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BECKMANN FRAGMENTATION AND SUCCESSIVE CARBON-CARBON BOND FORMATION OF α-ALKOXYCYCLOALKANONE OXIMES CATALYZED BY TRIMETHYLSILYL TRIFLUOROMETHANESULFONATE

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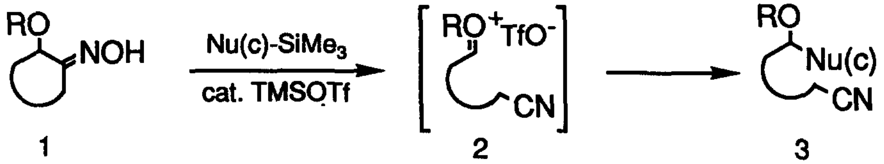
Summary: Title reaction occurred in the presence of silicon-containing carbon nucleophiles and various types of functionalized ω-nitrile compounds (3) were obtained from the oximes (1) in one-pot operation.

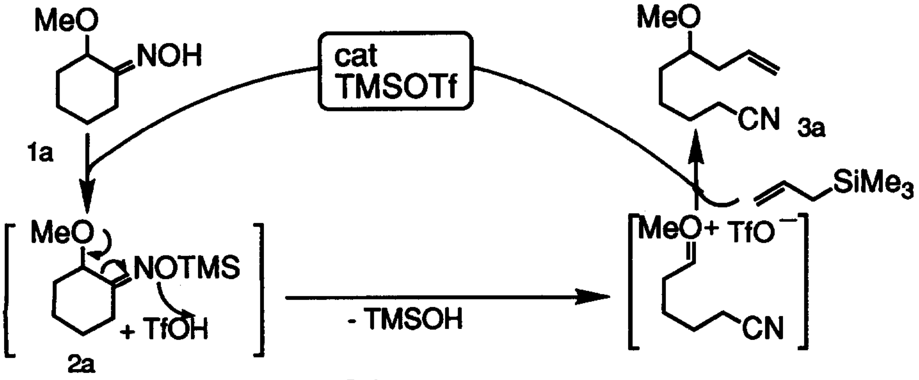
The oximes having α-substituents, such as hydroxy, alkoxy, carbonyl, amino, imino, and sulfenyl groups, undergo fragmentation reaction under Beckmann rearrangement conditions.[1] The Beckmann fragmentation is a very useful reaction to give functionalized ω-nitriles in cyclic systems. The reaction has been recognized to proceed *via* onium ion intermediates,[1b-1d,2] very active electrophiles. Although several kinds of nucleophiles seem to react with these intermediates, the use of carbon nucleophiles, which provides a new carbon-carbon bond formation, is quite few.[3] We wish to disclose here a novel Beckmann fragmentation of α-alkoxycycloalkanone oximes (1) and successive carbon-carbon bond formation of the intermediates with silicon-containing carbon nucleophiles (allylsilane, silyl cyanide, and silyl enol ethers) catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf). The overall transformation is illustrated in Scheme 1.



Scheme 1

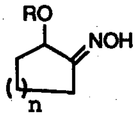
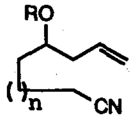
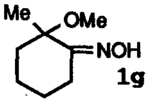
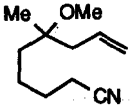
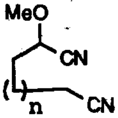
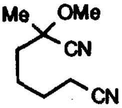
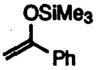
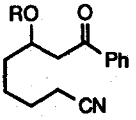
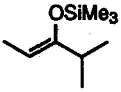
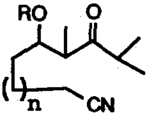
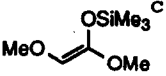
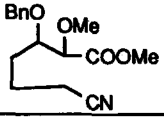
The results are summarized in the Table. The detailed study on the reaction was performed by use of allyltrimethylsilane (entries 1-8). Thus, various α-alkoxycycloalkanone oximes were allowed to react with 5 equivalents of allyltrimethylsilane in dichloromethane (CH_2Cl_2) in the presence of TMSOTf[4] and the nitrile compounds[5] having ω-vinyl fuctionality were obtained in one-pot operation. Several aspects are noteworthy. First, a catalytic amount of TMSOTf works well (entries 1 *vs* 2-8). Secondly, both methyl and benzyl ethers can be available (entries 2-5). Thirdly, the reaction works in medium to large ring systems, (entries 6,7). In these cases, however, the reactions were sluggish and refluxing is necessary. Fourthly, even in tertiary alkoxy system the reaction works (entry 8), but in this case a fair amount of 6-oxoheptyronitrile was accompanied. This catalytic reaction was also applicable to the other silicon-containing carbon nucleophiles. That is, the reactions of trimethylsilyl cyanide and oximes proceeded in a similar manner to give the dinitrile compounds[5] (entries 9-11), and several silyl enol ethers also reacted in a catalytic system to give the ω-cyano-β-alkoxy carbonyl compounds[5] (entries 12-16).

A possible mechanism of the catalytic cycle is shown in Scheme 2; illustrated by the reaction of 1a and allyltrimethylsilane. Reaction of 1a with TMSOTf generates a silylated compound (2a),[6] accompanied with trifluoromethanesulfonic acid (TfOH), which in turn is detrimethylsilanolated with TfOH and subjected to the fragmentation reaction to afford the oxonium ion intermediate.[7] Condensation of it with allyltrimethylsilane gives the desired functionalized ω-nitrile compound (3a) and regenerates TMSOTf, which recycles the reaction. In support of this mechanism, the silylated compound 2a, which was obtained by silylation of 1a under $TMSOTf/Et_3N/CH_2Cl_2$ condition, was treated with allyltrimethylsilane in the presence of a catalytic amount of TfOH to afford 3a.



Scheme 2

Table. Reaction of α-Alkoxycycloalkanone Oximes and Silicone-Containing Carbon Nucleophiles [Nu(c)-SiMe$_3$] in the Presence of TMSOTf in CH$_2$Cl$_2$.

Entry	Oximes [a]	Nu(c)-SiMe$_3$	Conditions		Products	Yields(%) [b]
			TMSOTf,	temp.		
						
1	1a(R=Me,n=2)		1.2 eq.	0°C	3a(R=Me,n=2)	51
2	1a		0.1 eq.	0°C	3a	66
3	1b(R=Bn,n=2)		0.1 eq.	0°C	3b(R=Bn,n=2)	68
4	1c(R=Me,n=1)		0.1 eq.	0°C	3c(R=Me,n=1)	54
5	1d(R=Bn,n=1)		0.1 eq.	0°C	3d(R=Bn,n=1)	71
6	1e(R=Me,n=4)		0.1 eq.	reflux	3e(R=Me,n=4)	57
7	1f(R=Me,n=8)		0.1 eq.	reflux	3f(R=Me,n=8)	83
8	 1g		0.1 eq.	0°C	 3g	29
9	1a	Me$_3$SiCN	0.1 eq.	0°C	 3h(n=2)	73
10	1e		0.1 eq.	reflux	3i(n=4)	38
11	1g	Me$_3$SiCN	0.1 eq.	0°C	 3j	67
12	1a		0.1 eq.	r.t.	 3k(R=Me)	92
13	1b		0.1 eq.	r.t.	3l(R=Bn)	59
14	1a	 [c]	0.1 eq.	r.t.	 3m(R=Me,n=2)	65 [d]
15	1d		0.1 eq.	r.t.	3n(R=Bn,n=1)	62 [d]
16	1d	 [c]	0.1 eq.	0°C	 3o	85 [d]

a) Prepared by oximation (NH$_2$OH·HCl,NaOH,MgSO$_4$,MeOH) of the corresponding ketones and used without further purification.

b) Yield of the isolated product and not optimized.

c) Z-isomer was used.

d) Mixture of diastereoisomers: 3m(1/1.6), 3n(1/1.7), 3o(1/1.8).

A reperesentative procedure (entry 2) is as follows: TMSOTf (0.01 ml, 0.1 eq) was added to a stirred solution of **1a** (54 mg) and allyltrimethylsilane (0.3 ml, 5 eq.) in dry CH_2Cl_2 (2 ml) at 0°C and the resulting mixture was stirred for 6h at the same temperature under a nitrogen atmosphere. The reaction mixture was poured into aqueous saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with hexane/ether (1/1) as an eluent to give **3a** (41.6 mg, 66%).

In conclusion, a novel Beckmann fragmentation and a successive carbon-carbon bond formation were achieved in the presence of a catalytic amount of TMSOTf and a practical way to get various types of functionalized ω-nitrile compounds was opened. Since the nitrile group can undergo several transformations,[8] the present method provides a useful tool in organic synthesis.

References and Notes

1) For reviews, see:(a) L. G. Donaruma and W. Z. Heldt, *Org. React.*, 11, 1 (1960); (b) M. Ohno, Kagaku No Ryoiki, 22, 30 (1968); (c) C. A. Grob and P. W. Schiess, *Angew. Chem. Int. Ed. Engl.*, 6, 1 (1967); (d) C. A. Grob, *ibid.*, 8, 535 (1969); (e) C. G. McCarty, "The Chemistry of the Carbon-Nitrogen Double Bond" ed. by S. Patai, Wiely-Interscience, New York (1970), p.416-439; (f) R. E. Gawley, *Org. React.*, 35, 1 (1986).
2) J. March, in "Advanced Organic Chemistry", J. Wiley, 3rd Ed., 1985, p. 931.
3) M. Ohno and I. Terasawa, *J. Am. Chem. Soc.*, 88, 5683 (1966). An interesting C-C bond formation was attained *via* α-chloromethyl ether intermediate which was obtained by treatment of 2-methoxycyclohexanone oxime with thionyl chloride.
4) Other Lewis acids such as $BF_3 \cdot OEt_2$, $TiCl_4$, $SnCl_4$, and ZnI_2 did not give a satisfactory result.
5) Satisfactory spectroscopic data were obtained for all new compounds.
6) Formation of the silylated compound (**2a**) was observed by TLC in the course of the reaction and was confirmed on TLC in comparison with **2a** obtained by silylation ($TMSOTf/Et_3N/CH_2Cl_2$) of **1a**.
7) Possibility of formation of the acetal type intermediate was excluded because of poor electrophilicity of TfO^-.
8) For example, see: G. Tennant, in "Comprehensive Organic Chemistry", Vol. 2, ed. by I. O. Sutherland, Pergamon Press, 1979, p. 528.

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