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The Friedel-Crafts Arylation of α -Substituted Chalcones Revisited: Highly Stereospecific Synthesis of TRANS-2,3-Diphenyl-Indan-1-One Derivatives

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**THE FRIEDEL-CRAFTS ARYLATION OF α -SUBSTITUTED
CHALCONES REVISITED: HIGHLY STEREOSPECIFIC SYNTHESIS
OF *TRANS*-2,3-DIPHENYL-INDAN-1-ONE DERIVATIVES[†]**

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Abstract: The Lewis or protic acid promoted cycloisomerization of 1,2,3-triphenylpropenone in nitroethane as solvent has given *trans*-2,3-diphenyl-indan-1-one with complete diastereoselection in good to excellent chemical yield.

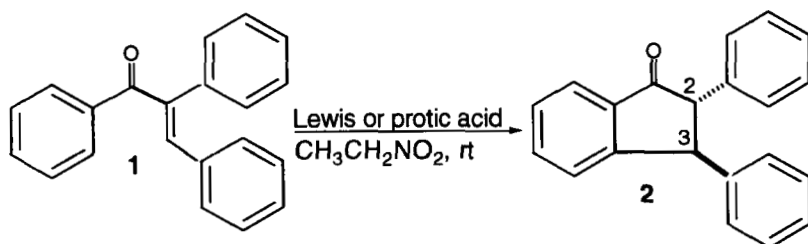
A recent report on the synthesis of 1-indanones *via* tandem Knoevenagel condensation-cycloalkylation of β -dicarbonyl compounds and aldehydes,¹ prompts us to disclose here our own results in the Friedel-Crafts arylation of α -substituted chalcones. Briefly, comparing with the results described previously² we have observed significant differences in the results obtained during the Lewis (AlCl₃, SnCl₄, BF₃·Et₂O) or protic acid (H₂SO₄ cc) promoted cycloisomerization of 1,2,3-triphenylpropenone (**1**) *using nitroethane as solvent*. Consequently, in this work we report that starting from compound **1**, *trans*-2,3-diphenyl-indan-1-one (**2**) could be prepared with complete diastereoselection and in good to excellent yield. Several efficient and selective chemical manipulations of indanone **2** are also described.

[†]This paper is dedicated with respect to Professor Manuel Bernabé Pajares on occasion of his 60th birthday

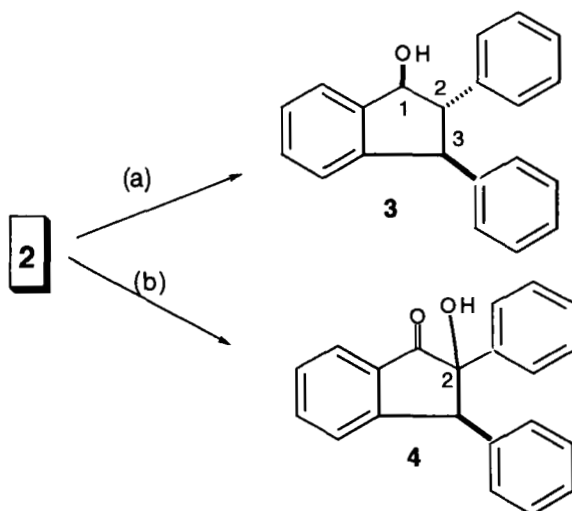
1-Indanones are currently used in medicinal chemistry for cell culture monitoring³ and as building blocks for antioxidants,⁴ acetylcholinesterase inhibitors,⁵ and chiral phase transfer agents.⁶ In the last years we have been actively working in the Michael additions to trisubstituted, highly deactivated olefins as Michael acceptors⁷ and in this context we had the opportunity to manipulate 1,2,3-triphenylpropenone (**1**) as a substrate of particular interest.⁸ In view of some recent reports¹ we have been attracted by the possibility of using this substrate as a convenient substrate for Friedel-Crafts arylation reactions, having in mind a potential synthesis of 1-indanones³⁻⁶ type of compounds from this precursor. A careful examination of the literature has shown that this reaction has been already described by Koelsch in 1961.² This author has performed this process in benzene as solvent, using AlCl_3 as catalyst, and has isolated "2,3-diphenylhydrindone, m.p. 98-100 °C" ² in 32% yield (configuration at C-2 and C-3 not assigned) and another compound (45% yield) "probably largely stereoisomeric form of 2,3-diphenylhydrindone..." ² To our knowledge, this protocol has never been reinvestigated again.

Now and very surprisingly, we have observed that, in contrast to this previous report,² when the cycloisomerization of α -chalcone **1** (Scheme) is carried out in nitroethane as solvent, using different Lewis or protic acids, the reaction proceeds very cleanly at room temperature, with complete diastereoselection, giving exclusive *trans*-product **2** (see Scheme; **Experimental**). The relative stereochemistry at C-2 and C-3 in compound **2** has been assigned by ¹H NMR analysis and by comparison of our values with those reported for this product.⁹ In fact, in the ¹H NMR spectrum H-2 appears at 4.59 ppm as a doublet ($J = 4.7$ Hz) and H-3 at 3.83 ppm. In the ¹³C NMR spectrum we could analyze also significant signals: C-1 (205.07 ppm, CO), C-2 (64.53 ppm) and C-3 (54.79 ppm). Our present results compare also very favourably, in terms of simplicity and chemical yield, with other protocols described previously for the preparation of 1-indanone **2**: a) Friedel-Crafts reaction of α,β,β -triphenylpropionic acid (P_2O_5 , AlCl_3 , benzene, reflux, 30 min, 60% yield);¹⁰ b) Reaction of diphenylethylene with benzaldehyde in the presence of boron trifluoride (in 1,2-dimethoxyethane, 7 h at reflux, 2 days at rt, 19% yield);¹¹ c) Stereospecific hydrogenation of 2,3-diphenylinden-1-one (Adams catalyst; yield not given);^{9,12} d) Acid dehydration of 2,2-diaryl-1,3-indanediols (50% yield);¹³ e) Reaction of

2,3-diphenylinden-1-one with lithium naphthalenide (70% yield);¹⁴ f) Reaction of morpholino chromium carbene complexes with alkynes (52% yield).¹⁵ In summary, it is obvious that the correct choice of the solvent has critical implications in the stereochemistry and in the chemical yields of this process.



<u>Lewis or protic acid</u>	<u>Yield (%)</u>
H_2SO_4	88
$\text{BF}_3 \cdot \text{Et}_2\text{O}$	96
SnCl_4	86
AlCl_3	67



Scheme.

Reagents: (a) NaBH_4 , MeOH (53%); (b) NaMeO , MeOH, (60%)

With the efficient method already described, we had in hands quantities of compound **2**. This moved us to explore some transformations of this material. Reduction with sodium borohydride in methanol gave the indan-1-ol **3** in 53% yield, as the only isolated and detected isomer. A compound with this structure has been described in the early years of this century,¹⁶ having as melting point 146 °C. These authors could not assign the relative stereochemistry at all the stereocenters. Careful examination of the ¹H NMR spectrum of our product (m.p.: 88-90 °C) allowed us to determine as *trans* the relative stereochemistry at C-1 and C-2 in our product. In fact, the two large coupling constants ($J_{1,2}$ = 8.6 Hz, $J_{2,3}$ = 10.0 Hz) suggest an *anti* relationship for protons H-1/H-2 and H-2/H-3. In addition, a crosspeak for H-1/H-3 is observed in the 2D NOESY spectrum, showing the *syn* arrangement for H-1 and H-3. Assuming, what is very reasonable, that in this reaction there is no possible epimerization at C-3, the final stereochemical assignment is as follows: C-1(OH) β /C-2(phenyl) α /C-3(phenyl) β (see Scheme). The exclusive formation of this isomer can be explained by the attack of the hydride to the ketone from the less hindered face, opposite to the vicinal phenyl group at C-2. In summary, from the melting point data, our product **3** has to be different from the compound described by Schlenk¹⁶ and to the best of our knowledge this the first time that compound **3** has been described.

The obtention of only *trans* **2** product in the cycloisomerization of compound **1**, moved us to prepare the *cis* isomer of **2**, in order to compare spectroscopic data and tlc behaviour. Obviously, with compound **2** in hands, a simple way to do that is the base catalyzed isomerization of the *trans* isomer.¹³ To our great surprise, however, when we treated the indanone **2** with sodium methoxide in methanol, at room temperature, we obtained a new product (**4**, see Scheme), in 60 % yield, whose analytical and spectroscopic data did not agree with those expected for the presumed *cis* isomer of **2**.⁹ On the contrary, in the ¹H NMR spectrum we observed, in addition to the aromatic signals between 8.00 and 6.70 ppm (14 H), a singlet at 4.85 ppm and a broad singlet at 3.25 ppm that disappears on shaking with D₂O. In agreement with this, in the ¹³C NMR spectrum plus DEPT experiment we detected also significant signals: 207.19 ppm (CO), 86.54 ppm (quaternary carbon) and 59.22 ppm (CH). These values coupled to the analytical data allowed us to propose **4** as the structure for this compound. However, we were unable to determine the relative stereochemistry at C-2 and C-3. In fact, a product with similar spectroscopic and physical properties has been

described previously in literature,^{14,17} although the relative stereochemistry at C-2 and C-3 could not be assigned. This product has been isolated in very low yield (8%) in the reaction of 2, 3-diphenylinden-1-one with lithium naphthalenide.¹⁴ This is in agreement with our results and confirms that in our basic conditions, traces of water in methanol probably promote the α -hydroxylation of ketone **2**, instead of the expected *trans/cis* isomerization.

In summary, in this paper we have described a reliable method for the preparation of *trans*-2,3-diphenylindan-1-one (**2**) in high yield, mild reaction conditions and complete diastereoselection. In addition we have reported some stereoselective manipulations that have resulted in some useful derivatives in this series.

Experimental

Reactions were monitored by TLC using precoated silica gel aluminium plates containing a fluorescent indicator (Merck, 5539). Detection was done by UV (254 nm) followed by charring with sulfuric-acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous Na₂SO₄ was used to dry organic solutions during workups and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using Kieselgel 60 (230-400 mesh, Merck) and hexane-ethyl acetate mixtures as eluent. ¹H and ¹³C NMR spectra were recorded with a Varian VXR-300S spectrometer, using tetramethylsilane as internal standard.

Cycloisomerization of 1, 2, 3-Triphenylpropenone (**1**). General Method.

To a solution of product **1** in nitroethane (0.13M) the Lewis acid (1 equiv) or concentrated sulfuric acid (several drops) were added at 0 °C and the reaction was warmed to room temperature (rt) and stirred for 4 h (AlCl₃, BF₃.Et₂O) or overnight (SnCl₄, sulfuric acid). Triethylamine (2 equiv) was added and the solvent evaporated. The residue was absorbed in silica gel and submitted to flash chromatography (hexane/EtOAc 5%) to give compound **2** (in the yields shown in Scheme; see text), whose spectroscopic data are in agreement with those recorded in literature.^{9,10}

(1 β , 2 α , 3 β)-2,3-Diphenyl-indan-1-ol (3).

Compound **2** (90 mg, 0.32 mmol) was dissolved in methanol (5 mL) and cooled at 0 °C. To this solution sodium borohydride (12 mg, 0.32 mmol, 1 equiv) was added and the reaction stirred at rt for 5 h. The solvent was removed and the residue suspended in ethyl acetate and washed with 5% aqueous solution of ammonium chloride. The organic phase was separated, dried (Na₂SO₄), filtered and evaporated. The residue was submitted to flash chromatography (hexane/EtOAc 10%) to give alcohol **3** (49 mg, 53% yield): m.p. 88-90 °C; IR (KBr) ν : 3.500-3.300, 3.020, 2.900, 1.600, 1.499, 1.455, 1.055, 910 cm⁻¹ ¹H NMR (200 MHz, CDCl₃) δ . 7.50-6.90 (m, 14 H, aromatic), 5.41 (dd, $J_{1,2}$ = 8.3 Hz, $J_{1,OH}$ = 1.0 Hz, 1 H, H-1), 4.35 (d, $J_{2,3}$ = 10.2 Hz, 1 H, H-3), 3.36 (dd, 1 H, H-2), 2.26 (br s, 1 H, OH). *Anal.* C₂₁H₁₈O. Calcd.: C, 88.08; H, 6.34. Found: C, 88.10; H, 6.25.

2-Hydroxy-trans-2, 3-diphenyl-indan-1-one (4).

Compound **2** (90 mg, 0.32 mmol) was dissolved in methanol (5 mL) and treated with a catalytic amount of sodium methoxide at rt for 18 h. Evaporation of the solvent and flash chromatography (hexane/EtOAc 10%) of the residue gave product **4** (57 mg, 60% yield; m.p. 123-126 °C; lit¹⁴ 126-128 °C) identical in all the spectroscopic data to the described product.¹⁴

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