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Graphical Abstract

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Transition metal free synthesis of Leave this area blank for abstract info. multifunctional thiomethylated-benzenes from aryl/heteroaryl/cyclopropyl methyl ketones Rahul Panwar,^a Ismail Althagafi,^b Shally, ^a Ranjay Shaw,^a Amr Elagamy,^a Chandan Shah,^a Pratik Yadav^c and Ramendra Pratap^a ^aDepartment of Chemistry, University of Delhi, North campus, Delhi, India-110007 ^bDepartment of Chemistry, Umm Al-Qura University, Makkah, Saudi Arabia ^cKirori Mal College, University of Delhi, Delhi, India-110007 CS₂. CHal SCH₃ High yield Mild condition Easily accessible precursor Groups can be modified further CHa NH2 ö



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Transition metal free synthesis of multifunctional thiomethylated-benzenes from aryl/heteroaryl/cyclopropyl methyl ketones

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ABSTRACT

A base-promoted strategic synthesis of various functionalized thiomethylated-benzenes has been established from acetophenones and cyclopropyl methyl ketone. We can directly access the thiomethylated-benzene nucleus embedded with diverse functional group by the reaction of 3,3-bis(methylthio)-1-arylprop-2-en-1-ones and 2-(1-aryl/cyclopropyl)ethylidene)malononitriles in the presence of sodium hydride in THF at reflux temperature. These precursors are easily accessible from aryl methyl ketones. Various functional groups like alkyl, aryl, nitrile, amine, aroyl and thiomethyl can be directly installed to the benzene ring. The one-pot approach for the construction of thiomethylated-benzene nucleus was also developed. The structure of the synthesized compound was confirmed by X-ray crystallography.

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1. Introduction

Benzene ring installed with various important functional groups is omnipresent and privileged structural motifs. They are found in a variety of natural products, pharmaceutical compounds, advanced functional materials and various organic ligands used for metal catalyzed chemistry.¹ Therefore, development of efficient and new synthetic methods toward multi-substituted benzenes have been paid tremendous attention during recent years. Over the years, electrophilic and nucleophilic aromatic substitution, benzannulation reactions,² transition-metal catalyzed cross-coupling reactions,^{3a} aryne intermediates^{3b} and arylation via C-H activation,^{3c} were used as powerful tools to construct the multi-substituted arenes.

Apart from these strategies various approaches have been developed to construct the functioned benzene directly from suitable precursors. Various diketones and enones have been studied for the construction of multifunctional benzenes through selective transformations under transition metal-free conditions.⁴ Benzannulation was also carried out by using Rhodium and Indium catalyzed reaction of enaminones.⁵ Very recently N-heterocyclic carbenes (NHC) have emerged as an efficient organocatalytic method to construct various multisubstituted benzenes. To achieve these transformations, various α,β -unsaturated electron deficient alkenes were activated using NHCs followed by addition of carbon nucleophile in the presence of oxidant and base. In the first report, Chi and coworkers used enals, ⁶ readily prepared in

three steps and unsaturated ketones as a carbon nucleophile to assemble benzene core via a formal [3+3] cycloaddition reaction.^{7a} This strategy was further utilized by Wang et *al.* via [4+2] benzannulation^{7b} and Ye and coworkers via [2+4] annulation^{7c} approach and both starting from enals and unsaturated ketones. In early 2015, Lupton et *al.* described another intramolecular NHC catalyzed strategy for the synthesis of functionalized benzaldehydes.^{7d} Chi and coworkers subsequently developed an elegant NHC catalyzed



Scheme 1: Previous approaches versus this approach to construction functionalized benzenes

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domino reaction triggered by a δ -LUMO activation of α , β + γ -re-p δ -diunsaturated enal for the formal [4+2] construction of multi-substituted benzenes (Scheme 1, entry i).⁸ Very recently, transition metal-free assembly of the benzene skeleton from enaminodiones was established through selfcondensation.⁸ A new Rh(III)-catalyzed approach for the construction of multifunctional benzenes through regioselective [4+2] C-annulation was developed.⁸ We have also established various ring transformation reactions for the construction of benzene nucleus by reaction of various functionalized 2-pyranones and carbon nucleophiles (Scheme 1, entry ii).⁹

Due to importance of suitably functionalized benzene nucleus, we became interested in the development of new basepromoted approach for their synthesis (Scheme 1, entry iii). Ketene dithioacetals are well known for the strong synthetic potential¹⁰ so we have further explored their synthetic potential.

2. Result and discussion

To start our study, we have synthesized the required precursors 3,3-bis(methylthio)-1-arylprop-2-en-1-ones and 2-(1-aryl)ethylidene)malononitriles by using earlier reported procedures. 3,3-Bis(methylthio)-1-arylprop-2-en-1-ones were synthesized by the reaction of functionalized acetophenones, carbon disulphide and methyl iodide under basic conditions.¹¹ The other precursor 2-(1-aryl)ethylidene)malononitriles was also synthesized by the reaction of alky/aryl methyl ketone and malononitrile in the presene of glacial acetic acid and ammonium acetate in toluene under reflux condition.¹²⁻¹⁴



Scheme 2: Synthesis of precursors 3,3-bis(methylthio)-1-arylprop-2-en-1ones (1) and 2-(1-aryl)ethylidene)malononitriles (2) [Compound 1 was synthesized by stirring aryl methyl ketone (10.0 mmol), carbon disulphide (11 mmol), methyl iodide (20.0 mmol) and NaH (30.0 mmol) in dry THF (50.0 ml) at 0 °C; Compound 2 was synthesized by stirring malononitrile (48.0 mmol), ammonium acetate (9.60 mmol) and ketone (48.0 mmol) and acetic acid (52.8 mmol) in toluene (30.0 ml) at reflux temperature]

In order to optimize the reaction condition 3.3bis(methylthio)-1-phenylprop-2-en-1-one and 2-(1-(ptolyl)ethylidene)malononitrile was selected as model substrate. We started the study using triethyl amine in DMSO at room temperature and 70 °C, but no product formation was observed (Table 1, entries 1 and 2). Further trial was made by using sodamide as base in DMSO at room temperature, 70 °C and 100 °C and 30-35% product was obtained at higher temperature (Table 1, entries 3-5). Then, we performed the reaction using sodamide in DMF at 100 °C and 35% of product was isolated (Table 1, entry 6). We used potassium tert.-butoxide and KOH at 100 °C and 30-36% product was formed (Table 1, entries 7,8). Then, we used sodium hydride in DMSO and DMF at 100 °C and 40 and 32% product was isolated respectively (Table 1, entries 9 and 10). When reaction was performed in THF using sodium hydride at reflux temperature, surprisingly 95% product was isolated (Table 1, entry 11). We proposed that due to high polarity of DMF, sodium hydride act as stronger base and cause decomposition of precursor and therefore low yield was obtained

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Entry	Base	Solvent	T (°C)	t (h)	Yield
					(%) 3
1	NEt ₃	DMSO	RT^{b}	12	_c
2	NEt_3	DMSO	70	12	_c
3	$NaNH_2$	DMSO	RT^{b}	12	_c
4	$NaNH_2$	DMSO	70	12	30
5	$NaNH_2$	DMSO	100	12	35
6	$NaNH_2$	DMF	100	12	35
7	KO ^t Bu	DMSO	100	12	30
8	KOH	DMSO	100	12	36
9	NaH	DMSO	100	12	40
10	NaH	DMF	100	12	32
11	NaH	THF	Reflux	6	95
12	NaNH ₂	THF	Reflux	12	42
13	Cs ₂ CO ₃	THF	Reflux	12	_c
14	кон	THF	Reflux	12	55

Table 1: Effect of base and solvent on the synthesis of **3a**^a

a] all reactions were performed by stirring 3,3-bis(methylthio)-1-phenylprop-2-en-1-one (0.5 mmol), 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol) and base (0.6 mmol) in solvent (5.0 mL) at different temperature; (b) Room temperature was ranging from 30-35 °C, (c) both starting material left unconsumed during the reaction.

Reflux

12

45

KO^tBu

15

THF



Scheme 3: Synthesis of various arylated benzenes **3** [Reactions were performed by stirring 3,3-bis(methylthio)-1-arylprop-2-en-1-one (0.5 mmol), 2-(1-aryl)ethylidene)malononitrile (0.5 mmol) and sodium hydride (0.6 mmol) in THF (5.0 mL) at reflux temperature]

in DMF. From the entry 11, we concluded that THF act as the best solvent for this reaction so tested the reactivity of some other bases in THF, such as sodamide, cesium carbonate, KOH and KO^tBu but none of them provided better results than sodium hydride (Table 1, entries 12-15). Thus, reaction of **1** and **2** in THF in the presence of sodium hydride at reflux

temperature provides the desired product in high yield and is the best reaction condition.

Then, we tested the generality of optimized reaction condition and performed the reaction using 2-(1-p-tolyl-ethylidene)malononitrile and various ketene dithioacetals containing differently functionalized aryl group and afforded the arylated benzene in 52-95% yield. The presence of different functional group in aryl ring of ketene dithioacetal affects the yield of the product, but does not follow any specific trends. 3,3-Bismethylsulfanyl-1-(pyridine/thiophen/furan-2-yl)-

propenones were also used as a precursor and good yields of the desired product was isolated.

Further, treatment of 3, 3-bis-methylsulfanyl-1-phenylpropenone with differently functionalized 2-(1-arylethylidene)-malononitriles afforded the functionalized benzenes in good yields. From these reactions, we observed that presence of different functional group in aryl ring of 2-(1aryl-ethylidene)-malononitriles have no significant effect on the yield of product under basic conditions. Apart from this, we tested many other combinations of ketene dithioacetals and 2-(1-aryl-ethylidene)-malononitriles under the same reaction conditions and all of them provide the desired product in moderate to good yields. It was interesting to note that presence of naphthyl group in either starting materials provides a lower yield probably due to electronic effect of naphthyl ring.



Scheme 4: Synthesis of various arylated benzene using 1-(halophenyl)-3,3bismethylsulfanylpropenones.[Reactions were performed by stirring 3,3bis(methylthio)-1-arylprop-2-en-1-one (0.5 mmol), 2-(1-aryl)ethylidene)malononitrile (0.5 mmol) and sodium hydride (0.6 mmol) in THF (5.0 mL) at reflux temperature]



Scheme 5: Synthesis of various heteroaryl substituted benzenes 6.[Reactions were performed by stirring 3,3-bis(methylthio)-1-arylprop-2-en-1-ones (0.5 mmol), 2-(1-aryl)ethylidene)malononitriles (0.5 mmol) and sodium hydride (0.6 mmol) in THF (5.0 mL) at reflux temperature.]

In order to perform the reaction at gram scale we have tried to synthesize compound **3a**. Surprisingly, we need to replace the base from NaH to KOH under similar reaction conditions, but lower yield 54% was obtained. We proposed that powdered KOH had better solubility than sodium hydride in THF and therefore at large scale KOH works better but low yield was obtained.

Interestingly, the use of 1-(halophenyl)-3,3 bismethylsulfanylpropenones as a precursor, provided the product **5** in which halide group was replaced with the methylthio group in addition to desired product (Scheme 4). If we increase the duration of reaction, yield of product **5** increased. Mechanistically, compound **4** can be converted in 5 through ipso attack by in situ generated methylthio group at position containing halide group followed by loss of halide to afford the product **5**.

To expand the scope of the reaction, we further synthesized heteroaryl substituted benzenes. We have synthesized the benzene functionalized with furan and thiophene in good yield by using 2-(1-heteroaryl)ethylidene)malononitriles as a precursor (Scheme 5).

We also planned to synthesize alkylated benzenes, but failed due to low yields of corresponding alkylidine malononitrile and various side reactions under basic conditions. Interestingly, we have synthesized 2-(1-cyclopropylethylidene)-malononitrile as a precursor and used it for further cyclization reaction. Treatment of ketene dithioacetal with 2-(1-cyclopropyl-ethylidene)-malononitrile under basic condition afforded cyclopropyl functionalized benzene in good yields (Scheme 6). We observed low yield of the desired product probably due to side reaction occurred under basic conditions, such as abstraction of protons from cyclopropyl ring or ring opening reaction. The cyclopropyl group can be used for further modification to develop new molecular entities.



In continuation, we became interested to develop the one-pot approach for the synthesis of functionalized benzenes. In this trial, we first performed the synthesis of ketene dithioacetal by stirring the acetophenone, carbon disulphide and methyl iodide under basic condition. Formation of ketene dithioacetal was monitored by TLC. Then 2-(1arylethylidene)-malononitriles and additional base was added to the same pot and the reaction mixture was refluxed until the reaction was completed. Usual work-up afforded the functionalized benzenes in good yield. We have synthesized some of the functionalized benzene in overall good yields (Scheme 7).



Mechanistically, we propose that reaction is initiated by Michael addition of carbanion generated from 2-(1-arylethylidene)-malononitrile on ketene dithioacetal **1** followed by elimination of methanethiol to afford the intermediate **A**. Further, in the presence of excess of base, carbanion generated from intermediate **A** undergoes isomerization to afford intermediate enolate **B**. Enolate **B** undergoes cyclization by involvement of nitrile group and carbon present at α -position to a carbonyl group to provide intermediate **C**. Intermediate **C** undergoes tautomerization to provide the desired product.

To probe the mechanistic pathway, we tried to isolate the intermediate **A**. For this purpose, we performed the reaction under similar condition using low concentrations of base, but only desired product **3** was isolated with the left starting material. This result demonstrates that intermediate **A** immediately converted to product due to presence of more activated proton than compound **2**.



Scheme 8: Proposed mechanistic pathway for the synthesis of highly functionalized thiomethylated-benzenes

The structure of the product **3a** was confirmed by X-ray crystallography (Fig. 1).¹⁵ Compound **3a** was crystallized in P-1 space group and contains two molecules in the triclinic unit cell. Both the phenyl ring of biaryl was not in the same plane. Both aryl rings of biaryl are planar and the dihedral



angle between the planes 34.69°.

Fig. 1 Ortep diagram of 3-amino-4-benzoyl-4'-methyl-5-methylsulfanyl-biphenyl-2-carbonitrile

Conclusions

In summary, we have developed a simple and efficient approach for the synthesis of highly functionalized thiomethylated-benzenes under basic condition. Atom economy of the reported reaction is very high. Various functional groups such as aryl, heteroaryl, aroyl, heteroaroyl, cyclopropyl, amino and nitrile group can be incorporated into the benzene nucleus. This reaction does not require any transition metal catalysts. We also successfully achieved onepot synthesis of functionalized thiomethylated-benzene from acetophenones. We tried to understand the mechanistic pathway, but not able to isolate the intermediate. All the synthesized compounds are characterized by spectroscopic techniques and one structure was confirmed by single crystal X-ray.

Experimental section

General remarks: All the reactions were performed by using commercially available reagents without any further purification. The sodium hydride (60% dispered in oil) was washed with hexanes to remove the oil before use. THF was dried over sodium under nitrogen atmosphere. ¹H and ¹³C NMR spectra were recorded on a 400 MHz NMR and 100 MHz NMR spectrometer. To perform the NMR spectroscopy, CDCl₃ was used as solvent. Chemical shifts values are reported as parts per million (δ -value) and for proton NMR peak of CDCl₃ (δ = 7.24 ppm for ¹H) or the middle peak of the CDCl₃ in ¹³C NMR (δ 77.00 ppm) was used as an internal reference. Characterization data shows signal patterns as s, singlet; d, doublet; dd, double doublet; t, triplet; bs, broad singlet; m, multiplets. Coupling constants (*J*) are given in hertz (Hz). During the period of reaction, room temperature was ranging from 30-35 °C.

General procedure for the synthesis of 3,3-bis(methylthio)-1arylprop-2-en-1-ones: To a vacuum dried RB flask sodium hydride (30.0 mmol) was taken in dry THF (50.0 ml) and cooled to 0 °C over ice bath. Then aryl methyl ketone (10.0 mmol) was added drop-wise with constant stirring until the solution at low temperature. Reaction mixture was stirred for 30 minutes. Then carbon disulphide (11 mmol) was added slowly and the mixture was again stirred for one hour. Further, methyl iodide (20.0 mmol) was added drop-wise at 0 °C. Then reaction mixture was stirred for another 1 hour at room temperature. After completion of the reaction, excess of THF was removed under reduced pressure and ice was added to the reaction mixture and obtained precipitate was filtered, dried and recrystallized with cold hexane to isolate the desired product.^{10,11}

General procedure for the synthesis of 2-(1-arylethylidene)malononitriles: To a vacuum dried RB flask malononitrile (3.17 g, 48.0 mmol, 1 equiv), ammonium acetate (0.740 g, 9.60 mmol, 0.2 equiv) and ketone (48.0 mmol, 1 equiv) was added. To the mixture acetic acid (3.0 ml, 52.8 mmol, 1.1 equiv) and toluene (30.0 ml) was added. The round-bottom was fitted with a Dean-Stark apparatus and reaction mixture was refluxed for 1-2 h. The reaction mixture was cooled to room temperature and diluted with toluene (50.0 mL). The organic layer was washed with saturated sodium bicarbonate solution (50.0 mLx3) and water (50.0 mLx2). The organic layer was dried with MgSO₄ and concentrated under vacuum and resulting solid was recrystallized in ethanol to isolate the compound.¹²⁻¹⁴

General procedure for the synthesis of multifunctional benzenes: To a vacuum dried RB flask 3,3-bis(methylthio)-1arylprop-2-en-1-ones (0.5 mmol) and 2 - (1 aryl)ethylidene)malononitriles (0.5 mmol) was placed. Then sodium hydride (0.6 mmol) was added followed by addition of THF (5.0 mL). The reaction mixture was refluxed till completion of the reaction. After completion of reaction, excess of THF was removed under reduced pressure followed by addition of ice water. Reaction mixture was neutralized by dilute HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent.

General procedure for the synthesis of multifunctional cyclopropylated benzenes: To a vacuum dried RB flask 3,3bis(methylthio)-1-arylprop-2-en-1-ones (0.5 mmol) and 2-(1cyclopropylethylidene)malononitrile (0.5 mmol) was placed. Then sodium hydride (1.0 mmol) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent.

General procedure for the gram scale synthesis of multifunctional benzenes: To a vacuum dried 100 ml RB flask 3,3bis(methylthio)-1-phenylprop-2-en-1-one (6.0 mmol) and 2-(1-(*p*-tolyl)ethylidene)malononitrile (6.0 mmol) was placed. Then potassium hydroxide (9.0 mmol) was added, followed by addition of THF (60 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent.

General procedure for one-pot synthesis of multifunctional benzenes (3): To a vacuum dried RB flask sodium hydride (3.0 mmol) was taken in dry THF (10.0 mL) and cooled to 0 °C over the ice bath. Then aryl methyl ketone (1.0 mmol) was added drop-wise with constant stirring to the solution at 0 °C. Reaction mixture was stirred for 10 minutes. Then carbon disulphide (1.1 mmol) was added slowly and mixture was again stirred for half hours. Then methyl iodide (2.0 mmol) was added drop-wise at 0 °C and reaction mixture was stirred for another hour at room temperature. Completion of reaction was monitored by TLC and then sodium hydride (1.0 mmol) and 2-(1-aryl)ethylidene)malononitriles (1.0 mmol) was added to the same mixture. The reaction bath was transferred to oil bath and refluxed till completion of the reaction. After completion of reaction, excess of THF was removed under reduced pressure followed by addition of ice water. Reaction mixture was neutralized by dilute HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent.

3-Amino-4-benzoyl-4'-methyl-5-(methylthio)-[1,1'-biphenyl]-

2-carbonitrile (3a): To a vacuum dried RB flask 3,3-bis(methylthio)-1-phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-(1-(ptolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed for 6 hours. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 95% (170 mg); light yellow solid; mp 150-152 °C; IR (KBr): 3395, 2210, 1645 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.36 (s, 3H, -SMe), 2.43 (s, 3H, -CH₃), 4.89 (s, 2H, -NH₂), 6.69 (s, 1H, ArH), 7.31 (d, J = 8 Hz, 2H, ArH), 7.49 (t, J = 8 Hz, 4H, ArH), 7.62-7.66 (m, 1H, ArH), 7.87 (d, J = 8 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.5, 21.3, 93.9, 115.9, 117.1, 120.9, 128.3, 128.9, 129.4, 129.6, 134.2, 135.2, 137.0, 139.2, 144.8, 147.2, 148.4, 196.5. HRMS (ESI): calculated for C₂₂H₁₉N₂OS, 359.1213 (MH⁺), found: *m/z*, 359.1214.

3-Amino-4-(3-bromobenzoyl)-4'-methyl-5-(methylthio)-[1,1'-

biphenyl]-2-carbonitrile (3b): To a vacuum dried RB flask 1-(3bromophenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.151 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 87% (190 mg); light yellow solid; mp: 148-150 °C; IR (KBr): 3471, 2208, 1691 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.37 (s, 3H, -SMe), 2.43 (s, 3H, -CH₃), 5.00 (s, 2H, -NH₂), 6.69 (s, 1H, ArH), 7.31-7.33 (m, 2H, ArH), 7.36 (t, J = 8 Hz, 1H, ArH), 7.49 (d, J = 8 Hz, 2H, ArH), 7.73-7.76 (m, 2H, ArH), 7.98-7.99 (m, 1H, ArH); 13 C NMR (100 MHz, CDCl₃): δ 16.6, 21.3, 94.1, 116.1, 117.0, 119.9, 123.1, 128.1, 128.3, 129.5, 130.4, 132.1, 135.0, 136.8, 139.1, 139.3, 145.0, 147.6, 148.7, 195.2. HRMS (ESI): calculated for $C_{22}H_{18}BrN_2OS$, 437.0318, (MH⁺+2); found: m/z, 439.0326.

3-Amino-4'-methyl-4-(4-methylbenzoyl)-5-(methylthio)-[1,1'-

biphenyl]-2-carbonitrile (3c): To a vacuum dried RB flask 3,3bis(methylthio)-1-(p-tolyl)prop-2-en-1-one (0.5 mmol, 0.119 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 86% (160 mg); light yellow solid; mp: 170-172 °C; IR (KBr): 3427, 2208, 1698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H, -SMe), 2.41 (s, 3H, -CH₃), 2.42 (s, 3H, -CH₃), 4.79 (s, 2H, -NH₂), 6.66 (s, 1H, ArH), 7.28 (t, J = 8 Hz, 4H, ArH), 7.46 (d, J = 8 Hz, 2H, ArH), 7.76 (d, J = 8 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.4, 21.3, 21.9, 93.8, 115.9, 117.2, 121.3,

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128.3, 129.4, 129.7, 129.8, 134.3, 135.3, 139.2, 144.5, 145.5, 147.0, 148.1, 196.0. HRMS (ESI): calculated for $C_{23}H_{21}N_2OS$, (373.1369 (MH⁺); found: *m/z*, 373.1367.

3-Amino-4'-methoxy-4-(4-methylbenzoyl)-5-(methylthio)-

[1,1'-biphenyl]-2-carbonitrile (3d): To a vacuum dried RB flask 1-(4-methoxyphenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.127 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 68% (132 mg); light yellow solid; mp: 165-167 °C; IR (KBr): 3369, 2210, 1728 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.38 (s, 3H, -SMe), 2.43 (s, 3H, -CH₃), 3.89 (s, 3H, -OMe), 4.77 (s, 2H, -NH₂), 6.68 (s, 1H, ArH), 6.95-7.00 (m, 2H, ArH), 7.25-7.32 (m, 2H, ArH), 7.46- 7.50 (m, 2H, ArH), 7.86-7.88, (m, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.2, 21.3, 55.6, 93.7, 114.2, 115.7, 117.2, 128.3, 129.4, 129.6, 129.7, 132.2, 135.3, 139.1, 144.3, 146.8, 148.0, 164.6, 194.6. HRMS (ESI): calculated for C₂₃H₂₁N₂O₂S, 389.1318 (MH⁺); found: *m/z*, 389.1326.

3-Amino-4-(2-methoxybenzoyl)-4'-methyl-5-(methylthio)-[1,1'-

biphenyl]-2-carbonitrile (3e): To a vacuum dried RB flask 1-(2methoxyphenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.127 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 95% (184 mg); light yellow solid; mp: 180-182 °C; IR (KBr): 3359, 2208, 1726 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.29 (s, 3H, -SMe), 2.40 (s, 3H, -SMe), 3.78 (s, 3H, -OMe), 5.46 (s, 2H, -NH₂), 6.57 (s, 1H, ArH), 6.95 (d, J = 8 Hz, 1H, ArH), 7. 00 (t, J = 8Hz, 1H, ArH), 7.27 (d, J = 8 Hz, 2H, ArH), 7.44-7.57 (m, 4H, ArH). ¹³C NMR (100 MHz, CDCl₃): δ 16.7, 21.2, 56.4, 93.6, 112.0, 115.5, 120.7, 121.9, 128.2, 128.7, 129.3, 130.8, 131.2, 132.4, 134.3, 135.3, 139.2, 147.2, 149.5, 159.0, 195.4. HRMS (ESI): calculated for $C_{23}H_{21}N_2O_2S$, 389.1318 (MH⁺); found: m/z, 389.1326.

4-(1-Naphthoyl)-3-amino-4'-methyl-5-(methylthio)-[1,1'-

biphenyl]-2-carbonitrile (3f): To a vacuum dried RB flask 3,3bis(methylthio)-1-(naphthalen-1-yl)prop-2-en-1-one (0.5 mmol, 0.137 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 53% (108 mg); light yellow solid, mp: 175-177 °C; IR (KBr): 3469, 2208, 1660 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.31 (s, 3H, -SMe), 2.42 (s, 3H, -CH₃), 4.94 (s, 2H, -NH₂), 6.71 (s, 1H, ArH), 7.30 (d, J = 8 Hz, 2H, ArH), 7.49-7.55 (m, 3H, ArH), 7.61 (t, J = 8Hz, 1H, ArH), 7.87-7.99 (m, 4H, ArH), 8.31 (s, 1H, ArH); 13 C NMR (100 MHz, CDCl₃): δ 16.4, 21.3, 93.8, 115.9, 117.1, 121.0, 124.2, 126.9, 127.8, 128.3, 128.9, 129.0, 129.4, 129.8, 132.2, 132.5, 134.2, 135.2, 136.5, 139.2, 144.8, 147.1,

 $\begin{array}{l} \textbf{Pre-148.4, 196.3. HRMS (ESI): calculated for C_{26}H_{21}N_2OS, 409.1369} \\ \textbf{(MH^+); found: } \textit{m/z, 409.1361.} \end{array}$

$\label{eq:2.1} 3-Amino-4-(3,4-dimethoxybenzoyl)-4'-methyl-5-(methylthio)-$

[1,1'-biphenyl]-2-carbonitrile (3g): To a vacuum dried RB flask 1-(3,4-dimethoxyphenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.142 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 64% (134 mg); light yellow solid, mp: 155-157 °C; IR (KBr): 3322, 2210, 11698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.32 (s, 3H, -SMe), 2.46 (s, 3H, -CH₃), 3.89 (s, 3H, -OMe), 3.97 (s, 3H, -OMe), 6.82 (s, 1H, ArH), 6.85-6.87 (m, 1H, ArH), 6.92-6.94 (m, 1H, ArH), 7.14 (d, J = 4 Hz, 2H, ArH), 7.35 (d, J = 12 Hz, 2H, ArH), 7.61 (d, J = 8 Hz, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 17.7, 21.3, 55.9, 56.0, 105.9, 110.6, 112.9, 121.6, 121.9, 122.1, 123.6, 128.8, 129.5, 131.7, 135.3, 139.2, 147.2, 147.4, 148.5 149.5, 149.7, 161.8. HRMS (ESI): calculated for C₂₄H₂₃N₂O₃S, 419.1424 (MH⁺); found: *m/z*, 419.1423.

3-Amino-4-(furan-2-carbonyl)-4'-methyl-5-(methylthio)-[1,1'-

biphenyl]-2-carbonitrile (3h): In a vacuum dried RB flask 1-(furan-2-yl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.107 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 78% (136 mg); light yellow solid, mp: 160-162 °C; IR (KBr): 3561, 3459, 2210, 1665 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.42 (s, 6H, -SMe, -CH₃), 4.93 (s, 2H, -NH₂), 6.60-6.61 (m, 1H, ArH), 6.70 (s, 1H, ArH), 7.23-7.30 (m, 1H, ArH), 7.31 (d, J = 8 Hz, 2H, ArH), 7.47 (d, J = 8 Hz, 2H, ArH), 7.70 (s, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.7, 21.3, 94.0, 113.0, 116.5, 117.0, 120.5, 121.4, 128.3, 129.4, 135.2, 139.3, 145.0, 147.5, 148.2, 148.4, 152.4, 182.7. HRMS (ESI): calculated for C₂₀H₁₇N₂O₂S, 349.1005 (MH⁺); found: *m*/*z*, 349.1008.

3-Amino-4'-methyl-5-(methylthio)-4-(thiophene-2-carbonyl)-[1,1'-biphenyl]-2-carbonitrile (3i): To a vacuum dried RB flask 3,3-bis(methylthio)-1-(thiophen-2-yl)prop-2-en-1-one (0.5 mmol, 0.115 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 80% (146 mg); light yellow solid, mp: 165-167 °C; IR (KBr): 3473, 2208, 1612 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.41 (s, 3H, -SMe), 2.43 (s, 3H, -CH₃), 4.80 (s, 2H, -NH₂), 6.70 (s, 1H, ArH), 7.15 (t, J = 8 Hz, 1H, ArH), 7.31(d, J = 8 Hz, 2H, ArH), 7.47 (d, J = 8 Hz, 2H, ArH), 7.61-7.62 (m, 1H, ArH), 7.79-7.80 (m, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.5, 21.3, 93.9, 116.1, 117.0, 121.6, 128.3, 128.6, 129.4, 129.5, 135.2, 135.8, 136.4, 139.2, 143.6, 144.3, 147.147.8, 187.9. HRMS (ESI): calculated for C₂₀H₁₇N₂OS₂, 365.0777 (MH⁺); found: *m/z*, 365.0775.

(3j): To a vacuum dried RB flask 3,3-bis(methylthio)-1phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-(1phenylethylidene)malononitrile (0.5 mmol, 0.084 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 85% (146 mg); light yellow solid, mp: 140-142 °C; IR (KBr): 3345, 2210, 1625 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.37 (s, 3H, -SMe), 4.89 (s, 2H, -NH₂), 6.70 (s, 1H, ArH), 7.43-7.55 (m, 5H, ArH), 7.57-7.59 (m, 2H, ArH), 7.62-7.66 (m, 1H, ArH), 7.88 (d, J = 8 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.6, 93.8, 115.9, 117.1, 121.6, 128.6, 128.9, 129.0, 129.3, 129.7, 134.4, 136.8, 138.0, 144.8, 147.4, 148.5, 196.6. HRMS (ESI): calculated for $C_{21}H_{17}N_2OS$, 345.1056 (MH⁺); found: m/z, 345.1059.

3-Amino-4-benzoyl-4'-fluoro-5-(methylthio)-[1,1'-biphenyl]-2carbonitrile (3k): To a vacuum dried RB flask 3,3-bis(methylthio)-1phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-(1-(4fluorophenyl)ethylidene)malononitrile (0.5 mmol, 0.093 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 89% (161 mg); light yellow solid, mp: 145-147 °C; IR (KBr): 3579, 2210, 1648 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.37 (s, 3H, -SMe), 4.90 (s, 2H, -NH₂), 6.60 (s, 1H, ArH), 7.17-7.22 (m, 2H ArH), 7.48-7.52 (m, 2H, ArH), 7.54-7.58 (m, 2H, ArH), 7.64 (t, J = 8 Hz, 1H, ArH), 7.87 (d, J = 4 Hz, 2H); ¹³C NMR $(100 \text{ MHz}, \text{CDCl}_3)$: δ 16.6, 94.0, 116.1, (d, J = 20 Hz), 117.0, 121.4, 129.3 (d, J = 60 Hz), 130.4, 130.5, 134.2, 134.3, 134.4, 137.0, 145.1, 146.2, 148.5, 163.3 (d, J = 250 Hz), 196.4. HRMS (ESI): calculated for C₂₁H₁₆FN₂OS, 363.0962 (MH⁺); found: *m/z*, 363.0964.

3-Amino-4-benzoyl-4'-chloro-5-(methylthio)-[1,1'-biphenyl]-2carbonitrile (31): To a vacuum dried RB flask 3,3-bis(methylthio)-1phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-(1-(4chlorophenyl)ethylidene)malononitrile (0.5 mmol, 0.101 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 74% (140 mg); light yellow solid, mp: 130-132 °C; IR (KBr): 3571, 2210, 1660 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.36 (s, 3H, -SMe), 4.87 (s, 2H, -NH₂), 6.64 (s, 1H, ArH, 7.45-7.51 (m, 6H, ArH), 7.63 (t, J = 8 Hz, 1H, ArH), 7.85 (d, J = 8 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.4, 93.7, 115.8, 116.7, 121.4, 129.0, 129.0, 129.6, 129.8, 134.3, 135.4, 136.5, 136.8, 145.1, 145.8, 148.4, 196.3. HRMS (ESI): calculated for C₂₁H₁₆ClN₂OS, 379.0666 (MH⁺); found: *m/z*, 379.0668.

3-Amino-4-benzoyl-4'-bromo-5-(methylthio)-[1,1'-biphenyl]-

2-carbonitrile (3m): To a vacuum dried RB flask 3,3-bis(methylthio)-1-phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-(1-(4bromophenyl)ethylidene)malononitrile (0.5 mmol, 0.123 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 72% (152 mg); light yellow solid, mp: 170-172 °C; IR (KBr): 3409, 2208, 1635 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.41 (s, 3H, -SMe), 4.89 (s, 2H, -NH₂), 6.66 (s, 1H, ArH), 7.36-7.40 (m, 1H, -ArH), 7.47-7.54 (m, 4H, ArH), 7.60-7.62 (m, 1H, ArH), 7.65-7.69 (m, 1H, ArH), 7.87 (d, *J* = 8 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.4, 93.7, 115.8, 121.6, 122.8, 127.2, 129.0, 129.6, 130.3, 131.3, 132.1, 134.4, 140.1, 145.1, 145.4, 148.3, 196.3. HRMS (ESI): calculated for C₂₁H₁₆BrN₂OS, 423.01461 (MH⁺+2); found: *m*/*z*, 425.01459.

3-Amino-4-benzoyl-4'-methoxy-5-(methylthio)-[1,1'-

biphenyl]-2-carbonitrile (3n): To a vacuum dried RB flask 3,3bis(methylthio)-1-phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-1-(4-methoxyphenyl)ethylidene)malononitrile (0.5 mmol, 0.099 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 91% (170 mg); light yellow solid, mp: 120-122 °C; IR (KBr): 3427, 2208, 1603 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.34 (s, 3H, -SMe), 3.85 (s, 3H, -OMe), 4.88 (s, 2H, -NH₂), 6.65 (s, 1H, ArH), 6.99-7.01 (m, 2H, ArH), 7.45-7.53 (m, 4H, ArH), 7.59-7.63 (m, 1H, ArH), 7.85 (d, *J* = 8 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): *δ* 16.4, 55.3, 93.7, 114.1, 115.8, 117.2, 120.6, 128.9, 129.5, 129.7, 130.3, 134.1, 137.0, 144.7, 146.8, 148.4, 160.3, 196.4. HRMS (ESI): calculated for C₂₂H₁₉N₂O₂S, 375.1162 (MH⁺); found: *m*/*z*, 37.1164.

3-Amino-4-benzoyl-4'-methyl-5-(methylthio)-[1,1'-biphenyl]-2-

carbonitrile (30): To a vacuum dried RB flask 3,3-bis(methylthio)-1phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-(1-(ptolyl)ethylidene)malononitrile (0.5 mmol, 0.122 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 95% (170 mg); light yellow solid; mp: 150-152 °C; IR (KBr): 3395, 2210, 1645 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): ¹H NMR (400 MHz, CDCl₃): δ 2.36 (s, 3H, -SMe), 2.43 (s, 3H, -CH₃), 4.89 (s, 2H, -NH₂), 6.69 (s, 1H, ArH), 7.31 (d, J = 8 Hz, 2H, ArH), 7.49 (t, J = 8 Hz, 4H, ArH), 7.62-7.66 (m, 1H, ArH), 7.87 (d, J = 8.0 Hz, 2H, ArH);; ¹³C NMR (100 MHz, CDCl₃); δ 16.3, 22.0, 93.8, 115.8, 117.1, 121.2, 128.3, 129.4, 129.7, 129.8, 134.3, 135.3, 139.1, 144.5, 145.5, 147.0, 148.1, 196.0.. HRMS (ESI): calculated for C₂₂H₁₉N₂OS, 359.1213 (MH⁺); found: *m/z*, 359.1214.

3-Amino-4-benzoyl-5-(methylthio)-[1,1':4',1''-terphenyl]-2-

carbonitrile (3p): To a vacuum dried RB flask 3,3-bis(methylthio)-1-phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-(1-([1,1'biphenyl]-4-yl)ethylidene)malononitrile (0.5 mmol, 0.122S g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 78% (164 mg); light yellow solid, mp: 190-192 °C; IR (KBr); 3579, 2208, 1648 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.38 (s, 3H, - SMe), 4.92 (s, 2H, -NH₂), 6.75 (s, 1H, ArH), 7.39-7.41 (m, 1H, ArH), 7.46-7.52 (m, 4H, ArH), 7.62-7.68 (m, 5H, ArH), 7.71-7.74 (m, 2H, ArH), 7.88-7.90 (m, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.4, 93.8, 116.0, 117.0, 121.2, 127.1, 127.4, 127.7, 128.8, 128.9, 129.6, 134.2, 136.9, 140.2, 142.0, 144.9, 146.7, 148.4, 196.4. HRMS (ESI): calculated for $C_{27}H_{21}N_2OS$, 421.1369 (MH⁺); found: *m*/*z*, 421.1372.

3-Amino-4-benzoyl-2',4'-dichloro-5-(methylthio)-[1,1'-

biphenyl]-2-carbonitrile (3q): To a vacuum dried RB flask 3,3bis(methylthio)-1-phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-(1-(2,4-dichlorophenyl)ethylidene)malononitrile (0.5 mmol, 0.118 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 68% (140 mg): light vellow solid, mp: 133-135 °C; IR (KBr): 3473, 2210, 1658-1; ¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H, -SMe), 4.83 (s, 2H, -NH₂), 6.61 (s, 1H, ArH), 7.33-7.35 (m, 1H, ArH), 7.37-7.40 (m, 1H, ArH), 7.50-7.53 (m, 2H, ArH) 7.56-7.56 (m, 1H, -ArH), 7.66 (t, J = 8 Hz, 1H, ArH), 7.88 (d, J = 8 Hz, 2H, -ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.4, 95.3, 116.0, 116.6, 122.0, 127.4, 129.0, 129.6, 130.0, 131.5, 134.4, 135.4, 135.7, 136.6, 143.4, 144.8, 147.8, 196.2. HRMS (ESI): calculated for $C_{21}H_{15}Cl_2N_2OS$, 413.0277 (MH⁺); found: m/z, 413.0279.

3-Amino-4-benzoyl-3'-bromo-5-(methylthio)-[1,1'-biphenyl]-2-

carbonitrile (3r): To a vacuum dried RB flask 3,3-bis(methylthio)-1phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-(1-(3bromophenyl)ethylidene)malononitrile (0.5 mmol, 0.123 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 78% (165 mg); light yellow solid, mp: 148-150°C; IR (KBr): 3409, 2208, 1635 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.41 (s, 3H, -SMe), 4.89 (s, 2H, -NH₂), 6.66 (s, 1H, ArH), 7.36-7.40 (m, 1H, -ArH), 7.47-7.54 (m, 4H, ArH), 7.60-7.62 (m, 1H, ArH), 7.65-7.69 (m, 1H, ArH), 7.87 (d, J = 8 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.4, 93.7, 115.8, 116.5, 121.6, 122.8, 127.2, 129.0, 129.6, 130.3, 131.3, 132.1, 134.4, 136.7, 140.1, 145.1, 145.4, 148.3, 196.3. HRMS (ESI): calculated for C₂₁H₁₆BrN₂OS, 425.0161 (MH⁺); found: *m/z*, 425.0158.

2-Amino-3-benzoyl-4-(methylthio)-6-(naphthalen-1-

yl)benzonitrile (3s): To a vacuum dried RB flask 3,3-bis(methylthio)-1-phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-(1-(naphthalen-1yl)ethylidene)malononitrile (0.5 mmol, 0.109 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 45% (89 mg); light yellow solid, mp: 178-180°C; IR (KBr): 3469, 2210, 1665 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.31 (s, 3H, -SMe), 4.87 (s, 2H, -NH₂), 6.74 (s, 1H, ArH), 7.50-7.60 (m, 6H, ArH), 7.66 (t, *J* = 8 Hz, 1H, ArH), 7.73 (d, *J* = 8 Hz, 1H, ArH), 7.93-7.97 (m, 4H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.2, 96.1, 116.3, 117.2, 121.3, 125.1, 126.2, 126.7, 127.0, 128.5, 129.0, 129.3, -129.6, 131.1, 133.6, 134.3, 135.8, 136.8, 144.5, 146.0, 147.9, 196.5. HRMS (ESI): calculated for $C_{25}H_{19}N_2OS$, 395.1213 (MH⁺); found: m/z, 395.1215.

2-Amino-3-benzoyl-4-(methylthio)-6-(naphthalen-2-

yl)benzonitrile (3t): To a vacuum dried RB flask 3,3-bis(methylthio)-1-phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-(1-(naphthalen-2yl)ethylidene)malononitrile (0.5 mmol, 0.109 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 48% (95 mg); light yellow solid, mp: 178-180 °C; IR (KBr): 3469, 2210, 1665 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.39 (s, 3H, -SMe), 4.93 (s, 2H, -NH₂), 6.81 (s, 1H, ArH), 7.49-7.58 (m, 5H, ArH), 7.63-7.70 (m, 2H, ArH), 7.89-7.92 (m, 2H, ArH), 7.93-7.97 (m, 1H, ArH), 7.99 (s, 1H, ArH), 8.06 (s, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.5, 94.1, 116.3, 121.1, 125.9, 126.7, 126.9, 127.7, 128.0, 128.4, 128.6, 129.0, 129.6, 133.0, 133.3, 134.3, 135.4, 136.9, 147.1, 148.5, 196.5. HRMS (ESI): calculated for C₂₅H₁₉N₂OS, 395.1213(MH⁺); found: *m/z*, 395.1215.

3-Amino-4-benzoyl-3',4'-dimethoxy-5-(methylthio)-[1,1'biphenyl]-2-carbonitrile (3u): To a vacuum dried RB flask 3,3bis(methylthio)-1-phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-1-(3,4-dimethoxyphenyl)ethylidene)malononitrile (0.5 mmol, 0.114 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 78% (147 mg); light yellow solid, mp: 153-155 °C; IR (KBr): 3317, 2210, 1697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.40 (s, 3H, -SMe), 3.95 (s, 3H, -OMe), 3.99 (s, 3H, -OMe), 4.92 (s, 2H, -NH₂), 6.70 (s, 1H, ArH), 6.99 (d, J = 8 Hz, 1H, ArH), 7.12-7.17 (m, 2H, ArH), 7.47-7.51 (m, 2H, ArH), 7.61-7.65 (m, 1H, ArH), 7.87 (d, J = 4 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.5, 55.9, 56.0, 93.8, 111.1, 111.6, 115.9, 117.2, 120.8, 121.1, 128.9, 129.5, 130.6, 134.1, 137.0, 144.7, 146.9, 148.4, 148.8, 149.8, 196.4. HRMS (ESI): calculated for C23H21N2O3S, 405.1267 (MH⁺); found: *m*/*z*, 405.1271.

3-Amino-4-(2-chlorobenzoyl)-4'-methyl-5-(methylthio)-[1,1'biphenyl]-2-carbonitrile (4a): To a vacuum dried RB flask 1-(2chlorophenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.129 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 65% (127 mg); light yellow solid, mp: 185-187 °C; IR (KBr): 3511, 3341, 2210, 1660 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.30 (s, 3H, -SMe), 2.42 (s, 3H, -CH₃), 6.07 (s, 2H, -NH₂), 6.56 (s, 1H, ArH), 7.29 (s, 1H, ArH), 7.31-7.35 (m, 2H, ArH), 7.44-7.45 (m, 2H, ArH), 7.46 (s, 2H, ArH), 7.48 (s, 1H, ArH); $^{13}{\rm C}$ NMR (100 MHz, CDCl₃): δ 17.0, 21.3, 93.8, 115.4, 117.1, 118.7, 126.9, 128.2, 129.4, 130.5, 130.7, 132.4, 132.6, 135.0, 139.3, 139.5, 148.1, 148.7, 151.2, 195.3. HRMS (ESI): calculated for C₂₂H₁₈ClN₂OS, 393.0823 (MH⁺); found: *m/z*, 393.0826.

[1,1'-biphenyl]-2-carbonitrile (5a): To a vacuum dried RB flask 1-(2-chlorophenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol. 0.128 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 25% (51 mg); light yellow solid, mp: 180-182 °C; IR (KBr): 3365, 2208, 1603 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.32 (s, 3H, -SMe), 2.41 (s, 3H, -SMe), 2.50 (s, 3H, -CH₃), 5.10 (s, 2H, -NH₂), 6.62 (s, 1H, ArH), 7.13 (t, J = 8 Hz, 1H, ArH), 7.28 (d, J = 8 Hz, 2H, ArH), 7.36-7.38 (m, 1H, ArH), 7.45-7.47 (m, 2H, ArH), 7.49-7.55 (m, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 15.7, 16.5, 21.2, 93.8, 115.8, 117.1, 121.0, 123.7, 128.3, 129.4, 129.5, 132.4, 133.1, 134.6, 135.2, 139.2, 143.4, 145.5, 147.4, 149.0, 196.3. HRMS (ESI): calculated for C₂₃H₂₁N₂OS₂, 405.1090 (MH⁺); found: *m*/*z*, 405.1089.

3-Amino-4-(2-bromobenzoyl)-4'-methyl-5-(methylthio)-[1,1'biphenyl]-2-carbonitrile (4b): To a vacuum dried RB flask 1-(2bromophenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.151 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 67% (146 mg); light yellow solid, mp: 182-184°C; IR (KBr): 3471, 2208, 1694 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.23 (s, 3H, -SMe), 2.35 (s, 3H, -CH₃), 6.06 (s, 2H, -NH₂), 6.48 (s, 1H, ArH), 7.23 (d, J = 8 Hz, 2H, ArH), 7.28-7.30 (m, 2H, ArH), 7.35-7.37 (m, 1H, ArH), 7.40 (d, J = 8 Hz, 2H, ArH), 7.57-7.59 (m, 1H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.5, 21.3, 93.9, 115.8, 117.1, 121.0, 123.8, 125.2, 128.3, 129.4, 132.5, 133.1, 134.6, 135.3, 139.3, 143.4, 145.5, 147.4, 149.0, 196.3. HRMS (ESI): calculated for C₂₂H₁₈BrN₂OS, 437.0318 (MH⁺); found: *m*/*z*, 437.0319.

3-Amino-4-(4-fluorobenzoyl)-4'-methyl-5-(methylthio)-[1,1'biphenyl]-2-carbonitrile carbonitrile (4c): To a vacuum dried RB flask 1-(4-fluorophenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5)mmol, 0.121 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added followed by addition of THF (5.0 mL). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 65% (122 mg); light yellow solid, mp: 145-147 °C; IR (KBr): 3579, 2208, 1648 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.37 (s, 3H, -SMe), 2.43 (s, 3H, -CH₃), 4.89 (s, 2H, -NH₂), 6.68 (s, 1H, ArH), 7.13-7.18 (m, 2H, ArH), 7.31 (d, J = 8 Hz, 2H, ArH), 7.47 (d, *J* = 8 Hz, 2H, ArH), 7.88-7.91 (m, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.4, 21.3, 94.1, 116.0 (d, J = 10Hz), 116.3, 117.0, 120.6, 126.4, 128.3, 129.5, 132.3 (d, J = 10 Hz), 135.2, 139.3, 144.7, 147.3, 148.4, 166.4 (d, J = 270 Hz), 194.8. HRMS (ESI): calculated for $C_{22}H_{18}FN_2OS$, 377.1118 (MH⁺); found: m/z, 377.1114.

3-Amino-4'-methyl-5-(methylthio)-4-(4-(methylthio)benzoyl)-[**1,1'-biphenyl]-2-carbonitrile (5b):** To a vacuum dried RB flask 1-(4-fluorophenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.121 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 26 % (41 mg); light yellow solid, mp: 160-162 °C; IR (KBr): 3360, 2208, 1610 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ ¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H, -SMe), 2.41 (s, 3H, -SMe), 2.51 (s, 3H, -CH₃), 4.80 (s, 2H, -NH₂), 6.66 (s, 1H, ArH), 7.24 (d, J = 4 Hz, 2H, ArH), 7.27-7.30 (m, 2H, ArH), 7.44-7.46 (m, 2H, ArH), 7.76 (d, J = 8 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 14.8, 16.4, 21.3, 93.9, 115.9, 117.1, 121.1, 125.0, 128.3, 129.4, 130.0, 130.1, 135.3, 139.2, 144.4, 147.0, 147.9, 148.2, 195.2. HRMS (ESI): calculated for $C_{23}H_{21}N_2OS_2$, 405.1090 (MH⁺); found: m/z, 405.1097.

3-Amino-4-(4-chlorobenzoyl)-4'-methyl-5-(methylthio)-[1,1'biphenyl]-2-carbonitrile (4d): To a vacuum dried RB flask 1-(4chlorophenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.129 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 61% (120 mg); light yellow solid, mp: 144-146 °C; IR (KBr): 3471, 2210, 1660 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.35 (s, 3H, -SMe), 2.41 (s, 3H, -CH₃), 4.92 (s, 2H, -NH₂), 6.66 (s, 1H, ArH), 7.29 (d, J = 8 Hz, 2H, ArH), 7.43-7.47 (m, 4H, ArH), 7.77-7.99 (m, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): *δ* 15.7, 21.3, 94.0, 115.9, 116.9, 120.2, 128.3, 129.2, 129.5, 130.9, 135.1, 135.4, 139.2, 140.5, 144.7, 147.4, 148.5, 195.2. HRMS (ESI): calculated for C₂₂H₁₈ClN₂OS, 393.0823 (MH⁺); found: *m*/*z*, 339.0828.

3-Amino-4-(4-bromobenzoyl)-4'-methyl-5-(methylthio)-[1,1'biphenyl]-2-carbonitrile (4e): To a vacuum dried RB flask 1-(4bromophenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.151 g) and 2-(1-(p-tolyl)ethylidene)malononitrile (0.5 mmol, 0.091 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 72% (157 mg); light yellow solid, mp: 143-145 °C; IR (KBr): 3473, 2210, 1658 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.27 (s, 3H, -SMe), 2.40 (s, 3H, -CH₃), 4.88 (s, 2H, -NH₂), 6.60 (s, 1H, ArH), 7.18-7.25 (m, 2H, ArH), 7.40 (d, J = 8 Hz, 2H, ArH), 7.54-7.56 (m, 2H, ArH), 7.63-7.66 (m, 2H, ArH); 13 C NMR (100 MHz, CDCl₃): δ 16.4, 21.3, 94.0, 115.9, 117.0, 120.1, 128.3, 129.2, 129.5, 131.0, 132.2, 135.1, 135.9, 139.3, 144.8, 147.5, 148.5, 195.5. HRMS (ESI): calculated for C₂₂H₁₈BrN₂OS, 437.0318 (MH⁺); found: *m*/*z*, 437.0317.

3-Amino-4-(2-chlorobenzoyl)-4'-methoxy-5-(methylthio)-[1,1'biphenyl]-2-carbonitrile (4f): To a vacuum dried RB flask 1-(2chlorophenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.129 g) and 2-(1-(4-methoxyphenyl)ethylidene)malononitrile (0.5 mmol, 0.099 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 62% (128 mg); light yellow solid, mp: 133-135°C; IR (KBr): 3471, 2208, 1660 cm⁻¹; ¹HNMR (400MHz, CDCl₃): δ 2.29 (s, 3H, -SMe), 3.85 (s, 3H, -OMe), 6.07 (s, 2H, -NH₂), 6.52 (s, 1H, ArH), 6.99 (d, *J* = 8 Hz, 2H, ArH), 7.30-7.44 (m, 4H, ArH), 7.51 (d, *J* = 8 Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.5, 55.3, 93.7, 114.1, 115.6, 117.3, 120.7, 123.7, 125.1, 129.7, 130.4, 132.5, 133.1, 134.6, 143.4, 145.5, 147.0, 149.0, 160.3, 196.3. HRMS (ESI): calculated for C₂₂H₁₈ClN₂O₂S, 409.0772 (MH⁺); found: *m/z*, 409.0775.

3-Amino-4'-methoxy-5-(methylthio) -4-(2-(methylthio)benzoyl)-[1,1'-biphenyl]-2-carbonitrile (5c): To a vacuum dried RB flask 1-(2-chlorophenyl)-3,3-bis(methylthio)prop-2en-1-one 0.128 (0.5)mmol, g) and 2-(1-(4methoxyphenyl)ethylidene)malononitrile (0.5 mmol, 0.099 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 25% (53 mg); light yellow solid, mp: 170-180 °C; IR (KBr): 3473, 2208, 1604 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.32 (s, 3H, -SMe), 2.49 (s, 3H, -SMe), 3.85 (s, 3H, -OMe), 5.12 (s, 2H, -NH₂), 6.60 (s, 1H, ArH), 6.99 (d, J = 8Hz, 3H, ArH), 7.13 (t, J = 8 Hz, 1H, ArH), 7.37 (d, J = 8 Hz, 1H, ArH), 7.51 (d, J = 8 Hz, 3H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 15.6, 16.5, 55.3, 93.7, 114.1, 115.6, 117.3, 120.7, 123.7, 125.1, 129.7, 130.4, 132.5, 133.1, 134.6, 143.4, 145.5, 147.0, 149.0, 160.3, 196.3. HRMS (ESI): calculated for C₂₃H₂₁N₂O₂S₂, 421.1039 (MH⁺); found: *m/z*, 421.1040.

2-Amino-3-benzoyl-6-(furan-2-yl)-4-(methylthio)benzonitrile

(6a): To a vacuum dried RB flask 3,3-bis(methylthio)-1-phenylprop-2en-1-one (0.5 mmol, 0.112 g) and 2-(1-(furan-2yl)ethylidene)malononitrile (0.5 mmol, 0.079 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 84% (140 mg); light yellow solid, mp: 158-160 °C; IR (KBr): 3454, 2208, 1629 cm $^{-1}$; $^{1}\mathrm{H}$ NMR (400 MHz, CDCl₃): δ 2.42 (s, 3H, -SMe), 4.95 (s, 2H, -NH₂), 6.58-6.59 (m, 1H, ArH), 7.14 (s, 1H, ArH), 7.37 (d, J = 4 Hz, 1H, ArH), 7.46-7.50 (m, 2H, ArH), 7.58-7.64 (m, 2H, ArH), 7.82-7.84 (m, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.5, 89.1, 111.5, 112.0,112.4, 117.4, 120.6, 128.9, 129.5, 134.1, 134.3, 137.1, 143.6, 145.4, 148.8, 149.5, 196.3. HRMS (ESI): calculated for $C_{19}H_{15}N_2O_2S$, 335.0849 (MH⁺); found: m/z, 335.0854.

2-Amino-3-benzoyl-4-(methylthio)-6-(thiophen-2-

yl)benzonitrile (6b): To a vacuum dried RB flask 3,3bis(methylthio)-1-phenylprop-2-en-1-one (0.5 mmol, 0.112 g) and 2-(1-(thiophen-2-yl)ethylidene)malononitrile (0.5 mmol, 0.087 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 76% (133 mg); light yellow solid, mp: 156-158 °C; IR (KBr): 3685, 2212, 1648 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.39 (s, 3H, -SMe), 4.95 (s, 2H, -NH₂), 6.81 (s, 1H, ArH), 7.18 (t, *J* = 8 Hz, 1H, ArH), 7.46- 7.47 (m, 1H, ArH), 7.50 (d, *J* = 8 Hz, 2H, ArH), 7.62-7.67 (m, 2H, ArH), 7.85-7.87 (m, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.5, 92.5, 115.6, 126.4, 127.5, 128.0, 128.2, 128.4, 128.9, 129.5, 130.2, 134.2, 136.9, 139.0, 139.3, 148.8, 196.2. HRMS (ESI): calculated for C₁₉H₁₅N₂OS₂, 351.0620 (MH⁺); found: *m/z*, 351.0616.

2-Amino-6-(furan-2-yl)-3-(4-methoxybenzoyl)-4-

(methylthio)benzonitrile (6c): To a vacuum dried RB flask 1-(4methoxyphenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.127 g) and 2-(1-(furan-2-yl)ethylidene)malononitrile (0.5 mmol, 0.079 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 74% (137 mg); light yellow solid, mp: 149-151 °C; IR (KBr): 3395, 2208, 1674 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.40 (s, 3H, -SMe), 3.89 (s, 3H, -OMe), 4.82 (s, 2H, -NH₂), 6.80 (s, 1H, ArH), 6.95-6.96 (m, 1H, ArH), 6.97-6.97 (m, 1H, ArH), 7.16-7.18 (m, 1H, ArH), 7.44-7.46 (m, 1H, ArH), 7.64-7.65 (m, 1H, ArH), 7.84-7.85 (m, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): *δ* 16.2, 55.6, 92.4, 114.2, 115.4, 117.2, 121.7, 127.3, 127.8, 128.2, 129.5, 132.2, 138.7, 139.4, 144.7, 148.4, 164.7, 194.3. HRMS (ESI): calculated for $C_{20}H_{17}N_2O_3S$, 365.0954 (MH⁺); found: m/z, 365.0957.

2-Amino-3-(4-methoxybenzoyl)-4-(methylthio)-6-(thiophen-2yl)benzonitrile (6d): To a vacuum dried RB flask 1-(4methoxyphenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.127 g) and 2-(1-(thiophen-2-yl)ethylidene)malononitrile (0.5 mmol, 0.087 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 72 % (137 mg); light yellow solid, mp: 149-151 °C; IR (KBr): 3395, 2208, 1674 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.40 (s, 3H, -SMe), 3.89 (s, 3H, -OMe), 4.82 (s, 2H, -NH2), 6.80 (s, 1H, ArH), 6.95-6.96 (m, 1H, ArH), 6.97-6.97 (m, 1H, ArH), 7.16-7.18 (m, 1H, ArH), 7.44-7.46 (m, 1H, ArH), 7.64-7.65 (m, 1H, ArH), 7.84-7.85 (m, 2H, ArH); ¹³C NMR (100 MHz, CDCl₃): δ 16.2, 55.6, 92.4, 114.2, 115.4, 117.2, 121.7, 127.3, 127.8, 128.2, 129.5, 132.2, 138.7, 139.4, 144.7, 148.4, 164.7, 194.3. HRMS (ESI): calculated for C₂₀H₁₇N₂O₂S₂, 381.0726 (MH⁺); found: *m/z*, 381.0729.

2-Amino-3-benzoyl-6-cyclopropyl-4-(methylthio)benzonitrile (8a): To a vacuum dried RB flask 3,3-bis(methylthio)-1-phenylprop-2en-1-one(0.5 0.112 mmol. g) and 2 - (1 cyclopropylethylidene)malononitrile (0.5 mmol, 0.066 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent.

2-Amino-6-cyclopropyl-3-(4-methylbenzoyl)-4-

(methylthio)benzonitrile (8b): To a vacuum dried RB flask 3,3bis(methylthio)-1-(p-tolyl)prop-2-en-1-one (0.5 mmol, 0.119 g) and 2-(1cyclopropylethylidene)malononitrile (0.5 mmol, 0.066 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 61 % (100 mg); light yellow solid, mp: 149-151 °C; IR (KBr): 3395, 2208, 1674 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.81-0.82 (m, 2H), 1.12-1.14 (m, 2H), 2.15-2.22 (m, 1H). 2.29 (s, 3H, -CH₃), 2.40 (s, 3H, -SMe), 4.73 (s, 2H, -NH₂), 6.17 (s, 1H, ArH), 7.24 (d, J = 8Hz, 2H, ArH), 7.68 (d, J 8Hz, 2H, ArH); ¹³C NMR (100 MHz, CDCl₂): δ 9.5, 14.9, 16.7, 22.0, 96.2, 111.0, 117.0, 120.7, 129.7, 129.8, 134.7, 144.7, 145.3, 147.8, 149.8, 196.1; HRMS (ESI): calculated for C₁₉H₁₉N₂OS, 323.1213 (MH⁺); found: *m/z*, 323.1220.

2-Amino-6-cyclopropyl-3-(4-methoxybenzoyl)-4-

(methylthio)benzonitrile (8c): To a vacuum dried RB flask 1-(4methoxyphenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.127 g) and 2-(1-cyclopropylethylidene)malononitrile (0.5 mmol, 0.066 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 56% (95 mg); light yellow solid, mp: 149-151 °C; IR (KBr): 3395, 2208, 1674 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.79-0.83 (m, 2H), 1.10-1.15 (m, 2H), 2.13-2.21 (m, 1H), 2.30 (s, 3H, -SMe), 3.86 (s, 3H, OMe), 4.68 (s, 2H, -NH₂), 6.17 (s, 1H, ArH), 6.89-6.92 (m, 2H, ArH), 7.76-7.78 (m, 2H, ArH); ^{13}C NMR (100 MHz, CDCl₃): δ 9.4, 14.7, 16.7, 55.6, 96.0, 110.9, 114.2, 116.8, 120.8, 130.0, 132.2, 144.4, 147.6, 149.6, 164.6, 194.8; HRMS (ESI): calculated for C₁₉H₁₉N₂O₂S, 339.1162 (MH⁺); found: *m/z*, 339.1166.

2-Amino-6-cyclopropyl-3-(3,4-dimethoxybenzoyl)-4-

(methylthio)benzonitrile (8d): To a vacuum dried RB flask 1-(3,4dimethoxyphenyl)-3,3-bis(methylthio)prop-2-en-1-one (0.5 mmol, 0.142 g) and 2-(1-cyclopropylethylidene)malononitrile (0.5 mmol, 0.066 g) was placed. Then sodium hydride (0.6 mmol, 0.0144 g) was added, followed by addition of THF (5.0 ml). The reaction mixture was refluxed till completion of the reaction. After completion of the reaction, excess of THF was removed under reduced pressure followed by the addition of ice water. Reaction mixture was neutralized by diluting HCl and obtained precipitate was filtered and dried. The crude product was purified on silica gel column chromatography by using 20% EtOAc in hexane as an eluent. Yield 56% (95 mg); light yellow solid, mp: 149-151 °C; IR (KBr): Yield 72 % (137 mg); light yellow solid, mp: 149-151 °C; IR (KBr): 3395, 2208, 1674 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.79-0.85 (m, 2H), 1.10-1.15 (m, 2H), 2.15-2.20 (s, 1H, -CH₂) 2.31 (S, 3H, -SMe), 3.91 (s, 6H), 4.65 (s, 2H, -NH₂), 6.18 (s, 1H, ArH), 6.80-6.89 (m, 1H, ArH), 7.50-7.56 (m, 1H, ArH). ¹³C NMR (100 MHz, CDCl₃): δ 9.4, 15.0, 16.6, 56.1, 96.0, 110.1, -110.4, 110.4, 111.0, 112.3, 116.9, 120.9, 125.8, 130.0, 147.5, 149.6, 154.5, 194.9. HRMS (ESI): calculated for $C_{20}H_{21}N_2O_3S$, 369.1267 (MH⁺); found: *m/z*, 369.1275.

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4. References and notes

Electronic Supporting Information: ¹H and ¹³C spectra of the entire synthesized compound are provided in ESI.

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- 15. Crystal data for C₂₂H₁₈N₂OS: A white crystal (0.240 x 0.220 x 0.200 mm3) was mounted on a capillary tube for indexing and intensity data collection at 298(2) K on an Oxford Xcalibur Sapphire3 CCD single-crystal diffractometer (MoKα radiation, $\lambda = 0.71073$ Å). Routine Lorentz and polarization corrections were applied, and an absorption correction was performed using the ABSCALE 3 program [CrysAlis Pro software system, Version 171.34; Oxford Diffraction Ltd., Oxford, U.K., 2011]. Patterson methods were used to locate the heavy metal atoms (SHELXS-86), and the remaining atoms were located from successive Fourier maps (SHELXL-97). All the non-hydrogen atoms were refined anisotropically; hydrogen atoms were located at calculated position using a riding model. All hydrogen atoms were calculated after each cycle of refinement using a riding model, with C–H =

0.93 Å + Uiso(H) = 1.2Ueq(C) for aromatic H atoms, and with C–H = 0.97 Å + Uiso(H) = 1.2Ueq(C) for methylene H atoms. Crystal data: CCDC No: 1857029; C22 H18 N2 O S; Mr = 358.44, crystal system: triclinic; space group P-1, a = 9.1224(8) Å, b = 10.0199(10) Å, c = 11.1240(8) Å, α = 74.343(8)°, β = 67.093(8)°, γ = 80.916(8)°, V = 900.25(15) Å3, Z = 2, pcalcd = 1.322 Mg/m3 g cm-3, μ = 0.193 mm-1, F(000) = 376, R1 = 0.0472 and wR2 = 0.1313 for I>2σ(I) and 226 parameters, R1= 0.0606 and wR2 = 0.1417, gof = 0.904 for all data.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

□The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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