# Synthetic Methods

# Straightforward Synthesis of 1,2-Dicyanoalkanes from Nitroalkenes and Silyl Cyanide Mediated by Tetrabutylammonium Fluoride

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**Abstract:** A straightforward synthesis of 1,2-dicyanoalkanes by reacting nitroalkenes with trimethylsilyl cyanide in the presence of tetrabutylammonium fluoride is described. The reaction proceeds through a tandem double Michael addition under mild conditions. Employing the hypervalent silicate generated from trimethylsilyl cyanide and tetrabutylammonium fluoride is essential for achieving this transformation. Mechanistic studies suggest that a small amount of water included in the reaction media plays a key role. This

# Introduction

Nitriles are undoubtedly an important class of compounds in organic synthesis and they have been recognized as versatile synthetic intermediates for the preparation of other useful building blocks.<sup>[1]</sup> Therefore, numerous efforts have been dedicated to the development of methods for introducing cyano groups into organic molecules.<sup>[2]</sup> Despite the significant achievements made in cyanation reactions, there are only a limited number of examples of dicyanation reactions. Such reactions can provide 1,2-dicyanoalkanes (succinonitrile derivatives) that could be transformed into highly valuable compounds such as 1,2-dicarboxylic acids,<sup>[3a]</sup> 1,2-diamides,<sup>[3b]</sup> 1,4-diamines,<sup>[3c,d]</sup> and various heterocycles (pyrrolidines, succinimides, and pyrroles).<sup>[3d-]</sup> Bailey and Jackson reported on the synthesis of 1,2dicyanoalkanes by the sequential one-pot Michael addition of lithium cyanide (LiCN) to a vinyl sulfone.<sup>[4]</sup> However, only one example of a substrate was described and this gave only moderate yield. Although Arai and Nishida recently reported on the palladium-catalyzed 1,2-dicyanation of alkynes, and also demonstrated the reduction of the resulting dicyanoalkene to provide a 1,2-dicyanoalkane, the method requires a two-step protocol involving a transition-metal-catalyzed reaction.<sup>[5]</sup> To our

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	Supporting information for this article is available on the WWW und

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201404780.

protocol is applicable to various types of substrates including electron-rich and electron-deficient aromatic nitroalkenes, and aliphatic nitroalkenes. Moreover, vinyl sulfones were found to be good alternatives, particularly for electrondeficient nitroalkenes. The broad substrate scope and functional group tolerance of the reaction makes this approach a practical method for the synthesis of valuable 1,2-dicyanoalkanes.

knowledge, no straightforward synthesis of 1,2-dicyanoalkanes has yet been established.

Nitroalkenes, which are easily prepared by nitro-aldol reactions,<sup>[6]</sup> have been widely used as Michael acceptors in organic synthesis.<sup>[7-9]</sup> Conjugate addition of a cyanide anion to a nitroalkene derivative is the simplest route to  $\beta$ -nitronitriles,<sup>[10]</sup> which are suitable precursors of cyanoalkenes. Corey and Estreicher reported that the Michael addition of sodium cyanide (NaCN) to 1-nitrocyclohexene under acidic conditions provided the corresponding  $\beta$ -nitronitrile, which, after treatment with 1,8diazabicyclo[5.4.0]undec-7-ene (DBU), gave the corresponding 1-cyanocycloalkene.<sup>[11]</sup> Although a few examples of the Michael addition of cyanide anions to nitroalkenes to produce cyanoalkenes through the elimination of HNO<sub>2</sub> in situ have been reported,<sup>[12]</sup> the direct use of such cyanoalkenes in further transformations has not been recorded. We have now designed a new strategy for the straightforward synthesis of 1,2-dicyanoalkanes from nitroalkenes by a tandem double Michael addition. The first Michael addition involves the addition of a cyanide anion to nitroalkene I (Scheme 1, I to II) and the second involves the addition of a cyanide anion to cyanoalkene III formed in situ from the  $\beta$ -nitronitrile **II** through the elimination of HNO<sub>2</sub> (Scheme 1, III to IV). Thus, we report a novel synthetic method for the preparation of 1,2-dicyanoalkanes from nitroal-



**Scheme 1.** Strategy for the straightforward synthesis of 1,2-dicyanoalkanes from nitroalkenes.

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kenes by using two equivalents of silyl cyanide mediated by tetrabutylammonium fluoride (TBAF).

#### **Results and Discussion**

We initially chose trimethylsilyl cyanide (TMSCN) as a cyanide source to examine the 1,2-dicyanation reaction using *trans*- $\beta$ -nitrostyrene (**1a**) at room temperature, as shown in Table 1.

Table 1. Optimization of reaction conditions. <sup>[a]</sup>							
Ph	NO <sub>2</sub>	+ cyanide - (2 equiv)	additive (x equiv) MeCN, RT	- Ph	CN	CN +	CN Ph 2a'
Entry	Cyanide	Additive [equiv]	Time [h]	Yie [% 2 a	ld ] <sup>(ه)</sup> 2 a′	Recov [%] <sup>[b]</sup>	ery of <b>1 a</b>
1 2 <sup>[c]</sup>	TMSCN TMSCN	none TBAF (0,2)	24 24	0 11	0 24	92 61	
3 <sup>[c]</sup>	TMSCN	(0.2) TBAF (0.5)	2	52	24	24	
4 <sup>[c]</sup>	TMSCN	TBAF (1.0)	2	95 (93)	0	0	
5	TMSCN	CsF (1.0)	2	29	9	16	
6	TMSCN	KF (1.0)	2	5	16	63	
7	TMSCN	KF/[18]crown-	62	38	27	27	
8 <sup>[d]</sup>	TMSCN	KF/[18]crown-	62	55	22	14	
9	NaCN	[15]crown-5 (2.0)	2	39	0	0	
10	Bu₄NCN	none	2	21	0	0	
[a] Reaction conditions: <b>1a</b> (0.5 mmol), cyanide (1.0 mmol), additive, MeCN (10 mL), RT. [b] Determined by <sup>1</sup> H NMR spectroscopic analysis of the crude product using mesityrene or 1,1,2,2-tetrachloroethane as an in- ternal standard. The value in parenthesis is the isolated yield. [c] TBAF (1 $\mu$ in THF) was used. [d] H <sub>2</sub> O (1% v/v MeCN) was added.							

When the reaction was run without an additive, no product was obtained, and the starting material 1a was recovered (entry 1). To enhance the reactivity of TMSCN, the addition of a catalytic amount of TBAF (1м in THF)<sup>[13]</sup> was examined, which resulted in the formation of the corresponding 1,2-dicyanoalkane 2a in low yield together with cyanoalkene 2a', with no  $\beta$ -nitronitrile product being observed (entry 2). Increasing the amount of TBAF was effective (entry 3), and the use of one equivalent of TBAF provided 2a in excellent yield (entry 4).<sup>[14]</sup> In contrast, low to moderate yields were observed when CsF or KF were used (with or without added [18]crown-6) as a fluoride anion instead of TBAF (entries 5-8). Other cyanide sources such as sodium cyanide (NaCN) and tetrabutylammonium cyanide (Bu<sub>4</sub>NCN), the cyanide anion of which is strongly nucleophilic, resulted in low yields, and unidentified by-products that might have been formed from the polymerization of 1a (entries 9 and 10). These results suggest that the hypervalent silicate generated from TMSCN and TBAF was an appropriate nucleophile for the dicyanation reaction.  $^{\left[15\right]}$ 

We then investigated the origin of the proton source in the dicyanation (cf. Scheme 1). The solution of TBAF (1  $\mbox{m}$  in THF, 0.2 mL) in acetonitrile (4 mL) contained 4218 ppm of H<sub>2</sub>O, as determined by Karl Fischer titration (the average of two experiments), demonstrating that 0.76 mmol of H<sub>2</sub>O was present in the reaction mixture under the standard conditions on a 0.2 mmol scale. Indeed, the reaction of **1a** with TMSCN employing TBAF·3H<sub>2</sub>O instead of TBAF (1  $\mbox{m}$  in THF) gave **2a** in a comparable yield (92%).<sup>[16]</sup> Thus, deuterium labeling experiments were carried out, in an attempt to gain more insights into the reaction mechanism under the "moist" conditions. When the deuterated substrate [D]-**1a** was used in the reaction, no deuterium incorporation in the product **2a** was detected (Scheme 2, Eq. 1). In contrast, the reaction of **1a** in ace-



Scheme 2. Mechanistic experiments.

tonitrile containing 5% D<sub>2</sub>O by volume afforded the 1,2-dideuterated product [D<sub>2</sub>]-**2a** (Scheme 2, Eq. 2). When the nondeuterated product **2a** was exposed to identical conditions, deuterium was incorporated into the  $\alpha$ -position, whereas no H/D exchange was detected at the  $\beta$ -position (Scheme 2, Eq. 3). Taken together, the proton at the  $\beta$ -position of **2a** appears to be incorporated through protonation by water rather than as result of a proton transfer from the  $\alpha$ -position.<sup>[4]</sup> Under the standard conditions, a small amount of water was included in the reaction media due to the use of TBAF in a THF solution, and this water appears to serve as a proton source in the reaction.

Based on the experimental results, a plausible reaction mechanism is depicted in Scheme 3. First, the silicate V generated from TMSCN and TBAF reacts with nitroalkene I to provide intermediate VI, which is then protonated by water to give  $\beta$ -nitronitrile II. When the resulting hydroxide anion abstracts the  $\alpha$ -proton from II, elimination of the nitro group occurs to provide cyanoalkene III, along with Bu<sub>4</sub>NNO<sub>2</sub>, which is stable under the reaction.<sup>[17]</sup> Finally, the second Michael addition of a cyanide anion to III leads to the formation of dicyanated product IV. To establish the precise mechanism of the

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Scheme 3. Plausible reaction mechanism.

second Michael addition, we investigated the effect of an additive on the reaction of cyanoalkene, 2-methylene-4-phenylbutanenitrile (5 a'), with TMSCN.<sup>[18]</sup> Interestingly, the results showed that the cyanation reaction was promoted in the presence of a catalytic amount of fluoride anion, but not nitrite or hydroxide ions. Therefore, we propose a reaction mechanism that involves silicate V, which reacts with cyanoalkene III to afford the product IV through protonation of intermediate VII by water. However, the dicyanation proceeded smoothly in the presence of TMSCN and a half equivalent of TBAF. According to the reaction profile of 4a, one equivalent of silicate V generated at the start of the reaction would be rapidly consumed in the first Michael addition,<sup>[18]</sup> indicating that the resulting trimethylsilyl fluoride (TMSF) and Bu<sub>4</sub>NOH would participate in the equilibrium to regenerate TBAF, which then triggers the catalytic second Michael addition.<sup>[19]</sup> Based on the mechanism, most of the added TBAF is converted into inert Bu<sub>4</sub>NNO<sub>2</sub> via Bu₄NOH during the reaction. Therefore, an appropriate amount of TBAF is required to complete the dicyanation (Table 1, entries 2-4). Moreover, it is noteworthy that the "moist" conditions are a key factor for suppressing the polymerization by rapid protonation of anion intermediates (VI and VII), and regeneration of fluoride anion by the hydrolysis of TMSF.<sup>[20]</sup> As mentioned above, in this dicyanation, the hypervalent silicate V is a suitable nucleophile, but not Bu<sub>4</sub>NCN, which may form from V.

With optimized conditions in hand, we next explored the scope of the reactions with respect to aromatic *trans*- $\beta$ -nitroalkenes 1 (Table 2). Substrates bearing electron-donating groups provided the corresponding products 2 in excellent yields (entries 1–6). The reaction of 4-fluoro-*trans*- $\beta$ -nitrostyrene (**1h**) proceeded efficiently, whereas 4-Cl analogue 1i resulted in a lower yield (entries 7 and 8). Although reactions with highly electron-deficient substrates containing trifluoromethyl, cyano, and ester groups resulted in low yields due to the polymerization of the nitroalkenes, the addition of 1% water by volume was found to suppress the side reactions and improve the

product yields (entries 9-11).<sup>[21]</sup> Substrates bearing 2,6-dichloro or 3,4-dioxo functional groups, and a polycyclic aromatic moiety performed well (entries 12-16). Heteroaromatic moieties including pyridyl, thienyl, furyl, and indolyl groups were also compatible with the reaction (entries 17-20). Moreover, the introduction of four cyano groups in one treatment could be accomplished when the bis-nitroalkene 1v was used (entry 21).

In the case of the reaction of  $\alpha$ -methyl- $\beta$ -nitrostyrene (**1** w),  $\beta$ -nitronitrile **3** was obtained (Scheme 4, Eq. 1). This is attribut-

$$Ph \xrightarrow{\beta} NO_{2} \xrightarrow{\text{TMSCN (2 equiv)}}_{\text{BAF (1 equiv)}} Ph \xrightarrow{\beta} NO_{2} \xrightarrow{\text{TMSCN (2 equiv)}}_{\text{MeCN, RT, 2 h}} Ph \xrightarrow{\text{CN}} NO_{2} 375\%$$
(1)

$$Ph \xrightarrow{\alpha} NO_{2} \xrightarrow{\text{TMSCN (2 equiv)}}_{\substack{\text{TBAF (1 equiv)} \\ \text{MeCN, RT, 2 h}}} Ph \xrightarrow{\text{CN}} 2x \, 98\%^{[a]}$$
(2)

Scheme 4. Reactions of  $\alpha$ - or  $\beta$ -methyl- $\beta$ -nitrostyrenes. [a] The d.r. value could not be determined because of the overlap of the signals in the NMR spectra.

ed to the absence of a hydrogen atom at the  $\alpha$ -position, which is required for the production of the cyanoalkene intermediate. In contrast,  $\beta$ -methyl- $\beta$ -nitrostyrene (**1 x**) was smoothly converted into 1,2-dicyanoalkane 2x as a mixture of diastereomers (Scheme 4, Eq. 2); unfortunately, the diastereomeric ratio (d.r.) could not be determined because of overlap of the signals in the NMR spectra.

The successful transformation of aromatic nitroalkenes into 1,2-dicyanoalkanes prompted us to investigate the reactions of aliphatic nitroalkenes. When the simple aliphatic nitroalkene 4a was reacted under the standard conditions for 2 h, 1,2-dicyanated product 5a was obtained in low yield (22% yield), along with the corresponding cyanoalkene 5a' and  $\beta$ -nitronitrile 5 a".<sup>[18]</sup> Gratifyingly, these intermediates were nearly completely consumed when the reaction was conducted for 40 h, providing 5a in 80% yield (Table 3, entry 1). Sterically bulkier secondary benzyl, isopropyl, and tert-butyl substituted nitroalkenes were converted into the corresponding products in good yields (entries 2-4). Various types of functional groups,



Scheme 5. Representative transformations of dicvanoalkane 5i.

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including cyclopropane, olefin, epoxide, and alcohol moieties, were all well tolerated (entries 5–8). Fortunately, cyclic nitroalkene **4i** was also smoothly converted into the corresponding product under heating conditions (entry 9); performing this reaction at room temperature provided only the cyanoalkene. Although the latter reaction afforded **5i** as a mixture of diastereomers, a change in the ratio was observed during purification by flash column chromatography on silica gel, affording one stereoisomer predominantly. In addition, we found that the obtained dicyano compound **5i** could be further transformed into imide, dicarboxylic acid, and amidine derivatives (Scheme 5). Thus the developed method provides efficient access to valuable compounds from readily available nitro alkenes.

In addition to nitroalkenes, vinyl sulfones **6** were also suitable substrates for the dicyanation reaction (Table 4).<sup>[4]</sup> The reaction of vinyl sulfone **6a** with TMSCN in the presence of TBAF furnished **2a** in high yield (entry 1). The simplest terminal vinyl sulfone **6b** afforded succinonitrile (**7b**; entry 2). Although reactions using electron-deficient nitroalkenes such as  $\beta$ nitroacrylates and  $\beta$ -nitroacrylamides failed due to polymerization, use of the corresponding vinyl sulfones **6c** and **6d** led to the formation of 1,2-dicyano products **7c** and **7d**, respectively (entries 3 and 4).

## Conclusion

The straightforward synthesis of 1,2-dicyanoalkanes by the reaction of nitroalkenes with TMSCN in the presence of "moist" TBAF under mild conditions has been developed. A wide range of substrates, including electron-rich and electron-deficient aromatic nitroalkenes, and aliphatic nitroalkenes, are tolerated in the reaction. Moreover, vinyl sulfones were found to be good alternatives, particularly for electron-deficient nitroalkenes. The reaction system is very useful and practical from the point of view of the availability of starting materials. In addition, detailed mechanistic studies suggest a unique mechanism for the dicyanation under "moist" conditions.

#### **Experimental Section**

#### General procedure for dicyanation

TBAF (1  $\mbox{m}$  in THF, 0.2 mmol) was added to a mixture of nitroalkene (0.2 mmol) and TMSCN (0.4 mmol) in MeCN (4 mL), under an atmosphere of N<sub>2</sub>. The mixture was stirred for 2 h at RT, then the reaction was quenched by elution through a short column of silica gel with ethyl acetate. The solution was concentrated to give the crude product, which was purified by flash column chromatography (silica gel) to give the product.

#### Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research (No. 25288047 and No. 26105735) from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT), Japan.

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Table 3. Scope of the reaction with respect to aliphatic nitroalkenes. <sup>[a]</sup>							
	R NO <sub>2</sub> +	TMSCN (3 equiv)	TBAF (1 equiv) MeCN, RT, 40 h				
Entry	4		5		Yield [%] <sup>[b]</sup>		
1 <sup>[c]</sup>	Ph NO <sub>2</sub>	4a		5 a	80		
2 <sup>[c]</sup>	Ph NO <sub>2</sub>	4 b	Ph CN	5 b	74 <sup>[d]</sup>		
3	NO <sub>2</sub>	4c		5 c	70		
4	NO <sub>2</sub>	4 d		5 d	67		
5	NO <sub>2</sub>	4e		5 e	77		
6	NO <sub>2</sub>	4 f		5 f	65		
7	O NO <sub>2</sub>	4 g		5 g	70 <sup>[e]</sup>		
8 <sup>[f]</sup>		0 <sub>2</sub> 4h		N 5 h	83 <sup>[e]</sup>		
9 <sup>[g]</sup>	NO <sub>2</sub>	4i		5i	89 <sup>[e]</sup>		

[a] Reaction conditions: nitroalkene (0.2 mmol), TMSCN (0.6 mmol), TBAF (1  $\mu$  in THF, 0.2 mL), MeCN (4 mL), RT, 40 h. [b] Isolated yield. [c] TMSCN (2 equiv) was used. [d] A d.r. of 1:1 was determined by <sup>1</sup>H NMR spectroscopic analysis. [e] The d.r. value could not be determined because of the overlap of signals in the NMR spectra. [f] Reaction performed on 0.05 mmol scale. [g] Reaction was carried out at 80 °C for 20 h.

Table 4. Scope of the reaction with respect to vinyl sulfones. <sup>[a]</sup>							
Entry	6		Time [h]	Product		Yield [%] <sup>[b]</sup>	
1 <sup>[c]</sup>	Ph SO <sub>2</sub> Ph	6a	20		2 a	80	
2 <sup>[c]</sup>	SO <sub>2</sub> Ph	6 b	20	CN CN	7 b	98	
3		6 c	2		7 c	83	
4	Me <sub>2</sub> N Ts	6 d	6	Me <sub>2</sub> N CN	7 d	85	

[a] Reaction conditions: vinyl sulfone (0.2 mmol), TMSCN (0.4 mmol), TBAF (1  ${\rm M}$  in THF, 0.2 mL), MeCN (4 mL), RT. [b] Isolated yield. [c] TMSCN (3 equiv) and TBAF (2 equiv) were used.

**Keywords:** cyanides • fluoride • Michael addition • reaction mechanism • synthetic methods

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- [17] The ammonium nitrite, Bu<sub>4</sub>NNO<sub>2</sub>, was isolated quantitatively by silica gel column chromatography after the reaction. See the Supporting Information for details.
- [18] See the Supporting Information for details.
- [19] The use of Bu<sub>4</sub>NOH as a catalyst in combination with PhMe<sub>2</sub>SiF promoted the reaction of 2-methylene-4-phenylbutanenitrile (5 a') with TMSCN. See the Supporting Information for details. The hydrolysis of TMSF under basic conditions has been reported, see: J. A. Gibson, A. F. Janzen, *Can. J. Chem.* 1972, *50*, 3087.
- [20] Although it is unlikely that TMSF can function as a Lewis acid in the reaction system, the possibility cannot be ruled out at this stage.
- [21] Without the addition of water, 1 j, 1 k, and 1 l were obtained in 61, 45, and 27%, respectively. See the Supporting Information for details.

Received: August 8, 2014 Published online on ■■ ■, 0000



# **FULL PAPER**

**Direct cyanation**: A straightforward synthesis of 1,2-dicyanoalkanes by the reaction of nitroalkenes with trimethylsilyl cyanide in the presence of tetrabutylammonium fluoride (TBAF) is reported (see scheme). The method has wide substrate scope and tolerates a wide variety of functional groups. Mechanistic studies suggest that a small amount of water present in the reaction media plays a key role in the reaction.



## Synthetic Methods

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Straightforward Synthesis of 1,2-Dicyanoalkanes from Nitroalkenes and Silyl Cyanide Mediated by Tetrabutylammonium Fluoride