



**Organic Preparations and Procedures International** 

The New Journal for Organic Synthesis

ISSN: 0030-4948 (Print) 1945-5453 (Online) Journal homepage: http://www.tandfonline.com/loi/uopp20

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**To cite this article:** Behrooz Maleki, Massomeh Raei, Elahe Akbarzadeh, Hassan Ghasemnejad-Bosra, Alireza Sedrpoushan, Samaneh Sedigh Ashrafi & Mohammad Nabi Dehdashti (2016) Chemoselective Synthesis of 2,2'-Arylmethylene bis-(3-Hydroxy-2-cyclohexenes) ("Tetraketones") in Hexafluoro-2-propanol, Organic Preparations and Procedures International, 48:1, 62-71, DOI: <u>10.1080/00304948.2016.1127102</u>

To link to this article: <u>http://dx.doi.org/10.1080/00304948.2016.1127102</u>



Published online: 29 Jan 2016.

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# Chemoselective Synthesis of 2,2'-Arylmethylene bis-(3-Hydroxy-2-cyclohexenes) ("Tetraketones") in Hexafluoro-2-propanol

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Some fluorous alcohols are useful as solvents, co-solvents, and additives because of their very useful properties in synthesis, in various formulations and of the ease of isolation of products. Fluorinated alcohols possess interesting physiochemical properties such as lower boiling points and higher melting points than their non-fluorinated counterparts; they are also strong hydrogen bond donors and have high polarity and the propensity to solvate water. The use of fluorinated solvents as reaction media instead of conventional volatile organic solvents, has grown dramatically in recent years.<sup>1–3</sup> Among several fluorinated alcohols, the most inexpensive and commonly utilized are 2,2,2-trifluoroethanol (*TFE*) and 1,1,1,3,3,3-hexafluoro-2-propanol (*HFIP*) which are available commercially. In spite of the strong electron-withdrawing power of the trifluomethyl group, these compounds are essentially non-acidic (pK<sub>a</sub> 9.3 and 14.4 respectively).<sup>4</sup> These fluorinated alcohols are neither nucleophilic nor hydrogen bond acceptors. Compared to other solvents, HFIP (bp. 59°C) and TFE, (bp. 74°C) are unique due their due to the extensive hydrogen bonding inter-network between the fluorines and the hydroxy groups. In addition, they can be easily separated from reaction mixtures and re-used subsequenly.<sup>5</sup>

2,2'-Arylmethylene *bis*-(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (**3**) are important for the synthesis of xanthenes which display biological and therapeutic properties such as anti-bacterial and anti-viral activities and also are useful in laser technology.<sup>6,7</sup> One of the simplest and general method for the preparation of this type of compounds involves the condensation of aromatic aldehydes (1 equiv.) with 1,3-cyclohexanediones (2 equiv.) under a variety of con-ditions. This reaction has been carried out using a number of catalysts such as sodium dodecylsulfate (SDS),<sup>8</sup> HClO<sub>4</sub>–SiO<sub>2</sub> or PPA–SiO<sub>2</sub>,<sup>9</sup>

Received July 5, 2015; in final form August 15, 2015.

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Scheme 1

molecular iodine, <sup>10</sup> *L*-histidine in an ionic liquid, <sup>11</sup> SmCl<sub>3</sub>, <sup>12</sup> polyvinylpyrrolidone(PVP)stabilized nickel nanoparticles, <sup>13</sup> KF/Al<sub>2</sub>O<sub>3</sub>, <sup>14</sup> catalyst-free, <sup>15,16</sup> triethylbenzylammonium chloride (TEBA), <sup>17,18</sup> FeCl<sub>3</sub>.6H<sub>2</sub>O/TMSCl/[bmim]-[BF<sub>4</sub>], <sup>19</sup> In(OTf)<sub>3</sub>, <sup>20</sup> Yb(OTf)<sub>3</sub>-SiO<sub>2</sub>, <sup>21</sup> cetyltrimethylammonium bromide (CTMAB), <sup>22</sup> nano-particles of Pd, <sup>23</sup> choline chloride/urea (2:1), <sup>24</sup> silica/HBF<sub>4</sub>, <sup>25</sup>ultrasonic, <sup>26–28</sup> and microwave. <sup>29,30</sup> However, many of these catalysts have disadvantages such as low yields, the utilization of expensive reagents of toxic metals and harsh reaction conditions, tedious work-up procedures, the need to use high catalyst loading, high temperature and of alternative energy source (ultrasonic and microwave). The development of methods that involve the use of reusable catalysts under mild and environmentally friendly conditions is one of the major goals in green and sustainable chemistry. Methods that lead to various organic compounds are in high demand for both academic and industrial applications. <sup>31–35</sup> As a continuation of our development of efficient and environmentally benign and catalyst, <sup>36–49</sup> we now report that the reaction of aldehydes with 1,3-cyclohexanediones proceeds at reflux in *HFIP* without any catalyst to give **3** in excellent yields and without the formation of by-products.

 Table 1

 Various Conditions Used for the Synthesis of 3f



Entry	Conditions	Time (min)	Yield (%)
1	HFIP/Reflux	140	95
2	HFIP/50°C	180	82
3	HFIP/40°C	210	81
4	HFIP/25°C	330	82
5	_a	360	_b
6	TFE/Reflux	140	89

<sup>a</sup>In the absence of HFIP at 60°C.

<sup>b</sup>No reaction.

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In our initial experiments, the condensation of 3-nitrobenzaldehyde (1 equiv.), dimedone (2 equiv.) in 1 mL of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was performed as a model reaction under different conditions (*Table 1*, *Entries 1–4*). *Table 1* shows that heating at reflux (59°C) afforded the best yield (95%) after 140 min. In the absence of HFIP, the reaction did not proceed at all. even upon prolonged heating (*Entry 5*).

Since 2,2,2-trifluoroethanol (TFE) has similar physicochemical properties as 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP),. its catalytic activity in this reaction was examined with 3-nitrobenzaldehyde at reflux (74°C). After 120 min, **3f** was obtained in 90% yield (*Table 1, Entry 6*).

Based on these results, the reaction of various aldehydes with cyclic 1,3-dicarbonyl compounds was carried out under these optimized conditions. The results are summarized in *Table 2*. In all cases, the corresponding products **3a-r** were obtained in good to excellent yields (76–95%) as well. Formaldehyde and acetaldehyde (*Entries 14 and 15*) as well as cinnamaldehyde (*Entry 13*) also gave good yields of the expected products. However, butyralde-hyde, isobutyraldehyde and crotonaldehyde gave only poor yields (26%, 32% and 37% re-spectively) of the expected products. The reaction did not proceed with acetylacetone, a non-cyclic  $\beta$ -diketone.

Chemoselectivity is one of the most desirable aspects in organic synthesis. In all the cases, the expected compounds (**3a-r**) were obtained in high yields as the major products. For example, none of the corresponding xanthene (**4g**) was formed on heating 2,2'-[(3-nitrophenyl)-methylene] *bis*-(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one) (**3g**, 1 equiv.) in HFIP (1 mL) at reflux; only starting material was recovered (*Figure 1*).

Upon completion of the reaction, HFIP is easily separated (by distillation) and may be re-used without decrease in its activity. For example, the reaction of dimedone (2 equiv.) with 3-nitrobenzaldehyde (1equiv.) afforded the corresponding 2,2'-(3-nitrophenylmethylene) *bis*-(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3g**) in 95%, 95%, 94%, 92%, and 90% yields over five cycles.

In order to illustrate the efficacy of our procedure, results for the preparation of 2,2'-arylmethylene *bis*-(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) derivatives reported previous-ly are compared with our data (*Table 3*). Our process using HFIP offers several advantages such as excellent yields, a simple procedure, facile work-up and recyclability.

In conclusion, we have developed an efficient procedure for the synthesis of "tetraketone" derivatives **3** *via* the condensation of various aldehydes and 1,3-cyclic dicarbonyl compounds catalyzed by HFIP. The main advantages of this procedure are that it (*i*) avoids the use of any base, metal, or Lewis acid catalysts, (*ii*) involves an facile separation and re-use of the catalyst from the reaction medium, (*iii*) leads to the easy isolation of the product without aqueous work-up, (*iv*) proceeds in high chemoselectivity and (*v*) there are no side-reactions.

### **Experimental Section**

All reagents were obtained from commercial sources and were used without purification. IR spectra were recorded as KBr pellets on a Shimadzu 435-U-04 spectrophotometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were determined on a Bruker DRX-300 Avance spectrometer in DMSO-d<sub>6</sub> or CDCl<sub>3</sub>, and shifts are given in  $\delta$  downfield from tetramethylsilane (TMS) as an internal standard. Melting points were determined using an Electrothermal 9200 apparatus and are uncorrected.

 Table 2

 Synthesis of Tetraketone Derivatives



				mp (°C)	
Entry	Products (3a-r)	Yield (%)	Time (min)	Found	Lit.
1	OH OH Me OO Me Me	90	180	190–191	186–188 <sup>12</sup>
2	OH OH Me Me	92	120	142–143	146–148 <sup>12</sup>
3	3b OH OH	90	180	156–158	158–159 <sup>13</sup>
4	Me Me 3e OH OH OH	88	180	143–145	142–144 <sup>12</sup>
5	Me Me 3d OH OH OH	93	180	167–168	167–168 <sup>13</sup>
6	Me Me 3e	90	120	190–192	194–196 <sup>12</sup>

(Continued on next page)

 Table 2

 Synthesis of Tetraketone Derivatives (Continued)

				mp (°C)	
Entry	Products (3a-r)	Yield (%)	Time (min)	Found	Lit.
	OH Me Me 3f				
7	OH Me Me 3g	95	140	199–200	201–203 <sup>12</sup>
8	OMe OH OH Me Me Me	90	120	175–177	178–180 <sup>12</sup>
9	3h	82	150	188–190	185–187 <sup>9</sup>
	OH Me Me 3i				
10	OH OH Me Me 3j	80	240	138–140	139–141 <sup>12</sup>
11	OH OH Me OH Me OH Me Me	79	240	192–194	195–196 <sup>13</sup>
12		90	240	140–142	139–141 <sup>12</sup>

(Continued on next page)

				mp (°C)	
Entry	Products (3a-r)	Yield (%)	Time (min)	Found	Lit.
	Me Me 31				
13	$\bigcirc$	85	300	204–206	20413
	OH OH Me OO Me				
14	3m	87	300	190	192–193 <sup>15</sup>
	Me Me 3n				
15	Me Me 30	76	360	180–182	182–184 <sup>15</sup>
16		92	120	209–212	207-20816
	ON ON OO 3p				
17	Br	90	110	238–240	240-24116
	OH OH OH OO 3q				

 Table 2

 Synthesis of Tetraketone Derivatives (Continued)

(Continued on next page)

 Table 2

 Synthesis of Tetraketone Derivatives (Continued)

Entry	Products ( <b>3a-r</b> )	Yield (%)	Time (min)	mp (°C)	
				Found	Lit.
18	OH OH OH OH OH	90	90	198–200	194–196 <sup>13</sup>

# Typical Procedure for the Synthesis of Compounds 3

Hexafluoroisopropanol (1 mL) was added to a mixture of the aldehyde (1 mmol), and 1,3-cyclohexanedione (0.23 g, 2 mmol) in a 5 mL flask fitted with a reflux condenser. The resulting mixture was heated to reflux (an oil bath) for the time shown in *Table 2* with stirring (spin bar). After the completion of the reaction as determined by TLC (hexane-ethyl acetate, 4:1), the products were isolated by distillation of HFIP and

 Table 3

 Comparison of the Efficiency of Various Catalysts in the Synthesis of Tetraketone Derivatives

Entry	Tetraketones	Conditions	Time (min)	Yield (%)
<b>3</b> a	~	HClO <sub>4</sub> –SiO <sub>2</sub> /acetonitrile/reflux <sup>9</sup>	360	54
3g	OH Me Me OO OH Me Me Me Me Me	SmCl <sub>3</sub> /water/rt <sup>12</sup>	30	91
		KF/Al <sub>2</sub> O <sub>3</sub> /solvent-free/rt <sup>14</sup>	840	86
		Catalyst-free/solvent-free/rt <sup>15</sup>	2880	86
		<i>p</i> -Dodecylbenzenesulfonic acid/ water/us/25–30°C <sup>28</sup>	60	89
		Present work	180	90
		SmCl <sub>3</sub> /water/rt <sup>12</sup>	30	91
		PVP-Ni NPs/ ethylene glycol/rt <sup>13</sup>	10	90
		KF/Al <sub>2</sub> O <sub>3</sub> /solvent-free/rt <sup>14</sup>	840	91
		Catalyst-free/water/rt <sup>16</sup>	2880	88
		Pd(0) NPs/water/rt <sup>23</sup>	25	88
		<i>p</i> -Dodecylbenzenesulfonic acid/ water/us/25–30°C <sup>28</sup>	60	94
		Present work	140	95



Figure 1

recrystallization of the solid residue from 96% ethanol (8 ml) to afford the pure "tetraketone" derivatives.

### Analytical Data for Selected Compounds

**2,2'-Phenylmethylene** *bis*(**3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one**) (**3a**): IR: 3080, 2956, 2929, 2870, 1610, 1520, 1400, 1350, 850; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.11 (s, 6H), 1.24 (s, 6H), 2.31–2.47 (m, 8H), 5.56(s, 1H), 7.10 (d, 2H), 7.18 (t, 1H), 7.28 (t, 2H), 11.91 (s, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  27.62, 29.86, 31.63, 32.96, 46.66, 47.28, 115.80, 126.05, 126.98, 128.42, 138.27, 189.59, 190.66.

**2,2'-[(4-nitrophenyl)methylene]** *bis*(3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one) (**3f**): IR: 3325, 3060, 2956, 1725, 1634, 1380, 1200, 1050, 950; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  1.12 (s, 6H), 1.24 (s, 6H), 2.32–2.51 (m, 8H), 5.55(s, 1H), 7.24 (d, 2H), 8.13 (d, 2H), 11.80 (s, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  27.62, 29.79, 31.63, 32.62, 46.64, 47.26, 115.55, 128.r0, 128.55, 131.80, 136.91, 189.63, 190.84.

# Acknowledgements

The author thanks the Research Council of Hakim Sabzevari University for partial support of this work.

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