Facile Conversion of Acetals to Nitriles

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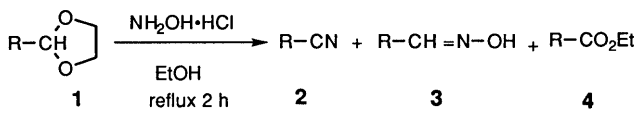
Aliphatic and aromatic acetals are easily and efficiently converted to the corresponding nitriles by reaction with hydroxylamine hydrochloride in refluxing absolute ethanol.

Keywords nitrile; acetal; hydroxylamine hydrochloride

Many methods have been developed to prepare nitriles[1] because of the importance of nitrile as a functional group. Among them, the elimination reactions of aldoximes or their derivatives have been well studied.[2] However, dehydration of aldoximes requires severe conditions and therefore many reagents have been examined in attempts to overcome this drawback. Aliphatic aldehydes have been converted directly into nitriles with hydroxylamine hydrochloride in refluxing 95% ethanol containing a few drops of hydrochloric acid.[3] We have now found that the acetals of both aliphatic and aromatic aldehydes can be converted into the corresponding nitriles in a simple one-step process.

The ethylene acetals of aldehydes were treated with hydroxylamine hydrochloride in refluxing absolute ethanol for 2 h under three different reaction conditions (A, without acid; B, with 0.01 eq of TsOH; with *ca.* 10 eq of hydrogen chloride) to afford the corresponding nitriles (**2**). As shown in the Table I, in all cases the reactions were accompanied by the formation of the corresponding oximes (**3**), which were easily separated by column chromatography. Aliphatic acetals gave the corresponding nitriles with or without acids in good yields (entries 1—8). Since the acetal of 4-tolyl aldehyde gave the nitrile (**2e**) in low yield without acid (entry 11), the reactions of other aromatic acetals were not carried out under condition A. Generally, the yields of the nitriles under condition C were higher than those under the other conditions, but gave the corresponding esters (**4**), which were formed by solvolysis of the nitriles and were difficult to separate from the nitriles, as by-products. Furthermore, the aromatic acetals having electron-donating substituents gave good results compared with those having electron-withdrawing substituents (entries 18—27). The acetal of cuminaldehyde gave the nitrile (**2g**) predominantly (entry



1 **2** **3** **4**

1—4	R	1—4	R	1—4	R
a	$CH_3(CH_2)_6$	f	2-$CH_3C_6H_4$	j	3,4-$(CH_3O)_2C_6H_3$
b	cyclohexyl	g	4-$(CH_3)_2CHC_6H_4$	k	4-ClC_6H_4
c	$C_6H_4CH_2CH_2$	h	4-$CH_3OC_6H_4$	l	4-$NO_2C_6H_4$
d	C_6H_5	i	3-$CH_3OC_6H_4$	m	1-naphthyl
e	4-$CH_3C_6H_4$				

Chart 1

TABLE I. The Reaction of Acetals with Hydroxylamine Hydrochloride

Entry	R	Reaction condition	Yield (%)[a]		
			2	3	4
1	$CH_3(CH_2)_6$	A	93	Trace	—
2		B	88	4	—
3		C	97	Trace	—
4	Cyclohexyl-	A	75	Trace	—
5		B	81	8	—
6		C	71	Trace	Trace
7	$C_6H_4CH_2CH_2$-	A	97	Trace	—
8		B	97	Trace	—
9	C_6H_5-	B	16	41	—
10		C	65	10	15
11	4-CH_3-C_6H_4-	A	36	56	—
12		B	57	29	—
13		C	65	17	8
14	2-CH_3-C_6H_4-	B	51	25	—
15		C	75	9	—
16	4-$(CH_3)_2CH$-C_6H_4-	B	75	18	—
17		C	96	Trace	—
18	4-CH_3O-C_6H_4-	B	71	22	—
19		C	84	10	—
20	3-CH_3O-C_6H_4-	B	43	49	—
21		C	70	22	—
22	3,4-$(CH_3O)_2$-C_6H_3-	B	83	9	—
23		C	92	Trace	—
24	4-Cl-C_6H_4-	B	Trace	80	—
25		C	77	Trace	20
26	4-NO_2-C_6H_4-	B	—	84	—
27		C	50	22	14
28	1-Naphthyl-	B	51	38	—
29		C	65	22	—

a) Isolated yields.

TABLE II. Physical Constants of Nitriles (**2**)

2	mp (°C) or bp (°C)/Torr	
	Found	Reported
2a	87—89/10	90—92/13[4]
2b	70—72/15	67/12[5]
2c	101—103/10	92/4[6]
2d	78—82/15	86/20[7]
2e	27	26—27[8]
2f	85—87/12	94—96/20[9]
2g	88—90/13	100/20[10]
2h	58—60	58—61[11]
2i	115—118/13	116—120/13[12]
2j	68—69	67—68[8]
2k	93—94	93—94[11]
2l	145—146	146—147[11]
2m	150—152/12	166—169/18[13]

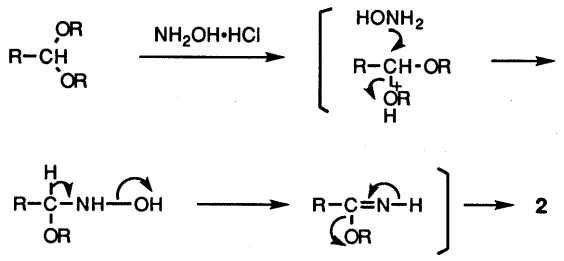


Chart 2

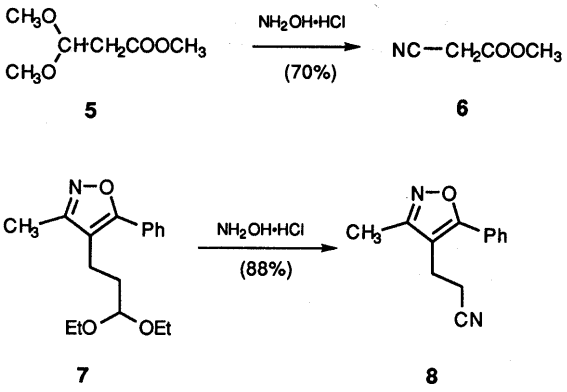


Chart 3

16), whereas cuminaldehyde afforded exclusively the corresponding aldoxime (**3g**) on reaction with hydroxylamine hydrochloride under condition B. Furthermore, the aldoxime (**3g**) was not converted into the nitrile (**2g**) under the same condition. This suggests that neither aldehydes, which might be formed by prior hydrolysis of the acetals, nor the aldoximes serve as intermediates en route to the nitriles. A plausible mechanism for the conversion of the acetals into the nitriles is shown in Chart 2. As the dimethyl and diethyl acetals (**5** and **7**[14]) were also converted to the corresponding nitriles (**6**[15] and **8**[14]), this method can be applied to various kinds of acetals.

Experimental

All reagents were commercial products, purchased from Tokyo Kasei Kogyo Co., and were used without further purification. Ethanol was used after distillation from sodium. All of the acetals were prepared by the reaction of the corresponding aldehydes and ethylene glycol in refluxing benzene in the presence of a catalytic amount of TsOH. Melting points were measured on a Yanaco micro-melting point apparatus and are uncorrected.

Reaction of the Acetals with Hydroxylamine Hydrochloride. General Procedure Method A (for Acetals **1a—c**): A mixture of acetal (10 mmol) and hydroxylamine hydrochloride (903 mg, 13 mmol) in absolute ethanol (50 ml) was refluxed for 2 h. The solvent was evaporated *in vacuo* and water (30 ml) was added to the residue. The organic phase was separated and extracted with ether (20 ml × 3). The ether layer was washed with brine (20 ml × 2), dried ($MgSO_4$) and evaporated. The resulting residue was subjected to column chromatography to give the products listed in Table I.

Method B (for All Acetals): A mixture of acetal (10 mmol), hydroxylamine hydrochloride (903 mg, 13 mmol), and TsOH (17 mg, 0.1 mmol) in absolute ethanol (50 ml) was refluxed for 2 h. The same work-up as described above gave the products listed in Table I.

Method C (for All Acetals except **1c**): A mixture of acetal (10 mmol) and hydroxylamine hydrochloride (903 mg, 13 mmol) in absolute ethanol (50 ml) containing *ca.* 7% dry hydrogen chloride was refluxed for 2 h. The same work-up as described above gave the products listed in Table I.

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