Basic Ionic Liquid Promoted Domino Knoevenagel–Thia-Michael Reaction: An Efficient and Multicomponent Strategy for Synthesis of 1,3-Thiazines

I. R. Siddiqui,* Rahila, Shayna Shamim, Pragati Rai, Shireen, Malik A. Waseem, Arjita Srivastava, and Anjali Srivastava

Laboratory of Green Synthesis, Department of Chemistry, University of Allahabad, Allahabad 211002, India
*E-mail: dr.irsiddiqui@gmail.com
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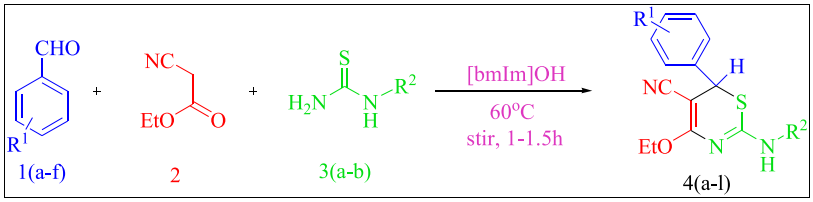

An efficient, three-component strategy for synthesis of 1,3-thiazines with high atom economy in one-pot mediated by room temperature basic ionic liquid is described here. The strategy involves basic ionic liquid, [bmim]OH-catalyzed Knoevenagel condensation between ethyl cyanoacetate and aromatic aldehyde and subsequent thia-Michael addition with substituted thioureas. The reaction sequence is smooth and quantitative under ambient temperature. [bmim]OH was recovered and reused four times without any appreciable decrease in its reactivity and product yield.

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INTRODUCTION

1,3-Thiazines constitute an important class of compounds possessing diverse biological activities such as antibacterial, insecticidal, fungicidal, antitumor, antioxidant, antipyretic, and calcium channel modulator [1]. In addition, it is the active core of cephalosporins that are among the widely used β-lactam antibiotics [2] and are also known as antiradiation agents and used as radiation sickness drugs [3].

In addition, ionic liquids (ILs), have received substantial interest from the synthetic community owing to their properties like negligible vapor pressure, lack of flammability, wide solvation ability, and high stability. ILs are also associated with enhancement of yields, increase in chemoselectivity, regioselectivity, and stereoselectivity, easy recovery and reuse [4–12]. The basic IL [bmim]OH has been successfully applied to catalyze Knoevenagel condensations of aliphatic and aromatic carbonyl compounds [13] as well as Michael additions of active methylene compounds to conjugated ketones, carboxylic esters, and nitriles [14]. It has very successfully replaced conventional bases as it is flexible, non-volatile and non-corrosive.

Knoevenagel condensation followed by hetero-Michael addition has considerably attracted attention as a versatile, expeditious and cost-effective strategy for synthesis of heterocycles for drug discovery process [15–18]. Multicomponent reactions in which three or more reactants are combined in a single vessel to generate new molecule that contain portions of each reactants undoubtedly maintain great importance in organic and medicinal chemistry as a result of synthetic efficiency and molecular diversity required in the discovery of new lead compounds [19].

Although number of protocols are reported for formation of 1,3-thiazines [20] but except very few, all of them involves volatile organic solvents, number of steps, low yield, high temperature, longer reaction time etc. Thus, there is still need to develop simple, clean eco-efficient method that offers wider flexibility with maximum functional group tolerating ability. Buoyed from the previous facts and as part of our ongoing program aimed at the development of simple, efficient, eco-compatible protocols for the synthesis of biodynamic heterocyclic scaffolds [21], we report herein an efficient synthesis of 1,3-thiazines mediated by tailor made, task-specific, room temperature basic ionic liquid (RTBIL), [bmim]OH (Scheme 1).

RESULTS AND DISCUSSION

Based on our progressive endeavors in exploring novel and practical multicomponent reactions to synthesize biodynamic heterocyclic compounds, we present, herein, the result of a novel three-component RTBIL-mediated cascade reaction for the efficient synthesis of 1,3-thiazines.

To find the best reaction condition for the synthesis of 1,3-thiazines, thiophene-2-carboxaldehyde **1a**, ethyl cyanoacetate **2** and *N*-allylthiourea **3b** were selected as model reactants. The reaction condition was optimized using different solvent as well as bases. Of the bases tested,

Scheme 1. RTBIL-mediated one-pot synthesis of 1,3-thiazines.

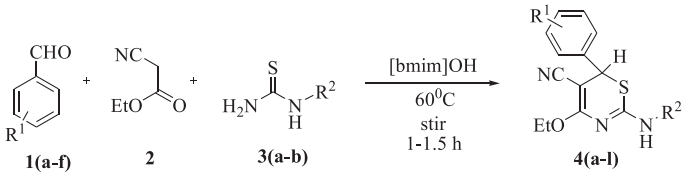
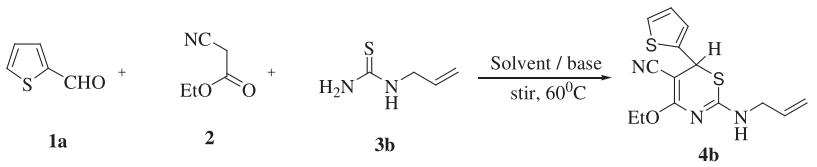


Table 1

Optimization of reaction condition for the synthesis of 1,3-thiazine in one-pot[a].



Entry	Solvent	Base (mol%)	Time (h)	Yield (%)[b]
1	Ethanol	NaOH (10)	1	55
2	THF	NaOH (10)	1	30
3	Acetone	NaOH (10)	1	35
4	Acetonitrile	NaOH (10)	1	45
5	Ethanol	Et_3N (10)	1	35
6	Ethanol	K_2CO_3 (10)	1	30
7	[bmim]OH (15)	—	1	88
8	[bmim]Cl (15)	—	2	32
9	[bmim]Br (15)	—	2	36

[a]Reaction conditions: 5.5 mmol thiophene-2-carboxaldehyde, 5 mmol ethyl cyanoacetate, 5 mmol thiourea.
[b]Yield of isolated and purified product.

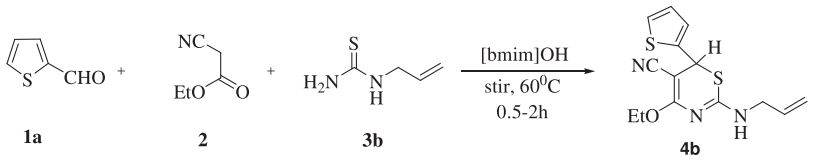
NaOH was found to be the best base, and with respect to the solvent-base system, the best results were achieved using ethanol and NaOH (Table 1, entry 1). In order to make the synthesis more eco-friendly and from the reports of ILs in organic transformation, a three-component reaction was performed using different ILs without any inorganic base in one-pot.

It can be inferred from Table 1 that the result of reaction for the synthesis of 1,3-thiazines in one-pot using different ILs as base as well as reaction media favor for use of [bmim]OH because the yield of product was excellent. It was also observed from the table that the reaction of aldehyde with ethyl cyano acetate and thiourea that are easily achieved by [bmim]OH, proceeded to very small extent under the catalysis of [bmim]Cl or [bmim]Br. This shows the vital role of the hydroxyl counter ion of this RTBIL in this transformation. The yield observed in case of [bmim]Br and [bmim]Cl might be because of the possibility of charged and polar intermediates in the reaction pathways, and it is reasonable to envisage ion-pairing formation of those species with ionic components (cations and anions) [22].

With [bmim]OH as the best promoter, we next intended to optimize its amount, necessary enough to furnish the desired product in maximum yield **4a**. We analyzed the reaction by varying the loading amount to 5, 10, 15, 20 and 25 mol% of [bmim]OH, and the results are summarized in Table 2. The optimum loading amount of [bmim]OH was found to be 15 mol% (entry 3), as no improvement in the yield was observed on increasing the loading amount to 20 and 25 mol% (entries 4 and 5). Whereas, when the amount of [bmim]OH was 5 or 10 mol%, the yield observed was drastically low (entries 1 and 2). Reaction efficiency was also investigated by varying the reaction temperatures. The results demonstrated that the reaction proceeds smoothly at 60°C; increasing the reaction temperature to 70°C (entry 6) had no effect in the yield, while on decreasing the reaction temperature to 50°C, yield of the product **4a** reduces (entry 7). At room temperature, the reaction took longer time and furnished the product in low yield (entry 8). Finally, the reaction time was investigated, the desired product was obtained in good yield in 1 h stirring time, on decreasing reaction time the yield obtained was relatively

Table 2

[bmim]OH-mediated three-component synthesis of 1,3-thiazine in one-pot[a].



1a **2** **3b** **4b**

Entry	[bmim]OH (mol %)	Time (h)	Temp (°C)	Yield (%)[b]
1	5	1	60	53
2	10	1	60	61
3	15	1	60	88
4	20	1	60	88
5	25	1	60	88
6	15	1	70	88
7	15	1	50	65
8	15	2	rt	38
9	15	0.5	60	60
10	15	2	60	88

[a]Reaction conditions: 5.5 mmol thiophene-2-carboxaldehyde, 5 mmol ethyl cyano acetate,5 mmol thiourea.
[b]Yield of isolated and purified product.

low (entry 9), and no change was observed in the product yield when stirring time was increased from 1.5 to 2 h (entry 10). Thus, the optimized set of conditions for the synthesis of 1,3-thiazine in one-pot was achieved employing 15 mol% of [bmim]OH as promoter, 1 h stirring time at 60°C.

After having the optimized set of conditions in hand, we were set about evaluating the scope of this new protocol by using various aromatic aldehydes, ethyl cyanoacetate and substituted thioureas. The results of this study are summarized in Table 3.

A wide range of aromatic aldehydes underwent condensation with active methylene compound ethyl cyano acetate and *N*-substituted thioureas by this procedure in one-pot in the presence of [bmim]OH yielding corresponding 1,3-thiazines. All of the reactions proceeded smoothly under the optimal conditions, affording annulated products with good to excellent yields. Aldehydes having both electron-donating and electron-withdrawing substituents that were well tolerated, providing the desired products. However, those with electron-donating substituent offered the products with slightly lower yields and took longer to form the respective products (Table 3, entries 6 and 7). In addition, thioureas with different substituents (3a, b) worked well. Heteroaromatic aldehydes such as thiophene-2-carboxaldehyde and furan-2-carbaldehyde (entries 1, 2, 9, and 10) also underwent smooth condensation. Thus, the IL [bmim]OH efficiently promoted the reaction as base as well as acted as alternative reaction media. Compared with other reported methods for the preparation of 1,3-thiazines, the methodology presented herein provides a novel, convenient, efficient, eco-compatible and cost effective access to a wide variety of 1,3-thiazines.

After the successful application of 15 mol% of [bmim]OH in promoting the reaction, we addressed the issue of its recyclability. [bmim]OH was recovered and reused four times without any appreciable decrease in its activity and yield of the product (Fig. 1).

First recycled [bmim]OH gave no product loss, and only 3, 3 and 5% product loss occurred after second, third, and fourth recycling. The IL remained intact as evidenced by ^{1}H NMR.

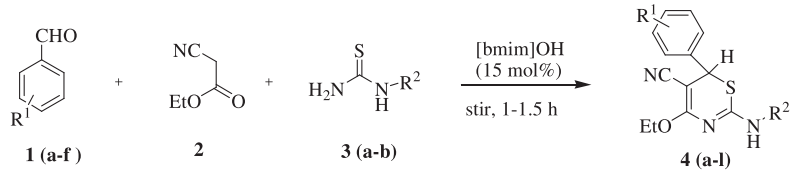
On the basis of previous observations, a mechanistic sequence is proposed for this [bmim]OH-catalyzed reaction. The strategy involves formation of intermediate **I** from Knoevenagel condensation between aromatic aldehyde and enolate ion of ethyl cyanoacetate. The activated olefinic group of intermediate ethyl 2-cyano-3-phenyl acrylate acted as acceptor in nucleophilic conjugate addition with thiourea effecting on thia-Michael addition. Hetero-Michael product **II** on subsequent dehydrative intramolecular nucleophilic addition yielded 2-amino-4-ethoxy-6-phenyl-6H-1,3-thiazine-5-carbonitrile (Scheme 2).

CONCLUSIONS

In conclusion, the present procedure using RTBIL [bmim]OH provides an efficient and convenient method for the three-component domino reaction of aldehydes, ethyl cyanoacetate and thioureas without the requirement

Table 3

RTBIL-mediated three-component synthesis of 1,3-thiazines[a].



1 (a-f) **2** **3 (a-b)** **4 (a-l)**

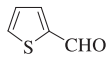
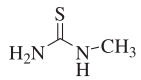
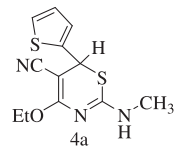
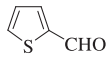
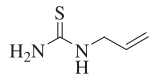
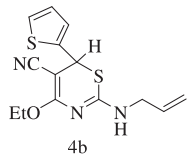
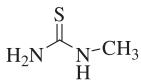
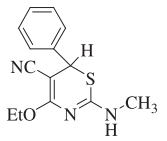
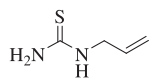
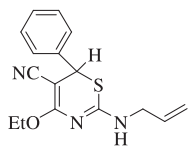
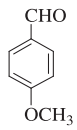
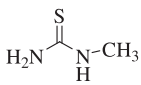
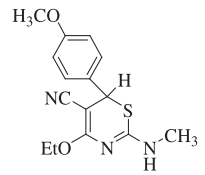
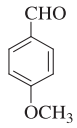
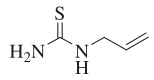
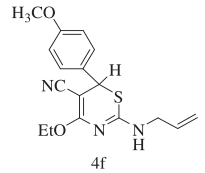
Entry	**1**(a–f)	**3**(a–b)	Product **4**(a–l)	Time (h)	Yield (%)[b]
1	 1a	 3a	 4a	1	84
2	 1a	 3b	 4b	1	86
3	 1b	 3a	 4c	1	76
4	 1b	 3b	 4d	1	77
5	 1c	 3a	 4e	1.5	76
6	 1c	 3b	 4f	1.5	78

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Table 3
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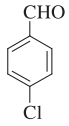
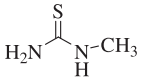
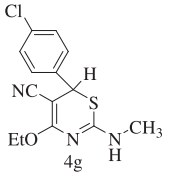
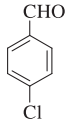
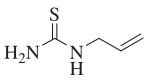
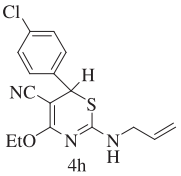
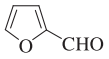
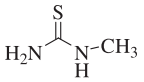
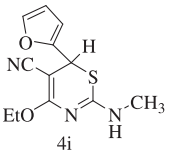
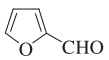
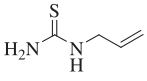
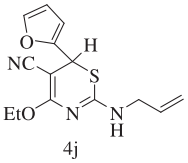
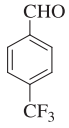
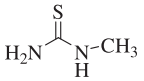
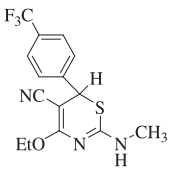
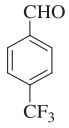
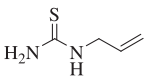
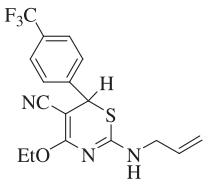
7	 1d	 3a	 4g	1	85
8	 1d	 3b	 4h	1	86
9	 1e	 3a	 4i	1	80
10	 1e	 3b	 4j	1	82
11	 1f	 3a	 4k	1	87
12	 1f	 3b	 4l	1	88

[a]Reaction conditions: 5.5 mmol aldehyde, 5 mmol ethyl cyano acetate, 5 mmol thiourea mixed in 15 mol% [bmim]OH stirred at 60°C for 1–1.5 h.
[b]Yield of isolated and purified product.

of any other inorganic base, catalyst and additional solvent. The efficiency, simplicity and milder reaction conditions of the protocol are the additional attributes in the context of green chemistry. In addition, general applicability and avoidance of hazardous organic solvent and toxic catalysts, excellent yield of products with high selectivity, makes the protocol preferable for the synthesis of 1,3-thiazines and other related biodynamic heterocyclic scaffolds.

EXPERIMENTAL

Materials and method. All chemicals were used as received without further purification. NMR spectra were recorded on a Bruker Avance DPX-400 FT Spectrophotometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) using $CDCl_3$ as solvent and TMS as internal reference. Mass spectra were recorded on a JEOL SX-102(FAB) mass spectrophotometer at 70 ev. Elemental analyses were carried out in Coleman

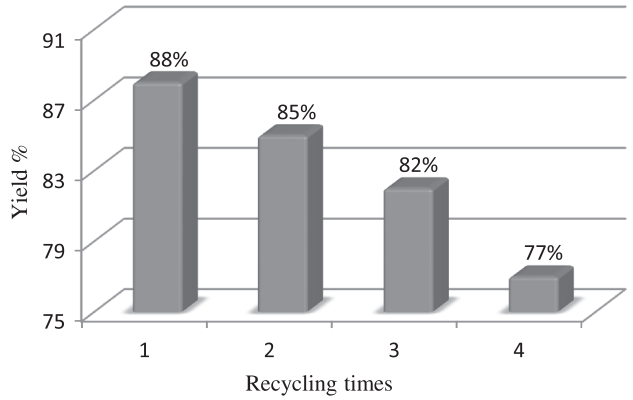


Figure 1. Recycling of [bmim]OH.

automatic carbon, hydrogen and nitrogen analyzer. Silica gel-G was used for TLC. Melting points were determined by open glass capillary method and are uncorrected.

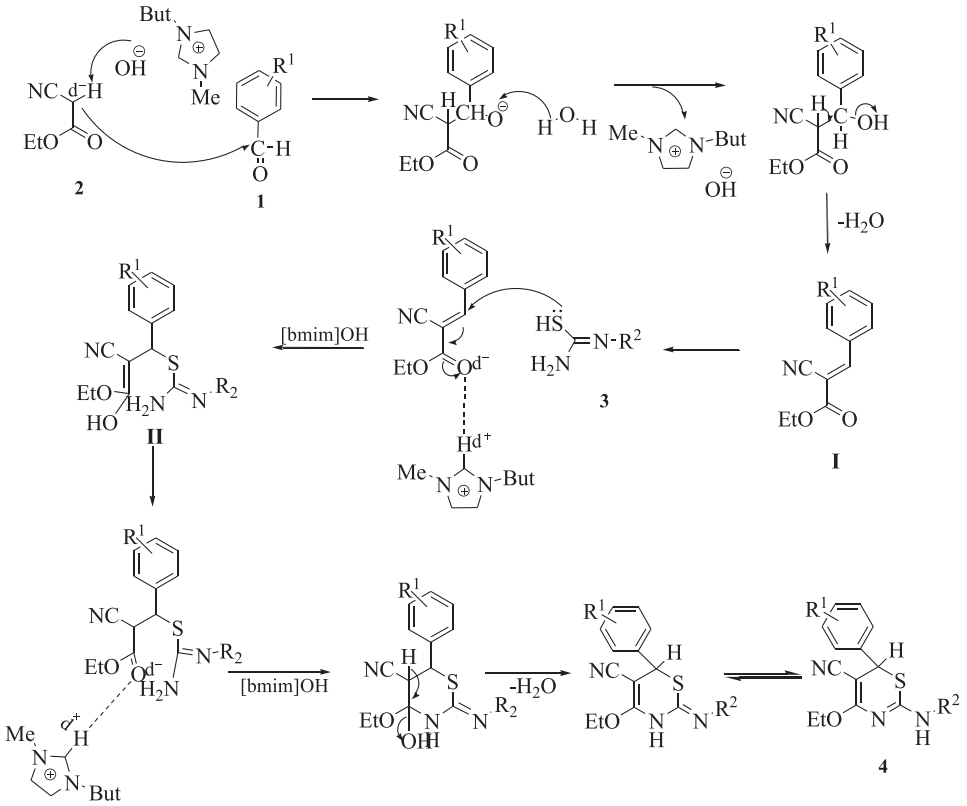
Preparation of 1-butyl-3-methylimidazolium hydroxide [bmim]OH. The basic IL was synthesized according to an earlier reported procedure [14].

4-Ethoxy-6-(phenyl)-6H-[1,3]thiazine-5-carbonitrile derivative: typical procedure. A mixture of thiophene-2-carboxaldehyde (5.5 mmol) and ethyl cyanoacetate (5.0 mmol) in [bmim]OH was stirred at 60°C for approximately 10–15 min. After formation of Knoevenagel adduct as evidenced by TLC, *N*-allyl thiourea (5 mmol) was added. After completion of the reaction, 20 mL of water was added and stirred well. The product was extracted with EtOAc (3 × 20 mL). The residue was purified by silica gel (mesh 60–120) chromatography (hexane–EtOAc) to afford the analytically pure compound **4** in 88% yield. After isolation of the product, the remaining aqueous layer containing the IL was washed with $(C_2H_5)_2O$ (2 × 10 mL), to remove organic impurity and filtered. The filtrate was extracted with CH_2Cl_2 (2 × 10 mL), dried over $MgSO_4$ and evaporated under reduced pressure to afford [bmim]OH, which was reused four times.

Characteristic data of products. ***4a. 4-Ethoxy-2-methylamino-6-thiophen-2-yl-6H-[1,3]thiazine-5-carbonitrile.*** Yellowish solid; IR (KBr, cm^{-1}): $\nu_{max} = 3370$, 3332, 3079, 3032, 2225, 1645, 1540, 1460, 1375, 1045; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12–6.80 (m, $3H_{arom}$), 8.21 (br s, 1H, NH), 4.80 (s, 1H, thiazine–H), 4.16 (q, 2H, $J = 7.1$ Hz, methylene H of O–CH_2CH_3), 3.73 (s, 3H, N–CH_3), 1.18 (t, 3H, $J = 7.1$ Hz, methyl H of O–CH_2CH_3); ^{13}CNMR ($CDCl_3$, 100 MHz): $\delta = 173.7$, 169.5, 139.4, 126.4, 125.3, 123.4, 117.3, 69.4, 57.8, 30.1, 26.5, 14.8. EIMS: (*m/z*): 279 (M^+), *Anal.* Calcd. For $C_{12}H_{13}N_3OS_2$: C 51.59, H 4.69, N 15.04; found C 51.51, H 4.61, N 15.11.

4b. 2-Allylamino-4-ethoxy-6-thiophen-2-yl-6H-[1,3]thiazine-5-carbonitrile. Yellowish solid; IR (KBr, cm^{-1}): $\nu_{max} = 3369$, 3325, 3071, 3025, 2230, 1631, 1542, 1445, 1370, 1040; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.14–6.76 (m, $3H_{arom}$), 5.74–5.06 (m, 5H, allylic H), 8.25 (br s, 1H, NH), 4.80 (s, 1H, thiazine–H), 4.27 (q, 2H, $J = 7.4$ Hz, methylene H of O–CH_2CH_3), 1.19 (t, 3H, $J = 7.4$ Hz, methyl H of O–CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.9$, 169.8, 139.6, 134.4, 126.5, 125.1, 123.5,

Scheme 2. Tentative mechanism of the [bmim]OH-mediated three-component synthesis of 1,3-thiazines in one-pot.



117.4, 115.3, 69.3, 57.8, 45.8, 30.1, 14.9. EIMS: (*m/z*): 305 (M^+), *Anal.* Calcd. For $C_{14}H_{15}N_3OS_2$: C 49.79, H 4.18, N 15.84; found C 49.71, H 4.25, N 15.77.

4c. 4-Ethoxy-2-methylamino-6-phenyl-6H-[1,3]thiazine-5-carbonitrile. Yellowish solid; IR (KBr, cm^{-1}): $\nu_{max} = 3388$, 3331, 3082, 3030, 2225, 1644, 1539, 1475, 1376,1040; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.72–7.25 (m, $5H_{arom}$), 8.17 (br s, 1H, NH), 4.23 (s, 1H, thiazine–H), 4.23 (q, 2H, $J = 6.9$ Hz, methylene H of O–CH_2CH_3), 3.69 (s, 3H, N–CH_3), 1.20 (t, 3H, $J = 6.9$ Hz, methyl H of O–CH_2CH_3). ^{13}CNMR ($CDCl_3$, 100 MHz): $\delta = 173.4$, 169.7, 141.1, 128.4, 127.8, 117.3, 69.4, 57.8, 29.6, 26.5, 14.9. EIMS: (*m/z*): 273 (M^+), *Anal.* Calcd. For $C_{14}H_{15}N_3OS$: C 61.51, H 5.53, N 15.37; found C 61.59, H 5.45, N 15.31.

4d. 2-Allylamino-4-ethoxy-6-phenyl-6H-[1,3]thiazine-5-carbonitrile. Yellowish solid; IR (KBr, cm^{-1}): $\nu_{max} = 3405$, 3349, 3070, 3026, 2240, 1614, 1542, 1440, 1370, 1032; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.69–7.23 (m, $5H_{arom}$), 5.72–5.11 (m, 5H, allylic H), 8.25 (br s, 1H, NH), 4.26 (s, 1H, thiazine–H), 4.16 (q, 2H, $J = 7.3$ Hz, methylene H of O–CH_2CH_3), 1.20 (t, 3H, $J = 7.3$ Hz, methyl H of O–CH_2CH_3). ^{13}CNMR ($CDCl_3$, 100 MHz): $\delta = 173.7$, 169.2, 141.2, 134.4, 128.6, 128, 127.9, 117.3, 115.3, 69.6, 57.6, 45.8, 29.5, 15.2. EIMS: (*m/z*): 299 (M^+), *Anal.* Calcd. For $C_{16}H_{17}N_3OS$: C 64.19, H 5.72, N 14.04; found C 69.09, H 5.79, N 14.08.

4e. 4-Ethoxy-6-(4-methoxy-phenyl)-2-methylamino-6H-[1,3]thiazine-5-carbonitrile. Yellowish solid; IR (KBr, cm^{-1}): $\nu_{max} = 3398$, 3358, 3083, 3029, 2210, 1644, 1545, 1470, 1370, 1039; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.19–6.95 (m, $4H_{arom}$), 8.16 (br s, 1H, NH), 4.24 (s, 1H, thiazine–H), 4.30 (q, 2H, $J = 7.6$ Hz, methylene H of O–CH_2CH_3), 3.72 (s, 3H, O–CH_3), 3.56 (s, 3H, N–CH_3), 1.19 (t, 3H, $J = 7.6$ Hz, methyl H of O–CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.6$, 169.2, 160.1, 133.4, 128.7, 117.1, 114.4, 69.4, 57.8, 56.1, 29.5, 26.5, 14.9. EIMS: (*m/z*): 303 (M^+), *Anal.* Calcd. For $C_{15}H_{17}N_3O_2S$: C 59.38, H 5.65, N 13.85; found C 59.31, H 5.57, N 13.92.

4f. 2-Allylamino-4-ethoxy-6-(4-methoxy-phenyl)-6H-[1,3]thiazine-5-carbonitrile. Yellowish solid; IR (KBr, cm^{-1}): $\nu_{max} = 3388$, 3323, 3085, 3028, 2220, 1630, 1539, 1450, 1373, 1042; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21–6.96 (m, $4H_{arom}$), 5.72–5.09 (m, 5H, allylic H), 8.25 (br s, 1H, NH), 4.24 (s, 1H, thiazine–H), 4.11 (q, 2H, $J = 6.9$ Hz, methylene H of O–CH_2CH_3), 3.72 (s, 3H, O–CH_3), 1.20 (t, 3H, $J = 6.9$ Hz, methyl H of O–CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.7$, 169.1, 160.3, 134.4, 133.4, 128.8, 117.3, 115, 114.3, 69.1, 57.8, 56.3, 46.2, 29.5, 15.1. EIMS: (*m/z*): 329 (M^+), *Anal.* Calcd. For $C_{17}H_{19}N_3O_2S$: C 61.98, H 5.81, N 12.76; found C 61.88, H 5.88, N 12.68.

4g. 6-(4-Chlorophenyl)-4-ethoxy-2-methylamino-6H-[1,3]thiazine-5-carbonitrile. Yellowish solid; IR (KBr, cm^{-1}): $\nu_{max} = 3394$, 3318, 3089, 3023, 2230, 1635, 1560, 1475, 1376, 1022, 737; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.22–7.05 (m, $4H_{arom}$), 8.22 (br s, 1H, NH), 4.26 (s, 1H, thiazine–H), 4.19 (q, 2H, $J = 7.3$ Hz, methylene H of O–CH_2CH_3), 3.71 (s, 3H, N–CH_3), 1.22 (t, 3H, $J = 7.3$ Hz, methyl H of O–CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.7$, 168.8, 139.2, 132.1, 129.4, 128.9, 117.3, 69.3, 57.8, 29.3, 26.5, 14.8. EIMS: (*m/z*): 307 (M^+), *Anal.* Calcd. For $C_{14}H_{14}ClN_3OS$: C 54.63, H 4.58, N 13.65; found C 54.52, H 4.65, N 13.58.

4h. 2-Allylamino-6-(4-chloro-phenyl)-4-ethoxy-6H-[1,3]thiazine-5-carbonitrile. Yellowish solid; IR (KBr, cm^{-1}): $\nu_{max} = 3380$, 3328, 3086, 3023, 2225, 1630, 1540, 1460, 1375, 1030, 730; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21–7.06 (m, $4H_{arom}$), 5.72–5.08 (m, 5H, allylic H), 8.25 (br s, 1H, NH), 4.26 (s, 1H, thiazine–H), 4.12 (q, 2H, $J = 7.5$ Hz, methylene H of O–CH_2CH_3), 1.19 (t, 3H, $J = 7.5$ Hz, methyl H of O–CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.9$, 169.4, 139.3, 134.4, 132.4, 129.4, 128.8, 117.6, 115, 69.6, 58.2, 45.8, 29.3, 14.9. EIMS: (*m/z*): 333 (M^+), *Anal.* Calcd. For $C_{16}H_{16}ClN_3OS$: C 57.56, H 4.83, N 12.59; found C 57.49, H 4.88, N 12.51.

4i. 4-Ethoxy-6-furan-2-yl-2-methylamino-6H-[1,3]thiazine-5-carbonitrile. Yellowish solid; IR (KBr, cm^{-1}): $\nu_{max} = 3384$, 3322, 3079, 3019, 2235, 1620, 1566, 1467, 1370, 1035; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.18–6.79 (m, $3H_{arom}$), 8.20 (br s, 1H, NH), 4.66 (s, 1H, thiazine–H), 4.31 (q, 2H, $J = 7.2$ Hz, methylene H of O–CH_2CH_3), 3.50 (s, 3H, N–CH_3), 1.20 (t, 3H, $J = 7.2$ Hz, methyl H of O–CH_2CH_3). ^{13}CNMR ($CDCl_3$, 100 MHz): $\delta = 173.5$, 168.7, 152.6, 141.3, 117.3, 110.8, 105.6, 69.6, 57.8, 30.4, 26.5, 14.9. EIMS: (*m/z*): 263 (M^+), *Anal.* Calcd. For $C_{12}H_{13}N_3O_2S$: C 54.74, H 4.98, N 15.96; found C 54.83, H 4.91, N 15.91.

4j. 2-Allylamino-4-ethoxy-6-furan-2-yl-6H-[1,3]thiazine-5-carbonitrile. Yellowish solid; IR (KBr, cm^{-1}): $\nu_{max} = 3390$, 3330, 3083, 3026, 2230, 1640, 1542, 1470, 1376, 1030; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.22–6.83 (m, $3H_{arom}$), 5.74–5.12 (m, 5H, allylic H), 8.25 (br s, 1H, NH), 4.64 (s, 1H, thiazine–H), 4.30 (q, 2H, $J = 6.8$ Hz, methylene H of O–CH_2CH_3), 1.20 (t, 3H, $J = 6.8$ Hz, methyl H of O–CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.3$, 169.1, 152.7, 141.3, 134.4, 117.6, 115.3, 111.2, 105.8, 69.4, 58.2, 45.8, 30.6, 15.4. EIMS: (*m/z*): 289 (M^+), *Anal.* Calcd. For $C_{14}H_{15}N_3O_2S$: C 58.11, H 5.23, N 14.52; found C 58.18, H 5.29, N 14.59.

4k. Ethoxy-2-methylamino-6-(4-trifluoromethyl-phenyl)-6H-[1,3]thiazine-5-carbonitrile. Yellowish solid; IR (KBr, cm^{-1}): $\nu_{max} = 3387$, 3331, 3086, 3029, 2220, 1633, 1545, 1463, 1377, 1230, 1040; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.70–7.26 (m, $4H_{arom}$), 8.25 (br s, 1H, NH), 4.45 (s, 1H, thiazine–H), 4.10 (q, 2H, $J = 7.6$ Hz, methylene H of O–CH_2CH_3), 3.78 (s, 3H, N–CH_3), 1.17 (t, 3H, $J = 7.6$ Hz, methyl H of O–CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.8$, 168.5, 144.7, 129.5, 128.4, 125.9, 119.2, 117.6, 69.5, 57.6, 29.3, 26.5, 14.9. EIMS: (*m/z*): 333 (M^+), *Anal.* Calcd. For EIMS: (*m/z*): 341 (M^+), *Anal.* Calcd. For $C_{15}H_{14}F_3N_3OS$: C 52.78, H 4.13, N 12.31; found C 52.66, H 4.19, N 12.38.

4l. 2-Allylamino-4-ethoxy-6-(4-trifluoromethyl-phenyl)-6H-[1,3]thiazine-5-carbonitrile. Yellowish solid; IR (KBr, cm^{-1}): $\nu_{max} = 3377$, 3325, 3087, 3038, 2239, 1635, 1550, 1470, 1370, 1241, 1036; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.26–7.02 (m, $4H_{arom}$), 5.71–5.20 (m, 5H, allylic H), 8.25 (br s, 1H, NH), 4.43 (s, 1H, thiazine–H), 4.20 (q, 2H, $J = 7.5$ Hz, methylene H of O–CH_2CH_3), 1.19 (t, 3H, $J = 7.5$ Hz, methyl H of O–CH_2CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 173.9$, 169.2, 144.5, 134.4, 129.6, 128.5, 126.5, 119.4, 117.3, 115.6, 69.9, 58.5, 45.8, 29.5, 14.8. EIMS: (*m/z*): 367 (M^+), *Anal.* Calcd. For $C_{17}H_{16}F_3N_3OS$: C 55.58, H 4.39, N 11.44; found C 55.48, H 4.31, N 11.52.

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