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# Convenient synthesis and characterization of molecules containing multiple β-keto ester units

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### ABSTRACT

Three compounds containing two  $\beta$ -keto ester units and one containing three were obtained in good yields from sebacyl, terepthaloyl, isophthaloyl, and trimesoyl chlorides. In this one pot procedure the acid chlorides were first treated with ethyl acetoacetate and barium oxide and then with ethyl alcohol. The aliphatic ester exists mainly as keto ester with a very small amount of the enol tautomer. In the case of aromatic esters, all possible tautomers were found in considerable concentrations in deuterochloro-form solution. Theoretical chemical shifts were estimated from GIAO/WP04/aug—cc-pVDZ/SCRF calculations, for a probable signal assignation for the corresponding tautomeric species. Our theoretical results are in agreement with experimental findings and account for negligible stability differences between the tautomers of each aromatic compound.

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β-Keto esters represent very valuable precursors in organic synthesis,<sup>1-4</sup> being widely used to prepare heterocycles,<sup>4-6</sup> ketones,<sup>3</sup> and  $\beta$ -hydroxyesters.<sup>3</sup> These chemicals are important for agrochemical, pharmaceutical, and dye industries.<sup>2</sup> They have been used in the syntheses of complex natural products too.<sup>2,7</sup>  $\beta$ -Keto esters can also be valuable in condensation reactions as stabilized enolates or active methylene equivalents.<sup>8</sup> This wide variety of applications and the fact that a rather small number of them are commercially available,<sup>4</sup> have probably provided the driving force to develop a significant number of procedures to obtain them,<sup>1,9</sup> ever since the first reports by Claisen.<sup>10,11</sup> Molecules containing multiple β-keto ester moieties have been used in polymerization reactions by poly-Michael condensation, yielding analogues to carbon monoxide copolymers.<sup>12</sup> They also represent attractive synthetic building blocks, for instance in asymmetric reductions to polyols.<sup>13</sup> Since  $\beta$ -keto esters are able to chelate metal ions they could be used to obtain metal-organic supramolecular assemblies in a similar way it has been reported for molecules with several  $\beta$ -diketone units.<sup>14</sup> However, molecules containing more than one  $\beta$ -keto ester unit are seldom reported.<sup>15-17</sup> Their syntheses represent an extra challenge because procedures that are suitable to obtain mono β-keto esters will not necessarily furnish the same results trying to obtain molecules with a superior number of this moiety.

Our interest in molecules containing several  $\beta$ -keto ester units stems from the idea of using them in condensation reactions with hydrazines in order to obtain molecules that incorporate several

5-pyrazolone rings in its structure. To date, condensation of hydrazines with  $\beta$ -keto esters is still the most general and practical reaction to obtain pyrazolones. The models in this objective are some related structures containing heterocyclic moieties already reported in the literature.<sup>18,19,15c</sup>

There are some previous reports regarding aromatic homologues. Compound **1** (Scheme 1) was easily obtained in a one pot procedure and with good vield from therephtalaldehyde and ethyl diazoacetate, using montmonirrollite K-10 as catalyst.<sup>15b</sup> However, the diazo reagent raises some safety concerns for large scale syntheses. Besides, the procedure was used to synthesize small amounts of the product. Compound 2 (Scheme 1) was obtained by a several step route.<sup>15c</sup> Dimethyl m-phenylenediacrylate acid was brominated and then transformed into dimethyl m-phenylenedipropiolate acid which by sulfuric acid catalyzed hydration afforded the target product. The main drawback of the synthesis is the number of steps, which is especially important if the diester is prepared to be used as a starting material in a subsequent reaction or synthesis. The availability and the price of the starting material is a second problem with this synthesis. In these two cases, spectroscopic data were not reported and therefore no information regarding tautomerism is known. For compound 2 the situation is absolutely understandable considering the date it was reported. In this Letter the successful application of one procedure to prepare some di- $\beta$ -keto esters and one tri- $\beta$ -keto ester from readily available and not expensive reagents is reported. The tautomerism observed is also discussed.

The fact that a reaction between two functional groups can be carried out successfully with high yields does not necessarily imply





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Scheme 1. Reagents and conditions: (a) BaO, H<sub>2</sub>O, ethyl acetoacetate, toluene, rt, (b) EtOH, H<sub>2</sub>SO<sub>4</sub> 5%, toluene, rt, yields: 1 (78%), 2 (73%), 3 (73%), and 4 (78%).

that the same result will be observed for the same reaction taking place simultaneously at several points in one substrate. This situation makes relevant the search for new procedures or to study which ones among those already known are suitable to obtain multifunctional counterparts. In the case of obtaining molecules with several  $\beta$ -keto ester units, reports are not as general as they could be expected. Random results have been reported in some cases.<sup>15a,20</sup> In order to obtain the target compounds, our attention was focused on procedures characterized by fairly good vields and at a convenient scale, considering that the products would be used as starting materials in other reactions. Thus, in the first experiments the procedure described by Yonemitsu<sup>21</sup> that gives  $\beta$ -keto esters in good yields starting from an acid chloride and Meldrum's acid followed by solvolysis with an alcohol was tried. The procedure was useless in trying to obtain aromatic di- or tri-\beta-keto esters. It is interesting to mention that Mahulikar and Mane<sup>20</sup> serendipitously isolated di-β-keto esters from glutaroyl or adipoyl dichlorides and Meldrum's acid. Kosower<sup>15a</sup> has also reported good results following the same procedure in the synthesis of diethyl 3.8-dioxodecanedioate, but he also failed with other aliphatic diacid dichlorides. After the bad results obtained with Meldrum's acid. the procedure reported by Yuasa and Tsuruta<sup>22</sup> was tried (Scheme 1). It was this procedure that finally furnished the desired products. As it can be seen, it worked for aromatic and aliphatic acyl halides. The reaction was repeated increasing up to four times the amounts of reagents described in the Supplementary data without noticeable effect in the yields. The limit was the size of the flask to carry out the reaction and the stirring system.

Organic chemists are quite familiar with keto–enol tautomerism.<sup>23–26</sup> Particularly in the case of di- $\beta$ -keto esters, Langer et al. studied the synthesis and tautomerism of 3,5-dioxopimelates.<sup>17</sup> In the present case several tautomers can be envisaged for compounds **1** to **4** (Scheme 2).

According to the solubility of the compounds the <sup>1</sup>H NMR spectra were recorded in  $CDCl_3$ .<sup>27</sup> Since our goal was the synthesis and the rapid characterization of the products, trials in other solvents were not attempted. For the di-esters **1** and **2**, two singlets around **4** ppm are observed, corresponding to the methylenic hydrogens between the carbonyls. This result indicates that compounds **1** and **2** exist in two different tautomeric forms (**1a/1b** and **2a/2b**), which share a common connectivity in the methylenic hydrogen region. Additionally, two signals are observed near 6 ppm corresponding to the vinylic hydrogens of enolized tautomers, which indicate the coexistence of tautomers **1b/1c** for compound **1**, and tautomers **2b/2c** for compound **2** (Fig. 1).

Other important signals that account for the presence of enol tautomers appear over 12 ppm. These signals correspond to OH groups that are strongly shifted downfield by intramolecular hydrogen bonding. Compound **1** is the easiest to analyze, considering the symmetry of structures **1a** and **1c**, which should be detected as two singlets in the aromatic region, respectively. Those

signals are observed at 8.04 and 7.82 ppm. However, with the available information it is not possible to unequivocally assign each signal to the corresponding tautomer. Signals corresponding to the aromatic hydrogens of tautomer **1b** can be identified without any doubt, because they constitute an AA'BB' spin system that gives rise to a doublet of doublets centered at 7.94 ppm. The spectrum of compound **2** also supports the presence of three tautomers in the aromatic region; however, establishing which hydrogen is responsible for each signal is again not straightforward with the present information.

The small variations in the structure on going from one tautomer to the other, makes it difficult to assign the signals with their corresponding protons. In order to provide complementary information to help in NMR signal assignments, DFT computational chemistry calculations were carried out with the method GIAO/ WP04/aug-cc-pVDZ/SCRF,<sup>28</sup> which has been described in the literature as a reliable method to obtain theoretical chemical shifts comparable with experimental values.<sup>29</sup> Tables SI1, SI2 and SI3 summarize these results for compounds 1, 2, and 3, respectively. As it can be concluded the hydrogen atoms in the aromatic rings of the di- or tri-keto structures are less shielded than the di- or tri-enol. Calculations also indicated that the vinvlic protons are more shielded as the number of enolized groups in a molecule increase. Although in some cases theoretical calculations clearly differ from experimental shifts and in other cases, the differences in calculated values for related hydrogen atoms are too small to be reliable, the fact that enolization produces a shielding was used as a guide for the assignation. But, it is important to consider that with the information available an unequivocal assignation based on the calculated data is not possible in all the cases and the assignments are only likely ones. Additional experiments are required to get fully reliable assignments. Thus, the chemical shift for the vinyl proton is smaller for the dienol 1c, than for the monoenol 1b, 5.72 and 5.74 ppm, respectively (see Fig. 1) and it follows that the concentration of dienol is lower than that of the monoenol. On the other side, methylenic hydrogens of tautomers 1a and 1b, 4.02 and 4.01 ppm, respectively. As previously stated, assigning the signals corresponding to the aromatic part is easier owing to symmetry. Besides, due to the better resolution of these signals, it is possible to ingrate their areas in order to estimate the relative abundances of the tautomers.

Chemical shift of the aromatic protons in tautomer **1a** is 8.04 ppm, while in tautomer **1c** the value is 7.82 ppm. For tautomer **1b** the values are 7.99 ppm and 7.87 ppm. The abundances as obtained from the areas are 54% of **1b**, 36% of **1a**, and 10% for **1c**. Chemical shifts for the OH protons are in agreement with the assignment based on the relative abundance for tautomer **1b** and **1c**.

Regarding compound **2** (Fig. 1) the signals at 5.73 and 5.72 ppm can be assigned to **2b** and **2c**, respectively. The methylenes between the carbonyls in tautomers **2a** and **2b** are observed at 4.03



Figure 1. Selected areas of <sup>1</sup>H NMR of compounds 1 and 2. Each signal shows the corresponding experimental and (calculated) chemical shifts.

and 4.02 ppm, correspondingly. As concluded from the previous result for **2b** and **2c**, the methylene in **2b** must have a smaller chemical shift than in **2a**. The protons in the aromatic ring are not well resolved, rendering integration not accurate; this in turn makes unreliable any calculation of the tautomers concentration. Regarding the OH protons, calculations predict that they are more shielded in **2c** than in **2b**. The corresponding experimental values are 12.61 and 12.59 ppm. Thus, for this compound it is possible



**Figure 2.** Selected <sup>1</sup>H NMR signals of compound **3** (calculated values between parentheses). Insert: patterns of the aromatic region in <sup>1</sup>H NMR spectrum for the tautomers of compound **3**.

to affirm that **2b** is the most abundant species followed by **2a** and finally **2c**; but, again, the percentages cannot be obtained owing to the low resolution.

Compound **3** exhibits three singlets around 4 ppm, corresponding to the methylenic hydrogen,  $\alpha$  to the carbonyl groups. This result agrees with the presence of tautomers **3a**, **3b**, and **3c**. Three signals near 6 ppm corresponding to three vinylic hydrogens are also observed. This result shows that there are three tautomers with different enolic groups as is the case of structures **3b**, **3c**, and **3d**. Three signals between 12 and 13 ppm corresponding to the three OH are also observed and support the coexistence of the different tautomeric species (Fig. 2).

Figure 2 shows that for compound **3** the vinylic hydrogen in tautomer **3d** is the most shielded, then in tautomer **3c** and finally in tautomer **3b**. Following the tendency of the calculated values, the experimental chemical shifts at 5.82, 5.79, and 5.77 ppm were assigned to the vinylic protons of tautomers **3b**, **3c**, and **3d**, correspondingly. In a similar way the signals at 4.08, 4.07, and 4.05 ppm were assigned to the methylenic hydrogens between the carbonyls in tautomers **3a**, **3b**, and **3c**, correspondingly. The signals at 8.24 and 8.71 ppm were assigned to the aromatic hydrogen of tautomers **3d** and **3a**, the tri-enol, and the tri-keto, respectively (Fig. 2, insert). The other signals in the aromatic region were assigned following the guide provided by the calculated chemical shifts.

The abundances of the tautomers, as calculated from the aromatic signal areas, are 48% of **3b**, 27% of **3a**, 21% of **3c**, and 4% of **3d**. Finally the signals corresponding to the hydroxyl protons (Fig. 2) can be assigned considering the relative abundances of the tautomers provided by the aromatic signals, beside the information provided by the calculated chemical shifts. Additionally, this assignation agrees with that of the vinylic protons.

<sup>13</sup>C NMR data are in well agreement with the mixture of tautomers. A first inspection of the spectra indicates that there are some missing signals. However, the relative intensities of some of them show that this may be due to overlapping. Table 1 summarizes the <sup>13</sup>C signal for compound **1**, **2**, **3**, and **4**.

Table 1	
Selected <sup>13</sup> C NMR chemical shifts (ppm) of <b>1</b> , <b>2</b> , <b>3</b> , and <b>4</b>	

Compound	C=O (keto)	C=O (ester)	=С-ОН	=C-H (vinyl)
1	192.0	173.1 172.9 170.1 169.5	167.3 167.1	89.4(8) 89.4(9)
2	191.9 191.7	172.9 172.8 170.9 169.6	167.2 167.1	88.2 87.9
3	191.3 191.2 191.0	174.7 172.7(2) 172.6(9) 172.6(5) 168.7 168.4 168.2	166.8(4) 166.7(7) 166.7(3)	$89.1(7)^a$ 88.9(7) $88.8(4)^a$
4	202.9	167.3	n.o. <sup>b</sup>	89.0

<sup>a</sup> More intense.

<sup>b</sup> Not observed.

Regarding the aliphatic ester, the proton spectrum shows that compound **4** exists mainly as the di-keto compound (**4a**). However it is still possible to observe a tiny signal for the OH at 12.08 ppm and two signals at 4.95 and 5.57 ppm for vinylic hydrogens. The area of the signal corresponding to the OH group duplicates the one of the vinylic protons. Comparing with the area of the CH<sub>2</sub> between the carbonyls at 3.41 ppm, the signal of the OH represents almost 1%. Another clue for enolization is that all the other important signals in the spectrum are accompanied by a small replication of them. For instance, the quartet that corresponds to OCH<sub>2</sub> that appears at 4.18 ppm and is accompanied by a small quartet slightly shifted downfield and appears at 4.25 ppm. The singlet for the methylene between the carbonyls appears at 3.41 ppm and it is also accompanied by a small singlet at 3.43 ppm. The triplet for the C-4 and C-11 methylene groups appears at 2.51 ppm and his partner at 2.63 ppm. The bigger difference in chemical shift in this case can be due to the nearness respect to the changing part of the molecule. There is a multiplet at 1.57 ppm corresponding to the methylene group of C-5 and C-10. In this case the partner signal is only a small shoulder. The last signal, at 1.26, corresponds to the two CH<sub>3</sub> and the rest of the CH<sub>2</sub> at the center of the molecule (C-6, C-7, C-8, and C-9). This signal is a distorted triplet and it is accompanied by a small triplet at 1.35. The coupling constant is 7.25 Hz, and this signal cannot be integrated because the small signal lies at the base of the bigger one. Other authors have also described that the di-keto tautomer is the most abundant for homologous di-esters.<sup>12,14,26</sup> The <sup>13</sup>C NMR for compound **4** is also consistent with the presence of the di-keto tautomer as the main species in the solution.

The FTIR spectra of compounds **1** and **2** show a characteristic band between  $1740-1745 \text{ cm}^{-1}$  for C=O of the ester. The ketone C=O appears between 1685 and 1690 cm<sup>-1</sup>. In the case of compound **3** the values are 1736 and 1690 cm<sup>-1</sup>, correspondingly. There is also another very intense signal around 1633 and 1640 cm<sup>-1</sup> that may correspond to C=C stretching of the enol moiety.

As a consequence of enolization, C=O bands appear to be broadened, C=C-OH bands are more intense and broad than conventional C=C bands, which are of moderate intensity. In these spectra a wide signal from around 3500 cm<sup>-1</sup> until 2400 cm<sup>-1</sup> that corresponds to the O-H involved in hydrogen bonding. This signal is overlapped with those corresponding the different C-H stretching.

Further results including more detailed NMR experiments with a more powerful spectrometer in order to obtain unambiguous assignations of the chemical shifts will be reported in due time.

## Conclusions

The acylation of ethyl acetoacetate using BaO as base has been successfully extended to obtain compounds with more than one  $\beta$ -keto ester units. The synthesized products were conveniently isolated from the reacting mixture and purified by crystallization or column chromatography. The large volumes of solvent and ethyl acetoacetate are recovered and can be reused. This alternative allows overcoming the difficulties that appeared following the conventional pathway with Meldrum's acid which turned out to be unsuitable with several aromatic diacyl or triacyl chlorides that were included in the study; despite the good yields that have been reported in the syntheses of compounds with one  $\beta$ -keto ester functionality. Thus, the presented results widen the scope of procedures so far reported in the synthesis molecules containing multiple  $\beta$ -keto ester moieties and open possibilities to prepare novel derivatives.

Results obtained show that the condensation of Meldrum's acid di or tri acyl chlorides is not as general as the condensation with mono acyl halides.

Computational calculations were employed as an auxiliary tool to guide the assignment of probable chemical shifts in the experimental <sup>1</sup>H NMR spectra.

NMR data support the existence of several tautomers in solution. The main tautomer in CDCl<sub>3</sub> solution in the case of aromatic keto esters is the monoenol, in the case of the non-aromatic homologue the main tautomer is largely the diketo.

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07. 025.

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- 27. Compounds were characterized by FTIR (Nicolet, Magna 550), <sup>1</sup>H and <sup>13</sup>C NMR (Bruker AC 250P; 250 MHz for <sup>1</sup>H and 62.9, operating temperature was 28 °C) and using TMS as internal standard. CDCl<sub>3</sub> from Merck Chemicals was used without further treatment. Concentrations roughly 10 to 15 mg per ml for <sup>1</sup>H and 40–50 mg per ml for <sup>13</sup>C were used.
- 28. Geometry optimization of each tautomeric species was carried out at B3LYP/6-311++G(d,p) level of theory without imposing any symmetry restriction. Conformational analysis was performed in order to identify the most stable conformation of the β-keto ester units related to the aromatic ring. Theoretical chemical shifts were obtained from the standard GIAO/WP04/aug-cc-pVDZ/ SCRF method, using TMS as reference compound. More specifications see in Supplementary data.
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