



Original Research article

A Rapid and Highly Effectual Protocol for the Synthesis of Bis-coumarins using Triethylaminium-*N*-sulfonic Acid Tetrachloroaluminate under Solvent-Free Conditions



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KEYWORDS

Bis-coumarin

4-Hydroxycoumarin

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Triethylaminium-*N*-sulfonic acid

tetrachloroaluminate (TSAT)

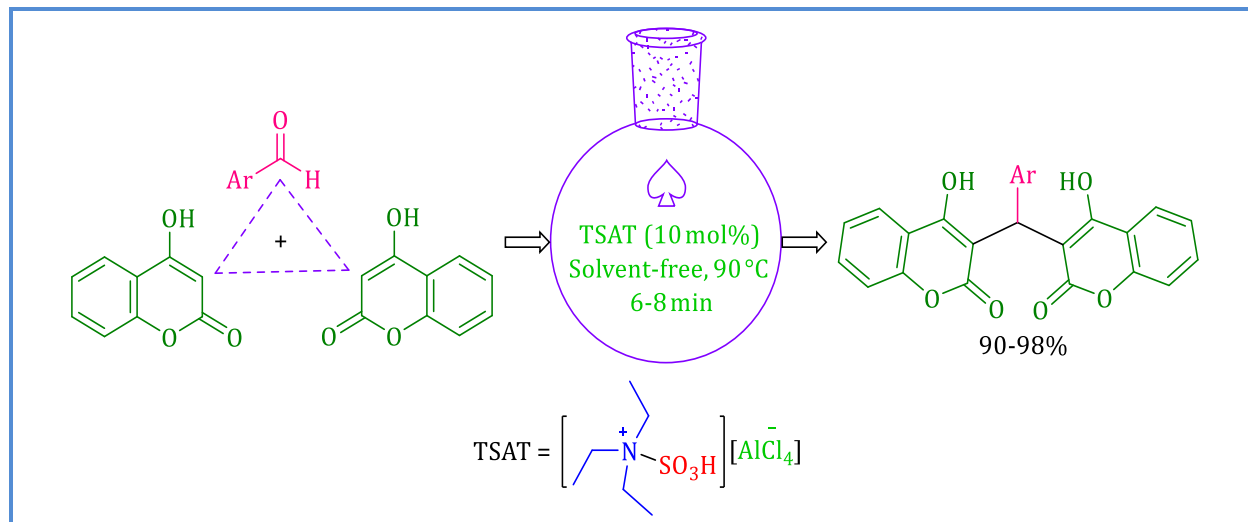
Solvent-free

ABSTRACT

In this work, a rapid and highly effectual protocol for the synthesis of bis-coumarins has been developed. The one-pot quasi three-component reaction of aromatic aldehydes (1 eq.) with 4-hydroxycoumarin (2 eq.) in the presence of catalytic amount of protic acidic ionic liquid triethylaminium-*N*-sulfonic acid tetrachloroaluminate (TSAT) under solvent-free conditions afforded the mentioned compounds in high yields and short reaction times.

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Graphical Abstract



Introduction

Ionic liquids (ILs) are defined as organic salts, which melt at room temperature or below 100 °C [1]. These compounds are of importance in organic synthesis field and extensively used as solvent, reagent and catalyst [1-9]. These extensive applications are related to their unique properties such as suitable thermal and chemical stability, non-volatility, wide liquid-state temperature range, non-flammability, large electrochemical window, enhanced reactivity, favorable solvation behavior, and aptitude to modify physical and chemical properties with functionalization of their cation and anion [1-9]. Among the kinds of ILs, protic acidic ones are appropriate candidate to utilize as effective catalysts for organic transformations [4-9].

Solvent-free reactions have been used as a practical technique in organic synthesis. This technique has usually various advantages in comparison to classical solution conditions, *e.g.* compliance with green chemistry protocols, easier work-up, shorter reaction time, higher yield, and enhancing regio- and stereoselectivity of reaction [10-14].

The compounds containing coumarin core have a wide range of pharmacological and biological activities; *e.g.* anticancer, anticoagulant, antifungal, antihelminthic, antibacterial, spasmolytic insecticidal, HIV protease inhibition, phytoalexin, hypnotic, urease inhibitory, antioxidant and antinociceptive properties [15-21]. Bis-coumarins are important group of coumarin derivatives which could prepare by the one-pot quasi three-component reaction of aldehydes (1 eq.) with 4-hydroxycoumarin (2 eq.) in the presence of a catalyst [22-31]. Despite potential efficacy of the reported methods, many of them suffer from some disadvantages or at least one limitation, such as

moderate yields, application of volatile organic solvents as reaction media, application of expensive, non-available or toxic catalysts, relatively long reaction times, poor agreement with green chemistry protocols, and harsh conditions.

In this research, we introduce protic acidic ionic liquid triethylammonium-*N*-sulfonic acid tetrachloroaluminate (TSAT) as a highly effectual catalyst for the rapid synthesis of bis-coumarins *via* the reaction of arylaldehydes (1 eq.) and 4-hydroxycoumarin (2 eq.) under solvent-free conditions. This method has solved almost all of the above-mentioned drawbacks.

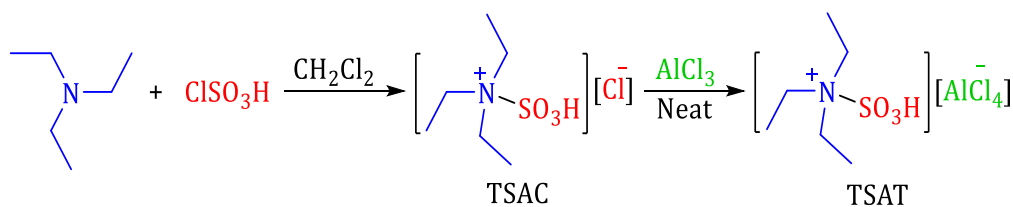
Experimental

General

All reactants and solvents were bought from Merck, Fluka or Acros Chemical Companies. The known compounds were identified by comparing their melting points/spectroscopic data with those reported in the literature. Monitoring progress of the reactions was achieved by thin layer chromatography (TLC). The melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. ¹H NMR (250 or 400 MHz) and ¹³C NMR (62.5 or 100 MHz) spectra were recorded on Bruker Avance DPX, FT-NMR spectrometer.

Preparation of catalyst triethylammonium-*N*-sulfonic acid tetrachloroaluminate (TSAT)

A solution of triethylamine (0.50 g, 5 mmol) in CH₂Cl₂ (20 mL) was added dropwise to a stirring solution of chlorosulfonic acid (0.58 g, 5 mmol) in dry CH₂Cl₂ (20 mL) over a period of 10 min at 10 °C. Afterward, the reaction mixture was allowed to heat to room temperature (accompanied with stirring), and stirred for another 4 h. The solvent was evaporated, and the liquid residue was triturated with diethyl ether (5 mL), and dried under vacuum at 90 °C to give triethylammonium-*N*-sulfonic acid chloride (TSAC) as a viscous pale yellow oil. Next, aluminum chloride (0.667 g, 5 mmol) was added slowly to TSAC (1.09 g, 5 mmol) over a period of 5 min at room temperature, and the resulting mixture was stirred at 70 °C for 4 h to afford TSAT as a white solid; m.p. 96-97 °C (lit. 97-98 °C) (Scheme 1) [9].



Scheme 1. The preparation of TSAT

Spectroscopic data of TSAT

FT-IR (KBr): 3650-2350 (OH), 1103 (S-OH bending), 945 (N-S) cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6):

δ (ppm) 1.18 (t, $J=5.8$ Hz, 9H, 3 CH_3), 3.04 (q, $J=5.8$ Hz, 6H, 3 CH_2), 10.17 (br., 1H, SO_3H); ^{13}C NMR (100 MHz, DMSO- d_6): δ (ppm) 8.9, 45.8; MS: m/z 352 ($\text{M}^+ + 1$), 351 (M^+).

General procedure for the synthesis of bis-coumarins

A mixture of aromatic aldehyde (1 mmol), 4-hydroxycoumarin (0.32 g, 2 mmol) and TSAT (0.035 g, 0.1 mmol) was stirred magnetically at 90 °C, and after solidification of the reaction mixture, it was stirred by a small rod at the same temperature. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled to room temperature, and the resulting precipitate was recrystallized from EtOH (95%) to give the pure product.

Selected spectral data of the synthesized bis-coumarins**Compound 1d**

^1H NMR (400 MHz, DMSO- d_6): δ (ppm) 3.59 (s, 6H, 2 CH_3), 3.66 (s, 3H, CH_3), 6.27 (s, 1H, methine CH), 6.47 (s, 2H, H_{Ar}), 7.31-7.38 (m, 4H, H_{Ar}), 7.60 (t, $J=8.4$ Hz, 2H, H_{Ar}), 7.93 (d, $J=7.9$ Hz, 2H, H_{Ar}); ^{13}C NMR (100 MHz, DMSO- d_6): δ (ppm) 36.8, 56.5, 60.4, 104.9, 105.1, 116.6, 117.9, 124.4, 124.5, 132.4, 135.6, 136.7, 152.7, 153.1, 165.2, 165.3.

Compound 1f

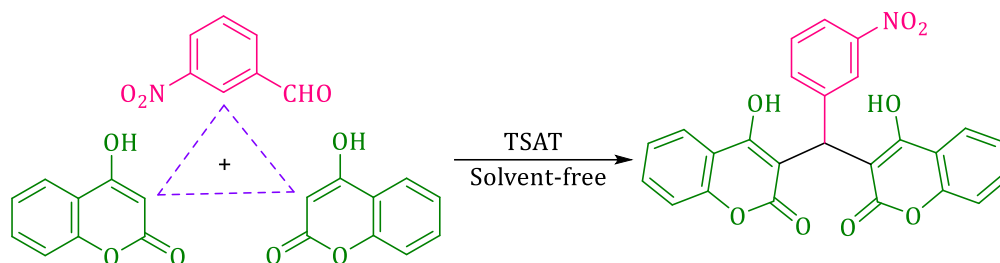
^1H NMR (250 MHz, DMSO- d_6): δ (ppm) 5.03 (br, 2H, 2OH), 6.34 (s, 1H, methine CH), 7.21-7.30 (m, 4H, H_{Ar}), 7.45-7.59 (m, 4H, H_{Ar}), 7.82 (d, $J=7.8$ Hz, 2H, H_{Ar}), 7.88 (s, 1H, H_{Ar}), 7.98 (d, $J=7.9$ Hz, 1H, H_{Ar}).

Compound 1h

^1H NMR (250 MHz, DMSO- d_6): δ (ppm) 6.26 (s, 1H, methine CH), 6.47 (br., 2H, 2OH), 6.93 (t, $J=5.3$ Hz, 1H, H_{Ar}), 7.10-7.31 (m, 7H, H_{Ar}), 7.53 (t, $J=7.3$ Hz, 2H, H_{Ar}), 7.84 (d, $J=7.5$ Hz, 2H, H_{Ar}).

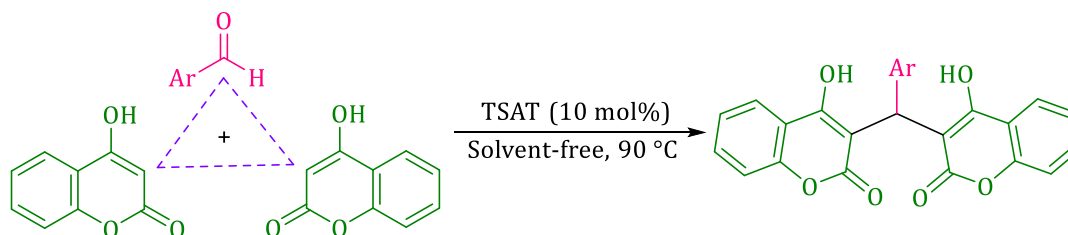
Results and discussion

To attain the optimal reaction conditions, the one-pot quasi three-component condensation of 3-nitrobenzaldehyde (1 mmol) and 4-hydroxycoumarin (2 mmol) was chosen as a model reaction (Scheme 1), and studied in the presence of different amounts of TSAT (5, 10 and 15 mol%) at a range of 80-100 °C in the absence of solvent. The best results were acquired when the reaction was performed using 10 mol% of the catalyst at 90 °C (time: 6 min, yield: 98%).



Scheme 2. The model reaction

The effectuality and generality of the protocol was recognized by performing the reaction of different aromatic aldehydes with 4-hydroxycoumarin under the optimal conditions; the results are depicted in Table 1. As the data in Table 1. indicate, high yields of the desired products were obtained in short reaction times in the case of all aldehydes, including benzaldehyde and arylaldehydes having electron-donating, electron-withdrawing and halogen substituents. These excellent results confirmed high effectiveness and generality of the method.



Product	Ar	Time (min)	Yield ^a (%)	M.p. (°C) [Lit.]
1a	C ₆ H ₅	8	96	232-234 (230-232) [29]
1b	4-CH ₃ C ₆ H ₄	6	94	270-271 (268-270) [28]
1c	4-CH ₃ OC ₆ H ₄	6	93	245-247 (246-248) [29]
1d	3,4,5-(CH ₃ O) ₃ C ₆ H ₂	8	91	241-243 (239-240) [28]
1e	4-NO ₂ C ₆ H ₄	6	94	233-235 (232-234) [27]
1f	3-NO ₂ C ₆ H ₄	6	98	213-215 (214-215) [22]
1g	4-FC ₆ H ₄	7	97	214-216 (213-215) [29]
1h	2-ClC ₆ H ₄	8	94	198-200 (201-203) [22]
1i	2-BrC ₆ H ₄	8	90	260-262 (259-261) [28]
1j	4-BrC ₆ H ₄	8	92	267-269 (265-267) [29]

^aIsolated yield

To illustrate the merit of our method with respect to the reported ones for the preparation of bis-coumarins, the reaction times and yields of these methods on the condensation of benzaldehyde and 4-hydroxycoumarin are tabulated in Table 2. As it is clear from the Table, our protocol afforded the product in shorter reaction time relative to the other methods; moreover, the yield was higher than most of the others.

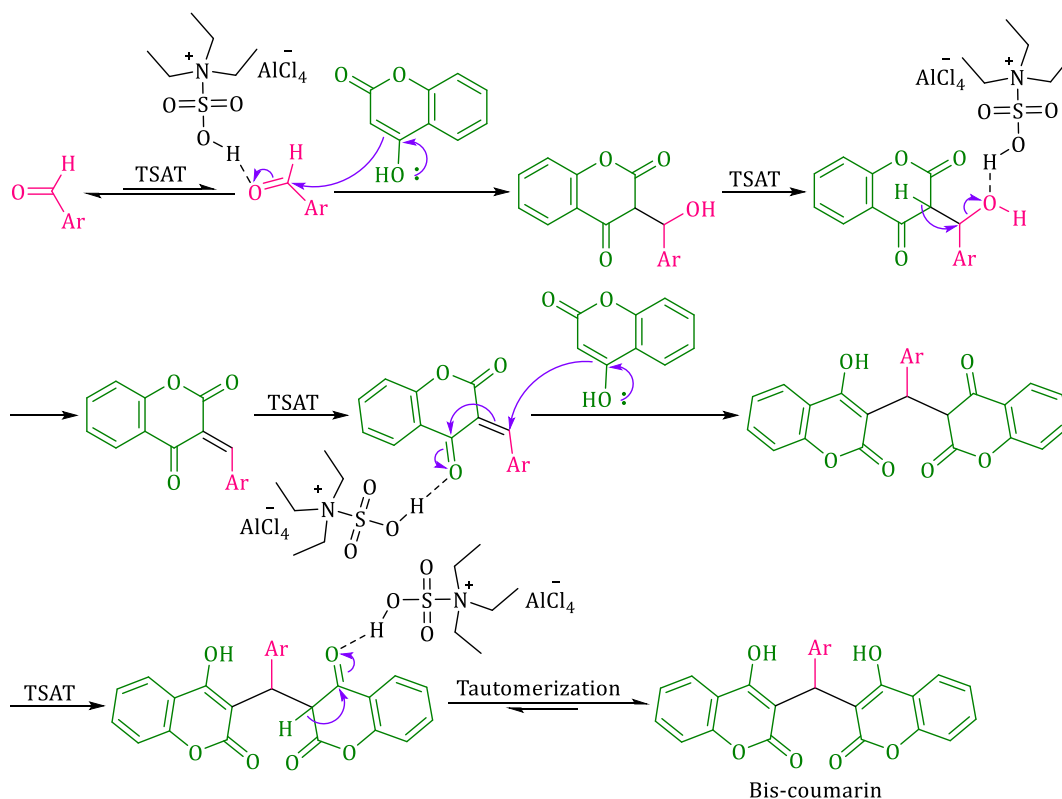
Table 2. Comparison of our method with the reported ones on the condensation of benzaldehyde and 4-hydroxycoumarin

Catalyst	Time (min)	Yield (%)	Ref.
TSAT	8	96	This work
[MIM(CH ₂) ₄ SO ₃ H][HSO ₄] ^a	30	92	[22]
I ₂	25	97	[23]
APVPB ^b	17	88	[24]
Choline hydroxide	60	99	[25]
Phthalimide- <i>N</i> -sulfonic acid	10	96	[26]
Isatin- <i>N</i> -sulfonic acid	10	96	[26]
Phosphotungstic acid	20	93	[27]
Melamine trisulfonic acid	20	95	[28]
Sodium dodecyl sulfate	140	90	[29]
Trityl bromide	20	92	[30]
Fe ₃ O ₄ @SiO ₂ @(CH ₂) ₃ -Im-SO ₃ H	12	93	[30]
Fe ₃ O ₄ @SiO ₂ @VB1-Ni ²⁺	30	95	[31]

^a 3-Methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulfate

^b Acetic acid functionalized poly(4-vinylpyridinium)bromide

A plausible mechanism, based on the literature [26-28], was proposed for the reaction (Scheme 3). As it is shown in this Scheme, the acidic group of TSAT activates the carbonyl groups to accept nucleophilic attacks, and also helps removing of H₂O and tautomerization.

**Scheme 3.** The proposed mechanism for the synthesis of bis-coumarins

Conclusions

In summary, we have introduced an ionic-liquid catalyst namely triethylammonium-*N*-sulfonic acid tetrachloroaluminate for the rapid synthesis of bis-coumarins. The advantages of this method consist of performing the reactions in solvent-free conditions, effectuality, generality, short reaction times, high to excellent yields, simple production of the catalyst, and good agreement with green chemistry protocols.

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