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Synthesis of coumarin derivative using polymer supported reagents

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ABSTRACT

Recently, there has been a surge in use of polymer-supported reagents and catalysts become common tools for organic synthesis in what is known as polymer-assisted synthesis since they can simplify product isolation and purification. In this context, coumarin derivative **3** was prepared in good yield and high purity, starting from 3-methoxy salicylaldehyde, using reagents supported on a macroporous ion exchange resin. For this purpose, iminocoumarin and unsaturated nitrile were used as starting materials. The synthesized compounds were characterized by IR, NMR and mass spectrometry.

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1. Introduction

Solution-phase synthesis using solid-phase reagents or scavengers has been termed polymer-assisted solution phase synthesis, and the developments in this field have been subject of several reviews [1]. The interest in this field has caused a recent explosion in the number of scientific papers describing the development of novel support bound reagents, catalysts and methods for purification. Supported reagents are reactive species, which are associated with a support material. The most important advantage in using a polymer-supported reagent in an organic reaction is the simplification of reaction workup, i.e. product separation and isolation. In the case of an insoluble polymeric reagent, filtration and repeated washing with suitable solvents can be generally used at the end of the reaction to isolate the product and therefore the need for complex chromatographic techniques can be avoided [2]. Monitoring the progress of the reactions is easy by applying TLC, NMR or LC/MS techniques. The use of an excess of reagent is also allowed without the need for additional purification steps [3]. Regeneration and reuse of the recovered polymer supported reagents are possible, thus providing an environmentally benign system [4]. On the other hand, the synthesis, characterization, and properties of 2-imino-coumarin derivatives have been studied intensively. This considerable attention of investigators to these products is connected on the one hand to their high reactivity toward both electrophiles and nucleophiles and on the other hand to their many applications in agricultural and pharmacological industries. For example, some 3-hetaryl coumarins and imino-coumarins have been proposed as anticancer [5], anti-asthmatic [6], antibacterial [7], and antiallergic [8-12] agents. They exhibit strong fluorescence in the UV-VIS region that makes them suitable to use as colorants, dye laser media and nonlinear optical chromophore. Taking these facts into consideration, we were interested in developing an efficient synthetic route to iminocoumarins (**1**) and activated nitrile (**2**) by the extension of our preceding strategy [13] (Scheme 1). Herein, we report firstly a successful utilization of 3-methoxy salicylaldehyde as a convenient starting material for a synthesis of novel iminocoumarin derivative (**1**) and unsaturated nitrile (**2**) then the hydrolysis of the obtained compounds **1** and **2** afforded the coumarin derivative **3**.

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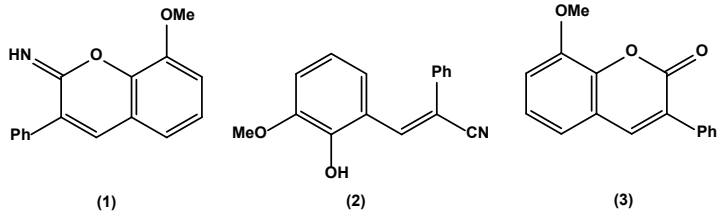
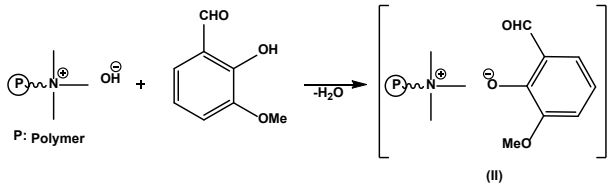
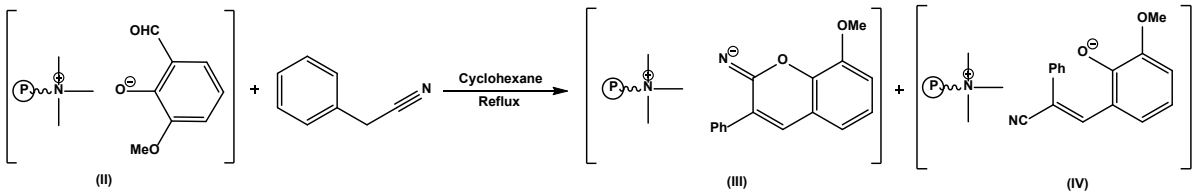


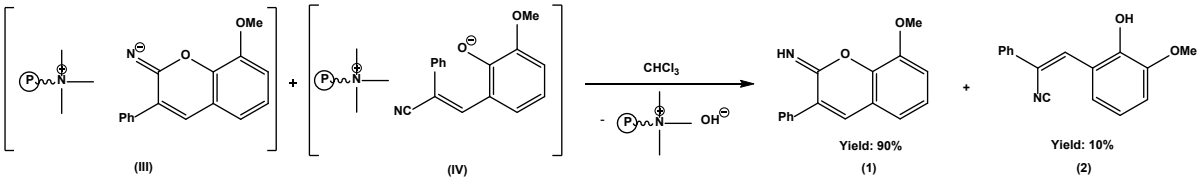
Scheme 1. Structures of iminocoumarins (**1**), unsaturated nitrile (**2**) and hydrolysis product (**3**).



1st step - Preparation of polymer supported phenate anions (II)



2nd step - Reaction of phenylacetonitrile with polymer supported reagents (II).



3rd Step: Deablock of iminocoumarin (**1**) and unsaturated nitrile (**2**) from the resin.

Scheme 2. Selective synthesis of iminocoumarin (**1**) and unsaturated nitrile (**2**) from the resin using 3-methoxy salicylaldehyde and phenylacetonitrile as starting materials.

2. Experimental

2.1. Instrumentation

Chemicals and solvents were purchased from Sigma-Aldrich. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 MHz for (^{1}H) and 50 MHz for (^{13}C), respectively, in $CDCl_3$ with TMS as an internal reference. The melting points of the compounds were determined using Stuart automatic melting point apparatus (SMP-40). Mass spectra were measured on a DI analysis Shimadzu Qp-2010 plus spectrometer; IR spectra were recorded with a Perkin Elmer Spectrum 100 Gladi ATR FT/IR spectrophotometer.

2.2. Synthesis

2.2.1. General procedure for the selective synthesis of iminocoumarin (1) and unsaturated nitrile (2)

Under nitrogen atmosphere, a mixture of the 3-methoxy salicylaldehyde (0.02 mol), Amberlite IRA 900 resin (0.02 mol) and cyclohexane (25 mL) was refluxed with the use of a Dean-Stark water separator. Acid-base reaction progress between Amberlite IRA 900 resin and aldehyde. It was monitored by GC technique. After completion of this reaction, the phenyl-acetonitrile (0.02 mol) was added and the mechanically stirred mixture was refluxed during 8 hours. After that, the reaction mixture was separated from the solid catalyst. Treatment of the resin beads by elution with chloroform, allows the recuperation of 90% from the synthesized iminocoumarin (**1**) and unsaturated nitrile (**2**). The organic phase was then evaporated under reduced pressure, leading to the recuperation of the resting iminocoumarin (**1**) and unsaturated nitrile (**2**) (10%). Finally, the obtained iminocoumarin (**1**) and unsaturated nitrile (**2**) were purified by crystallization with hexane. The purity of the synthesized compounds was examined by spectroscopic investigations.

8-Methoxy-3-phenyl-2H-chromen-2-imine (**1**): FT-IR (KBr, ν, cm^{-1}): 3330-3300 (NH), 1600 (C=C), 1640 (C=N). ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 6.91-7.97 (m, 8H, Ar-H + H5,6,7), 7.16 (s, 1H, H4), 3.94 (s, 3H, OCH_3), 3.25 (s, 1H, NH). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 112.4 (1C, C7), 119.4 (1C, C5), 123.3 (1C, C6), 133.5 (1C, C4), 128.0-129.0 (5C, Ci (3-Ph)), 56.3 (3C, OCH_3), 120.6, 131.0, 136.3, 142.6, 146.5 (Cq). MS (EI, *m/z* (%)): 251 (M+, 100).

3-(2-Hydroxy-3-methoxyphenyl)-2-phenylacrylonitrile (**2**): FT-IR (KBr, ν, cm^{-1}): 3530 (OH), 2215(CN), 1600 (C=C). ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 7.98 (s, 1H, H4), 6.91-7.97 (m, 8H, Ar-H + H5,6,7), 3.90 (s, 3H, OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 112.9 (1C, C7), 119.9 (1C, C6), 126.1 (1C, C5), 136.4 (1C, C4), 128.0-129.0 (5C, Ci (3-Ph)), 56.3 (3C, OCH_3), 113.5, 116.3, 120.7, 134.8, 145.2, 146.6 (Cq).

2.2.2. Synthesis of 8-methoxy-3-phenyl-2H-chromen-2-one (3)

The acid hydrolysis of the mixture of compound **1** and **2** in ethanol leads to the corresponding coumarin derivative (**3**).

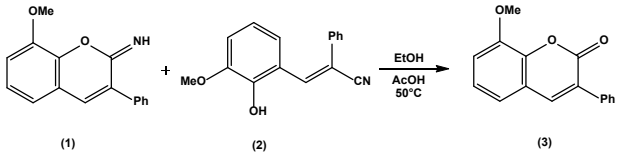
8-Methoxy-3-phenyl-2H-chromen-2-one (**3**): Color: Yellow. Yield: 95%. FT-IR (KBr, ν, cm^{-1}): 1727 (C=O), 1610 (C=C). ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.78 (s, 1H, H4), 7.73-7.38 (m, 5H, Ar-H), 7.19 (t, 1H, H6), 7.11 (dd, 1H, H5), 7.09 (dd, 1H, H7), 3.97 (s, 3H, OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 113.3 (1C, C7), 119.4 (1C, C5), 124.4 (1C, C6), 128.5-128.9 (5C, Ci (3-Ph)), 140.0 (1C, C4), 56.3 (3C, OCH3), 120.3, 128.57, 134.7, 143.5, 147.0, 160.0 (Cq).

3. Results and discussion

The synthetic procedure was accomplished in three-steps as given in Scheme 2. *Step 1*, Preparation of polymer supported phenate anions (II): Treatment of 3-methoxy salicylaldehyde with Amberlite IRA 900 (under its OH form) in cyclohexane solvent by the use of a Dean-Stark water separator, afforded the polymer supported phenate anions. *Step 2*, Reaction of phenylacetonitrile with polymer supported reagents (II): Phenylacetonitrile was combined with phenate resin beads, under reflux conditions, leading to the polymer supported anions (III) and (IV). *Step 3*, Deblock of the iminocoumarin (**1**) from the resin: Treatment of resin beads by elution with chloroform, afforded the iminocoumarins (**1**) and unsaturated nitrile (**2**).

Standard spectroscopic data of each compound are consistent with the proposed structures. The FT-IR spectrum of compound **1** showed absorption bands in 3330-3300 cm^{-1} (NH) and 1640 cm^{-1} (-C=N str.). The mass spectra of compounds **1** and **2** confirmed the proposed structure by the presence of molecular ion peaks [M] at *m/z* 251. The use of Amberlite IRA 900 resin beads as a solid support offers a practical alternative to the classical Knoevenagel methods. Using our procedure, the iminocoumarin (**1**) is generated *in situ* with no presence of free water and their hydrolyze does not take place. The key feature of this strategy is the use of strong anion exchange resin as a polymeric solid support [14,15].

The acid hydrolysis of the mixture of compound **1** and **2** in ethanol leads to the corresponding coumarin derivative (**3**) according to Scheme 3. The characterization of compound **3** was confirmed by different spectroscopic methods, ^1H NMR: the proton H_4 appears around δ 7.78 ppm; FT-IR: the carbonyl group absorbs was observed at 1727 cm^{-1}.



Scheme 3. The acid hydrolysis of the reaction mixture of compound **1** and **2** in ethanol.

4. Conclusion

In summary, we have used a supported polymer that can serve as a foundation for the preparation of iminocoumarin (**1**) and unsaturated nitrile (**2**). The acid hydrolysis of compounds **1** and **2** afforded the correspondent coumarin derivative (**3**) with high purity. The method developed in this work is particularly interesting for the simplicity of providing this iminocoumarin compounds in good yield.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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