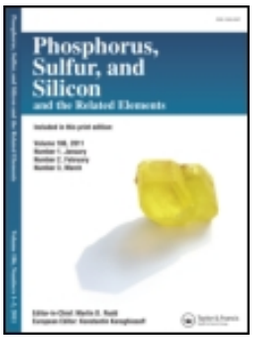

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A Facile One-Step Multi-Component Approach toward the Synthesis of 3-(2-Amino-4-Thiazolyl)Coumarins by using Trimethylsilyl Isothiocyanate and their Antioxidant and Anti-Inflammatory Activity

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A FACILE ONE-STEP MULTI-COMPONENT APPROACH TOWARD THE SYNTHESIS OF 3-(2-AMINO-4-THIAZOLYL)COUMARINS BY USING TRIMETHYLSILYL ISOTHIOCYANATE AND THEIR ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITY

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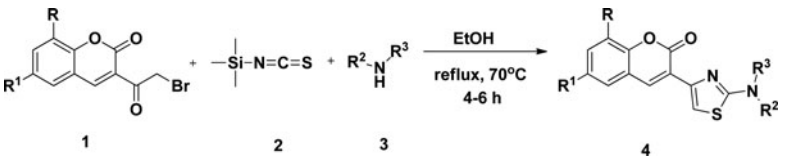
GRAPHICAL ABSTRACT



Abstract *A multi-component synthesis of 3-(2-amino-4-thiazolyl)coumarins has been reported from 3-(2-bromoacetyl)-2H-chromen-2-ones primary amines and using commercially available trimethylsilyl isothiocyanate. The structures of newly synthesized compounds were characterized by their analytical and spectral data. All the title compounds were screened for antioxidant and anti-inflammatory activity. Among the screened compounds, 4b exhibited highest free radical scavenging activity and also 4b was found to be effective in inhibiting the protein denaturation at all tested concentrations.*

Keywords Trimethylsilyl isothiocyanate; coumarin; multi-component reaction; primary amines

INTRODUCTION

Synthetically prepared substituted thiazoles are known to possess pharmacological properties[1–3] including antitumoral[4] and antimicrobial[5] activities and also other applications such as liquid crystals, cosmetic sunscreens.[6,7] Coumarin and its derivatives show antibacterial,[8,9] antifungal,[10,11] herbicidal,[12] antitumoral[13], cytotoxic,[14] and anti-HIV activity.[15,16] The compounds containing the coumarin motif are widely used as luminescent materials.[17]

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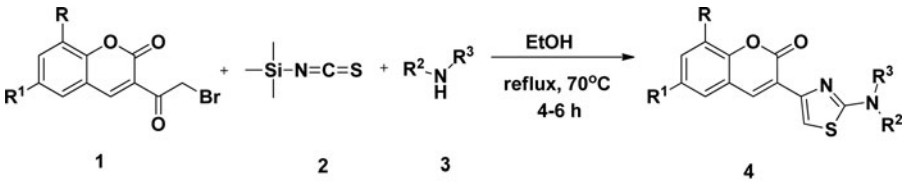
They also act as anticoagulants,[18] free radical scavengers,[19] antioxidant[20], lipoxygenase,[21] and cyclooxygenase inhibitors.[22]

In the literature, numerous methods were reported for the preparation of 4-substituted 2-amino thiazoles based on Hantzsch-type[23] condensation of alpha halo carbonyl compounds with various thioureas. In this paper, we report a novel method for the development of 2-amino thiazolyl coumarins using commercially available trimethylsilyl isothiocyanate (TMSNCS), along with readily available primary amines and 3-(2-bromoacetyl)-2H-chromen-2-ones via multi-component approach.

RESULTS AND DISCUSSIONS

Chemistry

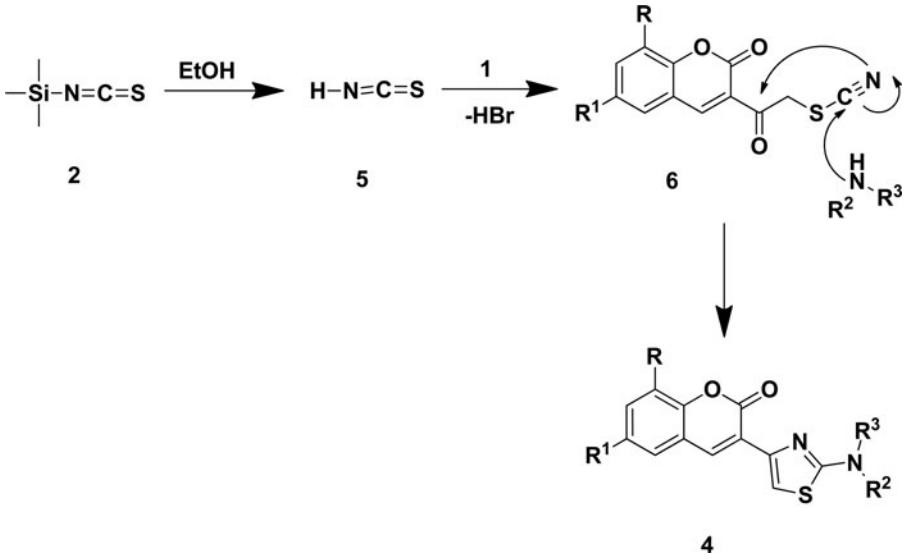
Condensation of 3-(2-bromoacetyl)-2*H*-chromen-2-one **1,** TMSNCS **2** with different primary amines **3** in ethanol gave the corresponding 3-(2-amino-4-thiazolyl)coumarins **4** in good yields. All the synthesized compounds are new and not reported in the literature except compounds **4c** and **4d** (Scheme 1). In the literature, these two compounds were synthesized using different methods[24] and their melting points were found identical with newly synthesized compounds.



4 (a) R =OCH_3, R^1=H, R^2= p-Tolyl, R^3=H
(b) R =OCH_3, R^1 =Br, R^2= p-Tolyl, R^3=H
(c) R =, R^1=H, R^2= p-Tolyl, R^3=H
(d) R =, R^1= 5,6 benzo, R^2 = p-Tolyl, R^3=H
(e) R=R^1=H, R^2 = p-Anisyl, R^3=H
(f) R= OCH_3, R^1=H, R^2 = p-Anisyl, R^3=H
(h) R= H,, R^1=Br, R^2= p-Anisyl, R^3=H
(i) R= R^1=H, R^2= p-Chloro phenyl, R^3=H

Scheme 1 Scheme for the preparation of 3-(2-amino-4-thiazolyl)coumarins **4a-i** using TMSNCS.

The mechanism for the formation of product was discussed in Scheme 2. In this procedure, we have modified the known Hantzsch method for thiazole synthesis involving the reaction of TMSNCS, primary amines and 3-(2-bromoacetyl)-2*H*-chromen-2-ones. We tried to develop the present a novel one pot multi-component synthesis of the title compounds using TMSNCS. This procedure may find extensive applications in the synthesis of a wide variety of substituted thiazoles. The structures of compounds **4a-i** were confirmed by their IR, ^{1}H NMR, and ^{13}C NMR spectral data. The ^{1}H NMR spectrum of **4a** in $CDCl_3$ showed thiazole proton as singlet at 7.76, C_4 proton of coumarin as singlet at 8.63 and NH proton appeared as singlet at 10.24 δ ppm. In the ^{13}C NMR spectrum of **4a** the thiazole and carbonyl carbon resonates at 110.1 and 164.5 δ ppm, respectively. The mass spectrum of **4a** exhibited the $[M+H]^+$ peak at *m/z* 365. When exposed to ethanol, TMSNCS rapidly releases isothiocyanic acid[25] **5** which could react with the compound **1** to form the respective thiocyanate[26] **6.** Then **6** reacts with primary amines to give the end products. (Full characterization and sample ^{1}H and ^{13}C NMR spectra are presented in the Supplemental Materials, Figure S 1–S 4)



Scheme 2 plausible mechanism for the formation of 3-(2-amino-4-thiazolyl)coumarin **4a-i.**

BIOLOGICAL ACTIVITY

Results

DPPH Radical Scavenging Activity. Among the screened compounds, 4b exhibited highest free radical scavenging activity. On the other hand **4g** and **4h** were proven to possess significant antioxidant properties. The results were compared with known standard BHA. The inhibition percentage of the compounds **4a, 4c, 4d, 4e, 4f, 4g, 4h, 4i** at 150 μg/mL.

Anti-inflammatory Activity. Among the various compounds tested, **4b** was found to be effective in inhibition of protein denaturation of all tested concentrations. The highest inhibition percentage 93% was obtained at 150 μg/mL and compared with standard Diclofenac sodium 96% at 20 μg/mL concentration. On the other hand, **4g** and **4h** also showed significant inhibition of protein denaturation. The percentage of inhibition noticed for **4a, 4c, 4d, 4e, 4f, 4g**, **4h, 4i** at 150 μg/mL concentrations are 80, 52, 39, 59, 79, 89, 85, and 76, respectively. However, inhibition concentration IC_{50} of 4b was found to be less than 50 μg/mL (Figures S5 and S6 Supplemental Materials).

CONCLUSION

This paper reports an efficient, one-pot three component method for the synthesis of 3-(2-amino-4-thiazolyl)coumarins by TMSNCS in good yields. The experimental conditions are simple, inexpensive, with easy work up and cleaner reaction profiles. The antioxidant and anti-inflammatory activities of the synthesized compounds were evaluated. Among them, **4b, 4g,** and **4h** showed good antioxidant as well as anti-inflammatory activities and emerged as potential molecules for further development.

EXPERIMENTAL

All the reagents and solvents were pure and purchased from commercial sources and were used without further purification unless otherwise stated. 3-(2-Bromo-acetyl)-2*H*-chromen-2-ones were prepared by the literature procedure.[29] Melting points were determined in open capillaries with a 'Cintex' melting point apparatus (Mumbai, India) and were uncorrected. CHN analysis was carried out by Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by TLC plates (E. Merck Mumbai, India). IR spectra were recorded on a thermo Nicolet Nexus 670 Q8 instrument (KBr pellets). ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using TMS as the standard. Mass spectra (EI-MS) were determined on a Perkin Elmer spectrometer (SCIEX API-2000, ESI) at 12.5 eV.

General Procedure for 4a-i

A mixture of 3-(2-bromoacetyl)-2*H*-chromen-2-one **1** (1 mmol), trimethylsilyl isothiocyanate **2** (1 mmol) and primary amine **3** (1 mmol) in ethanol (10 mL) was refluxed. After completion of the reaction, the reaction mixture was cooled, filtered, and solid was recrystallized from methanol. Complete characterization of 4b–4h and sample spectra for 4a and 4b are presented in the Supplemental Materials (Figures S1–S4).

8-Methoxy-3-(2-(p-tolylamino)thiazol-4-yl)-2H-chromen-2-one (4a). Color: yellow; mp: 172–174 °C; Yield: 87(%); IR (KBr) υ (cm^{-1}): 1538 (−C=C), 1603 (-C=N), 1708 (lactone −C=O), 3316 (−NH); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.28 (s, 3H, methyl), 3.94 (s, 3H, methoxy), 7.18 (d, 2H, J = 8 Hz, Ar-H), 7.30-7.36 (m, 2H, Ar-H), 7.47–7.50 (m, 1H, Ar-H), 7.62 (d, 2H, J = 8.4 Hz, Ar-H), 7.76 (s, 1H, thiazole), 8.63 (s, 1H, C-4 of coumarin), 10.24 (s, 1H, N-H); ^{13}C NMR (DMSO-d_6) δ (ppm): 20.8, 50.2, 110.1, 113.1, 119.1, 119.7, 120.3, 121.1, 124.3, 130, 133.4, 137.6, 138.8, 142.5, 144, 146.9, 159.1, 164.5; ESI-MS *m/z* (%): 365[M+H]$^+$; Anal. Calcd (%) for $C_{20}H_{16}N_2O_3S$: C, 65.92; H, 4.43; N, 7.69. Found: C, 65.90; H, 4.47; N, 7.60.

SUPPLEMENTARY DATA

Figures S1–S6 can be accessed on the publisher's website at http://dx.doi/10.1080/10426507.2014.990016

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