Solvent-Free Synthesis of Diaryl α-Tetralones via Michael Addition under Microwave Irradiation

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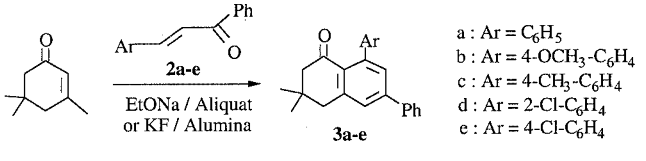
A one-pot synthesis of diaryldimethyl-α-tetralones via Michael addition and subsequent Robinson annulation reactions of isophorone with chalcones was carried out in solvent-free conditions under microwave irradiation. The reagents were either supported on basic mineral solid supports or mixed with a phase-transfer catalyst in basic medium. Substantial rate enhancements were observed and much shorter reaction times were needed upon microwave irradiation than by conventional heating.

Introduction

The hydronaphthalene ring is particularly important in the cosmetic and fragrance industries, in pharmacology and agrochemistry, and it is found in a number of drugs and natural products. However, synthetic *gem*-dimethylhydronaphthalene derivatives, obtained from isophorone, are rather rare, although some of them have been used in fragrance chemistry.[1−3] In pharmacology, such systems have been studied for their use as hypotensive agents,[4,5] bronchodilators [4] and antibacterials;[6] in agrochemistry they are involved in pest control as antifeedants against the spruce budworm.[7] Thus, polyhydronaphthalene derivatives, and especially α-tetralones, have attracted much attention due to their biological activities. Moreover, tetralones play a crucial role in the chemistry of polycyclic fused systems[8,9] and in the building of the anthracycline skeleton.[10−13] In this context, we have developed a new strategy for the synthesis of diaryl-*gem*-dimethyl-α-tetralones starting from isophorone.

The most significant approaches to the formation of α-tetralone ring involve either Diels−Alder reactions between cyclohexenones as dienophiles and various dienes, or tandem Michael addition/Robinson reactions. Some condensations of α,β-unsaturated ketones with chalcones to obtain carbocyclic rings have been described.[14] The aryne condensation of α,β-unsaturated ketone enolates (including isophorone) is also a good way of preparing naphthalene derivatives.[15−18] Isophorone has also been used in an ene reaction, followed by thermolysis, to prepare a *trans*-decalin derivative.[19] However, only a few reactions are known for the synthesis of aryl tetralones. Monoaryl tetralones have been obtained by a Friedel−Crafts reaction between α-tetralone and arenes in the presence of $AlCl_3$.[20]

We report here our strategy for the preparation of diaryltetralones in a one-pot reaction. It involves, in a first step, the Michael addition of isophorone with various chalcones in a basic medium followed by cyclization (Robinson annulation; Scheme 1). For this purpose we used nonclassical procedures[21,22] such as dry media conditions[23−25] or solvent-free phase-transfer catalysis (PTC),[26] which avoid the use of solvent during the reaction, both coupled with microwave activation [27] (MW) in order to: i) operate under a "green approach" in safe conditions minimizing pollution,[28−30] ii) take advantages of MW activation mainly resulting in shortened reaction times, enhanced yields and purities of products, iii) save starting materials (no solvent) and energy (significantly less energy is required in MW heating systems than with a thermostatted oil bath or stirrer hotplates).



Scheme 1

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Results and Discussion

It has been reported that isophorone undergoes a base-catalyzed self-condensation reaction at 155−160 °C in the presence of an alkaline hydroxide in water or sodium amide in a boiling aprotic solvent (Et_2O or benzene).[33−35] At room temperature, it reacts with arylaldehydes in a basic medium (NaOH/H_2O or KOH/MeOH) to give aldol condensation products.[36−39] In our investigations, we have chosen NaOEt as the base and first examined the reaction with chalcones in refluxing ethanol for 24 hours. Under these conditions, only compounds **3** were obtained with moderate yields (52%); no product resulting from self-condensation was observed.

Next, all the reactions were performed in open glass vessels under solvent-free conditions in a focused microwave monomode reactor (Synthewave 402® reactor from Prolabo).[27,31] This system has a number of advantages with regard to electric field homogeneity, temperature control, thanks to infrared,[32] low emitted power (from 15 to 300 Watts), and the possibility of carrying out reactions under atmospheric pressure in open vessels.

In the case of reactions using solid supports in “dry media”, the reactants were first dissolved in dichloromethane and impregnated onto basic inorganic solid supports (KF/alumina); the solvent was then removed under vacuum. In the phase-transfer catalysis (PTC) technique, the reagents were mixed with a catalytic amount of the phase-transfer agent (Aliquat 336, 4 mol %) and an excess of base (NaOEt, 2 equivalents). The mixtures were then exposed to microwave irradiation with mechanical stirring to ensure a good temperature homogeneity inside the reaction mixture. At the end of the reaction, the products were dissolved in an organic solvent and analyzed by GC-MS and NMR spectroscopy. In order to check the possible intervention of specific (non-thermal) effects of the electromagnetic field, the results were compared with those obtained from reactions performed under classical heating (thermostatted oil bath) under identical conditions (profiles temperature change, time, pressure, medium and reaction vessels, mechanical stirring).

Solid-Liquid PTC Solvent-Free Conditions

The use of NaOEt as the base under PTC conditions led exclusively to compounds **3** (Table 1). Microwave irradiation was successful and gave excellent yields (86−89%) of isolated pure tetralones within 5 to 6 minutes, whereas classical heating afforded only 51−56% of the desired product. To achieve similar yields, the reactions needed at least 60 minutes at the same temperatures under classical heating. Comparison of the two activating methods shows clearly the superiority of the solvent-free PTC conditions when coupled with focused microwave irradiation.

Mineral Solid Supported Reactions

The use of KF/alumina acting both as the basic catalyst and the mineral solid support coupled to microwaves in a

Table 1. Synthesis of compounds **3a−e** from reaction of isophorone **1** with chalcones **2a−e** by classical heating or under microwave activation; solid-liquid PTC solvent-free conditions (NaOEt, 2 equiv. and Aliquat 336, 4%)

	Reaction conditions	Time (min)	Temp (°C)[a]	Activ. Mode[b]	Product **3** (%)[c]
2a	EtOH	1440	78	CH	50
	Solvent-free PTC	5	110	MW	86
	Solvent-free PTC	5	110	CH	51
	Solvent-free PTC	60	110	CH	82
2b	EtOH	1440	78	CH	52
	Solvent-free PTC	5	108	MW	86
	Solvent-free PTC	5	108	CH	51
	Solvent-free PTC	120	108	CH	76
2c	EtOH	1440	78	CH	40
	Solvent-free PTC	6	120	MW	89
	Solvent-free PTC	6	120	CH	52
	Solvent-free PTC	90	120	CH	79
2d	EtOH	1440	78	CH	56
	Solvent-free PTC	5	110	MW	88
	Solvent-free PTC	5	110	CH	54
	Solvent-free PTC	90	110	CH	81
2e	EtOH	1440	78	CH	46
	Solvent-free PTC	6	110	MW	86
	Solvent-free PTC	6	110	CH	56
	Solvent-free PTC	75	110	CH	81

[a] Temperature is evaluated by IR detection (calibrated via an optical fiber) for the MW method and with a digital thermometer inside the reaction mixture for classical heating using a thermostatted oil bath. [b] MW = Microwave activation, CH = Classical heating. Under both conditions, temperature homogeneity was ensured by mechanical stirring. [c] Yields refer to pure isolated products (complements is constituted only from starting materials).

Table 2. Synthesis of compounds **3a−e** from reaction of isophorone **1** with chalcones **2a−e** by classical heating or under microwave activation using KF/alumina

	Time (min)	Temp (°C)[a]	Activ. Mode[b]	Product **3** (%)[c]
2a	8	108	MW	92
	8	108	CH	65
	60	108	CH	84
2b	5	110	MW	79
	5	110	CH	61
	120	110	CH	80
2c	8	112	MW	90
	8	112	CH	68
	120	112	CH	86
2d	5	115	MW	86
	5	115	CH	49
	90	115	CH	81
2e	8	115	MW	90
	8	115	CH	50
	90	115	CH	82

[a] Temperature is evaluated by IR detection (calibrated with an optical fiber) for the MW method and with a digital thermometer inside the reaction mixture for classical heating using a thermostatted oil bath. [b] MW = Microwave activation, CH = Classical heating. Under both conditions, temperature homogeneity was insured by mechanical stirring. [c] Yields refer to pure isolated products.

monomode reactor led to rather similar results as those obtained under the PTC conditions (Table 2). The reaction times ranged from 5 to 8 minutes and the yields were very high. It has been reported that in the absence of solvent the Michael addition is very efficient when the reactants are supported on basic alumina.[40,41] The cumulative effects of solid support and MW irradiation in the anionic condensation of methylbenzylidene cyanoacetate and nitromethane gave quantitative yields in the Michael reaction.[42]

In our investigations, only moderate yields (50−60%) were obtained when compounds **3** and KF-alumina were reacted under solvent-free classical heating, whereas excellent yields were obtained (up to 92%) when the supported reactants were submitted to MW irradiation. MW and conventional heating rates were identical due to, in the first case, the possibility of the modulation of the emitted power in order to maintain a constant temperature. Typical curves are given in Figure 1. These results reveal an important specific (non-thermal) microwave effect.

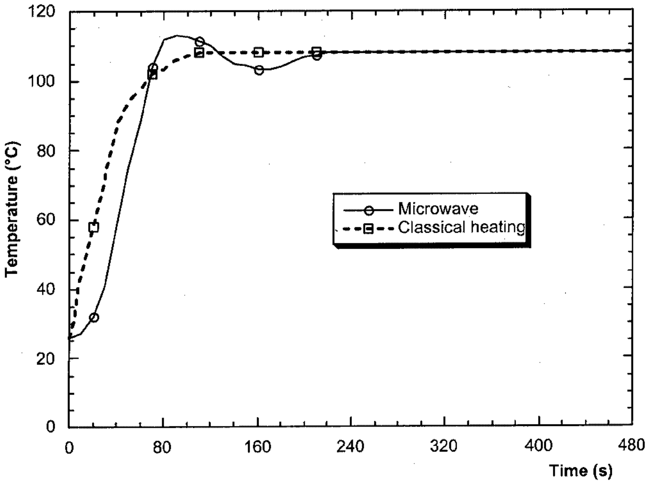
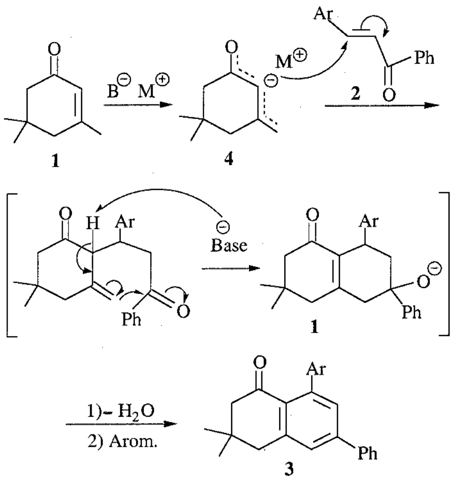


Figure 1. Temperature rise profiles under microwave or classical heating conditions for the reaction with KF-alumina (**1** + **2a**)

Reaction Mechanisms

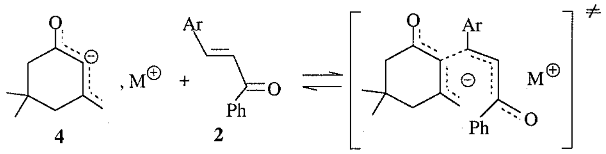
The structural assignment of the various tetralones deserves some explanation. One of the problems in the basic condensation with isophorone lies in the fact that it is an α,β-unsaturated ketone possessing acidic protons at C_6 (α′-position) and C_7 (γ-position). Under kinetic control, the α′-position would be the most reactive one,[43] whereas deprotonation under thermodynamic control would take place at the γ-position.[44] It is clear that an aldol condensation takes place between the α-C of isophorone and chalcones since only compounds **3** were formed. They are formed by nucleophilic attack at the 2-position of the mesomeric enolate ion **4** (already reported in the case of the reaction of acrylonitrile or methyl acrylate[45]) followed by dehydration and thermal aromatization (Scheme 2).



Scheme 2

Origins of Specific Microwave Effects

In these reactions, specific non-thermal MW effects are evidenced after direct comparisons between MW activation and conventional heating. These results can easily be rationalized by considering the enhancement in the polarity of the system during the reaction.[46] The transition states are composed of very loose ion pairs due to extension of the negative charge delocalization (Scheme 3), thereby conferring a polarity enhancement due to an increase in ionic dissociation. As the magnitude of the MW effect is amplified with the polarity of the materials by electrostatic (dipole-dipole type) interactions, the stabilization of the transition state is more effective than for the ground state and the energy of activation is therefore reduced when such a mechanism is involved.

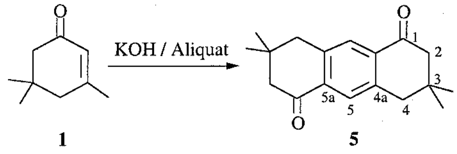


Scheme 3

When the reaction is performed in "dry media" using KF/alumina, another additional effect can intervene due to the use of mineral solid. Mineral oxides are generally poor conductors of heat. Using conventional means, heating is difficult and non-homogeneous, with large temperature gradients and overheating on the vessel walls. In contrast, however, they are very efficient MW absorbers,[47] resulting in very rapid and homogeneous heating. Improvements in temperature homogeneity and heating rates therefore mean faster reactions and less degradation of final products. This contributes to produce important effects when compared to classical heating in the case of supported reagents under MW.[48]

Formation of a Self-Condensation Product of Isophorone

When KOH was used instead of NaOEt, an unexpected and new self-condensation product **5** (25%) was obtained together with tetralone **3a** (70%). The conversion rate was 95% within 1 min at 120 °C. This result prompted us to examine the self-condensation of isophorone under PTC conditions with KOH as the base. Under these conditions, compound **5** was formed in 42% yield after 4 min at 126 °C under microwave irradiation. The yield falls to only 8% when the reaction mixture is heated in an oil bath under the same conditions (Scheme 4).



MW, 650W, 4 min, 126°C : 42%
Oil bath, 4 min, 126°C : 8%

Scheme 4

A similar tricyclic structure was obtained by Freer et al. in a base-catalyzed condensation of oxidized isophorone derivatives.[49,50]

Conclusion

In conclusion, the use of isophorone as a nucleophilic reagent in a basic medium for Michael addition and subsequent Robinson annulation with chalcones opens up a new method for a one-pot synthesis of diaryltetralones. The combination of MW irradiation and heterogeneous reactions under solvent-free conditions (PTC or supported reagents) proved to be very efficient in these syntheses since it gave high yields and pure products with very short reaction times under safe and improved conditions.

Experimental Section

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Analytical TLC were performed using Merck silica gel $^{60}F_{254}$ precoated on aluminum sheets; analytical GC was performed on a FID Carlo Erba, CG 6000 apparatus, fitted with a capillary column OV_1 (15 m). IR spectra were taken as KBr disks or as liquid films inserted between NaCl plates for oily compounds using a Perkin−Elmer 1600 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker instrument (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR) as $CDCl_3$ solutions. Chemical shifts are expressed in δ units (ppm) and quoted downfield from TMS as an internal standard. Mass spectra were measured with a Delsi-NerMag spectrometer with an ionising energy of 70 eV coupled to a gas chromatograph.

Focused MW irradiations were carried out at atmospheric pressure with a Synthewave S402 Prolabo microwave reactor (300 W, monomode system). Irradiation was monitored by a PC computer, infrared measurement and continuous feedback temperature control by modulation of the emitted MW power. The reactor was fitted with an external stirring system to ensure homogeneity in temperature. Yields and relative amounts of products were evaluated by GC (using an internal standard).

Reaction of Isophorone with Chalcones in Ethanolic Solution. General Procedure: Isophorone (0.66 g, 4.8 mmol) was added to a vigorously stirred solution of sodium ethoxide (20 mL, 0.5 M). Chalcone (0.5 g, 4.8 mmol) was dissolved in a minimum amount of absolute ethanol and then added to this solution. The mixture was then refluxed for *t* minutes, cooled to room temperature, concentrated under vacuum and then diluted with water (30 mL). The aqueous solution was extracted with dichloromethane. The combined extracts were dried over Na_2SO_4 and the solvent was removed. The crude mixture was purified through a silica gel column with hexane/ethyl acetate (8:2) to give 0.391 g (1.2 mmol, 50%) of pure **3a**. Tetralones **3** were recrystallized from an appropriate solvent.

Reaction of Isophorone with Chalcones Under Solvent-Free Conditions. General Procedure using NaOEt/Aliquat 336: NaOEt (0.34 g, 5 mmol) was closely blended with isophorone (0.33 g, 2.4 mmol), Aliquat 336 (40 mg, 0.1 mmol), and chalcone (0.5 g, 2.4 mmol). The mixture was heated whilst stirring in an oil bath or irradiated with microwaves. At the end of the reaction, the mixture was extracted with dichloromethane (3 × 10 mL), the combined extracts were filtered through Florisil to remove mineral salts and remaining Aliquat. The filtrate was then evaporated to dryness. The residue was chromatographed on a silica gel column with hexane/ethyl acetate (8:2) to give 0.672 g (2.06 mmol, 86%) of pure **3a** under MW conditions, and 0.398 g (1.22 mmol, 51%) of pure **3a** under classical heating. KOH was used under the same conditions.

General Procedure using KF/Al_2O_3: Basic alumina (20 g) was mixed with an aqueous solution of KF (15 g KF/150 mL H_2O) and stirred for 15 min. The mixture was then concentrated to dryness under vacuum and kept at 100 °C for 30 min. Isophorone (0.33 g, 2.4 mmol) and chalcone (0.5 g, 2.4 mmol) were dissolved in dichloromethane (15 mL). KF/Al_2O_3 (4 g) was quickly added to the solution at room temperature whilst stirring, then the solvent was evaporated to dryness and the residue immediately heated in an oil bath or exposed to microwave irradiation. At the end of the reaction, the products were eluted from the solid support by washing with dichloromethane (3 × 30 mL) and the solvent was removed. The crude mixture was purified through a silica gel column with hexane/ethyl acetate (8: 2) to give 0.72 g (2.21 mmol, 92%) of pure **3a** under MW conditions, and 0.508 g (1.56 mmol, 65%) of pure **3a** under classical heating.

3,3-Dimethyl-6,8-diphenyl-1-tetralone (3a): Yellow crystals: m.p. 150−151 °C from ethanol. $C_{24}H_{22}O$ (326.4): calcd. C 88.31, H 6.79, O 4.90; found C 88.17, H 6.69, O 4.89. IR: $\tilde{\nu}$ = 3100−3010 (C−H), 2970−2850 (C−H), 1675 (C=O), 1610 (C=C) cm^{-1}. ^{1}H NMR: δ = 1.11 (s, 6 H, gem-CH_3), 2.48 (s, 2 H, C-2H), 2.97 (s, 2 H, C-4H), 7.25−7.45 (m, 10 H, H-ar), 7.55 (s, 1 H, C-5H), 7.60 (s, 1 H, C-7H) ppm. ^{13}C NMR: δ = 27.4 (gem-CH_3), 32.8 (C-3), 44.0 (C-4), 53.2 (C-2), 124.9−143.6 (C-ar), 197.2 (C-1) ppm. MS: *m/z* (%) = 326 [$M^{+\cdot}$] (59.4), 325 (100), 270 (38.4), 241 (26.5).

3,3-Dimethyl-8-(*p*-methoxyphenyl)-6-phenyl-1-tetralone (3b): Yellow crystals: m.p. 106−107 °C from hexane. $C_{25}H_{24}O_2$ (356.5): calcd. C 84.24, H 6.79, O 8.98; found C 84.18, H 6.67, O 8.96. IR: $\tilde{\nu}$ = 3080−3000 (C−H), 2990−2850 (C−H), 1680 (C=O), 1614 (C=C) cm^{-1}. ^{1}H NMR: δ = 1.10 (s, 6 H, gem-CH_3), 2.49 (s, 2 H, C-2H), 2.96 (s, 2 H, C-4H), 3.83 (s, 3 H, ar-OCH_3); 6.45−7.20 (AA′ BB′ system, 4 H, H-ar), 7.35−7.50 (m, 5 H, H-ar), 7.60 (s, 1 H, C-5H), 7.64 (s, 1 H, C-7H) ppm. ^{13}C NMR: δ = 28.7 (gem-CH_3), 31.9 (C-

3), 45.4 (C-4), 53.6 (C-2), 55.7 (OCH_3), 111.0−158.2 (C-ar), 196.6 (C-1) ppm. MS: *m*/*z* (%) = 356 $[M^{+\cdot}]$ (20.7), 355 (100), 300 (39.0), 257 (14.5), 239 (11.7), 228 (18.7).

3,3-Dimethyl-6-phenyl-8-(*p*-tolyl)-1-tetralone (3c): White crystals: m.p. 95−96 °C from hexane. $C_{25}H_{24}O$ (340.5): calcd. C 88.20, H 7.11, O 4.70; found C 87.94, H 7.02, O 4.59. IR: $\tilde{\nu}$ = 3100−3010 (C−H), 2980−2860 (C−H), 1682 (C=O), 1600 (C=C) cm^{-1}. ^1H NMR: δ = 1.10 (s, 6 H, gem-CH_3), 2.39 (s, 3 H, ar-CH_3), 2.48 (s, 2 H, C-2H), 2.96 (s, 2 H, C-4H), 7.15−7.28 (AA′ BB′ system, 4 H, H-ar), 7.36−7.43 (m, 5 H, H-ar),7.60 (s, 1 H, C-5H), 7.64 (s, 1 H, C-7H) ppm. ^{13}C NMR: δ = 21.1 (CH_3), 28.7 (gem-CH_3), 44.8 (C-4), 54.0 (C-2), 126.2−144.2 (C-ar), 198.1 (C-1) ppm. MS: *m*/*z* (%) = 340 $[M^{+\cdot}]$ (87.6), 325 (13.3), 284 (11.4), 239 (37.1).

3,3-Dimethyl-8-(*o*-chlorophenyl)-6-phenyl-1-tetralone (3d): White crystals: m.p. 108−109 °C from ethanol. $C_{24}H_{21}ClO$ (360.9): calcd. C 79.88, H 5.87, O 4.43; found C 79.49, H 5.75, O 4.49. IR: $\tilde{\nu}$ = 3090−3010 (C−H), 2990−2850 (C−H), 1680 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR: δ = 1.12 (s, 3 H, gem-CH_3), 1.13 (s, 3 H, gem-CH_3), 2.51 (AB system, J = 16.2 Hz, 2 H, C-2H), 2.98 (s, 2 H, C-4H), 7.23−7.50 (m, 9 H, H-ar), 7.62 (s, 1 H, C-5H), 7.66 (s, 1 H, C-7H) ppm. ^{13}C NMR: δ = 28.1 (gem-CH_3), 33.2 (C-3), 44.6 (C-4), 53.1 (C-2), 126.5−144.8 (C-ar), 197.6 (C-1) ppm. MS: *m*/*z* (%) = 360 $[M^{+\cdot}]$ (42.2), 325 (100), 295 (13.3).

3,3-Dimethyl-8-(*p*-chlorophenyl)-6-phenyl-1-tetralone (3e): White crystals: m.p. 152−153 °C from ethanol. $C_{24}H_{21}ClO$ (360.9): calcd. C 79.88, H 5.87, O 4.43; found C 79.62, H 5.93, O 4.47. IR: $\tilde{\nu}$ = 3100−3020 (C−H), 2985−2850 (C−H), 1680 (C=O), 1610 (C=C) cm^{-1}. ^1H NMR: δ = 1.10 (s, 6 H, gem-CH_3), 2.49 (s, 2 H, C-2H), 2.98 (s, 2 H, C-4H), 7.15−7.65 (m, 11 H, H-ar) ppm. ^{13}C NMR: δ = 28.1 (gem-CH_3), 33.6 (C-3), 44.8 (C-4), 54.0 (C-2), 127.2−144.6 (C-ar), 198.1 (C-1) ppm.

3,3,7,7-Tetramethyl-1,5-dioxo-1,2,3,4,5,6,7,8,-octahydroanthracene (5): Yellowish crystals: m.p. 58−59 °C from hexane. $C_{18}H_{22}O_2$ (270.4): calcd. C 79.96, H 8.20, O 11.83; found C 80.23, H 8.08, O 11.98. IR: $\tilde{\nu}$ = 3025 (C−H), 2990−2855 (C−H), 1685 (C=O), 1620 (C=C) cm^{-1}. ^1H NMR: δ = 1.07 (s, 12 H, 2 × gem-CH_3); 2.52 (s, 4 H, C-2H, C-6H), 2.87 (s, 4 H, C-4H, C-8H), 7.88 (s, 2 H, C-9H, C-10H) ppm. ^{13}C NMR: δ = 28.5 (gem-CH_3), 34.1 (C-3), 43.5 (C-4), 52.9 (C-2), 128.1, 135.4, 140.8 (C-ar), 198.8 (C-1) ppm. MS: *m*/*z* (%) = 270 $[M^{+\cdot}]$ (33.0), 214 (100).

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