

# Potassium phthalimide-*N*-oxyl: An efficient catalyst for cyanosilylation of carbonyl compounds under mild conditions

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## Abstract

Potassium phthalimide-*N*-oxyl was used as an effective, easy to handle and readily available Lewis basic organocatalyst for the facile addition of trimethylsilyl cyanide to various carbonyl compounds at room temperature under mild conditions to afford corresponding cyanohydrin trimethylsilyl ethers in high to quantitative yields. The high yields of products, high turnover numbers of the catalyst, compatibility of other functional groups, and simplicity in the operation are the advantages of this method.

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**Keywords:** Cyanohydrins; Carbonyl compounds; Potassium phthalimide-*N*-oxyl; Nucleophilic catalyst

## 1. Introduction

Cyanohydrins and corresponding trimethylsilyl ethers are versatile intermediates in the preparation of a wide range of pharmaceuticals, agrochemicals and insecticides [1–4]. They can easily be converted into various functionalized  $\alpha$ -hydroxy acids,  $\alpha$ -hydroxy aldehydes,  $\beta$ -amino alcohols and other polyfunctional compounds [4]. The addition of trimethylsilyl cyanide (TMSCN) to carbonyl compounds, including aldehydes and ketones is a well-established route to afford trimethylsilylated cyanohydrins of which the preparation is difficult by the traditional methods [1–17]. The reaction is catalyzed by Lewis acids [8] as well as Lewis bases [9] or double activating catalytic systems. It is therefore not surprising that many catalysts have been developed for this transformation [8–10].

On the other hand, the past few years have witnessed major advances in new catalytic methods based on organic compounds as organocatalysts to replace the traditional transition metal–ligand catalytic systems [10,11]. Hence, various organocatalysts have also been applied to catalyze addi-

tion of TMSCN to carbonyl compounds at the threshold of their application in organic synthesis [9–17]. Among them, trisaminophosphines [9], stable *N*-heterocyclic carbenes (NHCs) [10], imidazolium-carbodithioate zwitterions [11], alkali metal salts of amino acids [12], *N*-oxides and their combination with quaternary ammonium salt [13], tetrabutylammonium cyanide [14], substituted guanidines [15], tertiary amines [16], derivatives of thia-urea [17] are worthwhile to be mentioned. However, most of these catalytic systems require multi-step preparation, the use of strong bases such as potassium *t*-butoxide, high catalyst to substrate mole ratio, inert atmosphere, long reaction times and laborious work-up procedure [9–17]. Therefore, development of new catalysts which operate under milder conditions is a challenge attracting much attention.

Recently, we have reported the first catalytic cyclotrimerization of aryl and alkyl isocyanates using potassium phthalimide-*N*-oxyl (PPINO) [18]. On the basis of our previous results and to develop the catalytic scope of the phthalimide-*N*-oxyl (PINO) nucleophile, we decided to examine the feasibility and efficiency of the PINO-catalyzed cyanosilylation of carbonyl compounds. Herein, we disclose the application of PPINO as an efficient organocatalyst to the addition of TMSCN to carbonyl compounds under mild conditions affording various cyanohydrin trimethylsilyl ethers.

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## 2. Experimental

### 2.1. General

FT IR spectra were recorded as KBr pellets on a Shimadzu FT IR-8400S spectrometer.  $^1\text{H}$  NMR (500 MHz) and  $^{13}\text{C}$  NMR (125 MHz) spectra were obtained using a Bruker DRX-500 AVANCE spectrometer. All NMR spectra were determined in  $\text{CDCl}_3$  at ambient temperature. GC chromatograms were recorded on a Shimadzu 2010 instrument. All chemicals were purchased from Merck or Aldrich and used as received except for benzaldehyde which a fresh distilled sample was used. Commercially available  $\text{CH}_3\text{CN}$  and  $\text{CH}_2\text{Cl}_2$  were respectively distilled from  $\text{CaCl}_2$  and dried on 4 Å molecular sieve supplied by Carl Roth GmbH + Co, 76185 Karlsruhe, Germany. Catalysts were powdered and dried at 70 °C for 1 h under reduced pressure [18]. All reactions were protected from moisture using a  $\text{CaCl}_2$  guard tube. Analytical TLC was carried out using Merck 0.2 mm silica gel 60 F-254 Al-plates. All compounds well characterized by GC analysis, IR and NMR spectral data by comparison with those obtained from authentic samples or reported in the literature [8b,c,10a,d].

### 2.2. General procedure for cyanosilylation of carbonyl compounds

TMSCN (1.2 mmol, 0.15 mL) was added to the stirred mixture of 1.0 mmol of a carbonyl compound dissolved in 5.0 mL  $\text{CH}_2\text{Cl}_2$  and 5.0 mg of PPINO. The mixture was stirred at room temperature for 20–240 min. The reaction was monitored by TLC. Then, the reaction mixture was quenched by water (2.5 mL) and the organic materials were extracted with  $\text{CH}_2\text{Cl}_2$  (2 mL  $\times$  5.0 mL). The obtained organic phase was washed with brine and water (5.0 mL), respectively and dried over  $\text{MgSO}_4$ . The solvent was evaporated on a rotary evaporator to afford the desired products which in some cases were essentially pure cyanohydrin TMS ethers. Further purification of the products was performed by silica gel column chromatography (EtOAc-Hexane, 1:10). The isolated yields were in good agreement with those obtained by GC analysis.

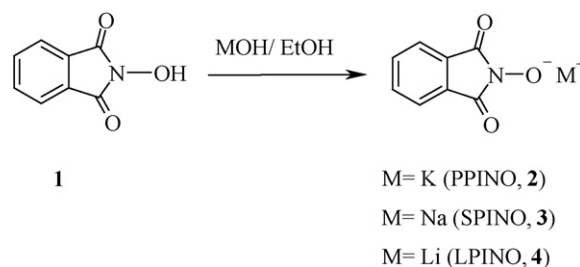
### 2.3. Selected spectroscopic data

#### 2.3.1. 2-(4-Chlorophenyl)-2-(trimethylsilyloxy) acetonitrile (**9a**)

Yield 100%;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.28 (s, 9H), 5.53 (s, 1H), 7.41–7.42 (d,  $J$  = 8.50, 2H), 7.45–7.46 (d,  $J$  = 8.50, 2H).  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ ):  $\delta$  -0.3, 62.9, 118.8, 127.7, 129.1, 134.8, 135.2.

#### 2.3.2. (2-Nitrophenyl)-2-(trimethylsilyloxy) acetonitrile (**9b**)

Yield 100%;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.31 (s, 9H), 6.25 (s, 1H), 7.61–7.65 (t,  $J$  = 8.20, 1H), 7.79–7.82 (t,  $J$  = 7.80, 1H), 8.04–8.06 (d,  $J$  = 7.80, 1H), 8.16–8.18 (d,  $J$  = 8.20, 1H);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.0, 60.6, 117.5, 125.9, 129.5, 130.9, 131.0, 134.9, 147.0.



Scheme 1.

#### 2.3.3. (4-Methoxyphenyl)-2-trimethylsilyloxy acetonitrile (**9i**)

Yield 93%;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.08 (s, 9H), 3.77 (s, 3H) 5.40 (s, 1H) 6.88–6.90 (d,  $J$  = 8.70, 2H), 7.37–7.39 (d,  $J$  = 8.70, 2H).  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.86, 55.47, 62.99, 114.51, 119.39, 127.78, 128.36, 160.54.

## 3. Results and discussions

Since *N*-hydroxyphthalimide **1** has a  $\text{p}K_a$  of 6.1, its alkali-metal salts **2–4** were simply prepared in quantitative yields by the reaction of *N*-hydroxyphthalimide **1** with an equivalent amount of the corresponding metal hydroxide in ethanol at room temperature or under reflux conditions (Scheme 1) [18].

A series of preliminary exploratory experiments revealed that 2.5 mol% of PPINO **2** can promote the addition of TMSCN to 4-chlorobenzaldehyde **5a** in dichloromethane at room temperature with a quantitative yield, demonstrating it as catalyst of choice for this transformation (Entry 4, Table 1). No reaction was observed under similar reaction conditions in the absence of PPINO. Further experiments were carried out by using sodium phthalimide-*N*-oxyl **3** and lithium phthalimide-*N*-oxyl **4** to compare their catalytic activities with PPINO in similar conditions. These salts showed lower activity than PPINO in this process (Entries 6,7, Table 1). The reactivity of different alkali metal salts of phthalimide-*N*-oxyl followed the sequence of  $\text{K} > \text{Na} > \text{Li}$ .

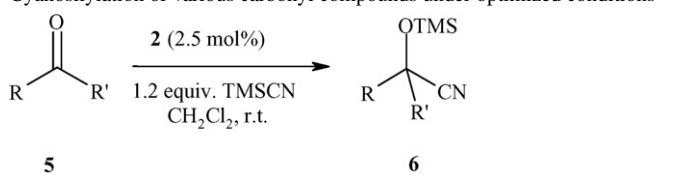
Having optimal conditions of this reaction (2.5 mol% of PPINO, TMSCN/aldehyde = 1.2 equiv.,  $\text{CH}_2\text{Cl}_2$ , r.t.) in hand, the reactivity of various aldehydes were investigated in the next step. The results have been summarized in Table 2. Aromatic, heterocyclic and aliphatic aldehydes have been efficiently converted. The data in Table 2 clearly show that all substrates react

Table 1  
Optimization of the cyanosilylation of 4-chlorobenzaldehyde catalyzed by PINO salts at room temperature<sup>a</sup> (Entry 1, Table 2)

Entry	Catalyst	mol%	Solvent	Time	Yield
1	PPINO <b>2</b>	10.0	$\text{CH}_3\text{CN}$	3.0 h	99
2	PPINO <b>2</b>	5.0	$\text{CH}_3\text{CN}$	3.0 h	97
3	PPINO <b>2</b>	2.5	$\text{CH}_3\text{CN}$	3.0 h	96
4	PPINO <b>2</b>	2.5	$\text{CH}_2\text{Cl}_2$	20 min	100
5	–	–	$\text{CH}_2\text{Cl}_2$	3.0 h	0.0
6	SPINO <b>3</b>	2.5	$\text{CH}_2\text{Cl}_2$	40 min	88
7	LPINO <b>4</b>	2.5	$\text{CH}_2\text{Cl}_2$	3.0 h	86

<sup>a</sup> All reactions were performed in the shown solvent (0.2 M solution of the aldehyde).

Table 2  
Cyanosilylation of various carbonyl compounds under optimized conditions



Entry	Carbonyl compound (5)	Time	Product (9)	Yield (%)
1	4-Chlorobenzaldehyde ( <b>5a</b> )	20 min	<b>9a</b>	100
2	2-Nitrobenzaldehyde ( <b>5b</b> )	20 min	<b>9b</b>	99
3	4-Cyanobenzaldehyde ( <b>5c</b> )	20 min	<b>9c</b>	100
4	3-Nitrobenzaldehyde ( <b>5d</b> )	30 min	<b>9d</b>	98
5	4-Bromobenzaldehyde ( <b>5e</b> )	90 min	<b>9e</b>	99
6	Benzaldehyde ( <b>5f</b> )	90 min	<b>9f</b>	98
7	4-Methylbenzaldehyde ( <b>5g</b> )	60 min	<b>9g</b>	95
8	2-Methoxybenzaldehyde ( <b>5h</b> )	60 min	<b>9h</b>	96
9	4-Methoxybenzaldehyde ( <b>5i</b> )	4.0 h	<b>9i</b>	93
10	Furfural ( <b>5j</b> )	4.0 h	<b>9j</b>	92
11	Thiophen-2-carbaldehyde ( <b>5k</b> )	4.0 h	<b>9k</b>	90
12	2-Naphthaldehyde ( <b>5l</b> )	30 min	<b>9l</b>	96
13	Cinnamaldehyde ( <b>5m</b> )	60 min	<b>9m</b>	100
14	3-Phenylpropanal ( <b>5n</b> )	60 min	<b>9n</b>	96
15	Octanal ( <b>5o</b> )	4.0 h	<b>9o</b>	94
16	Acetophenone ( <b>5p</b> ) <sup>a</sup>	4.0 h	<b>9p</b>	90
17	Cyclohexanone ( <b>5q</b> ) <sup>a</sup>	4.0 h	<b>9q</b>	93

<sup>a</sup> 7.5 mol% of the catalyst **2** was used.

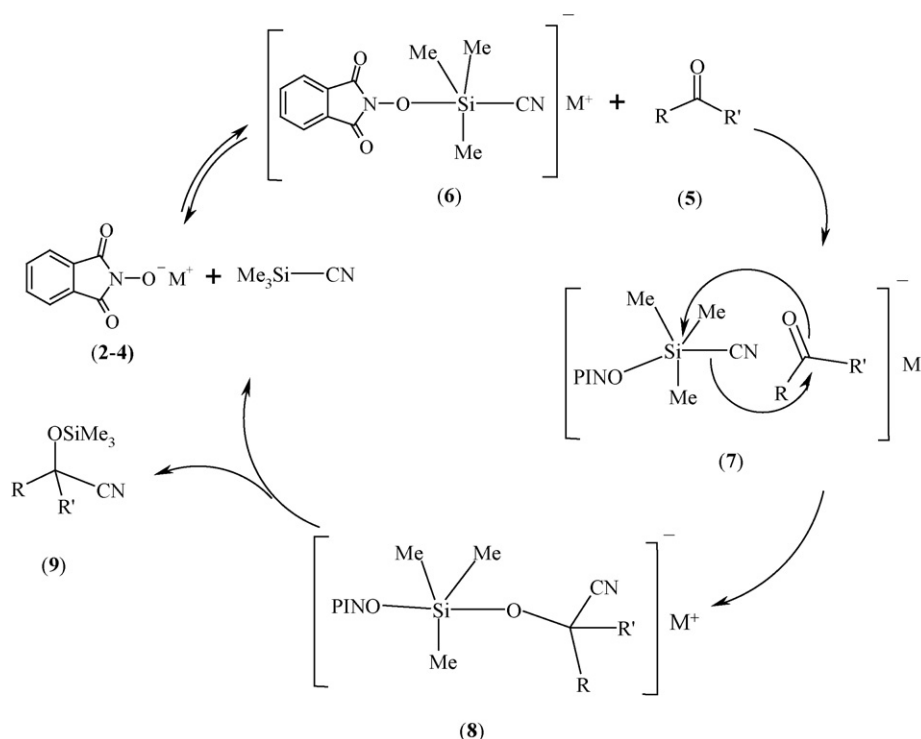
smoothly under optimal conditions to give the desired products in high to quantitative yields.

No by-products such as product of benzoin condensation or desilylation have been isolated. Furthermore, cinnamaldehyde

as an  $\alpha,\beta$ -unsaturated aldehyde reacted solely in the 1,2-mode and no Michael addition product was detected. On the other hand, this protocol is especially suitable for substrates such as furfural, thiophene-2-carbaldehyde and cinnamaldehyde which are polymerized or decomposed under acidic conditions. In general, the reaction conditions are mild and catalyst could be easily separated by aqueous extraction from the reaction mixture.

As shown in Table 2, electronic effects and the nature of the substituents on the aromatic ring showed relatively strong effects on the required reaction time for the complete conversion of aldehydes. In general, substrates containing electron-withdrawing groups (Entries 2–5) react much faster than ones bearing electron-donating groups (Entries 7–15). However, 4-bromobenzaldehyde **5e** did not demonstrate any substantial substituent effect and its reaction was completed after 90 min. Whereas 4-methoxybenzaldehyde **5i** required 4 h, 2-methoxybenzaldehyde **5h** completed cyanosilylation only after 1 h due to the “*ortho effect*”. Interestingly, 2-naphthaldehyde **5l** required short reaction time. On the other hand, due to the steric bulk, ketones such as acetophenone and cyclohexanone required higher catalyst loading (7.5 mol%) and longer reaction times than aldehydes to obtain the corresponding cyanohydrin trimethylsilyl ethers in near quantitative yields (Entries 16,17).

The mechanism of the PINO-catalyzed cyanosilylation probably involves the initial activation of TMSCN by its coordination with the most basic oxygen of the PINO anion and subsequent release of the nucleophilic cyanide ion to add to the carbonyl moiety in a rate-determining step followed by silylation and formation of the product **9** (Scheme 2).



Scheme 2. Postulated mechanism of the reaction.

Table 3  
Comparison of the results obtained by cyanosilylation of aldehydes with TMSCN in the presence of PPINO (1), with those catalyzed by NHCs (2), imidazolium-carbodithioate zwitterions (3) and K<sub>2</sub>CO<sub>3</sub> (4)

Entry	Substrate	Method [mol%/ Time (min)/ Yield (%)]			
		1	2	3	4
1	Benzaldehyde	2.5/90/98	10/180/95	10/960/99	3/40/99
2	4-Chlorobenzaldehyde	2.5/20/100	5/120/80	–	3/20/99
3	4-Methoxybenzaldehyde	2.5/240/93	10/180/90	10/3300/82	3/360/93
4	2-Naphthaldehyde	2.5/30/96	5/30/69	10/900/99	–
5	Cinnamaldehyde	2.5/60/100	5/30/75	–	3/180/82
6	3-Phenylpropanal	2.5/60/96	10/5/90	–	–

Considerable advancement has been made during the recent years in the Lewis base catalyzed reactions, using silylated reagents. On the other hand, among the various silicon derivatives, trimethylsilyl compounds are the most common reagents in organic synthesis. Therefore, it is anticipated that base-promoted reactions using trimethylsilyl compounds will be expanded in the future. Oxygen-containing nucleophiles are more efficient catalysts due to high bond strength as well as the kinetic lability of the silicon–oxygen bond. As a consequence, development of more efficient oxygen-containing nucleophiles such as the PINO anion, which are catalytic in nature, less basic, cost-effective, and simple to use, is very important [19,20].

To illustrate the efficiency of the proposed method, Table 3 is shown to compare our results with those reported in the literature [10a,10c,11,12b].

#### 4. Conclusion

In conclusion, potassium phthalimide-*N*-oxyl was found to be an excellent and readily available catalyst for cyanosilylation of various carbonyl compounds under mild conditions. It compares favorably with and represents a valid alternative to the existing methods. Attractive features of the method include the general application, high turnover numbers under mild conditions and simplicity in the preparation, operation and separation of the catalyst. The catalytic ability of PINO anion has been developed for the addition of TMSCN to carbonyl compounds for the first time and this would be useful in other reactions using trimethylsilyl compounds. Further studies on preparation of other useful PINO salts and development of its catalytic scope are in progress and would be presented in due course.

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