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ARTICLE

# On Water: Iodine-Mediated Direct Construction of 1, 3-Benzothiazines from *ortho*-Alkynylanilines by Regioselective 6-Exo-dig Cyclization

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Kapil Mohan Saini, Rakesh K. Saunthwal, Shiv Kumar and Akhilesh K. Verma*

Herein, we report the *6-exo-dig* ring closure of *ortho*-alkynylanilines with readily available aroyl isothiocyanate. An environmentally benign, metal- and base-free, iodine promoted cascade synthesis of highly functionalized benzo[1,3]thiazin-2-yl)benzimidic acids has been accomplished *via* in situ generated ortho-alkynylthiourea. The established methodology employs the abundant chemical feed stocks of ortho-alkynylanilines and aroyl isothiocyanates and could be applied in the late-stage synthesis of pharmaceutically active 1,3-benzothiazine containing molecules. Furthermore, the discovered protocol exclusively delivers the bis (benzo[1,3]thiazin-2-yl)dibenzimidic acid products and preserves the iodo-olefin substitution pattern which can be exploited by further derivatization.

## Introduction

Iodine-mediated transformations have become ubiquitous in the functionalizations and assembly of biological and pharmaceuticals molecules.[1] Most of the reported methods converts carbon-carbon triple bond into the carbon-carbon double bond using organic solvents[2] in the presence of base and iodine due to the high stability of the resulting iodonium ions in organic solvents and the presence of soft-soft interactions between iodine and alkyne bond compared to the C-C double bond counterparts. Carbon-carbon triple bond activation in water has become a subject of intensive research due to the unprecedented reactivity of alkyne bonds in water and the development of new environment-friendly methods for the synthesis of biologically active molecules.

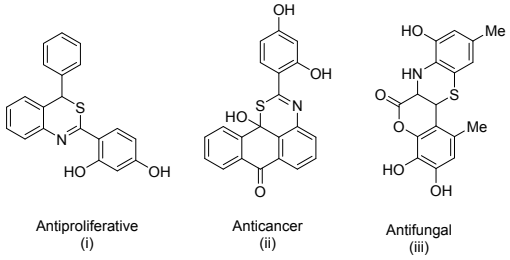
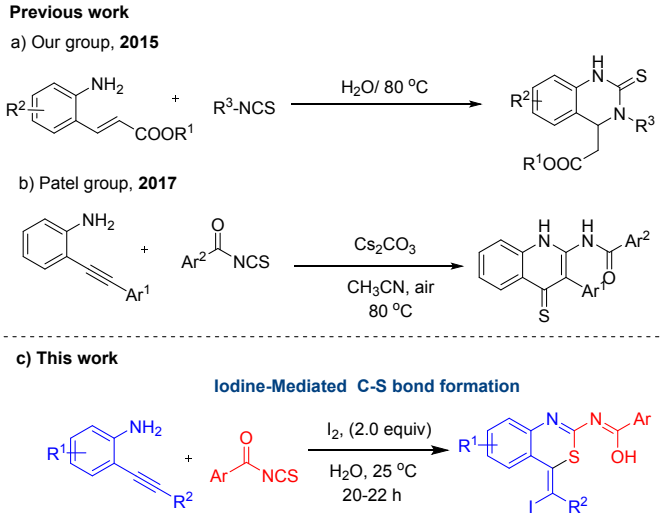



**Fig 1**.Biologically active benzothiazines cores

Nitrogen and sulphur-containing compounds, widely used as organic electroluminescent devices[3] and pharmaceutical drug candidates,[4] play an important role in modern organic synthesis. 1,3-benzothiazines derivatives have shown significant antiproliferative and anticancer activity (Fig. 1, i, and ii).[5] The benzothiazine core moiety has found many applications, such as it required for the protein *N*-acetylation in Aspergillusnidulans (Fig. 1, iii). Due to the biological importance of these compounds, over the past several years, significant effort has been devoted[6] and are still demanding for the development of an efficient approach for the synthesis.




**Scheme 1** Synthetic approaches for utilizing isothiocyanate

In recent years, the iodocyclization of C-C triple bonds using base and organic solvents has received widespread attention, [7] yet the use of water as a solvent in this context remains

*Mr. Kapil Mohan Saini, Dr. Rakesh K. Saunthwal, Mr. Shiv Kumar and Prof Akhilesh K. Verma*
*Synthetic Organic Chemistry Research Laboratory, Department of Chemistry, University of Delhi, Delhi–110007, India*
E-mail:averma@acbr.du.ac.in
† Footnotes relating to the title and/or authors should appear here.
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underdeveloped. In pioneering studies, Katritzky[8] reported the synthesis of [1,3]benzothiazine*viaortho*-lithiation of thiophenols by the using *N*,*N*-bis[(benzotriazol-1-yl) methyl]amines as 1,3-biselectrophile synthons. Later Wu and co-workers[9] reported the tandem synthesis of 1,3-benzothiazines from 2-alkynylbenzenamines under silver catalysis. Valliribera,[10] Reboul[11a], and our group[12] have also been involved in developing synthetic approaches towards the synthesis of 1,3-benzothiazines. Sashida group also demonstrated the synthesis of 1,3-benzothiazines using iodine-base system in organic solvent, however in the absence of $Cs_2CO_3$ the reaction gave the trace amount of product.[13]

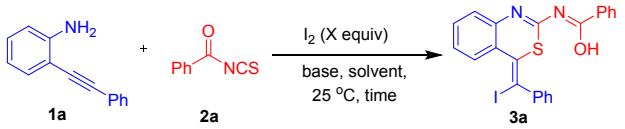
In 2015, we reported the synthesis of tetrahydroquinazolines from 2-aminophenylacrylate and aryl isothiocyantes in presence of water under heating (Scheme 1a).[14] Most of the existing synthetic strategies do not rely on the use of iodine in water as activating reagent. In 2017, Patel group describe the $Cs_2CO_3$-$CH_3CN$-promoted synthesis of quinoline-thiones from *ortho* - alkynylanilines and aroylisothiocyanates (Scheme 1b).[15] Interestingly, replacement of $Cs_2CO_3$-$CH_3CN$ with iodine-water completely changed the course of the reaction and the product outcome, giving a benzo[1,3]thiazin-2-yl)benzimidic acid *via* formation of the iodonium ion and followed by *6-exo-dig* ring closure at ambient temperature (Scheme 1b *vs* 1c).

## Results and discussion, Experimental

Based on this initial concept,[16] we started screening coupling partners 2-(phenylethynyl)aniline **1a** with aroylisothiocyanate **2a** as the standard substrates. When **1a** and aroylisothiocyanates **2a** employed with iodine (1.0 equiv) as the activating reagent in the presence of $K_2CO_3$ in dichloromethane at room temperature, no *6-exo-dig* ring closure product (**3a**) was detected (Table 1, entry 1). Increase of iodine loading did not provide the product **3a** (entry 2). We screened the other bases such as $Cs_2CO_3$, $KHCO_3$, $NaHCO_3$ and organic base $Et_3N$, which were found to be ineffective for the reaction (entries 3–6).

A similar result was observed using dichloroethane and ethanol as a solvent (entries 7–8); nevertheless, superior results were observed when the reaction was performed in water (entry 9). Based on these facts, we increased the reaction time, and formation of benzo[1,3]thiazin-2-yl)benzimidic acid product was observed in good yields (entries 10–12). Surprisingly, when the reaction was performed in the absence of the base under iodine (2.0 equiv) and water as a solvent, the desired product **3a** was obtained in 90% yield (entry 13). Lowering of iodine loading leads to the incomplete conversion of substrate (entries 14 and 15). Use of other electrophile like ICl provided the cyclized product comparatively in lower yield (entry 16). KI and NaI gave the isothiourea intermediate instead of the final product (entries 17 and 18). Reaction of benzoyl isocyanate with **2a** failed to provide the desired product.

**Table 1**. Optimization of the reaction condition[a]




| entry | reagent (equiv) | solvent | base (2.0 equiv) | time (h) | yield (%)[b]**3a** |
|---|---|---|---|---|---|
| 1 | $I_2$ (1.0) | $CH_2Cl_2$ | $K_2CO_3$ | 10 | 00 |
| 2 | $I_2$ (2.0) | $CH_2Cl_2$ | $K_2CO_3$ | 10 | 00 |
| 3 | $I_2$ (2.0) | $CH_2Cl_2$ | $Cs_2CO_3$ | 10 | 00 |
| 4 | $I_2$ (2.0) | $CH_2Cl_2$ | $KHCO_3$ | 10 | 00 |
| 5 | $I_2$ (2.0) | $CH_2Cl_2$ | $NaHCO_3$ | 10 | 00 |
| 6 | $I_2$ (2.0) | $CH_2Cl_2$ | $Et_3N$ | 10 | 00 |
| 7 | $I_2$ (2.0) | DCE | $NaHCO_3$ | 10 | 00 |
| 8 | $I_2$ (2.0) | EtOH | $NaHCO_3$ | 10 | 00 |
| 9 | $I_2$ (2.0) | $H_2O$ | $NaHCO_3$ | 10 | 65 |
| 10 | $I_2$ (2.0) | $H_2O$ | $NaHCO_3$ | 15 | 82 |
| 11 | $I_2$ (2.0) | $H_2O$ | $NaHCO_3$ | 20 | 90 |
| 12 | $I_2$ (2.0) | $H_2O$ | $NaHCO_3$ | 30 | 88 |
| 13 | $I_2$ (2.0) | $H_2O$ | - | 20 | 90 |
| 14 | $I_2$ (1.0) | $H_2O$ | - | 20 | 50[c] |
| 15 | $I_2$ (1.0) | $H_2O$ | - | 20 | 50[d] |
| 16 | ICl (1.0) | $H_2O$ | - | 20 | 70 |
| 17 | KI | $H_2O$ | - | 20 | 00 |
| 18 | NaI | $H_2O$ | - | 20 | 00 |

[a]Unless otherwise noted all reactions were carried out using 2-(phenylethynyl)aniline **1a** (0.50 mmol), aroylisothiocyanate **2a** (0.52 mmol), and $I_2$ in 2 mL solvent, [b]Isolated yield, [c]50% conversion of substrate into the product. [d]Under oxygen atmosphere at 80 °C.

Having established the optimum reaction condition in hand, we next explored the scope and generality of cascade reaction using an eco-friendly solvent (Scheme 2). The reaction of electron-neutral and electron-donating substrate **1a**–**d** bearing functional groups, such as 2-Me, 3-Me and 4-Me on the benzene ring of the alkyne, afforded the corresponding products **3a**–**d** in 84–93% yield. Alkynes bearing *n*-butyl and *tert*-butyl group on the para position of benzenering, provided the desired products **3e**–**f** in 88% and 86% yield respectively. Electron-withdrawing and sterically hindered groups, such as 4-F and 2-F, were also well-suited, leading to **3g** and **3h** in good yields. Electron-rich thienyl alkyne **1i** gave the cyclized product **3i** in 82% yield. Isothiocyanates bearing electron-donating group **2b** and **2c**, afforded the corresponding products **3j**–**o** in 82-90% yield. Electron-withdrawing groups bearing aroylisothiocyanates **2d**, was also compatible, leading to **3p** in 84% yields.

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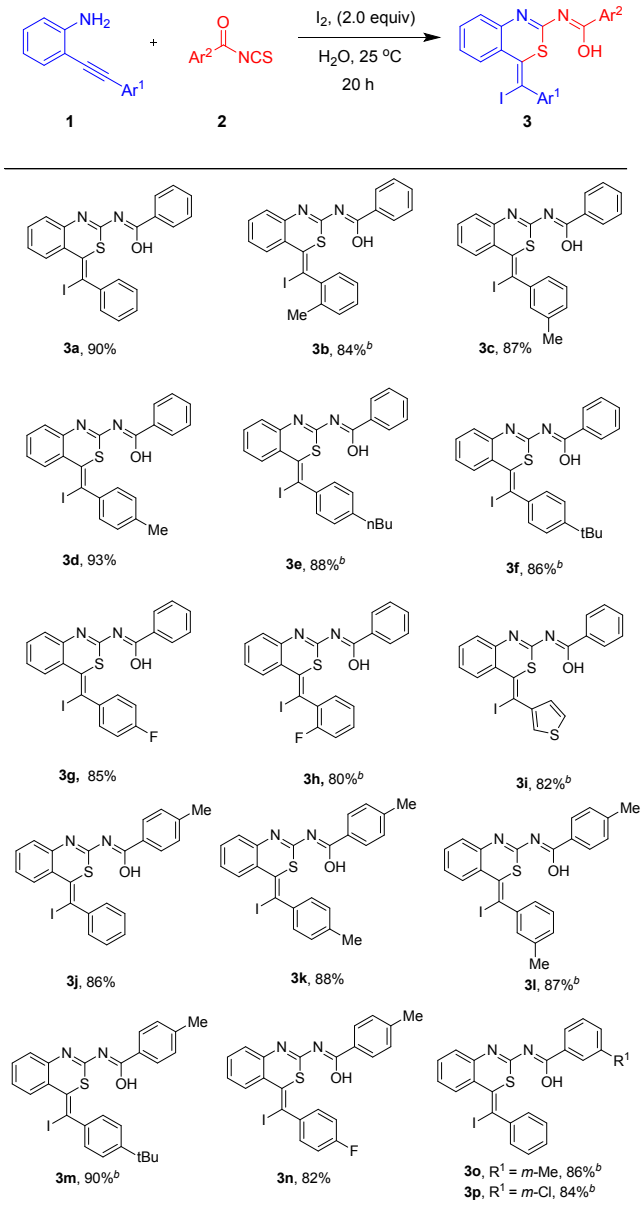
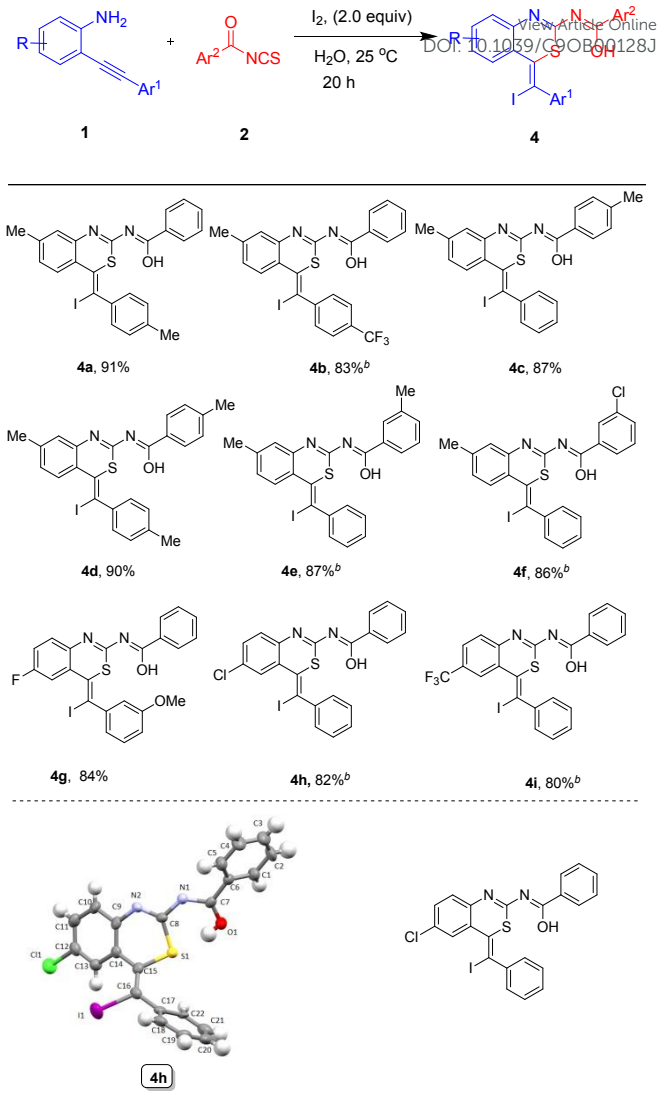



**Scheme 2** Scope of acyl isothiacynate, [b]Time 22 h

Additionally, we explored the scope of ortho-alkynylanilines for the green cascade approach (Scheme 3). 5-Me substituted *ortho*-alkynylanilines analogues **1j**–**l** reacted smoothly with aroylisothiocyanates bearing electron-neutral and electron-donating group **2a**–**c**, provided the corresponding products **4a**–**f** in 83-91% yields. The regioselectivity of the products was unambiguously assigned by X-ray crystallographic study[17] of product **4h**. Substrates (**1m**–**o**) having electron-withdrawing functional groups, such as fluoro, chloro, and trifluoromethyl at the 4-positon of the aniline moiety, afforded the desired product **4g**–**i** in 80-84% yield.




**Scheme 3** Scope of aniline

Next, the generality of aliphatic alkyne bearing aniline was evaluated (Scheme 4). *ortho*-Alkynylaniline **1p** having long aliphatic chain, afforded the desired product **5a** in good yield with excellent regioselectivity. 5-Chloropentyne substituted aniline **1q**, provided the cyclized product **5b** in 80% yield. *tert*-Butyl group substituted alkyne **1r**, was well tolerated to give the desired product in good yields. *ortho*-Alkynylanilines having aliphatic carbocyclic group such as cyclopropyl (**1s**), cyclohexane (**1t**) and cyclohexene (**1u**) gave the desired products **5d**–**f** in 65–78% yields.

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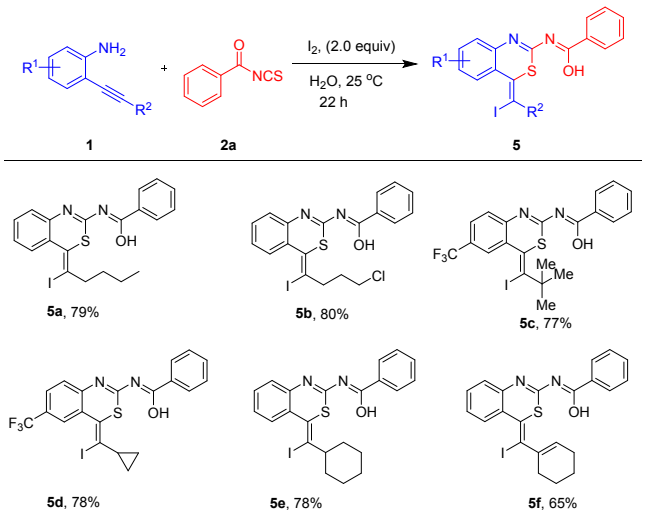
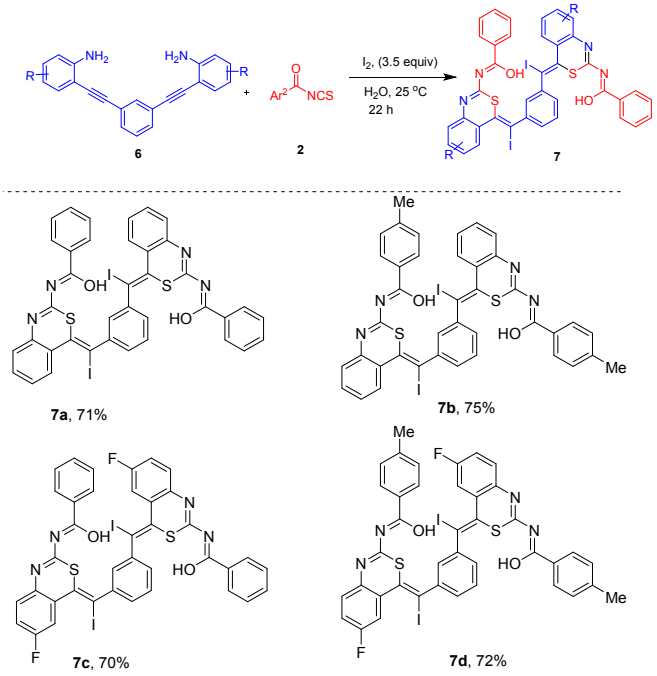



**Scheme 4.** Scope of aliphatic alkyne

Encouraged by above results, we pushed the scope of 1,3-dialkyne further and found that the double *6-exo-dig* ring closures of **6a** could be performed with aroylisothiocyanate**2a** to produce **7a** in the 71% yield. With 1, 3-dialkyne, the reaction of **2b** using the 3.5 equiv of iodine in water afforded the cyclized products **7b** in 75% yield. Finally, electron-withdrawing 4-F substituent at the benzene ring of 1,3-dialkyne, was also effectively employed in this protocol and gave the desired products **7c** and **7d** in good yields (Scheme 5).




**Scheme 5**. Scope of dialkynes

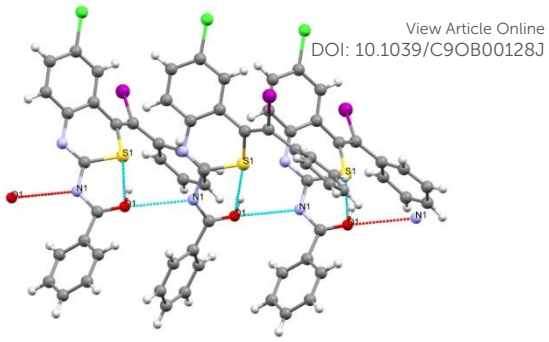
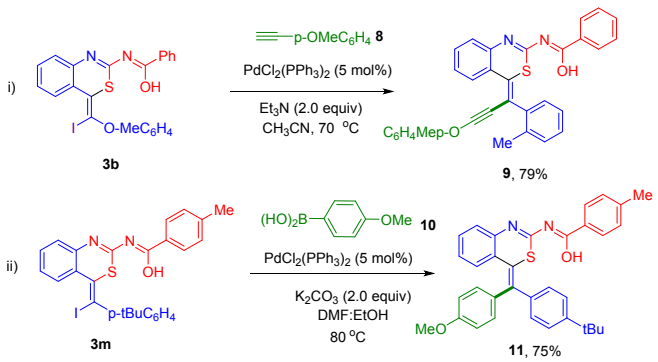


**Fig** 2 Stability of enol over keto due to hydrogen bonding (**4h**)

The structure and enol conformation of the benzo[1,3]thiazin-2-yl)benzimidic acid products were investigated in the solid state. Crystals appropriate for X-ray analysis were obtained for structure and enol confirmation, thus disclosing the solid-state confirmation of **4h** (Figure 2). The clear intra and intermolecular hydrogen bonding was observed in the molecule. The $O^1$-H-$S^1$ distances 1.958 Å, shows strong intramolecular hydrogen bonding, therefore, the hydrogen of $O^1$ is tilt towards the $S^1$ and $O^1$-H-$N^1$ distance 2.904 Å, shows moderate intermolecular hydrogen-bonding. This crystallography study suggested an intermolecular transannular hydrogen-bonding between the two benzo[1,3]thiazin-2-yl)benzimidic acid molecule, a characteristic of attention for the development of biologically active molecules with "hidden hydrophilicity".[17b]




**Scheme 6**. Synthetic utility of products

Because of the synthetic utility of alkyne and aryl groups, a mild and selective method for late-stage introduction of alkyne and aryl group in benzothiazine molecules will be highly desirable in synthetic chemistry. Thus, we employed the product **3b** and **3m** under Sonogashira (scheme 6i) and Suzuki coupling (scheme 6ii) reaction conditions, affording the coupling products **9** and **11** in good yields (Scheme 6).

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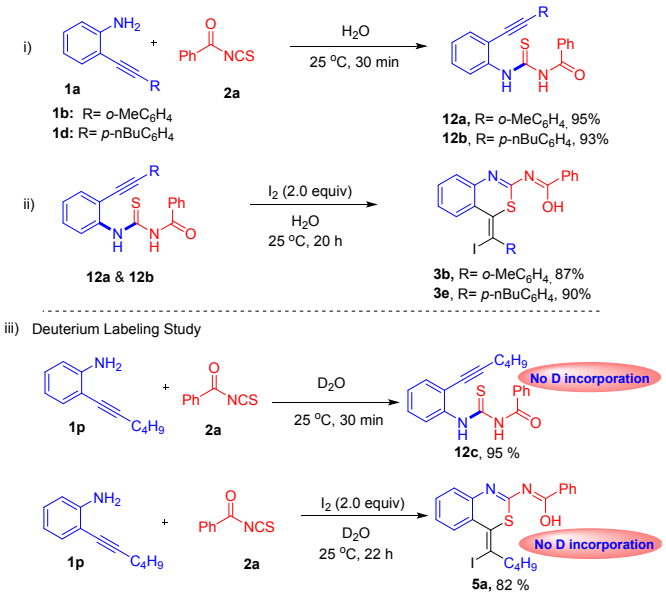
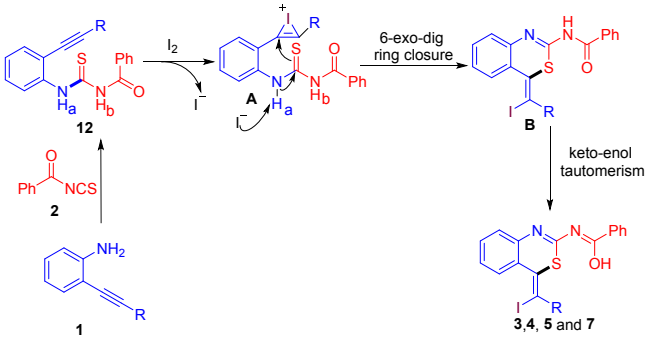



**Scheme 7**. Mechanistic control experiments

To validate the mechanism of iodine-mediated *6-exo-dig* ring closure several control experiments has been performed in Scheme 7. The reaction of **1b** and **1d** with aroylisothiocyanate **2b** in water at 25 °C, provided the urea intermediate **12** (Scheme 7i), further we employed these intermediate with optimized reaction condition to afford the final product **3b** and **3e** in good yield (Scheme 7ii). Moreover, intermolecular cyclization experiments indicated that reaction would compete in a cascade manner. In deuterium labeling study, H-D exchange was not observed which infer that the solvent is not responsible for protonation (Scheme 7 iii).




**Scheme 8**. Plausible reaction pathway

Based on the control experiments and literature studies, we envisaged the plausible mechanism for above-mentioned iodocyclization reactions in Scheme 8. First, this process would be initiated by the reaction between alkynylanilines **1** and aroylisothiocyanate **2**, which would form thiourea intermediate **12**. Further, alkyne bond coordinate with $I^+$, therefore enhancing the electrophilicity of the carbon-carbon triple bond to generate iodonium species **A** and liberate an iodine anion at the same time. With the support of the iodine anion, intramolecular nucleophilic attack of sulfur in the thiourea group on the more electron deficient carbon of iodonium intermediate, in the favoured *6-exo-dig* mode provided the species **B**, which after keto-enoltautomerisation, give the final products. The enol form would be stabilized by intermolecular transannular hydrogen bonding.

## Conclusions

In summary, we have disclosed a mild, one-pot, organic solvent-free and base-free methodology for the regioselective ring closure of *ortho*-alkynylanilines with aroylisothiocyanate enabled by the carbon-carbon triple bond activation using iodine. A variety of readily available *ortho*-alkynylanilines were reactive, including electron-withdrawing and electron-donating alkynylanilines. Additionally, the substrate scope was extended for the double *6-exo-dig* cyclization of 1,3-dialkynylanilines. Aromatic and aliphatic alkynylanilines are equally reactive and selective and can be cyclized in the presence of iodine. We anticipate that this protocol is useful for the synthesis of highly functionalized benzothiazine derivatives, which could find further application in the synthesis of biologically active compound. To the best of our knowledge, this work represents the first example of iodine-mediated alkyne activation without using any base on water.

## Experimental Section

**General Procedure for the Synthesis of Starting Substrate 1a-o**: To a solution of substituted 2-iodoaniline (0.5 mmol) in MeCN (2 mL), 3 mol% of $Pd(PPh_3)_2Cl_2$ was added. The reaction vial was then sealed and flushed with nitrogen. Then, 1.5 equiv of $Et_3N$ and 0.51 mmol of alkyne were added to the reaction mixture. The reaction was then stirred at 70°C until TLC revealed complete conversion of the starting material. The reaction mixture was then allowed to cool, was diluted with $H_2O$, and was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $Na_2SO_4$, concentrated under vacuum, and purified by column chromatography using 100–200 mesh size silica gels (hexane: ethyl acetate) to afford the corresponding product. The structure and purity of known starting materials **1a**-**o** were confirmed by comparison of their physical and NMR-spectral data ($^1$H NMR and $^{13}$C NMR) with those reported in the literature.[18-21]

**General Procedure for the Synthesis of Starting Substrate 1p-u:** To a solution of substituted 2-iodoaniline (0.5 mmol) in $Et_3N$ (3 mL), 3 mol% of $Pd(PPh_3)_2Cl_2$ and 1 mol% of CuI were added. The reaction vial was then sealed and flushed with nitrogen. Then 0.51 mmol of alkyne was added to the reaction mixture. The reaction was then stirred at 25 °C until TLC revealed complete conversion of the starting material. The reaction mixture was then allowed to cool, was diluted with $H_2O$, and was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $Na_2SO_4$, concentrated under vacuum, and purified by column chromatography using

100−200 mesh size silica gels (hexane: ethyl acetate) to afford the corresponding product. The structure and purity of known starting materials **1p**, **1q**, **1t**, **1u** were confirmed by comparison of their physical and NMR-spectral data ($^1$H NMR and $^{13}$C NMR) with those reported in the literature.[18-21]

**General experimental procedure for green one-pot synthesis of benzo[1,3]thiazin-2-yl)benzimidic acid 3-5:** To a solution of *ortho*-alkynlanilines **1** (0.5 mmol), aroy lisothiocyanates **2** (0.52 mmol) and 2.0 equiv of $I_2$ was added in water (2.0 mL). The reaction was then stirred at room temperature until TLC revealed a complete conversion of the starting material. After the completion of the reaction, the reaction mixture was quenched with saturated aq sodium thiosulfate solution and extracted with EtOAc (3X10 mL). The combined organic layers were dried over $Na_2SO_4$, concentrated under vacuum, and purified by column chromatography using 100−200 mesh size silica gels (EtOAc: hexane) to afford the corresponding product.

**General experimental procedure for green one-pot synthesis of Bisbenzo[1,3]thiazin-2-yl)di benzimidic acid 7**: To a solution of *ortho*-haloanilines **1** (0.5 mmol), aroylisothiocyanates **2** (1.04 mmol) and 3.5 equiv of $I_2$ were added in water (2.0 mL). The reaction was then stirred at room temperature until TLC revealed complete conversion of the starting material. After the completion of the reaction, the reaction mixture was quenched with saturated aq sodium thiosulfate solution and extracted with EtOAc (3X10 mL). The combined organic layers were dried over $Na_2SO_4$, concentrated under vacuum, and purified by column chromatography using 100−200 mesh size silica gels (EtOAc:hexane) to afford the corresponding product.

## Conflicts of interest

There are no conflicts of interest to declare.

## Acknowledgements

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## Notes and references

1. T. Aggarwal, S. Kumar and A. K. Verma, *Org. Biomol. Chem*., 2016, **14**, 7639–7653.
2. (a) F. Yang, T. Jin, M. Baoc and Y. Yamamoto, *Chem. Commun*., 2011, **47**, 4541–4543; (b) Y. X. Xie, X. Y. Liu, L. Y. Wu, Y. Han, L. B. Zhao, M. J. Fan and Y. M. Liang, *Eur. J. Org. Chem*., 2008, 1013–1018; (c) Z. Chen, G. Huang, H. Jiang, H. Huang and X. Pan, *J. Org. Chem.*, 2011, **76**, 1134–1139.
3. R. Hull, M. P. J. van den Broek, M. L. Swain and *J. Chem. Soc., Perkin Trans.1*, 1975, 922–925.
4. (a) S. Sabatini, F. Gosetto, S. Serritella, G. Manfroni, O. Tabarrini, N. Iraci, J. P.Brincat, E. Carosati, M. Villarini, G. W. Kaatz and V. Cecchetti, *J. Med. Chem*., 2012, **55**, 3568−3572; (b) A. Gangjee, Y. Zeng, T. Talreja, J. J. McGuire, R. L. Kisliuk, S. F. Queener and *J. Med. Chem*., 2007, **50**, 3046–305.
5. (a) J. Matysiak, *Bioorg. Med. Chem*., 2006, **14***,* 2613–2619; (b) A. Napolitano, L. Panzella, L. Leone and M. d'Ischia, *Acc. Chem. Res.*, 2013, **46**, 519–528; (c) K. Scherlach, H. W. Ntzmann, V. Schroeckh, H.-M. Dahse, A. A. Brakhage and C. Hertweck, *Angew. Chem. Int. Ed*., 2011, **50**, 9843 – 9847.
6. (a) N. Yongpruksa, S. Pandey, G. A. Baker and M. Harmata, *Org. Biomol. Chem*., 2011, **9**, 7979–7982; (b) M. Harmata, K. Rayanil, V.R. Espejo and C. L. Barnes, *J. Org. Chem.*, 2009, **74**, 3214–3216; (c) M. Harmata, Y. Chen and C. L. Barnes, *Org. Lett.*, 2007, **9**, 4701–4704.
7. (a) H. T. Zhu, K. G. Ji, F. Yang, L. J. Wang, S. C. Zhao, S. Ali, X. Y. Liu and Y. M. Liang, *Org. Lett.*, 2011, **13**, 684–687; (b) T. S. Jiang, X. G. Zhang and J. H. Li, *Synthesis* 2009, **18**, 3029–3038; (c) R. M. Gai, R. F. Schumacher, D. F. Back and G. Zen, *Org. Lett.*, 2012, **14**, 6072–6075.
8. A. R. Katritzky, Y. J. Xu and R. Jain, *J. Org. Chem.*, 2002, **67**, 8234–8236.
9. Q. Ding and J. Wu, *J. Comb. Chem.*, 2008, **10**, 541–545.
10. C. Gimbert and A. Vallribera, *Org. Lett.*, 2009, **11**, 269–271.
11. (a) C. Spitz, J. F. Lohier, V. Reboul and P. Metzner, *Org. Lett.*, 2009, **11**, 2776–2779.
12. R. K. Saunthwal, M. Patel, S. Kumar and A. K. Verma, *Tetrahedron Lett.,* 2015, **56**, 677–681.
13. H. Sashida, M. Kaname, M. Minoura, *Tetrahedron*, 2013,**69**, 6478–6487.
14. R. K. Saunthwal, M. Patel, R. K. Tiwari, K. Parang and A. K. Verma, *Green Chem*. 2015, **17**, 1434–1441.
15. A. Modi, P. Sau and B. K. Patel, *Org. Lett*., 2017, **19**, 6128–6131.
16. (a) S. P. Shukla, J. Singh and V. Rustagi, *J. Org. Chem*. 2011, **76**, 5670–5684; (b) A. K. Verma, V. Rustagi, T. Aggarwal and A. P. Singh, *J. Org. Chem*., 2010, **75**, 7691–7703; (c*)* A. K. Verma, T. Aggarwal, V. Rustagi and R. C. Larock, *Chem. Commun*., 2010, **46**, 4064–4066; (d) R. K. Saunthwal, A. K. Danodia, M. Patel, S. Kumar and A. K. Verma, *Chem. Asian J.,* 2016, **11**, 3001–3007; (e) H. H. Zhang, Y. Q. Wang, L. T. Huang, L. Q. Zhu, Y. Y. Feng, Y. M. Lu, Q. Y. Zhao, X. Q. Wang, Z. Wang, *Chem. Commun*., 2018, **54**, 8265–8268; (f) Y. Jiang, J. X. Zou, L. T. Huang, X. Peng, J. D. Deng, L. Q. Zhu, Y. H. Yang, Y. Y. Feng, X. Y. Zhang, Z. Wang,*Org. Biomol. Chem.*, 2018, **16**, 1641–1645.
17. Crystallographic data for the compound **4h** has been deposited with the Cambridge Crystallographic Data Centre. CCDC deposit number for compound **4h** is 1872209, contains all crystallographic details of this publication and is available free of charge at

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DOI: 10.1039/C9OB00128J

www.ccdc.cam.ac.uk; (b) R. Costil, Q. Lefebvre and J. Clayden, *Angew. Chemie Int. Ed.* 2017, **56**, 14602–14606.

18. (a) X. Wang, J. Li, Y. Huang, J. Zhu, R. Hu, W. Wu and H. Jiang, *J. Org. Chem.* 2018, **83**, 10453−10464; (b) C. M. Le, T. Sperger, R. Fu, X. Hou, Y. H. Lim, F. Schoenebeck and M. Lautens, *J. Am. Chem. Soc.,* 2016, **138**, 14441−14448; (c) L. Z. Yu, Y. Wei and M. Shi, *Chem. Commun*., 2017, **53**, 8980−8983.
19. F. Gao, J. T. Wang, L. L. Liu, N. Ma, C. Yang, Y. Gao and W. Xia, *Chem. Commun*., 2017, **53**, 8533−8536; (b) Y. Zhao,Y. Hu,H. Wang, X. Li and B. Wan, *J. Org. Chem.,* 2016, **81**, 4412−4420. (c) P. Li, Y. Weng, X. Xu and X. Cui, *J. Org. Chem.,* 2016, **81**, 3994−4001; (d) R. J. Liu, P. F. Wang, W. K. Yuan, L. R. Wen and M. Li, *Adv. Synth. Catal*., 2017, **359**, 1373–1378.
20. (a) L. Tang, C. Wu, Q. Hu, Q. Li and Zhang, *ApplOrganometal Chem.,* 2018, **32**, 3980. (b) X. F. Xia, G. W. Zhang, D. Wang and S. L. Zhu, *J. Org. Chem.,* 2017, **82**, 8455−8463; (c) F. D. Zhuang, J. M. Han, S. Tang, J. H. Yang, Q. R. Chen, J. Y. Wang and J. Pei, *Organometallics,* 2017, **36**, 2479−2482; (d) C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid and P. Knochel, *Tetrahedron,* 2003, **59**, 1571–1587.
21. (a) C. Peng, Y. Wang, L. Liu, H. Wang, J. Zhao and Q. Zhu, *Eur. J. Org. Chem.,* 2010, 818–822; (b) X. F. Xia, L. L. Zhang, X. R. Song, X. Y. Liu and Y. M. Liang, *Org. Lett*., 2012, **14**, 2480–2483; (c) A. Carpita and A. Ribecai, *Tetrahedron Lett.,* 2009, **50**,204–207; (d) J. S. Kim, J. H. Han, J. J. Lee, Y. M. Jun, B. M. Lee and B. H.Kim, *Tetrahedron Lett.,* 2008, **49**, 3733–3738.