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Advanced Synthesis & Catalysis

Transition Metal-Free Synthesis of Substituted Isothiazoles *via* Three-Component Annulation of Alkynones, Xanthate and NH_4I

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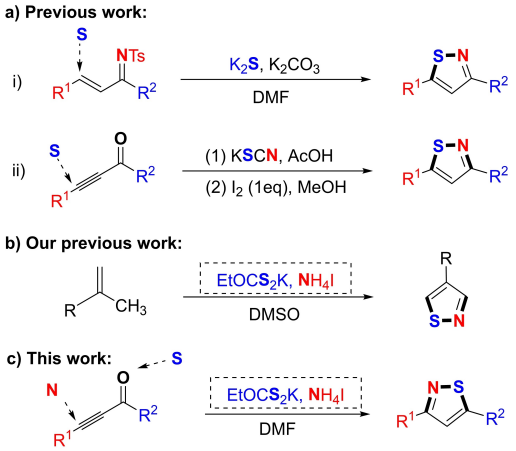
Abstract: A protocol was described to access diverse isothiazoles with functionalization potential *via* transition metal-free three-component annulation of alkynones, potassium ethylxanthate ($EtOCS_2K$) and ammonium iodide (NH_4I). A sequential regioselective hydroamination/thiocarbonylation/intramolecular cyclization cascade achieved the efficient formation of consecutive C–N, C–S and N–S bonds in a one-pot process.

Keywords: Isothiazole; Sulfur heterocycle; Xanthate; Cyclization; Regioselective

Introduction

Isothiazole is a valuable five-membered heterocycle, extensively found in natural products, synthetic intermediates and functional materials as a key structural unit.[1–2] Substituted isothiazoles with special structures have medical value due to their biological and therapeutic activities[3] as well as commercial importance due to various industrial applications.[4] Among them, the 3,5-disubstituted isothiazole skeletons have appeared in a variety of pharmaceutical active molecules, such as GPR agonists, mGluR1 antagonists.[5] As a consequence, the value of substituted isothiazoles has prompted more attention to their synthesis and application, and several effective synthesis methods have been reported.[6–7] Though transition metal-catalyzed reactions have proven to be highly efficient,[7] the use of expensive metal catalysts or specially designed ligands can increase the cost of the reactions and limit their applications. By comparison, metal-free strategies have been more extensively studied as being considered environmentally friendly. [8] For example, Wang and Ji et al.[8c] developed a cascade $S_3^{\bullet-}$ addition/electron detosylation reaction of in situ formed α,β-usaturated *N*-sulfonylimines and K_2S, in which only a few conventional isothiazole products were listed with low yields (Scheme 1a, i). Reddy[8b] described the synthesis of isothiazole from ynones and KSCN by two-step conversions, where the positions of S and N atoms are determined by the thiocyanative/



Scheme 1. Methods to Synthesize Substituted Isothiazoles.

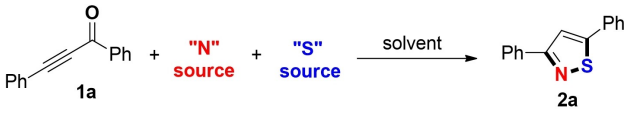
decyanative cyclization in the first step (Scheme 1a, ii). As most of methods for constructing substituted isothiazoles are still have limitations, it's urgently needed to develop novel metal-free reactions to efficien tly construct substituted isothiazoles by using eco-friendly conditions and inexpensive and easily available substrates.

As versatile precursors, xanthates can be applied to a variety of organic transformations,[9] and their reactive exploration has attracted our long-standing attention.[10] Recently, our group had achieved one-pot synthesis of 4-substituted isothiazoles through a cascade annulation of isopropene derivatives, NH_4I and $EtOCS_2K$ (Scheme 1b),[11] in which $EtOCS_2K$/NH_4I was first discovered to be an excellent combination for isothiazole synthesis. The continuation to explore the reactivity of $EtOCS_2K$/NH_4I combination for the synthesis of diverse substituted isothiazoles is valuable and challenging. Herein, we propose a transition metal-free synthesis of substituted isothiazoles *via* three-component annulation of alkynones and $EtOCS_2K$/NH_4I combination (Scheme 1c). The proposal is highly reliable because alkynones required are readily accessible and the reaction system is simple and efficient. Notably, consecutive C–N, N–S and C–S bonds can be formed efficiently and regioselectively through a one-pot method, and the structure of obtained isothiazoles is inconsistent with that reported by Reedy.

Results and Discussion

We commenced to use 1,3-diphenylprop-2-yn-1-one (**1a**) as the model substrate for condition optimization (Table 1). Initially, a series of investigations were conducted to determine the most suitable combination of "N" and "S" sources (entries 1–9). With NH_4I as the "N" source, a series of sulfur-containing compounds were tested, including thioacetamide, thiourea, Na_2S (entries 1–6). The results showed that the dimer of xanthates is effective (entry 2), and the reaction proceeded best when $EtOCS_2K$ was used as the "S" source to give the product **2a** in the yield of 73% (entry 6). With $EtOCS_2K$ as "S" source, the examination of different ammonium salts showed that NH_4I was the best choice of "N" sources (entries 6–10). Other solvents, such as DMSO, DMAc and xylenes, could not increase the yield of **2a** (entries 11–13). Pleasingly, an excellent yield of 89% was obtained when NH_4I was increased to 4 equivalents while $EtOCS_2K$ was decreased to 1.2 equivalents (entry 15). Furthermore, reducing the reaction time or lowering the reaction temperature led to a decrease in yield (entries 16–18). Under a N_2 atmosphere, the yield of the reaction decreased to 51%, indicating that the presence of air promotes the cyclization reaction. Based on the above results, the optimized reaction conditions were 0.5 mmol **1a**, 2.0 mmol NH_4I and 0.6 mmol of $EtOCS_2K$ in 2.0 mL DMF at 130 °C for 12 h.

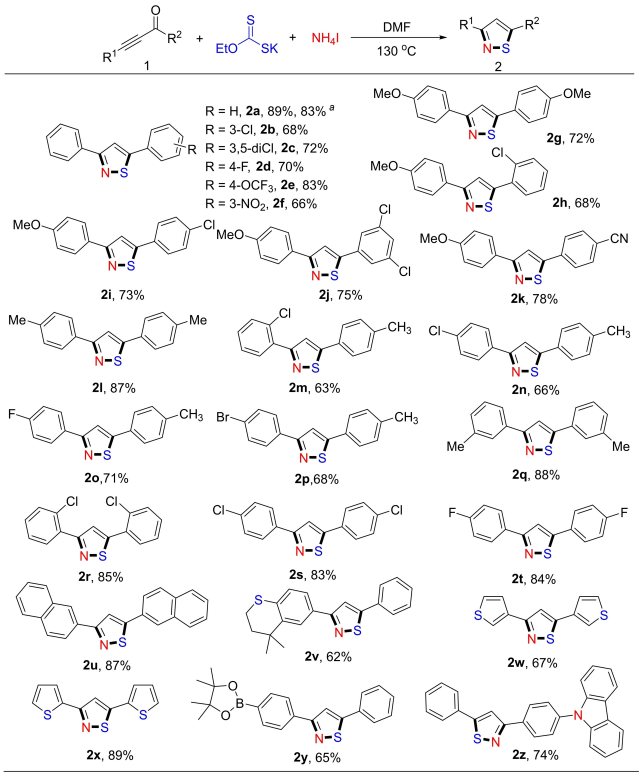
Table 1. Optimization of reaction conditions.[a]



Entry	"N" source (equiv.)	"S" source (equiv.)	Solvent	Yield (%)
1	NH_4I (3)	thioacetamide (2)	DMF	52
2	NH_4I (3)	isopropylxanthic disulphide (2)	DMF	68
3	NH_4I (3)	thiourea (2)	DMF	54
4	NH_4I (3)	S_8 (2)	DMF	53
5	NH_4I (3)	Na_2S (2)	DMF	57
6	NH_4I (3)	$EtOCS_2K$ (2)	DMF	73
7	NH_4Cl (3)	$EtOCS_2K$ (2)	DMF	< 5
8	NH_4Br (3)	$EtOCS_2K$ (2)	DMF	32
9	CH_3COONH_4 (3)	$EtOCS_2K$ (2)	DMF	28
10	$NH_3{\cdot}H_2O$ (3)	$EtOCS_2K$ (2)	DMF	< 5
11	NH_4I (3)	$EtOCS_2K$ (2)	DMSO	33
12	NH_4I (3)	$EtOCS_2K$ (2)	DMAc	53
13	NH_4I (3)	$EtOCS_2K$ (2)	xylenes	< 5
14	NH_4I (4)	$EtOCS_2K$ (2)	DMF	82
15	NH_4I (4)	$EtOCS_2K$ (1.2)	DMF	89
16[b]	NH_4I (4)	$EtOCS_2K$ (1.2)	DMF	73
17[c]	NH_4I (4)	$EtOCS_2K$ (1.2)	DMF	68
18[d]	NH_4I (4)	$EtOCS_2K$ (1.2)	DMF	54
19[e]	NH_4I (4)	$EtOCS_2K$ (1.2)	DMF	51

[a] Reaction conditions: 1,3-diphenylprop-2-yn-1-one **1a** (0.5 mmol), "N" source, "S" source and H_2O (0.5 mmol) in solvent (2.0 mL), 130 °C, 12 h. Isolated yield.
[b] 130 °C, 8 h.
[c] 110 °C, 12 h.
[d] 90 °C, 12 h.
[e] under a N_2 atmosphere.

Under the optimized conditions, we subsequently investigated the substrate scope of this three-component annulation reaction as shown in Scheme 2. Firstly, we explored reactivities of alkynones by changing the substituents on the R^2 group. The reactions of alkynone substrates bearing different substituents (halo-, trifluoromethoxy- and nitro-) on the R^2 group proceeded smoothly, and the desired products (**2a–2f**) were produced in good to excellent yields. We also studied the preparation of isothiazole **2a** on a 1.0 mmol-scale, obtaining 3,5-diphenylisothiazole in 83% yield, which confirmed the practicability of this cyclization reaction (See experimental section). Replacing R^1 group with 4-methoxyphenyl, both electron-rich substituents (methoxy-) or electron-poor substituents (halo- and cyano-) were well tolerated, the reactions delivered the target products (**2g–2k**) in 68–78% yields. Subsequently, the reactivities of alkynones



Scheme 2. Substrate scope of alkynones. Reaction conditions: alkynones **1** (0.5 mmol), NH_4I (2.0 mmol), $EtOCS_2K$ (0.6 mmol) and H_2O (0.5 mmol) in DMF (2.0 mL), 130 °C, 12 h. [a] Reaction carried on 1.0 mmol-scale.

with different substituents on the R^1 groups were investigated. Among them (**2 l**–**2 p**), product containing a methyl substituent on the R^1 group produced higher yield (87%) than those containing a halo substituent. When R^1 group was the same as R^2 group, the reaction of alkynone bearing 3-methylphenyl, 2-chlorophenyl, 4-chlorophenyl or 2-fluorophenyl substituent proceeded smoothly to produce the isothiazole products (**2 q**–**2 t**) in 83–88% yields, proving that halo substituents were tolerated in the reaction system. The naphthalene substrate (**1 u**) was also suitable for this annulation reaction and was converted to **2 u** in 87% yield. By comparison, the conversion of 2-thiophene substrate (**1 x**) was better than that of 3-thiophene substrate (**1 w**), probably because the 3-thiophene substituent contained active sites for side reactions, resulting in a lower yield. Particularly, the alkynone substrates with a complex R^1 group, such as 4,4-dimethylthiochroman, 4-dioxaborolanephenyl or 4-carbazolephenyl moiety, also participated well in the reactions, delivering the desired isothiazoles (**2 v**, **2 y**–**2 z**) in good yields. The structure of **2 z** was further confirmed by X-ray crystallographic analysis (Figure 1, CCDC: 2025711).

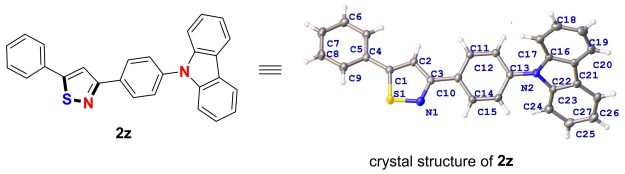
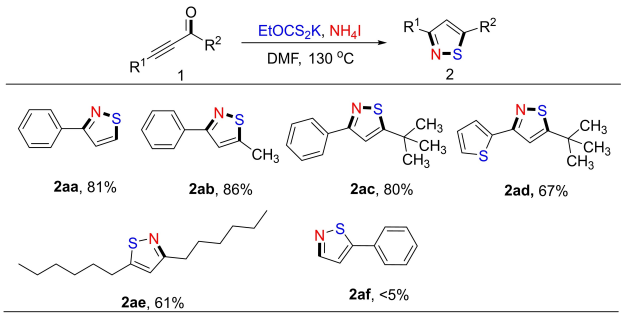


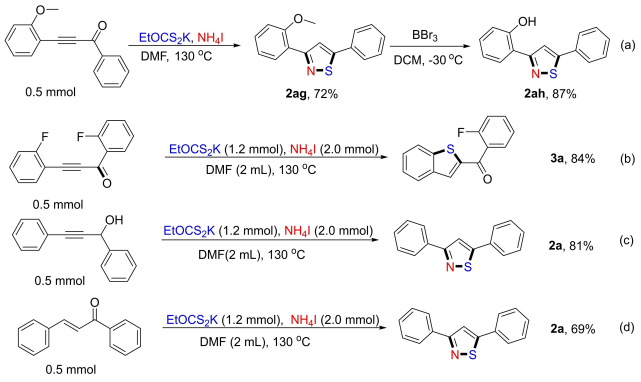
Figure 1. Molecular Structures of **2 z** by X-ray Crystallographic Analysis.

Next, A series of alkyl alkynones were investigated and the results were shown in Scheme 3. When the R^1 group was a phenyl group and the R^2 group was H or an alkyl group (Me or ^{t}Bu), the corresponding substrates had good reactivities, and the target products (**2 aa**–**2 ac**) were formed in excellent yields. The R^1 group was subsequently substituted with a 2-thiophene group, and the reaction gave **2 ad** in 67% yield. The dialkyl ynones such as pentadec-8-yn-7-one also successfully completed the cyclization reaction to give the corresponding product **2 ae** in 61% yield. Unfortunately, the reaction of terminal alkynones, such as 1-phenylprop-2-yn-1-one, produced a mixture of products (Scheme 3, **2 af**).

Other special transformations were discovered during the reaction process, as shown in Scheme 2. The reaction of the alkyne containing a 2-methoxyphenyl group under optimal conditions gave **2 ag** in 72% yield, which could be converted to **2 ah** by further demethylation with a yield of 87% (Scheme 4, eq. a). Interestingly, when using 1,3-bis(2-fluorophenyl)prop-2-yn-1-one as a substrate, the reaction gave the benzothiophene product (**3 a**) in 84% yield instead of the isothiazole product (Scheme 4, eq. b). The alkynols such as 1,3-diphenylprop-2-yn-1-ol successfully completed the cyclization reaction to give the isothiazole **2 a** in 81% yield (Scheme 4, eq. c). When a chalcone was used as reaction substrate, the cyclization reaction also gave the corresponding isothiazole **2 a** in 69% yield. (Scheme 4, eq. d).



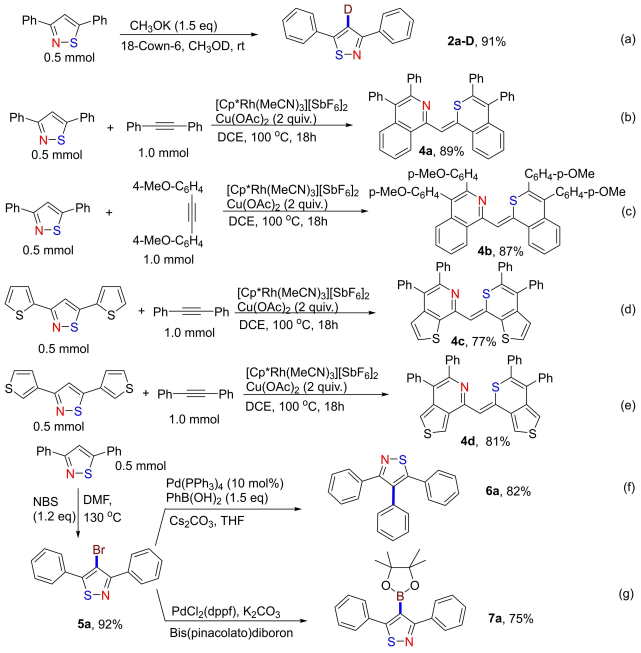
Scheme 3. Substrate scope of alkyl alkynones. Reaction conditions: alkyl alkynones **1** (0.5 mmol), NH_4I (2.0 mmol), $EtOCS_2K$ (0.6 mmol) and H_2O (0.5 mmol) in DMF (2.0 mL), 130 °C, 12 h.



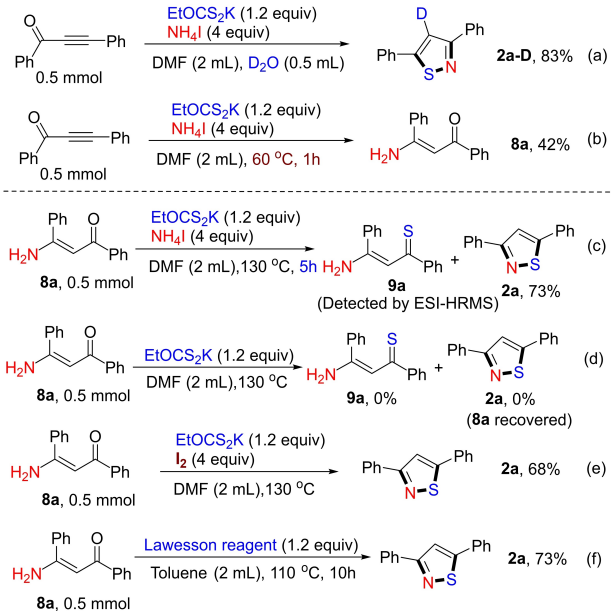
Scheme 4. Other Transformations.

As important type of building blocks, the newly formed isothiazoles could be utilized in various synthetic transformations (scheme 5). First, 4-deuterio-3,5-diphenylisothiazole (**2 a**–**D**) could be obtained through base-catalyzed deuteration reaction in 91% yield (eq. a). Forthermore, 3,5-diphenylisothiazole could undergo Rh(III)-catalyzed annulative coupling with alkynes smoothly and converted into different isoquinoline-isothiochromene conjugates (**4 a** and **4 b**) in 89% and 87% yields, respectively.[12] The transformation above was also applicable to 2-thiophene-substituted and 3-thiophene-substituted alkynones, and their reactions with 1,2-diphenylethyne furnished compounds (**4 c** and **4 d**) with novel structures in 77% and 81% yields, respectively (eq. b–d). The bromination of 3,5-diphenylisothiazole prepared 4-bromo-3,5-diphenylisothiazole (**5 a**), which could then be effectively transformed into the desired products **6 a** and **7 a** by Suzuki-Miyaura and Miyaura boronation reactions, respectively (eq. f–g).

In order to get insight into the reaction mechanism, several control experiments were then carried out, as shown in Scheme 6. First, it was noteworthy that when using DMF/D_2O (4:1) as a solvent mixture, 83% of 4-deuterio-3,5-diphenylisothiazole (**2 a**–**D**) was obtained, which indicated that a protonation process happened in the reaction (Scheme 6, eq. a). Since 1,3-diphenylprop-2-yn-1-one could react with NH_4I be converted to enamine **8 a** in 42% yields under 60 °C for 1 hours, respectively, they were considered to be possible reaction intermediates (Scheme 6, eq. b). Then, the reaction was conducted with enamine **8 a** as a substrate, $EtOCS_2K$ as "S" source and NH_4I as an addition to obtain the target product (**2 a**) in 73% yield, from which we speculated that enamine **8 a** might be the reaction intermediate. At the same time, we can detect thioketone **9 a** by ESI-HRMS, but it cannot be isolated independently. (Scheme 6, eq. c). In the absence of NH_4I, the reaction of enamine **8 a** with $EtOCS_2K$ did not gave the envisaged intermediate thioketone **9 a** or desired isothiazole **2 a**, instead of recycled raw material **8 a**. It shows that in the absence of NH_4I, it is difficult for $EtOCS_2K$ to react with carbonyl to obtain thioketones intermediates. (Scheme 6, eq. d). When replacing NH_4I with I_2, gave the **2 a** in 68% yield, proving that NH_4I not only acted as a "N" source, its iodine element could also effectively promote the reaction for synthesis of isothiazole **2 a** (Scheme 6, eq. e). When try to use the



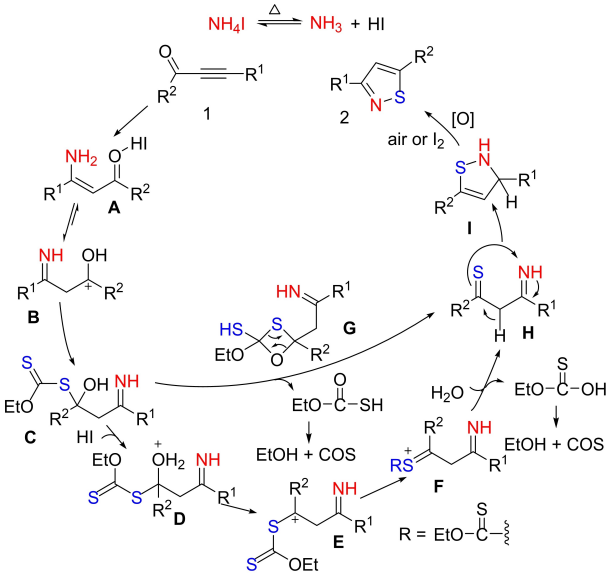
Scheme 5. Synthetic Utilization.



Scheme 6. Control Experiments.

Lawesson's reagent as thionating agent for preparation of thioketone **9a**, the reaction direct gave the isothiazole products **2a** in 73% yields. It shows that the sulfur cyclization of thioketone **9a** can be completed spontaneously without catalyst under high-temperature conditions (Scheme 6, eq. f).

On the basis of observed experimental results and the previous work,[11] the plausible mechanism for transition metal-free synthesis of substituted isothiazoles is proposed in Scheme 7. As described in published work, the thermal decomposition of NH_4I can release NH_3, which will preferentially undergo nucleophilic addition to alkynone through regioselective hydroamination to form enamine intermediate **A**.[13] After undergoing the nucleophilic attack of $EtOCS_2K$ on the carbonyl group with the aid of HI to form thioketone intermediate **H**.[14] Alternative, the thioketone intermediate **H** may be formed through a process similar to Lawesson's reaction.[15] The reaction underg a nucleophilic attack of $EtOCS_2K$ on the carbonyl group and subsequent intramolecular cyclization, intermediate **G** is formed with an unstable four-membered heterocycle, followed by the instantaneous departure of EtOCSOH to form thioketone intermediate **H**. Subsequently, the thioketone intermediate **H** undergoes an intramolecular nucleophilic attack of sulfur on the imine nitrogen (C=NH), forming the N – S bond to generate dihydroisothiazole intermediate **I**.[6c,8a] Subsequent aerial or I_2 oxidation of intermediate **I** gives the desired product **2**, in which I_2 is obtained by decomposition of NH_4I.[16]



Scheme 7. Possible Reaction Mechanism.

Conclusions

In conclusion, a one-pot synthesis protocol for the efficient synthesis of substituted isothiazoles through three-component annulation of alkynones, $EtOCS_2K$ and NH_4I has been established. Under transition metal-free conditions, the reaction delivers a series of isothiazoles in moderate to excellent yields through the efficient formation of C–N, N–S and C–S bonds, basing on a sequential regioselective hydroamination/thiocarbonylation/intramolecular cyclization cascade reaction. Simple operations, inexpensive and readily available substrates, broad substrate scopes and synthetic utilization of diversity make the method highly feasible in application. Further efforts are currently underway to further elucidate the mechanism and further expand the synthetic applications of isothiazole compounds in advanced materials.

Experimental Section

General information

Chemicals and solvents were purchased from commercial suppliers and used as received unless noted. All products were purified by flash chromatography on silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on 500 MHz Bruker spectrometers. Chemical shifts of ^{1}H were reported in part per million relative to the $CDCl_3$ residual peak (δ 7.260). Chemical shifts of ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.00). The used abbreviations are as follows: s (singlet), d (doublet), t (triplet), quart. (quartet), quint (quintet), m (multiplet), br (broad). Multiplets which arise from accidental equality of coupling constants of magnetically non-equivalent protons are marked as virtual (*virt.*). High resolution mass spectra (HRMS) data were measured on a ESI- microTOF II. Melting points were measured on a SGW® X-4B and are not corrected. Reactions were monitored by TLC analysis using silica gel 60 Å F-254 thin layer plates and compounds were visualized with a UV light at 254 nm or 365 nm. All the other chemicals were purchased from Aldrich Chemicals, Energy Chemical and Leyan Chemical. Commercial reagents were used without further purification.

General procedures for synthesis of 1,3-diphenylprop-2-yn-1-one: In a nitrogen atmosphere, add $PdCl_2(PPh_3)_2$ (23 mg, 5 mol%), CuI (9.5 mg, 4 mol%), THF (15 mL), terminal alkynes (2.5 mmol) and acid chloride (3 mmol). After stirring for 2 minutes, Et_3N (5 mL) was added and the reaction was stirred at room temperature for 5 h. After the reaction was completed, the reaction was diluted with ethyl acetate and washed with saturated brine (10 mL*3). The organic layer was then extracted, all organics were combined and dried with Na_2SO_4, The organic phase is concentrated and purified by flash chromatography to afford the 1,3-diphenylprop-2-yn-1-one.

General procedures for synthesis of 3,5-diphenylisothiazole: A mixture of 1,3-diphenylprop-2-yn-1-one (0.5 mmol), NH_4I (2.0 mmol, 290 mg), $EtOCS_2K$ (0.6 mmol, 96 mg), H_2O (0.5 mmol), DMF (2.0 ml) was added successively in a 20 mL Schlenk tube. The Schlenk tube was then immersed in an oil

bath at 130 °C stirring for 12 h. After cooling down to room temperature, the solution was filtered through a small amount of silica gel. Then the residue was concentrated in vacuo and the crude was purified by flash chromatography with n-hexane/ethyl acetate (20/1, v/v) to afford the 3,5-diphenylisothiazole (**2 a**) as a white solid in 89% yield.

General procedures for synthesis of 3 a-3 d:[12] To an oven-dried Schlenk tube were added isothiazole **2** (0.2 mmol), 1,2-diphenylethyne (0.4 mmol), $[Cp^*Rh(MeCN)_3]$ $[SbF_6]_2$ (6.6 mg, 4.0 mol%), and $Cu(OAc)_2$ (72.6 mg, 0.4 mmol). The tube was flushed with N_2, and DCE (3.0 mL) was added via syringe. The mixture was hated with oil bath at 100 °C for 18 h. The resulting suspension was diluted with water and was extracted with EtOAc (10 mL*3). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo.The crude material was subjected to silica gel chromatography give the corresponding coupling product **3 a**–**3 d**.

General procedures for synthesis of 4 a: A mixture of 3,5-diphenylisothiazole **2 a** (0.5 mmol), NBS (1.2 eq, 107 mg), DMF (2.0 ml) was added successively in a 20 mL Schlenk tube. The Schlenk tube was then immersed in an oil bath at 130 °C stirring for 8 h. After cooling down to room temperature, the solution was filtered through a small amount of silica gel. Then the residue was concentrated in vacuo and the crude was purified by flash chromatography with n-hexane/ethyl acetate (20/1, v/v) to afford the **4 a** as a white solid in 92% yield.

General procedures for synthesis of 5 a: A mixture of **4 a** (0.5 mmol), $PhB(OH)_2$ (1.5 eq, 92 mg), Cs_2CO_3 (1.2 eq,196 mg), THF (2.0 ml), H_2O (0.2 ml) was added successively in a 20 mL Schlenk tube. The Schlenk tube was then immersed in an oil bath at 60 °C stirring for 10 h. After cooling down to room temperature, the solution was filtered through a small amount of silica gel. Then the residue was concentrated in vacuo and the crude was purified by flash chromatography with n-hexane/ethyl acetate (4/1, v/v) to afford the **5 a** as a white solid in 82% yield.

General procedures for synthesis of 6 a: A mixture of **4 a** (0.5 mmol), CH_3COOK (2 eq, 98 mg), [1,1′Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (3 mol%, 11 mg), Bis (pinacolato)diboron (1 equiv, 127 mg), DMF (3 ml) was added successively in a 20 mL Schlenk tube. The Schlenk tube was then immersed in an oil bath at 90 °C stiring for 12 h. After cooling down to room temperature, the solution was filtered throu-gh a small amount of silica gel. Then the residue was concentrated in vacuo and the crude was purified by flash chromatography with *n*-hexane/ethyl acetate (20/1, v/v) to afford the **6 a** as a yellow liquid in 93% yield.

Synthesis of 3,5-diphenylisothiazole (2 a) in mmol-scale: A 25 mL Schlenk tube was charged with 1,3-diphenylprop-2-yn-1-one **1 a** (1.0 mmol, 206 mg), potassium xanthate (1.2 mmol, 190 mg, 1.2 equiv), NH_4I (4.0 mmol, 580 mg), H_2O (1.0 mmol, 18 mg), DMF (3.0 ml) and a magnetic stirring bar. The Schlenk tube was then immersed in an oil bath at 130 °C stirring for 12 h. After the reaction finished, the reaction mixture was diluted with ethyl acetate and passed through Celite. After evaporation of the solvent the residue was adsorbed on silica gel and the crude product was purified by column chromatography using n-hexane/ethyl acetate (20/1, v/v) the eluent, affording the3,5-diphenylisothiazole (**2 a**) as a white solid in 83% yield (196.7 mg).

3,5-diphenylisothiazole (2 a). White solid (105 mg, 89% yield); MP: 82–84 °C; R_f = 0.48 (Hexane/EtOAc = 30:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03–7.98 (m, 2H), 7.76 (s, 1H), 7.69–7.63 (m, 2H), 7.51–7.41 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 168.19, 134.8, 130.9, 129.6, 129.2 (3 C), 128.8 (2 C), 126.8 (2 C), 126.5 (2 C), 117.5. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{12}NS$, 238.0685, found 238.0685.

5-(3-chlorophenyl)-3-phenylisothiazole (2 b). Light yellow solid (92 mg, 68% yield); MP: 85–87 °C; R_f = 0.6 (Hexane /EtOAc = 30:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 2.0 Hz, 1H), 7.87 (dt, J = 6.7, 2.1 Hz, 1H), 7.73 (s, 1H), 7.65 (dd, J = 8.1, 1.4 Hz, 2H), 7.49–7.43 (m, 3H), 7.43–7.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 166.7, 136.4, 134.8, 130.8, 130.1, 129.8, 129.3 (2 C), 129.2, 127.0, 126.6 (2 C), 124.9, 117.5. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{11}NSCl$, 272.0295, found: 272.0294.

5-(3,5-dichlorophenyl)-3-phenylisothiazole (2 c). Black solid (110 mg, 72% yield); MP: 110–112 °C; R_f = 0.6 (Hexane/EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 8.4 Hz, 2H), 7.74 (s, 1H), 7.52 (d, J = 1.8 Hz, 2H), 7.50–7.40 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 165.0, 135.9 (2 C), 134.4, 133.6, 129.5, 129.2, 128.9 (2 C), 126.8 (2 C), 124.9 (2 C), 118.7. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{10}NSCl_2$, 305.9906, found:305.9902.

5-(4-fluorophenyl)-3-phenylisothiazole (2 d). Yellow solid (89 mg, 70% yield); MP: 112–114 °C; R_f = 0.6 (Hexane /EtOAc = 15:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 7.3 Hz, 2H), 7.70 (s, 1H), 7.64 (dd, J = 8.6, 5.2 Hz, 2H), 7.54–7.33 (m, 3H), 7.16 (t, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 167.0, 163.4 (d, J = 248.7 Hz, 1 C), 134.7, 129.3, 128.8, 128.5, 128.5 (d, J = 8.2 Hz, 2 C), 127.3 (d, J = 3.5 Hz, 1 C), 126.8, 117.7, 116.3 (d, J = 23 Hz, 2 C); HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{11}NSF$, 256.0591, found: 256.0591.

3-phenyl-5-(4-(trifluoromethoxy)phenyl)isothiazole(2 e). Yellow solid (133 mg, 83% yield); MP: 108–110 °C; R_f = 0.45 (Hexan/EtOAc = 30:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.7 Hz, 2H), 7.73 (s, 1H), 7.70–7.63 (m, 2H), 7.60–7.41 (m, 3H), 7.32 (d, J = 8.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 166.8, 149.8 (d, J = 3.0 HZ, 1 C), 133.4, 130.7, 129.8, 129.3 (2 C), 128.3 (2 C), 126.6(2 C), 122.4 (q, J = 256.1 HZ, 1 C), 121.2 (2 C), 117.4. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{11}F_3NOS$, 322.0508, found: 322.0506.

5-(3-nitrophenyl**)-3-**phenylisothiazole **(2 f)**. Yellow solid (93 mg, 66% yield); MP: 162–164 °C; R_f = 0.5 (Hexane /EtOAc = 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.28 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 7.0 Hz, 3H), 7.86 (s, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.59–7.38 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 165.2, 148.7, 134.3, 132.6, 132.4, 130.4, 129.6, 128.9 (2 C), 126.9 (2 C), 124.0, 121.3, 118.9. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{11}N_2O_2S$, 283.0536, found: 283.0531.

3,5-bis(4-methoxyphenyl)isothiazole (2 g). Yellow solid (107 mg, 72% yield); MP: 183–185 °C; R_f = 0.6 (Hexane/EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, J = 17.9, 8.8 Hz, 2H), 7.66–7.52 (m, 3H), 6.98 (dd, J = 8.6, 6.4 Hz, 4H),

3.87 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 167.8, 160.6, 160.4, 129.1, 128.2 (2 C), 127.9 (2 C), 123.8, 116.2, 114.5 (2 C), 114.1 (2 C), 55.4, 55.3. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{16}NO_2S$, 298.0896, found:298.0895.

5-(2-chlorophenyl)-3-(4-methoxyphenyl)isothiazole (2 h). Yellow solid (102 mg, 68% yield); MP: 91–93 °C; R_f = 0.45 (Hexane/EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 2.8 Hz, 1H), 7.74 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 9.3 Hz, 1H), 7.36 (d, J = 3.7 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 166.2, 160.7, 134.5, 132.0, 131.4, 130.2, 130.0, 128.0 (2 C), 127.0, 123.6, 120.3, 114.6 (2 C), 55.4. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{13}ONSCl$, 302.0401, found: 302.0402.

5-(4-chlorophenyl)-3-(4-methoxyphenyl)isothiazole (2 i). Pink solid (110 mg, 73% yield); MP: 152–154 °C; R_f = 0.6 (Hexane/EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.7 Hz, 2H), 7.65 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 166.5, 160.5, 135.4, 129.5, 129.4 (2 C), 128.2 (2 C), 127.8 (2 C), 127.7, 117.4, 114.1 (2 C), 55.3. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{13}ONSCl$, 302.0401, found: 302.0401.

5-(3,5-dichlorophenyl)-3-(4-methoxyphenyl)isothiazole (2 j). Brown solid (126 mg, 75% yield); MP: 146–148 °C R_f = 0.55 (Hexane /EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 1.9 Hz, 2H), 7.64–7.54 (m, 3H), 7.39 (t, J = 1.9 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 164.7, 160.7, 135.8 (2 C), 133.7, 129.2, 128.3 (2 C), 127.4, 124.9 (2 C), 118.3, 114.2 (2 C), 55.4. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{12}ONSCl_2$, 336.0011, found: 336.0009.

4-(3-(4-methoxyphenyl)isothiazol-5-yl)benzonitrile (2 k). Yellow solid (114 mg, 78% yield); MP: 103–105 °C; R_f = 0.35 (Hexane/EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.8 Hz, 2H), 7.75 (s, 5H), 6.99 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 165.4, 160.7, 135.2, 133.0 (2 C), 128.3 (2 C), 127.3, 127.1 (2 C), 118.4, 118.3, 114.2 (2 C), 112.9, 55.4. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{13}N_2OS$, 293.0743, found: 293.0742.

3,5-di-p–tolylisothiazole (2 l). White solid (115 mg, 87% yield); MP: 124–126 °C; R_f = 0.5 (Hexane/EtOAc = 15:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 8.1 Hz, 2H), 7.69 (s, 1H), 7.54 (d, J = 8.1 Hz, 2H), 7.29–7.25 (m, 4H), 2.41 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 168.1, 139.7, 139.2, 132.2, 129.8 (2 C), 129.5 (2 C), 128.2, 126.7 (2 C), 126.4 (2 C), 117.0, 21.3 (2 C). HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{16}NS$, 266.0998, found: 266.0999.

3-(2-chlorophenyl)-5-(p–tolyl)isothiazole (2 m). Yellow solid (90 mg, 63% yield); MP: 61–63 °C; R_f = 0.55 (Hexane /EtOAc = 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.1 Hz, 2H), 7.85 (s, 1H), 7.66 (d, J = 9.4 Hz, 1H), 7.54 (d, J = 9.3 Hz, 1H), 7.36 (d, J = 7.3 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 164.0, 139.2, 132.3, 132.1, 130.7, 130.3, 130.1, 130.1, 129.5 (2 C), 127.2, 126.8 (2 C), 121.1, 21.4. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{13}ClNS$, 286.0452, found 286.0446.

5-(4-chlorophenyl)-3-(p–tolyl)isothiazole (2 n). Yellow solid (94 mg, 66% yield); MP: 169–171 °C; R_f = 0.55 (Hexane /EtOAc = 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.5 Hz, 2H), 7.68 (s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.27(d, J = 9.5 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 166.9, 140.0, 135.2, 133.3, 129.9 (2 C), 129.0 (2 C), 128.1 (2 C), 128.0, 126.5 (2 C), 116.9, 21.4. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{13}ClNS$, 286.0452, found: 286.0455

3-(4-fluorophenyl)-5-(p–tolyl)isothiazole (2 o). Yellow solid (95 mg, 71% yield); MP: 158–160 °C; R_f = 0.55 (Hexane /EtOAc = 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.6, 5.5 Hz, 2H), 7.67 (s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.27(d, J = 8.5 Hz, 2H), 7.15 (t, J = 8.6 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 167.1, 163.3 (d, J = 247.4 Hz, 1 C), 139.9, 131.2 (d, J = 3.8 Hz, 1 C), 129.9, 128.7 (d, J = 8.8 Hz, 2 C), 128.0, 126.4, 116.8, 115.8 (d, J = 21.2 Hz, 2 C), 21.4. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{13}FNS$, 270.0747, found: 270.0746.

3-(4-bromophenyl)-5-(p–tolyl)isothiazole (2 p). Yellow solid (112 mg, 68% yield); MP: 186–188 °C; R_f = 0.55 (Hexane /EtOAc = 3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.1 Hz, 2H), 7.70 (s, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 166.6, 139.4, 132.4 (2 C), 132.0, 129.9, 129.5 (2 C), 128.0 (2 C), 126.7 (2 C), 123.6, 117.7, 21.4. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{13}BrNS$, 329.9946, found: 329.9948.

3,5-di-m–tolylisothiazole (2 q). Yellow solid (117 mg, 88% yield); MP: 117–119 °C R_f = 0.5 (Hexane /EtOAc = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.74 (s, 1H), 7.47 (d, J = 9.1 Hz, 2H), 7.36 (dt, J = 12.5, 7.6 Hz, 2H), 7.27–7.21 (m, 2H), 2.44 (d, J = 11.4 Hz, 6H); 13 C NMR (125 MHz, $CDCl_3$) δ 168.3, 168.2, 138.9, 138.4, 134.7, 130.8, 130.3, 129.9, 129.0, 128.6, 127.4, 127.1, 123.9, 123.6, 117.4, 21.4, 21.3. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{16}NS$, 266.0998, found: 266.0994.

3,5-bis(2-chlorophenyl)isothiazole (2 r). Yellow solid (130 mg, 85% yield); MP: 77–79 °C; R_f = 0.6 (Hexane /EtOAc = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.83 (dd, J = 7.2, 2.1 Hz, 1H), 7.70–7.64 (m, 1H), 7.56–7.52 (m, 1H), 7.49 (dd, J = 7.3, 1.8 Hz, 1H), 7.39–7.32 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 163.2, 134.1, 132.3, 132.0, 131.5, 130.7, 130.3, 130.2, 130.2, 130.1, 129.9, 127.2, 127.0, 124.7. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{10}Cl_2NS$, 305.9906, fuond: 305.9902.

3,5-bis(4-chlorophenyl)isothiazole (2 s). Yellow solid (127 mg, 83% yield); MP: 137–139 °C; R_f = 0.6 (Hexane /EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 8.5 Hz, 2H), 7.68 (s, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.4 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 167.1, 135.7, 135.3, 133.1, 129.5 (2 C), 129.2, 129.0 (2 C), 128.1 (2 C), 127.8 (2 C), 117.6. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{10}Cl_2NS$, 305.9906, found: 305.9905.

3,5-bis(4-fluorophenyl)isothiazole (2 t). Yellow solid (115 mg, 84% yield); R_f = 0.6 (Hexane /EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, J = 8.5, 5.6 Hz, 2H), 7.62 (dd, J = 8.5, 5.3 Hz, 2H), 7.16 (t, J = 8.5 Hz, 2H), 7.10 (t, J = 8.6 Hz,

2H), 6.03 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.63, 165.4 (d, J=57.5 Hz, 1 C), 163.4 (d, J=57.5 Hz, 1 C), 161.9, 136.3, 136.3, 133.6, 133.6, 129.4 (d, J=8.8 Hz, 1 C), 128.4 (d, J=8.6 Hz, 1 C), 116.1 (d, J=21.6 Hz, 1 C), 115.2 (d, J=21.5 Hz, 1 C), 91.5. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{10}F_2NS$, 274.0496,found: 274.0495.

3,5-di(naphthalen-2-yl)isothiazole (2 u). Yellow solid (147 mg, 87% yield); MP: 116–118 °C; R_f=0.35 (Hexane /EtOAc=20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, J=8.3 Hz, 1H), 8.29 (d, J=9.7 Hz, 1H), 7.98 (dt, J=6.2, 3.1 Hz, 4H), 7.87 (d, J=7.0 Hz, 1H), 7.75 (s, 1H), 7.71 (d, J=6.1 Hz, 1H), 7.65–7.53 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 165.5, 133.9, 133.7, 133.1, 131.1, 130.8, 129.8, 129.5, 128.6, 128.5, 128.4, 127.9, 127.6, 127.1, 126.8, 126.4, 126.0, 125.7, 125.7, 125.2, 125.2, 125.0. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{16}NS$, 338.0998, found: 338.0999.

3-(4,4-dimethylthiochroman-6-yl)-5-phenylisothiazole (2 v). Yellow liquid (104 mg, 62% yield); R_f=0.4 (Hexane /EtOAc=10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, J=7.1 Hz, 2H), 7.69 (s, 1H), 7.61 (d, J=1.9 Hz, 1H), 7.50–7.39 (m, 3H), 7.32 (dd, J=8.2, 2.0 Hz, 1H), 7.17 (d, J=8.2 Hz, 1H), 3.08 (d, J=12.2 Hz, 2H), 1.99 (d, J=12.2 Hz, 2H), 1.40 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 168.2, 142.8, 134.9, 134.5, 129.2, 128.8 (2 C), 127.3, 126.8 (2 C), 126.7, 124.4, 124.1, 116.8, 37.1, 33.1, 30.0 (2 C), 23.1. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{20}NS_2$, 338.1032, found: 338.1026.

3,5-di(thiophen-3-yl)isothiazole (2 w). Yellow solid (83 mg, 67% yield); MP: 117–119 °C; R_f=0.4 (Hexane /EtOAc=10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J=2.7 Hz, 1H), 7.64 (d, J=5.0 Hz, 1H), 7.59 (d, J=2.6 Hz, 1H), 7.53 (s, 1H), 7.48–7.42 (m, 1H), 7.39 (dd, J=5.0, 3.0 Hz, 1H), 7.33 (d, J=5.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 162.0, 137.2, 131.6, 127.2, 126.4, 126.4, 126.1, 123.7, 122.9, 117.8. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{11}H_8NS_3$, 249.9813, found: 249.9813.

3,5-di(thiophen-2-yl)isothiazole (2 x). Brown solid (111 mg, 89% yield); MP: 85–87 °C; R_f=0.6 (Hexane /EtOAc=20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.48 (m, 2H), 7.39 (dd, J=10.6, 5.1 Hz, 2H), 7.33 (d, J=3.5 Hz, 1H), 7.10 (q, J=4.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 160.4, 138.7, 132.3, 128.2, 127.7, 127.2, 127.2, 126.6, 125.9, 117.1 HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{11}H_8NS_3$, 249.9813, found: 249.9812.

5-phenyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl)isothiazole (2 y). Yellow liquid (118 mg, 65% yield); R_f = 0.5 (Hexane /EtOAc=5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 8.03 (d, J=7.3 Hz, 2H), 7.88 (d, J=7.4 Hz, 1H), 7.84 (s, 1H), 7.77 (d, J=7.8 Hz, 1H), 7.53–7.43 (m, 4H), 1.41 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 136.0 (2 C), 134.8, 132.6 (2 C), 130.4, 129.4, 129.2, 128.8 (2 C), 128.6, 126.9 (2 C), 117.7, 84.2 (2 C), 24.9 (4 C). HRMS (ESI-TOF) (*m/z*): $[M+Na]^+$ calcd for $C_{21}H_{22}BNNaO_2S$, 385.1393, found 385.1394.

3-(4-(9H-carbazol-9-yl)phenyl)-5-phenylisothiazole (2 z). Yellow solid (149 mg, 74% yield); MP: 138–140 °C, R_f = 0.5 (Hexane /EtOAc=5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J=8.4 Hz, 2H), 8.17 (d, J=7.8 Hz, 2H), 7.84 (s, 1H), 7.74–7.66 (m, 4H), 7.54–7.42 (m, 7H), 7.33 (t, J=7.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 167.3, 140.6, 138.4, 133.7, 130.8, 129.7, 129.3, 128.3, 127.2 (2 C), 126.6 (2 C), 126.0 (2 C), 123.5 (2 C), 120.3 (2 C), 120.1 (2 C), 117.5 (2 C), 109.8 (2 C). HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{19}N_2S$, 403.1263, found: 403.1253.

3-phenylisothiazole (2 aa). Brown solid (65 mg, 81% yield); MP: 45–47 °C; R_f=0.6 (Hexane /EtOAc=10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, J=1.6 Hz, 1H), 7.63–7.58 (m, 2H), 7.47–7.37 (m, 4H); ^{13}C NMR (125 MHz $CDCl_3$) δ 167.3, 158.2, 130.7, 129.5, 129.2 (2 C), 126.7 (2 C), 119.8. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for C_9H_8NS, 162.0372, found: 162.0371.

5-methyl-3-phenylisothiazole (2 ab). Brown solid (75 mg, 86% yield); MP: 67–69 °C; R_f=0.6 (Hexane /EtOAc=5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J=6.8 Hz, 2H), 7.41 (dd, J=12.8, 7.2 Hz, 3H), 7.20 (s, 1H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 167.4, 131.0, 129.4, 129.2 (2 C), 126.5 (2 C), 19.1. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{10}H_{10}NS$, 176.0528, fund: 176.0530.

5-(tert-butyl)-3-phenylisothiazole (2 ac). Yellow liquid (87 mg, 80% yield); R_f = 0.6 (Hexane /EtOAc=5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J=7.1 Hz, 2H), 7.41 (dt, J=14.6, 7.0 Hz, 3H), 7.33 (s, 1H), 1.42 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 167.1, 131.2, 129.2, 129.1 (2 C), 126.5 (2 C), 117.4, 36.6, 30.1 (3 C); HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{16}NS$, 218.0998, found: 218.0993.

5-(tert-butyl)-3-(thiophen-2-yl)isothiazole (2 ad). Brown liquid (75 mg, 67% yield); R_f=0.6 (Hexane /EtOAc=5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 1H), 7.29–7.26 (m, 1H), 7.19 (s, 1H), 7.06 (dd, J=5.1, 3.7 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2, 159.4, 133.1, 128.1, 126.6, 126.1, 117.9, 36.6, 30.0 (3 C); HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{11}H_{14}NS_2$, :224.0562, found: 224.0561.

3,5-dihexylisothiazole (2 ae). Yellow liquid (77 mg, 61% yield); R_f=0.7 (Hexane /EtOAc=30:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (s, 1H), 2.86 (t, J=7.7 Hz, 2H), 2.81–2.68 (m, 2H), 1.73–1.65 (m, 4H), 1.32 (ddt, J=10.6, 6.8, 5.4 Hz, 12H), 0.88 (q, J=6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 169.3, 121.4, 33.32, 31.6, 31.4, 30.9, 29.0, 28.96, 28.8, 27.9, 22.5, 22.5, 14.04, 14.01. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{28}NS$, 254.1937, found: 254.1938.

3-(2-methoxyphenyl)-5-phenylisothiazole (2 ag). Yellow solid (96 mg, 72% yield) MP: 110–112 °C; R_f=0.5 (Hexane /EtOAc=20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J=7.2 Hz, 2H), 7.97 (s, 1H), 7.85 (d, J=7.8 Hz, 1H), 7.48 (t, J=7.5 Hz, 2H), 7.44–7.36 (m, 2H), 7.11–7.03 (m, 2H), 4.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 162.5, 155.9, 135.0, 130.4, 128.9, 128.7 (2 C), 127.0, 126.8 (2 C), 121.1, 120.2, 116.9, 111.5, 55.6; HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{14}NOS$, 268.0791, found: 268.0784.

2-(5-phenylisothiazol-3-yl)phenol (2 ah). Yellow solid (110 mg, 87% yield); MP: 80–82 °C; R_f=0.5 (Hexane/EtOAc=20:1); ^{1}H NMR (500 MHz, Acetone) δ 11.6 (s, 1H), 8.38-8.37 (m, 1H), 8.02 (d, J=7.5 Hz, 1H), 7.79-7.86 (m, 2H), 7.56-7.51 (m, 3H), 7.36-7.33 (m, 1H), 7.02-6.96 (m, 2H); ^{13}C NMR (125 MHz, Acetone) δ 170.4, 167.8, 158.7, 132.2, 131.2, 130.4 (2 C), 129.2, 127.6 (2 C), 120.2 118.7, 118.3. HRMS (ESI-

TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{12}NOS$, 254.0634, found:254.0629.

benzo[*b*]thiophen-2-yl(2-fluorophenyl)methanone (3 a). Pink solid (108 mg, 84% yield); MP: 127–129 °C; R_f=0.4 (Hexane /EtOAc=4:1); 1H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, J= 8.0 Hz, 1H), 7.63 (d, J=3.3 Hz, 2H), 7.55 (m, J=5.4 Hz, 2H), 7.47 (m, J=7.5 Hz, 1H), 7.27 (m, J=11.3 Hz, 2H), 7.24–7.16 (m, 2H).^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 159.1 (d, J= 251.3 Hz, 1 C), 147.0, 138.0, 132.0 (d, J=8.4 Hz, 1 C), 131.6, 130.7, 130.0 (d, J=1.8 Hz, 1 C), 128.6, 127.8, 1126.8 (d, J= 3.8 Hz, 1 C), 126.3, 124.7 (d, J=3.8 Hz, 1 C), 124.3 (d, J= 12.5 Hz, 1 C), 1116.7 (d, J=21.2 Hz, 1 C). HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{10}FOS$, 257.0431, found: 257.0430.

(Z)-1-((3,4-diphenyl-1H-isothiochromen-1-ylidene)methyl)-3,4-diphenylisoquinoline (4 a).[12] Yellow solid (263 mg, 89% yield); R_f=0.5 (Hexane /EtOAc=10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, 1H), 8.06 (d, J=7.0 Hz, 2H), 7.82–7.49 (m, 5H), 7.48–7.26 (m, 9H), 7.24–7.04 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 140.1, 138.4, 137.6, 137.5, 136.6, 135.3, 132.1, 131.5 (2 C), 131.4 (2 C), 130.9 (2 C), 130.8, 130.4, 130.13, 129.9, 129.3 (2 C), 129.1, 128.3 (2 C), 128.2, 128.1 (2 C), 128.0, 127.8 (2 C), 127.4, 127.3, 127.2 (2 C), 127.0, 126.8, 126.7, 126.4, 125.7, 125.6, 124.6, 116.1.

Z)-1-((3,4-bis(4-methoxyphenyl)-1H-isothiochromen-1-ylidene)methyl)-3,4-bis(4-methoxyphenyl)isoquinoline (4 b).[12] Yellow solid (309 mg, 87% yield); R_f=0.5 (hexane/ EtOAc=3:1); ^{1}H NMR (500 MHz, $CDCl_3$) 8.40–8.43 (m, 1H), 8.01–8.05 (m, 2H), 7.71–7.73 (m, 1H), 7.57–7.59 (m, 2H), 7.51 (d, J=9 Hz, 2H), 7.41–7.44 (m, 1H), 7.30–7.33 (m, 1H), 7.18–7.20 (m, 2H), 7.12–7.14 (m, 3H), 7.04 (d, J=8.5 Hz, 2H), 6.93 (d, J=8.5 Hz, 2H), 6.80 (d, J=8.5 Hz, 2H), 6.70 (d, J= 8.5 Hz, 2H), 6.64 (d, J=8.5 Hz, 2H), 3.86 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.746 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 158.6, 158.5, 158.2, 152.5, 137.0, 135.6, 132.5 (2 C), 132.4 (2 C), 132.2 (2 C), 130.9, 130.9, 130.7, 130.7 (2 C), 130.2, 130.1, 129.0, 128.0, 127.9, 127.8, 126.3, 126.27, 125.6, 125.5, 124.7, 115.9, 113.9 (2 C), 113.5 (2 C), 113.2 (2 C), 112.8 (2 C), 55.2, 55.12, 55.09, 55.05.

(Z)-7-((4,5-diphenyl-7H-thieno[2,3-*c*]thiopyran-7-ylidene) methyl)-4,5-diphenylthieno[2,3-*c*]pyridine (4 c). Yellow solid (256 mg, 85% yield); MP: 269–271 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64–7.59 (t, J=7.0 Hz, 3H), 7.34 (dt, J=15.3, 7.6 Hz, 6H), 7.30–7.25 (m, 4H), 7.25–7.22 (m, 2H), 7.22–7.17 (m, 5H), 7.13 (t, J=7.3 Hz, 1H), 7.09 (s, 1H), 7.04 (t, J= 7.6 Hz, 2H), 6.83 (d, J=5.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 148.8, 145.9, 139.9, 139.6, 138.8, 138.3, 137.3, 136.8, 136.4, 134.1, 132.2, 130.9 (2 C), 130.7 (2 C), 130.6 (2 C), 130.1 (2 C), 129.6, 128.8, 128.3 (2 C), 128.1 (2 C), 128.0, 127.8 (2 C), 127.8, 127.2 (2 C), 127.1, 127.0, 126.9, 125.8, 125.4, 124.4, 106.7. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{39}H_{25}NS_3$, 604.1222, found: 604.1215.

(Z)-4-((6,7-diphenyl-4H-thieno[3,4-*c*]thiopyran-4-ylidene) methyl)-6,7-diphenylthieno[3,4-*c*]pyridine (4 d). Yellow solid (244 mg, 81% yield); MP: 177–179 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J=5.6 Hz, 1H), 7.69 (d, J=5.5 Hz, 1H), 7.65 (d, J=7.2 Hz, 2H), 7.52–7.47 (m, 2H), 7.42–7.34 (m, 6H), 7.31–7.26 (m, 7H), 7.22–7.19 (m, 3H), 7.14 (t, J=7.3 Hz, 1H), 7.05 (t, J=7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 143.8, 139.0, 138.3, 137.7, 137.2, 135.3, 132.3, 131.2, 131.1 (2 C), 130.5 (2 C), 130.3, 130.3, 130.1 (2 C), 130.0 (2 C), 129.5, 128.7 (2 C), 128.3 (2 C), 127.9, 127.9 (2 C), 127.8, 127.8, 127.3 (2 C), 127.2, 127.2, 126.7, 126.0, 125.4, 124.2, 122.0, 107.8. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{39}H_{25}NS_3$, 604.1222, found: 604. 604.1215.

4-bromo-3,5-diphenylisothiazole (5 a). [2d] White solid (144 mg, 92% yield); MP: 127–129 °C; R_f=0.5 (Hexane /EtOAc=20:1) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, J=7.8, 1.8 Hz, 2H), 7.67 (dd, J=7.9, 1.6 Hz, 2H), 7.58–7.43 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 162.9, 134.7, 130.1, 129.8, 129.4, 129.0 (2 C), 128.9 (2 C), 128.8 (2 C), 128.2 (2 C), 106.0. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{11}BrNS$, 315.9790, found: 315.9788.

3,4,5-triphenylisothiazole (6 a). [2d] Yellow solid (128 mg, 82% yield); MP: 217–219 °C; R_f=0.5 (Hexane /EtOAc=3:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J=6.9 Hz, 2H), 7.37–7.26 (m, 7H), 7.26–7.20 (m, 4H), 7.09 (d, J=6.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 164.0, 135.7, 134.2, 134.1, 131.0, 130.6 (2 C), 128.9 (2 C), 128.8, 128.7 (2 C), 128.7 (2 C), 128.6 (2 C), 128.4, 128.0 (2 C), 127.5; HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{16}NS$, 314.0998, found: 314.0997.

3,5-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) isothiazole (7 a). Brown liquid (136 mg, 75% yield); R_f=0.5 (Hexane /EtOAc=5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J=7.8 Hz, 2H), 7.63–7.60 (m, 2H), 7.42 (dd, J=8.0, 2.2 Hz, 6H), 1.19 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 172.4, 136.7, 131.9, 129.3, 128.8, 128.7 (2 C), 128.5 (2 C), 128.5 (2 C), 128.2 (2 C), 127.5, 84.4 (2 C), 24.7 (4 C). HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{23}BNO_2S$, 363.1573, found: 363.1563.

3,5-diphenylisothiazole-4-d (2 a-D). White solid (108 mg, 91% yield); R_f=0.5 (Hexane /EtOAc=30:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J=7.5 Hz, 2H), 7.66 (d, J=7.3 Hz, 2H), 7.46 (dq, J=20.4, 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 168.1, 134.8, 130.9, 129.6, 129.2 (3 C), 128.8 (2 C), 126.8 (2 C), 126.5 (2 C), 117.3 (t, J=27.5 Hz, 1 C); HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{11}DNS$, 239.0748, found: 239.0746.

(E)-3-amino-1,3-diphenylprop-2-en-1-one (8 a).[17] Yellow liquid (47 mg, 42% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.44 (s, 1H), 7.95 (d, J=7.8 Hz, 2H), 7.65 (d, J=7.6 Hz, 2H), 7.58–7.40 (m, 6H), 6.16 (s, 1H), 5.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.2, 162.9, 140.3, 137.6, 131.04, 130.7, 129.0 (2 C), 128.3 (2 C), 127.2 (2 C), 126.3 (2 C), 91.9. HRMS (ESI-TOF) (*m/z*): $[M+H]^+$ calcd for $C_{15}H_{14}NO$, 224.1070, found: 224.1065.

CCDC-2025711 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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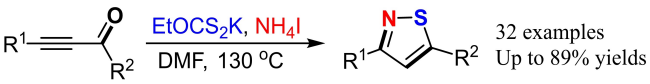
FULL PAPER

Transition Metal-Free Synthesis of Substituted Isothiazoles *via* Three-Component Annulation of Alkynones, Xanthate and NH_4I



* *One-pot synthesis*
* *Metal-free*
* *Readily available reactants*
* *C-N, C-S and N-S bond formations*

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