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SYNTHESIS AND CHARACTERIZATION OF 3-ACETYLCOUMARIN DERIVATIVE AND AZO COUMARIN DYE

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Abstract: Highly efficient synthetic method for 3-acetylcoumarin has been developed using piperidine (20 mol%) at 78°C through an optimized Knoevenagel condensation reaction. This method resulted in the successful synthesis of 3-acetylcoumarin with an excellent yield of 85%. Additionally, we have synthesized a stable red-colored azocoumarin dye, (E)-4-((2-nitrophenyl)diazenyl)-2H-chromen-2-one, using coumarin.

Keywords – Coumarins, Knoevenagel condensation, Piperidine, Azo coumarin dye.

I. INTRODUCTION

Coumarins are very important heterocyclic compounds with a benzo-α-pyrone moiety. They are derived from natural and synthetic origin. They are very abundant in plants, especially in species like tonka bean (Dipteryx odorata Wild), and have been widely studied in pharmaceutical science.[1] Coumarins are widely found in plant families such as Rutaceae and Umbelliferae, as well as in essential oils like cinnamon bark oil and lavender oil. Coumarins have a very significant influence on plant physiology and biochemistry and participate in essential processes like photosynthesis, respiration, plant growth regulation, and defense mechanisms against infections.[2] However, coumarins and their derivatives show remarkable pharmacological properties, including antimicrobial[3], antidepressant[4], anti-inflammatory[5], antiasthmatic[6], antitumor[7], and antiviral activities[8]. Important coumarin derivatives like Osthole, Umbelliferone, Warfarin, Dicoumarol, and Scoparone have important applications, such as sunscreens, fluorescence indicators, and dye indicators.[10] Due to their biological significance different synthetic methods have been developed.[11-14] Synthesis of azocoumarin dye holds importance due to the occurrence of coumarin moieties in many natural compounds. These dyes find various applications in physical, chemical, and biological science, making them very important for different industries such as food, textiles, paper, and pharmaceuticals.

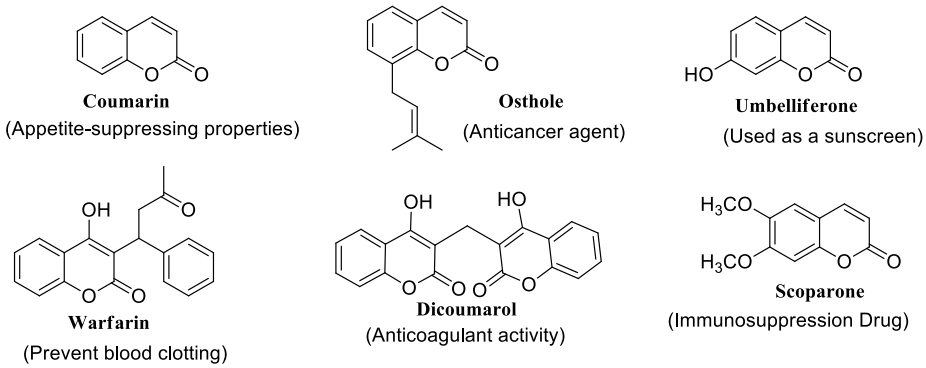


Figure 1: Bioactive compounds having coumarin motif.

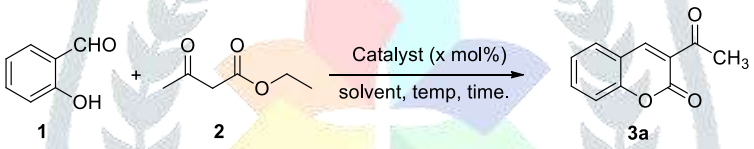
Herein we wish to report the optimized method for the synthesis of 3-acetylcoumarin from salicylaldehyde and ethyl acetoacetate using an optimized Knoevenagel condensation reaction and the synthesis of azocoumarin dye.

II. Results and discussions

1. Synthesis of coumarin *via* Knoevenagel condensation

In our preliminary studies we have screen different catalysts, solvents and varied reaction conditions to obtained desired product in optimum yields (Table 1.1, entry 1-9). In catalyst screening, we found that

Table 1.1 Optimization of reaction conditions for Knoevenagel condensation[a]



Sr. No.	Salicylaldehyde (in mmol)	Ethyl acetoacetate (in mmol)	Catalyst (x mol%)	Solvent	Temp. (ºC)	Time (h)	Yield[b] (%)
1	10	10	Piperidine (10)	Methanol	65	2.5	40
2	10	10	Pyrrolidine (10)	Methanol	65	2.5	15
3	10	20	Piperidine (10)	Ethanol	78	2	83
4	10	10	Pyrrolidine (10)	Ethanol	78	2.5	23
5	**10**	**10**	**Piperidine (20)**	**Ethanol**	**78**	**2**	**85**
6	10	10	Piperidine (10)	Ethanol	r.t.	18	N.R.[c]
7	20	10	Piperidine (10)	Ethanol	78	1.5	84
8	10	10	Piperidine (10)	Isopropanol	80	2.5	76
9	10	10	Pyrrolidine (10)	Isopropanol	80	2.5	20
10	10	10	No catalyst	Ethanol	78	6	N.R.[c]

[a]Reaction conditions: Salicyldehyde (10 mmol), ethyl acetoacetate (10-20 mmol) and catalyst (10-20 mol%) was added solvent under an open atmosphere at room temperature, the reaction mixture refluxed at a specified temperature and stirred for a specified time; the progress of the reaction was monitored by TLC. [b]Isolated yield after recrystallization. [c]N.R.- No Reaction.

piperidine (10 mol%) facilitate the desired transformation and furnish the product in good yield (Table 1.1,

entry 5). Ethanol was found to be the best solvent for this transformation. When we carried out reactions in other solvents such as methanol and isopropanol the desired product obtained in comparatively low yields (Table 1.1, entries 1-2, 8-9). When we carried out the reaction at room temperature, we did not observe any isolable desired product (Table 1.1, entry 6). While in the absence of catalyst, we did not observed any desired product formation (Table 1.1, entry 10). Preliminary studies indicate that the optimum reaction condition for this transformation is salicylaldehyde (10 mmol) and ethyl acetoacetate (10 mmol) undergoes Knoevenagel condensation in the presence of piperidine (10 mol%) at 78 ºC in ethanol to afford the desired product 3-acetylcoumarin **3a** in good yield (Table 1.1, entry 5).

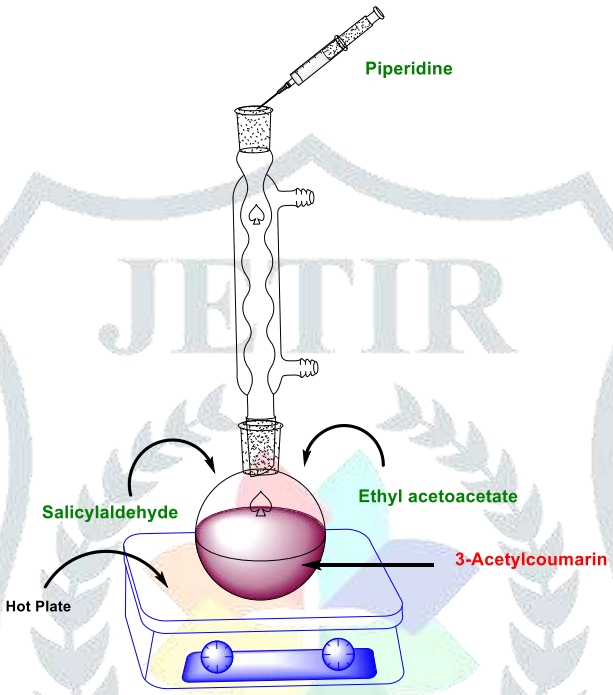
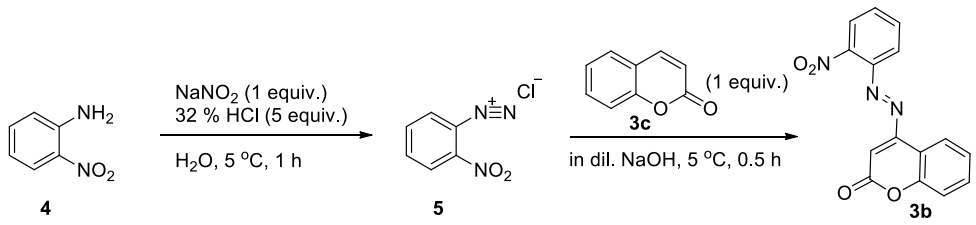


Figure 2: Synthesis of 3-acetylcoumarin

2. Synthesis of azo coumarin dye

Herein we wish to report the synthesis of azocoumarin dye. To synthesize azocoumarin dye, we have carried out diazotization of 2-nitroaniline **(4)** in the presence of sodium nitrite and hydrochloric acid at 0 ºC. This diazonium salt was utilized in the next step without further purification. This diazonium salt **5** was added to an alkaline solution of coumarin (**3c**) at 0 ºC to furnish the desired product red-colored azocoumarin dye (E)-4-((2-nitrophenyl)diazenyl)-2H-chromen-2-one **(3b)**.



Scheme 1.1 Synthesis of azocoumarin dye

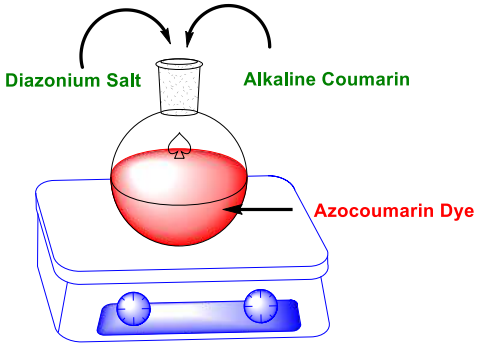


Figure 3: Synthesis of azocoumarin dye

III. Conclusions

In conclusion, we have successfully synthesized 3-acetylcoumarin *via* an optimized Knoevenagel condensation reaction. We have also successfully synthesized red-colored azocoumarin dye (E)-4-((2-nitrophenyl)diazenyl)-2H-chromen-2-one using coumarin which is stable under ordinary conditions.

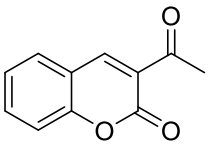
IV. Experimental Section

1. General

Unless otherwise noted, all reactions were carried out with distilled and dried solvents using oven-dried glassware. All reagents were purchased from commercial sources and used as received unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF254 pre-coated aluminum backed plates (2.5 mm) with detection by UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$. Chemical shifts in ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard or from the residual solvent peak as the internal standard and *J* values are given in Hz. ^{13}C NMR spectra are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by high-resolution mass spectrometry using HRMS ESI TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as neat and reported in cm^{-1}.

2. Procedure A for synthesis of coumarin *via* Knoevenagel condensation

In a round bottom flask, salicylaldehyde **1** (10 mmol) and ethyl acetoacetate **2** (10 mmol) was added in 25 mL ethanol. To this solution, piperidine (10 mol%) was added, and the whole reaction mixture was refluxed for 2 h. Then the reaction mixture allowed to cool at room temperature and the precipitate formed on cooling were filtered, washed with cold ethanol and dried. The solid product formed was purified by recrystallization from aqueous ethanol to give **3**-acetyl-coumarin **3a** as dark brown solid in 85% yield.



3-Acetyl-coumarin (3a):

Compound **3a** was synthesized following the procedure (A). The product was obtained as dark brown crystals (1.6 g, 85% yield): Melting point: 119-121 ºC.

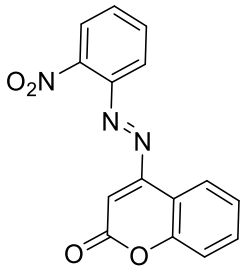
IR (neat) cm^{-1}: 3785, 3654, 3479, 3181, 3019, 2233, 1793, 1738, 1607, 1491, 1444, 1214, 1157, 855, 818, 651.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 7.67-7.62 (m, 2H), 7.37-7.31 (m, 2H), 2.72 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 159.4, 155.4, 147.6, 134.5, 130.4, 125.1, 124.6, 118.3, 116.8, 30.7.
HRMS (ESI TOF): Calculated for $C_{11}H_9O_3$ $(M + H)^+$: 189.0551, Found: 189.0555.

3. Procedure B for the synthesis of azo coumarin dye

Step –I: In a round bottom flask 2-nitroaniline **4** (0.138 g, 1 mmol) was added in 2.4 mL ice cold water. To this solution, 0.6 mL 32% hydrochloric acid (5 mmol) and 20% $NaNO_2$ (0.069 g, 1 mmol) was added in the above solution under stirring at 5 ºC. The reaction mixture was stirred at further for an hour. The above solution of diazonium salt **5** further utilized in the next step without purification.

Step II: In a round bottom flask, coumarin **3c** (1 mmol) was dissolved in sodium hydroxide solution (1 g NaOH in 10 mL water), and this solution was cooled to 5 ºC. The previously prepared diazonium salt **5** solution was added dropwise with stirring in an alkaline solution of coumarin **3c** in 30 minutes at 0 ºC. The above reaction mixture allowed to warm at room temperature and filtered. The residue was washed with cold water. The crude product was further purified with recrystallization in aqueous ethanol (ethanol: water, 1:10) to obtained azocoumarin dye **3b** in 70% yield.



(E)-4-((2-nitrophenyl)diazenyl)-2H-chromen-2-one (3b):

Compound **3b** was synthesized following the general procedure (B). The product was obtained as a red coloured dye (0.21 g, 70% yield).

IR (neat) cm^{-1}: 3742, 3601, 3429, 3385, 3318, 3162, 2950, 2819, 2719, 2223, 1909, 1614, 1542, 1394, 1097, 708, 612.

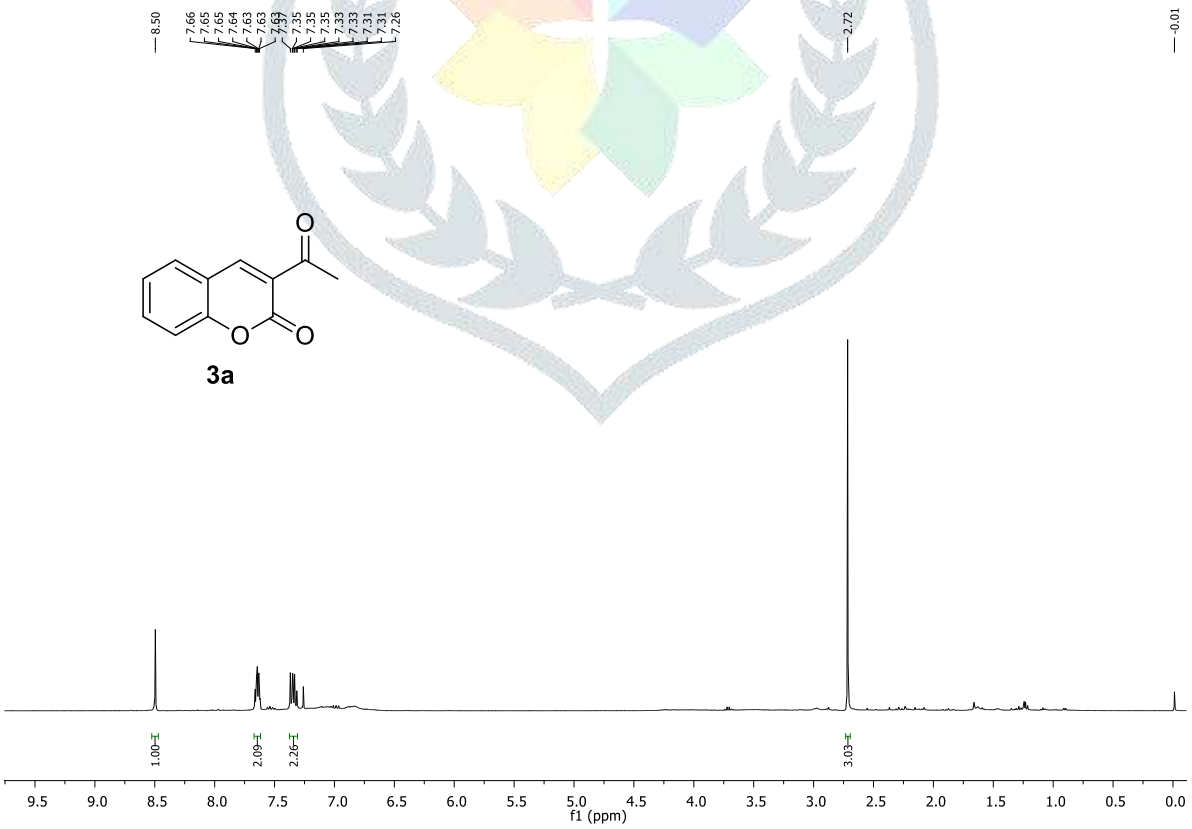


Figure 4.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3a**

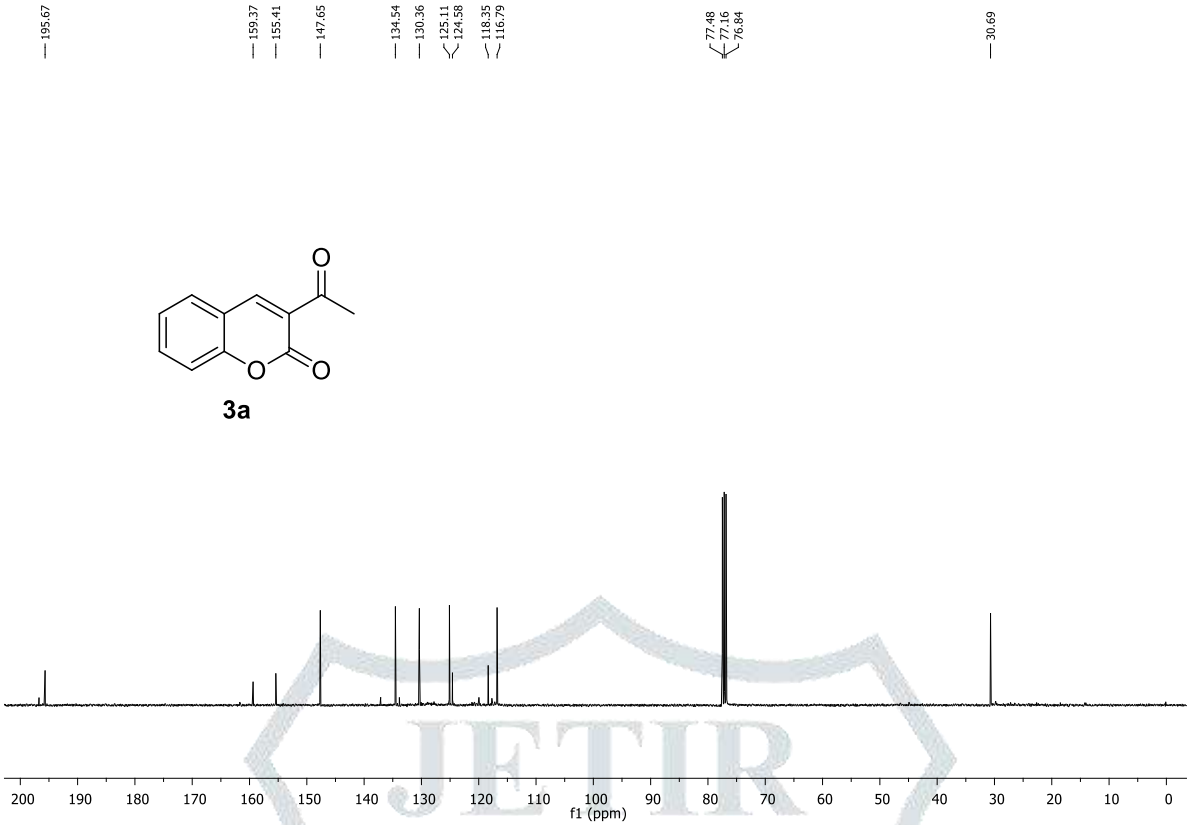


Figure 4.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3a**

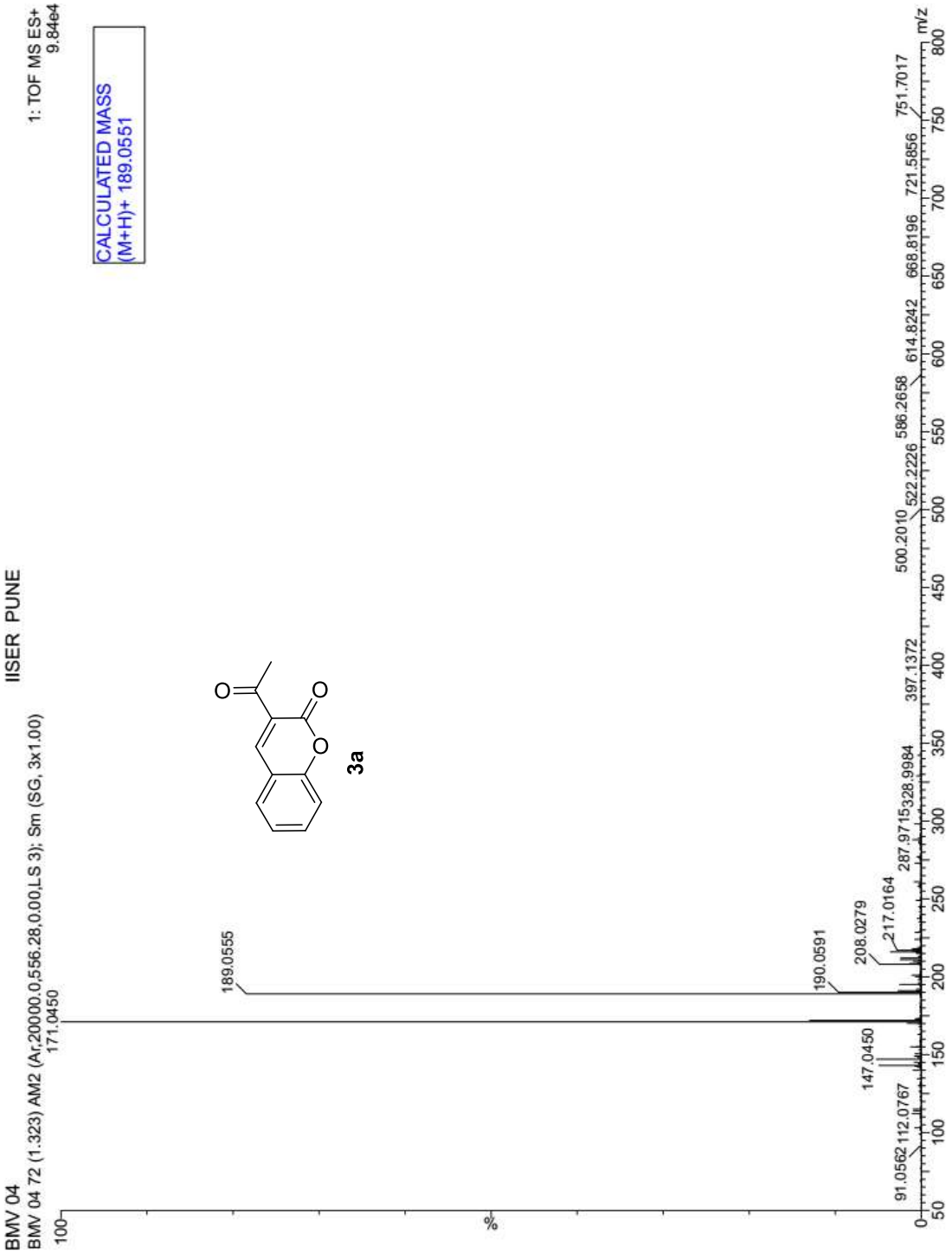


Figure 4.3: H.R.M.S. spectra of compound **3a**

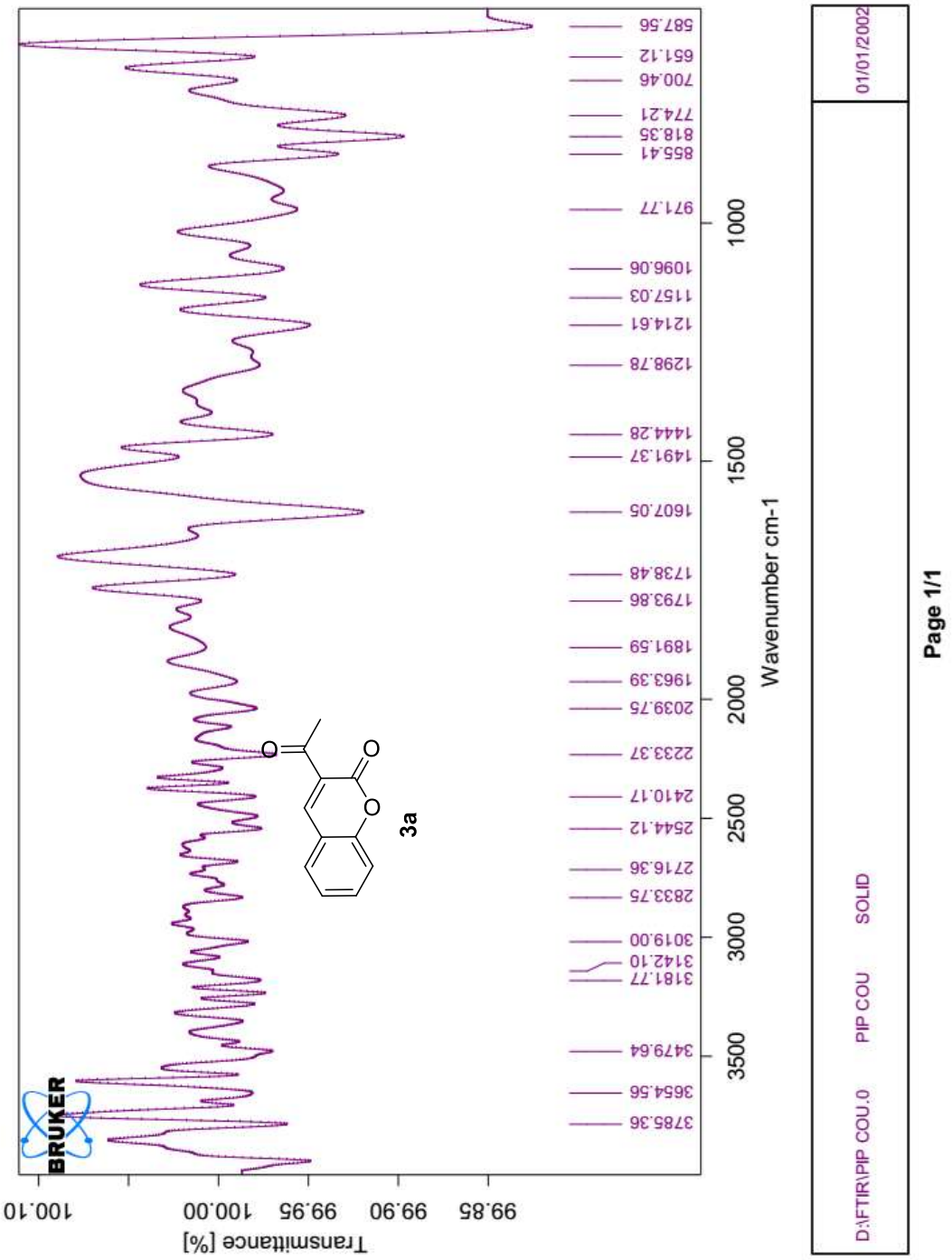


Figure 4.4: I.R. spectra of compound **3a**

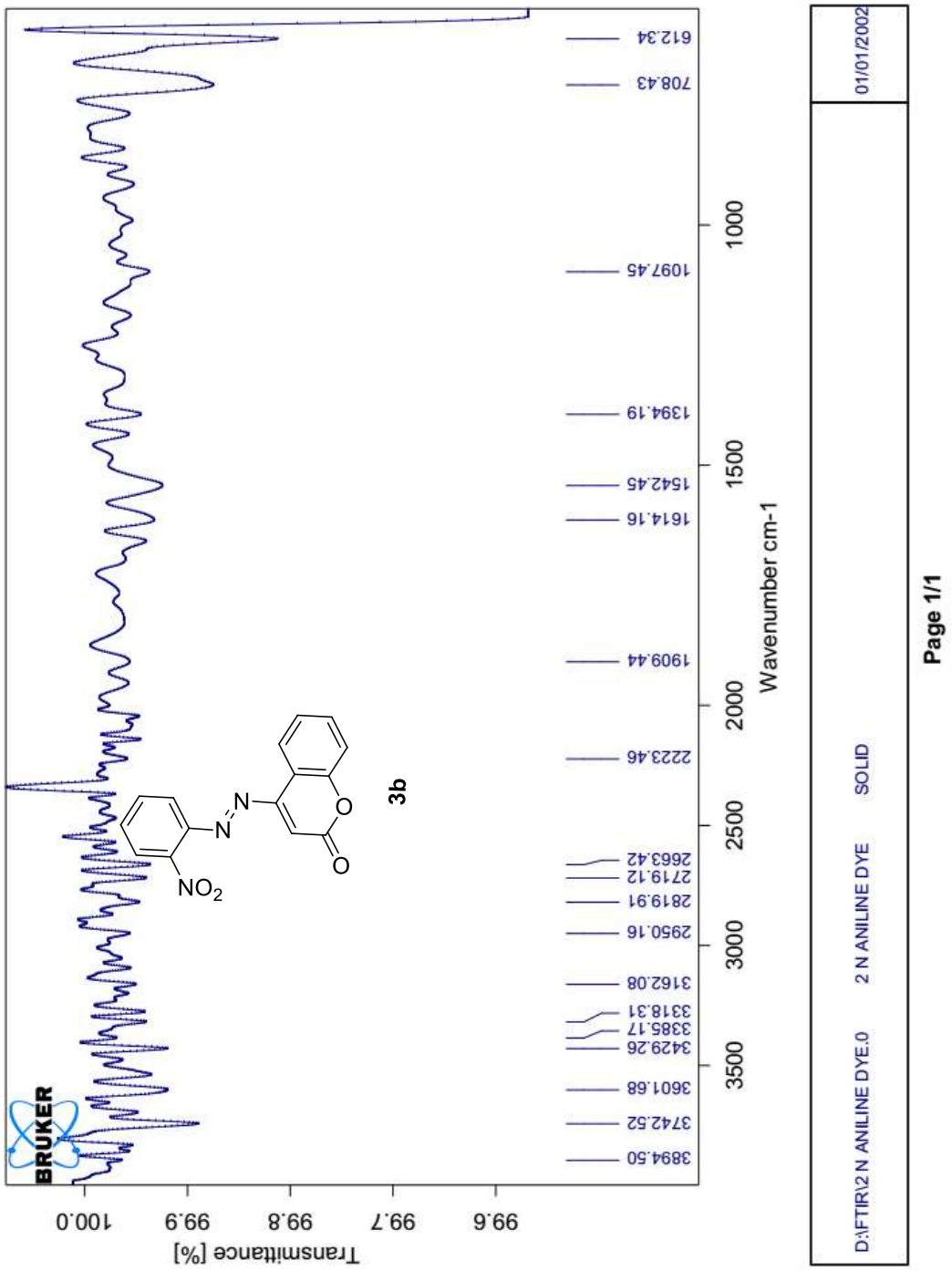


Figure 4.5: I.R. spectra of compound **3b**

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VI. Notes

The authors declare no competing financial interest.

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