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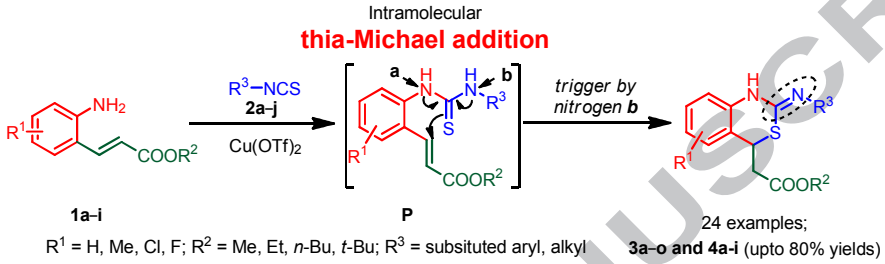

R^1 = H, Me, Cl, F; R^2 = Me, Et, *n*-Bu, *t*-Bu; R^3 = subsituted aryl, alkyl

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Rakesh K. Saunthwal, Monika Patel, Sushil Kumar and Akhilesh K. Verma[b]*

Synthetic Organic Chemistry Research Laboratory, Department of Chemistry, University of Delhi, Delhi 110007, India

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ABSTRACT

An efficient copper-catalyzed tandem approach for the synthesis of 2-imino[1,3]benzothiazines by the reaction of easily accessible 2-aminoaryl acrylates with isothiocyanates via in situ thioamidation and concomitant chemoselective intramolecular thia-Michael addition is described. Intramolecular cyclization was selectively triggered by the nitrogen **'b'** of the thiourea intermediate **P**.

Nitrogen and sulfur-containing compounds are privileged heterocyclic moieties due to their significant biological and pharmaceutical activities[1] and their applications as an organic electroluminescent devices.[2] Benzothiazine core moiety is present in pheofungins which is require for the protein *N*-acetylation in aspergillus nidulans (Figure1, i). The derivatives of 1,3-benzothiazines have shown significant antiproliferative and anticancer activity[3] (Figure 1, ii and iii). Because of the important biological activities of these compounds, significant efforts are being continued and are still require for the development of an efficient methods for their synthesis. Though various synthetic approaches are available for the construction of benzothiazines nucleus,[4] a need for novel and versatile protocols for their efficient synthesis attracts the interest of an organic chemist.

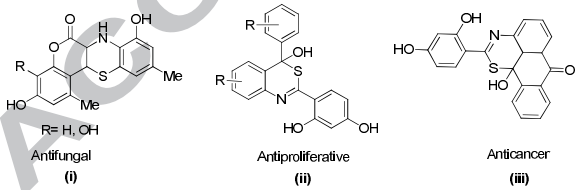
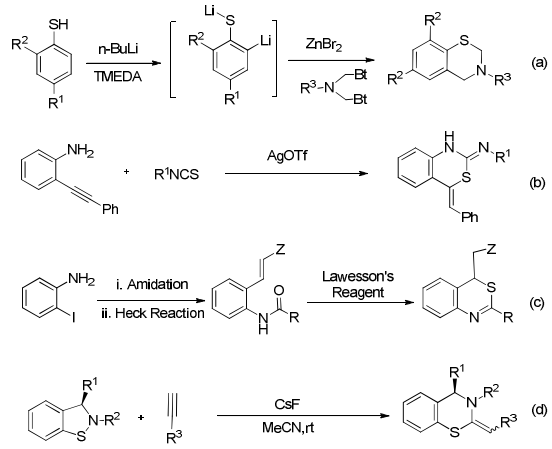


Figure 1. Significant examples of biologically active benzothiazines**.**

Literature survey revealed that in recent years, synthesis of heterocycles by tandem/domino approach[5] has been emerged as an attractive strategy in the field of organic synthesis. Copper-catalyzed conjugate addition (Michael-addition)[6] is one of the most powerful carbon-carbon bond forming reaction and has been extensively explored for the synthesis of wide variety of biologically active heterocycles and natural products[7].

* Corresponding author. Tel.: +91 1127666646 (Ext. 175)
E-mail address: averma@acbr.du.ac.in (Akhilesh K. Verma)

Significant advances have been made for the conjugate addition of amines (aza-Michael addition)[8] and thiols (thia-Michael addition)[9] to prepare their respective β-addition products. Intermolecular conjugate additions of amines and thiols have been well recognized; however intramolecular conjugate additions of thiols have not been much explored.



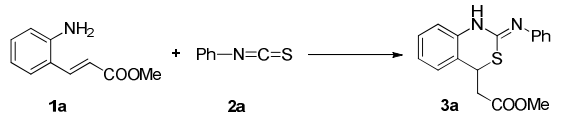
Scheme 1. Previous synthetic approaches

In 2002, Katritzky[10a] reported an elegant approach for the synthesis of [1,3]benzothiazine by direct *ortho*-lithiation of thiophenols by reacting with *N*,*N*-bis[(benzotriazol-1-yl)methyl]amines as 1,3-biselectrophile synthons (Scheme 1, a). Later in 2008 Wu and co-workers reported tandem synthesis of 1,3-benzothiazines starting from 2-alkynylbenzenamines under silver catalysis (Scheme 1, b).[10b] Valliribera[10c] reported synthesis of 4*H*-3,1-benzothiazines from amidoaryl acrylates using

Lawesson's reagent (Scheme 1, c). Recently Reboul and co-workers developed interesting approach for the synthesis of enantiopure 1,3-benzothiazines by the reaction of cyclic sulfenamides with terminal alkynes (Scheme 1, d).[10d]

In continuation of our ongoing research on the synthesis of heterocycles by tandem approach,[11] and our interest to expand the scope of the intramolecular thia-Michael addition;[12] herein we wish to report an efficient tandem approach for the synthesis of 2-imino[1,3]benzothiazines by the reaction of easily accessible 2-aminophenyl acrylates with isothiocyanates via in situ formation of thioamides and concomitant chemoselective intramolecular thia-Michael addition.

Table 1. Optimization of reaction conditions[a]



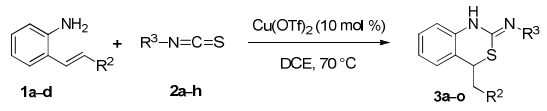
1a **2a** **3a**

Entry	Solvent	Cat./mol%	Time[h]	*T* (°C)	Yield (%)[b]
1	MeCN	AgOTf/5	12	25	00
2	MeCN	AgOTf/5	12	70	10
3	MeCN	AgOTf/5	18	70	15
4	MeCN	AgOTf/10	12	70	25
5	DMF	AgOTf/10	12	70	25
6	THF	AgOTf/10	12	25	32
7	THF	AgOTf/10	36	25	50
8	THF	AgOTf/10	36	50	55
9	DCE	AgOTf/10	36	70	55
10	**DCE**	**$Cu(OTf)_2$/10**	**36**	**70**	**70**
11	THF	$Cu(OTf)_2$/10	36	70	25
12	DCE	$Cu(OTf)_2$/10	18	70	54
13	DCE	$Cu(OTf)_2$/10	36	50	30
14	DCE	$Cu(OTf)_2$/5	36	70	45
15	DCE	CuI/10	36	70	35
16	DCE	$Pd(OAc)_2$/10	36	70	20
17	DCE	$PdCl_2$/10	36	70	30
18	DCE	$AgNO_3$/10	36	70	50
19	DCE	$AgSbF_5$/10	36	70	45
20	DCE	AgOAc/10	36	70	48
21[15]	DCE	-	36	70	00

[a] Reactions were performed using 0.5 mmol of **1a**, isothiocyanates **2a** (0.5 mmol) in 2.0 mL solvent. [b] Isolated yield.

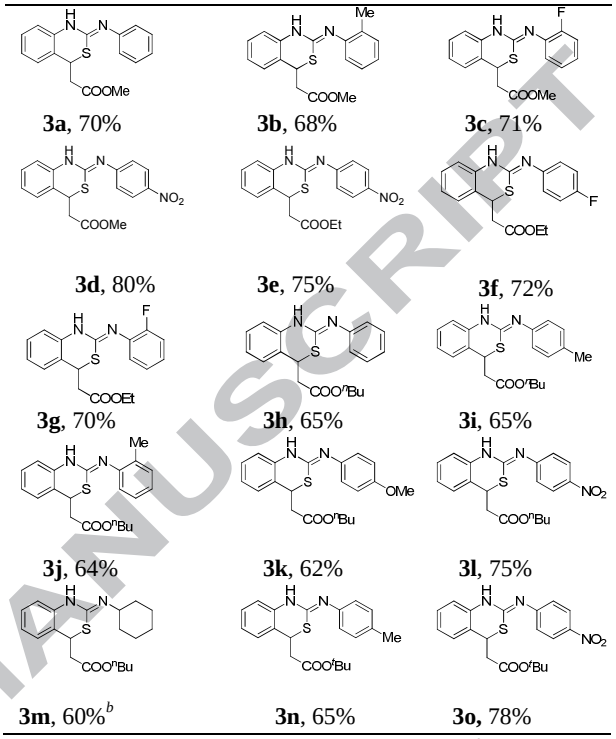
To identify the optimal conditions for the reaction, a number of catalyst reported in the literature such as Ag(I),[10b] Cu(II)[13] and Pd(II)[14] catalyst with various protic/aprotic organic solvents were examined in the reaction of 2-aminophenyl acrylate **1a** with phenylisothiocyanate (**2a**) (Table 1). When 5 mol % of AgOTf was used as catalysts in MeCN at 25 °C for 12 h, the desired product was not obtained (Table 1, entry 1). Increase in the reaction temperature and time provided the product **3a** in 10 and 15% yields respectively (Table 1, entries 2–3). Increase of the catalyst loading provided the product **3a** in improved yield (Table 1, entry 4). Similar result was observed using DMF as solvent; however THF and DCE provided the product in improved yield (Table 1, entries 5–9). Use of $Cu(OTf)_2$ in DCE was found more effective in comparison to AgOTf, and afforded the desired product in 70% yields (Table 1, entry 10). Inferior results were observed when reaction was performed using $Cu(OTf)_2$ in THF (Table 1, entry 11). Lowering of the reaction time, temperature and catalyst loading leads to the incomplete conversion of the substrate (Table 1, entries 12–14). Other catalysts such as CuI, $Pd(OAc)_2$, $PdCl_2$, $AgNO_3$, $AgSbF_5$ and AgOAc were found inferior for the reaction (Table 1, entries 15–20). In the absence of metal-catalyst the desired product **3a** was not obtained (Table 1, entry 21).[15]

Table 2. Synthesis of 2-imino[1,3]benzothiazines[a,b]



1a–d **2a–h** **3a–o**

R^2 = CO_2Me, CO_2Et, $CO_2{}^nBu$, $CO_2{}^tBu$; R^3 = substituted aryl, alkyl group



3a, 70% **3b**, 68% **3c**, 71%

3d, 80% **3e**, 75% **3f**, 72%

3g, 70% **3h**, 65% **3i**, 65%

3j, 64% **3k**, 62% **3l**, 75%

3m, 60%[b] **3n**, 65% **3o,** 78%

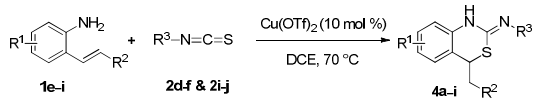
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $Cu(OTf)_2$ (10 mol %), 70 °C, 2 mL DCE, 36 h. [b] 48 h. [c] Isolated yields.

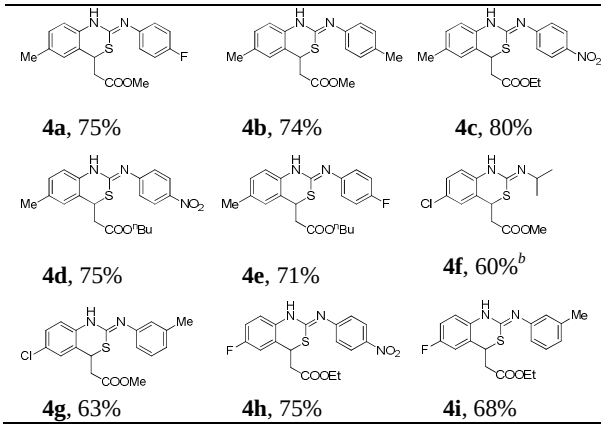
After optimizing the reaction conditions, we examined the substrate scope of the developed chemistry by using a variety of 2-aminoaryl acrylates **1a**–**d** and isothiocyanates **2a**–**h** (Table 2). The substrates **1a**–**d** required for the reaction was readily prepared by the Heck coupling[14] of the respective bromo/iodoanilines with acrylates. Reaction of acrylate **1a** with phenylisothiocyanate **2a** provided the desired product **3a** in 70% yield. Isothiocyanate **2b** bearing electron-donating substituents at *ortho* position of the phenyl ring provided the products **3b** in 68% yield. However, isothiocyanates **2c**, **2d** and **2e** bearing electron−withdrawing groups afforded the products **3c**–**g** comparatively in higher yields. In the case of *n*-butyl acrylate **1c,** product **3h**–**l** was obtained in moderate yields (Table 2, compare **3h** *vs* **3a**; **3j** *vs* **3b** and **3l** *vs* **3d**). The reaction of **1c** with cyclohexyl substituted isothiocyanate **2h** required longer reaction time for the completion of the reaction and afforded the desired product **3m** in 60% yield. Reaction of *tert*-butyl acrylate **1d** with 4-methylphenylisothiocyanate **2f** and **2d** afforded the desire product **3n** and **3o** in 65% and 78% yield respectively.

Success of the chemoselective addition of the unsubstituted aminoacrylates onto isothiocyanates encouraged us for the addition of the substituted acrylates onto isothiocyanates to synthesize functionalized benzothiazines. Under the optimized reaction conditions (Table 1, entry 10); the reaction of the acrylates **1e**−**i** with isothiocyanates **2d**−**f** and **2i**−**j** provided the corresponding products **4a**−**i** in good yields (Table 3). During the course of the reaction it was observed that the nature of the substituent's attached to the aryl ring of isothiocyanates and the acrylates were responsible for the success of the reaction.

Substrates **1e**−**g** bearing electron-releasing substituent's provided the respective products **4a**–**e** comparatively in higher yields.

Table 3. Synthesis of substituted 2-imino[1,3]benzothiazines[a]





[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $Cu(OTf)_2$ (10 mol %), 70 °C, 2 mL DCE, 36 h. [b] 48 h. [c] Isolated yields.

The substrate **3h** bearing chloro substituent, on reaction with isopropyl isothiocyanate **2i** afforded the desired product **4f** in 60% yield in 42 h. However, the reaction of substrate **3h** with isothiocyanate **2j** bearing an electron-releasing methyl group provided the desired product in 63% yields. The substrate **1i** bearing fluoro substituent afforded the desired products **4h**–**i** in moderate to good yields.

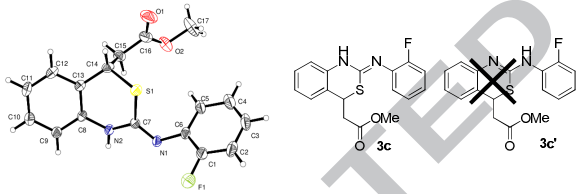
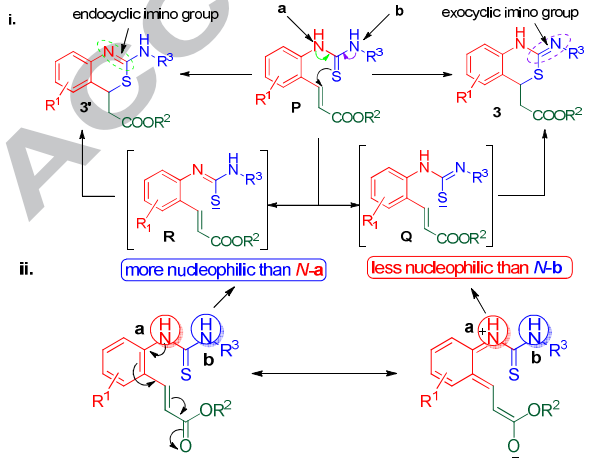


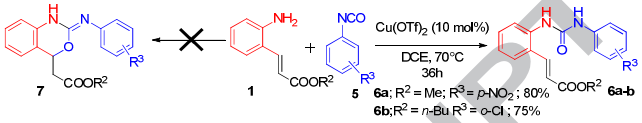
Figure 2. ORTEP drawing of compound **3c** drawn at 50% probability level.

The structure of the synthesize benzothiazines was fully characterized by the ^{1}H, ^{13}C NMR, HRMS and finally by the X-ray crystallographic studies of compound **3c** (Figure 2).[16]



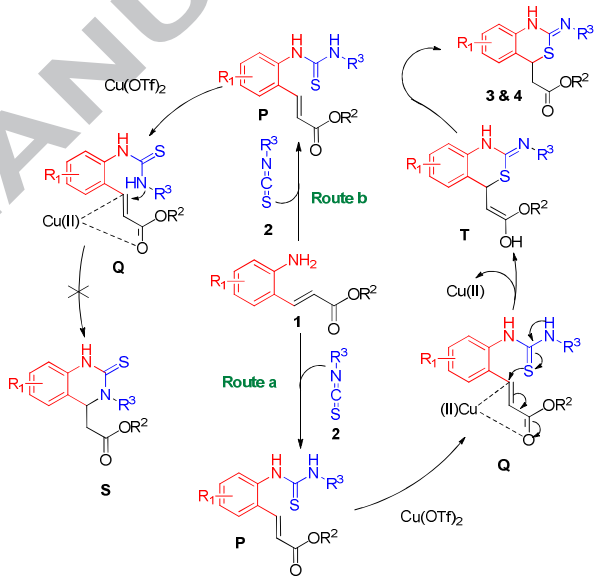
Scheme 2. Explanation for the preferential formation of exocyclic imine (**3**) over endocyclic imine (**3'**).

The crystal structure of product **3c** clearly indicates the formation of products **3** with exocyclic imino group. From intermediate **P** cyclization can occur by involving nitrogen **a** through intermediate **R**; ii) by involving nitrogen **b** via intermediate **Q** (Scheme 2, i). The possible reason for the preferential involvement of the nitrogen **b** over nitrogen **a**, could due to the difference in the nucleophilicity. The lone pair of nitrogen '**a**' are delocalized with adjacent acrylate and making it less nuclophilic than nitrogen **b** (Scheme 2, ii).



Scheme 3. Reaction of phenylisocyanate with acrylate **1**.

After obtaining the successful results with arylisothiocyanates, we tried to synthesize benzoxazines **7** by the reaction of isocyanates **5** with 2-aminoaryl acrylates **1a** and **1c**; unfortunately we did not obtained the desired product. The careful spectral analysis of the reaction shows the formation of the urea intermediate **6**. The probable reason could be the low nucleophilicity of oxygen in comparison to the sulfur (Scheme 3).



Scheme 4. Plausible mechanism.

A plausible mechanism for the above transformation based on the previously reported copper chemistry[17] is described in Scheme 4. Reaction of 2-aminoaryl acrylates with isothiocyanates would form the intermediate **P**, which can attack on acrylate intramolecularly by two routes. Presumably, $CuO(Tf)_2$ and intermediate **P** generates copper complex **Q**, which renders the acrylate susceptible to attack by the nucleophile. Sulfur being more nucleophilic than nitrogen triggers the intramolecular attacks at β-carbon of acrylate and generates intermediate **T**, which tautomerizes to give product **3** and **4** (Scheme 4).

In conclusion, the chemistry described herein provides a facile and direct synthesis of medicinally useful benzothiazines from easily accessible starting material in good yields under mild reaction conditions. The chemistry appears to involve the *in situ* thioamidation by the reaction of 2-aminoaryl acrylates with isothiocyanates followed by successive chemoselective intramolecular thia-Michael addition. Further investigation of the

scope and application of the developed chemistry are currently underway and will be reported in due course.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.125.

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(16) Crystallographic data of compounds **3d** have been deposited at the Cambridge Crystallographic data centre with file number **971535**, respectively, and Copies of these data can be obtained free of charge on application to CCDC, email: deposit@ccdc.cam.ac

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(18) **General procedure for the synthesis of 1,3−benzothiazine (3a-3o and 4a-4i)**. An oven-dried Schlenk tube with a Teflon screw valve was charged with 0.5 mmol of isothiocyanates, 0.5 mmol of the 2-aminophenylacrylate **1a-i** and $Cu(OTf)_2$ (10 mol %). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with nitrogen. The septum was then replaced with a Teflon screw valve, and the Schlenk tube was sealed. The reaction mixture was heated to 70 °C until 2-aminophenylacrylate **1a-i** had been completely consumed (36 h) (as determined by TLC) and was allowed to cool at room temperature. The reaction mixture was diluted with ethyl acetate (10 mL) and water (15 mL). Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel using hexane-ethyl acetate mixture (80: 20). **(*Z*)-Methyl 2-(2-(phenylimino)-2,4-dihydro-1*H*-benzo[*d*][1,3]thiazin-4-yl) acetate (3a).** The product was obtained as a yellow needles (DCM/Ether), (109.2 mg, 70%): mp 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.3 Hz, 2H), 7.31 (t, J = 8.0 Hz, 2H), 7.26–7.24 (m, 1H), 7.19–7.13 (m, 2H), 7.06 (t, J = 7.3 Hz, 2H), 4.47 (dd, J = 8.8 and 5.9 Hz, 1H), 3.66 (s, 3H), 2.87–2.80 (m, 1H), 2.77–2.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 148.6, 142.9, 141.0, 128.9, 128.7, 126.4, 124.3, 123.6, 122.2, 120.5, 51.9, 41.3, 40.3; IR spectrum in film (ν_{max}, cm^{-1}) 3344, 2951, 1731, 1655, 1614, 1580, 1537, 1480, 1439, 1314, 1231, 1150, 753; HRMS (ESI) $(M)^+$ Calcd for $C_{17}H_{16}N_2O_2S$ 312.0932, found 312.0930.

Highlights

- The manusript appears to involve the *in situ* thioamidation by the reaction of 2-aminoaryl acrylates with isothiocyanates followed by successive chemoselective intramolecular thia-Michael addition.
- A facile and direct synthesis of medicinally useful benzothiazines from easily accessible starting material in good yields under mild reaction conditions.
- A novel access to substituted 1,3-benzothiazines embedded with exocyclic imine groups which could be useful for the medicinal utility of the molecule and could be easily diversified.
- The mechanism of the reaction is supported by isolating the **P** intermediate (Thiourea).
- This chemistry involved the preferential intramolecular conjugate additions of thiourea (generated in situ in the reaction) to form 1,3-benzothiazines. The structure of the cyclized product was confirmed by X-ray crystallographic studies.