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Efficient Method for the Preparation of (Z)-α-Alkoxy-β,γ-unsaturated Nitriles Starting from the Corresponding Acetals of (E)-Chalcone Derivatives

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In the presence of a catalytic amount of $[Rh(COD)Cl]_2$ or trityl perchlorate, trimethylsilyl cyanide smoothly reacts with (E)-chalcone dimethyl acetal to yield (Z)-2,4-diphenyl-2-methoxy-3-butenenitrile accompanying isomerization of double bond.

Isomerization of double bond is one of the important tools for selective preparation of either E or Z-isomer of olefinic compounds. However, there appeared few examples on the effective isomerization of double bond especially from E-isomer to Z-isomer of an α, -unsaturated carbonyl compound except in case of an α,β-unsaturated ester by photochemical method.$^{1)}$

In the previous paper,$^{2)}$ we reported that in the presence of a catalytic amount of transition metal salt such as $NiCl_2$, $CoCl_2$ or di-μ-chloro-bis(1,5-cyclooctadiene)dirhodium ($[Rh(COD)Cl]_2$), trimethylsilyl cyanide (TMS-CN) smoothly reacts with various acetals under almost neutral conditions.

In the continuing study on the exploration of new synthetic methods by the use of the above catalysts, an interesting result was observed concerning effective isomerization of (E)-α,β-unsaturated carbonyl compound to the corresponding Z-isomer; that is, when (E)-chalcone dimethyl acetal (1) was allowed to react with TMS-CN (1.5 equiv.) in the presence of a catalytic amount of $[Rh(COD)Cl]_2$ (2 mol%) in CH_2Cl_2 at room temperature for 40 h, a mixture of (E) and (Z)-2,4-diphenyl-2-methoxy-3-butenenitrile (2) resulted in 89% yield (E:Z = 20:80). To our knowledge, this is the first example that E to Z isomerization of double bond takes place during the nucleophilic substitution of an acetal of (E)-α,β-unsaturated ketone. The above result made us to study further on the problem of double bond isomerization in the above reaction.

After screening the detailed reaction conditions taking the above acetal 1 as a model substrate, it was made clear that (Z)-2 was obtained in good yield when the reaction was carried out in CH_3CN by the use of $[Rh(COD)Cl]_2$ or trityl perchlorate ($TrClO_4$)$^{3)}$ as a catalyst (Table 1).

It was shown there that, in the initial stage of the present reaction (5 h in CH_2Cl_2), the cyanation took place to form only (E)-2,4-diphenyl-2-methoxy-3-butenenitrile, which in turn is isomerized to Z-isomer on kept standing the mixture for a long time.

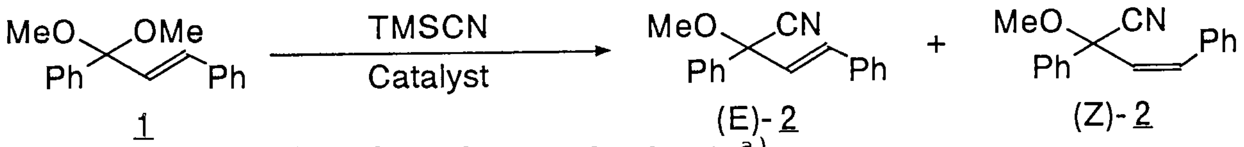


Table 1. Examination of Catalysts and Solvents[a]

Entry	Catalyst[b]	Solvent	Time/h	Yield/%	Ratio of E:Z[c]
1[d]	$[Rh(COD)Cl]_2$	CH_2Cl_2	5	86	100 : 0
2[d]	$[Rh(COD)Cl]_2$	CH_2Cl_2	10	83	64 : 36
3[d]	$[Rh(COD)Cl]_2$	CH_2Cl_2	40	89	20 : 80
4[d]	$[Rh(COD)Cl]_2$	CH_3CN	5	86	39 : 61
5[d]	$[Rh(COD)Cl]_2$	CH_3CN	20	85	0 :100
6	$NiCl_2$	CH_3CN	20	64	100 : 0
7	$CoCl_2$	CH_3CN	20	83	81 : 19
8	$Pd(acac)_2$	CH_3CN	20	77	100 : 0
9	$Pd(OAc)_2$	CH_3CN	20	95	100 : 0
10	$SnCl_2$	CH_3CN	3	98	96 : 4
11	$BF_3 \cdot Et_2O$	CH_3CN	3	98	100 : 0
12	$SnCl_4$	CH_3CN	3	quant.	24 : 76
13[e]	$AlCl_3$	CH_3CN	3	76	100 : 0
14	$TiCl_4$	CH_3CN	3	97	88 : 12
15	$TrClO_4$	CH_3CN	3	92	0 :100
16	$TrCl\text{-}SnCl_2$[4]	CH_3CN	15	86	0 :100
17	$TMSCl\text{-}SnCl_2$[5]	CH_3CN	15	85	0 :100

a) Reactions were carried out by using 1.5 equiv. of TMS-CN at room temperature.
b) 5 mol% of catalyst was used except for entries 1,2,3,4,5, and 13.
c) Determined by ^1H NMR measurement.
d) 2 mol% of catalyst was used.
e) 25 mol% of catalyst was used.

It was also found that the same isomerization took place to afford Z-isomer when the isolated E-isomer was treated with a catalytic system consisted of $[Rh(COD)Cl]_2$ and TMS-CN.

After screening various solvents, it was shown that CH_3CN is the best solvent and isomerization from (E)-2 to (Z)-2 was achieved within 20 h by using $[Rh(COD)Cl]_2$ as a catalyst. Isomerization proceeded slowly in the case of using other transition metal salts such as $NiCl_2$, $CoCl_2$, $Pd(acac)_2$ and $Pd(OAc)_2$ as a catalyst.

Further, it was found that the isomerization took place very rapidly when Lewis acids such as $TrClO_4$ was used as a catalyst. It is interesting to note that thermodynamically stable E-isomer perfectly isomerized to Z-isomer under the above conditions, because such an isomerization is not commonly known. On the other hand, isomerization proceeded more slowly in the case of using generally known strong Lewis acids such as $BF_3 \cdot Et_2O$ and $AlCl_3$.

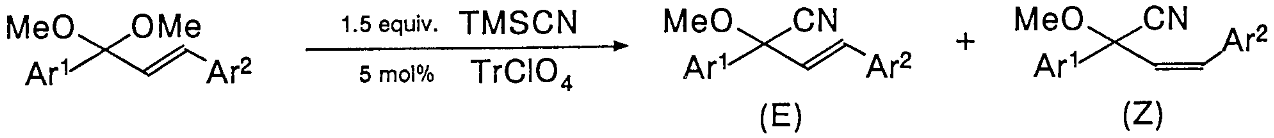
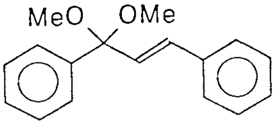
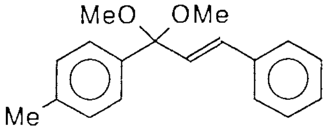
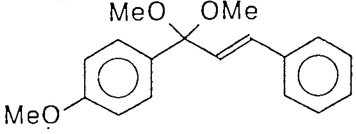
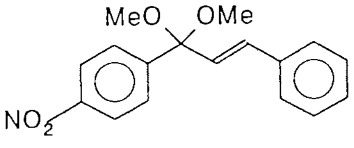
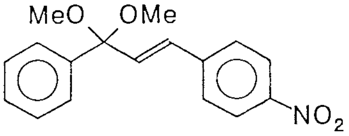
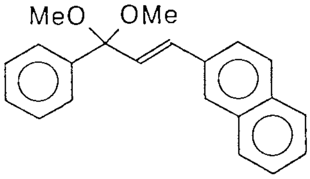
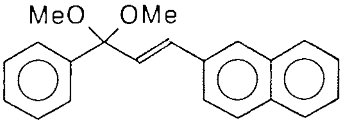
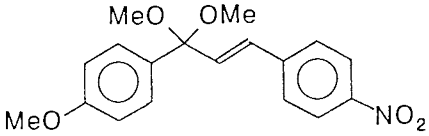


Table 2. Synthesis of α-Methoxy-β,γ-unsaturated Nitriles[a]

Entry	Substrate	Time/h	Yield/%	Ratio of E : Z[b]
1		3	92	0 :100
2		5	98	0 :100
3		8	81	0 :100
4		5	quant.	82 : 18
5		20	91	53 : 47
6		5	42	100 : 0
7		20	97	81 : 19
8		20	73	47 : 53
9		15	67	0 :100
10		20	94	0 :100

a) Reactions were carried out by using 1.5 equiv. of TMS-CN and 5 mol% of $TrClO_4$ in CH_3CN at room temperature.
b) Determined by ^1H NMR measurement.

Next, the similar reactions of various acetals of substituted chalcone derivatives with TMS-CN were tried in the presence of a catalytic amount of $TrClO_4$ (Table 2). One of the important notes of these reactions is that electronic effect of substituents contained in aromatic rings of chalcone derivatives is influential in the rate of isomerization.

Typical procedure is described for the reaction of (E)-chalcone dimethyl acetal 1 with TMS-CN by the use of $TrClO_4$ as a catalyst (Table 1, entry 15): Under an argon atmosphere, $TrClO_4$ (0.01 mmol) and TMS-CN (0.35 mmol) were stirred in acetonitrile (3 ml) at room temperature for 15 min, to which was added (E)-chalcone dimethyl acetal (0.208 mmol) in acetonitrile (1 ml). The reaction mixture was stirred for 3 h at room temperature, then quenched with pH 7 phosphate buffer. The organic materials were extracted with ethyl acetate and the combined extract was dried over Na_2SO_4. After evaporation of the solvent, the residure was purified by preparative TLC (silica gel, hexane : AcOEt = 5 : 1) to afford (Z)-2,4-diphenyl-2-methoxy-3-butenenitrile (0.192 mmol, 92%).

It is noted that the use of a catalytic amount of $[Rh(COD)Cl]_2$ or $TrClO_4$ promotes the cyanation of (E)-chalcone dimethyl acetal derivatives with TMS-CN accompanying perfect E to Z isomerization of the double bond. Further studies to clarify the mechanism of the isomerization and the reason for the preferential formation of thermodynamically unstable Z-isomer and also the possible use of the other nucleophiles and acetals of α,β-unsaturated ketone are currently in progress.

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References

1) For examples, R. E. Lutz and R. H. Jordan, J. Am. Chem. Soc., 72, 4090 (1950); Y. S. Rao and R. Filler, J. Chem. Soc., Chem. Commun., 1973, 55; F. D. Lewis and J. D. Oxman, J. Am. Chem. Soc., 103, 7345 (1981).
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