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Scope of the formal [3+2] cycloaddition for the synthesis of five-membered ring of functionalized indanes

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ABSTRACT

We report our research about the synthesis of functionalized indanes in the pentagonal ring by a formal [3+2] cycloaddition using benzhydrols and styrene derivatives with electron-withdrawing groups joined to C-β, such as carboxyl, carboxymethyl, carbonyl of ketones, and nitro groups. We also report the configurational assignment of the indanic structures synthesized using several experiments of NMR.

1. Introduction

The dihydroindene ring system is a structural subunit found in a large number of naturally occurring compounds with anti-tumor activity, such as 'secaloside' A (I).[1] In addition, several synthetic compounds with this skeleton, show a broad range of biological activities, such as the hydroxylated derivative of 3-(3,4-dichlorophenyl)-1-*N*-methylindanamine (II), which has high affinity for the serotonin transporter, dopamine, and norepinephrine.[2] Furthermore, indan-2-carboxylic acid with aryl groups at C-1 and C-3, such as compounds SB-209670 and SB-217242 (III),[3] are potent antagonists of endothelin receptors. Endothelin ET-1 and closely related compounds, such as the isopeptides ET-2 and ET-3, cause a profound vasoconstriction and mitogenic activity in the cardiovascular system[4,5] and play an important role in the pathogenesis of cardiovascular diseases (Fig. 1).

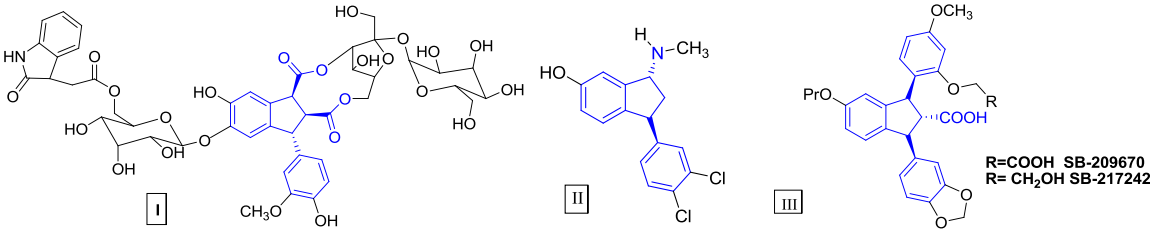

Fig. 1. Natural and synthetic products with dihydroindene ring system.

A variety of synthetic strategies to obtain this type of systems have been developed. These range from the dimerization of propenylbenzenes in acid medium[6] to multi-step synthesis of polycyclic indane structures,[7] among other syntheses.[8] The synthesis of functionalized indane structures in the pentagonal ring is complex, requires several steps, and generally results in low total yield.

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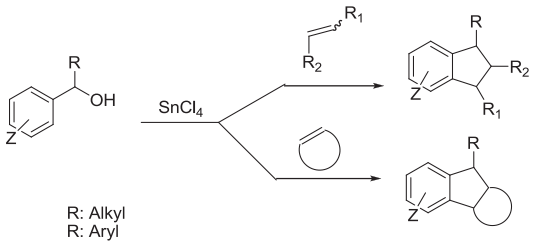
Therefore, the discovery of new synthetic strategies has become an interesting challenge. A reaction that has been very successful in the synthesis of highly substituted indanes[9] and indanic structures in three and tetracyclic systems[10] has been the formal [3+2] cycloaddition (FCA [3+2]) from benzyl alcohols and benzhydrols with styrenes, stilbenes, and cycloalkenes. This reaction offers the possibility to form three stereogenic centers in one step, exhibiting excellent regiochemistry (Scheme 1).[9,10]

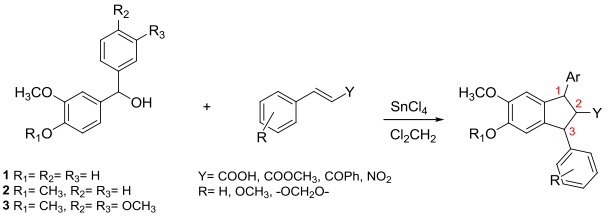


Scheme 1. Formal [3+2] cycloaddition.

In this paper, we report our research and results that led to the synthesis of functionalized indanes in the pentagonal ring, using benzhydrols and styrene derivatives with electron-withdrawing groups joined to C-β, such as carboxyl, carboxymethyl, carbonyl of ketones, and nitro groups. We also report the configurational assignment of the indanic structures synthesized using ^{1}H and ^{13}C NMR analysis and a set of two-dimensional experiments (NOESY, ROESY, HMQC, and HSQC).

2. Results and discussion

The benzhydrols (**1**–**3**) and substituted styrenes used were synthesized according to techniques previously described.[11] The catalyst used for the cycloaddition reaction was $SnCl_4$,[9,12] and methylene chloride as solvent (Scheme 2). The temperature and reaction time are indicated in each case. Other acid catalysts, which had shown good results in obtaining indanic structures [$H_3PMo_{12}O_{40}$ (MPA), MPA supported on C (MPA/C), $H_3PW_{12}O_{40}$ (TPA), TPA supported on SiO_2 (TPA/S)],[13] as well as other catalysts, such as $AlPMo_{12}O_{40}$ (MPAl) and $HClO_4$ supported on SiO_2 ($HClO_4$/S) were also tested in this work.



Scheme 2. Synthesis of functionalized indanes in the pentagonal ring.

2.1. Reaction of benzhydrols with styryl carboxylic acids, esters, and ketones

Table 1 shows the results obtained from benzhydrols **1**, **2** and carbonyl derivatives of styrenes.

Alcohol **2** did not react with cinnamic acid (**4**) (entry 1); instead, substituted cinnamic acids **5** and **6** showed a very good performance. In these cases, a mixture of diastereoisomers were obtained: 1,2-*cis*-2,3-*trans* (**7** and **9**) and *trans*–*trans* (**8** and **10**), in a proportion 2:1, respectively (entry 2, 3).

The reaction between benzhydrol **2** and methyl cinnamate (**11**) afforded indane **12** with trans–trans configuration as a single product, whereas with the substituted esters **13** and **14**, mixtures of diastereomers *trans*–*trans* (**16** and **18**) and 1,2-*cis*-2,3-*trans* (**15** and **17**) were obtained (entry 4–6).

A single stereoisomer (trans–trans configuration) was obtained from chalcone **19** and benzydrols **1** and **2** (entry 7,8), while three indane diastereoisomers were obtained from chalcones **22** and **23**. The main product in both cases presented the *trans*–*trans* configuration (**24** and **27**), while the minority products presented the 1,2-*cis*-2,3-*trans* (**25** and **28**) and 1,2-*trans*-2,3-*cis* (**26** and **29**) configurations (entry 9,10).

This reaction was also performed using other acid catalysts (Table 2). We tested this catalyst with benzhydrol **2** and cinnamic acid **5**, which turned out to be one of the most reactive in previous reactions. Chloroform was used as a solvent at reflux temperature for 24 h with substoichiometric amounts of catalyst. The products obtained in all the cases were the same as those obtained using $SnCl_4$ as catalyst and in the same rate (Table 2 entry 2).

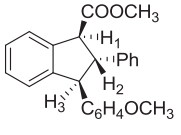
2.2. Reaction of benzhydrols 1, 2, and 3 with nitrostyrenes

Table 3 shows the results obtained by the reaction between benzhydrols and nitrostyrenes **30** and **31**. Nitrostyrene **30** did not react with any of the benzhydrols used. However, nitrostyrene **31** reacted with benzhydrols **1** and **2**, giving two stereoisomers, *trans*–*trans* (**32** and **33**) and 1,2-*cis*-2,3-*trans* (**34** and **35**), in identical proportion (entry 3,4). When the reaction was carried out at rt, a third minor isomer, 1,2-*trans*-2,3-*cis* diastereomer (**36** and **37**) (entry 5,6), was obtained. The reaction between **3** and **31** afforded indanes **38** and **39** (2:1 ratio) (entry 7).

2.3. Structural and configurational assignment of the indanes obtained

The regiochemistry of reaction FCA [3+2] and the stereochemical assignment of all compounds were carried out taking into consideration the data NMR spectra (chemical shifts, coupling constants, and a set of two-dimensional experiments: NOESY, ROESY, HMQC, HSQC). Table 4 summarizes the chemical shift data of protons, carbons, and coupling constants of the compounds obtained from benzhydrols and cinnamic acids, methyl esters, and ketones.

Compounds **8**, **10**, **12**, **16**, **18**, **20**, **21**, **24**, and **27**, showed very similar values of δ_H for the hydrogen atoms H-1 and H-3 ($\Delta\delta \leq 0.05$ ppm). Identical situation was observed for the chemical shifts of the carbon atoms C-1 and C-3 ($\Delta\delta \leq 0.07$ ppm). These data indicate that the regioisomers formed are those with phenyl and/or aryl residues linked to C-1 and C-3. Another evidence that supports the 1,3 diaryl substitution is that the values of δ_C published by Appelbe et al.[14] for *trans*–*trans* methyl 3-(4-methoxyphenyl)-2-phenylindan-1-carboxylate, are markedly different in the chemical shifts from those that appear in Table 4 for the esters **12**, **15**–**18**.



H_1: 4.38 J=10.0 Hz
H_2: 3.98 J=10.3 Hz
H_3: 4.35 J=10.0 Hz
C-1/C-3: 58.21, 59.78
C-2: 52.39
$COOCH_3$: 172.99

Moreover, this regiochemistry is consistent with the study of nucleophilicity of double bond carbons of chalcones **19** and **23**, conducted with the program Spartan 2.0.1.[15] The molecules were optimized using the density functional method (DFT), using the