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Synthesis of 2-azetidinones substituted coumarin derivatives

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Abstract: α-Naphthol was converted into 4-methyl-2*H*-benzo[*h*]chromen-2-one by reacting with ethyl acetoacetate in the presence of bismuth trichloride. The product was oxidized to 2-oxo-2*H*-benzo[*h*]chromene-4-carbaldehyde and then condensed with aromatic primary amines to give Schiff bases **3a**–**d**. These Schiff bases were then reacted with acid chlorides in the presence of a base in toluene to give 1,3,4-substituted 2-azetidinones.

Keywords: α-naphthol; selenium dioxide; aromatic amine; acid chloride; ethyl acetoacetate; tri-*n*-butylamine; 2-azetidinone.

INTRODUCTION

The β-lactam class of compounds has served an important and highly successful role in the pharmaceutical industry. Miracle drugs, such as penicillins and cephalosporins have significantly improved human health and life expectancy.

Developments in the field of β-lactams[1–4] during the last decades indicate that the only essential feature for antibacterial activity in these compounds is the presence of the β-lactam (2-azetidinone) ring. It was reported that the presence of an aliphatic substituent on the nitrogen and a carbonyl group on the imine carbon does not give any β-lactam *via* the di-anion–imine cycloaddition reaction.[5] However, van der Veen reported the formation of *cis*-β-lactams *via* [2+2] cycloaddition reaction involving an *in situ* prepared ketene and an imine derived from phenyl glyoxal and 2-phenylethylamine.[6] Azetidinone derivatives are also recognized as transcatheter arterial chemoembolization (TACE) inhibitors[7] and agents with new biological activities, such as anticancer,[8] anticoccidial,[9] cardiovascular,[10] antiviral,[11] mutagenic,[12] anticonvulsant and anti-inflammatory agents.[13,14]

A number of publications and patents have appeared in recent years discussing the synthesis of different types of coumarin derivatives and their antibacte-

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rial,[15] antifungal[16] and other biological[17] properties. The coumarin skeleton is also present in novobiocin[18] and other recently discovered antibiotics, such as coumermycin[19] and chartreusin.[20] Coumarins substituted with different heterocycles at the position 4 have been shown to possess promising antibacterial activity.[21] Bearing this in mind, it was decided to synthesize 2-azetidinones that have a coumarin moiety substituent at position 4.

RESULTS AND DISCUSSION

The 4-methyl coumarin derivative was obtained in excellent yield (92 %)[22] by reacting α-naphthol with ethyl acetoacetate in the presence of bismuth trichloride (5 mol %). The IR spectrum of compound **1** showed a band at 1711 cm^{-1} for C=O stretching along with other bands. The ^{1}H-NMR spectrum of compound **1** in $CDCl_3$ showed a doublet at δ 2.56 ppm for methyl protons and a quartet at δ 6.41 ppm for C_3–H. It was then oxidized to the corresponding formyl derivative **2** with selenium dioxide. The IR spectrum of compound **2** in KBr showed peaks at 1727 and 1706 cm^{-1} for the two carbonyl groups and the ^{1}H-NMR spectrum of **2** showed the presence of signal at δ 10.23 ppm for the aldehydic proton. The formyl compound **2** was condensed with various aromatic amines to yield the Schiff bases **3a**–**d**.[23] The IR spectra of the compounds **3a**–**d** showed an absorption for only one carbonyl group and band for C=N at 1634 cm^{-1}. The ^{1}H-NMR spectra showed the absence of an aldehydic proton and presence of the –CH=N– proton at δ 8.8 ppm. These Schiff bases were then reacted with acid chlorides in the presence of base to give the 1,3,4-substituted 2-azetidinones **4a**–**l**. The IR spectra of compounds **4a**–**l** showed absorptions for two carbonyls. In the ^{1}H-NMR spectra there were two doublets for C_3–H and C_4–H. The envisaged reaction sequence is depicted in Scheme 1.

Structures of the compounds **4a**–**l** were established by their IR and ^{1}H-NMR spectra. Their *cis*/*trans* stereochemistry depends mainly on the substituent present on the ketene part, as usually the imine is presumed to exist in the more stable *E*-configuration. The results can be better explained through a zwitter ion intermediate formed by the attack of the nitrogen lone pair of the imine on the ketene, occurring through the less hindered side of the latter.[24,25] The origin of the diastereoselectivity and influence of reaction conditions on the diastereoselectivity in the Staudinger syntyhesis have been carefully investigated recently.[26] The results indicated that:

1) The diastereoselectivity is controlled by the competition between the direct ring-closure and the isomerization of the imine moiety in the zwitter ionic intermediates generated from imines and ketenes;

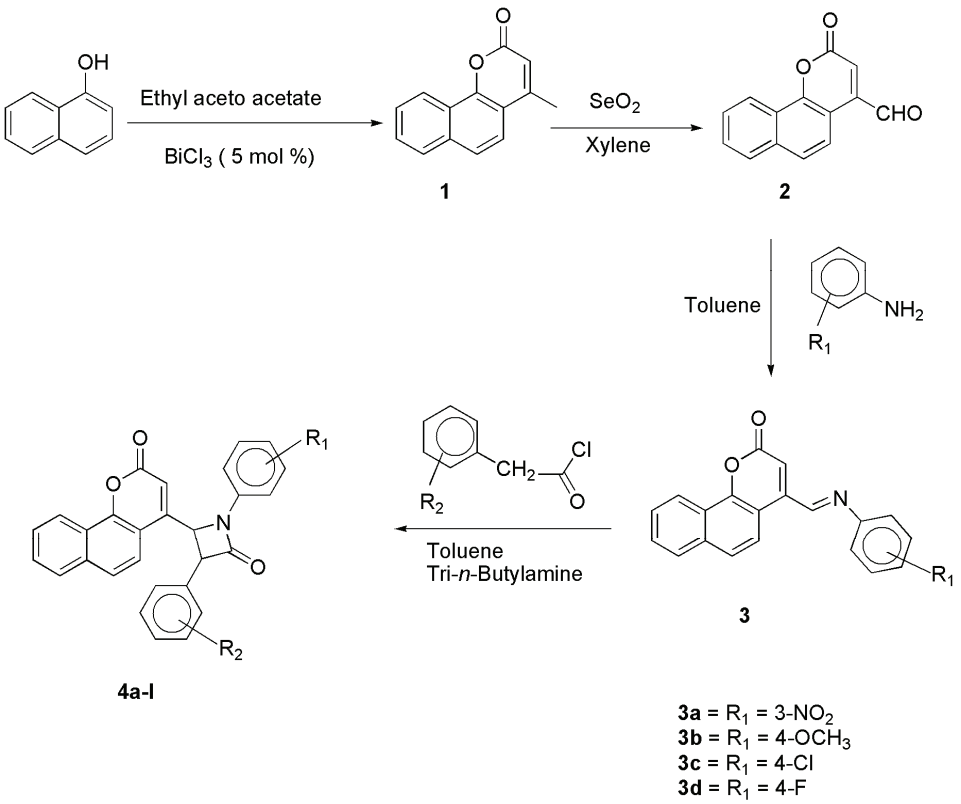
2) electron donating ketene substituents and electron withdrawing imine substituents accelerate the direct ring closure, leading to a preference for a *cis*-β-lactam formation, while electron withdrawing ketene substituents and electron do-

nating imine substituents slow the direct ring closure, leading to a preference for *trans*-β-lactam formation;

3) the electronic effect of the substituents on the isomerization is a minor factor in influencing the diastereoselectivity;

4) different ketene-generation pathways, solvent, additives usually existing in the reaction system, and photo- and microwave-irradiations do not affect the diastereoselectivity;

5) the reaction temperature really influences the diastereoselectivity for some reactions and can be used to tune the same. The stereoselectivity was determined by ^{1}H-NMR. The *cis* isomer shows a higher value of coupling constant than the *trans* isomer (Table I).[27]



Scheme 1. Synthesis route of 4-methylcoumarin derivative.

EXPERIMENTAL

All the compounds were identified by examination of their spectral data and physical properties. The reported yields refer to the isolated yields of the desired products. Melting points were determined on a Buchi-545 melting point apparatus and are uncorrected. The progress of the reaction was monitored by TLC. The IR spectra were recorded by Perkin

Elmer Spectrum-1 (FTIR) using the KBr disc technique, The ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ using a Bruker Avance 400 MHz spectrometer (chemical shifts, δ, are in ppm) with TMS as the internal standard. The mass spectra were recorded on a Thermo Finigan Ion Trap GCMS Polaris Q instrument. The dry reactions were performed under nitrogen with magnetic/mechanical stirring.

TABLE I. Stereochemistry of compounds **4a**–**l**

Compound	R_1	R_2	Isolated isomer
4a	4-F	H	*Trans*
4b	4-Cl	H	*Trans*
4c	4-OCH_3	H	*Cis*
4d	3-NO_2	H	*Trans*
4e	4-F	4-Cl	*Trans*
4f	4-Cl	4-Cl	*Trans*
4g	4-OCH_3	4-Cl	*Cis*
4h	3-NO_2	4-Cl	*Trans*
4i	4-F	4-OCH_3	*Cis*
4j	4-Cl	4-OCH_3	*Cis*
4k	4-OCH_3	4-OCH_3	*Cis*
4l	3-NO_2	4-OCH_3	*Trans*

*4-Methyl-2*H*-benzo[*h*]chromen-2-one (**1**)*

A mixture of α-naphthol (5 mmol) and ethyl acetoacetate (5 mmol) and $BiCl_3$ (5 mol %) was heated at 110 °C for 2 h. The completion of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and poured into 10 g of crushed ice. The crystalline product was collected by filtration under vacuum suction and washed with cold water. The pure product was obtained by recrystallization from hot ethanol.

*2-Oxo-2*H*-benzo[*h*]chromene-4-carbaldehyde (**2**)*

Compound **1** (0.10 mmol) was dissolved in xylene (50 ml) at 60–70 °C, and then SeO_2 (0.13 mmol) was added to the solution, which was refluxed for 6–7 h. The hot reaction mixture was filtered to remove the insoluble selenium. The filtrate gave fine crystalline product on cooling to 10 °C.

*General procedure for the synthesis of 4-[(phenylimino)methyl]benzo[*h*]chromen-2-ones (**3a**–**d**)*

An intimate mixture of the 4-formyl derivative compound (**2**) (10 mmol) and corresponding aromatic primary amine (11 mmol) was refluxed in toluene for 6–7 h with azeotropic removal of the water formed during the reaction. The reaction was monitored by TLC. After completion of the reaction, the reaction mass was cooled to 10 °C and the product was washed with cold toluene to obtain the solid products.

*General procedure for synthesis of 4-(2-oxo-2*H*-benzo[*h*]chromen-4-yl)-1,3-diphenylazetidin--2-ones (**4a**–**l**)*

An intimate mixture of the 4-imino coumarin derivatives (10 mmol) (**3a**–**d**), the required acid chloride (20 mmol) and tri-*n*-butylamine (30 mmol) in toluene was refluxed for 3–4 h. The reaction was monitored by TLC until the absence of 4-imino coumarins. Reaction mass was then cooled to room temperature and 40–50 ml 1:1 HCl:H_2O added. The organic layer that separated was washed with water followed by $NaHCO_3$ solution and finally with water.

After drying over anhydrous Na_2SO_4, the solvent was removed under reduced pressure. Compound was isolated using flash chromatography and thereafter crystallized using ethanol.

CONCLUSION

In conclusion, novel 4-(2-oxo-2*H*-benzo[*h*]chromen-4-yl)-1,3-diphenylazetidin-2-ones were synthesized under mild conditions starting from *α*-naphthol.

SUPPLEMENTARY MATERIAL

Analytic and spectral data of the synthesized compounds are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

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ИЗВОД

СИНТЕЗА 2-АЗЕТИДИНОН-СУПСТИТУИСАНИХ ДЕРИВАТА КУМАРИНА

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У реакцији *α*-нафтола и етил-ацетоацетата, у присуству бизмут-трихлорида, добијен је 4-метилбензо[*h*]хромен-2-он. Оксидацијом производа добијен је 2-оксо-2*H*-бензо[*h*]-хромен-4-карбалдехид који кондензацијом са ароматичним примарним аминима даје Шифове базе **3a**–**d**. Шифове базе у реакцији са хлоридима киселина, у присуству базе, у толуену као производ дају супституисане 2-азетидиноне.

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