Soluble Polymer-Supported Synthesis of 4-Methyl Coumarin on Modified Poly(ethylene glycol)s[1]

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Abstract: A simple liquid phase synthetic method for the preparation of 4-methyl coumarin on modified poly(ethylene glycol)s by using the von Pechmann reaction is described.

Key words: von Pechmann condensation, multicomponent reaction, liquid phase synthesis, heterocycles, coumarins

In recent years the synthesis of small organic molecules on polymeric supports has become a significant field of interest in particular its application in the field of combinatorial chemistry.[2,3]

Much attention is now focused on liquid-phase synthesis because it combines the advantages of the classical homogeneous solution methodology (high reactivity and simple analytical procedures) with those of solid-phase synthesis (easy isolation and purification of the final products and high stability of the system polymer-supported molecule).[4–6]

In particular, among the soluble supports, poly(ethylene glycol)s (PEG) are the most interesting polymers because they can be functionalized with different spacers or reactive groups and are also commercially available, inexpensive, non toxic, highly resistant to drastic physical and chemical conditions, and are soluble in a wide variety of solvents.[6]

Due to these features, PEG chemistry has shown broad-based application over the last decade, which may be in large part attributed to the use of PEG-conjugates.

In fact, polymer conjugation is a field of increasing interest in pharmaceutical chemistry for delivering drugs with simple structures as well as more complex ones such as oligonucleotides or enzymes.[7]

Encouraged by these very interesting results and on the basis of some our previous experiences in PEG-supported synthesis[8] and in the characterization of coumarin derivatives,[9] we report herein the synthesis of the 4-methyl coumarin prepared, for the first time, by using the soluble support approach applied to the von Pechmann reaction.[10]

Coumarins are a well known class of heterocycles, that are very attractive due to their versatility in a large number of applications and are mainly investigated due to their important biological (anti-coagulant, anti-HIV, anti-hyperproliferative)[11] and photophysical properties (fluorescent tags).[12–14]

To date, many routes to coumarin derivatives have been studied, including the Perkin,[15] Knoevenagel,[16,17] Reformatsky,[18] and Wittig[19–21] reactions as well as innovative techniques such as microwave irradiation.[22]

Nevertheless, the von Pechmann reaction still remains the most widely applied method to synthesize coumarins and involves the condensation of phenolic substrates with β-keto esters in the presence of condensing agents such as protic or Lewis acids.[23,24]

In Schemes 1 and 2, we report the compounds synthesized in our study and the related synthetic routes. The polymers of choice were the mono methyl ether of PEG with M_w = 5000 and the dihydroxy PEG with M_w = 4600, used to obtain compounds **9**–**15** and **10**–**16**, respectively. The starting materials are the mesylates **3** and **4** which proved to be very good activated intermediates.[25]

The reaction involves 12 M sulfuric acid as acidic condensing agent (see typical procedure); if the reaction is carried out using a Lewis acid such as indium(III) chloride (for reaction conditions see reference[23]), the reaction does not occur. In fact, due to the high complexing ability of PEGs, indium(III) chloride is not free to act as catalyst.

In Scheme 1, we report in detail the synthesis of compounds **9** and **10**. The hydroxy derivative of choice is resorcinol; in fact, it is well known that among all mono-, di-, and tri-hydroxy phenols, resorcinol is the most reactive and condenses rapidly with many β-ketoesters.[26]

The synthetic procedure starts by anchoring the mono allylated resorcinol **2** to mesylates **3** or **4,** to give the intermediates **5** and **6** which were promptly deprotected using palladium diacetate and triphenylphosphine in absolute ethanol.[27] The phenolic substrates **7** and **8** so obtained were used to carry out the von Pechmann reaction with ethyl acetoacetate in 12 M sulfuric acid. Compounds **9** and **10** were obtained as pure products following classical precipitation–filtration technique typical for liquid-phase synthesis.[6,28]

Scheme 2 describes the synthesis of **15** and **16** from intermediates **3** and **4**, which were transformed in three steps[25] into mesylates **11** and **12** which gave rise to derivatives **15** and **16**, in a similar way as for compounds **9** and **10**.

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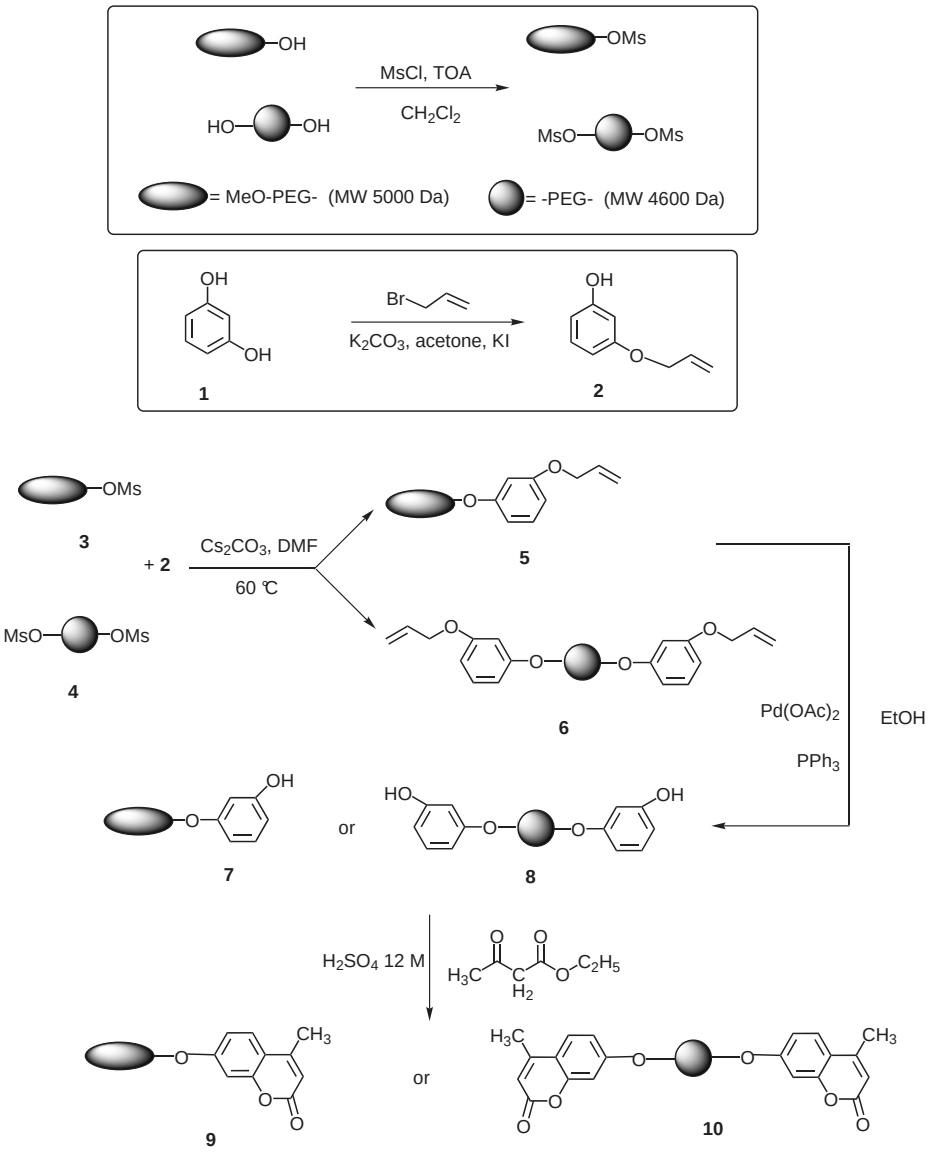


Scheme 1

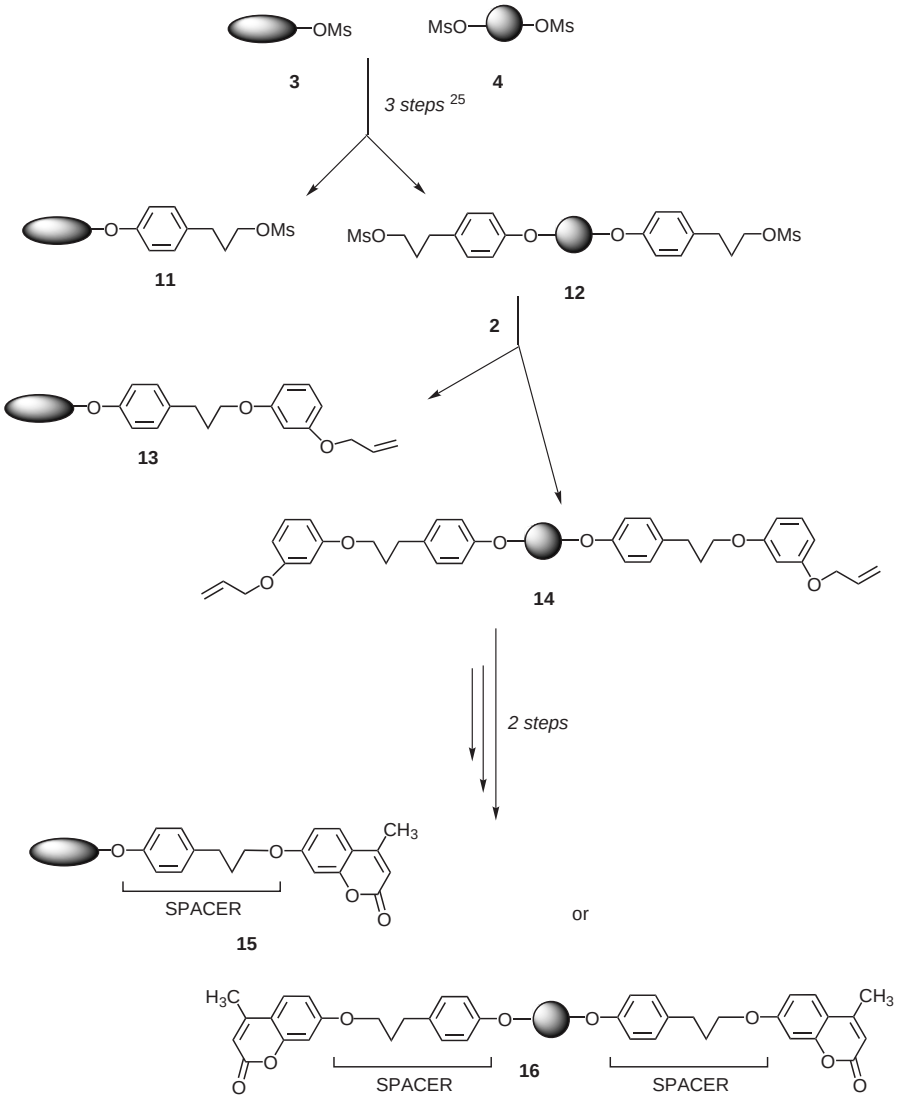
The overall yield from the commercially available unfunctionalized PEGs was ≥65% for **9** and **10** (4 steps), while yields ≥75% were observed for **15** and **16** (7 steps). The presence of the spacer, in the synthesis of **15** and **16**, which separates the reactive functionalities from the PEG core, could result in the higher yields.[8c]

Analysis of the ^{1}H NMR spectra of the obtained compounds showed that the von Pechmann reaction gave rise only to the linear coumarinic isomer, as expected. In fact, under the general von Pechmann reaction conditions, using sulfuric acid as condensing agent, the formation of the 7-hydroxy derivative is always preferred to the 5-hydroxy isomer.[26] In the case of our synthetic approach, the 7-PEG-supported derivative is the only product, probably also as a result of steric hindrance related to the polymer structure.

Together with the ^{1}H NMR investigations, a series of MALDI-MS analysis[29] of the PEG-conjugate derivatives **9**, **10**, **15**, and **16** have been performed. The MALDI spectrum for compound **16**, is shown in Figure 1 which consists of a wide distribution of peaks centred at about *m*/*z* 4800 and extending from *m*/*z* 4000 up to *m*/*z* 6000. These data clearly reveal the absence of degradation of the polymeric support and show that it is resistant to the drastic synthetic conditions. Indeed, the MALDI-MS methodology is an important tool for a qualitative determination of possible structural modifications of the polymers.

In conclusion, we succeeded in developing an innovative method to synthesize the coumarin nucleus, with an improvement in the yields[30] through a very stable C–O bond connection to the soluble support which was resistant to the drastic operating conditions.

Moreover, PEG conjugation could almost certainly improve the pharmacokinetics and bio-distribution, due to the efficient synthesis, stability and high water solubility of the supported coumarin. Also the PEG-coumarin



Scheme 2

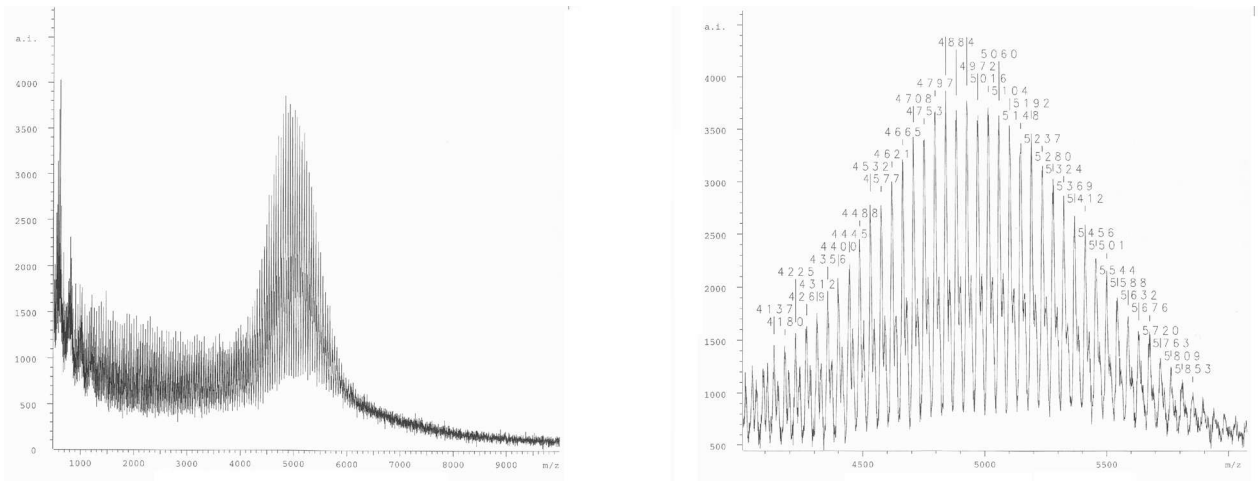


Figure 1 MALDI-MS spectrum of compound **16**

system could probably act as a prodrug, as has been seen for other active molecules (anti-tumor drugs, peptides, nucleic acids, and antibodies).[7]

All PEG samples (Aldrich and Fluka) were melted in vacuum at 90 °C for about 45 min before use, to remove any trace of moisture. After reaction, the crude mixture was concentrated in vacuum to eliminate the solvent. CH_2Cl_2 (6–7 mL) was added to completely dissolve the residue. Et_2O (50 mL per g of polymer) was added to the mixture, which was cooled to 0 °C. The suspension obtained was filtered through a sintered glass filter and the residue was washed repeatedly with Et_2O. All the samples were crystallized from *i*-PrOH. It is a well known fact, that PEGs, due to their helical structure, show a strong propensity to crystallize.[31] The yields of PEG-supported compounds were determined by weight. The indicated yields were for pure products after crystallization from *i*-PrOH. Their purity was confirmed by 300 MHz ^{1}H NMR spectroscopy[32] in $CDCl_3$ with pre-saturation of the methylene signals of the polymeric support at 3.60 ppm; a relaxation delay of 6 s and an acquisition time of 4 s were used to ensure complete relaxation and accuracy of integration. The integrals of the signals of the PEG CH_2OCH_3 fragment at δ = 3.30 and 3.36 ppm, were used as internal standards.

Matrix-assisted laser desorption/ionization (MALDI) measurements were performed on a Reflex time-of-flight instrument (Bruker-Franzen Analytik, Bremen, Germany), operating in positive ion mode. Ions, formed by a pulsed UV laser beam (nitrogen laser, λ = 337 nm) were accelerated to 25 kV. Pulsed ion extraction (PIE) was obtained applying a voltage of about 17 kV to the second grid for 200 ns. Samples were dissolved in water at a concentration of 1 mg/mL. The matrix was dihydroxybenzoic acid, saturated with aqueous 0.1% TFA; 5 µL samples of solution were mixed with the same volume of matrix solution. About 1 µL of the resulting solution was deposited on the stainless steel multiprobe and allowed to dry before being introduced into the mass spectrometer. Mass spectra were obtained by averaging 100 laser shots.

PEG-Supported von Pechmann Reaction; Typical Procedure (9)

To a solution of **7** (1 g, 0.196 mmol) in H_2SO_4 (12 M, 12 mL), cooled at 0 °C, was added dropwise ethyl acetoacetate (0.1 g, 0.097 mL, 0.784 mmol) and the mixture was stirred at r.t. for 48 h. The reaction mixture was poured into crushed ice (7 g) and stirred until the ice melted. Then the mixture was extracted with CH_2Cl_2 (5 ×), dried over Na_2SO_4, filtered, and then concentrated to a small volume.

The pure product **9** was obtained by precipitation with Et_2O filtration technique and then crystallized from *i*-PrOH.

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(32) Analytical details for compounds **9** and **15**. **9**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 3.36 (s, 3 H), 6.20 (s, 1 H), 6.80 (s, ^4J = 2.43 Hz, 1 H), 6.90 (d, ^3J = 8.50 Hz, ^4J = 2.43 Hz, 1 H), 7.60 (s, ^3J = 8.50 Hz, 1 H). **15**. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81 (m, 2 H), 2.40 (s, 3 H), 2.70 (t, 2 H), 3.36 (s, 3 H), 3.92 (t, 2 H), 6.18 (d, ^3J = 8.50 Hz, 2 H), 6.30 (s, 1 H), 6.81 (d, ^3J = 8.41, 1 H), 6.88 (s, 1 H), 6.98 (d, ^3J = 8.50, 2 H), 7.50 (d, ^3J = 8.41, 1 H).