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Efficient Activation of Acetals toward Nucleophiles by the Use of Transition Metal Salts. New Method for Cyanation of Acetals and Orthoester Derived from Aromatic and α,β-Unsaturated Carbonyl Compounds with Trimethylsilyl Cyanide under Neutral Condition

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In the presence of a catalytic amount of transition metal salts ($NiCl_2$, $CoCl_2$, $PdCl_2$, etc.), trimethylsilyl cyanide smoothly reacts with acetals or orthoester derived from aromatic and α,β-unsaturated carbonyl compounds to give the corresponding α-cyano derivatives under neutral condition.

Cyanation of carbonyl and related compounds is an imprortant tool for carbon-carbon bond formation. Trimethylsilyl cyanide (TMS-CN) is well known as one of the most popular reagents for cyanation of aldehyde, ketone, epoxide, etc.[1) Most of these reactions are carried out under acidic condition by the use of Lewis acids such as $TiCl_4$, $SnCl_4$, ZnI_2, etc., and there reported some examples for cyanation of acetal or ketal by the use of Lewis acids.[2) Now, we wish to report a new method for cyanation of acetals and orthoester derived from aromatic and α,β-unsaturated carbonyl compounds with TMS-CN under neutral condition by the use of a catalytic amount of transition metal salts. To our knowledge, this is a first example to activate acetals by using this type of catalyst to effectively perform cyanation reaction.[3)

First, in order to carry out the cyanation of the acetals with TMS-CN under very mild condition without use of commonly employed Lewis acids, the reaction of dimethyl acetal of (E)-cinnamaldehyde(1) with TMS-CN (1.5 equiv.) in CH_2Cl_2 was tried in the presence of a catalytic amount of $NiCl_2$ (10 mol%) at room temperature and it was found that (E)-1-methoxy-4-phenyl-3-butenenitrile(2) was obtained in

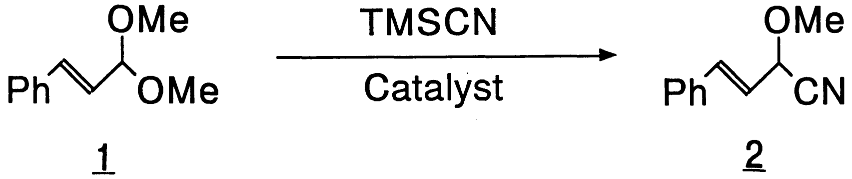


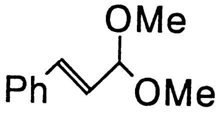
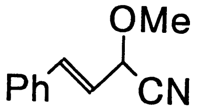
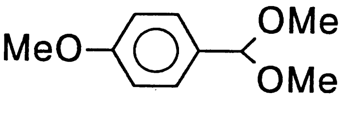
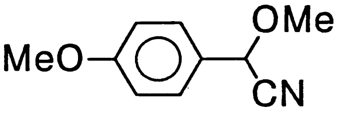
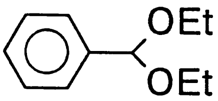
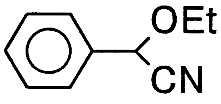
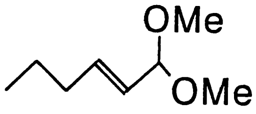
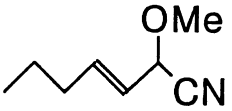
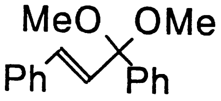
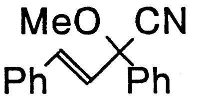
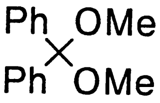
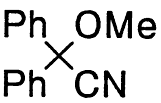
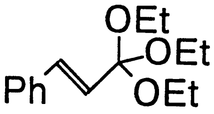
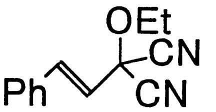
Table 1. Examination of catalysts and solvents[a)]

Entry	Catalyst[b)]	Solvent	Yield of 2/%
1	$NiCl_2$	CH_2Cl_2	96
2	$Ni(acac)_2$[c)]	CH_2Cl_2	84
3	$Ni(OAc)_2$	CH_2Cl_2	87
4	$CoCl_2$	CH_2Cl_2	82
5	$Co(acac)_2$	CH_2Cl_2	82
6	$PdCl_2$	CH_2Cl_2	95
7	$Pd(acac)_2$	CH_2Cl_2	78
8	$Co(acac)_2$	toluene	81
9	$Co(acac)_2$	CH_3CN	92
10	$Co(acac)_2$	Et_2O	92
11	$Co(acac)_2$	dioxane	90
12	$Co(acac)_2$	THF	89
13[d)]	$Co(acac)_2$	DMF	79

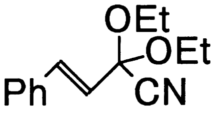
a) Reactions were carried out by using 1.5 equiv. of TMS-CN at room temperature for 3 h except for entry 13.
b) In all experiments, 10 mol% catalyst was used.
c) acac: acetylacetone
d) Reaction time is 44 h.

96% yield. After screening other transition metal salts and detailed reaction conditions taking the above acetal 1 as a model substrate, it was also found that 2 was obtained in good yield when a catalytic amount of the other transition metal salts such as $CoCl_2$, $Co(acac)_2$, $PdCl_2$, etc. were used. One of the important notes of these reactions is that ether, dioxane, THF and DMF can be used as a reaction solvent different from the commonly known Lewis acids mediated reactions.

Table 2. Synthesis of α-alkoxynitriles[a)]

Entry	Substrate	Catalyst[b)]	Time/h	Product	Yield/%
1		$NiCl_2$	3		81
2		$CoCl_2$	3		91
3		$NiCl_2$	3		N.R.
4		$CoCl_2$	1		90
5		$Co(acac)_2$	39		92
6		$NiCl_2$	6		N.R.
7		$CoCl_2$	41		98
8		$Co(acac)_2$	41		95
9		$NiCl_2$	18		N.R.
10		$CoCl_2$	18		96
11		$NiCl_2$	20		75
12		$CoCl_2$	18		99
13		$NiCl_2$	24		60
14		$CoCl_2$	24		94
15[c)]		$NiCl_2$	36		57[d)]
16[c)]		$CoCl_2$	55		91

a) Reaction was carried out by using 1.5 equiv. of TMS-CN in CH_2Cl_2 at room temperature except for entries 15 and 16.
b) In all experiments, 2 mol% catalyst was used.
c) 3 equiv. of TMS-CN was used.
d) Monocyano compound (see right) was obtained in 26% yield.



Next, various acetals including ketals and orthoester were treated with TMS-CN under the similar condition and the results are summarized as follows:

(1) Various acetals, ketals and orthoester smoothly react with TMS-CN to give the corresponding α-cyano derivatives by the use of a catalytic amount of

$NiCl_2$, $CoCl_2$ or $Co(acac)_2$ (2 mol%).

(2) $CoCl_2$ is more reactive compared with $NiCl_2$.

(3) Dicyano compound was obtained from orthoester (entries 15, 16).

Typical procedure is described for the reaction of TMS-CN with (E)-cinnamaldehyde dimethyl acetal 1 by the use of $NiCl_2$ as a catalyst (Table 1, entry 1): Under an argon atmosphere, a CH_2Cl_2(3 ml) suspension of $NiCl_2$ (0.04 mmol) and trimethylsilyl cyanide (0.6 mmol) was stirred for 30 min at room temperature (20°C), to which was added (E)-cinnamaldehyde dimethyl acetal (0.4 mmol) in CH_2Cl_2 (1 ml). The reaction mixture was stirred for 3 h at room temperature and quenched with pH 7 phosphate buffer. The organic materials were extracted with CH_2Cl_2 and combined extracts were dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by preparative TLC (silica gel, n-hexane:AcOEt=5:1) to afford (E)-1-methoxy-4-phenyl-3-butenonitrile (0.396 mmol, 96%).

Although the detailed mechanism is not yet clear, it is assumed that positively charged trimethylsilyl group could be generated by coordination of cyano group of TMS-CN to transition metal salts. The acetal would be activated by the interaction with the trimethylsilyl group and would be readily attacked by TMS-CN to result in the formation of α-alkoxynitrile.

It is noted that the use of a catalytic amount of transition metal salts promotes the cyanation of acetals and orthoester derived from aromatic and α,β-unsaturated carbonyl compounds with TMS-CN under neutral condition. Further studies directed to the possible use of the other transition metal salts and to the application to other types of carbon-carbon bond forming reactions are currently in progress.

References

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2) For examples, K. Utimoto, Y. Wakabayashi, Y. Shishiyama, M. Inoue, and H. Nozaki, Tetrahedron Lett., 22, 4279 (1981); K. Utimoto, Y. Wakabayashi, T. Horiie, M. Inoue, Y. Shishiyama, M. Obayashi, and H. Nozaki, Tetrahedron, 39, 967 (1983).

3) Addition of TMS-CN to allenes with the aid of a palladium or nickel catalyst has been reported. N. Chatani, T. Takeyasu, and T. Hanafusa, Tetrahedron Lett., 27, 1841 (1986).

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