Pergamon

Tetrahedron Letters, Vol. 38, No. 41, pp. 7203-7206, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01715-2

Effective Transformation of Aldoximes to Nitriles by Dehydration with 2-Methylene-1,3-dioxepane in the Presence of a Lewis Acid Catalyst

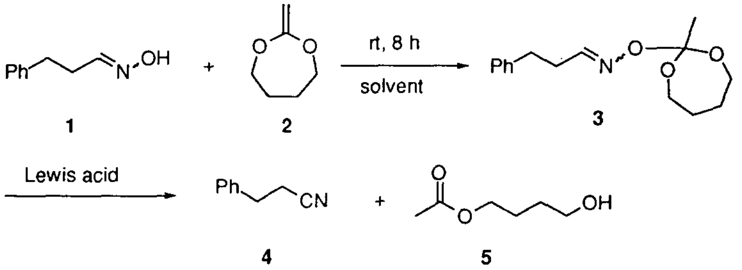
Shin-ichi Fukuzawa,* Yasuhiro Yamaishi, Hideki Furuya,
Keiji Terao,† and Fumiaki Iwasaki‡

Department of Applied Chemistry, Chuo University, Bunkyo-ku, Tokyo 112, Japan
† Wacker Chemicals East Asia Ltd., Shinjuku-ku, Tokyo 169, Japan
‡Tokuyama Research Laboratory, Tokuyama, Yamaguchi 745, Japan

Abstract: The dehydration of aldoximes with 2-methylene-1,3-dioxepane (MDO) proceeds smoothly in the presence of a catalytic amount of Lewis acid such as scandium(III) triflate to give corresponding nitriles in moderate to high yields under mild conditions.

Nitriles are important intermediates for fine chemicals such as medicines, agricultural chemicals, and dyes. One of the most general method for synthesis of alkyl nitriles is a nucleophilic substitution reaction of alkyl halides with inorganic cyanides. However, reactions with *sec*-alkyl halides are often accompanied by elimination of hydrogen halides. Since cyanides are violent poisons they must be treated very carefully. Nitrile synthesis by means of dehydration of amides or aldoximes with an appropriate dehydrating agent would be an alternative safe and efficient method.[1-2] Several mild dehydrating agents have been proposed for this transformation. Dehydration of aldoxime esters or ethers is also an efficient dehydration method.[1-2] We would like to present in this report a facile and safe method for the preparation of nitriles from aldoximes using 2-methylene-1,3-dioxepane (MDO)[3] in the presence of a Lewis acid under mild conditions.

Scheme 1



The reaction of 3-phenylpropanaldoxime (**1**) (a mixture of *cis* and *trans* isomers) with MDO (**2**) in CH_2Cl_2 proceeds smoothly at room temperature to give the corresponding oxime ortho ester (**3**),[5] as a thermally stable compounds in over 95 % yield. On treatment of the ortho ester with a catalytic amount of $Sc(OTf)_3$,[4] 3-phenylpropionitrile (**4**) was produced in 88 % yields at room temperature as a dehydrated product (Scheme 1). The dehydration of the aldoxime was conveniently carried out without isolation of the ortho ester; the nitrile was obtained by the reaction of 3-phenylpropanaldoxime with MDO followed by treatment with a Lewis acid in one pot. We first surveyed the dehydration of the aldoxime with MDO to nitriles using various acid catalysts. Table 1 summarizes the results of the reaction. As a Lewis acid catalyst, $Sc(OTf)_3$, $Sc(NTf_2)_3$, $Yb(OTf)_3$, and $AlCl_3$ were effective for the nitrile synthesis (entries 1-3 and 6); $Sc(OTf)_3$ was the most efficient catalyst for the dehydration. The reaction with other Lewis acids like $Nd(OTf)_3$, $Ti(OPr^i)_4$, $BF_3{\bullet}Et_2O$, and $ZnCl_2$ accompanied the simple hydrolysis of the ortho ester significantly to the original aldoxime (entries 5 and 7-9). We next examined the dehydration of various aldoximes with MDO using $Sc(OTf)_3$ as a Lewis acid in various solvents. The results asre summarized in Table 2. Tetrahydrofuran, diethyl ether, and acetonitrile can be used as a solvent instead of CH_2Cl_2, but toluene is not a suitable solvent.

Table 1. The Dehydration of 3-Phenylpropanaldoxime with MDO in the Presence of a Lewis Acid[a]

Entry	Catalyst	Yield of the nitrile (4) (%)[b]
1	$Sc(OTf)_3$	90
2	$Sc(NTf_2)_3$	75
3	$Yb(OTf)_3$	75
4	$Sm(OTf)_3$	60
5	$Nd(OTf)_3$	7[c]
6	$AlCl_3$	85
7	$Ti(OPr^i)_4$	trace
8	$BF_3{\bullet}Et_2O$	41[c]
9	$ZnCl_2$	16[c]

a) A mixture of 3-phenylpropanalodoxime (0.5 mmol) and MDO (1.0 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature for 8 h and the treated with a catalyst (0.1 mmol, 20 mol % to the oxime). b) Determined by GC. c) Starting 3-phenylpropanaodoxime was recovered.

Table 2. $Sc(OTf)_3$ Catalyzed Dehydration of 3-Phenylpropanaldoxime in Various Solvents[a]

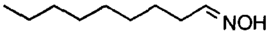
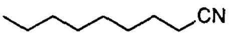
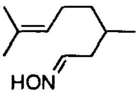
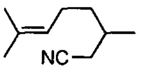
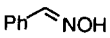
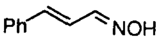
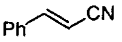
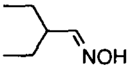
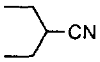
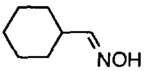
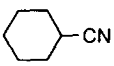
Entry	Solvent	Yield of the nitrile (4) (%)[b]
1	CH_2Cl_2	90
2	THF	75
3	Et_2O	75
4	CH_3CN	60
5	Toluene	7

a) A mixture of 3-phenylpropanalodoxime (0.5 mmol) and MDO (1.0 mmol) in solvent (5 ml) was stirred at room temperature for 8 h and then treated with $Sc(OTf)_3$ (0.1 mmol, 20 mol %) to the oxime.
b) Determined by GC.

No isonitrile was produced as a Beckmann rearrangement product during decomposition of the oxime ortho ester with each acid catalyst. While, it has been reported that *cis* aldoximes undergo the Beckmann rearrangement with methylketene diethylacetal on treatment with $BF_3 \bullet Et_2O/HgO$ to give isonitriles mainly.[6] The MDO method for selective transformation of aldoximes to nitriles is superior to the methylketene diethylacetal method with respect to simplicity and safety reaction procedures; the MDO method does not requires separation of *cis* and *trans*-isomers, and MDO is inexpensive and non-toxic.

Table 3 shows the typical results of the reaction with various aldoximes. Primary alkyl aldoximes such as nonylaldoxime and citraldoxime underwent dehydration effectively with MDO and $Sc(OTf)_3$ (Table 3, entries 1-2). The dehydration of benzaldoxime and cinnamaldoxime were not successful, yields of nitriles being low to moderate yields (entries 3-4). In these cases, significant amount of starting aldoximes were recovered. Secondary alkyl aldoximes such as diethylacetaldoxime and cyclohexancarbaldoxime could be converted into corresponding nitriles in good yields (entries 5-6).

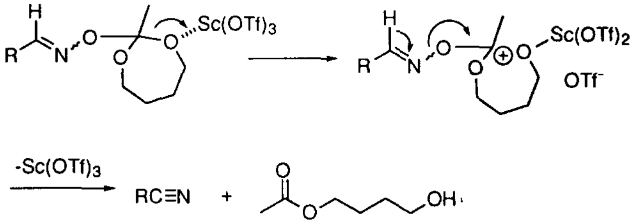
Table 3. $Sc(OTf)_3$ Catalyzed Dehydrationof Aldoximes with MDO[a]

Entry	Aldoxime	Product	Yield(%)[b]
1			85
2			81
3		Ph–CN	13
4			25
5			70
6			94

a) A mixture of alodoxime (0.5 mmol) and MDO (1.0 mmol) in CH_2Cl_2 (5 ml) was stirred at room temperature for 8 h and then treated with $Sc(OTf)_3$ (0.1 mmol, 20 mol % to the oxime). b) Determined by GC.

We propose a reaction mechanism as presented in Scheme 2. Coordination of $Sc(OTf)_3$ to the oxygen atom of the 1,3-dioxepane ring induces the carbon-oxygen bond cleavage to form the cationic intermediate. Then, elimination of hydrogen of the oxime and ortho ester part leads to production of the nitrile and the ester.

Scheme 2



The following provides a typical experimental procedure for the dehydration of aldoximes with MDO. A mixture of 3-phenylpropanaldoxime (**1**) (75.0 mg, 0.5 mmol) and MDO (**2**) (114 mg, 1.0 mmol) in CH_2Cl_2 (1 ml) was stirred at room temperature for 8 h, during which time over 95% **1** was converted into the ortho ester (3): The reaction was monitored by GC analysis. To the resulting solution was added $Sc(OTf)_3$ (100 mg, 0.2 mmol) slowly 0 °C and the mixture was stirred at room temperature for 3 h. The mixture was treated with water, extracted with diethyl ether (10 ml X 3), and then dried ($MgSO_4$). GC/MS analysis revealed the presence of 3-phenylpropionitrile (59.0 mg, 90% yield) using biphenyl as an internal standard.

References and notes

(1) For a review, Fatiadi, A. J. In *Preparation and synthetic applications of cyano compounds*, Patai, S.; Rapport, Z., Eds.; The Chemistry of Functional Groups, Supplement C, Wiley: New York, 1983; pp 1057-1302.

(2) For a review, Friedrich, K. In *Recent advances in the synthesis of triple-bonded groups*, Patai, S. ; Rapport, Z., Eds.; The Chemistry of Functional Groups, Supplement C, Wiley: New York, 1983; Wiley: New York, 1983; pp 1345-1390,

(3) MDO is commercially available, inexpensive compounds. It is thermally stable and can be handled easily. Pommerening, H.; Pflaum, S. *Chemistry Today* **1996**, 13.

(4) For a review for scandium(III) triflate in organic synthesis, Kobayashi, S. *Synlett* **1994**, 689.

(5)The oxime ortho ester **3**. ^{1}H NMR (400 MHz) δ 1.58 (s, 3H), 1.68 (m, 4H) 2.75 (m, 2H), 2.84 (t, 2H), 3.65 (m, 2H), 3.93 (m, 2H). 6.80 (t, 0.6H, J = 5.2 Hz), 7.17-7.32 (m, 5H), 7.46 (t, 0.4H, J = 5.9 Hz). ^{13}C NMR δ 21.7, 27.1, 28.8, 32.0, 63.1, 118.4, 126.0, 128.1, 128.3, 140.4, 151.6

(6) Mukaiyama, T.; Tonooka, K.; Inoue, K. *J. Org. Chem.* **1961**, *26*, 2203.

(*Received in Japan* 10 *July* 1997; *revised* 11 *August* 1997; *accepted* 18 *August* 1997)