

Facile new syntheses of substituted benzhydryl derivatives using trichloroacetimidate C-C bond formation method

Walid Fathalla

Department of Mathematics and Physics, Faculty of Engineering, Port-Said University, Port Said, Egypt

Email address:

walid3369@yahoo.com

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Abstract: An improved syntheses of substituted benzhydryl derivatives has been developed. This facile two-step procedure involves C-C bond formation from *O*-diphenylmethyltrichloroacetimidate and C-nucleophiles in the presence of TMSOTf. The C-nucleophiles include arenes, alkenes, alkene silylated C-nucleophiles and trimethylsiloxy alkenes to give a series substituted benzhydryl derivatives in excellent yields.

Keywords: Trichloroacetimidate Method, C-C Bond Formation, C-Nucleophiles, Benzhydryl Derivatives

1. Introduction

The benzhydryl motif is a fundamental component in drugs such antihistamines [1], antihypertensive agents antihistamines [2] and antiallergenic agents antihistamines [3]. Diphenhydramine (Benadryl); first generation antihistamine works by blocking the effect of histamine at H₁ receptor sites required to reduce the redness, hyperthermia and edema that occurs during an inflammatory reaction. Diphenhydramine also acts as a sodium channel blocker [4, 5] and inhibits the reuptake of the neurotransmitter serotonin. This discovery led to a search for viable antidepressants with similar structures and fewer side effects.

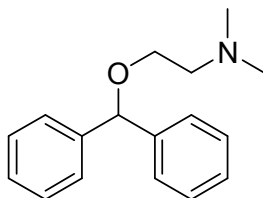


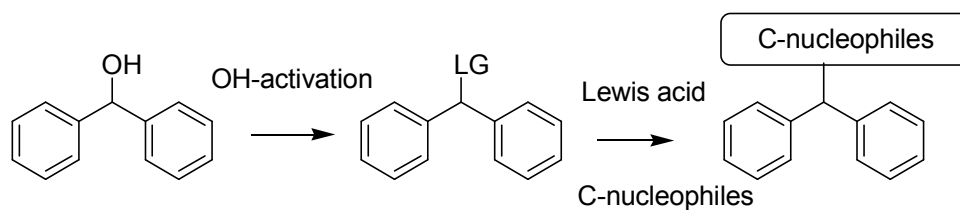
Fig. 1. Benadryl first generation antihistamine

Many C-C coupling reactions have found their way into pharmaceutical industry and into synthesis of conjugated organic materials used in dyestuff and perfume industries. Special attention were recognized for those C-C coupling where two hydrocarbon fragments are coupled with the aid

of a metal catalyst such as Negishi method [6], Suzuki reaction [7] and Heck reaction [8]. Nevertheless, metal-free and solvent-free C-C coupling methods gained more and more attention because of green chemistry awareness. The formation of C-C bonds was reported *via* cyclization of siloxy alkynes [9], intermolecular Friedel-Crafts reactions using aliphatic alcohols [10], acetate [11] and imines [12].

Trichloroacetimidate synthons are well recognized intermediates in synthetic organic chemistry [13, 14]. Trichloroacetimidate method have been widely used to activate the anomeric oxygen exchange reactions with the consequent glycoside bond formation; useful in the glycoside synthesis area [15, 16]. Ali & Fathalla [17, 18] showed in their work, the reaction of *O*-phthalimido-methyltrichloroacetimidate and methyl-2-benzamido-2-(2,2,2-trichloro-1-iminoethoxy) acetate with C-nucleophiles in the presence of TMSOTf to afford a series of *N*-substituted phthalimides and *N*-protected non-proteinogenic α -amino acid esters, respectively.

This research offers an interesting collective method for diphenylcarbinol structure modifications that could be useful in the field of synthetic organic chemistry. Structure modification is based on activation of *O*-diphenylcarbinol with good leaving group followed by forced generation of carbocation using Lewis acid and finally the reaction with a wide variety of C-nucleophiles, Scheme 1.



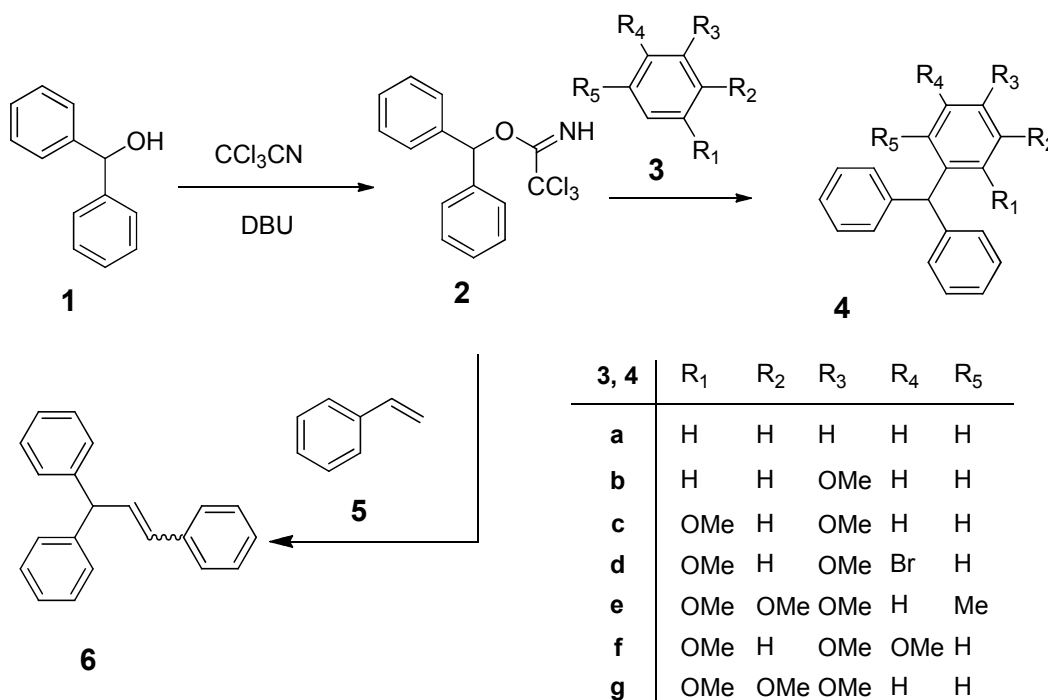
Scheme 1. Synthetic pathway of diphenylcarbinol structure modifications via C-C bond formation.

2. Results and Discussion

The precursor trichloroacetimidate **2** formed in the present study were synthesized by addition of trichloroacetonitrile to diphenylcarbinol [15, 19] in the presence of DBU, as shown in sequence outlined in Scheme 2. The reaction of **2** with arene C-nucleophiles in the presence of catalytic amount of TMSOTf at room temperature gave readily the benzhydryl products **4a-g** in good to moderate yield [20-26]. This method has the advantage of regioselective alkylation of a variety of π -electron rich benzene derivatives with diphenyl methane *via* C-C bond formation.

The alternative Freidal Craft alkylation of electron rich benzene derivative was somehow not practical due to

polymerization and by products [27]. Triphenyl methane **4a** was previously prepared by the standard Freidal Craft alkylation of benzene with carbon tetrachloride in the presence of AlCl_3 (34%) [20]. Benzhydryl 4-methoxy benzene **4b** and benzhydryl 2,4-dimethoxybenzene **4c** were earlier prepared by the reaction of diphenylcarbinol with anisole and 1,3-dimethoxy benzene in the presence of 5 mol% of triflic acid, the reaction time was 9 h. and the yield was 85 and 92 %, respectively [23]. Using a laser flash photolysis techniques as reported by MacKnight & McClelland [28] showed the isomeric conversion of benzhydryl 2,6-dimethoxybenzene to benzhydryl 2,4-dimethoxybenzene **4c** in 61 % yield.



Scheme 2. Sequential synthesis of benzhydryl arenes **4a-g** and 1-Benzhydryl 2-phenyl ethene **6**.

The structure assignment of the prepared benzhydryl derivatives **4a-g** is based on ^1H and ^{13}C NMR spectral and physicochemical analysis. The ^1H NMR spectra clearly confirm the selective aromatic electrophilic substitution reaction. Thus, the ^1H NMR spectrum of 5-bromo-1-benzhydryl-2,4-dimethoxybenzene (**4d**) gave two singlet signals at δ 7.01 and 6.53 ppm associated with two isolated aromatic protons, which confirms the regioselectivity in electrophilic aromatic substitution on 1-bromo-2,4-dimethoxy-benzene ring. ^1H NMR spectrum also reveals a

singlet signal at δ 5.82 ppm typically associated with benzhydryl CH proton, which confirms the generated C-C linkage. The ^{13}C NMR spectrum of **4e** displays signals at δ 60.11, 59.23, 55.41 and 49.26 ppm associated with 3OCH_3 and the benzhydryl CH carbon, respectively.

Furthermore, trichloroacetimidate method can be efficiently applied to the synthesis of 1-benzhydryl-2-phenyl ethene (**6**) by the reaction of styrene with **2** in the presence of TMSOTf at room temperature. The synthesis of **6** was performed in literature by dehydration of 1,3,3-

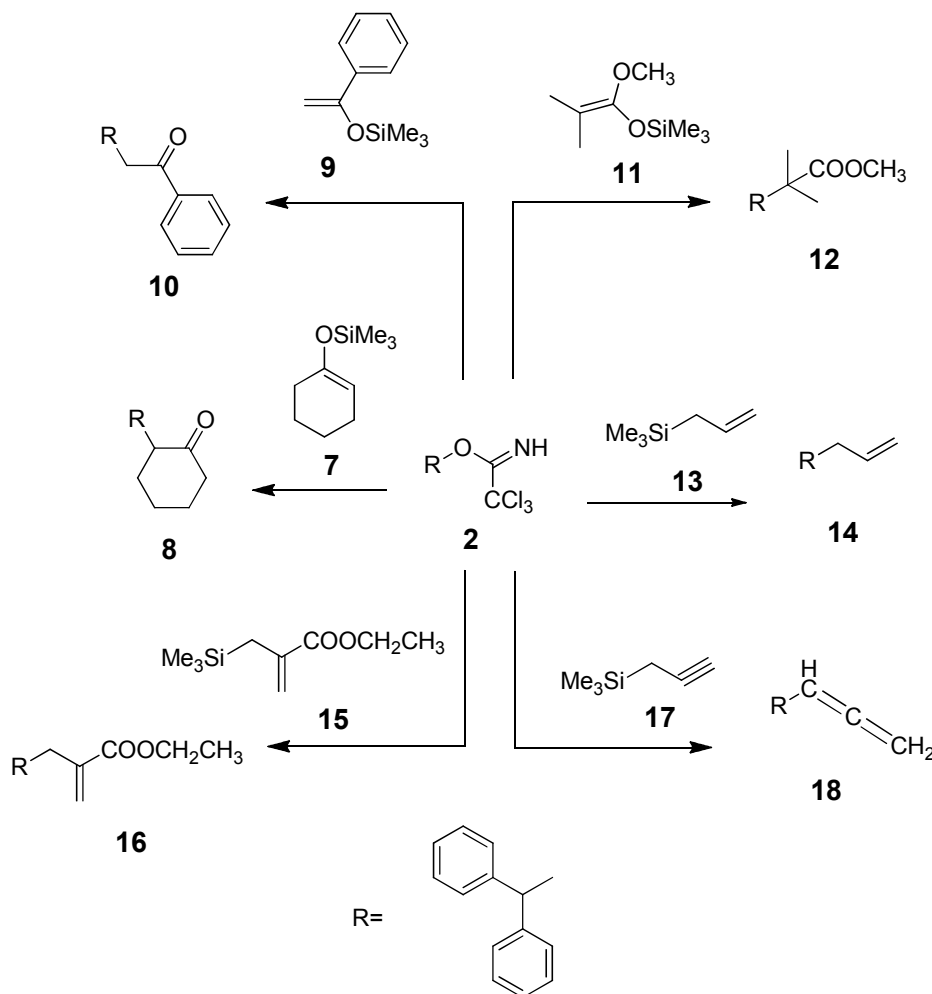
triphenylpropan-1-ol with 20% aqueous sulfuric acid (87% yield) [29]. Marcuzzi et al., [30] described the addition of diphenylmethyl chloride to styrene in the presence of $n\text{-Bu}_4\text{N}^+\text{Cl}^-$ in dichloromethane gave a mixture of 1-chloro-1,3,3-triphenylpropane (54 %) together with some 1,3,3-triphenylprop-1-ene 6 (8 %).

We have extended the scope of this process by developing a procedure for the conversion of diphenylcarbinol into functionalized compounds by an indirect trichloroacetimidate method. The trichloroacetimidate **2** has been found to be an excellent reagent for the benzhydryl alkylation at the α -position of ketones and esters as shown in Scheme 3. The reaction of trichloroacetimidate **2** with 1-trimethylsilyloxycyclohexene (**7**) as C-nucleophile in the presence of TMSOTf afforded benzhydrylcyclohexanone (**8**) in 84 % yield. Similarly, 1-benzhydryl 2-phenyl 2-ethanone **10** [31, 32] and methyl 2-benzhydryl-2-methylpropanoate **12** [33] were readily formed by the reaction of **2** with 1-phenyl-1-trimethylsiloxy-ethylene (**9**) and 1-methoxy-2-methyl-1-trimethyl-siloxy-propene (**11**), respectively Scheme 3.

Winthrop & Humber [34] earlier described the synthesis of 2-benzhydrylcyclohexanone **8** by the reaction of benzylidenecyclohexanone with phenyl Grignard reagent in the presence of cuprous chloride and trichloroacetic acid as a

solvent yielded 35 % **8**. Also 2-benzhydrylcyclohexanone **8** could be obtained in 61 % yield as reported by electroreduction of *S*-(2-methoxycarbonyl)-phenyl 5-hexene or 6-heptene thioates in an undivided cell containing tetraethylammonium perchlorate (TEAP), graphite plate and an aluminum rod as supporting electrolyte, cathode and anode, respectively [35]. The reaction of an excess of phenyllithium or phenylmagnesium bromide with either *cis*- or *trans*-styryl cyanide gives 1-benzhydryl 2-phenyl 2-ethanone **10** in 7 % yield and the known isomer of benzalacetophenone in 34 % yield [32].

The structure assignment of the prepared functionalized ester and ketone benzhydryl derivatives **8**, **10**, and **12** was based on NMR as well as physicochemical analysis. The ^1H NMR spectrum of **12** gave a singlet signal at δ 4.48 ppm typically associated with benzhydryl CH group and an indicator for C-C bond formation. The ^1H NMR spectrum of **12** also displays singlet signals at δ 3.54 and 1.35 ppm associated with OCH_3 and two CH_3 groups, respectively. The ^{13}C NMR spectrum of **12** displays signals at δ 58.78, 51.18, 46.07, 26.51 and 24.03 ppm associated with benzhydryl CH carbon, OCH_3 , aliphatic quaternary carbon and two methyl groups, respectively.



Scheme 3. Sequential synthesis of benzhydryl ketones **8**, **10**; esters **12**, **16**; alkene **14** and diene **18** derivatives.

Benzhydryl aliphatic terminal alkenes (alpha olefins) are starting materials for the preparation of many classes of organic compounds. The value-added, we convert an inexpensive raw material into a more highly functionalized compound with concomitant formation of one or more carbon-carbon bonds.

The *one-pot* trichloroacetimidate procedure can be efficiently applied to benzhydryl alkylation of alpha olefins to form benzhydryl aliphatic terminal alkenes *via* C-C bond formation using 3-trimethyl silylated alkenes. Thus, reaction of trichloroacetimidate 2 with the silylated C-nucleophile allyltrimethylsilane (13) and 2-trimethylsilylamylmethylacrylic acid methyl ester (15) in the presence of catalytic amounts of TMSOTf at room temperature gave benzhydryl-2-propene 14 [36, 37] and ethyl 2-benzhydrylmethyl prop-2-enoate 16, respectively scheme 3. In a similar mechanistic rationalization, benzhydrylpropandiene 18 is produced *via* reaction of 2 with 3-trimethyl-silylpropyne 17.

Benzhydryl-2-propene 14 was prepared earlier by alkylation of diphenylmethane with allyl chloride in the presence of liquid ammonia-ether to afford 14 in 87 % yield [38].

The structure assignment of the prepared benzhydryl aliphatic terminal alkene derivatives 14, 16 and 18 was based on NMR as well as physicochemical analysis. The ¹H NMR spectrum of 18 gave an interesting overlapping multiplet signal at δ 4.88-4.76 ppm associated with CH₂ group and benzhydryl CH group as an indicator for C-C bond formation. The ¹H NMR spectrum of 18 also shows a multiplet signal at δ 5.77-5.69 ppm typically associated with CH group. The ¹³C NMR spectrum of 18 displays signals at δ 94.01, 76.34 and 50.80 ppm associated with CH₂, CH and benzhydryl CH carbon, respectively.

3. Conclusion

A series of benzhydryl derivatives of promising biological activity have been prepared by trichloroacetimidate method from easily available diphenylcarbinol. *O*-diphenylmethyl-trichloroacetimidate (2) was treated with Lewis acid followed by reaction with C-nucleophiles that include arenes; alkenes; trimethylsilyloxyalkenes and alkenes silylated C-nucleophile to afford benzhydryl arenes 4a-g; 1-benzhydryl-2-phenyl ethane 6; ester and ketone functionalized benzhydryl derivatives 8, 10, 12; benzhydryl alkenes 14, 16 and benzhydrylpropdiene 18, respectively *via* C-C bond formation.

4. Experimental Section

General procedures.

Solvent were purified and dried by standard procedures. The boiling range of the petroleum ether used was 40-60 °C. Thin layer chromatography (TLC): silica gel 60 F₂₅₄ plastic plates (E. Merck, layer thickness 0.2 mm) detected by UV absorption. Elemental analyses were performed on a *Flash EA-1112* instrument at the Microanalytical laboratory,

Faculty of Science, Suez Canal University, Ismailia, Egypt. Melting points were determined on a Buchi 510 melting-point apparatus and the values are uncorrected. ¹H and ¹³C NMR spectra were recorded at 250 MHz and 62.5 MHz, respectively (Bruker AC 250) in CDCl₃ solution with tetramethylsilane as an internal standard.

General procedure for the preparation of O-benzhydryl 2,2,2-trichloroacetimidate (2) [15].

A stirred solution of diphenylcarbinol (1, 0.93 g, 5.0 mmol) in dry dichloromethane (30 mL) and trichloroacetonitrile (5 mL, 50 mmol) was treated with DBU (71 μL) at room temperature and then left for 2 h. The solvent was evaporated under reduced pressure and the product was purified by column chromatography 5 % triethylamine in toluene /ethylacetate, 25:1 to give 2 as white powder. (1.52 g, 93 %); mp 84-85 °C. ¹H NMR (CDCl₃), δ: 6.94 (1H, s, CH), 7.44-7.28 (10H, m, Ar-H), 8.40 (1H, bs, NH). Anal. Calcd. for C₁₅H₁₂Cl₃NO₃ (328.6): C, 54.82; H, 3.68; Found: C, 54.69; H, 3.52.

General procedure for the reaction of O-diphenylmethyl-trichloroacetimidate (2) with C-nucleophiles

A stirred solution of 2 (0.46 g, 1.4 mmol) and C-nucleophiles as acceptor (1.4 mmol) in dry dichloromethane (40 mL) under nitrogen was treated with TMSOTf (13 mL, 0.06 mmol) at room temperature. After completion of the reaction (TLC monitored), the reaction mixture was neutralized with solid sodium bicarbonate, filtered and concentrated in vacuo. The residue was purified by flash chromatography.

Benzhydrylbenzene (4a) [21].

Colorless crystals (0.27g, 78 %); mp 92-93 °C. ¹H NMR (CDCl₃), δ: 5.86 (1H, s, CH benzhydryl), 7.26-7.16 (15H, m, Ar-H). Anal. Calcd. for C₁₉H₁₆ (244.3): C, 93.40; H, 6.60; Found: C, 93.28; H, 6.56.

Benzhydryl-4-methoxybenzene (4b) [25].

Colorless crystals (0.25 g, 65 %); mp 60-61 °C. ¹H NMR (CDCl₃), δ: 3.73 (3H, s, OCH₃), 5.83 (1H, s, CH benzhydryl), 6.49 (1H, d, *J* = 6.5 Hz, CH), 7.06-6.99 (3H, m, Ar-H), 7.26-7.16 (10H, m, Ar-H). Anal. Calcd. for C₂₀H₁₈O (274.4): C, 87.56; H, 6.61; Found: C, 87.31; H, 6.54.

Benzhydryl-2,4-dimethoxybenzene (4c) [24].

Colorless crystals (0.25 g, 59 %); mp 135-136 °C. ¹H NMR (CDCl₃), δ: 3.85 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 6.01 (1H, s, CH benzhydryl), 6.49-6.65 (2H, m, ArH), 6.91 (1H, d, *J* = 8.5 Hz, ArH), 7.23-7.41 (10H, m, ArH). Anal. Calcd. for C₂₁H₂₀O₂ (304.4): C, 82.86; H, 6.62; Found: C, 82.74; H, 6.48.

5-Bromo-1-benzhydryl-2,4-dimethoxybenzene (4d).

Colorless crystals (0.30 g, 56 %); mp 124-125 °C. ¹H NMR (CDCl₃), δ: 3.76 (3H, s, OCH₃), 3.94 (3H, s, OCH₃), 5.82 (1H, s, CH benzhydryl), 6.53 (1H, s, Ar-H), 7.01 (1H, s, Ar-H), 7.23-7.18 (3H, m, Ar-H), 7.33-7.24 (7H, m, Ar-H). Anal. Calcd. for C₂₁H₁₉O₂Br (383.3): C, 65.81; H, 5.00; Br, 20.85; Found: C, 65.65; H, 4.98.

1-Benzhydryl 2,3,4-trimethoxy-6-methylbenzene (4e).

Colorless crystals (0.35 g, 71 %); mp 89-90 °C. ¹H NMR

(CDCl₃), δ : 2.24 (3H, s, CH₃), 3.24 (3H, s, OCH₃), 3.89 (3H, s, OCH₃), 3.91 (3H, s, OCH₃), 5.97 (1H, s, CH benzhydryl), 6.58 (1H, s, Ar-H), 7.36-7.22 (10H, m, Ar-H). ¹³C-NMR (CDCl₃), δ : 20.96 (CH₃), 49.26 (OCH₃), 55.41 (CH), 59.23 (OCH₃), 60.11 (OCH₃), 109.44 (CH_{Ar}), 125.41 (CH_{Ar}), 127.66 (CH_{Ar}), 128.18 (C_q), 128.84 (CH_{Ar}), 132.09 (C_q), 140.61 (C_q), 143.07 (CH_{Ar}), 151.58 (C_q), 152.30 (C_q). Anal. Calcd. for C₂₃H₂₄O₃ (348.4): C, 79.28; H, 6.94; Found: C, 79.01; H, 6.88.

1-Benzhydryl-2,4,5-trimethoxybenzene (4f)

Colorless crystals (0.31 g, 68 %); mp 116–117 °C. ¹H-NMR (CDCl₃), δ : 3.64 (3H, s, OCH₃), 3.82 (3H, s, OCH₃), 3.87 (3H, s, OCH₃), 5.91 (1H, s, CH benzhydryl), 6.49 (1H, s, Ar-H), 6.56 (1H, s, Ar-H), 7.28-7.12 (10H, m, Ar-H). ¹³C-NMR (CDCl₃), δ : 48.92 (OCH₃), 55.45 (OCH₃), 55.79 (CH), 56.32 (OCH₃), 102.71 (C_q), 114.72 (CH_{Ar}), 124.13 (C_q), 125.69 (CH_{Ar}), 127.77 (CH_{Ar}), 128.90 (CH_{Ar}), 142.60 (C_q), 143.77 (CH_{Ar}), 148.02 (C_q), 151.20 (C_q). Anal. Calcd. for C₂₂H₂₂O₃ (334.4): C, 79.02; H, 6.63; Found: C, 78.87 ; H, 6.61.

1-Benzhydryl-2,3,4-trimethoxybenzene (4g)

Yellowish oil. ¹H-NMR (CDCl₃), δ : 3.55 (3H, s, OCH₃), 3.85 (3H, s, OCH₃), 3.91 (3H, s, OCH₃), 5.91 (1H, s, CH benzhydryl), 6.59 (1H, d, J = 8.4 Hz, Ar-H), 7.04 (1H, d, J = 8.4 Hz, Ar-H), 7.34-7.14 (10H, m, Ar-H). ¹³C-NMR (CDCl₃), δ : 50.06 (OCH₃), 55.93 (CH), 60.56 (OCH₃), 60.64 (OCH₃), 106.80 (CH_{Ar}), 124.42 (CH_{Ar}), 126.15 (CH_{Ar}), 128.10 (C_q), 128.22 (CH_{Ar}), 129.25 (C_q), 129.47 (CH_{Ar}), 140.611 (C_q), 143.87 (CH_{Ar}), 144.12 (C_q), 152.14 (C_q). Anal. Calcd. for C₂₂H₂₂O₃ (334.4): C, 79.02; H, 6.63; Found: C, 78.69 ; H, 6.51.

1-Benzhydryl 2-phenylethene (6) [29]

Colorless crystals (0.26 g, 69 %); mp 91–92 °C. ¹H-NMR (CDCl₃), δ : 4.97 (1H, d, J = 7.5 Hz, CH), 6.43 (1H, d, J = 15.7 Hz, CH benzhydryl), 6.76 (1H, dd, J_{gem} = 15.8 Hz, $J_{1,2}$ = 7.5 Hz CH), 7.47-7.23 (15H, m, Ar-H). Anal. Calcd. for C₂₁H₁₈O (270.4): C, 93.29; H, 6.71; Found: C, 93.14; H, 6.66.

Benzhydrylcyclohexanone(8) [35]

Colorless crystals (0.31 g, 84 %); mp 104–105 °C. ¹H-NMR (CDCl₃), δ : 2.16-1.61 (6H, m, 3CH₂), 3.58-3.48 (1H, m, CH), 4.50 (1H, d, J = 10.8 Hz, CH), 7.49-7.24 (10H, m, Ar-H). Anal. Calcd. for C₁₉H₂₀O (264.4): C, 86.32; H, 7.63; Found: C, 86.25; H, 7.60.

1-Benzhydryl 2-phenyl 2-ethanone (10)

Colorless crystals (0.23 g, 58 %); mp 82 – 83 °C. ¹H-NMR (CDCl₃), δ : 3.79 (2H, d, J = 7.8 Hz, CH₂CO), 4.91 (1H, t, J = 8 Hz, CH), 7.72-7.19 (13H, m, Ar-H), 8.04-7.96 (2H, m, Ar-H). ¹³C-NMR (CDCl₃), δ : 45.89 (CH₂), 58.83 (CH), 126.24 (CH_{Ar}), 127.18 (CH_{Ar}), 127.73 (CH_{Ar}), 127.92 (CH_{Ar}), 128.42 (CH_{Ar}), 128.83 (CH_{Ar}), 129.08 (C_q), 132.89 (CH_{Ar}), 137.02 (C_q), 139.71 (C_q), 144.05 (CH_{Ar}), 197.84 (C=O). Anal. Calcd. for C₂₁H₁₈O (286.4): C, 88.08; H, 6.34; Found: C, 87.94; H, 6.30.

Methyl 2-benzhydryl-2-methyl propanoate (12)

Colorless crystals (0.17 g, 63%); mp 45-46 °C. ¹H-NMR (CDCl₃), δ : 1.35 (6H, s, 2CH₃), 3.54 (3H, s, OCH₃), 4.48 (1H, s, CH), 7.38-7.21 (10H, m, Ar-H). ¹³C-NMR (CDCl₃), δ :

24.03 (CH₃), 26.51 (CH₃), 46.07 (C_q), 51.18 (OCH₃), 58.78 (CH), 125.89 (CH_{Ar}), 126.53 (C_q), 126.87 (C_q), 127.56 (CH_{Ar}), 127.89 (C_q), 129.38 (CH_{Ar}), 141.17 (CH_{Ar}), 177.52 (C=O). Anal. Calcd. for C₁₈H₂₀O₂ (268.4): C, 80.56; H, 7.51; Found: C, 80.48; H, 7.43.

Benzhydryl-2-propene (14) [38]

Colorless crystals (0.20 g, 69 %); mp 114–115 °C. ¹H-NMR (CDCl₃), δ : 3.01 (2H, t, J = 8 Hz, CH₂), 4.20 (1H, t, J = 8 Hz, CH), 5.18 (2H, dd, J_{gem} = 17 Hz, $J_{1,2}$ = 8 Hz CH₂), 5.97-5.86 (1H, m, CH), 7.48-7.31 (10H, m, Ar-H). Anal. Calcd. for C₁₆H₁₆ (208.3): C, 92.26; H, 7.74; Found: C, 92.15; H, 7.72.

Ethyl 2-benzhydrylmethyl prop 2-enoate (16)

Yellowish oil. ¹H-NMR (CDCl₃), δ : 1.31 (3H, t, J = 7.0 Hz, CH₃), 3.08 (2H, d, J = 7.7 Hz, CH₂), 4.18 (2H, q, J = 7.0 Hz, OCH₂), 4.27 (1H, t, J = 7.8 Hz, CH), 5.31 (1H, s, CH₂), 6.07 (1H, s, CH₂), 7.38-7.13 (10H, m, Ar-H). ¹³C-NMR (CDCl₃), δ : 14.03 (CH₃), 37.86 (CH₂), 49.83 (CH), 60.45 (CH₂), 126.07 (C=CH₂), 126.60 (CH_{Ar}), 127.12 (CH_{Ar}), 127.90 (CH_{Ar}), 128.21 (CH_{Ar}), 138.47 (C_q), 143.91 (C=CH₂), 166.92 (C=O). Anal. Calcd. for C₁₉H₂₀O₂ (280.4): C, 81.40; H, 7.19; Found: C, 81.38; H, 7.18.

Benzhydrylpropdiene(18)

Yellowish oil. ¹H-NMR (CDCl₃), δ : 4.88-4.76 (3H, m, CH, CH₂), 5.77-5.69 (1H, m, CH), 7.42-7.25 (10H, m, Ar-H). ¹³C-NMR (CDCl₃), δ : 50.80 (CH), 76.34 (CH₂), 94.01 (CH₂), 126.45 (CH_{Ar}), 128.36 (CH_{Ar}), 143.52 (C_q), 208.77 (C=C=CH₂). Anal. Calcd. for C₁₆H₁₄ (206.3): C, 93.16; H, 6.84; Found: C, 93.01; H, 6.68.

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