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An unexpected tetracyclic product isolated during the synthesis of biscoumarins catalyzed by [MIM$(CH_2)_4SO_3H$][HSO_4]: Characterization and X-ray crystal structure of 7-(2-hydroxy-4-oxo-4H-chromen-3-yl)-6H,7H-chromeno[4,3-b]chromen-6-one

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ABSTRACT

Under solvent-free conditions and in the presence of 3-methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulfate [MIM$(CH_2)_4SO_3H$][HSO_4], a Brønsted acidic ionic liquid, the reaction of aromatic aldehydes with 4-hydroxycoumarin has been investigated. A wide range of aromatic aldehydes easily undergoes condensation with 4-hydroxycoumarin to afford biscoumarins with good purity in excellent yields. However, reaction of 2-hydroxybenzaldehyde with 4-hydroxycoumarin gave, not the corresponding biscoumarin, but a tetracyclic compound, 7-(2-hydroxy-4-oxo-4H-chromen-3-yl)-6H,7H-chromeno[4,3-b]chromen-6-one, in high yield.

Coumarins are a large group of heterocycles with diverse and interesting biological activities. These compounds are reported to possess significant anticoagulant, insecticidal, antihelminthic, hypnotic, antifungal, and HIV protease inhibition activities [1–3]. Biscoumarins, the bridge substituted dimers of 4-hydroxycoumarin, have enormous potential as anticoagulants [4,5]. A number of biscoumarins have also been found to be urease inhibitors [6]. Recently, a number of methods have been reported for the synthesis of biscoumarins by reaction of 4-hydroxycoumarin and various aldehydes [7–12]. Although these methods may be effective, some of them have relatively long reaction times and unsatisfactory yields. This finding prompted us towards further investigation in search for a new catalyst, which will carry out the synthesis of biscoumarins under simpler experimental set up and eco-friendly conditions.

Ionic liquids (ILs) are salt-type compounds, which are liquid at room temperature and possessing low vapor pressure. Due to the lack of evaporation, they are considered as promising "green solvents" for replacing the volatile – therefore flammable and harmful – conventional solvents. ILs are also known as environmentally benign catalysts and much attention has currently been focused on the organic reactions in the presence of these compounds as catalysts or solvents [13–16]. The introduction of Brønsted-acidic functional groups into cations or anions of the ILs, especially the SO_3H-functional groups, obviously enhanced their acidities and water solubilities [17–19]. Therefore, Brønsted-acidic ILs can be used as highly efficient acid catalysts and have been receiving extensive interest as green substitute for H_2SO_4, HF and $AlCl_3$ catalysts in chemical processes [20]. In fact, the use of Brønsted-acidic ILs as catalysts is an area of ongoing activity; however, development and exploration of Brønsted-acidic ILs are currently in the preliminary stage. To the best of our knowledge, there are no examples of the use of Brønsted-acidic ILs as catalyst for the synthesis of biscoumarin derivatives.

Thus, in continuation of our previous works on the applications of reusable acid catalysts in organic synthesis [21–29] we decided to investigate the synthesis of biscoumarins using 3-methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulfate [MIM$(CH_2)_4SO_3H$][HSO_4], a Brønsted-acidic IL, as catalyst.

1. Experimental

1.1. Chemicals and apparatus

All chemicals were available commercially and used without additional purification. The Brønsted-acidic ionic liquid [MIM$(CH_2)_4SO_3H$][HSO_4] was synthesized according to the literature [30]. Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a Tensor 27 Bruker

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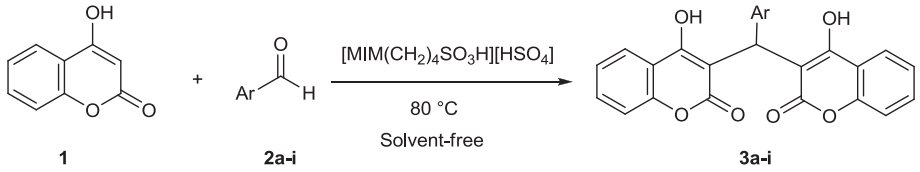


Scheme 1. Synthesis of biscoumarins catalyzed by $[MIM(CH_2)_4SO_3H][HSO_4]$.

Table 1
Synthesis of compound 3a in the presence of various amount of $[MIM(CH_2)_4SO_3H][HSO_4]$ at different temperatures under solvent-free conditions[a].

Entry	Catalyst (mol%)	*T* (°C)	Time/min	Yield/%[b]
1	None	120	120	Trace
2	5	60	30	51
3	10	60	20	67
4	15	60	15	74
5	5	80	15	67
6	10	80	10	84
7	15	80	8	92
8	20	80	10	93
9	5	120	15	71
10	10	120	10	85
11	15	120	10	92

[a] 5 mmol benzaldehyde, 10 mmol 4-hydroxycoumarin.
[b] Isolated yields.

Table 2
Synthesis of compound 3a in the presence of $[MIM(CH_2)_4SO_3H][HSO_4]$ (15 mol%) in different solvents[a].

Entry	Solvent	*T* (°C)	Time (min)	Yield (%)[b]
1	EtOH	Reflux	30	63
2	MeOH	Reflux	40	56
3	CH_3CN	Reflux	40	51
4	CH_2Cl_2	Reflux	60	26
5	Solvent-free	80	8	92

[a] 5 mmol benzaldehyde, 10 mmol 4-hydroxycoumarin.
[b] Isolated yields.

spectrophotometer as KBr disks. The ^{1}H NMR (500 MHz) spectra were recorded with a Bruker DRX500 spectrometer. The ^{13}C NMR (125 MHz) spectrum was recorded with a Bruker DRX500 spectrometer. Mass spectrum was recorded with a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was performed with a Thermo Finnigan Flash EA microanalyzer.

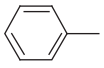
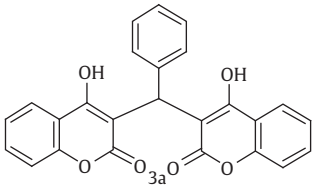
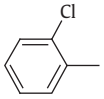
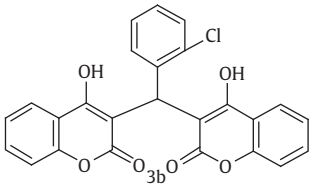
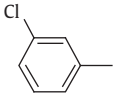
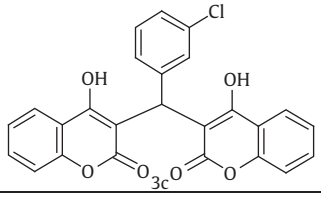
1.2. General procedure for the synthesis of biscoumarins 3a-i and compound 4

A mixture of an aromatic aldehyde (5 mmol), 4-hydroxycoumarin (10 mmol) and $[MIM(CH_2)_4SO_3H][HSO_4]$ (15 mol%) without solvent was heated on the oil bath at 80 °C for 18–30 min. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and water was added. The precipitate was filtered off and recrystallized from ethanol to give compounds 3a–i and 4 in high yields. The catalyst was recovered from the filtrate by evaporation of the water and reused for the similar reaction. The catalyst could be used at least three times with only slight reduction in catalytic activity.

1.3. Spectral and microanalytical data for compound 4

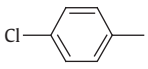
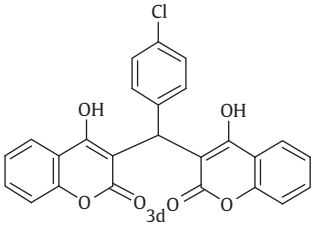
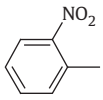
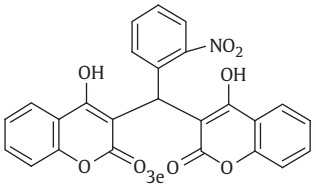
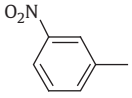
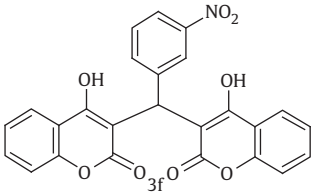
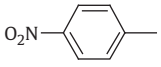
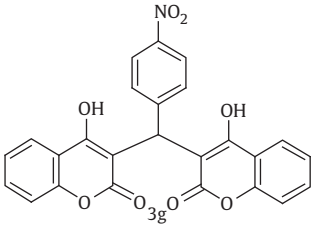
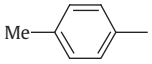
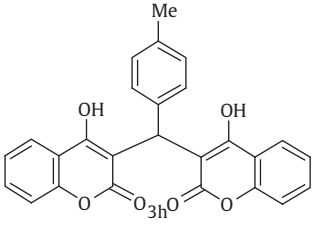
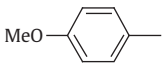
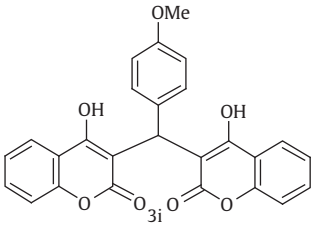
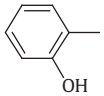
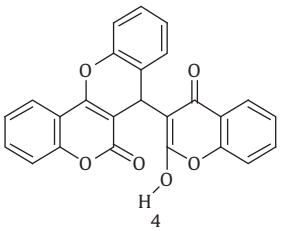
^{1}H NMR (500 MHz, $CDCl_3$, δppm): 5.41 (s, 1H, CH), 7.10–7.20 (m, 2H, arom-H), 7.23 (d, 1H, J = 8.0 Hz, arom-H), 7.30–7.38 (m, 3H, arom-H), 7.40–7.50 (m, 2H, arom-H), 7.53 (td, J = 7.5, 1.5 Hz, 1H, arom-H), 7.67 (td, J = 7.8, 1.5 Hz, 1H, arom-H), 8.07 (dd, J = 7.9,

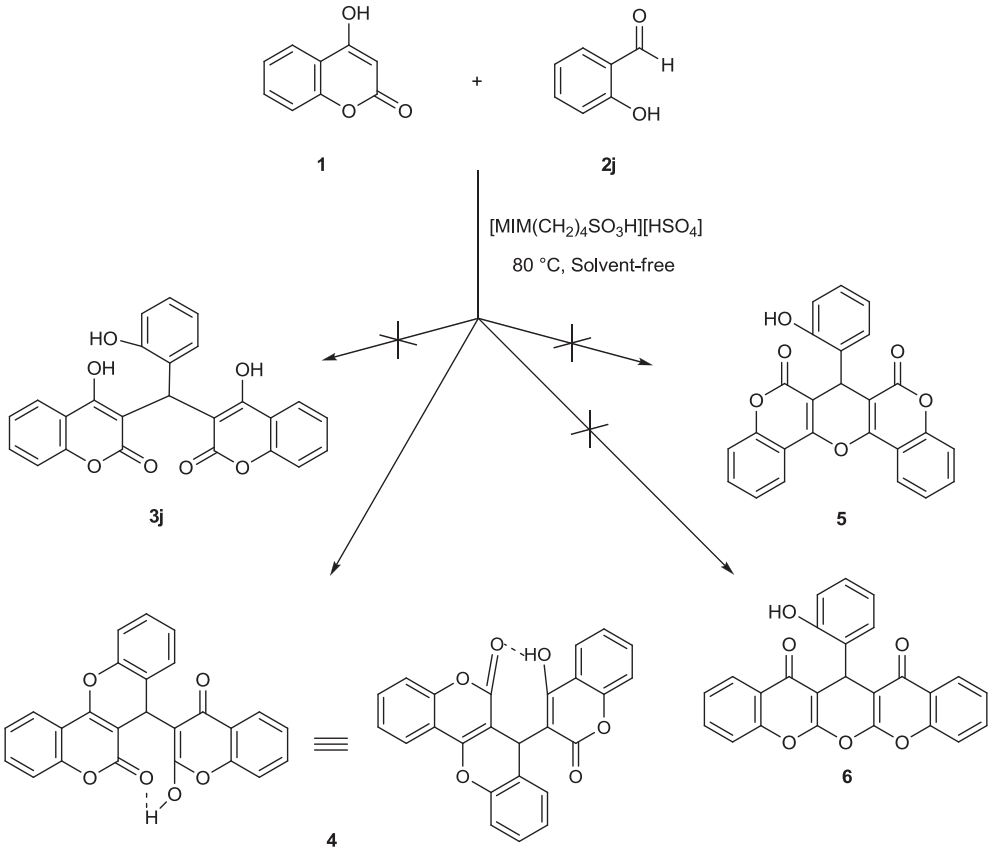
Table 3
$[MIM(CH_2)_4SO_3H][HSO_4]$ catalyzed synthesis of biscoumarins[a].

Entry	Ar	Product[b]	Time (min)	Yield (%)[c]	mp °C		Ref.
					Found	Reported	
1			30	92	229–231	228–230	8
2			30	88	201–203	198–199	10
3			25	89	221–223	222–224	10

(*continued on next page*)

Table 3 (*continued*)

Entry	Ar	Product[b]	Time (min)	Yield (%)[c]	mp °C		Ref.
					Found	Reported	
4			25	93	261–263	258–259	11
5			30	86	198–200	200–202	10
6			20	89	214–215	212–215	10
7			20	96	233–235	232–234	8
8			25	90	266–269	269–270	11
9			30	89	250–252	249–250	11
10			18	94	254–256	–	–



Scheme 2. Reaction of 2-hydroxybenzaldehyde with 4-hydroxycoumarin.

1.5 Hz, 1H, arom-H), 8.19 (dd, $J = 8.0$, 1.5 Hz, 1H, arom-H), 10.43 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$, δppm): 30.41, 100.64, 109.09, 115.04, 116.68, 116.76, 117.27, 117.40, 121.82, 123.84, 124.29, 124.78, 125.44, 125.98, 128.96, 129.16, 132.37, 133.19, 151.40, 152.52, 153.50, 159.22, 161.59, 161.84, 166.58; IR (KBr disk): υ 3419 (OH), 1717 (CO), 1689 (CO) cm^{-1}; MS, m/z: 410 (M^+), 289, 262, 249, 221, 165, 121, 92; Anal. calcd. for $C_{25}H_{14}O_6$ (410.37) (%): C, 73.17; H, 3.44. Found (%): C, 74.01; H, 3.51.

2. Results and discussion

The efficient synthesis of biscoumarins was achieved by condensation of aromatic aldehydes and 4-hydroxycoumarin in the presence of 3-methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulfate $[MIM(CH_2)_4SO_3H][HSO_4]$, a Brønsted-acidic IL, as catalyst (Scheme 1).

$[MIM(CH_2)_4SO_3H][HSO_4]$ was prepared according to the literature procedure [30]. Initially, the synthesis of compound 3a was selected as a model reaction to optimize the reaction conditions. The reaction was carried out by heating a mixture of benzaldehyde (5 mmol) and 4-hydroxycoumarin (10 mmol) in the presence of various amount of $[MIM(CH_2)_4SO_3H][HSO_4]$ at different temperatures under solvent-free conditions. As can be seen from Table 1, the shortest time and best yield were achieved in the presence of 15 mol% of catalyst at 80 °C (Entry 7).

Furthermore, the same model reaction in presence of 15 mol% of the catalyst was carried out at different solvents to assess the effect of solvent on the reaction. As shown in Table 2, the yield of the reaction under solvent-free conditions was greater and the reaction time was generally shorter than the conventional methods.

In order to evaluate the generality of this model reaction, we prepared a range of biscoumarin derivatives under optimized reaction conditions. In all cases (except for 2-hydroxybenzaldehyde), aromatic aldehydes with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the expected products in excellent yields and short reaction times. The type of aromatic aldehyde had no significant effect on the reaction. The results are shown in Table 3. The structure of the products (3a–i) was established from their IR spectral data and comparison of their melting points with those of authentic samples. Also, the structure of some products was confirmed by ^{1}H NMR spectral data.

When 2-hydroxybenzaldehyde was allowed to react with 4-hydroxycoumarin under optimized reaction conditions, surprisingly, the product was isolated that its ^{1}H NMR data did not show the formation of biscoumarin 3j (Scheme 2). While three hydroxyl groups are expected in ^{1}H NMR spectrum of compound 3j, the ^{1}H NMR spectrum of the isolated product showed only one hydroxyl group at 10.43 ppm which was removed on deuteration. We thus turned our attempt for the characterization of this compound by means of other spectroscopic methods. The MASS spectrum of this compound

Notes to Table 3
[a] 5 mmol aromatic aldehyde, 10 mmol 4-hydroxycoumarin, 0.75 mmol (15 mol%) $[MIM(CH_2)_4SO_3H][HSO_4]$ at 80 °C in solvent-free conditions.
[b] The products 3a–i were characterized by IR spectral data and comparison of their melting points with those of authentic samples. Also, the structures of some of them were confirmed by ^{1}H NMR spectral data. The product 4 was characterized by IR, ^{1}H NMR, ^{13}C NMR and MASS spectral and microanalytical data and also by single crystal X-ray crystallography.
[c] Isolated yields.

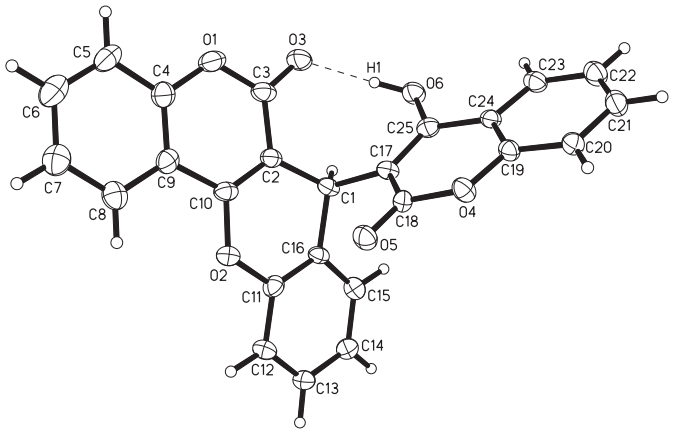


Fig. 1. X-ray crystal structure of compound 4.

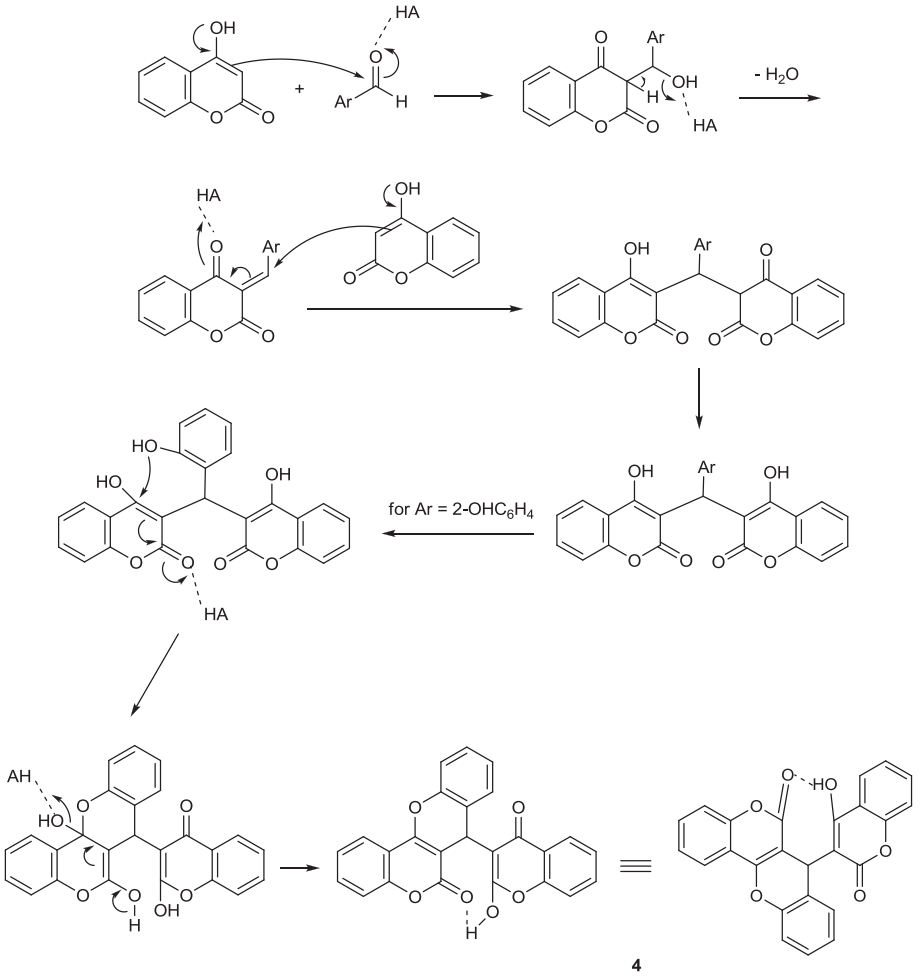
showed a molecular ion peak at m/z 410 which is in accordance with a cyclization reaction by the removal of one water molecule from corresponding biscoumarin 3j. Indeed, this compound gave satisfactory elemental analysis data corresponding to the molecular formula $C_{25}H_{14}O_6$.

Synthesis and cyclization reaction of some biscoumarins have been reported by Hamdi and co-workers [12]. Though, they did not investigate the synthesis and cyclization reaction of biscoumarin 3j, but in other cases, cyclization reactions have occurred by dehydration between two coumarin rings. However, for biscoumarin 3j, there are three alternatives for cyclization process. Distinguishing between the structures 4, 5 and 6 is not possible by MASS spectrum and microanalytical data.

The structure of the studied compound was finally proven by ^{13}C NMR spectrum and X-ray analysis. 25 Signals in ^{13}C NMR spectrum show that all carbon atoms are nonequivalent that is in accordance with structure 4. Also, an ORTEP representation of the structure has been shown in Fig. 1. As depicted in this figure, this compound has a tetracyclic structure containing two fused chromene rings along with an chromene substituent at 7 position that clearly shows the structure to be that of 4. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 819933. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: 44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

A plausible mechanism for the synthesis of biscoumarins and compound 4 in the presence of $[MIM(CH_2)_4SO_3H][HSO_4] \equiv HA$ may proceed as depicted in Scheme 3.

Reusability of the catalyst was also investigated. For this purpose, the same model reaction was again studied in the optimized conditions. After the completion of the reaction, the reaction mixture was cooled to room temperature and then water was added. The precipitated solid was filtered off and the catalyst was recovered from the filtrate by evaporation of the water and reused for the similar reaction. As it shown in Fig. 2, the catalyst could be used at least three times with only slight reduction in catalytic activity.



Scheme 3. Plausible mechanism for the formation of biscoumarins and compound 4 in the presence of $[MIM(CH_2)_4SO_3H][HSO_4] \equiv HA$ as catalyst.

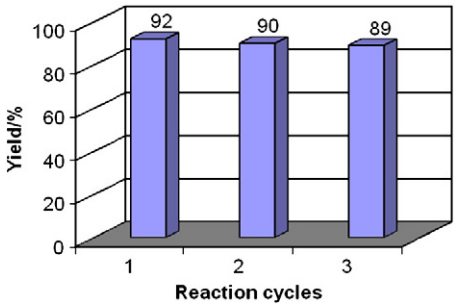


Fig. 2. Reusability of $[MIM(CH_2)_4SO_3H][HSO_4]$ for model reaction.

3. Conclusion

In conclusion, a reliable, rapid, and environmentally benign method for synthesizing biscoumarins via the reaction of aromatic aldehydes with 4-hydroxycoumarin has been developed, which involves the use of a Brønsted-acidic IL as catalyst. In addition to the purity of the products, the short reaction times and ease of work up make the method advantageous. However, reaction of 2-hydroxybenzaldehyde with 4-hydroxycoumarin gave, not the corresponding biscoumarin, but a tetracyclic compound, 7-(2-hydroxy-4-oxo-4H-chromen-3-yl)-6H,7H-chromeno[4,3-b]chromen-6-one, in high yield. This compound was characterized by IR, ^{1}H NMR, ^{13}C NMR and MASS spectral and microanalytical data and also by single crystal X-ray crystallography.

Acknowledgments

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