A New Preparation of Benzofurans Utilizing Trimethylsilyldiazomethane

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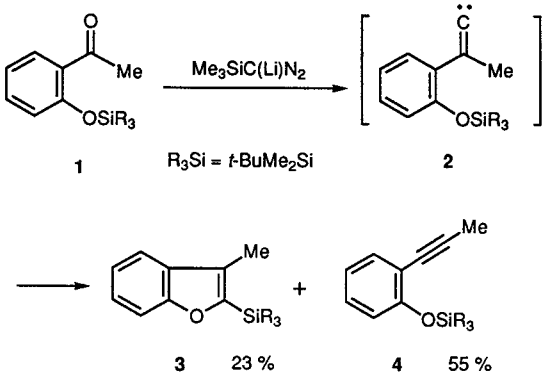
Abstract: *o*-Triisopropylsiloxyaryl ketones and aldehydes smoothly reacted with the lithium salt of trimethylsilyldiazomethane to give *o*-triisopropylsiloxyphenylacetylenes which were easily converted to benzofurans by treatment with tetra-n-butylammonium fluoride. 3-Benzofuranmethanols were also obtained when the reaction was conducted in the presence of carbonyl compounds.

We have already reported that the lithium salt of trimethylsilyldiazomethane (TMSC(Li)N_2), a useful reagent for generating alkylidene carbenes from carbonyl compounds,[1] smoothly reacted with β-trimethylsiloxyketones to give 5-trimethylsilyl-2,3-dihydrofurans via oxonium ylide intermediates.[1c] Under the same reaction conditions, *o*-tert-butyldimethylsiloxyacetophenone **1** also gave the desired benzofuran **3**, but the major product was the 1-(*o*-siloxyphenyl)propyne **4** generating by migration of the phenyl function in the alkylidene carbene intermediate **2**,[1a] as shown in Scheme 1. We thought that *o*-siloxyphenylacetylenes could be converted to benzofurans by treatment with a fluoride ion, because the reaction of *o*-hydroxyphenylacetylenes with sodium ethoxide is known to give benzofurans.[2]

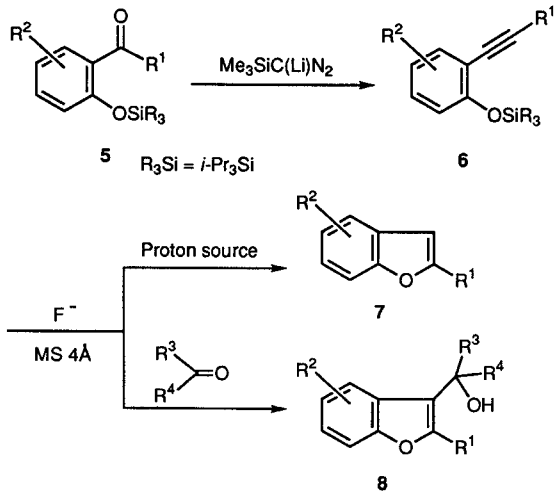


Scheme 1

This communication describes our results on the two-step preparation of benzofurans starting from *o*-siloxyaryl ketones and aldehydes **5** by use of TMSC(Li)N_2. The overall process is depicted in Scheme 2.

First, chemoselective preparation of *o*-siloxyphenylacetylenes was investigated.[3] Among several *o*-trialkylsiloxyacetophenones examined, *o*-triisopropylsiloxyacetophenone **5a** gave the best result. Thus TMSC(Li)N_2 reacted efficiently with **5a** in tetrahydrofuran (THF) to give the phenylacetylene **6a** in 78% yield, as shown in Table 1. Other *o*-triisopropylsiloxyaryl ketones and aldehydes **5b-e** also afforded the corresponding acetylenes **6b-e** in good yields. In some cases, small amounts of 2-triisopropylsilylbenzofurans analogous to **3** were formed as by-products.

We next investigated the conversion of the acetylenes **6** to the benzofurans **7**, and found that **6** smoothly underwent cyclization to furnish **7** in good yields by treatment with tetra-n-butylammonium fluoride (TBAF) in the presence of molecular sieves 4Å in THF.[4] The reaction has been found to have generality, as shown in Table 2. Interestingly, the use of cesium fluoride in place of TBAF in THF gave no benzofurans and only the desilylated products, *o*-hydroxyphenyl-



Scheme 2

Table 1.[a,b] Preparation of *o*-Triisopropylsiloxyphenylacetylenes **6**

Compd. No.	R^1	R^2	Yield (%)
a	Me	H	78[c]
b	Et	H	65[d]
c	H	H	69
d	H	5-Cl	55
e	H	3-MeO	74

a) The reaction of **5** (1 mmol) with TMSC(Li)N_2 (1.2 mmol) in THF (10 ml) was carried out at -78℃ for 1 h, from -78℃ to 0℃ during 1 h, and then at 0℃ for 1 h. b) All products gave satisfactory spectral data and elemental analysis. c) 3-Methyl-2-triisopropylsilylbenzofuran (19%) was also obtained. d) 3-Ethyl-2-triisopropylsilylbenzofuran (23%) was also obtained

Table 2.[a,b] Preparation of Benzofurans **7**

Run	Compd. No.	R^1	R^2	Yield (%)
1	**a**	Me	H	71
2	**a**	Me	H	93[c]
3	**b**	Et	H	75
4	**c**	H	H	56
5	**d**	H	5-Cl	76
6	**e**	H	3-MeO	75

a) All products gave satisfactory spectral data. b) The reaction was carried out at 50℃ for 2-6 h. c) The reaction was carried out in the presence of CsF (1.5 eq) in acetonitrile at 50℃ for 18 h

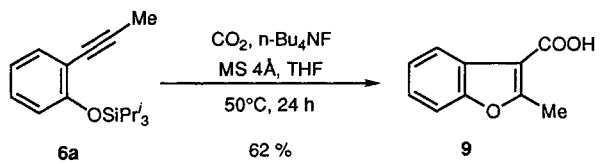
acetylenes, were formed. However, a dramatic solvent effect giving the benzofuran **7a** in high yield was observed in the use of acetonitrile as solvent, though the reaction proceeded more slowly (run 2 in Table 2).

In this benzofuran synthesis, 3-benzofuranmethanols **8**, the tandem cyclization-hydroxymethylation products, could also be obtained when the reaction was conducted in the presence of carbonyl compounds. The scope of the new preparation of **8** is summarized in Table 3. Various aromatic and heteroaromatic aldehydes smoothly reacted with **6** to give **8**. Although pivalaldehyde, acetone, and paraformaldehyde also afforded the corresponding 3-benzofurans **8k-m**, respectively, the major product was **7a**. Unfortunately, no hydroxymethylation occurred when aliphatic aldehydes bearing a hydrogen at α position of the carbonyl function were used as substrates.[5] Carbon dioxide also underwent the reaction with **6a** to give 3-benzofurancarboxylic acid **9** in good yield, as shown in Scheme 3. A slight excess of TBAF was required to conduct the reaction smoothly. THF seemed to be the solvent of choice. The use of acetonitrile gave **7** only and no hydroxymethylation products were obtained.

Table 3.[a,b] Preparation of 3-Benzofuranmethanols **8**

Starting acetylene **6**	R^1	R^2	R^3	R^4	Yield (%)	
6a	Me	H	Ph	H	**8a**	81
6b	Et	H	Ph	H	**8b**	80
6c	H	H	Ph	H	**8c**	67
6d	H	5-Cl	Ph	H	**8d**	77
6e	H	3-MeO	Ph	H	**8e**	86
6a	Me	H	4-$MeOC_6H_4$	H	**8f**	65
6a	Me	H	4-$ClOC_6H_4$	H	**8g**	81
6a	Me	H	2-Furyl	H	**8h**	76
6a	Me	H	2-Thienyl	H	**8i**	70
6a	Me	H	2-Pyridyl	H	**8j**	73[c]
6a	Me	H	t-Bu	H	**8k**	42[c]
6a	Me	H	Me	Me	**8l**	14[c]
6a	Me	H	H	H	**8m**	25[c]

a) All new products gave satisfactory spectral data and elemental analysis. b) The reaction was carried out at 50℃ for 2-8 h. c) 2-Methylbenzofuran **7a** was also formed in 13-50% yield.



6a 62 % **9**

Scheme 3

In conclusion, the method using commercially available trimethylsilyldiazomethane will provide a new and convenient method for the two-step preparation of benzofurans, 3-benzofuranmethanols, and 3-benzofurancarboxylic acids from *o*-triisopropylsiloxyaryl ketones and aldehydes.

A typical procedure for the preparation of **7** : A mixture of TBAF (0.6 M in THF, 0.75 ml, 0.45 mmol) and MS 4Å (500 mg) in THF (0.5 ml) was stirred at room temperature for 1h. Then a solution of **6a** (101 mg, 0.35 mmol) in THF (1.5 ml) was added and the whole was stirred at 50 °C for 5.5h under argon. The mixture was diluted with AcOEt/benzene (1:1) and filtered. The filtrate was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (BW-820 MH, 12g, hexane) to give **7a** (33 mg, 71%).

A typical procedure for the preparation of **8** : A mixture of **6e** (109 mg, 0.36 mmol), benzaldehyde (76 mg, 0.72 mmol), TBAF (0.45 mmol), and MS 4Å (500 mg) in THF (2 ml) was stirred at 50 °C for 8 h. After the reaction, the mixture was worked up as usual. The crude product was purified by column chromatography (BW 200, 30g, hexane : Et_2O = 5:1 to 1:1) to give **8e** (78 mg, 86%).

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References and Notes

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2. Toda, F.; Nakagawa, M. *Bull. Chem. Soc. Jpn.*, **1959**, *32*, 514.
3. Cf. Reference 1a.
4. In this reaction, TBAF may act partially as a source of proton since GLC analysis of the reaction mixture showed the presence of tri-n-butylamine resulting from the Hofmann degradation of TBAF.
5. For example, the reaction of **6a** with hydrocinnamaldehyde gave **7a** (43%) only and no hydroxymethylation product could be detected.