

Catching Elusive 2-Furyl Carbenes with Silanes: A Metal-Free Microwave-Assisted Silicon-Hydrogen Bond Functionalization

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Abstract: An efficient, metal-free, silicon–hydrogen bond functionalization based on the microwave-assisted reaction of readily available enynones and silanes is reported. This process seemingly proceeds through a 2-furyl carbene species, a particularly elusive intermediate. Preliminary studies on the metal-free oxygen–hydrogen and nitrogen–hydrogen bond functionalization of representative alcohols, azoles and sulfonamides are also provided.

Keywords: carbenes; furans; metal-free conditions; microwave-assisted reaction; silanes

2-Furyl carbenes are elusive intermediates and, for this reason, they have traditionally been regarded as synthetically useless intermediates.^[1] As a result, a plethora of transition metal-based alternatives have been reported in the last years.^[2]

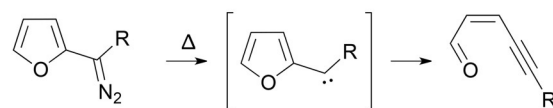
Generated from 2-furyl diazo compounds or 2-furyldiazirine derivatives, these intermediates undergo a rapid ring-opening reaction to give enynones, which precludes their capture when generated in the presence of potential trapping reagents (Scheme 1, A).^[3]

In a different approach, in 1995, Saito et al. managed the photochemical generation and subsequent intermolecular trapping by protic solvents of 2-furyl carbene intermediates arising from enynes featuring a conjugated α -diketone moiety (Scheme 1, B).^[4] The α -diketone structural motif was found to be crucial for the success of the cyclization step since substrates lacking the additional carbonyl group located adjacent to that one involved in the cyclization did not afford any product resulting from the trapping of the postulated carbene intermediate. Although this contribution represents the first high-yield trapping reaction of 2-furyl carbene intermediates, the need of a multistep sequence for the synthesis of the starting

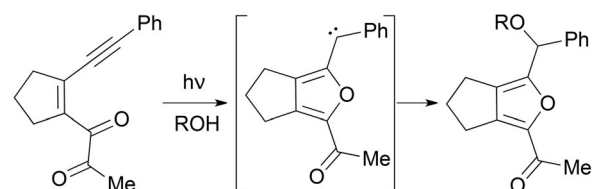
enynones and the exclusive use of protic solvents (water and alcohols) as trapping reagents impose significant limitations on the synthetic applicability of this methodology. In particular, silanes and alkenes were found to be completely unsuccessful trapping reagents.

Clearly, the development of readily available precursors for the generation of 2-furyl carbenes susceptible of being intercepted by suitable trapping reagents would be particularly appealing.

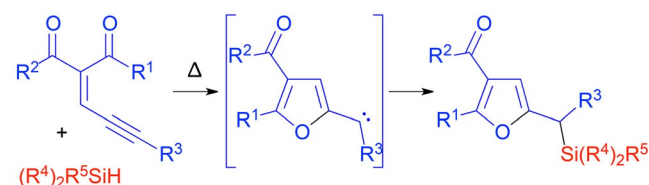
A)



B)



This work



- Metal-free Si–H bond functionalization
- Easily available starting substrates
- 100% atom economy
- Synthetically useful yields

Scheme 1. Generation and trapping of 2-furyl carbene intermediates.

Due to our recent interest in the silicon–hydrogen bond functionalization^[5] and inspired by a recent work of Bertrand and co-workers on the activation of Si–H bonds with stable singlet carbenes,^[6] we decided to test the thermal behaviour of readily available enynones in the presence of silanes. As a result, in this communication we report a facile, metal-free, silicon–hydrogen bond functionalization based on the trapping of 2-furyl carbene intermediates.^[7] Preliminary studies on the functionalization of other heteroatom–hydrogen bonds are also disclosed.

On the outset we studied the reaction of enynone **1a** with triethylsilane **2a** under a variety of reaction conditions (Table 1). First, we found that heating a mixture of **1a** and **2a** (6 equiv.) in toluene at 90 °C for 48 hours afforded the furan derivative **3a** in 20% yield after chromatographic purification (Table 1, entry 1). Gratifyingly, when the reaction was performed under microwave heating at 140 °C an improved yield was achieved (84% isolated yield, Table 1, entry 2). Next, we tried to reduce the amount of the silane component. Although the reaction worked well with a nearly stoichiometric amount of the silane component (Table 1, entry 4), the use of 3 equiv. proved optimal in terms of yield (quantitative by NMR; 91% isolated yield; Table 1, entry 3). The reaction could also be performed under standard oil-bath conditions, although these conditions required an extended reaction time to afford a comparable yield (Table 1, entries 5 and 6). The reaction also proceeded in the absence of solvent but in this case an

excess of triethylsilane was required (Table 1, entry 7).

Inductively coupled plasma mass spectrometry (ICP-MS) analyses ruled out the involvement of metal species arising from contamination of reactants and/or solvent.

These results represent a proof of concept demonstration of the feasibility of using enynones as 2-furyl carbene precursors for the metal-free silicon–hydrogen bond functionalization.

With the optimized reaction conditions in hand (microwave heating at 140 °C in toluene, 3 equiv. of silane), the substrate scope of this metal-free silicon–hydrogen bond functionalization was assessed using a range of enynones and silane derivatives (Table 2).

Regarding the enynone component, both electron-rich (enynone **1b**; R¹=R²=Me, R³=*p*-MeOC₆H₄) and electron-poor (enynone **1c**; R¹=R²=Me, R³=*p*-O₂NC₆H₄) aromatic groups at the acetylenic position (R³) were found to be well tolerated in this transfor-

Table 1. Optimization of the reaction conditions: summary.^[a]

Entry	n	Solvent	T [°C]	t [h]	Yield [%] ^[b]
1	6	toluene	90	48	20
2	6	toluene	140 (MW)	4	84
3	3	toluene	140 (MW)	4	91^[c]
4	1.5	toluene	140 (MW)	4	71
5	3	toluene	140	4	30 ^[d]
6	3	toluene	140	12	80
7	30	–	100	22	77

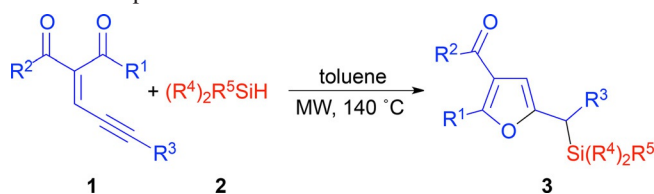
^[a] Unless otherwise stated, these exploratory experiments were performed on a 0.2 mmol scale.

^[b] Isolated yields unless otherwise specified.

^[c] 99% yield by NMR (dibromomethane as internal standard).

^[d] Crude yield by NMR (dibromomethane as internal standard).

Table 2. Microwave-assisted reaction of enynones **1** and silanes **2**: scope.^[a]



R ¹ , R ² , R ³	R ⁴ , R ⁵	3 , Yield ^[b]
Me, Me, Ph	Et, Et	3a , 91% (90) ^[5a]
Me, Me, <i>p</i> -MeOC ₆ H ₄	Et, Et	3b , 85% (86) ^[5a]
Me, Me, <i>p</i> -O ₂ NC ₆ H ₄	Et, Et	3c , 82% (69) ^[5a]
Me, Me, 1-cyclohexenyl	Et, Et	3d , 79% (59) ^[5a]
Me, Me, <i>n</i> -C ₅ H ₁₁	Et, Et	3e , 69% (77) ^[5a]
Me, Me, <i>n</i> -C ₈ H ₁₇	Et, Et	3f , 71%
Me, Me, CH ₂ CH ₂ Ph	Et, Et	3g , 54% (81) ^[5b]
Me, Me, (CH ₂) ₄ OTBS	Et, Et	3h , 55% (70) ^[5b]
Et, Et, Ph	Et, Et	3i , 54%
Me, OEt, Ph	Et, Et	3j , 53% (65) ^[5b]
Me, Me, Ph	Me, Bn	3k , 83% (71) ^[5b]
Me, Me, <i>p</i> -MeOC ₆ H ₄	Me, Bn	3l , 75%
Me, Me, <i>p</i> -O ₂ NC ₆ H ₄	Me, Bn	3m , 66%
Me, Me, <i>n</i> -C ₅ H ₁₁	Me, Bn	3n , 60%
Me, Me, Ph	Me, Ph	3o , 77% (67) ^[5b]
Me, Me, <i>n</i> -C ₅ H ₁₁	Me, Ph	3p , 71% (68) ^[5a]
Me, Me, Ph	Ph, Me	3q , 82% ^[c]
Me, Me, Ph	Ph, Ph	3r , 75% ^[c]
Me, Me, Ph	TMS, TMS	3s , 38% ^[c]
Me, Me, Ph	Et, H	3t , 91% ^[c] (54) ^[5b]

^[a] Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol, 3 equiv.), toluene (0.1 M), 140 °C (microwave heating).

^[b] Yield of isolated product after column chromatography. The values in parenthesis correspond to the yields reported in the literature for the zinc-catalyzed reaction.^[5]

^[c] Reaction run with 6 equivalents of silane.

mation providing furan derivatives **3b** and **3c** in good isolated yields (85 and 82%, respectively).

Similarly, a substrate bearing an alkenyl group at this position (enynone **1d**; R³=cyclohexenyl) posed no problems giving rise to furan derivative **3d** in 79% isolated yield.

Enynones **1e–g** with alkyl chains installed at the acetylenic position were also suitable substrates for this transformation affording the corresponding furan derivatives **3e–g** in moderate isolated yields. A protected alcohol in the alkyl chain [enynone **1h**; R³=(CH₂)₄OTBS] was also well tolerated.

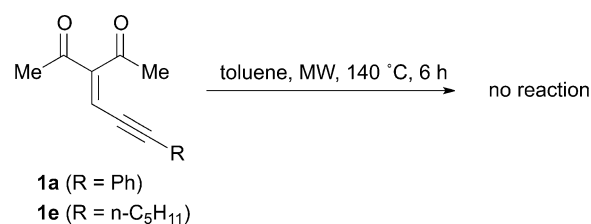
Some modifications on the structure of the enynone component were also realized. Thus, enynones **1i** (R¹=R²=Et, R³=Ph) and **1j** (R¹=Me, R²=OEt, R³=Ph) behaved similarly and afforded the expected furan derivatives **3i** and **3j** in moderate isolated yields.

Next, the scope of this metal-free silicon–hydrogen bond functionalization was expanded to other silanes. Indeed, benzyldimethylsilane (**2b**) and phenyldimethylsilane (**2c**) readily reacted with enynones **1** delivering the corresponding furan derivatives **3k–p** in good yields. Diphenyldimethylsilane (**2d**) and triphenylsilane (**2e**) also proved to be suitable silane counterparts in this microwave-mediated transformation providing the corresponding functionalized furan derivatives **3q** and **3r** in 82 and 75% yields, respectively. Even a highly sterically encumbered trisubstituted silane, namely tris(trimethylsilyl)silane (**2f**), was able to participate in this transformation although with a significant decrease in the yield. Finally, the reaction of enynone **1a** and diethylsilane (**2g**) posed no problems delivering the corresponding furan derivative **3t** in excellent isolated yield. In contrast, phenylsilane and triethoxysilane were not suitable reagents under our reaction conditions.

As shown in Table 2, in most cases the yields of this metal-free reaction are equivalent or superior to those reported in our previous zinc-catalyzed reaction.^[5]

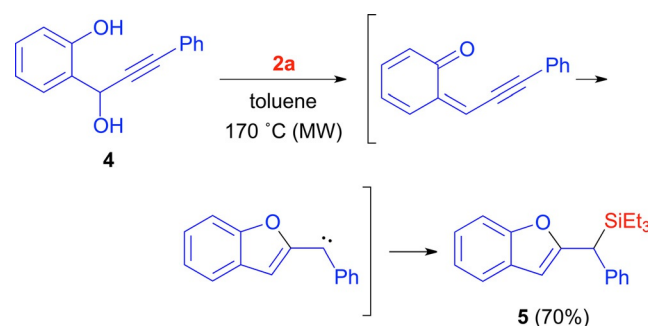
Next, we conducted some control experiments in absence of silane aimed at gaining insight into the structure of the intermediate involved in this transformation. Thus, when solutions of enynones **1a** (R¹=R²=Me, R³=Ph) and **1e** (R¹=R²=Me, R³=*n*-C₅H₁₁) in toluene were heated under microwave irradiation at 140°C for 6 h, neither a dimerization product nor (in the case of enynone **1e**) a vinylfuran derivative resulting from a 1,2-H shift were observed, with the majority of mass balance being unreacted enynone (Scheme 2). These observations are in full agreement with those previously reported by Shechter and co-workers in the generation of 2-furyl carbenes by vacuum pyrolyses of some tosylhydrazone sodium salts.^[8]

To further demonstrate the synthetic utility of this metal-free cyclization/silicon–hydrogen bond func-



Scheme 2. Control experiments performed in the absence of silane reagent.

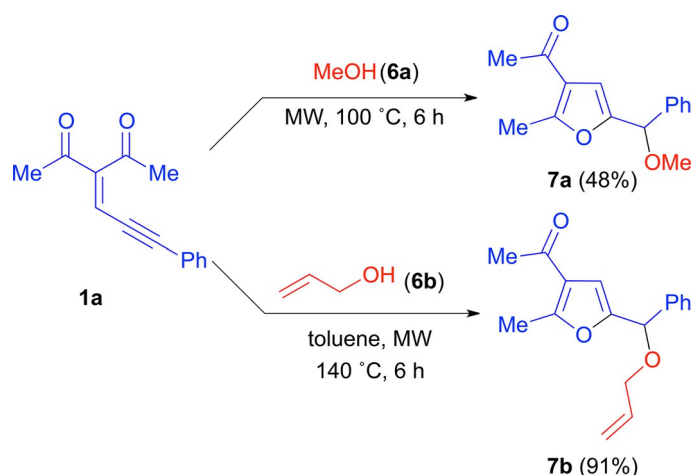
tionalization sequence, we decided to extend the study to the generation of the benzofused analogue intermediate, namely a benzofuran carbene intermediate. In this regard, we envisioned alkynyl-substituted *o*-hydroxybenzyl alcohol **4** as a suitable starting substrate. We surmised that initial microwave-assisted thermal dehydration to furnish the corresponding *o*-quinone methide,^[9] followed by cyclization and trapping of the resulting benzofuryl carbene could represent a convenient metal-free approach to silyl-substituted benzofuran derivatives. In fact, the formation of benzofuran derivative **5** in 70% isolated yield after heating a mixture of alkynyl-substituted *o*-hydroxybenzyl alcohol **4** and triethylsilane (**2a**) in toluene at 170°C clearly demonstrated the feasibility of this methodology (Scheme 3).



Scheme 3. Microwave-mediated, metal-free synthesis of benzofuran derivative **5**.

Having established the feasibility of using enynones **1** as 2-furyl carbene precursors, preliminary studies were also conducted to assess the potential of this metal-free methodology for the functionalization of oxygen–hydrogen bonds (Scheme 4).^[10]

Initially, we found that the reaction of enynone **1a** with methanol (**6a**) as the trapping reagent under the conditions developed for the silicon–hydrogen bond functionalization (3 equivalents of methanol, toluene as solvent, microwave heating at 140°C for 6 hours), afforded only traces of the corresponding ether **7a**. Pleasingly, the use of methanol as solvent at 100°C provided a significant improvement of the yield. On

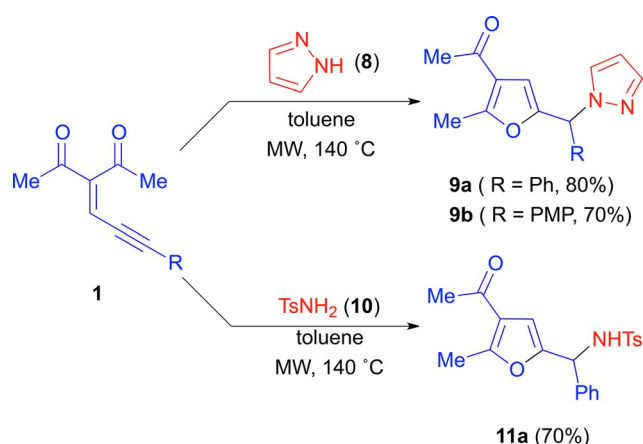


Scheme 4. Microwave-assisted O–H bond functionalization.

the other hand, reaction of enynone **1a** with allylic alcohol (**6b**, 3 equivalents) in toluene at 140 °C proceeded with complete chemoselectivity delivering furfuryl ether derivative **7b** in excellent isolated yield (91%). Significantly, under these reaction conditions neither cyclopropanation of the olefinic moiety nor insertion into the allylic carbon–hydrogen bonds were observed.

Finally, we also briefly examined the feasibility of a hydrogen–nitrogen bond functionalization. After some optimization, we found that reaction of enynones **1a** (R = Ph) and **1b** (R = *p*-MeOC₆H₄) with an excess of pyrazole (**8**) in toluene at 140 °C led to the formation of furfuryl- and pyrazolyl-containing triaryl-methane derivatives **9a** and **9b** in good isolated yields (Scheme 5). Extension of this protocol to 4-toluene-sulfonamide (**10**) produced the functionalized furan derivative **11a** in 70% isolated yield.

In short, we have described the microwave-mediated, metal- and additive-free reaction of readily avail-



Scheme 5. Microwave-assisted N–H bond functionalization.

able enynones and silanes to afford functionalized furfurylsilanes. This non-diazo silicon–hydrogen bond functionalization is believed to proceed by means of a 2-furyl carbene intermediate, which in turn would be trapped by the silane. It is worthy of note that, with a few notable exceptions, these intermediates have largely defied trapping. Notable aspects of our protocol are: (i) availability of the starting materials, (ii) easy execution, (iii) complete atom efficiency, and (iv) synthetically useful yields. Preliminary results demonstrated that this protocol could be used for the generation and trapping of other heteroaryl carbenes as well as for the functionalization of other heteroatom–hydrogen bonds. In our opinion, these preliminary findings could open up new pathways for the development of new metal-free methodologies, an attractive field in contemporary organic synthesis. In particular, our group is actively pursuing the development of new strategies for the metal-free C–C bond formation, a traditional domain of metal-based methodologies.

Experimental Section

Representative Procedure (3a)

A 2–5-mL microwave vial was charged with the enynone **1a** (42.4 mg, 0.2 mmol), triethylsilane **2a** (69.8 mg, 0.6 mmol, 3.0 equiv.), toluene (2 mL) and a stirring bar. The vessel was sealed with a septum, placed into the microwave cavity and irradiated to maintain the reaction at 140 °C for 4 hours in a Biotage Initiator microwave apparatus. The solvent was removed under reduced pressure. ¹H NMR (dibromomethane as internal standard) revealed the formation of furan derivative **3a** in quantitative yield. Purification by flash chromatography (SiO₂, hexane:EtOAc = 10:1) furnished **3a** as a pale yellow oil; yield: 59.8 mg (91%). ¹H NMR: (400 MHz, CDCl₃): δ = 0.61 (q, *J* = 8.0 Hz, 6H), 0.88 (t, *J* = 8.0 Hz, 9H), 2.37 (s, 3H), 2.58 (s, 3H), 3.63 (s, 1H), 6.23 (s, 1H), 7.14–7.22 (m, 3H), 7.26–7.30 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ = 2.9 (CH₂), 7.2 (CH₃), 14.5 (CH₃), 29.1 (CH₃), 35.2 (CH), 105.6 (CH), 122.2 (C), 125.3 (CH), 127.9 (CH), 128.4 (CH), 140.3 (C), 154.8 (C), 156.6 (C), 194.3 (C); HR-MS (EI): *m/z* = 328.1858, calculated for [C₂₀H₂₈O₂Si]⁺ (M⁺): 328.1859.

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