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A Facile One-Pot Multi-Component Synthesis of (E)-3-(2-((5-(benzylideneamino)-4H-1,2,4-triazole-3-yl)thio)acetyl) -2H-chromen-2-oneand its Derivatives

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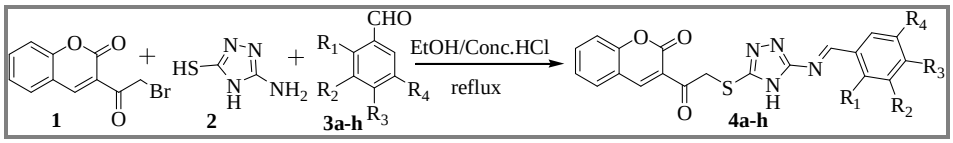
ABSTRACT

*An efficient one-pot multi-component method for the synthesis of (E)-3-(2-((5-(benzylideneamino)-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-ones(**4a-f**) have been described with good yields. It has been synthesized from 3-(2-bromo acetyl) chromen-2-ones (**1**) and 5-amino-4H-1,2,4-triazole-3-thiol (**2**), substituted benzaldehydes (**3**)in anhydrous ethanol and Conc. HCl resulted in the formation of title compounds. All the synthesized compounds have been characterized by analytical and spectral data.*

Graphical Abstract

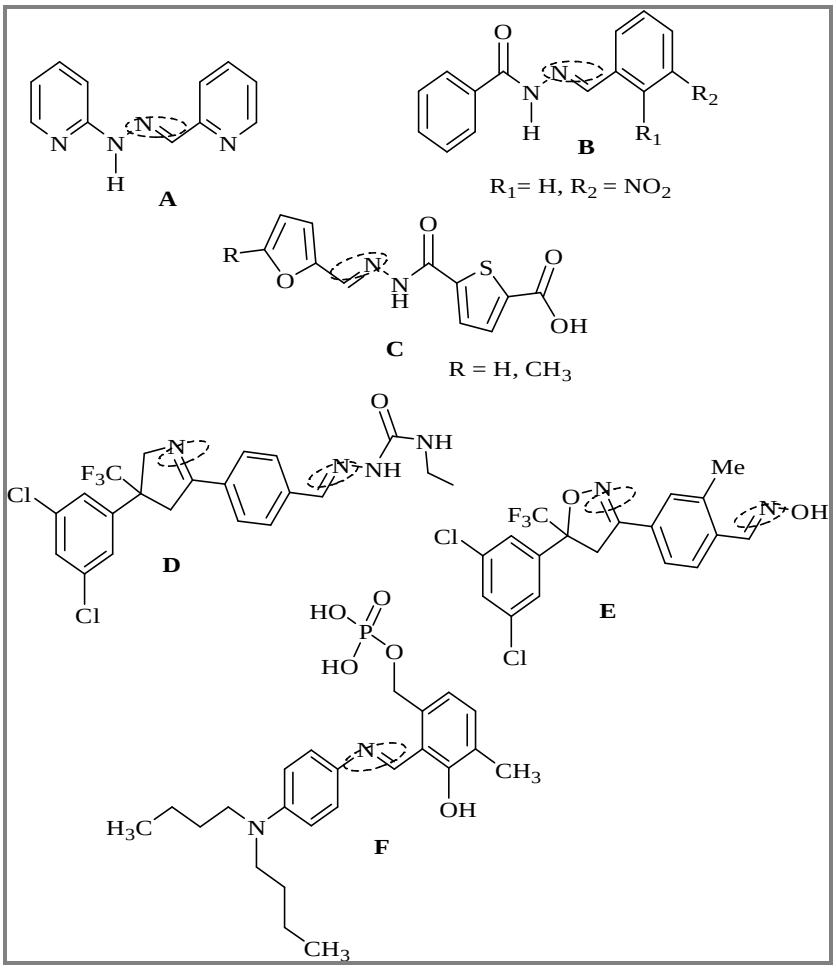


Keywords: Coumarin, 1,2,4-Triazoles, Schiff's base, One pot multi-component reaction.

INTRODUCTION

The 1,2,4-Triazole and its derivatives are the most significant class of heterocyclic compounds in the medicinal chemistry and pharmaceutical chemistry. The 1,2,4-triazole has been incorporated into a wide variety of interesting drugs including H_1/H_2 histamine receptor blockers, choline esterase activity agents, CNS stimulants, anti-anxiety agents and sedatives [1]. Which have been shown remarkable biological activities such as antibacterial, antifungal [2], antitumor [3], anti-inflammatory [4], ketol-acid reductoisomerase inhibitors [5], analgesic [6], antihypertensive [7], antiviral [8]. Theearlier literature survey has been stated that many coumarin derivatives are widely distributed in several drugs and have been shown significant biological activities among them anti-microbial [9, 10], antifungal [11], anti-inflammatory [12], anticancer [13, 14], anti-tubercular [15] and antitumor activity [16]. In observation the present study focused on (E)-3-(2-((5-(benzylideneamino)-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-ones.

Schiff's bases are imine or azomethine (-C=N-) functional group-containing compounds. These are formed by the condensation reaction of primary amines with carbonyl compounds and were first reported by Hugo Schiff. A Schiff base has an important class of the most widely used organic compounds and has a wide variety of applications [**17**] among them such as analytical, biological, biochemistry and inorganic chemistry. All these have gain importance in medicinal and pharmaceutical chemistry due to a wide range of biological activities such as antioxidant [**18**], anthelmintic [**19**], antimicrobial [**20**], anticonvulsant [**21**], antitubercular [**22**], anticancer [**23**], anti-inflammatory [**24, 25**]. Apart from that importance, Schiff bases have been used in different applications as antiglycation agents [A, B, C], pesticidal agents [D, E], as a reagent used in the assay determination of plasma homocysteine [F]. Some of these reported Schiff base containing scaffolds.



Schiff base containing scaffolds.

Because of their importance, many efficient methods have been developed for coumarin and 1,2,4-triazole derivatives. Among them, multi-component reactions (MCRs) [**26-28**] are the most excellent synthetic methods in organic chemistry. In a multi-componentreaction, three or more reactants combine to generate a single product in only one operation. These reactions can be performed under mild reaction conditions, shorter reaction times with maximum selectivity, atom economy and a high percentage of yields in a single synthetic operation [**29**]. Consequently, the MCRs are many advantages over the conventional linear stepwise synthesis. In view of this observation and our present study importance on the development of Schiff base containing new methodology for the synthesis (E)-3-(2-((5-(benzylideneamino)-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-ones.

MATERIALS AND METHODS

All the chemicals used in this present protocol were purchased from commercial sources used without further purification. The purity of prepared materials was checked by TLC on silica plates (E-Merk, Mumbai, India). Melting points were checked with an open capillary tube with a "Cintex" melting point apparatus, Mumbai, India and were uncorrected. IR spectra were recorded in KBr disks on a Bruker WM-200 MHz spectrometer. ^{1}H- and ^{13}C-NMR spectra were documented on a Bruker WM-400 spectrometer (in δ ppm) using TMS as an internal standard. Mass spectra (EI-MS) were determined on Jeol-D-300 spectrometer at 70 eV. CHN analyses were recorded on Carlo Erba 1108 Heraeus analyzer. The 3-(2-bromoacetyl)chromen-2-ones (**1**) were prepared by reported procedures [22].

General procedure for the synthesis of (E)-3-(2-((5-(benzylideneamino)-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-one (Method I)(4a-f): A mixture of 5-amino-4H-1,2,4-triazole-3-thiol **(**1 mmol), appropriate aromatic benzaldehyde(1 mmol) and 3-(2-bromoacetyl)-chromen-2-one (1 mmol), was taken in 5 mL of ethanol and catalytic amount of conc. HCl was added to reaction mixture. The reaction mixture was refluxed for 4 hours bymonitored TLC andallowed to cool room temperatureto get the solid, which was filtered, dried and recrystallized from ethanol to get title compounds (Table-1).

(E)-3-(2-((5-((4-methylbenzylidene)amino)-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-one 4a: IR (KBr) v cm-1;1608 (-C=N), 1679 (-C=O), 1717 (lactone, -C=O) and 3411 (triazole, -NH) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.15 (s,3H, -CH_3) 4.52 (s, 2H, -CH_2-),5.57 (s, 1H, triazole –NH-), 7.39-7.41 (m, 4H, Ar-H), 7.69 – 7.73 (m, 2H, of C_6&C_8-H coumarin), 7.79 (m, 1H, Ar-H of C_7-H), 7.81 (m, 1H, Ar-H of C_5-H), 8.61 (s, 1H, C_4-H of coumarin) and 11.64 (s, 1H, of –CH=N-);^{13}C NMR (400 MHz, DMSO-d_6): δ45.56, 112.50, 115.31, 116.50, 118.70, 124.24, 125.44, 128.72, 129.42, 131.12, 133.02, 135.35, 139.63, 152.81, 154.64, 157.97, 167.29, 191.47.

(E)-3-(2-((5-((3-(nitromethyl)benzylidene)amino)-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-one4b: IR (KBr) v cm-1;1607 (-C=N), 1636 (-C=O), 1726 (lactone, -C=O) and 3435 (triazole, -NH) cm^{-1} ; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.00 (s, 2H, -CH_2- of Sulfer), 5.57 (s, 1H, triazole –NH-), 7.39-7.43 (m, 3H, Ar-H), 7.63 – 7.75 (m, 2H,of C_6&C_8-H coumarin), 7.82 – 7.86 (m,1H, Ar-H), 8.17 (m, 1H, Ar-H of C_7-H), 8.28 – 8.30 (m, 1H, Ar-H of C_5-H), 8.49 - 8.51 (s, 1H, C_4-H of coumarin), 9.57 (s,1H, triazole NH) 10.16 (s, 1H, of –CH=N-);^{13}C NMR (400 MHz, DMSO-d_6): δ 45.56, 112.50, 115.31, 116.50, 118.70, 124.24, 125.44, 128.72, 129.42, 131.12, 133.02, 135.35, 139.63, 152.81, 154.64, 157.97, 167.29, 191.47.

(E)-3-(2-((5-((4-methoxybenzylidene)amino)-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-one 4c: IR (KBr) v cm-1;1608 (-C=N), 1679 (-C=O), 1725 (lactone, -C=O) and 3438 (triazole, -NH) cm^{-1} ; ^{1}H NMR (400 MHz, DMSO-d_6): δ3.30 (s, 3H, OCH_3), 4.52 (s, 2H, -CH_2-), 5.67 (s, 1H, triazole –NH-), 7.40-7.79 (m, 3H, of C_6, C_7 &C_8-H coumarin), 7.82 – 7.86 (m,4H, Ar-H), 7.98 (m, 1H,of C_5-H coumarin), 8.65 - 8.51 (s, 1H, C_4-H of coumarin), 11.70 (s, 1H, of –CH=N-);^{13}C NMR (400 MHz, DMSO-d_6): δ 45.56, 112.50, 115.31, 116.50, 118.70, 124.24, 125.44, 128.72, 129.42, 131.12, 133.02, 135.35, 139.63, 152.81, 154.64, 157.97, 167.29, 191.47.

(E)-3-(2-((5-((2,4-dichlorobenzylidene)amino)-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-one 4d: IR (KBr) v cm-1;1609 (-C=N), 1681(-C=O), 1724 (lactone, -C=O) and 3441 (triazole, -NH) cm^{-1} ; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.52 (s, 2H, -CH_2-), 5.52 (s, 1H, triazole –NH-), 7.43 – 7.47 (m, 2H, Ar-H of C_7 and C_8), 7.53 (m, 2H, Ar-H of C_5& C_6-H), 7.56 – 7.65 (m, 3H, Ar-H), 7.76 - 7.78 (m, 1H,Ar-H), 8.14 (d, 1H, *J* = 2 Hz, C_5-H of coumarin), 8.60 (s, 1H, C_4-H of coumarin) and 11.53 (s, 1H, of –CH=N-).

General Procedure for the Preparation of 3-(2-((5-amino-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-ones, (Method-II)(5): A mixture of 3-(2-bromoacetyl)chromen-2-one(1 mmol) and 5-

amino-4H-1,2,4-triazole-3-thiol(1 mmol) was refluxed for 1 h. The reaction mixture was checked by TLC, then allowed to cool room temperature to get the solid, was filtered. The crude product was recrystallized from ethanol.

3-(2-((5-amino-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-ones 5: IR (KBr) v cm-1;1604 (-C=N), 1712 (lactone, -C=O), 1750 (ester, –C=O), 3418 (-NH-) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6):δ4.75 (s,2H,-CH_2-),7.40 – 7.44 (m, 2H, C_6 &C_8H, Coumarin), 7.59 (m, 1H, C_7-H of Ar-H), 7.75 (d, 1H, C_5-H of coumarin), 7.77 – 7.88 (s, 2H, NH_2), 7.94 (s, 1H, NHof triazole), 8.7 (s, 1H, C_4-H of coumarin);^{13}C NMR (400 MHz, DMSO-d_6): δ42.79, 116.60, 118.24, 122.51, 125.48, 131.10, 135.40, 146.58, 149.54, 152.19, 155.28, 159.01, 189.76.

General Procedure for the Preparation of 4a-f from 5 (Method-II): A mixture of 3-(2-((5-amino-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-one **5** (1 mmol) and appropriate aromatic aldehyde (1 mmol) was taken in 5 mL of dry ethanol and a catalytic amount of Conc. HCl was refluxed for 4 h. The reaction mixture was checked by TLC than allowed to cool room temperature to get the solid, was filtered. The crude product was recrystallized from ethanol to get the title compounds (Table 1).

Table 1. Physical data of compounds (**4a-g**).

Compounds 4a-h	R_1	R_2	R_3	R_4	Molecular Formula	Molecular Weight g mol^{-1}	Yield (%) Method I, II		M.P. (^{0}C)
							I	II	
a	H	H	CH_3	H	$C_{21}H_{16}N_4O_3S$	404.44	85	78	225 - 227
b	H	H	H	NO_2	$C_{21}H_{15}N_5O_5S$	449.44	86	71	212 - 214
c	H	H	OCH_3	H	$C_{21}H_{16}N4_5O_4S$	420.44	88	68	217 - 219
d	Cl	H	Cl	H	$C_{20}H_{12}N_4O_3SCl_2$	459.31	81	65	235 - 237
e	Cl	H	H	H	$C_{20}H_{13}N_4O_3SCl$	424.86	83	70	231 - 232
f	H	H	H	OCH_3	$C_{21}H_{16}N_4O_4S$	420.44	84	76	220 -222
g	H	H	Br	H	$C_{20}H_{13}BrN_4O_3S$	469.31	85	73	40 - 242

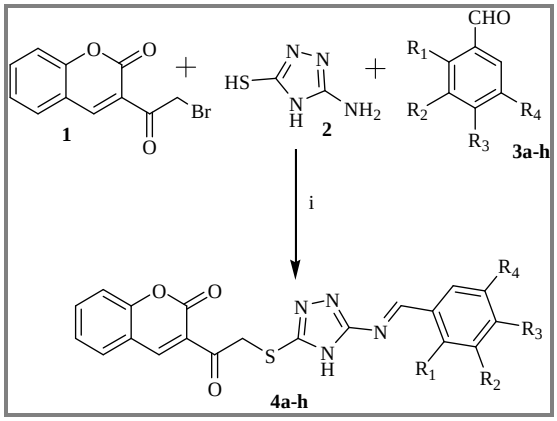
RESULTS AND DISCUSSION

The present protocol involved in one pot multi-component acid catalyzed condensation reaction of 3-(2-bromoacetyl)coumarins **1,** with 5-amino-4H-1,2,4-triazole-3-thiol **2** and benzaldehyde **3** in ethanol and a catalytic amount of Conc. HCl. The yields of the products **4a-**g are good (80%). The one pot multi-component method, it is believed that 3-(2-bromoacetyl)coumarins **1** react with 5-amino-4H-1,2,4-triazole-3-thiol **2** and benzaldehyde **3** in ethanol and conc. HCl to give (E)-3-(2-((5-(benzylideneamino)-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-ones. The first method (**Method-1**) has an efficient acid catalyzed condensation reaction and a simple, easy workup procedure, without any side products. The reaction takes place under reflux conditions (Scheme 1) **4** through immediately formed by s-alkylation after that condensation reaction takes place, as a result, Schiff base.

Title compounds **4a-g** can also be synthesized through an alternative method involving of 3-(2-bromoacetyl)chromen-2-one **1** with 5-amino-4H-1,2,4-triazole-3-thiol **2** in ethanol to yield the corresponding 3-(2-((5-amino-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-one **5**. This on further reaction with substituted benzaldehydes in ethanol and Conc. HCl resulted in the formation of **4a-g** through a two-step process (Method -2) by s-alkylation and condensation reaction. The yields of products (**Method-2**) **4a-g** are in between 78-65%. Both the methods obtained the title compounds were found to be identical by their mixed m.p. measurements, co-TLC and IR spectra (Scheme 2).

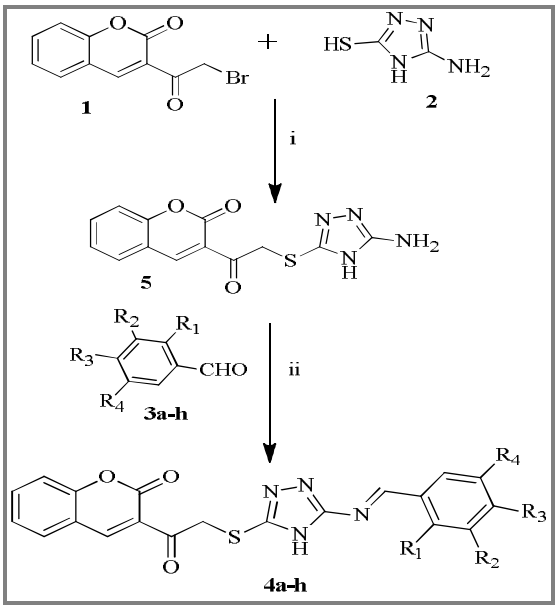
In the present method-1 was preferred over method-2, higher yields of the products and less time. Unlike the literature methods, we have first time synthesized title compounds **4a-g** in one step to

expand the scope of synthetic transformation and offer a new convenient method for synthesis of (E)-3-(2-((5-(benzylideneamino)-4H-1,2,4-triazol-3-yl)thio)acetyl)-2H-chromen-2-ones.



Experimental condition: (i) EtOH/Conc.HCl Reflux for 4 h.

Scheme 1. Method-1.



Experimental condition: (i) EtOH, Reflux for 1 h;
(ii) EtOH/Conc.HCl, Reflux for 4 h.

Scheme 2. Method -2.

All the synthesized materials were characterized by their analytical and spectral data for some representative compounds **4a-g** and **5** have given. The IR spectra of compounds **4a** showed prominent peaks 1608 (-C=N), 1679 (-C=O), 1717 (lactone, -C=O), 3411 (-NH) cm^{-1}, consistent with the assigned structures. The ^1H NMR (DMSO-d_6) spectrum of **4a** showed signals around δ 2.15 (s, 3H,-CH_3), 4.52 (s, 2H, -CH_2-), 5.57 (s,1H, -NH-), 7.39-7.41(m, 4H, Ar-H), 7.69 – 7.73 (m, 2H, of C_6 and C_8-H coumarin), 7.79 (m, 1H, Ar-H of C_7-H), 7.81 (m, 1H, Ar-H of C_5-H), 8.61 (s, 1H, C_4-H of coumarin) and 11.64 (s, 1H, of –CH=N-), in the mass spectrum **4a** showed the molecular ion peak at m/z 404 (100%). The IR spectra of compounds **5** showed prominent peaks at 1607(-C=N), 1679 (-C=O), 1725 (lactone, -C=O), 3441 (-NH) cm^{-1},CH_2 protons appeared around δ 4.56 in the ^{1}HNMR spectra and –NH- proton appeared at δ5.76 which is D_2O exchangeable. The methyl protons appeared at δ 2.16 as a singlet. The mass spectrum of 5 showed the molecular ion at m/z 302.

APPLICATION

In this present study, the title compounds have been synthesized from acid catalyzed one pot multi-component reaction.

CONCLUSION

In this protocol, we have described a Schiff base containing a different kind of heterocyclics were obtained by two methods from readily available starting materials. The advantages of this protocol Method-I was preferred over Method-II is, therefore, mild reaction conditions, single step, shorter reaction times, good yields and easy workup-up procedure, without any side products. All the synthesized compounds may be useful for drug improvement and the biological activity of these compounds is in progress.

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