Facile *Knoevenagel* and Domino *Knoevenagel/Michael* Reactions Using Gel-Entrapped Base Catalysts

by **Shital Shinde**, **Gajanan Rashinkar**, **Arjun Kumbhar**, **Santosh Kamble**, and **Rajashri Salunkhe***

Department of Chemistry, Shivaji University, Kolhapur, 416004, M.S., India
(phone: +91 2312609169; fax: +91 231 2692333; e-mail: rss234@rediffmail.com)

An efficient method for *Knoevenagel* condensation of arenecarbaldehydes with active methylene compounds such as barbituric acid and *Meldrum*'s acid in the presence of gel-entrapped base catalysts is reported. The method has been extended to the one-pot synthesis of arylmethylene-bis[3-hydroxycyclohex-2-en-1-one] derivatives from dimedone (= 5,5-dimethylcyclohexane-1,3-dione) and arenecarbaldehydes by using domino *Knoevenagel/Michael* reaction sequence.

Introduction. – *Knoevenagel* condensation is one of the most common and versatile reaction that is used for C,C bond formation. This reaction has been widely used for the preparation of several intermediates which are useful in perfumes, cosmetics, and bioactive compounds [1][2]. The products of *Knoevenagel* condensation also have widespread applications including inhibition of antiphosphorylation of EGF receptor and antiproliferative activity [3]. Due to their importance from a pharmacological, industrial, and synthetic point of view, several methods for the *Knoevenagel* condensation have been reported. These methods include both homogeneous as well as heterogeneous conditions, catalyzed by bases such as piperidine [4], ethylenediamines or their corresponding ammonium salts, 4-(dimethylamino)pyridine (DMAP), or organocatalyst such as glycine, L-proline, and alanine [5]. In recent years, resins [6], montmorillonite–KSF [7], $ZrCl_4$–SiO_2 [8], ionic liquids [9], microwave irradiation [10] and *Lewis* acids [11] have also been employed. Although the literature on *Knoevenagel* condensation contains a rich array of versatile methodologies, new approaches remain valuable additions to the contemporary arsenal of synthetic strategies.

The concept of Gel-Entrapped Base Catalysts (GEBCs) combines the advantages of alkali and organic bases with those of heterogeneous supports [12]. These catalysts are prepared by immobilization of alkali or organic bases by entrapping them in an aqueous gel matrix of agar–agar which is a polymer composed of repeating agarobiose units alternating between 3-linked β-D-galactopyranosyl (G) and 4-linked 3,6-anhydro-α-L-galactopyranosyl (LA) units as shown in *Fig. 1*. This method reduces the amount of bases used, and allows easy and efficient separation of products from the catalyst. Besides this, bases like alkalis, when exposed to air, absorb moisture and are spoiled. On the contrary, the GEBCs do not absorb moisture on exposure to air and remain intact. The use of GEBCs in organic synthesis also provides an excellent opportunity of recyclability and reusability, which is seldom possible using bases alone as catalysts.

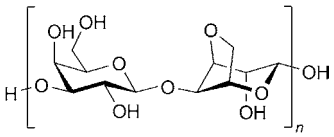


Fig. 1. *Stucture of agarose*

However, despite their well recognized advantages, there have been only limited and sporadic reports dealing with use of GEBCs in synthetic chemistry [13][14]. The interesting properties of GEBCs spurred us to probe their barely exploited potential in organic synthesis.

In our continuing search for novel catalysts in organic synthesis [15], we report herein the *Knoevenagel* condensation of arenecarbaldehydes with active methylene compounds like barbituric acid (= pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) and *Meldrum*'s acid (=2,2-dimethyl-1,3-dioxane-4,6-dione) and one-pot synthesis of arylmethylene-bis[3-hydroxycyclohex-2-ene-1-one] derivatives from dimedone and arenecarbaldehydes by using domino *Knoevenagel*/*Michael* reaction sequence in the presence of GEBCs.

Results and Discussion. – Initially, we focused our attention in the synthesis of various GEBCs. Morpholine, piperidine, and KOH were selected as bases for the synthesis of GEBCs. A series of experiments were conducted in which different concentrations of selected bases (5–25%) were dissolved in a varying amount of agar–agar in H_2O. Finally, we found that 20% (*w*/*w*) of agar–agar/aqua gel containing 10% bases resulted in the formation of soft gels that served as GEBCs in the present work. All the GEBCs were light-yellow jelly-like substances that could be cut into pieces (*Fig. 2*).

Fig. 2. *Photograph of KOH-GEBC*

Thermal behavior of GEBCs was studied by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC; *Fig. 3*). The TGA/DSC curves of KOH-GEBC (*Fig. 3*, *a*) revealed that degradation of gel occured with increase in temperature and was completed at 151° as evident from strong endothermic peak observed in DSC. The thermal decomposition of agar polymer started around 240° and was very slow up to 475°, indicating that the polymer matrix might have undergone some structural changes (which were slightly exothermic) leading to complete exothermic decomposition of polymer material around 500°, leaving only anhydrous KOH which decomposed above 800°. However, in the case of GEBCs containing morpholine and piperidine (*Fig. 3*, *b* and *c*), the decomposition of bases was observed before the degradation of polymer. The process of base degradation was slow due to intercalation of morpholine and piperidine in polymer matrix.

Our next task was to demonstrate the catalytic activity of GEBCs in the *Knoevenagel* condensation. As a trial case, equimolar mixture of barbituric acid and benzaldehyde (5 mmol each) was stirred in the presence of 1 g of various GEBCs in EtOH at ambient temperature until the completion of reaction as monitored by TLC. The results are compiled in *Table 1*. Among the various GEBCs, KOH-GEBC was found to be better than piperidine- and morpholine-GEBCs. The stupendous increase in the yield of product as well as reaction times of KOH-GEBC may be attributed to higher basicity of KOH as compared to piperidine and morpholine. Further, we have also studied the effect of solvents on a model reaction using KOH-GEBC. We observed that, in solvents such as EtOH, i-PrOH, MeOH, CH_2Cl_2, and toluene, the yields of the products were considerably higher in EtOH than in others (*Table 2*). It is worthy noting that, in a blank experiment, no reaction was observed under similar conditions in the absence of GEBC. The striking feature of all the reactions was the isolation of products. It was interesting to observe that, after a specified time, the product precipitated out of the mixture that could be isolated simply by filtration. The product obtained after sufficient washing with H_2O was found to be practically pure.

Table 1. *Screening of Various GEBCs for* Knoevenagel *Condensation*[a])

Entry	GEBC	Time [min]	Yield[b]) [%]
1	KOH-GEBC	10	92
2	Morpholine-GEBC	10	65
3	Piperidine-GEBC	10	70

[a]) The reaction of benzaldehyde with barbituric acid. [b]) Yields of isolated products.

Table 2. *Solvent Effect on the* Knoevenagel *Condensation Using KOH-GEBC*[a])

Entry	Solvent	Time [min]	Yield[b]) [%]
1	EtOH	15	92
2	i-PrOH	15	70
3	MeOH	15	60
4	CH_2Cl_2	15	55
5	Toluene	15	50

[a]) The reaction of benzaldehyde with barbituric acid. [b]) Yields of isolated products.

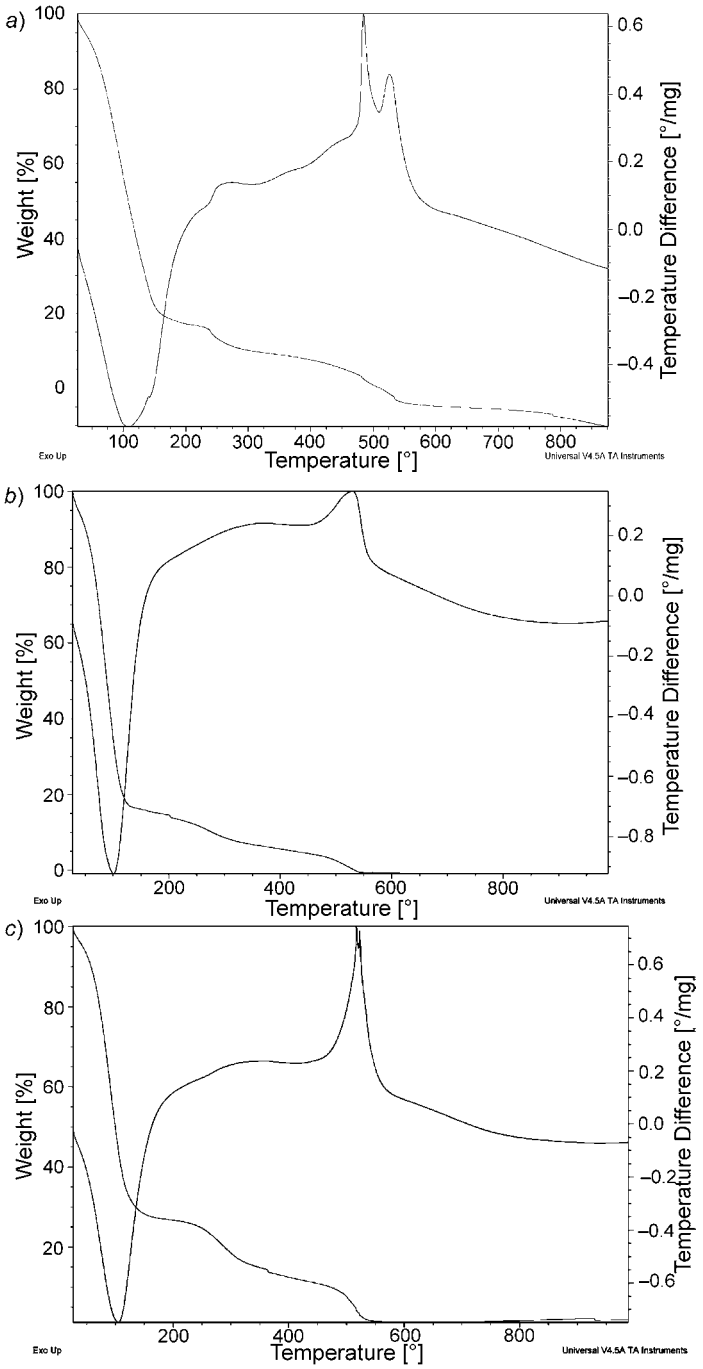
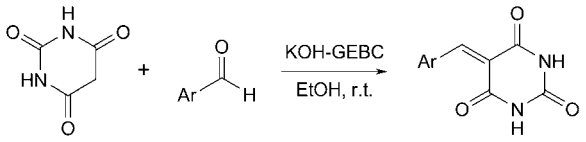


Fig. 3. *DSC-TGA graph of* a) *KOH-GEBC,* b) *Morpholine-GEBC, and* c) *Piperidine-GEBC*

Because excellent results were obtained with KOH-GEBC, we employed this particular catalyst for further studies. To investigate the feasibility of KOH-GEBC, a number of structurally diverse arenecarbaldehydes were reacted with barbituric acid (**1**) in EtOH. The results of the reactions are collected in *Table 3*. In all cases, arylmethylidene-barbituric acids were the sole products, and no anomalies were noted. With both electron-poor and electron-rich benzaldehydes, the corresponding products were obtained in good-to-excellent yields. The reaction of the sterically hindered 2-substitued benzaldehydes gave even higher yields, highlighting the general applicability of the protocol. The identity of all the compounds was ascertained on the basis of IR, ^{1}H- and ^{13}C-NMR, and MS data. The physical and spectroscopic data are in agreement with the proposed structures.

Table 3. *KOH-GEBC-Catalyzed* Knoevenagel *Condensation of Arenecarbaldehydes with Barbituric Acid*[a])



1 **2a – 2i** **3a – 3i**

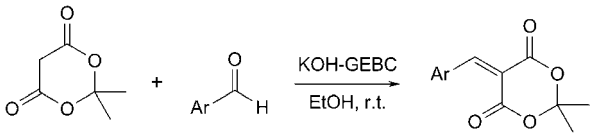
Entry	Ar	Aldehyde	Product	Time [min]	Yield[b]) [%]	M.p. [°][c])
1	Ph	**2a**	**3a**	10	92	271 (273 [16])
2	4-(Me_2N)–C_6H_4	**2b**	**3b**	10	89	265 (263 [16])
3	4-Cl–C_6H_4	**2c**	**3c**	8	79	280 (281 [16])
4	2-Cl–C_6H_4	**2d**	**3d**	10	80	252 (253 [17][18])
5	4-OH–C_6H_4	**2e**	**3e**	10	86	297 (299 [19])
6	3-MeO,4-OH–C_6H_3	**2f**	**3f**	10	76	290 (291 [19])
7	4-MeO–C_6H_4	**2g**	**3g**	10	91	276 (277 [17][18])
8	4-Me–C_6H_4	**2h**	**3h**	10	81	300 (298 [19])
9	Thiophen-2-yl	**2i**	**3i**	10	81	273 (27 [20])

[a]) All products were characterized by IR, ^{1}H- and ^{13}C-NMR, and MS analyses. [b]) Yields of isolated products. [c]) Literature values in parentheses.

To investigate the scope and limitations of the method, we applied similar conditions to *Knoevenagel* condensation of arenecarbaldehydes with other active methylene compound like *Meldrum*'s acid (**4**). We found that the reactions proceeded equally well forming the corresponding products in excellent yields within shorter duration reflecting the versatility of the method (*Table 4*).

Arylmethylene-bis[3-hydroxycyclohex-2-en-1-one] derivatives constitutes important class of scaffolds that are widely used for the syntheses of xanthenes and acridinediones [24]. In addition, they have also shown potent activities as antioxidants, lipoxygenase inhibitors [25], and a new clinical class of tyrosinase inhibitors against crucial dermatological disorders like hyperpigmentation skin melanoma [26]. Although a large number of synthetic protocols have been developed for arylmethylene-bis[3-hydroxycyclohex-2-en-1-one] derivatives using cyclic 1,3-dicarbonyl compounds and arenecarbaldehydes, in which the domino *Knoevenagel*/*Michael* addition reactions

Table 4. *KOH-GEBC-Catalyzed* Knoevenagel *Condensation of Arenecarbaldehydes with* Meldrum*'s Acid*[a])



4 **2a – 2h** **5a – 5h**

Entry	Ar	Aldehyde	Product	Time [min]	Yield[b]) [%]	M.p. [°][c])
1	Ph	**2a**	**5a**	10	88	84 (85 [21–23])
2	4-(Me_2N)–C_6H_4	**2b**	**5b**	10	89	173 (174 [21–23])
3	4-Cl–C_6H_4	**2c**	**5c**	10	76	163 (162 [21–23])
4	2-Cl–C_6H_4	**2d**	**5d**	10	87	135 (133 [21–23])
5	4-OH–C_6H_4	**2e**	**5e**	10	78	198 (197 [21–23])
6	3-MeO,4-OH–C_6H_3	**2f**	**5f**	10	77	128 (129 [23])
7	4-MeO–C_6H_4	**2g**	**5g**	10	75	127 (126 [23])
8	4-Me–C_6H_4	**2h**	**5h**	10	80	158 (159 [23])

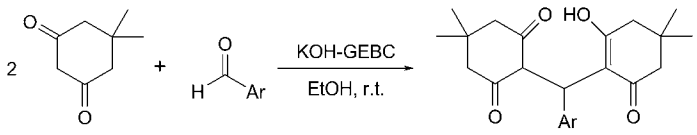
[a]) All products were characterized by IR, ^{1}H- and ^{13}C-NMR, and MS analyses. [b]) Yields of isolated products. [c]) Literature values in parenthesis.

are key steps [27], there is still a scope for improvement especially towards developing an efficient method using highly reusable catalyst. This prompted us to investigate the synthesis using KOH-GEBC. Accordingly, the reactions of dimedone (= 5,5-dimethylcyclohexane-1,3-dione; **6**; 1 mmol) with variety of arenecarbaldehydes (2 mmol) were examined in EtOH in the presence of KOH-GEBC at ambient temperature. As shown in *Table 5*, all the arenecarbaldehydes reacted readily with **6** to afford corresponding arylmethylene-bis[3-hydroxycyclohex-2-en-1-one] derivatives in 65–95% yields in a very short reaction time.

In the GEBCs, the reagent entrapped in the gel may leach into the solvent. To study the leaching of KOH in solvent, 1 g of KOH-GEBC was stirred in 5 ml of EtOH at room temperature. The KOH-GEBC was filtered, and H_2O (3 ml) was added to the filtrate. The KOH leached out was then determined by titrating against 0.1N succinic acid solution using phenolphthalein as an indicator. It was observed that only 1.5% KOH leached out from gel into EtOH. Using the same amount of KOH as that leached out, the reaction between barbituric acid (**1**)/*Meldrum*'s acid (**4**) and benzaldehyde (**2a**) did not give quantitative yield of the corresponding product. This clearly demonstrated that catalysis was solely due to intact KOH-GEBC rather than leached KOH.

The recovery and reuse of catalysts is highly preferable for the large-scale operations and from the industrial point of view. To check the possibility of GEBC recycling, the reaction of barbituric acid (**1**), *Meldrum*'s acid (**4**), and dimedone (**6**) with benzaldehyde (**2a**) using KOH-GEBC in EtOH was studied. After completion of the reaction, the KOH-GEBC was separated from mixture, washed with EtOH, and reused in another reaction with identical substrates. The catalyst showed a remarkable recyclability, as the yield of the product decreased only slightly from the first run to the fifth run (*Fig. 4*).

Table 5. *KOH-GEBC-Catalyzed Domino* Knoevenagel/Michael *Reaction Sequence of Arenecarbaldehydes with Dimedone*[a])



6 **2a – 2h** **7a – 7h**

Entry	Ar	Aldehyde	Product	Time [min]	Yield[b]) [%]	M.p. [°][c])
1	Ph	**2a**	**7a**	10	84	196 (192–194 [28])
2	4-(Me_2N)–C_6H_4	**2b**	**7b**	10	87	188 (186–188 [28])
3	4-Cl–C_6H_4	**2c**	**7c**	10	89	140 (140–142 [28])
4	2-Cl–C_6H_4	**2d**	**7d**	10	81	235 (238–240 [29])
5	4-OH–C_6H_4	**2e**	**7e**	10	85	200 (202–205 [28])
6	3-MeO,4-OH–C_6H_3	**2f**	**7f**	10	87	122 (122–124 [30])
7	4-MeO–C_6H_4	**2g**	**7g**	10	88	145 (146–148 [28])
8	4-Me–C_6H_4	**2h**	**7h**	10	83	129 (128–130 [28])

[a]) All products were characterized by IR, ^{1}H- and ^{13}C-NMR, and MS analyses. [b]) Yields of isolated products. [c]) Literature values in parenthesis.

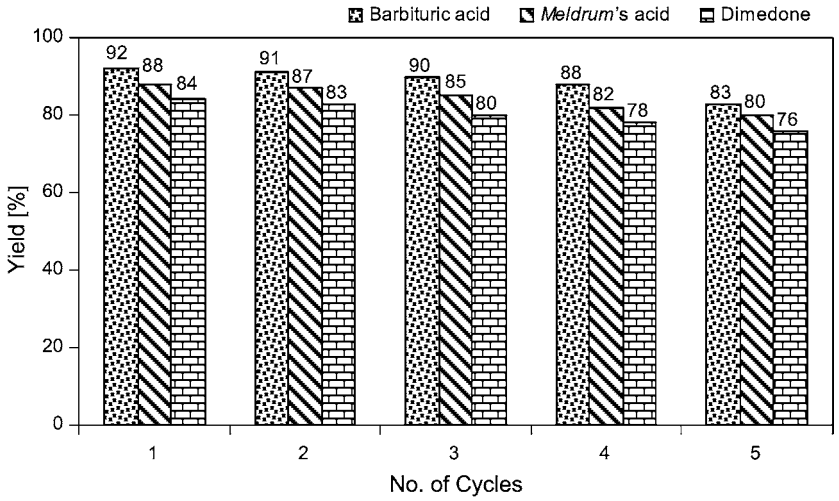


Fig. 4. *Recyclability of KOH-GEBC*

Conclusions. – In conclusion, a novel and highly efficient methodology for *Knoevenagel* condensation of arenecarbaldehydes with active methylene compounds has been developed using recyclable GEBC. The protocol has been successfully applied for the one-pot synthesis of arylmethylene-bis[3-hydroxycyclohex-2-en-1-one] derivatives from dimedone and arenecarbaldehydes by using domino *Knoevenagel*/*Michael* reaction sequence. The method offers several significant advantages, such as high

conversions, easy handling, clean reaction profile, and short reaction time, which render it a useful and an attractive addition to the existing methodologies for the synthesis of *Knoevenagel* condensation products.

Experimental Part

General. All chemicals were obtained from local suppliers and used without further purification. M.p.: Open capillary; uncorrected. IR Spectra: *Perkin-Elmer* FT-IR spectrometer; KBr discs. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avon 300* MHz spectrometer with DMSO or $CDCl_3$ as solvent, and TMS as internal reference. MS: *Shimadzu QP2010* GC/MS with an ion source temp. of 280°. Thermal gravimetric analysis (TGA): instrument *STA 1500* in the presence of static air at a linear heating rate of 10°/min from 25° to 1000°.

Preparation of GEBCs. To a boiling mixture of agar–agar (20 ml) in H_2O (60 ml) was added a mixture of base (10 g) in H_2O (10 ml). The resultant soln. was boiled with stirring for 5 min and cooled in ice bath to yield the desired GEBC.

General Procedure for Knoevenagel *Condensation of Arenecarbaldehydes with Active Methylene Compounds.* A mixture of arenecarbaldehyde (5 mmol) and active methylene compound (5 mmol) was stirred in the presence of GEBC (1 g) in 5 ml of EtOH at ambient temp. until the completion of the reaction as monitored by TLC. The resulting crude product was filtered off, washed with H_2O and recrystallized from EtOH to afford pure products.

General Procedure for the Synthesis of Arylmethylene-bis(3-hydroxycyclohex-2-en-1-one) Derivatives. A mixture of arenecarbaldehyde (5 mmol) and active methylene compound (10 mmol) was stirred in the presence of GEBC (1 g) in 5 ml of EtOH until the completion of the reaction as monitored by TLC. The resulting crude product was purified by recrystallization.

*Data of Representative Compounds. 5-[4-(Dimethylamino)benzylidene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**3b**). IR (KBr): 3196, 3073, 1715, 1649, 1611, 1505. ^{1}H-NMR (300 MHz, DMSO): 3.11 (*s*, 6 H); 6.69 (*s*, 1 H); 8.37–8.01 (*m*, 4 H); 10.80 (*s*, 1 H); 10.92 (*s*, 1 H). ^{13}C-NMR (75 MHz, DMSO): 40.0; 110.1; 111.6; 120.6; 139.5; 150.7; 154.2; 156.4; 162.9; 165.1. EI-MS: 259 (M^+).

*5-(4-Methoxybenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**3g**). IR (KBr): 3070, 1727, 1675, 1602, 1547, 1215. ^{1}H-NMR (300 MHz, DMSO): 3.84 (*s*, 1 H); 6.91 (*s*, 1 H); 7.73–8.31 (*m*, 4 H); 10.98 (*s*, 1 H); 11.09 (*s*, 1 H). ^{13}C-NMR (75 MHz, DMSO): 55.4; 113.9; 114.4; 127.7; 137.9; 150.4; 156.5; 162.3; 164.0; 164.2. EI-MS: 246 (M^+).

5-[4-(Dimethylamino)benzylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (**5b**). IR (KBr): 3090, 2980, 2921, 2850, 1720, 1698, 1610, 1399, 1262, 819. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.65 (*s*, 6 H); 3.10 (*s*, 6 H); 6.67 (*d*, $J = 9$, 2 H); 8.11 (*d*, $J = 9$, 2 H); 8.15 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 27.2; 40.0; 103.2; 104.5; 111.3; 119.7; 138.9; 154.7; 157.4; 161.2; 164.7. EI-MS: 275 (M^+).

5-(4-Methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (**5g**). IR (KBr): 3075, 2997, 2950, 2900, 1740, 1714, 1575, 1390, 1284, 837. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.80 (*s*, 6 H); 3.92 (*s*, 3 H); 7.01 (*d*, $J = 9$, 2 H); 8.24 (*d*, $J = 9$, 2 H); 8.27 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 27.5; 55.5; 103.9; 111.0; 114.3; 124.8; 137.6; 157.7; 160.1; 163.7; 164.5. EI-MS: 262 (M^+).

2-[(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)(phenyl)methyl]-5,5-dimethylcyclohexane-1,3-dione (**7a**). IR (KBr): 2962, 1594, 1447, 1374, 1299, 1249, 1165, 843. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.11 (*s*, 6 H); 1.24 (*s*, 6 H); 2.28 (*d*, 4 H), 2.50 (*d*, $J = 16.2$, 8 H); 5.55 (*s*, 1 H); 7.09–7.30 (*m*, 5 H); 11.92 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 25.3; 27.7; 29.3; 29.8; 38.7; 44.4; 110.6; 113.9; 123.5; 125.4; 146.7; 188.2; 164.7. EI-MS: 367 (M^+).

2-{[4-(Dimethylamino)phenyl](2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)methyl}-5,5-dimethylcyclohexane-1,3-dione (**7b**). IR (KBr): 2959, 1660, 1600, 1369, 1306, 1230, 1164, 1064, 910, 812. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.10 (*s*, 6 H); 1.23 (*s*, 6 H); 2.33 (*d*, 4 H), 2.42 (*d*, $J = 16.1$, 8 H); 2.90 (*s*, 6 H); 5.47 (*s*, 1 H); 6.65–7.26 (*m*, 4 H); 11.95 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 27.3; 29.7; 31.3; 31.8; 40.7; 46.4; 47.0; 112.6; 115.9; 125.5; 127.4; 148.7; 189.0; 190.2. EI-MS: 410 (M^+).

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