

# Synthesis of 6-Aroyl-3,3,5,5-tetramethyl-2,3,5,6-tetrahydropyran-2,4-diones and Their Reaction with Phenylhydrazine

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**Abstract**—Methyl 4-bromo-3-oxo-2,2,4-trimethylpentanoate reacts with zinc and arylglyoxals yielding 6-aryol-3,3,5,5-tetramethyl-2,3,5,6-tetrahydropyran-2,4-diones. The latter with phenylhydrazine afford 6-(1-aryl-2-phenylhydrazonomethyl)-3,3,5,5-tetramethyl-2,3,5,6-tetrahydropyran-2,4-diones.

In contrast to substituted 2,3,5,6-tetrahydropyran-2,4-diones no published data is available [1] on their analogs containing an aroyl group in 6 position of the pyran ring. Aiming to synthesize this kind of compounds we carried out a reaction of methyl 4-bromo-3-oxo-2,2,4-trimethylpentanoate (**I**) with zinc and arylglyoxals **III**. We established that the synthesis was successful when the process was performed stepwise along the following scheme.

Zinc enolate **II** was prepared in the first stage, from bromoderivative **I** and zinc in ethyl ether-ethyl acetate mixture, 3: 1, and then thereto arylglyoxal **III** was added. The reaction between zinc enolate **II** and arylglyoxal occurred exclusively at the aldehyde group to afford zinc bromide alcoholate **IV** that cyclized under the reaction conditions to furnish the target product, 6-aryol-3,3,5,5-tetramethyl-2,3,5,6-tetrahydropyran-2,4-dione (**Va-j**), in 80–93% yield (Table 1).

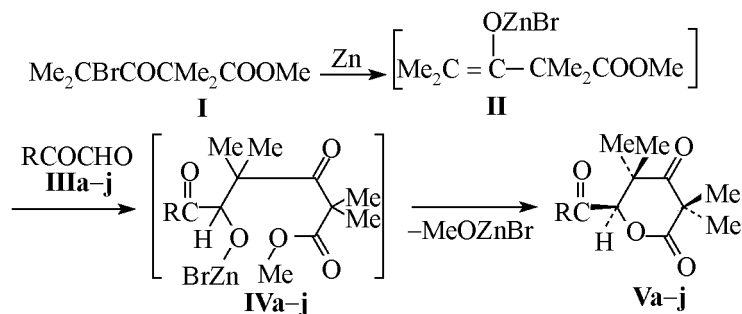
The composition and structure of compounds **Va-j** were proved by elemental analyses, <sup>1</sup>H NMR and IR

spectra. The <sup>1</sup>H NMR spectra contain characteristic proton signals (δ, ppm) in the regions 5.07–6.19 and 0.87–1.58 belonging respectively to the methine proton (CHO) and to the protons of four methyl groups (CMe<sub>2</sub>, CMe<sub>2</sub>). In the IR spectra (ν, cm<sup>-1</sup>) appear the absorption bands of the keto group from the aroyl moiety, of the keto and lactone groups from the heterocycle in the region 1680–1895, 1720–1725, 1745–1765 respectively.

In order to evaluate the reactivity of 6-aryol-3,3,5,5-tetramethyl-2,3,5,6-tetrahydropyran-2,4-diones and to obtain therefrom new nitrogen-containing derivatives we studied the reaction of compounds **Va, c, e-g** with phenylhydrazine.

The attack of nucleophilic reagent resulting further in formation of the corresponding phenylhydrazone may occur either at the carbon atom from the C=O group in the aroyl moiety or on the carbon atom of the C=O group in the heterocycle. The study revealed that the reaction **Va** took the first route, and as a result pyrandiones **Va, c, e-g** with phenylhydrazine give

## Scheme.



**III-V**, R = Ph (**a**), 4-MeC<sub>6</sub>H<sub>4</sub> (**b**), 4-EtC<sub>6</sub>H<sub>4</sub> (**c**), 4-(*t*-Bu)C<sub>6</sub>H<sub>4</sub> (**d**), 4-FC<sub>6</sub>H<sub>4</sub> (**e**), 4-ClC<sub>6</sub>H<sub>4</sub> (**f**), 4-BrC<sub>6</sub>H<sub>4</sub> (**g**), 4-PhC<sub>6</sub>H<sub>4</sub> (**h**), 2,4,6-Me<sub>3</sub>C<sub>6</sub>H<sub>2</sub> (**i**), 2,3,5,6-Me<sub>4</sub>C<sub>6</sub>H (**j**).

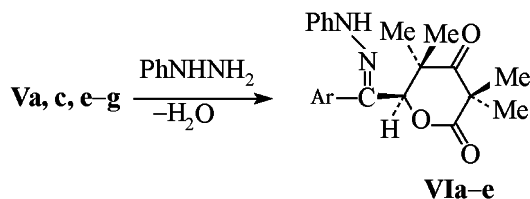
**Table 1.** Yields, melting points, IR and <sup>1</sup>H NMR spectra, and elemental analyses of 6-aryl-3,3,5,5-tetramethyl-2,3,5,6-tetrahydropyran-2,4-diones **Va–j**

Compd. no.	Yield, %	mp, °C	IR spectrum (ν, cm <sup>-1</sup> )			<sup>1</sup> H NMR spectrum (δ, ppm)					Found, %		Formula	Calcd., %	
			RCO	CO (ketone)	CO (lactone)	CMe <sub>2</sub> , CMe <sub>2</sub>	-CHO-	R	C	H	C	H			
<b>Va</b>	80	92–93	1680	1720	1750	0.93 s, 1.39 s, 1.45 s, 1.50 s	6.19 s	7.58 t, 7.75 t, 8.13 d (Ph)	69.84	6.53	C <sub>16</sub> H <sub>18</sub> O <sub>4</sub>	70.00	6.61		
<b>Vb</b>	84	124–125	1690	1720	1755	0.91 s, 1.40 s, 1.45 s, 1.52 s	6.15 s	2.44 s (Me), 7.38 d, 8.03 d (4-MeC <sub>6</sub> H <sub>4</sub> )	70.71	6.88	C <sub>17</sub> H <sub>20</sub> O <sub>4</sub>	70.82	6.99		
<b>Vc</b>	82	105–106	1680	1725	1750	0.87 s, 1.27 s, 1.33 s, 1.47 s,	5.58 s	1.13 t, 2.60 q (Et), 7.13 d, 7.77 d (4-EtC <sub>6</sub> H <sub>4</sub> )	71.41	7.26	C <sub>18</sub> H <sub>22</sub> O <sub>4</sub>	71.50	7.33		
<b>Vd</b>	91	149–150	1680	1715	1750	0.97 s, 1.37 s, 1.45 s, 1.57 s	5.57 s	1.22 s ( <i>t</i> -Bu), 7.40 d, 7.80 d (4- <i>t</i> -BuC <sub>6</sub> H <sub>4</sub> )	72.55	7.84	C <sub>20</sub> H <sub>26</sub> O <sub>4</sub>	72.70	7.93		
<b>Ve</b>	85	113–114	1680	1715	1760	0.91 s, 1.30 s, 1.37 s, 1.47 s	5.51 s	7.10 d.d, 8.00 d.d (4-FC <sub>6</sub> H <sub>4</sub> )	65.68	5.80	C <sub>16</sub> H <sub>17</sub> FO <sub>4</sub>	65.75	5.86		
<b>Vf</b>	86	125–126	1690	1720	1765	0.95 s, 1.39 s, 1.46 s, 1.49 s	6.17 s	7.62 d, 8.15 d (4-ClC <sub>6</sub> H <sub>4</sub> )	62.14	5.47	C <sub>16</sub> H <sub>17</sub> ClO <sub>4</sub>	62.24	5.55		
<b>Vg</b>	90	119–120	1690	1720	1765	0.94 s, 1.39 s, 1.47 s, 1.50 s	6.17 s	7.76 d, 8.08 d (4-BrC <sub>6</sub> H <sub>4</sub> )	54.30	4.75	C <sub>16</sub> H <sub>17</sub> BrO <sub>4</sub>	54.41	4.85		
<b>Vh</b>	89	152–153	1680	1720	1745	0.97 s, 1.41 s, 1.58 s 1.37 s,	5.61 s	7.20–7.60 m (C <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub> ), 7.65 d, 8.00 d (C <sub>6</sub> H <sub>5</sub> C <sub>6</sub> H <sub>4</sub> )	75.32	6.23	C <sub>22</sub> H <sub>22</sub> O <sub>4</sub>	75.41	6.33		
<b>Vi</b>	91	132–133	1695	1725	1755	1.00 s, 1.30 s, 1.42 s, 1.57 s	5.13 s	2.13 s (Me), 6.83 s (Me <sub>3</sub> C <sub>6</sub> H <sub>2</sub> )	70.90	7.84	C <sub>18</sub> H <sub>24</sub> O <sub>4</sub>	71.03	7.95		
<b>Vj</b>	93	163–164	1695	1720	1745	1.05 s, 1.33 s, 1.45 s, 1.58 s	5.07 s	2.03 s, 2.10 s (Me), 7.02 s (MeC <sub>6</sub> H <sub>4</sub> )	71.51	8.15	C <sub>19</sub> H <sub>26</sub> O <sub>4</sub>	71.67	8.23		

**Table 2.** Yields, melting points, IR and <sup>1</sup>H NMR spectra, and elemental analyses of 6-(1-aryl-2-phenylhydrazonomethyl)-3,3,5,5-tetramethyl-2,3,5,6-tetrahydropyran-2,4-diones **Vla–e**

Compd. no.	Yield, %	mp, °C	IR spectrum (ν, cm <sup>-1</sup> )			<sup>1</sup> H NMR spectrum (δ, ppm)					Found, %		Formula	Calcd., %	
			CO (ketone)	CO (lactone)	NH	CMe <sub>2</sub> , CMe <sub>2</sub>	-CHO-	Ph-NH-, Ar	C	H	C	H			
<b>Vla</b>	65	179–181	1720	1745	3330	1.27 s, 1.30 s, 1.35 s, 1.43 s	5.18 s	6.75 t, 6.94 d, 7.12 t (PhN), 7.47 m, 7.52 m (Ph), 9.02 s (NH)	72.35	6.52	C <sub>22</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub>	72.51	6.64		
<b>Vlb</b>	45	136–137	1720	1750	3360	1.20 s, 1.30 s, 1.45 s	4.93 s	1.20 t, 2.63 q (Et), 6.63–7.40 m (PhN, 4-EtC <sub>6</sub> H <sub>4</sub> ), 7.63 s (NH)	73.25	4.11	C <sub>24</sub> H <sub>28</sub> N <sub>2</sub> O <sub>3</sub>	73.44	7.19		
<b>Vlc</b>	61	191–192	1720	1750	3350	1.15 s, 1.30 s, 1.43 s	4.87 s	6.57–7.47 m (PhN, 4-FC <sub>6</sub> H <sub>4</sub> ), 7.50 s (NH)	69.01	5.98	C <sub>22</sub> H <sub>23</sub> FN <sub>2</sub> O <sub>3</sub>	69.10	6.06		
<b>Vld</b>	60	205–207	1720	1750	3345	1.16 s, 1.30 s, 1.43 s	4.88 s	6.57–7.55 m (PhN, 4-ClC <sub>6</sub> H <sub>4</sub> ), 7.58 s (NH)	66.03	5.70	C <sub>22</sub> H <sub>23</sub> ClN <sub>2</sub> O <sub>3</sub>	66.25	5.81		
<b>Vle</b>	64	202–204	1720	1750	3355	1.13 s, 1.23 s, 1.40 s	4.83 s	6.60–7.63 m (PhN, 4-BrC <sub>6</sub> H <sub>4</sub> ), 7.67 s (NH)	59.48	5.13	C <sub>22</sub> H <sub>23</sub> BrN <sub>2</sub> O <sub>3</sub>	59.60	5.23		

rise to 6-(arylphenylhydrazonomethyl)-3,3,5,5-tetramethyl-2,3,5,6-tetrahydropyran-2,4-diones (**VIa-e**).



**VI**, Ar = Ph (**a**), 4-EtC<sub>6</sub>H<sub>4</sub> (**b**), 4-FC<sub>6</sub>H<sub>4</sub> (**c**), 4-ClC<sub>6</sub>H<sub>4</sub> (**d**), 4-BrC<sub>6</sub>H<sub>4</sub> (**e**).

For interpretation of the results obtained we used simulation of phenylhydrazine nucleophilic attack on the carbons of keto groups in **Va** molecule by semi-empirical procedure SCF MO LCAO in AM1 approximation [2] applying the method of reaction coordinate. As the latter were chosen the interatomic distances  $l(\text{C}-\text{N})$ . We calculated the formation enthalpy  $\Delta H_f$  of a supermolecule (**Va**)...phenylhydrazine by scanning the interatomic distance  $l(\text{C}\cdots\text{N})$  from 3.00 to 1.55 Å with a step of 0.01 Å. It turned out that the  $\Delta H_f$  value increased monotonically from -348.6 to -195.7 kJ mol<sup>-1</sup> at the attack on benzoyl carbonyl, and from -333.3 to -148.8 kJ mol<sup>-1</sup> at the attack of the C<sup>4</sup>=O carbonyl. Since the second curve is located higher than the first as regards the  $\Delta H_f$  axis, the energy consumption at the attack on C<sup>4</sup> should be considerably greater apparently due to the steric hindrances from the methyl groups attached to C<sup>3</sup> and C<sup>5</sup>. This is the reason why among the reaction products we did not find phenylhydrazones alternative to the above mentioned.

The calculations also show that the phenylhydrazone with *syn*-orientation of the phenyl substituent and NH-Ph group with respect to C=N bond is by 30.09 kJ mol<sup>-1</sup> more stable than the corresponding *anti*-isomer.

The yields of phenylhydrazones **VIa-e** are 45–65% (Table 2).

Their composition and structure were confirmed by elemental analyses, <sup>1</sup>H NMR and IR spectra. In the <sup>1</sup>H NMR spectra (CDCl<sub>3</sub>, δ, ppm) appear characteristic signals at 7.50–7.67, 4.83–4.93, 1.13–1.45 from a proton of NH group, methine proton from CHO group, and from four methyl groups (CMe<sub>2</sub>, CMe<sub>2</sub>) respectively. In the IR spectra (ν, cm<sup>-1</sup>) are present the absorption bands of the keto and lactone groups in the heterocycle, and also those of the NH

group in the regions 1720, 1745–1750, 3330–3360 respectively.

## EXPERIMENTAL

<sup>1</sup>H NMR spectra of compounds **Vc-e**, **h-j**, **VIb-e** were registered in CDCl<sub>3</sub> solutions on spectrometer RYa-2310 (60 MHz), of compounds **Va**, **b**, **f**, **g**, **VIa** in DMSO-*d*<sub>6</sub> solutions on spectrometer Bruker DRX-500 (500 MHz). TMS was used as internal reference. IR spectra were measured on spectrophotometer UR-20 from individual compounds.

The quantum-chemical calculations were carried out on PC Pentium 200 MMX using a software package MOPAC 7.0 [3] with complete optimization of all geometrical parameters.

**6-Aroyl-3,3,5,5-tetramethyl-2,3,5,6-tetrahydropyran-2,4-diones (Va-j)**. To 4 g of fine zinc turnings in a mixture of 15 ml of anhydrous ethyl ether and 5 ml of anhydrous ethyl acetate was added 0.04 mol of methyl 4-bromo-3-oxo-2,2,4-trimethylpentanoate. On completion of the reaction the mixture was heated for 30 min. The reaction mixture was then cooled, 0.033 mol of arylglyoxal solution in 10 ml of anhydrous benzene was added, the mixture was boiled for 20 min, cooled, hydrolyzed with 5% hydrochloric acid, and the reaction products were extracted into ether. The organic layer was dried with anhydrous sodium sulfate, the solvents were distilled off, and compounds **Va-j** were recrystallized from methanol (Table 1).

**6-(Arylphenylhydrazonomethyl)-3,3,5,5-tetramethyl-2,3,5,6-tetrahydropyran-2,4-diones (VIa-e)**. To 0.004 mol of compound **Va**, **c**, **e-g** dissolved in 10–15 ml of glacial acetic acid was added 0.006 mol of phenylhydrazine. The mixture was stored at room temperature for 4–10 days, then the separated precipitate of phenylhydrazone was filtered off and twice recrystallized from methanol (Table 2).

## REFERENCES

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3. Stewart, J.J.P., *MOPAC. Version 7.0*, Frank J. Seiler Research Laboratory, US Air Force Academy-QOMP.