Dibutyltin Dibromide-catalyzed Trimethylsilylcyanation of Aldehydes and Imines

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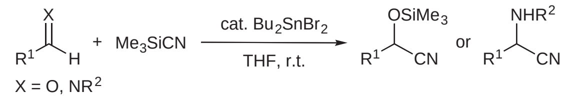
Dibutyltin dibromide efficiently catalyzes addition of trimethylsilyl cyanide to aldehydes and aldimines. Various trimethylsilylated cyanohydrins and α-aminonitriles are obtained in moderate to high yield by this method.

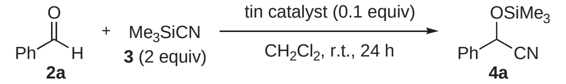
Organotin(IV) reagents such as trialkyltin enolates and allylic trialkyltins are known to have moderate nucleophilicity and have been often utilized for carbon–carbon bond forming reactions; however, their use in organic synthesis is somewhat limited because of their toxicity.[1] To overcome this difficulty, we attempted to develop the above-mentioned reactions promoted by a catalytic amount of organotin(IV) compounds and as a result, we found an aldol reaction of alkenyl trichloroacetates catalyzed by dibutyltin dimethoxide, which is efficiently recycled with the assistance of methanol.[2] By taking advantage of this catalytic system, the Mannich-type reaction of aldimines[3] and the Michael addition to *p*-benzoquinone[4] have been also achieved. As for these reactions, noteworthy is the fact that organotin(IV) enolates are generated catalytically and immediately undergo addition to the corresponding electrophiles. In addition, we have found a dibutyltin oxide-catalyzed allyl-transfer reaction from tertiary homoallylic alcohols to aldehydes, in which a catalytic amount of an allylic tin compound is formed in situ.[5] Our interest in the catalytic ability of these organotin(IV) compounds has led us to undertake a further investigation of related tin species. Here, we wish to describe a cyanation of aldehydes and imines with trimethylsilyl cyanide catalyzed by dibutyltin dibromide (Scheme 1).

Cyanohydrins are versatile synthetic intermediates for diverse natural products, which are further transformable into α-hydroxycarboxylic acids or α-hydroxyketones.[6] In order to construct the cyanohydrin moiety efficiently, various metal catalysts have been applied to silylcyanation of aldehydes.[7] As for organotin(IV) compounds, tributyltin cyanide has been found to catalyze addition of triethylsilyl cyanide to aldehydes[8] and relevant acylcyanation.[9] In 1996, Whitesell and Apodaca have reported that dibutyltin dichloride is an effective catalyst for trimethylsilylcyanation of aldehydes and ketones in the absence of solvent.[10] They measured a 1:1 mixture of Bu_2SnCl_2 and Me_3SiCN in $CDCl_3$ by ^{1}H NMR at room temperature and detected Me_3SiCl (ca. 5%) which suggests a tin cyanide as a catalytically active species. This result prompted us to examine Bu_2SnBr_2 (**1**), which is anticipated to show higher catalytic activity than that of Bu_2SnCl_2.[11] So, we carried out a reaction of benzaldehyde (**2a**) with Me_3SiCN (**3**) in the presence of 10 mol % Bu_2SnBr_2 (**1**) in CH_2Cl_2 under more diluted conditions than Whitesell's conditions and compared its catalytic activity with other organotin(IV) reagents (Table 1). As a result, Bu_2SnBr_2 (**1**) afforded the desired trimethylsilylated cyanohydrin **4a** in 52% yield in the reaction at room temperature for 24 h (Entry 1). In contrast, Bu_2SnCl_2 indicated lower reactivity under similar reaction conditions (Entry 2). $Bu_2Sn(OMe)_2$ and Bu_2SnO, which were effective catalysts for the aforementioned aldol reaction[2] and allyl-transfer reaction,[5] had almost no catalytic activity in the present cyanation (Entries 3 and 4).



Scheme 1. Bu_2SnBr_2-catalyzed cyanation of aldehydes and imines.

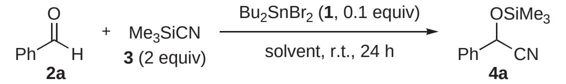
Table 1. Screening of tin catalysts in trimethylsilylcyanation of benzaldehyde (**2a**) with cyanotrimethylsilane (**3**)[a]



Entry	Tin catalyst	Yield/%[b]
1	Bu_2SnBr_2 (**1**)	52
2	Bu_2SnCl_2	14
3	$Bu_2Sn(OMe)_2$	3
4	Bu_2SnO	3
5	Bu_3SnBr	<1

[a] The reaction was carried out employing cyanotrimethylsilane (**3**, 2 equiv), benzaldehyde (**2a**, 1 equiv), and tin catalyst (0.1 equiv) in CH_2Cl_2 at room temperature for 24 h. [b] Isolated yield.

Table 2. Solvent effect on trimethylsilylcyanation of benzaldehyde (**2a**) with cyanotrimethylsilane (**3**) catalyzed by Bu_2SnBr_2 (**1**)[a]

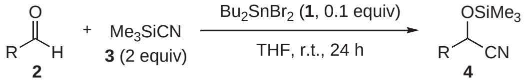


Entry	Solvent	Yield/%[b]
1	CH_2Cl_2	52
2	THF	78
3[c]	THF	<1
4	MeCN	62
5	DMF	<1
6	MeOH	<1
7	Toluene	<1

[a] The reaction was carried out employing cyanotrimethylsilane (**3**, 2 equiv), benzaldehyde (**2a**, 1 equiv), and dibutyltin dibromide (**1**, 0.1 equiv) in a specified solvent at room temperature for 24 h. [b] Isolated yield. [c] Bu_2SnCl_2 was used as a catalyst instead of Bu_2SnBr_2 (**1**).

In order to obtain a more satisfactory yield, we then investigated solvent effects (Table 2). Among the solvents tested, THF was found to furnish a higher yield than that given in CH_2Cl_2 (Entries 1 and 2), while Bu_2SnCl_2 did not promote the cyanation at all in the former solvent (Entry 3). Acetonitrile was also a promising solvent (Entry 4), however, use of DMF, MeOH, and toluene resulted in totally unacceptable yields (Entries 5–7).

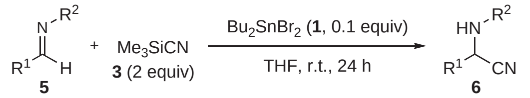
Table 3. Bu_2SnBr_2 (**1**)-catalyzed trimethylsilylcyanation of various aldehydes **2** with trimethylsilyl cyanide (**3**)[a]



Entry	Aldehyde	Yield/%[b]
1	PhCHO (**2a**)	78
2	*p*-$MeOC_6H_4CHO$ (**2b**)	65
3	*o*-$MeOC_6H_4CHO$ (**2c**)	70
4	2-$C_{10}H_7CHO$ (**2d**)	74
5	(*E*)-PhCH=CHCHO (**2e**)	68
6	$Ph(CH_2)_2CHO$ (**2f**)	74
7	*c*-$C_6H_{11}CHO$ (**2g**)	68

[a]The reaction was carried out using cyanotrimethylsilane (**3**, 2 equiv), aldehyde (**2**, 1 equiv), and dibutyltin dibromide (**1**, 0.1 equiv) in THF at room temperature for 24 h. [b]Isolated yield.

Table 4. Bu_2SnBr_2 (**1**)-catalyzed cyanation of various aldimines **5** with trimethylsilyl cyanide (**3**)[a]



Entry	R^1	R^2	Yield/%[b]
1	Ph	Ph (**5a**)	99
2	Ph	*p*-BrC_6H_4 (**5b**)	>99
3	Ph	*p*-$MeOC_6H_4$ (**5c**)	>99
4	*p*-$CF_3C_6H_4$	Ph (**5d**)	96
5	*p*-$MeOC_6H_4$	Ph (**5e**)	>99
6	*o*-$MeOC_6H_4$	Ph (**5f**)	95
7	*p*-$MeOC_6H_4$	*p*-BrC_6H_4 (**5g**)	95
8	1-Naphthyl	Ph (**5h**)	98
9	2-Furyl	Ph (**5i**)	97

[a]The reaction was carried out using cyanotrimethylsilane (**3**, 2 equiv), aldimine (**5**, 1 equiv), and dibutyltin dibromide (**1**, 0.1 equiv) in THF at room temperature for 24 h. [b]Isolated yield.

Under thus optimized reaction conditions, we finally performed cyanation of various aldehydes **2** with cyanotrimethylsilane (**3**) catalyzed by Bu_2SnBr_2 (**1**) in THF. The results are shown in Table 3. Not only aromatic aldehydes **2a**–**2d** but α,β-unsaturated aldehyde **2e** and aliphatic aldehydes **2f** and **2g** were also efficiently silylcyanated and the corresponding α-trimethylsiloxynitriles **4** were obtained in good yield. In the case of cinnamaldehyde (**2e**), only a 1,2-adduct was observed (Entry 5).

We further attempted addition of cyanotrimethylsilane (**3**) to aldimines **5** using Bu_2SnBr_2 (**1**) as a catalyst. The Strecker-type reaction is a beneficial route to α-amino acids or 1,2-diamines via α-aminonitriles.[7c,12] First, we tested the optimized reaction conditions for the above-mentioned trimethylsilylcyanation of aldehydes. When *N*-benzylideneaniline (**5a**) was treated with two equivalents of Me_3SiCN (**3**) in the presence of 0.1 equiv of Bu_2SnBr_2 (**1**) in THF at room temperature for 24 h, the targeted α-aminonitrile **6a** was obtained in 99% yield (Table 4, Entry 1). Thus, we carried out the cyanation of various aldimines **5** under the reaction conditions and Table 4 indicates representative examples. As a result, in addition to electron-deficient imines **5b** and **5d**, electron-rich imines **5c**, **5e**, and **5f** also gave the corresponding cyanated product **6** almost quantitatively (Entries 2–6).

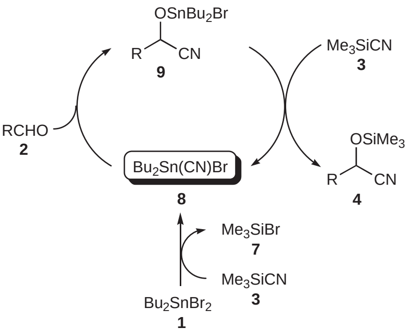


Figure 1. A probable catalytic cycle.

A possible catalytic mechanism for the present cyanation of aldehydes is shown in Figure 1.[10] First, Bu_2SnBr_2 (**1**) reacts with cyanotrimethylsilane (**3**) to give Me_3SiBr (**7**) and dibutyltin bromide cyanide (**8**). Subsequently, the tin cyanide **8** is allowed to add to aldehyde **2**, yielding tin alkoxide of cyanohydrin **9**. Finally, silylation of the tin alkoxide **9** with **3** completes the catalytic cycle by regenerating the tin bromide cyanide **8** and furnishing the desired product **4**. An alternative catalytic mechanism in which dibutyltin dicyanide is recycled in place of $Bu_2Sn(CN)Br$ (**8**) is also possible.

In summary, we have achieved a Bu_2SnBr_2-catalyzed addition reaction of Me_3SiCN to aldehydes and imines. The tin catalyst is efficiently regenerated via $Bu_2Sn(CN)Br$ under the mild reaction conditions and various trimethylsilylated cyanohydrins and α-aminonitriles can be obtained in satisfactory yield. The procedure is operationally simple and can be performed using readily available chemicals.

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