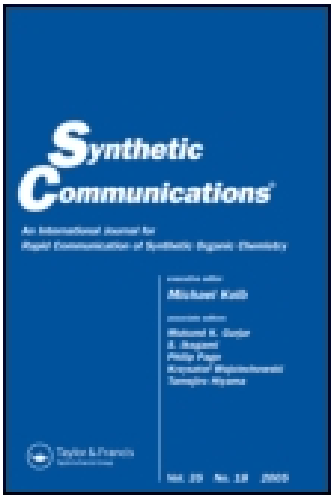

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Sonia Taktouk [a] , Jihène Ben Kraiem [a] & Hassen Amri [a]

[a] Laboratory of Selective Organic Synthesis and Biological Activity, Faculty of Science , El Manar University , Tunis , Tunisia

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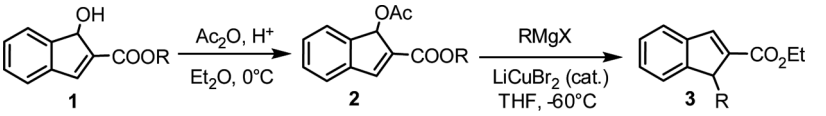
EFFICIENT SYNTHESIS OF SUBSTITUTED INDENE DERIVATIVES

Sonia Taktouk, Jihène Ben Kraiem, and Hassen Amri
Laboratory of Selective Organic Synthesis and Biological Activity, Faculty of Science, El Manar University, Tunis, Tunisia

GRAPHICAL ABSTRACT



Abstract *An efficient protocol for the synthesis of new functionalized indenes* ***3*** *was successfully realized. Thus the coupling reaction of allyl acetate* ***2*** *with Grignard reagents in the presence of a catalytic amount of* $LiCuBr_2$ *at low temperature afforded pure ethyl 1-alkyl-1H-indenes-2-carboxylate* ***3*** *in good yields.*

Keywords Allylic acetates; ethyl 1-alkyl-1*H*-indenes-2-carboxylate; Grignard reagents; indenols

INTRODUCTION

Substituted indene derivatives are valuable synthetic targets in organic[1–6] and medicinal chemistry[7,8] because of their important biological activities[9–11] and applications in functional materials.[12] They are also used as ligands in metallocene complexes, used in the catalyzing olefin polymerization.[13] In addition, indene scaffolds occupy an important place in the carbocyclic products because of the presence of these moieties in various natural products[14,15] and in a large number of drug candidates possessing potential estrogenic bioactivity. Consequently, much effort has been devoted to the construction of the indene ring system, embodying the use of catalysts based on transition metals,[16–20] phenyl-substituted allylic alcohols,[21,22] the ring expansion of suitably substituted cyclopropenes,[23] the reduction/dehydration of indanones[24] and $FeCl_3$-mediated intramolecular olefin–cationic cyclization of cinnamates reported very recently.[25] Although the methods mentioned above are quite effective in synthesizing simple indenes, some disadvantages accompany the preparation of functionalized indenes because of long reaction sequences and strong acidic conditions.[26] In continuation of our interest in the

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Address correspondence to Hassen Amri, Laboratory of Selective Organic Synthesis and Biological Activity, Faculty of Science, El Manar University, 2092 Tunis, Tunisia. E-mail: hassen.amri@fst.rnu.tn

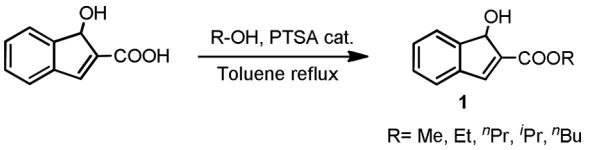
synthesis of carbocyclic compounds,[27] we herein report a facile two-step methodology for obtaining highly substituted indene derivatives by the use of new indene esters **1** as key intermediates.

RESULTS AND DISCUSSION

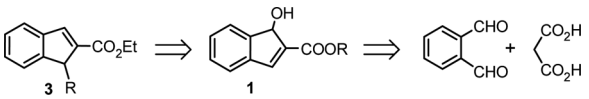
Very recently, we have uncovered a straightforward protocol for the preparation of new indenols derivatives **1** involving the coupling reaction of a wide variety of aliphatic alcohols with 1-hydroxy-1*H*-indene-2-carboxylic acid in the presence of *p*-toluenesulfonic acid (PTSA) as catalyst (Scheme 1). This methodology afforded an efficient entry to a variety of new indenol-based molecular models **1**,[27] identified as potent antibacterial agent against a panel of resistant pathogens. The assessment of radical scavenging capacity of the compounds **1** toward the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) was measured and these compounds were found to scavenge DPPH free radical efficiently.

We now report the use of bicyclic β−hydroxyesters **1** as ideal intermediates in the synthesis of new multiply substituted indenes **3**. In our approach, the construction of indene carbocycles is based on the acetylation of indenols compounds **1** followed by the displacement reaction of allylic acetates using magnesium dialkyl cuprates generated in situ. The retrosynthetic scheme of this approach is represented in Scheme 2.

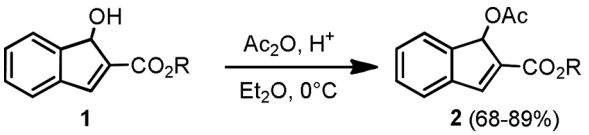
The starting synthetic sequence shown in Scheme 3 is based on the use of allyl acetates **2**, obtained from the conversion of the corresponding alcohols in the presence of acetic anhydride in the presence of a drop of concentrated sulfuric acid as a catalyst.[28] All reactions worked well to give the desired 1-acetoxy-1*H*-indene-2-carboxylates **2a–e** in moderate to good yields as shown in Table 1, whose characterization was performed



Scheme 1. Synthesis of indenols derivatives.



Scheme 2. Retrosynthetic analysis.

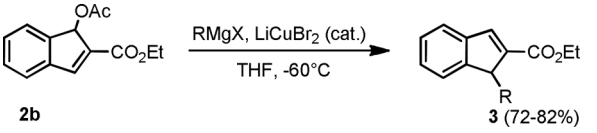


Scheme 3. Acetylation of bicyclic β-hydroxyesters **1**.

Table 1. Preparation of allyl acetates **2a–e** from the corresponding secondary alcohols **1**

R	Product	Yield[a] (%)
Me	**2a**	75
Et	**2b**	80
Pr	**2c**	89
^{i}Pr	**2d**	68
^{n}Bu	**2e**	78

[a]Yields refer to the pure isolated products characterized by ^{1}H NMR, ^{13}C NMR, and HRMS.



Scheme 4. Organocuprates addition to acetate **2b**.

by spectroscopic methods such as infrared (IR), ^{1}H NMR, ^{13}C NMR, and HRMS (Scheme 3, Table 1).

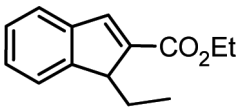
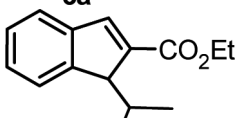
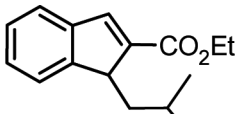
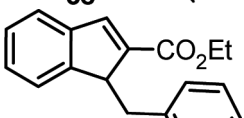
In this context, several years ago it was demonstrated that the application of various Morita–Baylis–Hillman acetates,[29–32] homologous to the allyl acetates **2**, served efficiently as useful substrates in some organic transformation protocols[31,33] and as an outstanding intermediates for allylic amination,[34–36] organo-catalytic allylic alkylation[30,31,33,37–41] and nucleophilic displacement.[32,42] On the basis of these applications, it occurred to us that it would be interesting to examine the electrophilic reactivity of the unprecedented 1-acetoxy-1*H*-indene-2-carboxylates **2a–e** toward organocuprates reagents, as such study will provide the desired indenes **3**. Indeed, we found that the conjugate addition of dialkyl organocuprates reagents, generated in situ at low temperature from Grignard reagents in the presence of a catalytic amount of $LiCuBr_2$, to the allylic acetate **2b** led to the corresponding ethyl 1-alkyl-1*H*-indenes-2-carboxylate **3a–d** in moderate to good yields through an usual displacement addition–elimination or nucleophilic S_N2'. The results are summarized in Scheme 4 and Table 2.

To the best of our knowledge, this is the first report in the synthesis of various functionalized indenes derivatives **3** from available indenol-based molecular models **1**. Nowadays the procedures for preparation of indene are widely developed with the use of expensive catalysts based on transition metals, palladium, platinum, ruthenium, and niobium, and hence the originality and the simplicity of our protocol in the synthesis of substituted and functionalized indenes **3**.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX 300 spectrometer working at 300 and 75 MHz respectively for the proton and ^{13}C with $CDCl_3$

Table 2. Synthesis of ethyl 1-alkyl-1*H*-indenes-2-carboxylate **3a–d**

Entry	RMgX (equiv)	Time (min)	Product **3**	Yields (%)[a]
1	EtMgBr (2.0)	10	 **3a**	81
2	^{i}PrMgBr (2.5)	12	 **3b**	82
3	^{i}BuMgBr (2.2)	15	 **3c**	72
4	$PhCH_2MgBr$ (2.0)	10	 **3d**	75

[a]Yields refer to the pure isolated products characterized by ^{1}H and ^{13}C NMR.

as solvent and Tetramethylsilane (TMS) as the internal standard. The chemical shifts (δ) and coupling constants (*J*) are, respectively, expressed in parts per million (ppm) and hertz (Hz). All NMR spectra were acquired at room temperature. Assignments of proton (^{1}H NMR) and carbon (^{13}C NMR) signals were secured by distortionless enhancement by polarization transfer (DEPT) 135, nuclear Overhauser effect spectroscopy (NOESY), heteronuclear multiple quantum correlation (HMQC), and heteronuclear multiple bond correlation (HMBC) experiments. Multiplicity of peaks is indicated by the following: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were recorded on an Equinox 55 spectrophotometer. HRMS analyses were performed with a Maldi-TOF-TOF technique on a Bruker Autoflex III Smartbeam. All reactions were monitored by TLC, performed on Merck aluminium-backed plates precoated with silica (0.2 mm, $60\,F_{254}$), which were visualized either by quenching of ultraviolet fluorescence ($\lambda max = 254$ nm) or by charring with $KMnO_4$ TLC dip. Flash chromatography (FC) was performed on silica gel (Merck Kieselgel $60\,F_{254}$, 230–400 mesh).

General Procedure for the Synthesis of 1-Acetoxy-1*H*-indene-2-carboxylic Acid Alkyl Ester 2a–e

A drop of concentrated sulfuric acid was added to a mixture of alcohol **1** (5 mmol) and acetic anhydride (25 mmol) in 40 mL of anhydrous ether cooled at 0 °C under stirring in a nitrogen atmosphere. After completion of the reaction, the mixture was hydrolyzed with ice water and extracted with ether (3×20 mL). The

organic layers were washed successively with sodium hydroxide solution (1.5 M) and brine until neutral pH then dried over $MgSO_4$ and concentrated in vacuo. After evaporating of the solvent, the residue was purified by silica-gel column chromatography (AcOEt/hexane, 7:3).

The spectral (^1H and ^{13}C NMR and HRMS) data of the unknown compounds **2a–e** are given.

Selected Data: 1-Acetoxy-1*H*-indene-2-carboxylic Acid Methyl Ester 2a

Yield: 75% as a white solid; mp 66–68 °C. IR (ATR): 1711, 1230 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 7.67 (s, 1H); 7.49–7.32 (m, 4H); 6.65 (s, 1H); 3.82 (s, 3H); 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 170.9; 163.6; 144.0; 143.6; 140.1; 136.2; 129.3, 129.1, 125.0, 123.9; 74.5; 51.7; 21.0. HRMS calculated for $C_{13}H_{12}O_4Na$ $[M+Na]^+$ 255.06278; found 255.06244.

Organocuprate Addition to Acetate 2b: Typical Procedure

A solution of alkylmagnesium halide RMgX (2–2.5 equiv.) was added dropwise over a period of 15 min to a mixture of ethyl 1-acetoxy-1*H*-indene-2-carboxylate **2b** (2 mmol) and a 1 M solution of $LiCuBr_2$ (0.15 mL) diluted in dry THF (10 mL) at − 60 °C under nitrogen. After a few minutes, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and then extracted with ether (3 × 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane, 1:9) to afford ethyl 1-alkyl-1*H*-indene-2-carboxylates **3a–d**.

Selected Data: 1-Ethyl-1*H*-indene-2-carboxylic Acid Ethyl Ester 3a

Yield: 81% as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): 7.69 (s, 1H); 7.48–7.29 (m, 4H); 4.30 (q, 2H, J = 6.0 Hz); 3.83 (t, 1H, J = 6.5 Hz); 2.18 (quintuplet, 2H, J = 6.5 Hz); 1.36 (t, 3H, J = 6.0 Hz); 0.55 (t, 3H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 164.8; 149.3; 142.0; 141.3; 140.5; 127.5; 126.9; 123.4; 123.3; 60.2; 50.2; 23.0; 14.4; 8.6. HRMS calculated for $C_{14}H_{17}O_2$ $[M+H]^+$ 217.12175; found 217.12231.

CONCLUSION

We reported in this paper a novel method to access to recent substituted indene esters using simple operational resources and inexpensive products. In addition, the synthesis protocol reported here is likely to provide access to several varieties of indene-based molecular models which can be used in the development of bioactive compounds, ligands precursors for metallocene catalyst systems, and some functional materials.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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