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New Synthetic Applications of 2-Benzylidene-1-indanones: Synthesis of 4b,10,10a,11-Tetrahydro-5*H*-indeno[1,2-*H*]quinoline and 1′-(Diisopropylamino)-2,2′-spirobi[indene]-1,3′(1′*H*,3*H*)-dione †

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Abstract

2-Benzylidene-1-indanones constitute a family of heterocyclic compounds with a wide range of pharmacological and material applications. Here we present preliminary results of new chemistry in this field. Thus, an acid-mediated aldolic condensation of 1-indanone with *o*-nitrobenzaldehyde provided *(E)*-2-(2-nitrobenzylidene)-2,3-dihydro-1*H*-inden-1-one, which, when subjected to catalytic hydrogenation, led directly to 4b,10,10a,11-tetrahydro-5*H*-indeno[1,2-*b*]quinoline, as a result of several successive spontaneous reactions. On the other hand, a base-mediated aldolic condensation of 1-indanone with *o*-methoxycarbonylbenzaldehyde yielded methyl (*E*)-2-((1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoate which, when treated with LDA, led to the formation of 1′-(diisopropylamino)-2,2′-spirobi[indene]-1,3′(1′*H*,3*H*)-dione.

Keywords: spiroketones; benzylideneindanones; quinolines

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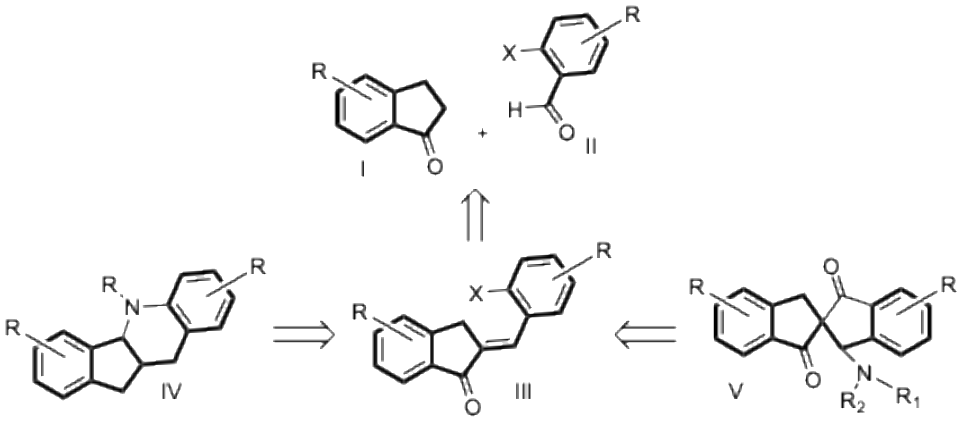
1. Introduction

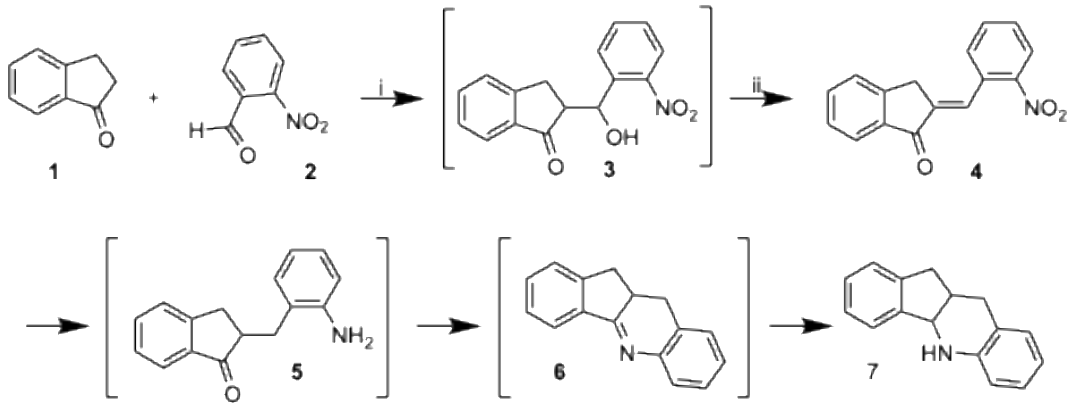
2-Benzylidene-1-indanones constitute a family of indanones [1,2] with a wide range of pharmacological and material applications [3]. Their structure, characterized by an indanone skeleton functionalized with a benzylidene group at the 2- position confers conjugated properties that promote biological activity, including antioxidant, anti-inflammatory, anticancer and antimicrobial effects [1]. In addition, their synthesis via Knoevenagel-type condensations is efficient and versatile, allowing for extensive structural modification. These characteristics make 2-benzylidene-1-indanones promising candidates in the design of new bioactive entities and functional materials [4]. Furthermore, 2-benzylidene 1-indanones could be useful scaffolds for the access of condensed tetracyclic derivatives in which their carbon skeleton is embedded, like indenoquinolines **IV** [5] and spiro compounds **V** [4,6,7] (Scheme 1).

Here we present preliminary results of new chemistry in this field. It consists of (a) the transformation of (*E*)-2-(2-nitrobenzylidene)-2,3-dihydro-1*H*-inden-1-one (**4**) into 4b,10,10a,11-tetrahydro-5*H*-indeno[1,2-*b*]quinoline/**7**) (Scheme 2) and (b) the

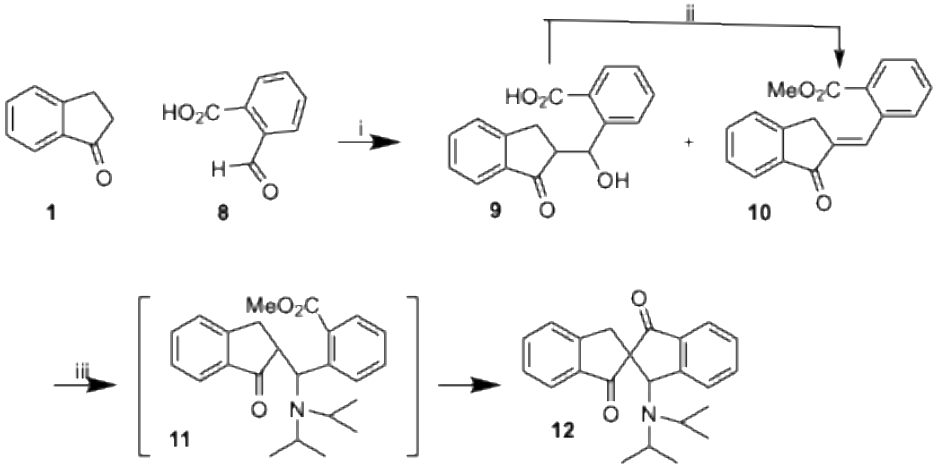
transformation of methyl (*E*)-2-((1-oxo-1,3-dihydro-2*H*-inden-2-ylidene)methyl)benzoate (**10**) into 1′-(diisopropylamino)-2,2′-spirobi[indene]-1,3′(1′*H*,3*H*)-dione (**12**). (Scheme 3).



Scheme 1. Caption.



Scheme 2. *Conditions*: (i) HCl, EtOH, reflux, 6 days (60%). (ii) H_2, Pd/C, EtOAc, rt, 2 h (65%).



Scheme 3. *Conditions*: (i) HCl, MOH, reflux, 13 days (30% of **9**, 40%of **10**). (ii) H_2SO_4, MeOH, reflux, 14 h (iii) LDA, THF, −78 °C, 4 h, rt 12 h (50%).

2. Results and Discussion

2.1. Synthesis of 4b,10,10a,11-Tetrahydro-5H-indeno[1,2-b]quinoline (7)

An acid-mediated aldolic condensation of 1-indanone with *o*-nitrobenzaldehyde provided indanone **3**, a process that is followed by a spontaneous dehydration to give the nitrobenzylideneindanone **4**, as it was established from its analytical and spectroscopic

data. His IR spectrum shows at 1700 cm^{-1} the C=O band and at 1512 and 1267 cm^{-1} the NO_2 bands. And the ^1H NMR spectrum included three signals at 7.35–7.65, 7.85–792 and 8.05 ppm, due to the eight aromatic and the vinyl protons, along with a doublet at 3.79 ppm, due to the methylene group.

Next, catalytic hydrogenation of **4** [2,8] directly yielded tetrahydroquinoline **7**, as deduced from its analytical and spectroscopic data. The most representative signal in this ^1H NMR spectrum is a broad singlet at 4.31 ppm, due to the amine proton. And the ^{13}C NMR spectrum shows three quaternary carbon signals at 146.2, 144.3 y 141.5 ppm and the signal of the C-N bond carbon at 121.5 ppm, along with signals of the aromatic CH groups at 128.,7, 127.5, 126.9, 126.7, 125.4, 123.8, 117.0, 113.2 ppm, the signal of the carbon of the CH-N group at 59.8 ppm, the signals from the -CH_2- groups at 37.2 and 30.2 ppm and the signal of a -CH- group at 36.8 ppm.

Formation of **7** [9] may be explaining assuming that the hydrogenation of **4** resulted in a cascade of reactions in which the reduction of the nitro group to amino and a spontaneous reduction of the exocyclic double bond provided aminoindanone **5**. This was followed by subsequent spontaneous intramolecular condensation of the amino and carbonyl groups of this intermediate and finally the reduction of the C=N bond of the resulting compound **6** led compound **7**.

2.2. Synthesis of 1'-(Diisopropylamino)-2,2'-spirobi[indene]-1,3'(1'H,3H)-dione

After a failed attempt of aldolic condensation of indanone **1** with 2-formylbenzoic acid **8** under basic conditions (EtONa/EtOH), satisfactory results were obtained when the reaction was undertaken in an acidic media (HCl, EtOH), under reflux for 13 days. This led to a mixture of compounds **9** (30%) and **10** (40%) (Scheme 3), which were isolated by column chromatography and identified from spectroscopic and analytical data.

The IR spectrum of compound **9** shows a broad band at 3716–3100 cm^{-1} and strong band at 1712 cm^{-1}, due to de carboxyl group, along with a strong band at 1665 cm^{-1}, due to the carbonyl group of the ketone. The representative signals present in its ^1H NMR are a singlet at **6.21** ppm, due to the proton at the carbon carrying the OH group, and a signal at 3.31 ppm and two double doublets at 2.89 and 2.53 ppm, correspond to the other three aromatic protons. And the ^{13}C NMR spectrum includes at 170 and 203.5 ppm the signals corresponding to carbonyl of the carboxylic acid and the ketone groups.

On the other hand, the IR spectrum of compound **10**[4] shows two strong bands a 1702 and 1635 cm^{-1}, corresponding to the ketone carbonyl and the methoxy carbonyl groups. The ^1H NMR spectrum confirms the esterification of the carboxyl group of compound **9**, as established by the presence of a singlet at 4.40 ppm, due to the methyl group. In addition, the signal of the vinylic proton appears at 8.23 ppm. The *E* configuration of the double bond was assigned by comparison with other similar 2-benzylideneindanones prepared by us, and the ^{13}C NMR spectrum includes signals corresponding to the carbonyl groups at 167.0 and 193.8 ppm.

The obtaining of the mixture **9** and **10** was explaining assuming that the hydroxyacid **9** resulting from the aldolic condensation of compounds **1** and **8** spontaneously underwent esterification and dehydration, giving rise to compound **10**. This was confirmed because compound **9** was transformed into compound **10** when subjected to the reaction conditions giving rise to mixture **9** + **10**.

Following our plan, the reaction of compound **10** with LDA produced the tetracyclic spirocompound **12** [4], as deduced from its analytical and spectroscopic data. Its IR spectrum shows a ketone carbonyl band at 1694 cm^{-1} and its ^1H NMR spectrum includes signals from eight aromatic protons, along with a singlet a 4.90 ppm, corresponding to the proton of the carbon carrying the amino group, a singlet of two protons, due to the methylene, and the following signals from the two isopropylidene groups: two signals at 3.31

and 2.43 ppm and four doublets at 1.32, 1.03, 0.82 and 0.56 ppm. In addition, representative signals present in its ^{13}C NMR spectrum are two pics at 203.3 and 202.2 ppm, of the two ketone carbonyls, a signal at 72.6 ppm, from the spiranic carbon, and four pics at 24.2, 23.8, 22.2 and 20.90 ppm, dues to the four methyl groups.

The formation of compound **12** can be explained in terms of a Michael-Claisen-like cascade involving a conjugated addition of LDA to the a,b-unsaturated carbonylic moiety of compound **10,** yielding enolate **11**, which spontaneously gives rise to **12** through an intramolecular attack of this enolate on the methoxycarbonyl subs*t*ituent.

3. Conclusions

These preliminary results on synthetic applications of 2-benzylideneindan-1-ones consist of a new synthesis of 10,10a,11-tetrahydro-5*H*-indeno[1,2-*b*]quinoline (**7**) and the synthesis of 1′-(diisopropylamino)-2,2′-spirobi[indene]-1,3′(1′*H*,3*H*)-dione (**12**) [10].

The interest and novelty of this work lie in the fact that type **7** indenoquinolines have hardly been considered (only one example has been described) and compound **12** is the first example described with an amino substituent at the C-1′ position. Also noteworthy is the direct access to these targets, based previously undescribed on cascade reactions 2-benzylideneindan-1-ones [11,12].

Future work in this field will include the stereoselective synthesis of libraries of compounds **7** and **12**, for chemical and biological studies.

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