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A novel one-pot synthesis of 3-acetyl- and 3-benzoylisoxazole derivatives using ammonium cerium nitrate (CAN)

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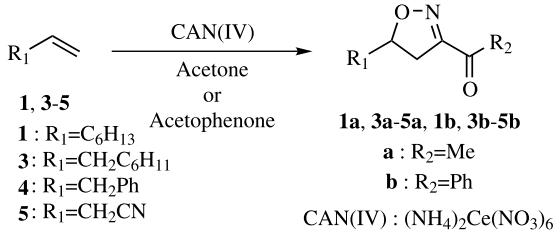
Abstract—The reaction of dipolarophiles (several alkenes and alkynes) with ammonium cerium(IV) nitrate ($(NH_4)_2Ce(NO_3)_6$, CAN(IV)) in acetone under reflux gave 3-acetylisoxazole derivatives. In the case of acetophenone, 3-benzoylisoxazole derivatives were obtained. Moreover, it was found that yields of isoxazole derivatives were improved using ammonium cerium(III) nitrate tetrahydrate ($(NH_4)_2Ce(NO_3)_5{\cdot}4H_2O$, CAN(III))–formic acid.

Isoxazole derivatives have been reported to possess interesting biological activities and pharmacological properties such as analgesic, anti-inflammatory and hypoglycemic.[1,2] In addition, 4,5-dihydroisoxazoles are recognized as useful intermediates in organic synthesis. For example, they can be converted into various important synthetic units such as β-hydroxy ketones,[3] γ-amino alcohols,[4] β,γ-unsaturated ketones[5] and β-hydroxy nitriles.[6] Isoxazole derivatives are usually prepared by one of the following methods: 1,3-dipolar cycloaddition of dipolarophiles (several alkenes and alkynes) with nitrile oxides from nitro compounds by dehydration using aqueous sodium hypochlorite with triethylamine in methylene chloride,[7] or from oxime compounds by dehydrogenation using sodium acetate in acetic anhydride.[8] In particular, the formation of nitrile oxide using hydroxylamine from β-keto esters or α,β-unsaturated ketones is known as a one-pot synthesis of isoxazole derivatives.[9,10]

CAN(IV) has been utilized extensively for a variety of oxidative transformations. We have investigated the development of some novel reaction systems using CAN. In a previous paper we reported a novel α-iodination of ketones in acetic acid or alcohol,[11] a new alkoxyiodination and nitratoiodination of olefins and α,β-unsaturated esters,[12] and a new α,α′-diiodination of ketones using iodine–CAN(IV).[13] One of our group reported a novel synthesis of 4,5-dihydroisoxazoles from alkenes using CAN(IV) or CAN(III)–formic acid.[14] However, the yields of products were unsatisfactory because of the formation of nitroalkene and nitroalcohol from alkene as by-products. So we tried a novel one-pot synthesis of isoxazole derivatives using CAN. In this paper, we report that the reaction of dipolarophiles (alkenes **1**–**5** and alkynes **6**–**8**) with CAN in acetone or acetophenone yields the corresponding isoxazole derivatives.

The reaction of several alkenes **1**–**5** with CAN(IV) in acetone under reflux gave 3-acetyl-4,5-dihydroisoxazoles[16] (**1a**–**5a**). In the case of acetophenone at 80°C, 3-benzoyl-4,5-dihydroisoxazoles (**1b**–**5b**) were obtained (Scheme 1). Moreover, a similar reaction using several alkynes **6**–**8** afforded the corresponding 3-acetylisoxazole (**6a**–**8a**) and 3-benzoylisoxazoles (**6b**–**8b**) (Scheme 2). These results are summarized in Table 1. As can be seen from Table 1, it was found that this



Scheme 1.

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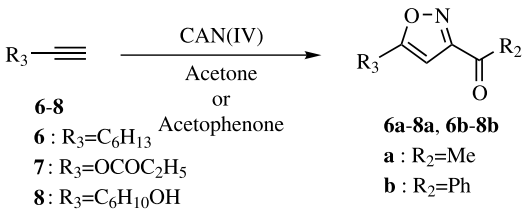


Scheme 2.

method is a novel one-pot synthesis of 3-acetyl- and 3-benzoylisoxazole derivatives from dipolarophiles (alkenes or alkynes) and acetone or acetophenone using CAN(IV).

We further attempted to elaborate the reaction conditions to improve the yields of the isoxazole derivatives. In the case of CAN(III)–formic acid, 3-acetyl- and 3-benzoylisoxazole derivatives were obtained in good yields. These results are summarized in Table 2. From these results, it is apparent that this reaction is general for the synthesis of 3-acetylisoxazole derivatives and 3-benzoylisoxazole derivatives in good yields.

CAN has the ability of nitration for alkenes and aromatic compounds.[15] Wade and co-workers reported that α-nitroketones were converted to nitrile oxide by acid-catalyst.[16] It is known that nitrile oxides dimerize to furoxans. If a furoxan is confirmed in this reaction, it is possible to prove the existence of nitrile oxide as an intermediate. The formation of the dimer (3,4-diacetyl-1,2,5-oxadiazole 2-oxide (furoxan) (**9**)) of nitrile oxide generated from acetone was confirmed (Scheme 3). This result suggests that acetone is converted into the corresponding nitrile oxide via a process involving a nitration of acetone by cerium(IV) or cerium(III), and then undergoes competitive dimerization and 1,3-dipolarcycloaddition with the alkenes or alkynes. From these viewpoints and results, we suggest the reaction mechanism in Scheme 4.

In conclusion, this method is simple and convenient to obtain 3-acetyl- and 3-benzoylisoxazole derivatives. It is particularly noteworthy that this reaction affords a new synthetic method for isoxazole and dihydroisoxazole derivatives that is more convenient than the methods used heretofore.

Table 2. Reaction of dipolarophiles (alkenes **1**–**5** and alkynes **6**–**8**) with CAN(III)–formic acid in acetone or acetophenone

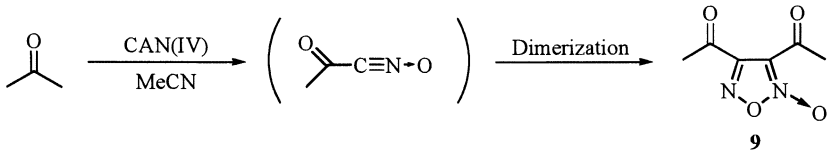
Entry[a]	Substrate	Solvent	Time (h)	Product (%)[b]
1	**1**	Acetone	10	**1a** (84)
2	**2**	Acetone	10	**2a** (73)
3	**3**	Acetone	10	**3a** (74)
4	**4**	Acetone	10	**4a** (81)
5	**5**	Acetone	8	**5a** (72)
6	**6**	Acetone	10	**6a** (85)
7	**7**	Acetone	8	**7a** (87)
8	**8**	Acetone	8	**8a** (83)
9	**1**	Acetophenone	15	**1b** (84)
10	**2**	Acetophenone	10	**2b** (80)
11	**3**	Acetophenone	12	**3b** (70)
12	**4**	Acetophenone	12	**4b** (66)
13	**5**	Acetophenone	5	**5b** (64)
14	**6**	Acetophenone	8	**6b** (85)
15	**7**	Acetophenone	5	**7b** (76)
16	**8**	Acetophenone	8	**8b** (57)

[a] Substrate (0.5 mmol), CAN(III) (0.5 mol), formic acid (10.0 mol) and solvent (3.0 ml) were employed under reflux.
[b] Determined by GLC analysis using *n*-dodecane as an internal hydrocarbon standard. All products were identified by satisfactory spectral data (IR, ^{1}H, ^{13}C NMR and MS).

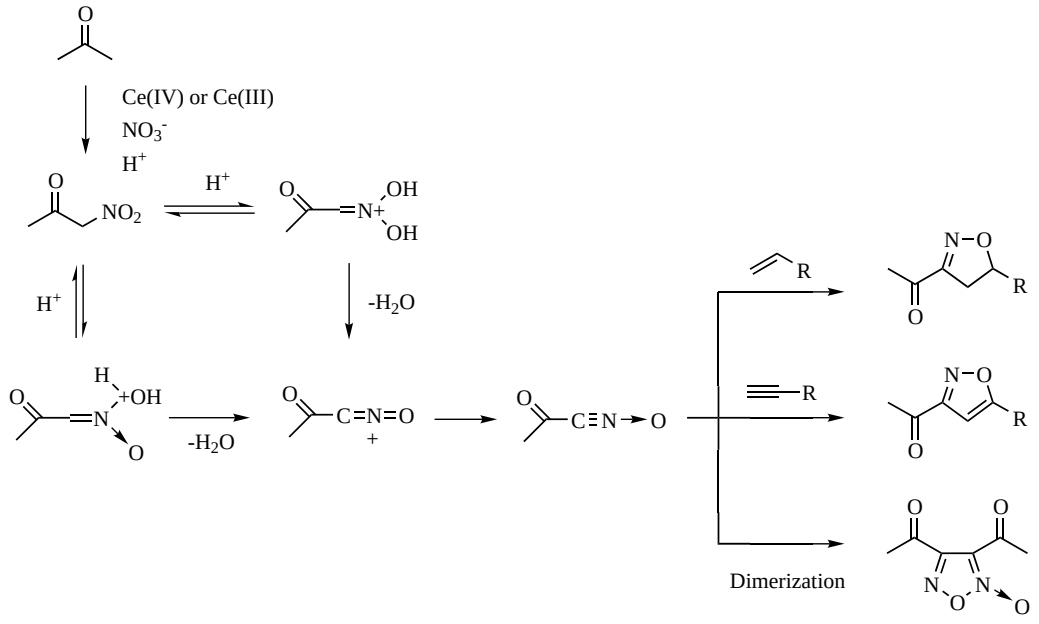
Table 1. Reaction of dipolarophiles (alkenes **1**–**5** and alkynes **6**–**8**) with CAN(IV) in acetone or acetophenone

Entry[a]	Substrate	Solvent	Time (h)	Product (%)[b]
1	1-Octene (**1**)	Acetone	14	**1a** (72)
2	Cyclooctene (**2**)	Acetone	12	**2a** (59)
3	Allylcyclohexane (**3**)	Acetone	10	**3a** (69)
4	Allylbenzene (**4**)	Acetone	5	**4a** (72)
5	Allylcyanide (**5**)	Acetone	12	**5a** (55)
6	1-Octyne (**6**)	Acetone	10	**6a** (59)
7	Ethyl acetylenecarboxylate (**7**)	Acetone	10	**7a** (49)
8	1-Ethynyl-1-cyclohexanol (**8**)	Acetone	14	**8a** (68)
9	**1**	Acetophenone	16	**1b** (77)
10	**2**	Acetophenone	10	**2b** (71)
11	**3**	Acetophenone	16	**3b** (67)
12	**4**	Acetophenone	16	**4b** (54)
13	**5**	Acetophenone	10	**5b** (60)
14	**6**	Acetophenone	12	**6b** (80)
15	**7**	Acetophenone	8	**7b** (71)
16	**8**	Acetophenone	10	**8b** (49)

[a] Substrate (0.5 mmol), CAN(IV) (0.5 mmol) and solvent (3.0 ml) were employed.
[b] Determined by GLC analysis using *n*-dodecane as an internal hydrocarbon standard. All products were identified by satisfactory spectral data (IR, ^{1}H, ^{13}C NMR and MS).



Scheme 3. *Reaction conditions*: acetone (0.5 mmol), CAN(IV) (1.0 mmol) and acetonitrile (3.0 ml) were employed under reflux for 10 h.



Scheme 4. Reaction mechanism.

Typical procedures: **Reaction of 1-octyne with CAN(IV) in acetone**. A mixture of 1-octyne (**6**) (0.0551 g, 0.5 mmol) and ammonium cerium(IV) nitrate (0.2791 g, 0.5 mmol) in acetone (3.0 ml) was stirred under reflux for 14 h. The mixture was extracted with diethyl ether (30 ml) and washed with aq. sodium hydrogencarbonate solution (2×2.0 ml), saturated aq. NaCl (2×2.0 ml) and water (2×2.0 ml). The ethereal solution was dried over Na_2SO_4 and concentrated in a vacuum. The resulting oil was chromatographed on silica gel. Elution with hexane–ether (3:1) gave 3-acetyl-5-hexylisoxazole (**6a**) as a pale-yellow oil (0.060 g, 62%). **3-Acetyl-5-hexylisoxazole** (**6a**): Pale-yellow oil; IR (NaCl) 1707 and 1593 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta = 6.36$ (s, 1H), 2.77–2.81 (s, 1H), 2.63 (s, 3H), 1.29–1.75 (m, 4H) and 0.89 (t, 3H); ^{13}C NMR ($CDCl_3$) $\delta = 192.5$, 175.7, 162.1, 99.2, 31.4, 28.7, 27.4, 26.8, 22.5 and 14.0; MS (EI) m/z 195 (M^+), 152, 134, 111, 83, 68, 55 and 43; MS (CI) m/z 196 ($[M+1]^+$).

References

1. Conti, P.; Dallanoce, C.; De Amici, M.; De Micheli, C.; Klotz, K.-N. *Bioorg. Med. Chem.* **1998**, *6*, 401.
2. Ko, D.-H.; Maponya, M. F.; Khalil, M. A.; Oriaku, E. T.; You, Z.; Lee, H. J. *Med. Chem. Res.* **1998**, *8*, 313.
3. Kim, B. H.; Chung, Y. J.; Ryu, E. J. *Tetrahedron Lett.* **1993**, *34*, 8465.
4. Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826.
5. Curran, D. P.; Kim, B. H. *Synthesis* **1986**, 312.
6. Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023.
7. Maugein, N.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 1547.
8. Lee, G. A. *Synth. Commun.* **1982**, *12*, 508.
9. Sørensen, U. S.; Falch, E.; Krogsgaard-Larsen, P. *J. Org. Chem.* **2000**, *65*, 1003.
10. Martin, M. A. P.; Flores, A. F. C.; Bastos, G. P.; Sinhorin, A.; Bonacorso, H. G.; Zanatta, N. *Tetrahedron Lett.* **2000**, *41*, 293.
11. Horiuchi, C. A.; Kiji, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 421.
12. Horiuchi, C. A.; Ochiai, K.; Fukunishi, H. *Chem. Lett.* **1994**, 185.
13. Horiuchi, C. A.; Takahashi, E. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 271.
14. Sugiyama, T. *Appl. Organomet. Chem.* **1995**, *9*, 399.
15. Ganguly, N.; Sukai, A. K.; De, S. *Synth. Commun.* **2001**, *31*, 301.
16. Wade, P. A.; Amin, N. V.; Yen, H.-K.; Price, D. T.; Huhn, G. F. *J. Org. Chem.* **1984**, *49*, 4595.