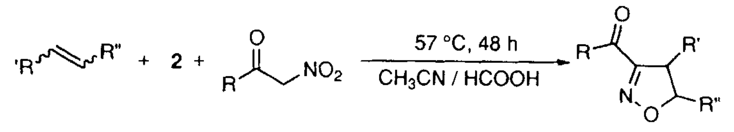
4-Methyl-1-pentene in trifluoroacetic acid at 55 °C in the presence of an appropriate amount of ammonium cerium(IV) nitrate (**1**) afforded 3-isovaleryl-5-isobutyl-2-isoxazoline (**3**) together with 4-methyl-1-nitro-1-pentene (**4**) and 4-methyl-1-nitro-2-pentanol (**5**) as side products. The structure of the product **3** was identified by

CCC 0268–2605/95/050399–13

Received 8 July 1994
Accepted 11 August 1994



[1]



[2]

1 : $Ce(NO_3)_4{\cdot}2NH_4NO_3$, 2 : $Ce(NO_3)_3{\cdot}2NH_4NO_3{\cdot}4H_2O$

^{1}H NMR, ^{13}C NMR, mass and IR spectroscopies, elemental analyses, and chemical conversion methods: ketalization of **3** gave 3-[(*E*)-3-methyl-1-methoxy-1-butenyl]-5-isobutyl-2-isoxazoline (**6**) and 3-[(*Z*)-3-methyl-1-methoxy-1-butenyl]-5-isobutyl-2-isoxazoline (**7**). The structures of **6** and **7** were confirmed by ^{1}H NMR and GC–MS spectroscopies. The formation of **6** and **7** may suggest the intermediacy of the ketal of **3**.

Comparison of ^{1}H NMR, ^{13}C NMR, and IR spectra of **3** and 2-isovaleryl-4-isobutyloxazoline (**8**) (provided by S. Oka), the corresponding oxazoline derivative, revealed that the ring structure of **3** is not oxazoline, but isoxazoline.

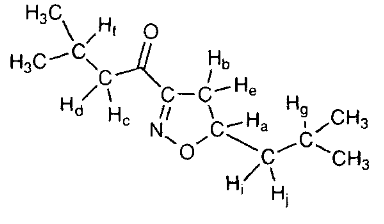
Effect of the solvent medium

The effect of solvent on the yields of products from the present reaction was examined by using 1-hexene as an alkene, and it was found that trifluoroacetic acid only was effective. No reaction took place in acetonitrile, water, acetic acid or tetrahydrofuran. The observation suggests a crucial role of the acid for facilitating a smooth reaction. Thus, the author decided to test the effectiveness of the acetonitrile/carboxylic acid (e.g. formic acid, acetic acid) system as the reaction medium. The results were, however, unsatisfactory and the expected 3-valeryl-5-butyl-2-isoxazoline (**9**) was not detected in the reaction mixture. Instead, 1-nitro-1-hexene (**10**) and 1-nitro-2-hexanol (**11**) were obtained in 6% and 1% yields, respectively.

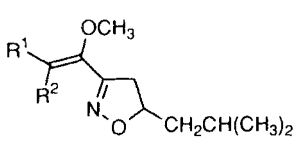
However, when a 0.25 equivalent amount of cyclohexanone, relative to **1**, was added to a reaction mixture in acetonitrile–formic acid, the yield of **9** increased to 19%. The results are summarized in Table 1 together with the results obtained from single-solvent systems in the presence of cyclohexanone.

It should be pointed out from Table 1 that there are two prominent features in the reaction. Firstly, this reaction requires a carboxylic acid of pK_a similar to that of formic acid or less. The second feature is that an additive is required to make the reactions go smoothly.

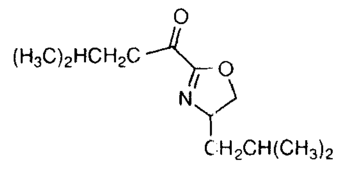
Several additives other than cyclohexanone were also examined. They were cyclopentanone, actylacetone, hexachloroacetone, 4-heptanone, dibutyl ether, tetra-hydrofuran, 1,4-hydroquinone, cumene, benzene, dibutyl sulfide, dimethyl sulfoxide and chloroform. Although all carbonyl compounds except hexachloroacetone exerted comparable results with that of cyclohexanone, others were ineffective (although hydroquinone is effective, it is thought that it is firstly oxidized to the corresponding carbonyl compound). Thus, carbonyl compounds having a certain basicity can promote the reaction. Hexachloroacetone, for example, does not promote the reaction to an appreciable extent. In addition, some metal powders can substitute for the carbonyl compound, provided they have a



3

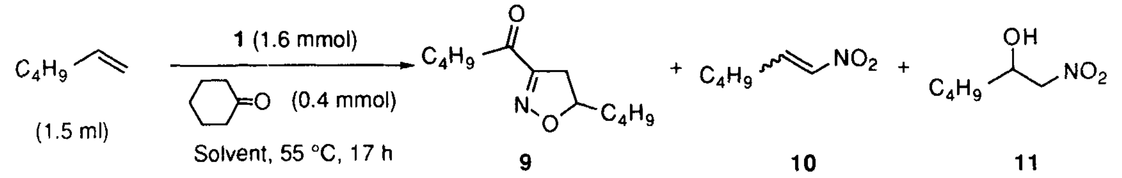


6 : $R^1 = (CH_3)_2CH$, $R^2 = H$
7 : $R^1 = H$, $R^2 = (CH_3)_2CH$



8

Table 1 Effect of the reaction medium in the reaction of 1-hexene with **1**



Solvent (ml)	Yield (%)[a] 9	10	11
$CH_3CN(1.0)-HCOOH(0.5)$[b]	0	6	1
$CH_3CN(1.0)-HCOOH(0.5)$	19	32	157
$CH_3CN(0.5)-HCOOH(1.0)$	13	8	20
$CH_3CN(1.0)-CH_3COOH(0.5)$	Trace	28	43
$CH_3CN(0.5)-CH_3COOH(1.0)$	4	8	16
$CH_3CN(1.0)-CH_3COOH(0.5)-H_2O(0.5)$	Trace	9	25
$CH_3CN(1.0)-(CH_3CO)_2O(0.5)$	Trace	19	32
$CH_3CN(0.5)-CF_3COOH(1.0)$	16	76	92
$CF_3COOH(1.5)$	16	58	39
$CH_3CN(1.0)-H_2O(0.5)$	Trace	17	26
$CH_3CN(1.0)$	Trace	18	22
1-Hexene(1.5)	0	3	3
DMSO(1.5)	0	1	1
$CH_3OH(1.5)$	0	Trace	Trace
HCOOH(1.5)	2	7	16

[a] The yields are based on the amount of **1** used. [b] Cyclohexanone is not present.

certain reduction potential. The effects of metal powders on the yield of product from the reaction of 1-octene with **1** are listed in Table 2.

The results from the reactions in the presence of cyclohexanone and without an additive are also listed in Table 2 as references. When nickel, silver, zinc or manganese was used as an additive, 3-heptanoyl-5-hexyl-2-isoxazoline (**12**) was obtained in 31–39% yields. Among these additives, nickel powder gave the best result, because it inhibits the formation of 1-nitro-2-octanol (**13**), giving the highest **12**/(**13**+**14**) ratio of 1.16.

Thus, the author has succeeded in preparing isoxazoline derivatives as major products directly from alkenes and **1**. However, the yields of products are still unsatisfactory, and closer investigation is required in order to improve the yield.

Characterization of the cerium compound formed after the reaction

The reaction of **1** with 1-hexene in acetonitrile–formic acid affords a precipitate, and it was found, by visual inspection, that practically no Ce(IV) ion was present in the precipitate. The result means that almost all cerium species present in the precipitate are cerium(III) ions. On the other hand, both wet and dry analysis methods showed the content of cerium element to be 41.5%. Furthermore, the X-ray diffraction pattern of an authentic sample of cerium(III) formate was the same as that of the precipitate. The result suggests that the precipitate contains the $Ce(HCOO)_3$ moiety.

All these results and elemental analyses of other elements revealed that the precipitate has an empirical formula of $Ce(HCOO)_3 \cdot 0.5NH_4NO_3 \cdot H_2O$.

Reactions of formic acid with ammonium cerium(IV) and cerium(III) nitrates

It has been confirmed that nitrate anions, the original ligands on the cerium atom, are replaced by formate anions during the reaction of **1** with an alkene under various conditions to give Ce(III) formate.

In order to discuss the subject in further detail, **1** and **2** were reacted with formic acid independently under various conditions. The results summarized in Table 3 reveal some interesting facts:

formic acid does not react with **1** even at 100 °C, and the presence of acetonitrile as a solvent does not assist the reaction. On the contrary, **2** reacts with formic acid slowly at 25 °C or higher temperatures without a solvent, and the reaction becomes vigorous at 55–57 °C to evolve NO_2 gas. In acetonitrile, the reaction proceeds mildly and the evolution of NO_2 gas is slow even at 56 °C. It seems probable that the central Ce(IV) ion in **1** in a nonaqueous medium is covered by coordinating nitrate anions and is protected from attack by formic acid.[6] Consequently no ligand exchange takes place. This result can explain the function of the aforementioned additives as well. It is obvious that **1** can react with formic acid after it is reduced to **2** by certain carbonyl compounds or metal powders. In other words, the ligand exchange essential to the isoxazoline synthesis occurs only after the reduction of Ce(IV) to Ce(III).

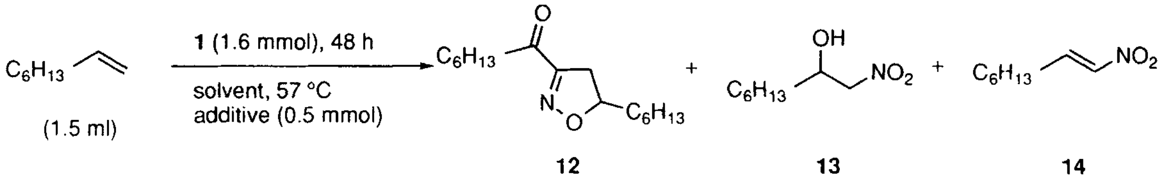
Reaction of nitro compound with alkene

The fact that **3**, prepared from 4-methyl-1-pentene and **1**, has a carbonyl group in the molecule suggests that the reaction proceeds with one molecule of primary *α*-nitro ketone and one molecule of an alkene. It has also been elucidated that **2** is effective as a promoter of the reaction.

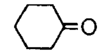
It is interesting to know whether the *gem*-nitro carbonyl moiety in the nitro compound is essential for the reaction or not. The reaction system composed of a certain nitro compound, allyl cyanide, **2**, and iso-octane (solvent) was chosen to elucidate the functional requirement. Two groups of nitro compounds were employed for this purpose. One consisted of nitro compounds that have various electron-donating or -withdrawing properties, and the other consisted of those that are assumed to be the intermediates of the reaction. Allyl cyanide and iso-octane were employed as an alkene and a solvent, respectively, because undesirable side reactions are prohibited with the combination of this reagent and solvent. The use of **2** in place of **1** has an advantage in that the reaction becomes simpler with **2** than with **1** because the former has no oxidizing ability, which the latter has. The results are summarized in Table 4.

The nitro compounds can be classified into three categories by their reactivities. The reaction proceeds easily with compounds that belong to the first class. Compounds that possess a carbonyl group *α* to the reaction center exert the highest reactivity. However, the presence of such a structure is not always essential for the reaction. For example, the reaction with cyanonitromethane afforded 3-cyano-5-cyanomethyl-2-isoxazoline (**17**) in 74% yield. It is concluded that the nitro

Table 2 Effect of metal powder in the reaction of 1-octene with **1**



solvent : $CH_3CN/HCOOH$ (1.0 ml / 0.5 ml)

Additive	Yield (%)[a] 12	13	14	$\frac{12}{13+14}$
—	0	1	6	0
	19	98	42	0.14
Ni	37	9	23	1.16
Ag	39	25	20	0.87
Zn	34	26	21	0.73
Mn	31	25	23	0.65
Pb	17	45	41	0.20
Nb	16	79	77	0.10

[a] Yield based on amount of **1** used.

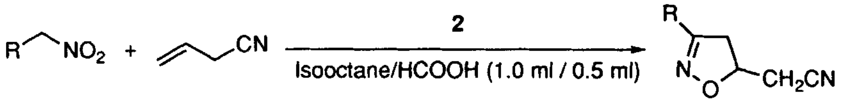
Table 3 Reaction of cerium compounds with formic acid

99% HCOOH (ml)	CH_3CN (ml)	$Ce(NO_3)_4 \cdot 2NH_4NO_3$ (g)	$Ce(NO_3)_3 \cdot 2NH_4NO_3 \cdot 4H_2O$ (g)	Result
6.0	0	10.5	0	No reaction at 100 °C
6.0	12.0	10.5	0	No reaction at 100 °C Slow reaction at 25 °C
3.0	0	0	5.2	Vigorous reaction at 56 °C NO_2 gas evolution
3.0	6.0	0	5.2	Slow reaction at 56 °C NO_2 gas evolution

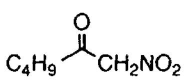
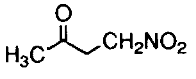
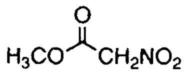
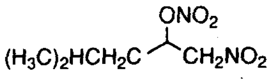
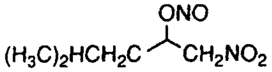
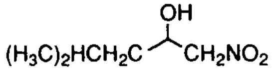
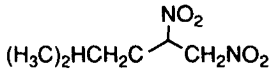
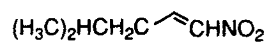
compounds that have a strong electron-withdrawing substituent are favorable to the present reaction.

Nitro compounds of very low reactivity belong to the second class. Among the compounds examined, chloronitromethane, bromonitromethane, and nitropropane belong to this class. The reaction of bromonitromethane with allyl cyanide gave 3-bromo-5-cyanomethyl-2-isoxazoline (**18**) in 27% yield, in contrast to yields of less than 5% from chloronitromethane and nitropropane. It was unexpected that the reactions of these three nitro compounds with allyl cyanide afforded **17** besides the normal product—especially in the reactions of chloronitromethane and nitropropane, where **17** becomes the major product. The structure of **17** was confirmed by GC–MS and ^1H NMR spectra from comparison with those of an authentic sample obtained from the reaction of cyanonitromethane with allyl cyanide under the

Table 4 The reaction of nitro compounds with allyl cyanide in the presence of **2**

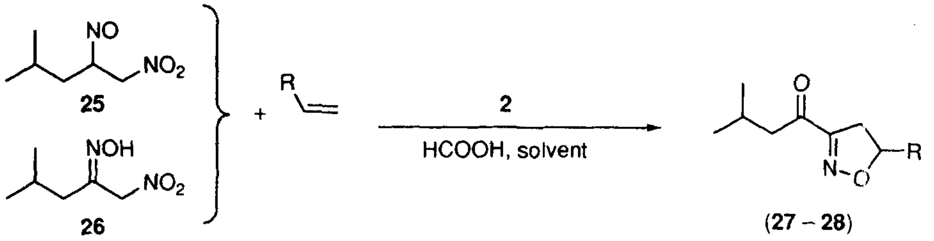


(15 – 20)

Substrate	Product	Yield (%)[a]	Substrate	Product (%)	Yield (%)
 $C_4H_9COCH_2NO_2$	**15**	100	 $H_3CCOCH_2NO_2$	**(21)**	0
 $H_3COCOCH_2NO_2$	**16**	100	 $(H_3C)_2HCH_2C(ONO_2)CH_2NO_2$	**(22)**	0
$NCCH_2NO_2$	**17**	74	 $(H_3C)_2HCH_2C(ONO)CH_2NO_2$	**(23)**	0
$BrCH_2NO_2$	**18**	27[b]	 $(H_3C)_2HCH_2C(OH)CH_2NO_2$	**(5)**	0
$ClCH_2NO_2$	**19**	<5[c]	 $(H_3C)_2HCH_2C(NO_2)CH_2NO_2$	**(24)**	0
$C_2H_5CH_2NO_2$	**20**	<5[c]	 $(H_3C)_2HCH_2C{=}CHNO_2$	**(4)**	0

[a] The yields are based on amount of cerium compound used. [b] 3-Cyano 5-cyanomethyl 2-isoxazoline was obtained as a by-product. [c] 3-Cyano 5-cyanomethyl 2-isoxazoline was major component of the mixture of products.

Table 5 Reaction of **25** and **26** with alkenes



2: 1.0 mmol; alkene: 0.94 ml (excess); solvent: 0.63 ml; HCOOH: 0.32 ml; temp: 58 °C; time: 48 h

25 (mmol)	**26** (mmol)	R	Solvent	Product	Yield (%)
1.0	0	CH_2CN	CH_3CN	**27**	25
1.0	0	C_6H_{13}	CH_3CN	**28**	28
0	1.0	CH_2CN	CH_3CN	**27**	28
0	1.0	C_6H_{13}	CH_3CN	**28**	23
1.0	0	CH_2CN	Iso-octane	**27**	26
1.0	0	CH_2CN	Iso-octane	**27**	24[a]

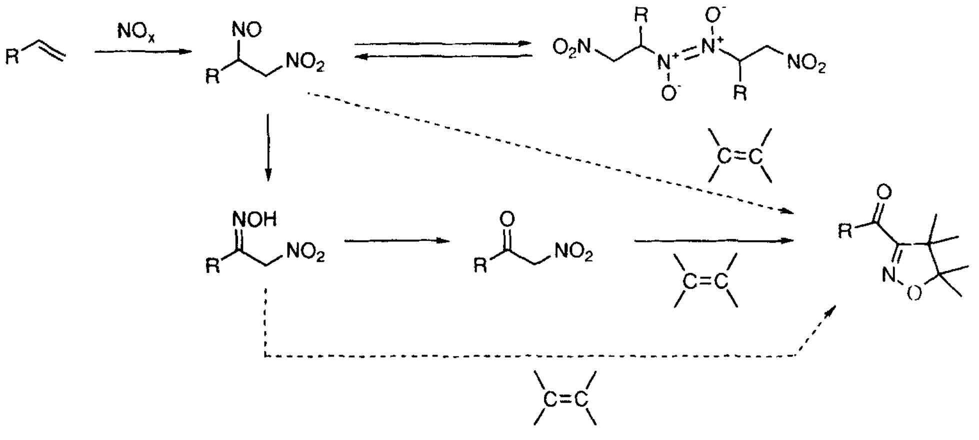
[a] At 80 °C.

same conditions.

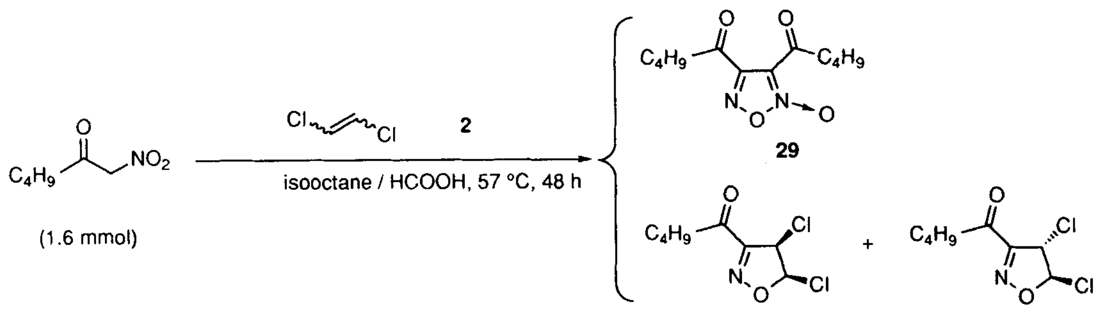
4-Nitro-2-butanone (**21**), 4-methyl-1-nitro-2-pentyl nitrate (**22**), 4-methyl-1-nitro-2-pentyl nitrite (**23**), 1,2-dinitro-4-methylpentane (**24**), **4** and **5** are included in the third class. All these compounds are inactive under the conditions employed. The result proves that these compounds cannot be intermediates in the direct synthesis of 2-isoxazolines from the corresponding alkene and ammonium cerium nitrate; the reaction proceeds by not only **1** but by **2** as well.

Contrary to the above results, both 4-methyl-1-nitro-2-nitrosopentane (**25**) and 4-methyl-1-nitro-2-pentanone oxime (**26**) react with allyl cyanide and 1-octene to give 3-isovaleryl-5-cyanomethyl-2-isoxazoline (**27**) and 3-isovaleryl-5-hexyl-2-isoxazoline (**28**), respectively. The results are summarized in Table 5

In both cases, although yields are moderate, the results suggest that the alkene reacts with NO_x arising from **1** to give either or both of nitro compounds, **25** and **26**, then these intermediates react with an alkene to give the corresponding isoxazoline derivatives as shown in Scheme 1.



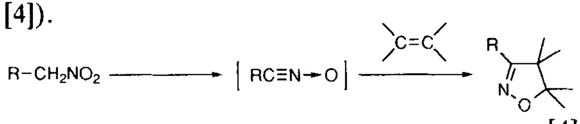
Scheme 1



[3]

Formation of furoxan

It is well-known that nitrile oxides dimerize to furoxans.[7] Therefore, if a furoxan is detected in the present reaction, it may prove the intermediacy of a nitrile oxide. Indeed, 3,4-divaleryl-1,2,5-oxadiazole 2-oxide (**29**) (furoxan) was detected as major and minor product, respectively, from the reactions in the presence of (*Z*)- and (*E*)-1,2-dichloroethylenes (Eqn [3]). The result reveals that 1-nitro-2-hexanone is converted into the corresponding nitrile oxide with the aid of **2**, which undergoes competitive dimerization and 1,3-cycloaddition to the alkene (Eqn [4]).



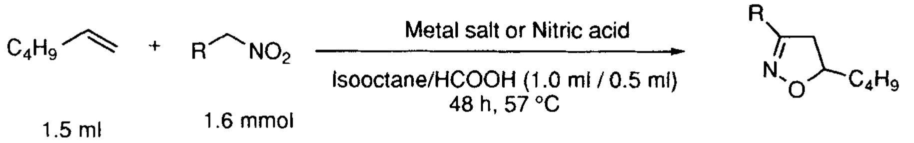
[4]

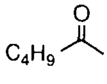
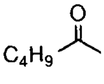
Effects of metal and ligand

The effects of metal ion and ligand on the yield of product were examined and compared with the effects of **2**. The stoichiometry of the nitrate anion was normalized to that of **2**. The results are summarized in Table 6

Several interesting points are evident from Table 6. Although the reaction also proceeded in the presence of iron(III) and copper(II) nitrates, the yields were 54% and 50%, respectively. The yield of isoxazoline was 63% with cerium(III) nitrate, $Ce(NO_3)_3 \cdot 6H_2O$. On the other hand, in the cases of cerium(III) chloride, cerium(IV) fluoride, and iron(II) sulfate, where nitrate anion is absent, the yields were less than 7%. The results suggest that nitrate anion plays an important role in this reaction. Despite the presence of nitrate anion, the yield was only 11% with lithium

Table 6 Effect of metals and ligands in metal salts and nitric acid



R	Metal mediator (mmol)	Yield (%)	R	Metal mediator (mmol)	Yield (%)
	$Ce(NO_3)_3 \cdot 2NH_4NO_3 \cdot 4H_2O$ (1.6)[b]	0		$FeSO_4 \cdot 7H_2O$ (1.6)	5
	$Ce(NO_3)_3 \cdot 2NH_4NO_3 \cdot 4H_2O$ (1.6)	100		94% HNO_3 (8.0)	48
	$Ce(NO_3)_3 \cdot 6H_2O$ (2.7)	63		94% HNO_3 (8.0)[b]	43
	$Cu(NO_3)_3 \cdot H_2O$ (4.0)	52		94% HNO_3 (8.0)[c]	23
	$Fe(NO_3)_3 \cdot 9H_2O$ (2.7)	54		94% HNO_3 (16.0)	15
	$LiNO_3$ (8.0)	11		94% HNO_3 (8.0) + $Ce(O_2CH)_3 \cdot H_2O$ (1.6)	80
	$LiNO_3$ (8.0) + $CeCl_3$ (1.6)	64	NC—	$Ce(NO_3)_3 \cdot 2NH_4NO_3 \cdot 4H_2O$ (1.6)[c]	74
	$CeF_4 \cdot H_2O$ (1.6)	4		94% HNO_3 (8.0)[c]	14
	$CeCl_3 \cdot 7H_2O$ (1.6)	7			

[a] Yields are based on the amount of metal compound used. [b] Without HCOOH. [c] At 80 °C.

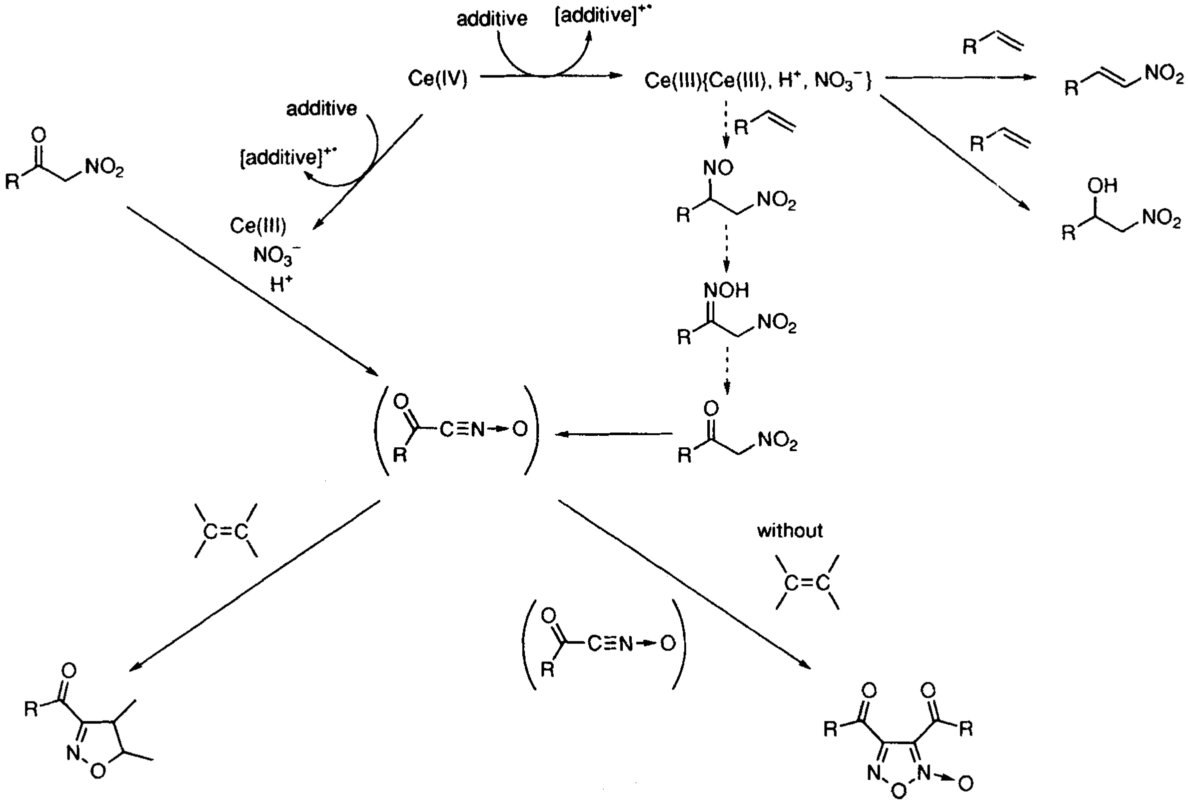
nitrate. However, coexistence of cerium(III) chloride with lithium nitrate increased the yield to 65%. It is thus apparent that the metal cation, besides the nitrate anion, also exerts an effect on the reaction. The metal cation and nitrate anion may have independent functions. Although closer investigation is required to understand the mechanism, the oxophilicity and large coordination number of the cerium metal appear to play crucial roles in the reaction.

Results from the reaction in the presence of nitric acid are worthy of mention. The reaction proceeded in the presence of 94% nitric acid, but the yield of product did not exceed 50%. The absence of formic acid does not affect the yield under the coexistence of nitric acid, in contrast to the reaction with ammonium cerium nitrate. Optimum conditions for the reaction with nitric acid, however, do not always coincide with those for the ammonium cerium nitrate system. In the case of nitric acid, elevated reaction temperatures (57–80 °C) and the use of a large excess of nitric acid are not favorable for the reaction. In the reaction with excess nitric acid at lower temperatures, the α-nitro ketone was consumed despite the yield of isoxazoline being kept as low as 7%. Coexistence of cerium(III) formate monohydrate affects the reaction promoted by nitric acid and the yield of product is improved dramatically. The results again support the idea that both nitrate anion and cerium metal act independently and cooperatively.

Summarized reaction scheme

The present reactions may be summarized as depicted in Scheme 2.

The author proposes that NO_x generated from nitrate anion acts as a source of the nitro group and an activator, and metal acts as an activator by chelation. Ammonium cerium nitrate is one of the best reagents to satisfy both requirements effectively. However, **1** cannot react with formate anion owing to its sterically hindered structure, and it must be converted into **2** before the ligand is exchanged for the formate. Therefore, certain carbonyl compounds or metal powder are necessary for the reaction to proceed smoothly when **1** is employed as one of the reagents.



Scheme 2

Studies on the stereochemistry of the reaction are in progress.

EXPERIMENTAL

Instruments

The ^1H and ^{13}C NMR spectra were recorded on Varian VXR-200 and JEOL JNM-GX400 spectrometers for $CDCl_3$ solutions. Mass spectra were recorded on GC-MS, Finigan-Mat ITD-800 ion trap detector. IR spectra were recorded on a Hitachi Model 260-50 grating spectrophotometer for pure liquid films or KBr pellets. X-ray diffraction spectra were obtained with a Shimadzu X-ray diffraction appratus XD 3A. GLC analyses were performed on a Shimadzu GC-14A gas chromatograph using 25 m × 0.25 mm i.d. PEG 20M and 25 m × 0.25 mm i.d. OV 1701 bonded capillary columns. Merck precoated silica gel sheets 60F-254 were used for TLC. Silica gel column chromatography was performed with Silica Gel 60 (70-230 mesh, Nacalai Tesque Inc.) with eluents of hexane–dichloromethane mixtures (10–1 : 1).

Products were identified by ^1H NMR, ^{13}C NMR, IR and MS spectra as well as elemental analyses, by direct comparison with those of the corresponding authentic specimens, if necessary.

Reagents

Ammonium cerium(IV) nitrate (**1**) and cerium(III) formate monohydrate were provided by SEIMI Chemical Co. Ltd. The former was used after drying at 80 °C for 2 h. 2-Isovaleryl-4-isobutyloxazoline (**8**) was provided by Professor Emeritus Oka.

β-Nitroalcohols (**5**, **11** and **13**) were prepared from nitromethane and the corresponding aldehydes according to the Henry method.[8] α-Nitroalkenes (**4**, **10** and **14**) were obtained from the corresponding β-nitro alcohols.[9] Cyanonitromethane was prepared by the procedure reported by Ried and Köhler using methagonic acid and thionyl chloride in ethyl ether.[10]

Chloronitromethane was prepared by the procedure reported by Heasley *et al.*[11] 4-Nitro-2-butanone (**21**) was prepared according to the literature procedure.[12] 4-Methyl-1-nitro-2-pentylnitrate (**22**) and 1,2-dinitro-4-methyl-pentene (**24**) were prepared by addition of dinitrogen tetraoxide to 4-methyl-1-pentene in ether saturated with oxygen according to Levy and Scaife's method.[13] 4-Methyl-1-nitro-2-pentyl nitrite (**23**) was prepared from 4-methyl-1-nitro-2-pentanol (**5**) and sodium nitrite in the usual way. 4-Methyl-1-nitro-2-nitrosopentane (**25**), which seems to exist in dimer form, and 4-methyl-1-nitro-2-pentanone oxime (**26**) were prepared by the procedure reported by Klamann *et al.*[14]

Each compound gave satisfactory results in ^1H NMR, mass and IR spectra. Other chemicals were obtained from commercial sources (Nacalai Tesque Inc., Wako Pure Chemical Industries Ltd, and Aldrich Chemical Co.) and were used after purification, if necessary.

Preparation of 1-nitro-2-hexanone

Into a mixture of **11** (12.9 mmol), tetrabutylammonium hydrogen sulfate (0.9 mmol), and dichloromethane (300 ml) cooled to −10 °C, were added 30% sulfuric acid (150 ml) and potassium dichromate (11.6 mmol). After stirring for 2 h at −10 °C, another portion of potassium dichromate (3.4 mmol) was added to the mixture, and the mixture was stirred for 1 h at −10 °C. The mixture was raised to room temperature, and after stirring for an additional 1 h, 100 ml of 10% aqueous iron(II) sulfate was added to the mixture. The reaction mixture was worked up by the usual method, then the crude 1-nitro-2-hexanone obtained was purified immediately by chromatography over Florisil (eluent: CH_2Cl_2); this procedure is important because the crude product is decomposed quickly by some unidentified impurities. The product was distilled for further purification: bp 80–82 °C (0.1 mmHg); yield 72%. ^1H NMR ($CDCl_3$): δ 0.90 (t, $J = 6.8$ Hz, 3H, CH_3), 1.08–1.80 (m, 4H, $2CH_2$), 2.54 (t, $J = 8.5$ Hz, 2H, CH_2), 5.26 (s, 2H, CH_2). GC–MS (CI): m/z 146 ($M + 1$, 7.23), 130 (25.0), 114 (17.8), 874 (16.4), 86 (16.4), 86 (47.0), 85 (100.0), 84 (21.1), 83 (14.3), 82 (11.8).

Reaction of 1 with 4-methyl-1-pentene in trifluoroacetic acid

A mixture of **1** (9.6 mmol), 4-methyl-1-pentene (9.0 ml), and trifluoroacetic acid (9.0 ml) was stirred for 17 h at 55 °C and the mixture was poured into 20 ml of water. Organic materials were extracted with dichloromethane (3 × 20 ml). The combined dichloromethane layer was washed with water, neutralized with sodium hydrogencarbonate, and dried over anhydrous sodium sulfate. The dichloromethane was removed from the solution at 50 °C under reduced pressure. The residue was subjected to column chromatography to obtain **3**, **4** and **5**.

3: ^{13}C NMR ($CDCl_3$): δ 22.289 (CH_3), 22.582 ($2CH_3$), 22.757 (CH_3), 25.079 (CH), 25.214 (CH), 37.558 (CH_2), 44.345 (CH_2), 47.855 (CH_2), 83.074 (CH), 158.133 (C=N), 195.633 (C=O). ^{1}H NMR ($CDCl_3$): δ 0.944–1.017 (3d, 12H, $4CH_3$) (the signals at δ 0.944–1.017 consist of three doublets, but the chemical shift of each peak is too close to evaluate the coupling constant), 1.412 (m, H_i or H_j), 1.709 (m, H_j or H_i), 1.809 (m, H_g), 2.292 (m, H_f), 2.723 (dd, $J = 17.1$ Hz, $J = 8.8$ Hz, H_e or H_b), 2.763 (d, $J = 7.3$ Hz, H_c and H_d), 3.187 (dd, $J = 17.1$ Hz, $J = 10.8$ Hz, H_e or H_b), 4.818 (m, H_a). Signals were assigned on the basis of the spin-decoupling method. GC-MS: *m/z* 211 (M^+, 24.9), 169 (10.7), 154 (7.5), 141 (5.7), 126 (16.4), 112 (8.8), 110 (7.3), 101 (5.5), 85 (38.5), 70 (15.7), 69 (13.2), 57 (100), 55 (11.1). IR: (ν_{max}, cm^{-1}): 1680 (C=O), 1575 (C=N). Analysis: calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02%; N, 6.63%. Found: C, 67.81; H, 10.05; N, 6.54%.

8, for comparison: ^{13}C NMR ($CDCl_3$): δ 22.055 (CH_3), 22.406 (CH_3), 22.640 (CH_3), 22.991 (CH_3), 23.986 (CH), 26.267 (CH), 41.361 (CH_2), 42.941 (CH_2), 56.652 (CH_2), 75.995 (CH), 156.553 (C=N), 163.164 (C=O). ^{1}H NMR ($CDCl_3$): δ 0.937 (d, $J = 6.8$ Hz, 3H, CH_3), 0.954 (d, $J = 6.8$ Hz, 3H, CH_3), 0.966 (d, $J = 6.8$ Hz, 3H, CH_3), 0.968 (d, $J = 6.8$ Hz, 3H, CH_3), 1.365–1.480 (m, 1H, CH_2), 1.674–1.740 (m, 1H, CH_2), 1.857–1.958 (m, 1H, CH), 2.195 (hept, $J = 7.5$ Hz, 1H, CH), 2.393–2.451 (m, 1H, CH_2), 2.580–2.645 (m, 1H, CH_2), 3.390–3.470 (m, 1H, CH_2), 3.935 (dd, $J = 16.8$ Hz, $J = 2.4$ Hz, 1H, CH_2), 4.404–4.472 (m, 1H, CH). GC-MS: *m/z* 211 (M^+, 7.2), 169 (10.7), 126 (16.1), 110 (6.5), 84 (100.0), 69 (23.9), 56 (26.3), 55 (37.6), and 54 (23.3). IR: (ν_{max}; cm^{-1}): 1730 (C=O), 1635 (C=N).

Ketalization of **3** was performed in the usual way. A mixture of **3**, methanol and p-toluenesulfonic acid was refluxed for 3 h. Separation and purification of the products with column chromtography afforded **6** and **7**.

6 (or **7**): ^{1}H NMR ($CDCl_3$): δ 0.951 (t, $J = 5.6$ Hz, 6H, $2CH_3$), 1.015 (d, $J = 13.2$ Hz, 3H, CH_3), 1.021 (d, $j = 13.2$ Hz, 3H, CH_3), 1.342–1.410 (m, 1H, CH_2), 1.661–1.711 (m, 1H, CH_2), 1.753–1.854 (m, 1H, CH), 2.729 (dd, $J = 17.1$ Hz, $J = 8.8$ Hz, 1H, CH_2), 2.999–3.064 (m, 1H, CH), 3.176 (dd, $J = 17.1$ Hz, $J = 10.0$ Hz, 1H, CH_2), 3.527 (s, 3H, OCH_3), 4.583–4.660 (m, 1H, CH), 4.726 (d, $J = 9.3$ Hz, 1H, CH).

6 (or **7**): GC-MS: *m/z* 225 (M^+, 55.0), 210 (37.0), 168 (25.7), 154 (27.5), 126 (21.4), 125 (30.4), 124 (77.4), 110 (24.2), 108 (33.0), 83 (59.0), 69 (49.4).

7 (or **6**): ^{1}H NMR ($CDCl_3$): δ 0.958 (t, $J = 7.3$ Hz, 6H, $2CH_3$), 1.026 (d, $J = 6.8$ Hz, 6H, $2CH_3$), 1.370–1.418 (m, 1H, CH_2), 1.679–1.749 (m, 1H, CH_2), 1.770–1.854 (m, 1H, CH_2) 2.655 (dd, $J = 16.1$ Hz, $J = 8.8$ Hz, 1H, CH_2), 2.886–2.990 (m, 1H, CH), 3.108 (dd, $J = 16.1$ Hz, $J = 10.3$ Hz, 1H, CH_2), 3.730 (s, 3H, OCH_3), 4.620–4.701 (m, 1H, CH), 5.099 (d, $J = 9.3$ Hz, 1H, CH).

7 (or **6**): GC-MS: *m/z* 225 (M^+, 43.9), 210 (33.0), 168 (22.4), 154 (24.5), 126 (19.5), 125 (25.1), 124 (66.7), 110 (19.6), 108 (26.9), 83 (47.5), 69 (49.5).

Reaction of 1 with 1-hexene in acetonitrile–formic acid mixture

Into a mixture of **1** (1.60 mmol), cyclohexanone (0.4 mmol), acetonitrile (1.0 ml), and 1-hexene (1.5 ml), was added 0.5 ml of formic acid. The mixture was stirred for 17 h at 55 °C. The reaction mixture was worked up in the same manner as described above for the reaction of **1** with 4-methyl-1-pentene in trifluoroacetic acid to afford **9**, **10** and **11**.

9: ^{13}C NMR ($CDCl_3$): δ 13.865 ($2CH_3$), 22.465 ($2CH_3$), 26.209 (CH_2), 27.379 (CH_2), 34.926 (CH_2), 37.032 (CH_2), 38.904 (CH_2), 84.478 (CH), 157.840 (C=N), 196.218 (C=O). ^{1}H NMR ($CDCl_3$): δ 0.921 (t, $J = 7.3$ Hz, 6H, $2CH_3$), 1.313–1.450 (m, 6H, $3CH_2$), 1.543–1.794 (m, 4H, $2CH_2$), 2.757 (dd, $J = 17.6$ Hz, $J = 8.8$ Hz, 1H, CH_2), 2.884 (t, $J = 7.3$ Hz, 2H, CH_2), 3.156 (dd, $J = 17.6$ Hz, $J = 10.7$ Hz, 1H, CH_2), 4.716–4.796 (m, 1H, CH). GC-MS: *m/z* 211 (M^+, 33.2), 169 (9.3), 154 (20.2), 126 (17.4), 112 (37.3), 85 (48.4), 70 (11.1), 57 (100.0). *IR*: (ν_{max}, cm^{-1}): 1690 (C=O), 1570 (C=N). Analysis: calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63%. Found: C, 68.06; H, 10.10; N, 6.45%.

10 and **11**: ^{1}H NMR and IR spectra of **10** and **11** agreed completely with those of the corresponding authentic samples.

Reaction of 1 with 1-octene in the presence of metal powder

The reaction was run in the same manner as described above for the reaction of **1** with 1-hexene in the presence of cyclohexanone except that 0.5 mmol of metal powder was employed in place of 0.4 mmol of cyclohexanone. The corresponding isoxazoline derivative, **12**, was obtained together with **13** and **14**.

12: ^{1}H NMR ($CDCl_3$): δ 0.881 (t, $J=6.8$ Hz, 3H, CH_3), 0.885 (t, $J=6.8$ Hz, 3H, CH_3), 1.186–1.463 (m, 14H, $7CH_2$), 1.537–1.775 (m, 4H, $2CH_2$), 2.754 (dd, $J=17.6$ Hz, $J=8.8$ Hz, 1H, CH_2), 2.878 (t, $J=7.3$ Hz, 2H, CH_2), 3.156 (dd, $J=17.6$ Hz, $J=10.7$ Hz, 1H, CH_2), 4.716–4.796 (m, 1H, CH). GC–MS: m/z 267 (M^+, 17.1), 182 (6.5), 154 (8.9), 113 (15.4), 98 (4.9), 85 (10.6), 69 (6.5), 55 (30.4), 43 (100.0).

13 and **14**: ^{1}H NMR and IR spectra of **13** and **14** agreed with those of the corresponding authentic samples.

Reaction of nitroalkane with allyl cyanide in the presence of 2

Into a mixture of nitroalkane (1.60 mmol), allyl cyanide (1.5 ml), **2** (1.92 mmol), and iso-octane (1.0 ml), 0.5 ml of formic acid was added. Other reaction conditions and work-up methods were the same as those described above. The product corresponding to each nitroalkane was obtained.

15 from 1-nitro-2-hexanone: ^{1}H NMR ($CDCl_3$): δ 0.926 (t, $J=7.3$ Hz, 3H, CH_3), 1.365 (hexa, $J=7.3$ Hz, 2H, CH_2), 1.643 (q, $J=7.3$ Hz, 2H, CH_2), 2.771 (*t*, $J=5.9$ Hz, 2H, CH_2), 2.896 (t, $J=7.3$ Hz, 2H, CH_2), 3.058 (dd, $J=18.1$ Hz, $J=7.1$ Hz, 1H, CH_2), 3.389 (dd, $J=18.1$ Hz, $J=10.7$ Hz, 1H, CH_2), 5.004–5.076 (m, 1H, CH). IR: (ν_{max}, cm^{-1}): 1690 ($C{=}O$), 1580 ($C{=}N$), 2250 ($C{\equiv}N$).

16 from methyl nitroacetate: ^{1}H NMR ($CDCl_3$): δ 2.743 (d, $J=5.6$ Hz, 2H, CH_2), 3.079 (dd, $J=18.2$ Hz, $J=7.2$ Hz, 1H, CH_2), 3.436 (dd, $J=18.2$ Hz, $J=10.8$ Hz, 1H, CH_2), 3.870 (s, 3H, OCH_3), 4.970–5.125 (m, 1H, CH). GC–MS: m/z 168 (M^+, 8.6), 137 (12.5), 128 (19.6), 70 (7.4), 59 (100.0), 56 (10.0).

17 from cyanonitromethane: ^{1}H NMR ($CDCl_3$): δ 2.800 (d, $J=7.5$ Hz, 2H, CH_2), 3.114 (dd, $J=17.3$ Hz, $J=7.7$ Hz, 1H, CH_2), 3.476 (dd, $J=17.3$ Hz, $J=10.9$ Hz, 1H, CH_2), 5.067–5.211 (m, 1H, CH). GC–MS: m/z 135 (M^+, 21.8), 95 (100.0), 78 (8.1), 67 (41.3), 52 (11.7), 51 (10.1).

18 from bromonitromethane: GC–MS: m/z 190 (M^+, ^{81}Br, 15.0), 188 (M^+, ^{79}Br, 16.1), 150 (98.1), 148 (100.0).

19 from chloronitromethane: GC–MS: m/z 146 (M^+, ^{37}Cl, 8.7), 144 (M^+, ^{35}Cl, 29.3), 106 (34.2), 104 (100.0), 78 (9.9), 76 (29.7).

20 from nitropropane: GC–MS: m/z 138 (M^+, 38.3), 98 (10.1), 70 (100.0), 68 (17.7), 55 (6.1), 54 (7.9), 53 (10.1).

The same reactions were run with metal salts as catalysts. The results are summarized in Table 6. The stoichiometry of the nitrate anion was normalized to that of **2**.

Reaction of 25 or 26 with an alkene

Into a mixture of a reagent (**25** or **26**, 1.0 mmol), **2** (1.0 mmol), an alkene (allyl cyanide or 1-octene, 0.94 ml) and a solvent (CH_3CN or iso-octane, 0.63 ml), 0.32 ml of formic acid was added. Other reaction conditions and work-up methods were the same as those described above. The corresponding isoxazoline derivative (**27** or **28**) was afforded (Table 5).

27: GC–MS: m/z 194 (M^+, 3.4), 152 (44.0), 137 (30.0), 126 (17.4), 124 (60.9), 97 (12.6), 83 (18.8), 70 (43.0), 57 (56.0).

28: GC–MS: m/z 239 (M^+, 16.1), 154 (6.6), 126 (11.4), 112 (15.3), 95 (8.0), 85 (52.5), 57 (100.0).

Reaction of 1-nitro-2-hexanone with (*E*) and (*Z*)-1,2-dichloroethylenes (formation of furoxan)

The reaction was run in the same manner as described above for the reaction of nitroalkane with allyl cyanide in the presence of **2**, except that (*E*) or (*Z*)-1,2-dichloroethylene was employed in place of allyl cyanide. The products afforded were

29, the corresponding isoxazoline derivatives and an unknown compound [in the case of (*Z*)-isomer]. In the absence of an alkene, **29**, was afforded as a sole product (54% yield).

The yields of the products were as follows: from the (*Z*)-isomer, **29** (32%), the corresponding isoxazoline derivative (2%), and an unknown compound as a major product; from the (*E*)-isomer, **29** (14%) and the corresponding isoxazoline derivative (42%).

29: ^{13}C NMR ($CDCl_3$): δ 13.705 ($2CH_3$), 21.963 (CH_2), 22.026 (CH_2), 24.877 (CH_2), 25.130 (CH_2), 40.716 (OCH_2), 41.139 (OCH_2), 111.499 (C═N), 153.788 (C═N), 188.440 (C═O), 191.655 (C═O). ^1H NMR ($CDCl_3$): δ 0.915 (t, $J = 7.2$ Hz, 3H, CH_3), 0.940 (t, $J = 7.0$ Hz, 3H, CH_3), 1.276–1.497 (m, 4H, $2CH_2$), 1.573–1.799 (m, 4H, $2CH_2$), 2.892 (t, $J = 8.3$ Hz, 2H, CH_2), 3.000 (t, $J = 8.5$ Hz, 2H, CH_2). IR: (ν_{max}, cm^{-1}): 1720 (C═O), 1710 (C═O), 1600 (C═N—O), 1475 ($=N^+—(O^-)—O$). Analysis: calcd for $C_{12}H_{18}N_2O_4$: C, 56.69; H, 7.09; N, 11.02. Found: C, 56.76; H, 7.23; N, 11.06%.

Analysis of Ce(IV) in the precipitate

The precipitate formed from the reaction of **1** with 1-hexene in the acetonitrile–formic acid system was filtered, washed with a small amount of dichloromethane and dried at 60 °C under reduced pressure. The precipitate (200 mg) was dissolved into 20 ml of conc. sulfuric acid–water (1/1, v/v) to prepare solution A. On the other hand, cerium(IV) nitrate (5.8 mg) was dissolved in 200 ml of conc. sulfuric acid–water (1/1, v/v) to make solution B. A comparison of each 20 ml of solutions A and B was performed by visual inspection. It was confirmed that solution A was colorless and clean, and solution B was pale yellow; the pale yellow color stems from solvated Ce(IV) ion. The content of cerium(IV) ion in the precipitate was thus calculated to be less than 0.10%.

Quantitative analyses of total cerium ion in the precipitate

Wet analysis

The precipitate (100 mg) was dissolved into 5 ml of conc. sulfuric acid–water (1/1, v/v), which was followed by dilution with water to 500 ml total volume. After a 100 ml aliquot was adjusted to pH 5.5–5.8 by addition of 5 g of hexamine, the solution was titrated with 0.01 M aqueous ethylenediaminetetra-acetic acid (EDTA) solution (indicator: xylenol orange). The total content of cerium ion in the precipitate was calculated to be 41.40%.

Dry combustion method

The precipitate (100 mg) was combusted for 1 h at 950 °C under atmospheric oxygen to obtain 51.0 mg of solid. The total content of cerium in the precipitate was calculated to be 41.52%, which is in excellent agreement with the value obtained from the wet method.

Analysis: calcd for $Ce(OOCH)_3 \cdot 0.5NH_4NO_3 \cdot H_2O$: C, 10.81; H, 2.12; N, 4.20%. Found: C, 11.22; H, 1.99; N, 4.89%.

Acknowledgement The author thanks Professor A. Ohno for useful discussions. He also thanks Mr S. Hiyama (SEIMI Chemical Co.) for providing ammonium cerium(IV) nitrate and cerium(III) formate monohydrate and Professor Emeritus S. Oka for providing 2-isovaleryl-4-isobutyloxazoline.

The present work was supported by a Grant-in-Aid for Scientific Research on Priority Areas 'New Development of Rare Earth Complexes' No. 06241242 from The Ministry of Education, Science and Culture, Japan.

REFERENCES

1. S. A. Lang, Jr and Y.-i. Lin, Isoxazoles and their benzo derivatives. In: *Comprehensive Heterocyclic Chemistry*, Potts, K. T. (ed.), Pergamon, Oxford, 1984, Vol. 6, Part 4B 4–16, pp. 127–130.
2. J. Shyhchen, V. A. Palaniswamy, P. Yorgey and S. J. Gould, *J. Am. Chem. Soc.* **108**, 6429 (1986); S. Mzengeza and R. A. Whitney, *J. Org. Chem.* **53**, 4074 (1988).
3. D. P. Curran, *J. Am. Chem. Soc.* **105**, 5826 (1983); S. Kanemasa and M. Nishiuchi, *Tetrahedron Lett.* **34**, 4011 (1993).
4. S. A. Lang, Jr and Y.-i. Lin, 'Isoxazoles and their benzo derivatives'. In: *Comprehensive Heterocyclic Chemistry*, Potts, K. T. (ed.), Pergamon, Oxford, 1984, Vol. 6, Part 4B 4–16, pp. 88–98.
5. T. Sugiyama, *Bull. Chem. Soc. Jpn* **54**, 2847 (1981); T. Sugiyama, *Chem. Lett.* 1013 (1987); T. Sugiyama, *Bull. Inst. Chem. Res., Kyoto Univ.* **67**, 112 (1989).
6. T. A. Beineke and J. Delgaudio, *Inorg. Chem.*, 1968, **7**, 715; A. Zalkin, *J. Chem. Phys.*, 1963, **39**, 2881.
7. P. Caramella and P. Grünanger, Nitrile oxides and imines. In: *1,3-Dipolar Cycloaddition Chemistry*, Padwa,

A. (ed.), John Wiley and Sons, New York, 1984, Vol. 1, Chapter 3, pp. 297–300.

8. F. I. Carroll, J. D. White and M. E. Wall, *J. Am. Chem. Soc.* **85**, 1236 (1963).
9. S. C. Austin and E. F. Degering, *J. Am. Chem. Soc.* **64**, 1063 (1942).
10. Von W. Ried and E. Köhler, *Liebigs Ann. Chem.* **598**, 145 (1956).
11. V. L. Heasley, G. E. Heasley, M. R. McConnell, K. A. Martin, D. M. Ingle and P. D. Davis, *Tetrahedron Lett.* 4819 (1971).
12. T. Miyakoshi, S. Saito and J. Kamanotani, *Chem. Lett.* 1677 (1981).
13. N. N. Levy and C. W. Scaife, *J. Chem. Soc.* 1100 (1946).
14. D. Klamann, W. Koser, P. Weyerstahl and M. Fligge, *Chem. Ber.* **98**, 1831 (1965).