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Synthesis of benzylidenecycloalkan-1-ones and 1,5-diketones under Claisen–Schmidt reaction: Influence of the temperature and electronic nature of arylaldehydes

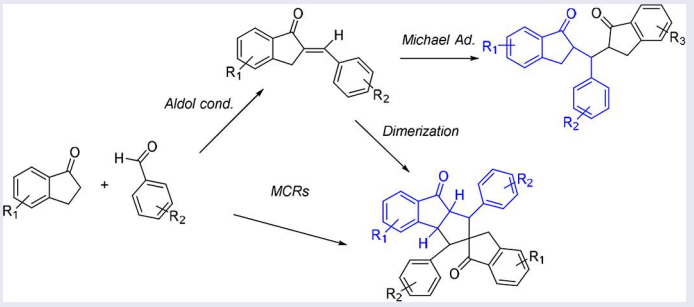
Beatriz Lantaño[a,b], José M. Aguirre[a,b], Eleonora V. Drago[a], Mariela Bollini[b], Diego J. de la Faba[a], and Jorge D. Mufato[a]

[a]Departamento de Ciencias Básicas, Universidad Nacional de Luján, Luján, Argentina; [b]Cátedra de Química Orgánica II, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, Argentina

ABSTRACT

Herein, we present the results of the influence of reaction temperature and the electronic nature of arylaldehydes in the reactions of benzocycloalkan-1-ones and arylaldehydes under classical Claisen–Schmidt condensation conditions. The products obtained, 2-arylidene derivatives of benzocycloalkan-1-ones and/or spiropolycyclic-1,5-diketones through multicomponent reactions, depended on the electronic nature of arylaldehyde and the reaction temperature. Besides, under identical conditions, 2-arylideneindan-1-ones afforded *bis*-indane-1,5-diketones through a process that involves Michael addition reaction, which is also dependent on the temperature. Theoretical studies using density-functional theory allowed understanding the chemical reactivity and the site selectivity of α,β-enones used in this work through the calculation of global and local electrophilicity on C–β. Both the electrophilicity of C-β and the temperature led the course of reaction toward the formation of aldol condensation, aldol condensation/Michael addition, and aldol condensation/dimerization products. This work is the first to perform the structural and configurational assignments of *bis*-indane-1,5-diketones.

GRAPHICAL ABSTRACT



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CONTACT Beatriz Lantaño lantanob@gmail.com Departamento de Ciencias Básicas, Universidad Nacional de Luján, Luján 6700, Argentina; Cátedra de Química Orgánica II, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín, Buenos Aires 956 (1113), Argentina.

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Supplemental data (full experimental and spectral details and characterization of title compounds) can be accessed on the publisher's website.

Introduction

Natural and synthetic α,β-unsaturated carbonyl compounds, especially chalcones, 2-benzylideneindanones, and 2-benzylidenetetralones, show significant biological activity.[1] Besides, 2-benzylideneindanone derivatives [BI] have been shown to be potent aromatase inhibitors in cancer therapy,[1a] potent and selective anticancer agents through the inhibition of tubulin polymerization,[1b] and multitarget-directed ligands against neurodegenerative diseases.[1c] In addition, Donepezil hydrochloride, an acetylcholinesterase inhibitor, has been approved by the FDA to treat mild to moderate Alzheimer's disease,[1d] and Indanocine and its analogs have been developed to combat drug-resistant malignancies (Fig. 1).[1e]

On the other hand, α,β-unsaturated ketones are versatile and convenient intermediates in the synthesis of a wide range of compounds. They can be used as starting materials in the synthesis of intermediate compounds of natural products, bioactive molecules, orthogonal estrogen receptor-based gene switch and semiconducting thin films.[2–6] Besides, the α,β-enone moiety of these molecules is a favorable unit for nucleophilic 1,4-addition and dipolar cycloaddition.[2–8]

The most common synthetic methods to obtain α,β-unsaturated ketones are based on classical Claisen–Schmidt condensation conditions (C–S), which involve appropriate ketones and aldehydes with NaOH or KOH in water–ethanol.[9] Under these conditions, high yields of several substituted chalcones[2] and benzylidenecycloalkanones from 1-indanone and 1-tetralone and arylaldehydes have been reported.[10] However, from arylketones with active methylenes, such as deoxybenzoin (**1**) and benzaldehyde or π–excessive and π–deficient arylaldehydes, using NaOH in EtOH/H_2O, we reported a single product, the 1,5-diketone **3** known as Benzamarone (Scheme 1). In the cases studied, the benzylidene derivative **2** was not isolated and the 1,5-diketones **3** were the result of a tandem aldol condensation–Michael addition sequence.[11]

From 1-indanones and different arylaldehydes using NaOEt in THF, Camps et al.[12] obtained α,β-enones and spiropolycyclic 1,5-diketones from multicomponent reactions (MCRs) (Scheme 2). Other researchers such as Berthelette et al.,[13a] Leblanc et al.,[13b]

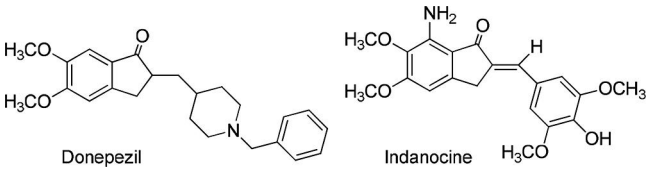
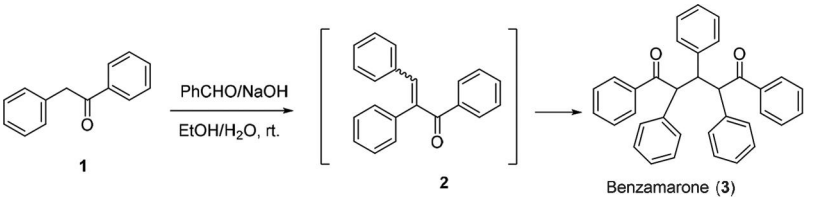
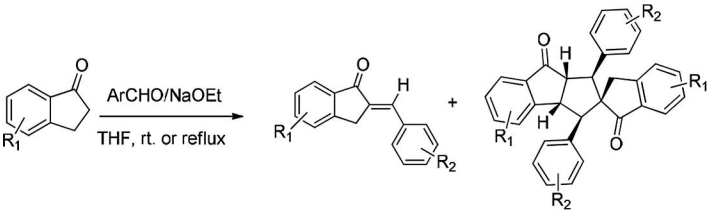


Figure 1. Benzilidene derivatives.



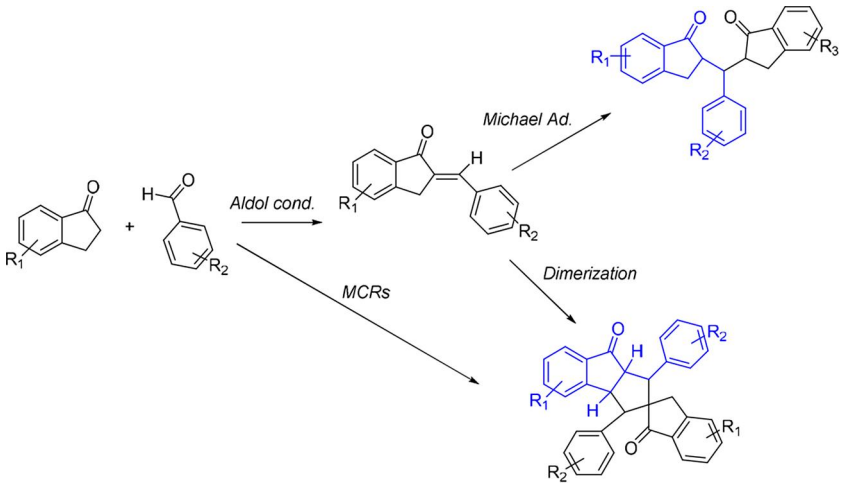
Scheme 1. Aldol condensation and Michael addition products from deoxybenzoin.



Scheme 2. Aldol condensation and MCR products from 1-indanone.

Gupta et al.,[13c] and Narang et al.[13d] used different bases and solvents (Cs_2CO_3/CH_3CN, KOH/MeOH at reflux temperature) and obtained principally spiropolycyclic compounds. These results clearly indicate that the expected α,β-enones show a particular reactivity toward active methylene compounds and then hinder the synthesis of BI under the classical C–S condensation thus limiting the scope of this methodology.

Based on the above, it is an interesting challenge to obtain BI with aryl groups attached to C–β with different electronic density due to their importance as precursors of several compounds, including *bis*-indane 1,5-diketones. These ketones are important synthetic intermediates and desirable starting materials for the preparation of heterocyclic and poly-functional compounds.[14] Bearing in mind the behavior of α,β-enones mentioned above, in the present study, we attempted to direct the course of reaction toward the formation of (i) benzylidenealkanones (aldol condensation), (ii) *bis*-indane and *bis*-tetraline 1,5-diketones (aldol condensation/Michael addition), and (iii) spiropolycyclic 1,5-diketones (aldol condensation/dimerization) (Scheme 3) and reported the behavior of benzocycloalkanones, 1-indanones and 1-tetralones, and arylaldehydes with different electronic nature using NaOH and $EtOH/H_2O$. Changes in temperature allowed us to direct the course of reaction toward the desired products. In addition, to rationalize the results obtained from BI, we analyzed local and global electrophilicity using density-functional theory (DFT) methods at the B3LYP/6-31G *[15] level and compared them with other benzylidene derivatives. This work is the first to show the structural and configurational assignments of *bis*-indane 1,5-diketones by 1D and 2D NMR.

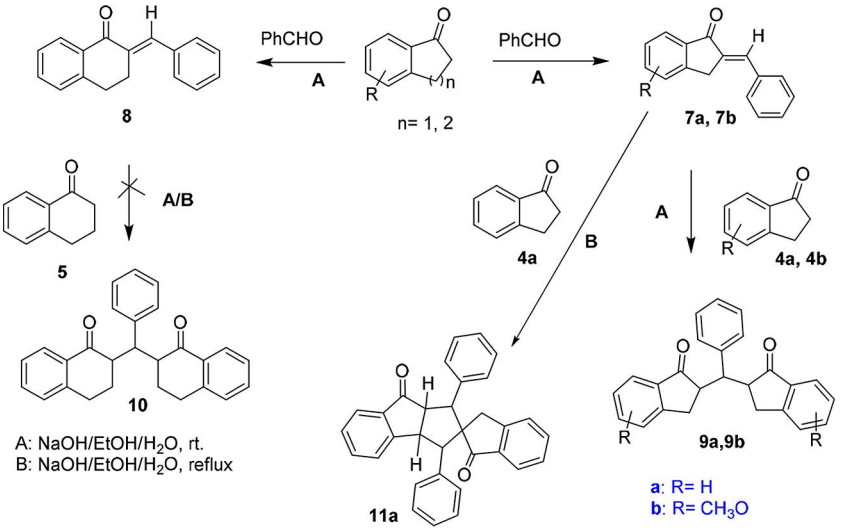


Scheme 3. Reactions of benzocycloalkanones and benzylidenealkanones.

Results and discussion

Reaction of benzocycloalkan-1-ones 4a, 4b, and 5 with benzaldehyde 6a under C–S

The ketones 1-indanone (**4a**), 5,6-dimethoxy-1-indanone (**4b**), and 1-tetralone (**5**) were treated with benzaldehyde (**6a**) at room temperature under classical C–S conditions (Scheme 4 and Table 1). The results of these reactions allowed us to compare the behavior of these ketones with that obtained from deoxybenzoin (**1**), which led to the formation of one 1,5-diketone (**3**) through aldol condensation followed by the Michael addition in tandem[11] (Scheme 1). The ketones **4a, 4b**, and **5** gave the 2-benzylidene derivatives **7a,**



Scheme 4. Reaction of benzocycloalkan-1-ones (**4a, 4b**, and **5**) with benzaldehyde.

Table 1. Reaction of 1-indanones **4a, 4b** and 1-tetralone **5** with arylaldehydes **6a–d**.

Entry	Ketone	Aldehyde	Ratio	Method*	Temp.	Reaction products (% isolated yields)
1	**4a**	**6a**	1:1	A	25 °C	**7a** (98%)
2	**4a**	**6a**	1:1	A	Reflux	**11a** (60%)
3	**4a**	**6a**	1:1	B	25 °C	**7a** (79%) **11a** (21%)
4	**4a**	**6a**	1:1	C	25 °C	**7a** (56%)
5	**4a**	**6a**	2:1	A	25 °C	**7a** (22%) **9a** (40%)/**9a*** (33%)
6	**4a**	**6b**	1:1	A	25 °C	**12a** (87%)
7	**4a**	**6b**	1:1	A	Reflux	**13a** (51%)
8	**4a**	**6c**	1:1	A	25 °C	**14a** (98%)
9	**4a**	**6c**	1:1	A	0 °C	**17a** (87%) **14a** (12%)
10	**4a**	**6c**	2:1	A	0 °C	**20a** (79%)
11	**4a**	**6d**	1:1	A	0 °C	**16a** (73%)
12	**4a**	**6d**	1:1	A	25 °C	**15a** (65%)
13	**4b**	**6a**	1:1	A	25 °C	**7b** (90%)
14	**4b**	**6a**	2:1	A	25 °C	**9b** (75%)
15	**4b**	**6c**	1:1	A	0 °C	**17b** (75%)
16	**4b**	**6c**	2:1	A	25 °C	**14b** (20%) **20b** (40%)
17	**5**	**6a**	1:1	A	25 °C	**8** (75%)
18	**5**	**6a**	2:1	A	25 °C	**8**
19	**5**	**6a**	2:1	A	Reflux	**8**

6a, benzaldehyde; **6b**, 4-MeO-benzaldehyde; **6c**, 4-PyCHO; **6d**, 3-PyCHO.
*A, NaOH/EtOH/H_2O; B, KOH/EtOH; C, NaOH/H_2O.

7b, and **8** in high yields [Entries 1, 13, 17]. In any case, the corresponding 1,5-diketones were isolated, as from ketone **1**.

In an attempt to assess the reactivity and to obtain the corresponding 1,5-diketones, the α,β-enones **7a, 7b**, and **8** were treated with one equivalent of the respective precursor benzocycloalkan-1-one under C–S conditions [Table 2, Entries 1, 2, 7]. Only enones **7a** and **7b** yielded the Michael addition, leading to the expected *bis*-indane 1,5-diketones (**9a, 9a***, and **9b**).

In addition, to favor Michael addition over compound **8**, the reaction was performed at reflux temperature but the expected 1,5-diketone (**10**) was not formed [Entry 18]. However, under these conditions, the benzylidene derivative **7a**, at reflux temperature, led to a spiropolycyclic 1,5-diketone (**11a**) [Entry 2]. Besides, to obtain the *bis*-tetraline 1,5-diketone **10**, a change in the stoichiometric ratio of ketone:benzaldehyde (2:1) did not lead to the expected product [Entry 19]. The same changes in the stoichiometric ratio (2:1) for ketones **4a** and **4b** resulted in the formation of expected products **9a, 9a***, and **9b**, at room temperature [Entries 5 and 14]. These facts indicate the different reactivity of α,β-enones **2, 7a, 7b**, and **8** with ketones with hydrogen at C–α under the conditions studied. The lack of reactivity of compound **8** can be attributed to the lower coplanarity of the enone moiety, which decreases the electrophilicity of C–β.[10]

We also studied the influence of solvent on the course of these reactions, which were performed in H_2O and EtOH. This assay was performed using ketone **4a**. The results, shown in Table 1, indicated that the main product in both solvents was the benzylidene derivative (**7a**) and that the EtOH/H_2O mixture led to the best result, since the only product formed was **7a** [Entries 1, 3, 4].

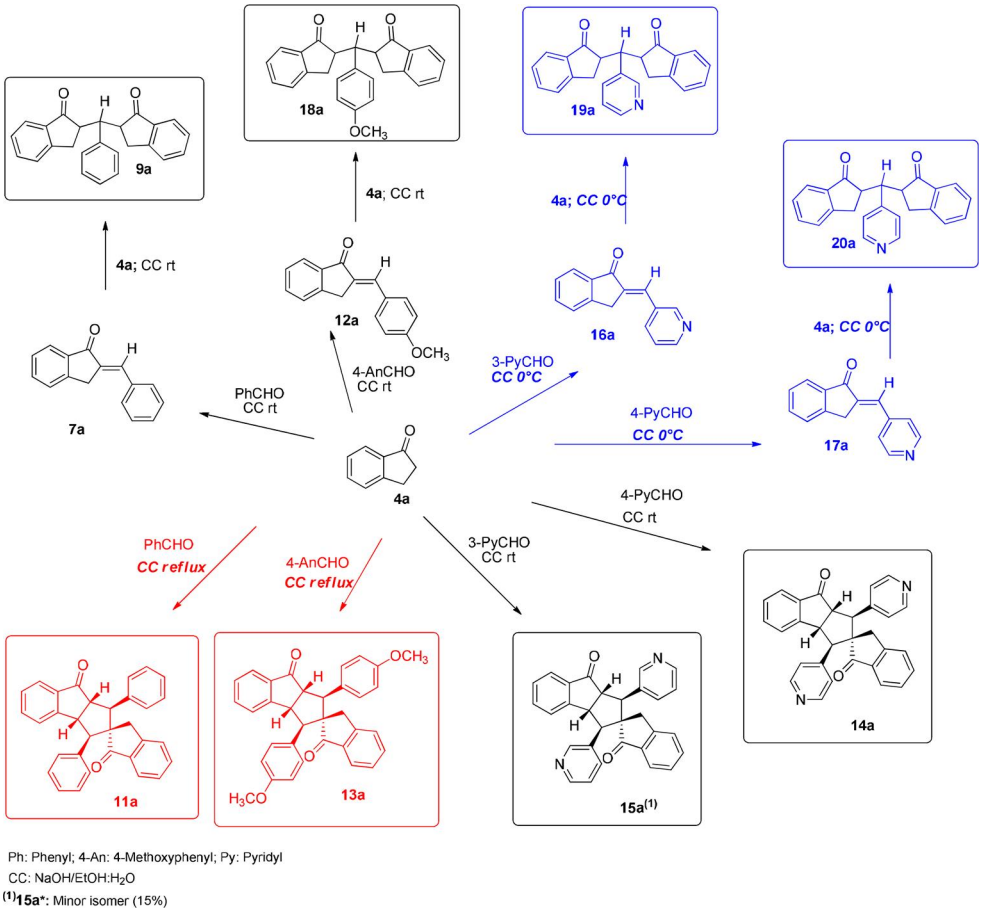
Reaction of 1-indanones 4a and 4b with arylaldehydes and 2-benzylideneindanone under C–S

The 1-indanones **4a** and **4b** were reacted with π-excessive and π-deficient arylaldehydes under C–S conditions (Schemes 5 and 6, Table 1). The results were analyzed comparatively with those reported by other researchers using bases and solvents different from those used in this work, as mentioned above. The ketones **4a** and **4b** reacted with benzaldehyde and π-excessive arylaldehydes at room temperature with high yields to give the corresponding benzylidene derivatives (**7a, 7b**, and **12a**) [Entries 1, 13, 6]. However, at reflux temperature, the spiropolycyclic 1,5-diketones **11a** and **13a**, which are the products of MCRs, as previously described,[12][13] were formed [Entries 2, 7].

The benzocycloalkan-1-ones **4a** and **4b** reacted at room temperature with π-deficient aldehydes, leading to the MCR products **14a, 14b**, and **15a** [Entries 8, 16, 12]. The benzylidenindanones **16a, 17a**, and **17b** were obtained only when the reaction was

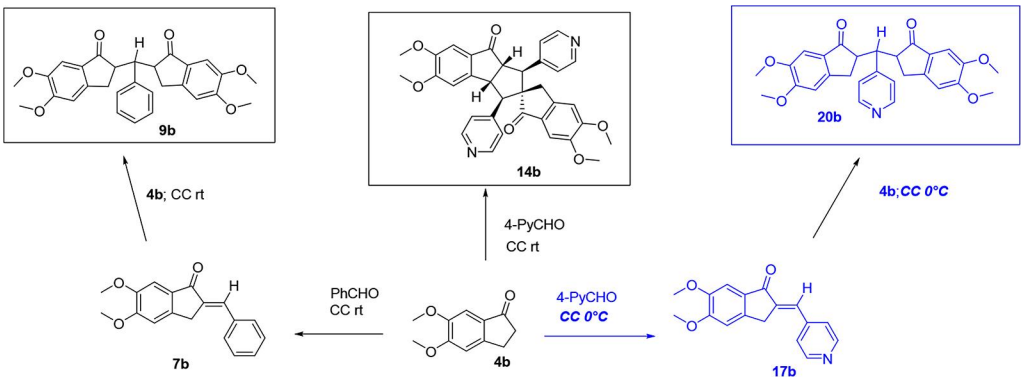
Table 2. Reaction of 2-benzylidencycloalkan-1-ones with ketones **4a, 4b**, and **5**.

Entry	2-Enones	Ketones	Temp.	Products
1	**7a**	**4a**	25 °C	**9a/9a*** (7:3)
2	**7b**	**4b**	25 °C	**9b**
3	**12a**	**4a**	25 °C	**18a**
4	**16a**	**4a**	0 °C	**19a**
5	**17b**	**4b**	25 °C	**14b/20b** (2:1)
6	**17b**	**4b**	0 °C	**20b**
7	**8**	**5**	25 °C	**8**



Scheme 5. Reactions of **4a** with arylaldehydes and 2-arylideneindanones.

performed at 0 °C [Entries 9, 11, 15]. In addition, using NaOH in EtOH/H_2O at different reaction temperatures, **7a, 7b, 12a, 16a**, and **17b** yielded *bis*-indane 1,5-diketones (Table 2). At room temperature, those having phenyl or 4-methoxyphenyl groups yielded the expected



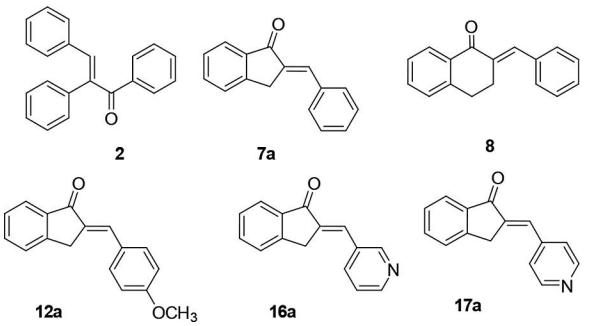
Scheme 6. Reactions of **4b** with arylaldehydes and 2-arylideneindanones.

Michael adducts (**9a, 9a***, **9b**, and **18a**). The 1,5-diketones **19a, 20a**, and **20b** from the BIs with a π-deficient aryl moiety bounded to the C–β (**16a, 17a**, and **17b**) were obtained only when the reaction was performed at 0 °C. It is noteworthy that the reactivity of this type of α, β-enones depends on the electronic characteristics of aryl moiety in C–β and that by changing the temperature conditions, different products can be synthesized (Schemes 5 and 6).

DFT study of the different reactivity of α,β-enones

Conceptual DFT has been widely used to understand the chemical reactivity and the site selectivity of molecular systems. Chemical potential (μ),[16] global hardness (η),[17] global softness (*S*),[16] electronegativity (χ),[16] and electrophilicity (ω)[18] are highly successful global reactivity descriptors used to predict global chemical reactivity trends. Fukui functions[19] and local softness are extensively applied to assess local reactivity and site selectivity. Global electrophilicity (ω), introduced by Parr et al.,[18] is a descriptor of reactivity which allows a quantitative classification of the global electrophilic nature of a molecule within a relative scale and is defined as $\omega = \mu^2/2\eta$. Chattaraj et al.[20] proposed the generalized concept of local philicity ω_k^+, which provides information about nucleophilic, electrophilic, and radical reactions.[21–22] The local electrophilicity index is defined as $\omega_k^\alpha = \omega f_k^\alpha$, where ω is the global electrophilicity and f_k^α is a Fukui function.[19] The most electrophilic site in a molecule provides the highest value of ω_k^+. We calculated global electrophilicity and local electrophilicity (C–*β*) for benzo α,β-enone both in acyclic and in cyclic compounds to analyze their reactivity (Tables 3 and 4) and to compare them with the experimental results obtained.

Table 3. Global (ω) and local (ω_k^+ of C–β) electrophilicity values of α,β-enones **2, 7a**, and **8**.



Compound	μ	η	ω	f_k^+	ω_k^+
2	−3.821	1.605	4.547	0.191	0.864
7a	−4.166	2.026	4.282	0.170	0.728
8	−4.045	1.961	4.173	0.165	0.667

Values are in eV.

Table 4. Global (ω) and local (ω_k^+ of C–β) electrophilicity values of benzylideneindanones **7a, 12a, 16a**, and **17a**.

Compound	Ar	μ	η	ω	f_k^+	ω_k^+
12a	4-CH_3OPh	−3.808	1.920	3.775	0.157	0.566
7a	Phenyl	−4.166	2.026	4.282	0.170	0.728
16a	3-Pyridyl	−4.366	2.026	4.704	0.172	0.799
17a	4-Pyridyl	−4.466	2.078	4.799	0.171	0.811

Values are in eV.

The calculated global and local electrophilicity for **2, 7a**, and **8** showed the values according to the reactivity of ketones with active hydrogens under the classical C–S conditions (4.547 to 4.173 and 0.864 to 0.667, respectively). The higher electrophilic values of the enones studied corresponded to ketone **2**, which led to tandem reactions, showing greater reactivity than enone **7a** in identical conditions (Table 3). Finally, the benzylidene derivative **8** was not reactive under these conditions and showed the lowest values of ω and ω_k^+. This is consistent with its low reactivity, mentioned above.

In the case of benzylideneindanones **7a, 12a, 16a**, and **17a**, the values of ω and ω_k^+ are consistent with their different reactivity since, at room temperature, the first two led to the formation of Michael adducts, while the enones **16a** and **17a**, with π-deficient groups bound to C–β, easily dimerized to the corresponding spiropolycyclic 1,5-diketones due to the higher values of electrophilicity ω and ω_k^+ (Scheme 4 and Table 4). The benzylideneindanones **16a** and **17a** were only synthesized at 0 °C.

Structural and configurational assignments of the compounds synthesized

Benzylidene derivatives and spiropolycyclic 1,5-diketones

The benzylidene derivatives **7a, 7b, 8, 12a, 16a, 17a**, and **17b** have been previously described and the NMR spectroscopic data agree with previously published data.[10,12,23,24] ^{1}H and ^{13}C NMR data of the spiropolycyclic compounds **11a, 15a, 14a**, and **14b** are consistent with those previously reported[12,13a] and the structure and stereochemistry of **13a** was assigned by comparison (See Supplemental data).

The structure of spiropolycyclic compound **15a*** (minor diasteroisomer of **15a**) was established by 1D and 2D NMR (See Supplemental data). Its relative configuration was determined by nuclear overhauser enhancement spectroscopy (NOESY) (Figure 2) and agrees with one of the minor isomers described by Berthelette et al.[13a] for the reaction of 1-indanone with benzaldehyde.

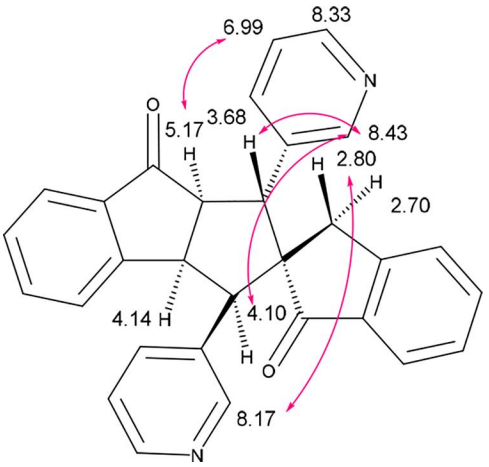


Figure 2. Representative NOE correlations of spiropolycyclic **15a***.

Bis-indane 1,5-diketones

These kinds of compounds can appear as four stereoisomers: two *meso* forms (*R,s,S* and *R,r,S*) and one pair of enantiomers (*R,R* and *S,S*) (Figure 3). Only in the case of Michael adducts from **7a**, two diastereomers (**9a** and **9a***) were obtained, one of which has already been reported by Pavel et al.[25] although its stereochemistry was not informed. All other *bis*-indane 1,5-diketones were obtained as a single stereoisomer. The structural and stereochemical assignments of these 1,5-diketones were determined by NMR, chemical shifts, coupling constants, and a set of 2D experiments: HSQC, HMBC, NOESY.

Based on the HSQC experiments, hydrogens in the methylene group were assigned to both stereoisomers of **9a** and **9a*** (See Supplemental data). Configurational assignment of the *meso* form was determined by NOE experiment. In this isomer, the H-3 at $\delta = 2.94$ ppm had NOE interactions with the H-10 at $\delta = 3.84$ ppm and with the H_{ortho} of phenyl group, while the other H-3 at $\delta = 3.38$ ppm had NOE interactions only with the H_{ortho} of phenyl group. The H-2 at $\delta = 3.68$ ppm had NOE interactions with the H_{ortho} ($\delta = 7.30$ ppm) of phenyl group attached to C-10. This correlation indicates that H-2 and the phenyl group of C-10 are in a *cis* arrangement. All these data show that the *meso*-structure of 1,5-diketone **9a** has the *R,s,S* configuration (Figure 4, see Supplemental data).

In the case of the other isomer **9a***, the H-3 at $\delta = 2.67$ ppm had NOE correlation with H-10 ($\delta = 3.55$) and with the H_{ortho} of phenyl group. Besides, the H-3′ at $\delta = 3.18$ ppm had NOE correlations with the H_{ortho} of phenyl group. The significant NOE correlation observed between H-2 ($\delta = 4.00$ ppm) and H-2′ ($\delta = 3.82$ ppm) is indicative of a *cis* arrangement. These correlations indicate that the structure of this isomer has the 2*R*,2′*R*/2*S*,2′*S* configuration (Figure 5, See Supplemental data).

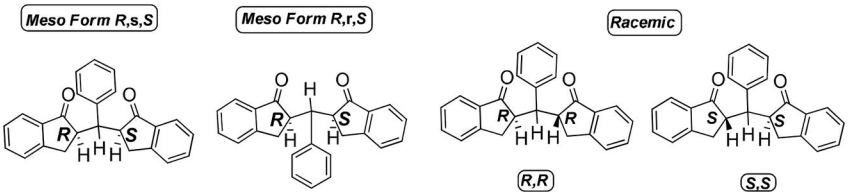


Figure 3. Stereoisomers of the *bis*-indane1,5-diketone **9**.

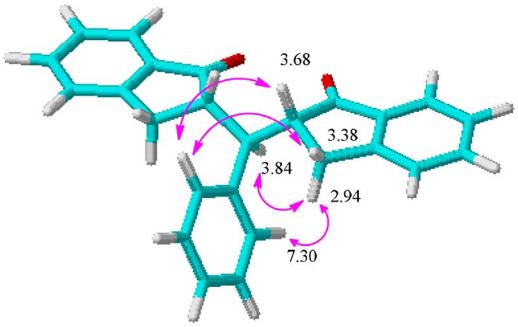


Figure 4. Representative NOE correlations of **9a** (meso **R,s,S**).

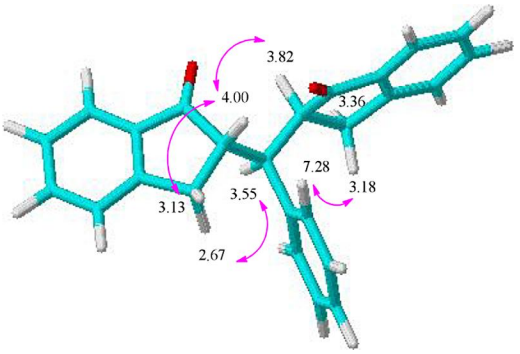


Figure 5. Representative NOE correlations of racemic **9a***(*2R,2′R/2S,2′S*).

Finally, the structure and configuration assignments of *bis*-indane 1,5-diketones obtained, **9b, 18a, 19a, 20a**, and **20b**, were performed by comparison of ^{1}H NMR data with those corresponding to **9a** and **9a*** (Supplemental data). All these spectroscopic data allowed us to assign the *meso* configuration (*R,s,S*) to the *bis*-indane 1,5-diketones.

Conclusion

We studied the behavior of benzocycloalkan-1-ones toward arylaldehydes under classical Claisen–Schmidt condensation conditions (NaOH in EtOH/H_2O). The products obtained, 2-benzylidene derivatives of benzocycloalkan-1-ones and/or spiropolycyclic 1,5-diketones, depend on the electronic nature of the arylaldehyde and on the reaction temperature. Besides, 2-arylideneindan-1-ones afforded *bis*-indane 1,5-diketones through a process involving Michael addition reaction, which is dependent on the temperature of the reaction. Theoretical studies using DFT allowed understanding the chemical reactivity and site selectivity of the α,β-enones used in this work through the calculation of global and local electrophilicity (C–β). Both the electrophilicity of C–β and the reaction temperature led the course of reaction toward the formation of aldol condensation, aldol condensation/Michael addition, and aldol condensation/dimerization products. The results of this research indicate that *bis*-indane 1,5-diketones could be synthesized with the three aryl groups with different substituents, which can be used as a starting material for the synthesis of different compounds. This work is the first to show the dependence of the course of reaction on both the temperature and the electrophilicity of C–β, on the reaction of benzoalkan-1-ones under C–S, NaOH in water–ethanol solution as well as the structural and stereochemical assignments of *bis*-indane 1,5-diketones.

Experimental

Reaction of benzocycloalkan-1-ones and benzaldehydes

General procedure A (Aldolic condensation)

Benzaldehyde (3.0 mmol) was added to a well-stirred solution of benzocycloalkan-1-one (3.0 mmol) and NaOH/H_2O 10% (1.6 mL) in ethanol (1.6 mL). After the mixture was stirred at ice bath or room temperature for 2–4 h, the solid was filtered and washed with water. 2-Arylidenebenzocycloalkan-1-ones **7a, 7b, 8, 12a, 16a, 17a**, and **17b** were prepared as per the mentioned procedure and identified by m.p. and ^{1}H NMR spectra.

(E)-2-(Phenylmethylene)indan-1-one[10]. Yield: 0.64 g (98%), mp 109–111 °C (MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.93 (d, $J = 7.6$ Hz, 1H); 7.71-7.69 (m, 3H); 7.64-7.56 (m, 2H); 7.51-7.39 (m, 4H); 4.07 (s, 2H).

General procedure B (Multicomponent reactions)

Benzaldehyde (3.0 mmol) was added to a well-stirred solution of benzocycloalkan-1-one (3.0 mmol) and NaOH/H_2O 10% (1.6 mL) in ethanol (1.6 mL). After the mixture was stirred at reflux or room temperature for 1–2 h, the reaction mixture was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by preparative TLC, to afford spiropolycyclic compounds. The compounds **11a, 13a, 15a, 15a*, 14a** were prepared as per the mentioned procedure and identified by m.p. and ^{1}H NMR spectra.

(1RS,2SR,3SR,3aRS,8aRS)-1,3-diphenyl-3a,8a-dihydrospiro{cyclopenta[a]indene-2,2′(1H,3′H)-indene}-1′,8(3H)-dione (11a)[13a]. Purified by preparative TLC ($CHCl_3$). Yield: 0.79 g. (60%). mp 235–236 °C (MeOH). ^{1}H NMR (300 Hz, $CDCl_3$) δ 7.77 (d, $J = 7.1$ Hz, 1H); 7.54 (d, $J = 7.6$ Hz, 1H); 7.48-7.40 (m, 2H); 7.31-7.09 (m, 13H); 6.94 (d, $J = 7.6$ Hz, 1H); 4.58 (dd, $J = 9.3$, 9.7 Hz, 1H); 4.10 (d, $J = 10.8$ Hz, 1H); 3.93 (dd, $J = 8.6$, 10.6 Hz, 1H); 3.84 (d, $J = 10.7$ Hz, 1H); 3.08 (d, $J = 17.4$ Hz, 1H); 2.99 (d, $J = 17.4$ Hz, 1H).

Reaction of 2-arylideneindan-1-ones and indan-1-ones

General procedure C (Michael addition)

2-Arylideneindan-1-one (3.0 mmol) was added to a well-stirred solution of 1-indanones (3.0 mmol) and NaOH/H_2O 10% (1.6 mL) in ethanol (1.6 mL). After the mixture was stirred at ice bath or room temperature for 3–5 h, the solid was filtered and washed with water. The product was purified by preparative TLC. The compounds **9a, 9a*, 9b 18a, 19a, 20a**, and **20b** were prepared as per the mentioned procedure. The structure of reaction products were established by spectroscopic data.

(2R,10s,2′S)-2,2′–(phenylmethylene)-bis-(2,3-dihydro-1H-inden-1-one) ($9a_{meso}$) and (2R/S, 2′R/S)-2,2′–(phenylmethylene)-bis-(2,3-dihydro-1H-inden-1-one) ($9a^*_{racemic}$). Purified by preparative TLC ($CHCl_3$). Yield: 0.77 g, (73%), diastereomers mixture **9a** and **9a*** (7:3) ratio determined by ^{1}H NMR. ***9a***: mp 213–215 °C[25] and ***9a****: mp 173–174 °C.

9a: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, $J = 7.6$ Hz, 2H, H-8); 7.53 (t, $J = 7.3$ Hz, 2H, H-6); 7.35 (d, $J = 8.2$ Hz, 2H, H-5); 7.34 (t, $J = 8.2$ Hz, 2H, H-7); 7.30 (d, $J = 7.0$ Hz, 2H, H-12); 7.23 (t, $J = 7.0$ Hz, 2H, H-13); 7.14 (t, $J = 7.0$ Hz, 1H, H-14); 3.84 (t, $J = 8.0$ Hz, 1H, H-10); 3.68 (dt, $J = 3.7$, 8.0, 8.0 Hz, 2H, H-2); 3.38 (dd, $J = 8.0$, 16.8 Hz, 2H, H-3); 2.94 (dd, $J = 3.7$, 16.8 Hz, 2H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): 207.5(C-1), 153.5 (C-4), 139.3 (C-11), 136.9 (C-9), 134.6 (C-6), 129.4 (C-12), 128.2 (C-14), 127.3 (C-13), 126.9 (C-7), 126.4 (C-5), 123.8 (C-8), 48.8 (C-2), 46.4 (C-10), 31.1 (C-3). Elemental analysis calcd. (%) for $C_{25}H_{20}O_2$ (352.15): C, 85.20; H, 5.72. Found: C, 85.22; H, 5.74.

9a*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, $J = 7.7$ Hz, 1H, H-8′); 7.75 (d, $J = 7.7$ Hz, 1H, H-8); 7.53 (t, $J = 8.3$ Hz, 1H, H-6′); 7.51 (t, $J = 7.5$ Hz, 1H, H-6); 7.38 (d, $J = 7.5$ Hz, 1H, H-5′), 7.36 (overlapped, H-7); 7.34 (overlapped, H-7′); 7.33 (overlapped, H-5); 7.28 (d, $J = 7.3$ Hz, 2H, H-12); 7.25 (t, $J = 7.3$ Hz, 2H, H-13); 7.21 (t, $J = 7.2$ Hz, 1H, H-14); 4.00 (ddd, $J = 7.9$, 10.6 Hz, 1H, H-2), 3.82 (ddd, $J = 3.6$, 5.1, 8.6 Hz, 1H, H-2′); 3.55

(dd, $J = 3.6$, 10.6 Hz, 1H, H-10); 3.36 (dd, $J = 8.0$, 16.7 Hz, 1H, H-3′b); 3.18 (dd, $J = 5.3$, 16.7 Hz, 1H, H-3′a); 3.13 (dd, $J = 7.8$, 17.4 Hz, 1H, H-3b); 2.67 (dd, $J = 4.5$, 17.4 Hz, 2H, H-3a). ^{13}C NMR (125 MHz, $CDCl_3$): 207.7 (C-1), 207.1 (C-1′), 153.1 (C-4), 152.8 (C-4′), 141.4 (C-11), 137.7 (C-9), 136.9 (C-9′), 134.6 (C-6), 134.2 (C-6′), 128.9 (C-7′), 128.5 (C-12), 128.3 (C-13), 127.3 (C-7), 127.2 (C-14), 126.9 (C-5), 126.2 (C-5′), 124.0 (C-8′), 123.6 (C-8), 50.2 (C-2′), 47.9 (C-10), 47.8 (C-2), 33.3 (C-3), 30.7 (C-3′). Elemental analysis calcd. (%) for $C_{25}H_{20}O_2$ (352.15): C, 85.20; H, 5.72. Found: C, 85.19; H, 5.71.

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