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Communication

Synthesis of 1,2-phenylenedimethanols by base-promoted reduction of isobenzofuran-1(3*H*)-ones with silane Bin Liu^{a,b}, Xigeng Zhou^{a,*}

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Graphical abstract



An efficient method for preparation of substituted 1,2-phenylenedimethanols and aliphatic 1,4-diols that are valuable intermediates in organic synthesis, has been developed by the base-promoted reduction of isobenzofuran-1(3H)-ones and γ -lactones with silane under mild conditions. Compared with traditional procedures using stoichiometric amounts of metal hydrides and alkyl reductants, the present method avoids the use of sensitive reagents and is operationally simple, and a broad variety of functional groups are tolerated.

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ABSTRACT

An efficient method for preparation of substituted 1,2-phenylenedimethanols and aliphatic 1,4diols that are valuable intermediates in organic synthesis, has been developed by the basepromoted reduction of isobenzofuran-1(3H)-ones and γ -lactones with silane under mild conditions. Compared with traditional procedures using stoichiometric amounts of metal hydrides and alkyl reductants, the present method avoids the use of sensitive reagents and is operationally simple and a broad variety of functional groups are tolerated.

1,2-Phenylenedimethanols and aliphatic 1,4-diols are valuable intermediates in organic synthesis. For example, 1,2-phenylenedimethanols can be used for preparing 1,3-dihydroisobenzofuran [1], 1,2-bis(bromomethyl)benzene [2], or *o*-phthalaldehyde [3]. Therefore, development of new methods for synthesis of substituted 1,4-diols is of broad interests.

Isobenzofuran-1(3*H*)-ones and γ -lactones are important heterocycles that are readily extracted from natural products or synthesized conveniently [4]. There was much interest in developing hydrogenative reduction of such types of substrates to 1,4-diols. Despite much progress in the catalytic hydrogenation of isobenzofuran-1(3*H*)-ones and γ -lactones to the corresponding 1,4-diols with the use of H₂ [5], in most cases high hydrogen pressure reaction conditions and expensive transition-metal catalysts were needed to obtain high yields. Alternatively, several methods without the presence of H₂ have also been developed, but these protocols require the use of stoichiometric amounts of water-sensitive metal hydrides such as DIBAL-H [6], LiAlH₄ [7], LiBH₄, NaH or metal alkyl complex [8] as the reducing agent or co-reductant, which not only produce large amounts of salt wastes and thus make product purification difficult,

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but also limit the substrate scope. Therefore, the development of new reducing systems for transformation of isobenzofuran-1(3*H*)-ones and γ -lactones into the corresponding 1,4-diols is still highly desirable.

Very recently, we reported that hydrosilanes are efficient reducing reagents for the transformation of 6H-isoindolo[2,1-a]indol-6ones to 2-(-1*H*-indol-2-yl)benzyl alcohols [9]. As a part of our continuing research on making use of hydrosilanes as a practical organic reagent, we become interested in the reduction of isobenzofuran-1(3*H*)-ones and γ -lactones to the corresponding 1,4-diols with hydrosilanes. Herein, we describe details of the hydrogenative reduction of of isobenzofuran-1(3*H*)-ones and γ -lactones with hydrosilanes to give various 1,4-diols.

We initiated our research on the model reaction of isobenzofuran-1(3H)-one (**1a**), base and PhSiH₃ under different reaction conditions (Table 1). We firstly elected KOH as the base. Screening several different reductants such as PhSiH₃, Ph₂SiH₂ and TMDS (1,1,3,3-tetramethyldisiloxane) (Table 1, entries 1-3), it was found that PhSiH₃ gave the best result with 98% yield (Table 1, entry 1). Shortening the time led to a decrease of yield (Table 1, entry 4). The further investigation results indicated that other bases examined, such as *t*-BuONa, NaOH, K₂CO₃ and Na₂CO₃, were less effective (Table 1, entries 5-8). Other solvents, such as 2-methyltetrahydrofuran and dioxane, were less effective (Table 1, entries 9-10). Decreasing amount of KOH (Table 1, entry 11) or PhSiH₃ used (Table 1, entries 12-14) led to a decrease of yields. Besides, decreasing the reaction temperature led to a decrease of yields (Table 1, entries 15-16). No desired reaction occurred without the presence of base or silane (Table 1, entries 17-18).

Table 1

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Base, silane, and solvent effects.^a

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	Base, Silane	\int	
	Solvent	OH	
1a		2a	
Entry	Additive (equiv.)	Reductant (equiv.)	Yield (%) ^b
1	KOH (1.0)	PhSiH ₃ (3.0)	98
2	KOH (1.0)	Ph ₂ SiH ₂ (3.0)	60
3°	KOH (1.0)	TMDS (3.0)	trace
4^{d}	KOH (1.0)	PhSiH ₃ (3.0)	62
5	t-BuONa (1.0)	PhSiH ₃ (3.0)	92
6	NaOH (1.0)	PhSiH ₃ (3.0)	88
7	$K_2CO_3(1.0)$	PhSiH ₃ (3.0)	70
8	Na ₂ CO ₃ (1.0)	PhSiH ₃ (3.0)	62
9 ^e	KOH (1.0)	PhSiH ₃ (3.0)	86
$10^{\rm f}$	KOH (1.0)	PhSiH ₃ (3.0)	85
11	KOH (0.5)	PhSiH ₃ (3.0)	58
12	KOH (1.0)	PhSiH ₃ (2.0)	65
13 ^g	KOH (1.0)	PhSiH ₃ (2.0)	78
14 ^h	KOH (1.0)	PhSiH ₃ (3.0)	89
15 ⁱ	KOH (1.0)	PhSiH ₃ (3.0)	60
16 ^j	KOH (1.0)	PhSiH ₃ (3.0)	trace
17	_	PhSiH ₃ (2.0)	\rightarrow
18	KOH (1.0)	_	- X-

OH

^a Substrate (0.4 mmol), base, reductant, dried THF (2 mL), N₂, refluxing for 4 h.

^b Isolated yield.

- ^c TMDS (1,1,3,3-tetramethyldisiloxane).
- ^d 2 h.

^e Dry 2-methyltetrahydrofuran as solvent.

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<sup>f</sup>Dry dioxane as solvent.
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^g 8 h.

^h Air humidity (60%-70%).

ⁱ45 °C.

^j25 °C.

With the optimum reaction conditions in hand, we subsequently explored the scope of the reaction to various substituted isobenzofuran-1(3H)-ones. As shown in Scheme 1, the presence of the substituent such as phenyl, methyl, *n*-propyl, *n*-butyl or benzyl group at the 3-position has a slightly negative impact on the reaction, leading to the formation of the corresponding 1,2-phenylenedimethanols in moderate to good yields (**2b**-**2f**), probably due to their steric effect. However, these substrates have the relatively low yields when the PhSiH₃ is replaced by LiAlH₄ [10].

Noticeably, reduction of 3-methoxyisobenzofuran-1(3H)-one (**1g**) with PhSiH₃ led to the simultaneous occurrence of demethoxylation, affording only the 1,2-phenylenedimethanol (Scheme 1, **2a**). The same phenomenon was also observed in other reducing systems [11]. Similarly, reacting 3-bromoisobenzofuran-1(3H)-one (**1h**) with PhSiH₃ afforded the tandem debromination/ lactone reduction product 1,2-phenylenedimethanol (**2a**). Interestingly, **2a** could also be obtained from 5-bromoisobenzofuran-1(3H)-one (**1i**) under the similar conditions, indicating that the debromination is also viable in company with reduction of lactone (**2a**). However, the chlorine substituent is tolerate under the present conditions (**2j**, **2k**). It is also noteworthy that 4-NO₂ or 4-CN-tolerance was also observed (**2l**, **2m**). This is in sharp contrast with the stoichiometric reactions between NC-substituted isobenzofuran-1(3H)-

ones and some strong reducing agents like LiAlH₄ or NaBH₄, wherein the CN group is usually reduced simultaneously [12]. In contrast to the methoxyl group at the 3-position, the methoxyl groups at the 5-, 6- and 7-positions are tolerated, affording the desired products in satisfactory yields (**2n**, **2o**, **2p**). Besides, (4-methyl-1,2-phenylene)dimethanol (**2r**) could be obtained from 6-methylisobenzofuran-1(*3H*)-one.

In addition, the presence of the electron-donating substituents on the benzene ring of isobenzofuran-1(3H)-ones had a less impact on the reductive ring-opening reaction, affording the corresponding substituted 1,2-phenylenedimethanols in 80% yields (Table 2, entry 1). Naphthalene-1,2-diyldimethanol was also obained in 67% yield from the corresponding naphtho[1,2-c]furan-1(3H)-one (Table 2, entry 2). Significantly, 2-(2-(hydroxymethyl)phenyl)ethanol could also be synthesized from isochroman-1-one or isochroman-3-one under the standard conditions (Table 2, entries 3-4). Besides, dodecane-1,4-diol could be obtained from 5-octyldihydrofuran-2(3H)-one in 89% yield (Table 2, entry 5). To our delight, benzene-1,2,4-triyltrimethanol could be synthesized from methyl 1-oxo-1,3-dihydroisobenzofuran-5-carboxylate in satisfactory yield (Table 2, entry 6). Unfortunately, other substrates such as benzofuran-2(3H)-one and isobenzofuran-1,3-dione gave a complex mixture or no corresponding product (Table 2, entries 7-8). Notably, 3-(2-(hydroxymethyl)phenyl)pentan-3-ol could also be synthesized from 3,3-diethylisobenzofuran-1(3H)-one under the standard conditions (Table 2, entry 9).



Scheme 1. KOH-promoted reduction of isobenzofuran-1(3*H*)-ones with PhSiH₃. Substrate (0.4 mmol), KOH (0.4 mmol), PhSiH₃ (1.2 mmol), Dried THF (2 mL), N₂, refluxing for 4 h. Isolated yield. ^a KOH (0.8 mmol), PhSiH₃ (1.6 mmol).

Table 2

KOH-promoted reduction of other isobenzofuran-1(3H)-ones with PhSiH₃.^a





Condition: a Substrate (0.4 mmol), KOH (0.4 mmol), PhSiH₃ (1.2 mmol), Dried THF (2 mL), N₂, refluxing for 4 h.

^b Isolated yield.

^c KOH (0.8 mmol), PhSiH₃ (2.4 mmol).

^d Complex mixture.

To test the scalability and practicality of the newly established method, a gram-scale experiment was conducted under the standard conditions (Scheme 2). Significantly, an excellent yield of 90% was achieved, which paves the way for further application of the current method in organic synthesis.





o-Phthalaldehyde can be used as an antibacterial disinfectant [13]. Recently, the applications of *o*-phthalaldehyde as the fluorescent probe [14], catalyst [15] and intermediate [16] are also discovered. Encouraged by the above results, we further examined the application of the method as a key step in transformation of isobenzofuran-1(3H)-one to *o*-phthalaldehyde. *o*-Phthalaldehyde could be obtained from **2a** with IBX as oxidant in 70% yield [17] (Scheme 3).



Scheme 3. Synthesis of *o*-phthalaldehyde (3a).

In summary, we have developed an efficient method for preparation of 1,2-phenylenedimethanols and linear aliphatic diols *via* the base-promoted reduction of isobenzofuran-1(3*H*)-ones and γ -lactones with hydrosilane. The present reducing system for transformation of lactones into 1,2-phenylenedimethanols or linear aliphatic diols is significantly complementary to the previously reported methods that require the use of stoichiometric amounts of water-sensitive reducing agents, such as DIBAL-H, LiAlH₄, LiBH₄ and NaH, or the high pressure hydrogen and special catalysts. For example, for the isobenzofuran-1(3*H*)-ones bearing the substituent at the 3-position, a improved yield is achieved. Further investigations on the synthetic applications of this method are underway in our lab.

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