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SYNTHESIS AND CHARACTERIZATION OF AZO DERIVATIVES OF COUMARIN-3-CARBOXYLIC ACID USING DEEP EUTECTIC SOLVENT

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ABSTRACT: Traditional solvents like most liquid organic solvents and inorganic solvents, many of the times results completion of chemical reactions, in a very long duration, several hours to days. In this study, ionic solvents are considered at the center which are also called as Deep Eutectic solvents (DES). Such an example of deep Eutectic mixture is Choline chloride and Urea used to reduce the time of condensation reaction. The azo derivatives of coumarin-3-carboxylic acid is prepared by Knoevenagel condensation of 5(substituted phenylazo) salicylaldehyde with meldrum's acid. The derivatives are characterized by using IR, HNMR and mass spectroscopy. The research articles show, mere, grinding of salicylaldehyde with meldrum's acid or using microwave results in Knoevenagel condensation but these methods become difficult to result in interested moiety when azo substituted derivatives are used. The reaction using ionic solvent results in a good yield with a very short duration of period to yield the condensation product. The best part of the use of DES can be regenerated and reused.

KEYWORDS: Coumarin, azo derivatives, eutectic solvent, choline chloride, Knoevenagel condensation, phenylazo.

INTRODUCTION:

Coumarin and its derivatives are the core of medicinal chemistry. Several derivatives of coumarin have wide variety of functionality whether it is obtained naturally or synthetically. Varied pharmacological properties of coumarins attracted researchers to synthesize various derivatives of coumarins and study its properties in various fields [i]. Coumarins and related compounds possessed wide variety of biological functionality and can be used for treatment of different kinds of cancer [ii-vii] and tumors [viii], also used as antibacterial, antituberculosis activity [ix], antifungal agent [x], antioxidant, antiviral, anti-inflammatory activities [xi]. Various derivatives of coumarin show different activities in perfumery, food and optical brighteners [xii] along with these pharmaceutical applications.

Mindboggling applications of coumarins and related compounds drag the attention to search for a novel molecule with coumarin moiety and study its behavioral properties. On the other hand, the researchers are also working on speeding up the reactions, increasing the product yield and greener synthesis. Most of the synthesis have severe conditions of the reactions,

deprived substituent acceptance and little products [xii]. The studies show the various methods employed which includes nano catalysis, metal catalysis [xiv], ionic liquids [xv], solid phase synthesis [xvii] have shown to increase in rate and yield of the reactions. Recently, the chemical reaction using Microwave activations created lots of interests as the reactions are not requiring drastic reaction conditions and also results in good yield and better rate of reactions in organic synthesis [xvi]. There are many ionic solvents which can be used for synthesis having a good yield, solubility and efficiency in the progress of reaction [xviii]. Ionic solvents offer several advantages over organic solvents which are expensive, hazardous, difficult to remove from the product in case of aprotic dipolar solvents with high boiling point and also causing chemical pollution [xix]. Various derivatives of coumarins were synthesized by reacting substituted salicylaldehyde and medrum's acid in choline chloride and urea as a deep eutectic solvent and have shown a wonderful result in respective to yield and rate [xix].

In continuation to this study and searching for a better solvent and catalyst, this research work includes deep eutectic solvent i.e., homogeneous mixture of choline chloride and urea, to synthesize the coumarin moiety from 5-(substituted phenylazo) salicylaldehyde resulting into 6-(substituted phenylazo) coumarin-3carboxylic acid by Knoevenagel condensation reaction. The ionic solvents have very good solubility and creates the medium for the reactants to undergo condensation yielding a desired product. For the reactants to undergo into a reacting condition, the most important criteria become solubility, when any of the reactant is insoluble in solvents like ethanol, methanol, acetone, water, chloroform etc., in such situation ionic solvents/deep eutectic solvents are very efficient.

EXPERIMENTAL:

Materials and methods: All the reagents and solvents which are used, were of AR grade and chemically pure. The chemicals and solvents were purchased from Spectrochem and Loba chemicals. The reagents and solvents were used without further purification. The melting points were measured using Thieles' apparatus showing a sharp melting of the crystals. The IR spectra was measured PerkinElmer Spectrum Version 10.5.2, HMNR were done using SA-AGILENT 400MHz in DMSO solvent and Mass spectra were measured using instrument NBHC-INS-EQP-10A. The completion of reaction was checked using ALUGRAM® SXtra Aluminum Sheet, SILGUR UV254 with visualization in UV light using 7:3 mixture of n-hexane/petroleum ether and ethyl acetate to run the spot.

Preparation of Deep Eutectic solvent (DES):

The ionic liquid is prepared by method as reported [xix]. The solid choline chloride and urea are taken 1:2 cc. Solids are heated together at 80^0C temperature with continuous stirring till a homogeneous solution is obtained. This homogeneous mixture is further used as a solvent medium as well as a catalyst to progress the reaction.

Method of preparation of Substituted phenylazo coumarin-3-carboxylic acid:

The synthesis reaction is carried out by adding substituted 5-phenylazo salicylaldehyde (0.005mol) (1) and meldrum's acid (0.005mol) (2) to hot DES at 80^0C (5 mole equivalent of homogeneous liquid). The temperature is maintained 140^0C for 1-2 hours. The completion of reaction is checked by using TLC. When the reaction is completed, the crystallization of the product was done in ice cold water. It is filtered. The crystals, obtained, washed with water several times and recrystallized in ethanol and ethyl acetate (1:1) to yield solids of *2-oxo-6-(substituted phenyldiazenyl)-2H-chromene-3-carboxylic acid* 3(a-e). The filtrate is used to regenerate the solids used for DES preparation and reused for further reactions [xix].

2-oxo-6-(phenyldiazenyl)-2H-chromene-3-carboxylic acid *(3a)*: Bright yellow crystalline solid**.** ^{1}H NMR (DMSO, 400MHz): δ 12.21 (s, 1H), 8.36 (s, 1H), 8.15 (dd, 1H), 7.53 (m, 5H),

7.10 (d, 2H). IR (Vmax/cm^{-1}) = 3197, 1735, 1698, 1648, 1596, 1572, 1459, 1429, 1394, 1275, 830. MS (m/z) = 295 (M+1).

2-oxo-6-(4-fluorophenyldiazenyl)-2H-chromene-3-carboxylic acid *(3b)*: Yellow crystalline solid**.** ^{1}H NMR (DMSO, 400MHz): δ 12.02 (s, 1H), 8.30 (s, 1H), 8.12 (dd, 1H), 7.98 (d, 2H), 7.85 (d, 2H), 7.75 (d, 2H). IR (Vmax/cm^{-1}) = 3332, 1724, 1690, 1620, 1580, 1501, 1480, 1433, 1262, 1157, 897, 766. MS (m/z) = 313.9 (M+1).

2-oxo-6-(4-bromophenyldiazenyl)-2H-chromene-3-carboxylic acid *(3c)*: Turmeric Yellow crystalline solid**.** ^{1}H NMR (DMSO, 400MHz): δ 12.05 (s, 1H), 8.30 (s, 1H), 8.16 (dd, 1H), 7.99 (d, 1H), 7.86 (d, 2H), 7.75 (d, 2H), 7.61 (d, 2H). IR (Vmax/cm^{-1}) = 3197, 1730, 1688, 1598, 1572, 1478, 1459, 1394, 1275, 1065, 1006, 898, 516. MS (m/z) = 374.9 (M+1).

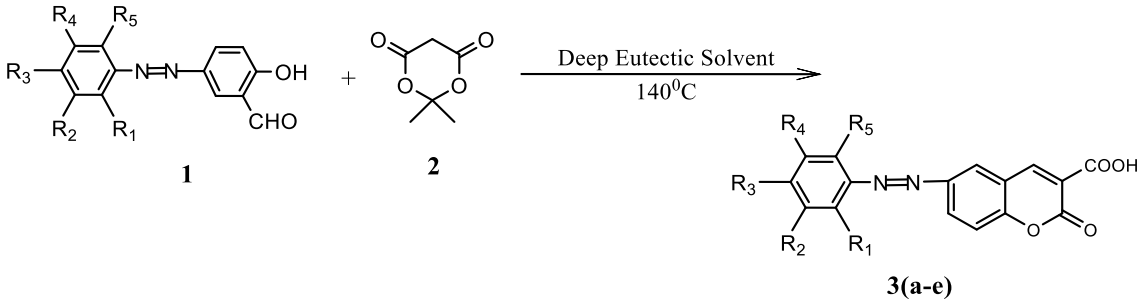
2-oxo-6-(2,4-dichlorophenyldiazenyl)-2H-chromene-3-carboxylic acid *(3d)*: Dark Brown crystalline solid**.** ^{1}H NMR (DMSO, 400MHz): δ 11.55 (s, 1H), 8.38 (s, 1H), 8.11 (d, 1H), 80.8 (d, 1H), 7.91 (d, 2H), 7.81 (d, 2H). IR (Vmax/cm^{-1}) = 3200, 1700, 1598, 1472, 1378, 1274, 1241, 1065, 1006, 950, 827, 760, 704 MS (m/z) = 365.26 (M+1).

2-oxo-6-(4-chlorophenyldiazenyl)-2H-chromene-3-carboxylic acid *(3e)*: Brown crystalline solid**.** ^{1}H NMR (DMSO, 400MHz): δ 11.95 (s, 1H), 8.48 (s, 1H), 8.36 (dd, 1H), 8.06 (d, 2H), 7.95 (d, 2H), 7.61 (d, 2H). IR (Vmax/cm^{-1}) = 3197, 1730, 1688, 1598, 1478, 1459, 1394, 1275, 1065, 980, 898, 750. MS (m/z) = 329.9 (M+1).

RESULTS AND DISCUSSION:

Initially, the experiments were carried out taking organic solvents like ethanol, methanol, ethyl acetate and DMF and found that the reaction time for synthesizing 2-oxo-6-(diazenyl)-2H-chromene-3-carboxylic acid using the methods reported in research articles, were taking time for completion more than a day or two with no success in conversion to the interested moiety. Some trials were yielding very less reaction product. This reaction was also carried out using Piperidine as a base [xx] and catalyst and found that the reaction was leading to formation of ester instead of carboxylic acid in the coumarin moiety.

The reaction of substituted azophenyl salicylaldehyde and meldrum's acid was carried out using deep eutectic solvent yielding a Knoevenagel condensation product. The homogeneous mixture of choline chloride and urea in the proportion yielding a favourable reacting medium converting the salicylaldehyde part of the reactant to coumarin-3-carboxylic acid with the substituents as it was present with reactant. Initially, it was confirmed using TLC and later IR, NMR and mass spectroscopy.



Scheme: Synthesis of substituted phenylazo coumarin-3-carboxylic acid (3a-e)

The reaction at lower temperatures took long duration to complete whereas that at 140^{0}C results in 45minutes to 2 hours (Table 2). The table also depicts the substituents are azophenyl, colour and melting points of the derivatives (Table 1).

Table 1 Substituents, colour and melting point of the compounds 3(a-e)

Compound	R_1	R_2	R_3	R_4	R_5	Colour	Melting point (^{0}C)
3a	H	H	H	H	H	Bright yellow	163
3b	H	H	F	H	H	Yellow	88 – 90
3c	H	H	Br	H	H	Turmeric yellow	158 – 160
3d	H	H	Cl	H	H	Dark brown	>360
3e	Cl	H	Cl	H	H	Brown	160

Table 2 Chemical formula, molecular weight, reaction time and percentage yield of the compounds 3(a-e)

Compound	Chemical Formulae	Molecular Weight	Reaction Time at 140^{0}C	% Yield
3a	$C_{16}H_{10}N_2O_4$	294.26	45 min.	90
3b	$C_{16}H_9N_2O_4F$	312.25	1 hr.	89
3c	$C_{16}H_9N_2O_4Br$	373.15	50 min.	85
3d	$C_{16}H_8N_2O_4Cl_2$	363.15	2 hr.	75
3e	$C_{16}H_9N_2O_4Cl$	328.70	1.30 hr.	85

CONCLUSION:

The method of preparation can be employed to several other derivatives of coumarins where aprotic solvents change the result of the reaction either by breaking apart the coumarin ring or difficult in removing the solvents completely from the reaction product. The deep eutectic solvents can be used in other moiety synthesis, as coumarins are synthesized and catalyzed in DES. It can be easily washed off from the product using plenty of water. Also suffice a criterion for green solvents so greener method of synthesis. The products can be used for further to study biological activities.

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