## Organic & Biomolecular Chemistry

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**RSC**Publishing

View Article Online View Journal | View Issue

Cite this: Org. Biomol. Chem., 2013, 11, 6703

Received 8th July 2013, Accepted 16th August 2013 DOI: 10.1039/c3ob41400k

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# Efficient synthesis of trifluoromethylated cyclopentadienes/fulvenes/norbornenes from divinyl ketones†

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The synthetic methods of trifluoromethylated cyclopentadienes/ fulvenes/norbornenes have been developed using  $3-CF_{3}-1,4$ -dien-3-ols as the synthons, which can be easily prepared by the regiospecific 1,2-addition of the Ruppert–Prakash reagent (TMSCF<sub>3</sub>) to divinyl ketones. All the reactions are carried out under mild, metal-free conditions to afford the corresponding products in high to excellent yields.

Divinyl ketones (DVKs) are important intermediates in [5 + 1] annulations<sup>1,2</sup> and Nazarov cyclizations.<sup>3,4</sup> Recently, we have developed the synthesis of substituted halocyclopentadienes (halo-Cps) *via* tandem Nazarov cyclization–halovinylation sequence of DVKs under Vilsmeier conditions (Scheme 1a).<sup>5*a*</sup> It has been reported that Nazarov cyclization can also be achieved using 1,4-dien-3-ols to afford Cp derivatives,<sup>6</sup> including the Gassman ligand (1,2,3,4-tetramethyl-5-(trifluoromethyl)cyclopentadiene) synthesized by acid mediated cyclization of (2*E*,5*E*)-3,5-dimethyl-4-(trifluoromethyl)hepta-2,5-dien-4-ol. Up to now, however, there has been no efficient



Scheme 1 Nazarov cyclizations of divinyl ketones and alcohols.

method for the synthesis of suitable substrates, such as CF<sub>3</sub>-1,4-dien-3-ols.<sup>7–13</sup> In Gassman's method, the only CF<sub>3</sub>-1,4-dien-3-ol intermediate ((2*E*,5*E*)-3,5-dimethyl-4-(trifluoromethyl)-hepta-2,5-dien-4-ol) was prepared in a two-step process from *trans*-2-butene and ethyl trifluoroacetate and involved the use of 2 equivalents of lithium metal (Scheme 1b).<sup>7</sup>

The introduction of a  $CF_3$  group into a molecule could profoundly modify its properties through alteration of its steric, electronic and lipophilic characteristics.<sup>8</sup> Thus,  $CF_3$ -containing compounds have attracted considerable attention in organic synthesis.<sup>9</sup> The introduction of the  $CF_3$  group into Cps, which are useful ligands in organometallic chemistry,<sup>10</sup> is an effective strategy for modulating the physical properties and chemical reactivities for the substituent effects.<sup>11</sup> In 1963 Wilkinson and Dickson reported the synthesis of tetrakis(trifluoromethyl)cyclopentadienone, prepared by the coupling of hexafluoro-2-butyne and CO mediated by  $[Rh(CO)_2Cl]_2$ .<sup>12</sup> Since then, several methods for synthesizing  $CF_3$ -Cps have been reported<sup>13</sup> and the Gassman ligand has been obtained as a mixture of double-bond isomers.<sup>7</sup>

As part of our continuing interest in developing useful synthetic methods using DVKs,<sup>1,2,5</sup> combining the utilization of (trifluoromethyl)trimethylsilane (TMSCF<sub>3</sub>, the Ruppert-Prakash reagent),<sup>14,15</sup> we herein wish to report the efficient and direct synthesis of CF<sub>3</sub>-Cps **4** and CF<sub>3</sub>-fulvenes **5** starting from 3-CF<sub>3</sub>-1,4-dien-3-ols **3**, which are easily prepared from DVKs **1** and Ruppert–Prakash reagent.<sup>5</sup> In addition, the synthesis of trifluoromethyl norbornenes **6** through the Diels–Alder reaction of CF<sub>3</sub>-Cps **4** with maleimide is also described.

It is known that the reactions of TMSCF<sub>3</sub> with enones tend to give the 1,2-adducts.<sup>14,15</sup> Therefore, we began our recent research by examining the efficiency and regioselectivity of nucleophilic addition of TMSCF<sub>3</sub> to DVKs **1**. We were pleased to find that the 1,2-adducts **2a–2n** could be obtained in high to excellent yields under optimal conditions (Table 1). For example, ((1*E*,4*E*)-1,5-ditolyl-3-(trifluoromethyl)penta-1,4dien-3-yloxy)trimethylsilane **2a** was obtained in 95% yield (Table 1, entry 1) upon treatment of a mixture of **1a** (2.0 mmol) and anhydrous NaOAc (2.0 eq.) in anhydrous DMF (2.0 mL) at

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<sup>†</sup>Electronic supplementary information (ESI) available: Detailed experimental procedures, analytical and spectral data for all the new compounds. CCDC 851500 (**5b**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob41400k

#### Table 1 Preparation of 2 and 3

Ar		F <sub>3</sub> C F <sub>3</sub> /NaOAc rt, 20 min Ar	OSiMe <sub>3</sub> R'aq. HO THF, rt, 2	EI F <sub>3</sub> 0 20-24 h Ar	C OH R' R	
1a-n		2	a-n	3a-n		
Entry	Ar	R	R'	Yield of $2^{a}$ (%)	Yield of $3^{a}$ (%)	
1	4-MeC <sub>6</sub> H <sub>4</sub>	4-MeC <sub>6</sub> H <sub>4</sub>	Н	<b>2a</b> 95	<b>3a</b> 92	
2	Ph	Ph	Н	<b>2b</b> 93	<b>3b</b> 93	
3	$3-MeC_6H_4$	$3-MeC_6H_4$	Н	<b>2c</b> 94	<b>3c</b> 91	
4	4-OMeC <sub>6</sub> H <sub>4</sub>	4-OMeC <sub>6</sub> H <sub>4</sub>	Н	2d 95	3d 96	
5	4-ClC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>	Н	<b>2e</b> 90	<b>3e</b> 95	
6	$4 - FC_6H_4$	$4 - FC_6H_4$	Н	<b>2f</b> 89	<b>3f</b> 90	
7	$2-FC_6H_4$	$2 - FC_6H_4$	Н	2g 88	3g 88	
8	$4\text{-BrC}_6H_4$	$4-BrC_6H_4$	Н	<b>2h</b> 91	<b>3h</b> 89	
9	$2,4-Cl_2C_6H_3$	$2,4-Cl_2C_6H_3$	Н	2i 85	<b>3i</b> 87	
10	$4 - ClC_6H_4$	$4\text{-BrC}_6H_4$	Н	2j 90	<b>3j</b> 90	
11	$4 - FC_6H_4$	4-MeC <sub>6</sub> H <sub>4</sub>	Н	<b>2k</b> 92	<b>3k</b> 88	
12	$4 - FC_6H_4$	Ph	Н	<b>2l</b> 89	<b>31</b> 85	
13	$4-ClC_6H_4$	Me	Н	<b>2m</b> 95	<b>3m</b> 94	
14	Ph	Ph	4-OMeC <sub>6</sub> H <sub>4</sub>	<b>2n</b> 86	<b>3n</b> 88	

room temperature for 5 min with subsequent addition of TMSCF<sub>3</sub> (1.5 eq.) in one portion and stirring for another 15 min. Furthermore, the corresponding CF<sub>3</sub>-1,4-dien-3-ols **3a–3n** were prepared in high to excellent yields by hydrolysis of **2a–2n** with aqueous HCl in THF at room temperature for 20–24 h (Table 1). It was noticed that, in the preparation of 2, no 1,4-adducts could be detected.

With the trifluoromethylated 1,4-dien-3-ols 3 at hand, the transformation of 3 to CF<sub>3</sub>-Cps 4 was first studied. Treatment of 3b with *p*-toluenesulfonic acid (TsOH, 5.0 eq.) in THF at reflux temperature for 5 h resulted in a symmetry-allowed cyclization to give CF<sub>3</sub>-Cp 4b in 90% yield. Under identical conditions but at room temperature, the above transformation required 3 days. Fortunately, it was found that CF<sub>3</sub>-Cps 4 could be prepared by the reaction of 3 in the presence of BF<sub>3</sub>·Et<sub>2</sub>O (2.0 eq.) in 1,2-dichloroethane (DCE) at 35 °C (Table 2). As a result, Cps 4a–4n were obtained in high to excellent yields (Table 2, entries 1–14). Among them, double-bond isomers of 4j–m/4j'-m', without further assignment, were obtained from unsymmetrical 1,4-dien-3-ols 3j–m due to the facile migration of the endocyclic double bonds.<sup>5a,7,16</sup>

Encouraged by the above results, we then turned to the onepot synthesis of CF<sub>3</sub>-fulvenes 5 starting from the corresponding 1,4-dien-3-ols 3. Fulvenes are an important class of cyclic cross-conjugated molecules and have attracted much attention due to their unique properties in the fields of organometallic and medicinal chemistry, as well as in organic synthesis.<sup>17,18</sup> Fulvenes are traditionally prepared by base mediated condensation of Cps with carbonyl compounds, a method which is typically limited by the availability of suitable Cps and the regioselectivity of the reaction.<sup>19</sup> In addition, to our knowledge, there has been no report on the synthesis of CF<sub>3</sub>-fulvenes.<sup>17-22</sup>

Table 2 Preparation of CF<sub>3</sub>-Cps 4 and CF<sub>3</sub>-fulvenes 5



Entry	t (min)	Yield of $4^{a}$ (%)	3	Entry	t (min)	Yield of $5^{a}$ (%)
1	20	<b>4a</b> 83	3a	1′	50	5a 78
2	20	4b 85	3b	2'	55	5b 83
3	30	<b>4c</b> 82	3c	3'	60	<b>5c</b> 80
4	20	<b>4d</b> 79	3d	4'	50	<b>5d</b> 76
5	30	<b>4e</b> 95	3e	5'	60	<b>5e</b> 94
6	35	<b>4f</b> 97	3f	6'	65	<b>5f</b> 84
7	50	4g 95	3g	7'	85	5g 92
8	30	<b>4h</b> 90	3ĥ	8'	55	<b>5h</b> 85
9	80	<b>4i</b> 89	3i	9'	110	<b>5i</b> 84
$10^b$	40	<b>4j+4j</b> ′ 96	3j	$10'^{b}$	70	5j+5j′ 92
$11^b$	25	4k+4k' 87	3k	$11'^{b}$	55	5 <b>k</b> +5 <b>k</b> ′ 81
$12^b$	25	4l+4l' 92	31	$12'^{b}$	55	<b>5l+5l</b> ′ 86
$13^{b,c}$	180	<b>4m+4m'</b> 86	3m	$13'^{d}$	30	<b>5m</b> 84
$14^c$	240	<b>4n</b> 83	3n			

<sup>*a*</sup> Isolated yields of **4** or **5**. <sup>*b*</sup> Mixture of double bond isomers with the ratios of  $4\mathbf{j}-\mathbf{l}:4\mathbf{j}'-\mathbf{l}'=1:1$ ;  $4\mathbf{m}:4\mathbf{m}'=3:1$ ;  $5\mathbf{j}:5\mathbf{j}'=1:1$ ;  $5\mathbf{k}:5\mathbf{k}'=1.5:1$ ;  $5\mathbf{l}:5\mathbf{l}'=1.1:1$ . <sup>*c*</sup> The reaction was carried out in THF in the presence of TsOH (5.0 eq.) at reflux temperature. <sup>*d*</sup> Synthesized from **4m**.

To our delight, it was found that highly functionalized  $CF_3$ fulvenes 5 could be synthesized from 1,4-dien-3-ols 3 directly by combining the  $BF_3 \cdot Et_2O$ -promoted Nazarov cyclization of 3 with subsequent functionalization under Vilsmeier conditions.<sup>5*a*</sup> For example, TFM-substituted fulvene **5b** was prepared in 83% yield upon treatment of **3b** with  $BF_3 \cdot Et_2O$  followed by addition of DMF and POCl<sub>3</sub> (Table 2, entry 2'). Under similar conditions, the desired  $CF_3$ -fulvenes **5a** and **5c-m** were prepared in high to excellent yields (Table 2, entries 1' and 3'-13').

According to the <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of fulvenes 5, the reactions of **3a-h** gave **5a-h** as a single isomer (Table 2, entries 1'-8').<sup>23</sup> Similar to the corresponding CF<sub>3</sub>-Cps **4**, CF<sub>3</sub>fulvenes **5j-l**/**5j'-l'** were obtained as a mixture of endocyclic double-bond isomers (Table 2, entries 10'-12'). However, the single isomer **5m** was produced from unsymmetrical 1,4-dien-3-ol **3m** bearing a β-alkyl and a β-aryl substituent, respectively (Table 2, entry 13', the configuration of **5m** was confirmed by the 2D <sup>1</sup>H-<sup>1</sup>H NOESY spectrum). In addition, inspection of the <sup>1</sup>H NMR spectrum of **5i** indicated the formation of two pairs of



Scheme 2 Proposed mechanism for formation of 4 and 5

atropisomers in the ratio of 1.2:1.0 due to the hindered rotation of the 2-chlorophenyl rings.

On the basis of the above results and related reports,<sup>1-5</sup> a possible mechanism for the formation of CF<sub>3</sub>-Cps 4 and CF<sub>3</sub>-fulvenes 5 is proposed in Scheme 2 (with 4b/5b as an example). The reaction begins with the generation of pentadienyl cation I from 1,4-dien-3-ol 3 induced by Lewis acid such as BF<sub>3</sub>·Et<sub>2</sub>O (or BF<sub>3</sub>·H<sub>2</sub>O generated *in situ*).<sup>24</sup> Then, cyclization of I (to give cyclopentenyl cation II) followed by the elimination of a proton from II leads to CF<sub>3</sub>-Cps 4.<sup>7</sup> Furthermore, the *N*,*N*-dimethylmethanamine intermediate V could be formed from the reaction of a tautomer of 4 with the Vilsmeier regent  $(4 \rightarrow III \rightarrow IV \rightarrow V)$ . Finally, further reaction of V under Vilsmeier conditions and subsequent hydrolysis result in the formation of fulvenes 5.

The formation of CF<sub>3</sub>-fulvenes **5** from CF<sub>3</sub>-Cps **4** was further supported by the reaction of CF<sub>3</sub>-Cp **4b** under Vilsmeier conditions to give **5b** in 95% yield. As another application of CF<sub>3</sub>-Cps **4**, the reactions of **4a** and **4e** with maleimide were also examined. As a result, the Diels–Alder adducts, 1,2-diaryl-4-(trifluoromethyl)norbornene derivatives **6a** and **6e** were obtained in excellent yields, respectively (Scheme 3).

In conclusion, a series of trifluoromethylated 1,4-dien-3-ols 3 were successfully synthesized in excellent yields from DVKs 1 and Ruppert–Prakash reagent. The reactions of 3 could lead to the formation of either CF<sub>3</sub>-Cps 4 *via* the BF<sub>3</sub>·Et<sub>2</sub>O mediated Nazarov cyclization or CF<sub>3</sub>-fulvenes 5 *via* the cyclofunctionalization, a combination of Nazarov cyclization, followed by *in situ* derivatization under Vilsmeier conditions. Additionally, CF<sub>3</sub>-norbornenes 6 were also obtained by the Diels–Alder



Scheme 3 Synthesis of trifluoromethyl norbornenes 6.

reaction of **3** with maleimide. All the reactions were carried out under mild, metal-free conditions with high to excellent yields. Further studies are in progress.

Financial support of this research by the National Natural Sciences Foundation of China (21072027, 21272034 and 21202015), the Project sponsored by SRF for ROCS, SEM are greatly acknowledged.

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