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Article

Heterocyclic Analogs of Thioflavones: Synthesis and NMR Spectroscopic Investigations †

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† Dedicated to Prof. Peter Stanetty with best personal wishes on the occasion of his 65th birthday.

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Abstract: The synthesis of several hitherto unknown heterocyclic ring systems derived from thioflavone is described. Coupling of various *o*-haloheteroarenecarbonyl chlorides with phenylacetylene gives 1-(*o*-haloheteroaryl)-3-phenylprop-2-yn-1-ones, which were treated with NaSH in refluxing ethanol to yield the corresponding bi- and tricyclic annelated 2-phenylthiopyran-4-ones. Detailed NMR spectroscopic investigations of the ring systems and their precursors are presented.

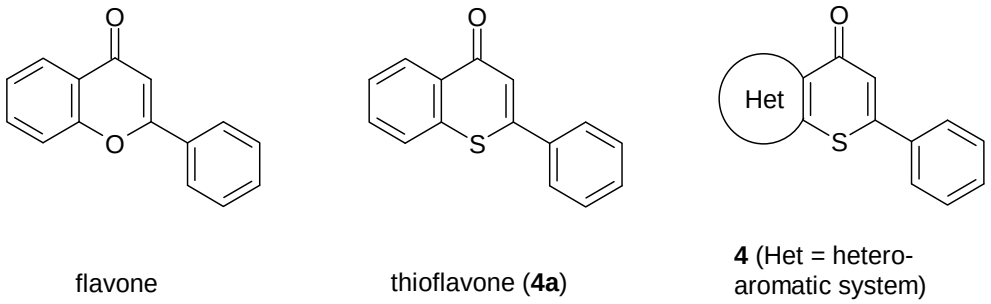
Keywords: thioflavone; Sonogashira coupling; ring closure reactions; NMR spectroscopy

1. Introduction

The flavone system (2-phenyl-4*H*-chromen-4-one, shown in Figure 1, is the core of many biologically active compounds which play important roles in numerous biological processes. The relevance of flavone-based molecules has been thoroughly described in the literature [1-5]. Replacement of the ring oxygen atom in flavone by a sulfur atom results in thioflavone (**4a**, Figure 1), whose derivatives also exhibit interesting biological properties [6-13]. Moreover, thioflavones are valuable precursors for the synthesis of other condensed heterocyclic systems, such as benzothiazepines [14]. Analogs of type **4** thioflavone-systems – in which the condensed benzene ring of **4a** is replaced by a heteroaromatic moiety (Figure 1) – seem to be of notable interest considering the

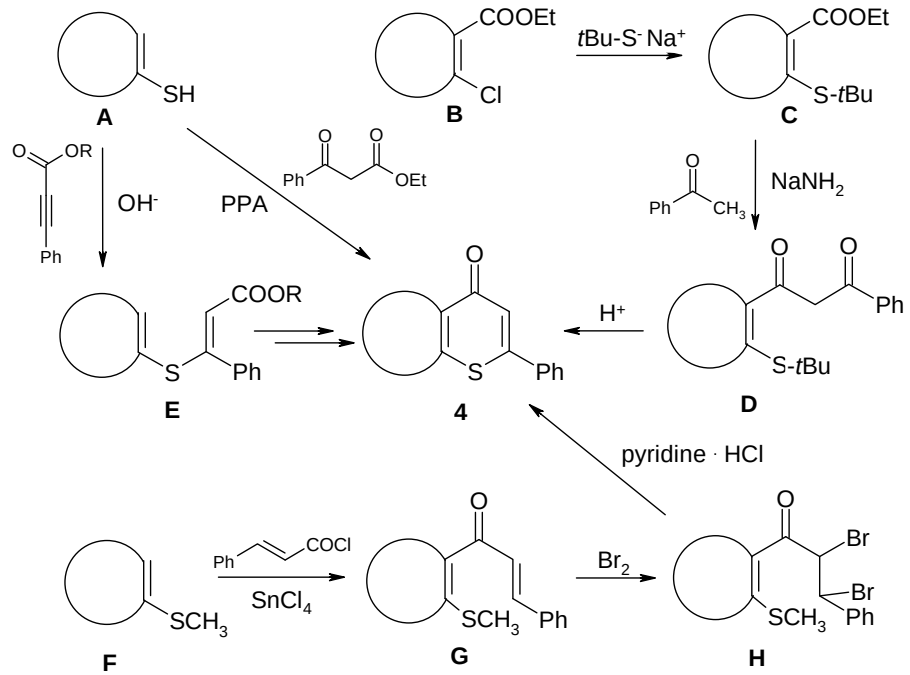
concept of bioisosterism [15-17]. Type **4** compounds with a pyridine, thiophene, benzo[*b*]thiophene or indole system annelated to the thiopyrane ring have been previously characterized.

Figure 1. Flavone, thioflavone and its heterocyclic analogs **4**.



Various approaches have been used to synthesize type **4** systems. Representative examples are given in Scheme 1.

Scheme 1. Traditional approaches to the title compounds **4**.

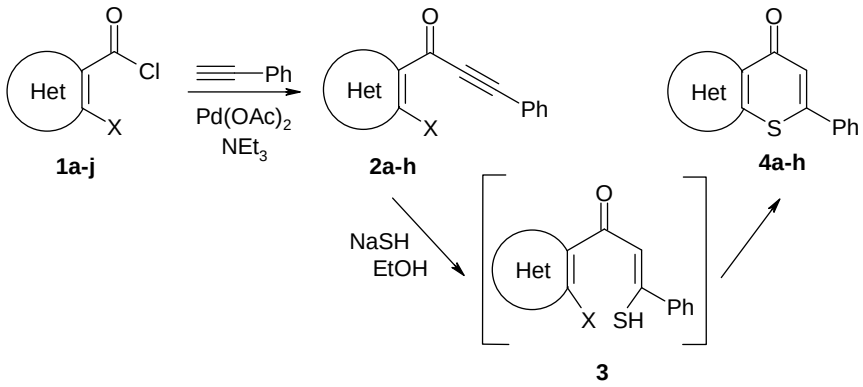


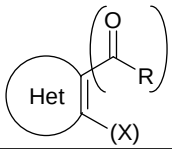
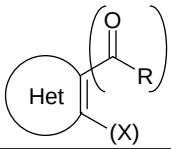
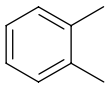
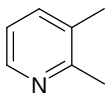
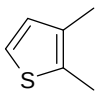
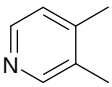
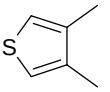
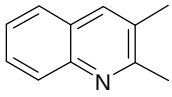
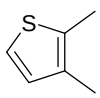
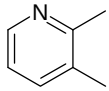
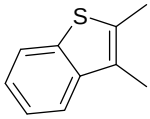
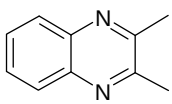
For instance, condensation of appropriate thiophenols **A** with ethyl benzoylacetate followed by subsequent cyclization of the obtained condensation products permits access to type **4** systems [18]. Another approach was employed by Becher in the synthesis of 2-phenyl-4*H*-thiopyrano[2,3-*b*]pyridin-4-one (**4f**) [19]. Ethyl 2-chloronicotinate (**B**) was transformed into the 2-*tert*-butyl congener **C**, which was condensed with acetophenone to yield **D**; the latter readily cyclized into **4f** in an acidic medium. Moreover, the reaction between phenylpropiolates and thiophenols **A** and subsequent ring closure reaction of the formed substituted cinnamates **E** has also been used [20-21], for instance, in the synthesis of indole annelated 2-phenylthiopyran-4-ones [22]. Variants of **4** containing a thiophene or a benzo[*b*]thiophene moiety have been prepared *via* Friedel–Crafts acylation of the corresponding

methylthio(benzo)thiophenes **F** with cinnamoyl chloride, to yield ketones **G**, and addition of bromine to the alkene double bond (compounds **H**) and subsequent cyclization with pyridine hydrochloride [23-25]. However, many of these methods require precursors that are neither commercially available nor readily synthesized. Moreover, the other above-mentioned approaches lack generality. For example, Friedel-Crafts-based methods are restricted to π-excessive heteroaromatic systems.

Here, we present a general approach for synthesizing heterocyclic analogs of type **4** based on a Sonogashira-type coupling of *o*-halo(hetero)aroyl chlorides **1** with phenylacetylene to yield alkynones **2** (Scheme 2). Reactions between **2** and NaSH in refluxing ethanol then yield the desired compounds **4** *via* an addition/cyclization step (Scheme 2). A related approach to thioflavone generation employing a microwave-assisted one-pot, three-component synthesis has been recently described by Müller [26] (based on an earlier report by Shvartsberg [27-28]). In the course of these investigations, the acetylenic component was varied to obtain different 2-substituted 4*H*-thiochromen-4-ones [26].

Scheme 2. Preparation of compounds **4a-h**.



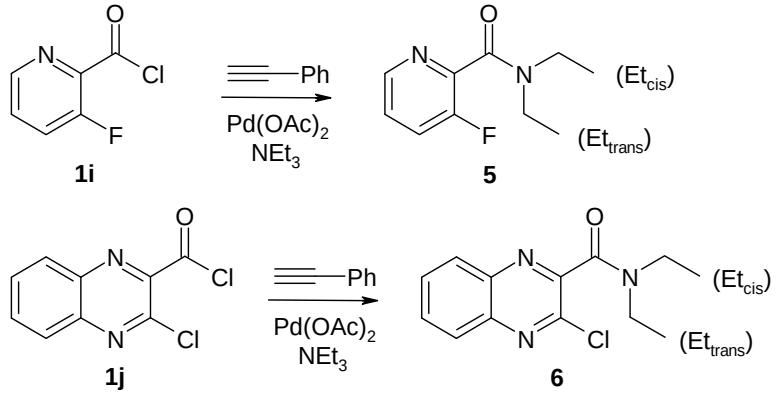
Compd. 1,2,(3),4		X in 1,2,(3)	Compd. 1,2,(3),4		X in 1,2,(3)
a		Cl (a1) F (a2)	f		Cl
b		Br	g		Cl
c		Br	h		Cl
d		Br	i		F
e		Cl	j		Cl

2. Results and Discussion

2.1. Chemistry

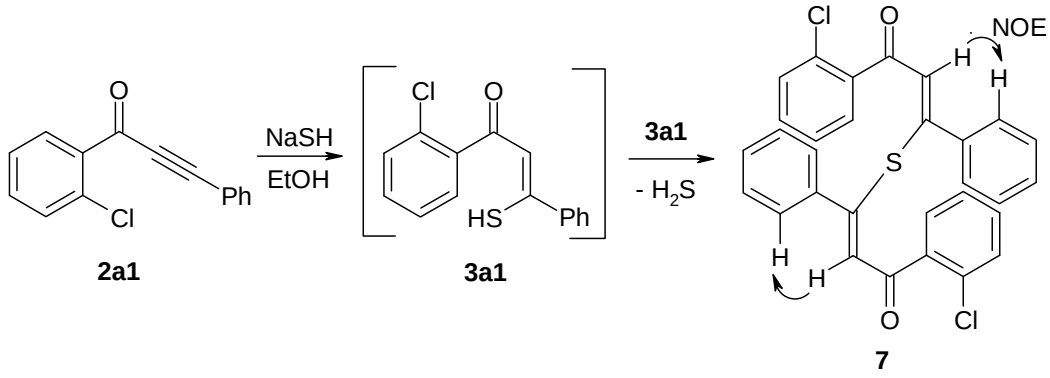
Synthesis of the target compounds **4** was accomplished *via* the sequence shown in Scheme 2. Precursors **1** are either commercially available or can be easily prepared by treatment of the corresponding carboxylic acids with thionyl chloride. Compounds **1** were transformed into **2** *via* Sonogashira-type coupling [29-30], a very important step in forming C-C bonds with terminal acetylenes [31]. A ligand- and copper-free Pd-catalyzed (Pd acetate, Et_3N) version of this method for the coupling of carboxylic acid chlorides with different terminal acetylenes has been recently described by Nájera [32] and Srinivasan [33]. In preliminary tests in which the solvent, amount of triethylamine and the acid chloride/phenylacetylene ratio were varied, we adapted the reaction conditions for synthesis of the desired *o*-halo(hetero)arylynones **2a–h**. The best results were obtained using two equivalents of acid chloride, a 3–14-fold molar excess of triethylamine, dichloromethane as the solvent and ambient temperature. Reasonably good yields of ynones **2a–h** were obtained applying these reaction conditions. However, using of **1i** and **1j** as starting materials (both having the COCl group attached in the *o*-position to a pyridine-type nitrogen atom), we did not obtain the corresponding coupling products **2i** or **2j**. Instead, the respective *N,N*-diethylamides **5** and **6** were isolated as the main reaction products from the complex reaction mixtures (Scheme 3). A few reports in the literature have described *N,N*-diethylamide formation from acid chlorides and triethylamine [30,34-35].

Scheme 3. Unexpected formation of *N,N*-diethylamides **5** and **6**.



NaSH in refluxing ethanol (96%) was used for the conversion of ynones **2a–h** into thiopyranones **4a–h** (Scheme 2). In principle, it is possible to use Na_2S as the SH donor [27-28]; however, poor results were obtained using this technique. Evidence of the proposed mechanism, a Michael addition of the hydrosulfide to the alkynone system [26], was obtained in the following experiment. When **2a1** was reacted with NaSH/ethanol at room temperature, we isolated a sulfur-containing product that contained a chlorine atom and an enone group. The high-resolution mass spectrum and the spectral data demonstrated that the product was not the expected intermediate **3a1**, but rather the thioether **7** (Scheme 4), formed following reaction between two units of **3a1** by elimination of hydrogen sulfide. The *cis*-position of alkene-H and the phenyl ring was confirmed by an NOE-difference experiment that employed irradiation of alkene-H resonance (Scheme 4).

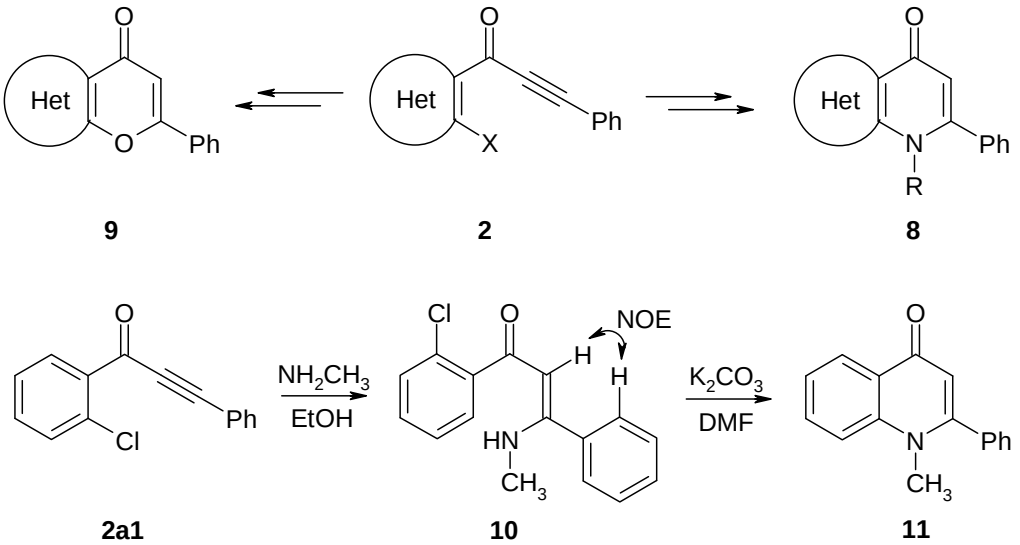
Scheme 4. Formation of thioether **7** from Michael addition intermediate **3a1**.



Initial attempts to synthesize **4a** and **4f** in a one-pot/two-step procedure (reactants: **1a** or **1f**, respectively, with phenylacetylene, by $Pd(OAc)_2$/triethylamine catalysis in solvent; then addition of Na_2S in DMF) gave low yields (<16%) of the desired thiopyranones.

The ynones **2** described here are valuable precursors in the synthesis of other condensed heterocyclic systems, such as annelated pyridin-4-ones **8** and pyran-4-ones **9** (Scheme 5). For example, **2a1** was reacted with methylamine to generate the corresponding Michael addition product **10** at a 73% yield (stereochemistry demonstrated by a NOESY experiment). Treatment of product **10** with K_2CO_3 in dry DMF gave 1-methyl-2-phenyl-4(1*H*)-quinolinone (**11**) at a good yield. This type of compound was reported to exhibit interesting biological properties, such as anti-platelet [36], anti-mitotic [37], and anti-HIV-replication activity [38]. Furthermore, the well-known class of fluoroquinolinone type [39] antibacterial drugs, such as ciprofloxacin [40] or enoxacin [41], are structurally similar to **11**. Investigations into the preparation of heterocyclic annelated pyridin-4-ones of type **8** are currently in progress and will be reported elsewhere.

Scheme 5. Further synthetic potential of ynones **2**.



2.2. Spectroscopic investigations

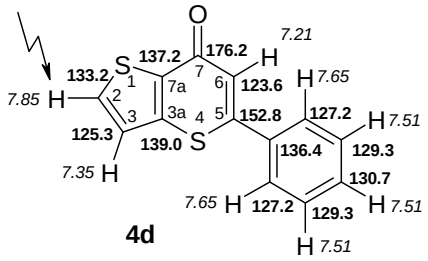
Alkynones **2** and thiopyranones **4** are predominantly novel structures. Representative structures (**2a1**, **2a2**, **4a**, **4d–f**) have not been thoroughly investigated by spectroscopic methods, such as NMR. In regards to ^{13}C-NMR spectroscopy – in cases where such data are available (**4a**, **4f**) – little [19] to no [27-28] signal assignments have been made. Hence, we present the results from an extensive NMR study (^{1}H, ^{13}C, ^{15}N) of compounds **2** and **4**. Reliable and unambiguously assigned chemical shift data are important reference material for NMR prediction programs, such as CSEARCH [42]/NMRPREDICT [43] and ACD/C + H predictor [44]. Such programs have become very popular in the last few years, particularly for predicting ^{13}C-NMR chemical shifts. However, the quality of such predictions is highly dependent on the availability of authentic reference data from related structures. This criterion is frequently unfulfilled for rare condensed heteroaromatic systems, such as those described here.

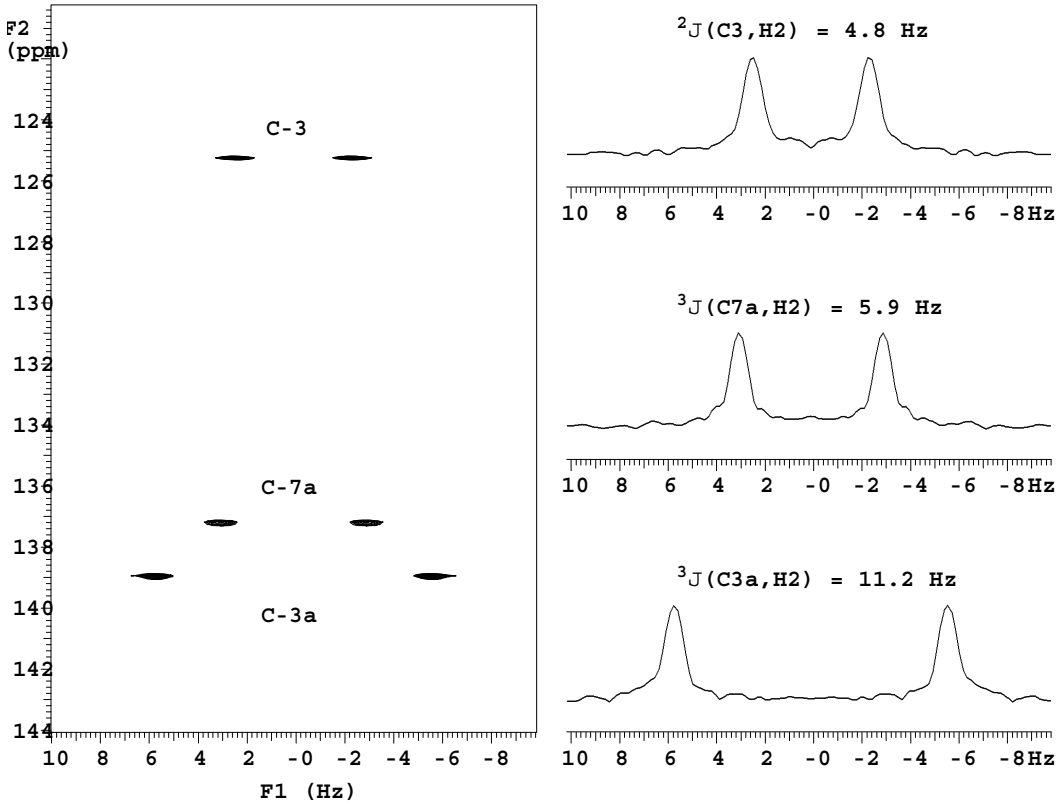
Full and unambiguous assignment of all ^{1}H, ^{13}C and ^{15}N resonances was achieved by combining standard NMR techniques [45], such as fully ^{1}H-coupled ^{13}C-NMR spectra, APT, HMQC, gs-HSQC, gs-HMBC, COSY, TOCSY, NOESY and NOE-difference spectroscopy. Moreover, experiments with selective excitation (DANTE) of certain ^{1}H-resonances were performed, such as long-range INEPT [46] and 2D(δ,*J*) long-range INEPT [47]. The latter experiments were indispensable for the unambiguous mapping of long-range ^{13}C,^{1}H coupling constants. Aside from the variable heteroaromatic system, the obtained data of the invariant parts of **2** and **4** show a high degree of consistency. Thus, the 3-phenyl-2-propyn-1-one substructure in **2a**–**h** exhibits a carbonyl C-1 shift of 168.3–176.7 ppm, a C-2 shift of 87.2–88.5 ppm, and a C-3 shift of 91.9–96.2 ppm. Alkyne C-atoms, C-2 and C-3, can be easily distinguished by their coupling patterns: the C-2 signal appears as a singlet in the ^{1}H-coupled ^{13}C-NMR spectrum, whereas the C-3 signal is a triplet due to ^{3}J coupling with phenyl protons H-2/6 (which is confirmed by a correlation signal from the involved nuclei in the HMBC spectrum). The signals from the phenyl-C atoms are Ph C-1: 119.3–120.1 ppm, Ph C-2/6: 133.1–133.3 ppm, Ph C-3/5: 128.6–128.8 ppm and Ph C-4: 130.9–131.6 ppm. The thiopyranone system in compounds **4a**–**h** is characterized by a chemical shift of 176.2–182.0 ppm for the carbonyl C-atom (split by a ~ 1 Hz ^{2}J coupling to the adjacent =C-H), 122.1–125.0 ppm for =C-H (^{1}J 163.3–164.8 Hz) and 151.5–155.1 ppm for S-C-Ph (^{2}J to =CH ~ 3 Hz). The =C-H proton gives rise to a characteristic singlet signal between 6.99 and 7.32 ppm. As observed with compounds **2**, systems **4** also exhibit small differences in Ph-C shifts within the series **a–h** (Ph C-1: 136.1–136.7 ppm, Ph C-2/6: 126.9–127.2 ppm, Ph C-3/5: 129.2–129.4 ppm, Ph C-4: 130.7–131.3 ppm). The descriptions of NMR spectra in the Experimental section were assigned based on systematic nomenclature and, hence, the numbering of atoms within the thiopyrane moiety is inconsistent.

The excellent utility of 2D (*δ*,J) long-range INEPT spectra with selective excitation for the definite mapping of ^{13}C,^{1}H coupling constants is demonstrated by an example presented in Figure 2. In the ^{1}H-coupled ^{13}C-NMR spectrum of **4d**, the signal of C-7a is split by a 7.1, 5.9 and 4.7 Hz coupling, whereas coupling occurs with H-2, H-3 and H-6. Unequivocal assignment of these coupling constants based on literature data for the thiophene system is unreliable. However, after selective excitation of the H-2 resonance, the C-7a signal appears as a doublet of 5.9 Hz, thus ^{3}J(C7a,H2) = 5.9 Hz (Figure 2). Moreover, the couplings ^{2}J(C3,H2) = 4.8 Hz and ^{3}J(C3a,H2) = 11.2 Hz emerge (Figure 2) (^{4}J(C7,H2)

= 1.1 Hz also appears, but it is not displayed in Figure 2). Further experiments with selective excitation of H-3 and H-6 assigned ^{3}J(C7a,H3) = 7.1 Hz and ^{2}J(C7a,H6) = 4.7 Hz.

Figure 2. Part of the long-range 2D (δ,*J*) INEPT spectrum of **4d** obtained upon selective excitation of the H-2 resonance; ^{1}H- (in *italics*) and ^{13}C-NMR chemical shifts in **4d.**





Furthermore, the NMR spectra of *N,N*-diethylcarboxamides **5** and **6**, respectively, two different signals sets for the ethyl moieties (Et_{cis}, Et_{trans}, see Scheme 3) were found for each case. As expected, this indicates that there is restricted rotation around the amide bond under the recording conditions ($CDCl_3$, ambient temperature).

In the IR spectra, the carbonyl C=O absorption from the ynones **2** appears in the range between 1,601 and 1,649 cm^{-1}, and those from the thiopyranones **4** between 1,606 and 1,635 cm^{-1}. Absorptions for the C≡C vibration in the IR spectra of compounds **2** appear from 2,196–2,202 cm^{-1}.

As reported for related structures [48], the mass spectra of **4** exhibit a fragmentation behavior that is characterized by the loss of CO, a pathway that is also observed for ynones **2**.

3. Conclusions

We have presented a widely applicable method for the preparation of heterocyclic annelated 2-phenylthiopyran-4-ones *via* a cross-coupling addition-cyclization approach starting from *o*-halo-heteroaroyl chlorides and phenylacetylene. Detailed NMR spectroscopic studies of the title compounds and their precursors were provided.

4. Experimental

4.1. General

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV), a Finnigan MAT 8230 instrument (EI, 70 eV, HRMS), and a Finnigan MAT 900S instrument (ESI, 4 kV, MeOH-acetonitrile). IR spectra (KBr unless otherwise stated) were recorded on a Perkin-Elmer FT-IR 1605 spectrophotometer or an ATI Mattson Genesis series FT-IR spectrophotometer. Elemental analyses (C, H, N and S) were performed at the Microanalytical Laboratory, University of Vienna, and were in good agreement (±0.4%) with the calculated values. ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian UnityPlus 300 spectrometer at 28 °C (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) or on a Bruker Avance 500 spectrometer at 293 K (500.13 MHz for ^{1}H, 125.77 MHz for ^{13}C). The center of the solvent ($CDCl_3$) signal was used as an internal standard, which was related to TMS with δ 7.26 ppm (^{1}H) and δ 77.0 ppm (^{13}C). ^{15}N-NMR spectra (50.68 MHz) and ^{19}F-NMR spectra (470.56 MHz) were obtained on a Bruker Avance 500 spectrometer with a 'directly' detecting broadband observe probe (BBFO). The spectra were referenced against external nitromethane (^{15}N) or against the absolute frequency scale (Ξ ratio, ^{19}F). The digital resolution was 0.25 Hz/data point in the ^{1}H spectra and 0.4 Hz/data point in the ^{13}C-NMR spectra. Systematic names were generated with ACD/Name [49] according to the IUPAC recommendations and were checked manually [50]. For chromatographic separations, Kieselgel 60 (70–230 mesh, Merck) was used. Light petroleum had a boiling point of 40–65 °C.

4.2. Synthetic procedures

4.2.1. General procedure for the synthesis of *o*-halo(hetero)aroyl chlorides **1b–h**

A suspension of the appropriate acid (2 mmol) in toluene (20 mL), DMF (5 drops) and $SOCl_2$ (20 mmol, 2.38 g) was refluxed for 3 h or overnight. The solvent and excess $SOCl_2$ were removed under reduced pressure. Additional toluene (4 × 5 mL) was added, and the solvent was removed under reduced pressure. The remaining acid chloride was immediately used in subsequent reaction steps (with no further purification).

4.2.2. General procedure for the synthesis of ynones **2a-h**

The appropriate acid chloride **1** (2 mmol) was dissolved in dry CH_2Cl_2 (3 mL). Triethylamine (2 mL), phenylacetylene (1 mmol, 102 mg) and Pd(II) acetate (10 μmol, 2 mg) were added to the

solution, which was stirred at room temperature under a N_2 atmosphere (N_2 balloon) for the indicated time. The solvent was removed under reduced pressure and water (20 mL) was added to the residue. The resulting solution was acidified with 5% HCl and extracted with CH_2Cl_2 or EtOAc (2 × 15 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution and a saturated NaCl solution and were then dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography through a silica gel column (eluent given below). An analytically pure sample was obtained by recrystallization from the appropriate solvent, which is indicated below.

1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-one (**2a1**). Reaction time: 2.5 h. Eluent: toluene/light petroleum, 1:1 v/v. Yield: 209 mg, 87%; orange oil; [51] ^{1}H-NMR (300 MHz): δ 8.08 (m, 1H, H-6), 7.65 (m, 2H, Ph H-2,6), 7.48 (m, 2H, H-3,4), 7.46 (m, 1H, Ph H-4), 7.41 (m, 2H, Ph H-3,5), 7.40 (m, 1H, H-5); ^{13}C-NMR (75 MHz): δ 176.7 (C=O, ^3J(CO,H6) = 5.3 Hz), 135.9 (C-1), 133.5 (C-2), 133.3 (C-4), 133.1 (Ph C-2,6), 132.4 (C-6), 131.5 (C-3), 130.9 (Ph C-4), 128.7 (Ph C-3,5), 126.8 (C-5), 120.1 (Ph C-1), 93.9 (COC≡C, ^3J(C,Ph H2,6) = 5.5 Hz), 88.3 (COC≡C); IR (liquid film): 2196 (C≡C), 1649 (C=O) cm^{-1}; MS *m/z* (%): 242/240 (M^+, 14/40), 214/212 ([M − C=O]$^+$, 25/72) 141/139 ([COC_6H_4Cl]$^+$, 12/34), 129 ([$COC{\equiv}CC_6H_5$]$^+$, 100), 101 ([$C{\equiv}CC_6H_5$]$^+$, 14).

1-(2-Fluorophenyl)-3-phenylprop-2-yn-1-one (**2a2**). Reaction time: 45 min. Eluent: CH_2Cl_2/light petroleum, 1:1 v/v. Yield: 164 mg, 73%; light orange oil; [52] ^{1}H-NMR (500 MHz): δ 8.11 (m, 1H, H-6), 7.67 (m, 2H, Ph H-2,6), 7.59 (m, 1H, H-4), 7.49 (m, 1H, Ph H-4), 7.42 (m, 2H, Ph H-3,5), 7.28 (m, 1H, H-5), 7.19 (m, 1H, H-3); ^{13}C-NMR (125 MHz): δ 174.2 (C=O), 162.1 (C-2, ^1J(C2,F2) = 261.7 Hz), 135.6 (C-4, ^3J(C4,F2) = 9.2 Hz), 133.2 (Ph C-2,6), 131.8 (C-6), 130.9 (Ph C-4), 128.6 (Ph C-3,5), 125.6 (C-1, ^2J(C1,F2) = 7.7 Hz), 124.2 (C-5, ^4J(C5,F2) = 3.9 Hz), 120.1 (Ph C-1), 117.1 (C-3, ^2J(C3,F2) = 21.9 Hz), 93.0 (COC≡C, J(C,F2) = 3.2 Hz), 88.5 (COC≡C); ^{19}F-NMR (470 MHz): δ −111.3 (F-2); IR (liquid film): 2200 (C≡C), 1647 (C=O) cm^{-1}; MS *m/z* (%): 224 (M^+, 17), 196 ([M − C=O]$^+$, 36), 129 ([$COC{\equiv}CC_6H_5$]$^+$, 100), 123 ([COC_6H_4F]$^+$, 84), 101 ([$C{\equiv}CC_6H_5$]$^+$, 21), 74 (83).

1-(2-Bromothiophen-3-yl)-3-phenylprop-2-yn-1-one (**2b**). Reaction time: 19 h. Eluent: CH_2Cl_2/light petroleum, 3:2 v/v. Yield: 147 mg, 67%; whitish needles, mp 66–67 °C (EtOH/H_2O); ^{1}H- NMR (500 MHz): δ 7.65 (m, 2H, Ph H-2,6), 7.57 (d, ^3J = 5.8 Hz, 1H, H-4), 7.48 (m, 1H, Ph H-4), 7.41 (m, 2H, Ph H-3,5), 7.28 (d, ^3J = 5.8 Hz, 1H, H-5); ^{13}C-NMR (125 MHz): δ 170.5 (C=O, ^3J(CO,H4) = 2.0 Hz), 138.2 (C-3, ^2J(C3,H4) = 4.5 Hz, ^3J(C3,H5) = 8.4 Hz), 133.0 (Ph C-2,6), 130.9 (Ph C-4), 129.9 (C-4, ^1J(C4,H4) = 173.4 Hz, ^2J(C4,H5) = 3.8 Hz), 128.7 (Ph C-3,5), 126.0 (C-5, ^1J(C5,H5) = 190.3 Hz, ^2J(C5,H4) = 6.0 Hz), 120.3 (C-2, ^3J(C2,H4) = 12.1 Hz, ^3J(C2,H5) = 6.8 Hz), 120.0 (Ph C-1, ^3J(Ph C1,Ph H3,5) = 8.5 Hz, ^4J(Ph C1,Ph H4) = 1.3 Hz), 93.1 (COC≡C), 88.0 (COC≡C); IR: 2202 (C≡C), 1630 (C=O) cm^{-1}; MS *m/z* (%): 292/290 (M^+, 22/23), 264/262 ([M − C=O]$^+$, 28/28), 139 (65), 129 ([$COC{\equiv}CC_6H_5$]$^+$, 100), 101 ([$C{\equiv}CC_6H_5$]$^+$, 16), 74 (79). Calcd. for $C_{13}H_7BrOS$: C, 53.63; H, 2.42; S, 11.01. Found: C, 53.31; H, 2.39; S, 10.92.

1-(4-Bromothiophen-3-yl)-3-phenylprop-2-yn-1-one (**2c**). Reaction time: 3 h. Eluent: CH_2Cl_2/light petroleum, 3:2 v/v. Yield: 148 mg, 25%; brownish oil; ^{1}H-NMR (500 MHz): δ 8.42 (d, ^4J = 3.5 Hz, 1H, H-2), 7.65 (m, 2H, Ph H-2,6), 7.49 (m, 1H, Ph H-4), 7.41 (m, 2H, Ph H-3,5), 7.36 (d, ^4J = 3.5 Hz,

1H, H-5); ^{13}C-NMR (125 MHz): δ 170.2 (C=O, ^{3}J(CO,H2) = 3.6 Hz, ^{4}J(CO,H5) = 0.6 Hz), 138.6 (C-3, ^{2}J(C3,H2) = 3.2 Hz, ^{3}J(C3,H5) = 7.9 Hz), 137.9 (C-2, ^{1}J(C2,H2) = 189.5 Hz, ^{3}J(C2,H5) = 5.3 Hz), 133.0 (Ph C-2,6), 130.9 (Ph C-4), 128.7 (Ph C-3,5), 126.1 (C-5, ^{1}J(C5,H5) = 192.9 Hz, ^{3}J(C5,H2) = 5.0 Hz), 119.9 (Ph C-1, ^{3}J(Ph C1,Ph H3,5) = 8.6 Hz, ^{4}J(Ph C1,Ph H4) = 1.3 Hz), 109.7 (C-4, ^{2}J(C4,H5) = 0.9 Hz, ^{3}J(C4,H2) = 11.2 Hz), 91.9 (COC≡C), 87.2 (CO<u>C</u>≡C); IR (liquid film): 2189 (C≡C), 1640 (C=O) cm^{-1}; MS *m/z* (%): 292/290 (M^+, 2/2), 264/262 ([M − C=O]$^+$, 2/1), 191/189 ([COC_4H_2SBr]$^+$, 65/61), 129 ([$COC{\equiv}CC_6H_5$]$^+$, 7), 101 ([$C{\equiv}CC_6H_5$]$^+$, 1), 81 (100). Calcd. for $C_{13}H_7BrOS$: C, 53.63; H, 2.42; S, 11.01. Found: C, 53.38; H, 2.50; S, 10.67.

1-(3-Bromothiophen-2-yl)-3-phenylprop-2-yn-1-one (**2d**). Reaction time: 23 h. Eluent: CH_2Cl_2/light petroleum, 3:2 v/v. Yield: 134 mg, 46%; colorless needles, mp 74–77 °C (EtOH/H_2O); ^{1}H- NMR (500 MHz): δ 7.69 (m, 2H, Ph H2,6), 7.62 (d, ^{3}J = 5.2 Hz, 1H, H-5), 7.50 (m, 1H, Ph H-4), 7.42 (m, 2H, Ph H-3,5), 7.18 (d, ^{3}J = 5.2 Hz, 1H, H-4); ^{13}C-NMR (125 MHz): δ 168.3 (C=O), 138.0 (C-2, ^{3}J(C2,H4) = 7.4 Hz, ^{3}J(C2,H5) = 4.8 Hz), 134.0 (C-4, ^{1}J(C4,H4) = 176.5 Hz, ^{2}J(C4,H5) = 4.1 Hz), 133.6 (C-5, ^{1}J(C5,H5) = 188.1 Hz, ^{2}J(C5,H4) = 6.1 Hz), 133.1 (Ph C-2,6), 131.0 (Ph C-4), 128.7 (Ph C-3,5), 119.9 (Ph C-1), 116.4 (C-3, ^{2}J(C3,H4) = 2.4 Hz, ^{3}J(C3,H5) = 12.2 Hz), 94.1 (COC≡<u>C</u>), 87.3 (CO<u>C</u>≡C); IR: 2198 (C≡C), 1627 (C=O) cm^{-1}; MS *m/z* (%): 292/290 (M^+, 25/22), 264/262 ([M − C=O]$^+$, 52/47), 139 (95), 129 ([$COC{\equiv}CC_6H_5$]$^+$, 97), 101 ([$C{\equiv}CC_6H_5$]$^+$, 22), 84 (73), 74 (77), 43 (100). Calcd. for $C_{13}H_7BrOS$: C, 53.63; H, 2.42; S, 11.01. Found: C, 53.63; H, 4.00; S, 10.85. HRMS Calcd. for $C_{13}H_7BrOS$: 289.9401. Found: 289.9403.

*1-(3-Chloro-1-benzo[*b*]thiophen-2-yl)-3-phenylprop-2-yn-1-one* (**2e**). Reaction time: 2.5 h. Eluent: toluene. Yield: 213 mg, 72%; light tan crystals, mp 117–120 °C (MeOH); ^{1}H-NMR (500 MHz): δ 8.03 (d, ^{3}J = 8.0 Hz, 1H, H-4), 7.85 (d, ^{3}J = 8.1 Hz, 1H, H-7), 7.72 (m, 2H, Ph H-2,6), 7.57 (m, 1H, H-6), 7.52 (m, 2H, H-5, Ph H-4), 7.45 (m, 2H, Ph H-3,5); ^{13}C-NMR (125 MHz): δ 169.3 (C=O), 139.3 (C-7a), 137.6 (C-3a), 136.4 (C-2), 133.2 (Ph C-2,6), 131.2 (Ph C-4), 129.0 (C-6), 128.7 (Ph C-3,5), 126.9 (C-3, ^{3}J(C3,H4) = 7.7 Hz), 125.7 (C-5), 124.4 (C-4), 122.9 (C-7), 119.9 (Ph C-1), 95.1 (COC≡<u>C</u>, ^{3}J(C,Ph H2,6) = 5.4 Hz), 88.0 (CO<u>C</u>≡C); IR: 2199 (C≡C), 1601 (C=O) cm^{-1}; MS *m/z* (%): 298/296 (M^+, 27/68), 270/268 ([M − C=O]$^+$, 40/100), 129 ([$COC{\equiv}CC_6H_5$]$^+$, 100), 101 ([$C{\equiv}CC_6H_5$]$^+$, 14). Calcd. for $C_{17}H_9ClOS{\bullet}0.2\ H_2O$: C, 67.98; H, 3.15. Found: C, 68.11; H, 2.82.

1-(2-Chloropyridin-3-yl)-3-phenylprop-2-yn-1-one (**2f**). Reaction time: 2.5 h. Eluent: CH_2Cl_2/EtOAc, 20:1 v/v. Yield: 123 mg, 51%; yellowish-brown crystals, mp 69–71 °C (MeOH); ^{1}H- NMR (500 MHz): δ 8.56 (dd, ^{3}J(H5,H6) = 4.7 Hz, ^{4}J = 1.9 Hz, 1H, H-6), 8.34 (dd, ^{3}J = 7.7 Hz, ^{4}J = 1.9 Hz, 1H, H-4), 7.65 (m, 2H, Ph H-2,6), 7.51 (m, 1H, Ph H-4), 7.42 (m, 3H, H-5, Ph H-3,5); ^{13}C-NMR (125 MHz): δ 175.5 (C=O, ^{3}J(CO,H4) = 5.3 Hz), 152.3 (C-6, ^{1}J(C6,H6) = 183.7 Hz, ^{2}J(C6,H5) = 3.8 Hz, ^{3}J(C6,H4) = 8.2 Hz), 149.5 (C-2, ^{3}J(C2,H4) = 8.8 Hz, ^{3}J(C2,H6) = 13.8 Hz, ^{4}J(C2,H5) = 1.5Hz), 140.7 (C-4, ^{1}J(C4,H4) = 166.2 Hz, ^{2}J(C4,H5) = 1.9 Hz, ^{3}J(C4,H6) = 6.7 Hz), 132.6 (C-3), 133.2 (Ph C-2,6), 131.3 (Ph C-4), 128.8 (Ph C-3,5), 122.4 (C-5, ^{1}J(C5,H5) = 168.2 Hz, ^{2}J(C5,H6) = 8.2 Hz), 119.5 (Ph C-1, ^{3}J(Ph C1,Ph H3,5) = 8.6 Hz, ^{4}J(Ph C1,Ph H4) = 1.4 Hz), 95.7 (COC≡<u>C</u>, ^{3}J(C,Ph H2,6) = 5.3 Hz), 87.9 (CO<u>C</u>≡C); ^{15}N-NMR (50 MHz): δ −70.3 (N-1); IR: 2199 (C≡C), 1636 (C=O) cm^{-1}; MS *m/z* (%):

243/241 (M^+, 6/15), 215/213 ([M − C=O]$^+$, 6/21), 129 ([COC≡CC_6H_5]$^+$, 100), 101 ([C≡CC_6H_5]$^+$, 13). Calcd. for $C_{14}H_8ClNO$: C, 69.58; H, 3.34; N, 5.80. Found: C, 69.59; H, 3.16; N, 5.67.

1-(3-Chloropyridin-4-yl)-3-phenylprop-2-yn-1-one (**2g**). Reaction time: 23 h. Eluent: CH_2Cl_2/EtOAc, 20:1 v/v. Yield: 70 mg, 19%; brown crystals, mp 77–79 °C (MeOH/H_2O, 5:1 v/v); ^{1}H- NMR (500 MHz): δ 8.76 (s, 1H, H-2), 8.68 (d, ^3J = 4.9 Hz, 1H, H-6), 7.81 (d, ^3J = 4.9 Hz, 1H, H-5), 7.65 (m, 2H, Ph H-2,6), 7.52 (m, 1H, Ph H-4), 7.43 (m, 2H, Ph H-3,5); ^{13}C-NMR (125 MHz): δ 175.3 (C=O), 151.6 (C-2, ^1J(C2,H2) = 188.0 Hz, ^3J(C2,H6) = 11.4 Hz, ^4J(C2,H5) = 1.0 Hz), 148.4 (C-6, ^1J(C6,H6) = 183.6 Hz, ^2J(C6,H5) = 2.3 Hz, ^3J(C6,H2) = 11.6 Hz), 141.8 (C-4, ^2J(C4,H5) = not resolved, ^3J(C4,H2) = 4.9 Hz, ^3J(C4,H6) = 6.9 Hz), 133.3 (Ph C-2,6), 131.6 (Ph C-4), 129.3 (C-3), 128.8 (Ph C-3,5), 124.0 (C-5, ^1J(C5,H5) = 167.1 Hz, ^2J(C5,H6) = 9.7 Hz), 119.3 (Ph C-1, ^3J(Ph C1,Ph H3,5) = 8.5 Hz, ^4J(Ph C1,Ph H4) = 1.4 Hz), 96.2 (COC≡C, ^3J(C,Ph H2,6) = 5.4 Hz), 87.8 (CO<u>C</u>≡C); IR: 2197 (C≡C), 1641 (C=O) cm^{-1}; MS *m/z* (%): 243/241 (M^+, 4/12), 215/213 ([M − C=O]$^+$, 4/8), 129 ([COC≡CC_6H_5]$^+$, 100), 101 ([C≡CC_6H_5]$^+$, 11). Calcd. for $C_{14}H_8ClNO$•0.2 H_2O: C, 68.56; H, 3.45; N, 5.71. Found: C, 68.69; H, 3.25; N, 5.63.

1-(2-Chloroquinolin-3-yl)-3-phenylprop-2-yn-1-one (**2h**). Reaction time: 200 min. Eluent: light petroleum/EtOAc, 4:1 v/v. Yield: 181 mg, 62%; brownish-yellow crystals, mp 100–101 °C (MeOH); ^{1}H-NMR (500 MHz): δ 8.87 (s, 1H, H-4), 8.08 (dd, ^3J = 8.5 Hz, ^4J = 1.1 Hz, 1H, H-8), 7.97 (dd, ^3J = 8.1 Hz, ^4J = 1.4 Hz, 1H, H-5), 7.88 (m, ^3J(H7,H6) = 7.0 Hz, ^3J(H7,H8) = 8.5 Hz, ^4J = 1.4 Hz, 1H, H-7), 7.68 (m, 2H, Ph H-2,6), 7.66 (m, 1H, H-6), 7.51 (m, 1H, Ph H-4), 7.44 (m, 2H, Ph H-3,5); ^{13}C-NMR (125 MHz): δ 175.3 (C=O, ^3J(CO,H4) = 5.7 Hz), 148.4 (C-8a), 147.0 (C-2, ^3J(C2,H4) = 9.7 Hz), 142.7 (C-4, ^1J(C4,H4) = 164.4 Hz, ^3J(C4,H5) = 4.6 Hz), 133.2 (C-7, Ph C-2,6), 131.3 (Ph C-4), 130.2 (C-3), 128.9 (C-5), 128.8 (Ph C-3,5), 128.5 (C-8), 128.0 (C-6), 126.0 (C-4a), 119.7 (Ph C-1, ^3J(Ph C1,Ph H3,5) = 8.5 Hz, ^4J(Ph C1,Ph H4) = 1.3 Hz), 95.2 (COC≡<u>C</u>, ^3J(C,Ph H2,6) = 5.3 Hz, ^4J(C,Ph H3,5) = 1.0 Hz), 88.0 (CO<u>C</u>≡C); ^{15}N-NMR (50 MHz): δ −78.4 (N-1); IR: 2197 (C≡C), 1632 (C=O) cm^{-1}; MS *m/z* (%): 293/291 (M^+, 6/15), 265/263 ([M − C=O]$^+$, 8/24), 239 (41), 129 ([COC≡CC_6H_5]$^+$, 90), 101 ([C≡CC_6H_5]$^+$, 45), 43 (100). Calcd. for $C_{18}H_{10}ClNO$•0.4 H_2O: C, 72.32; H, 3.64; N, 4.69. Found: C, 72.27; H, 3.37; N, 5.01.

4.2.3. General procedure for the synthesis of thiopyranones **4a–h**

A suspension of NaSH hydrate (~60%, 1.2 mmol, 112 mg) was refluxed in EtOH (20 mL) until a cloudy solution was formed. Ynone **2** (0.4 mmol) in EtOH (2 mL) was then added to the solution, which was refluxed for the indicated time. The solvent was removed under reduced pressure and water (20 mL) was added to the residue. The resulting solution was acidified with 5% HCl and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution and a saturated NaCl solution. They were then dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography through a silica gel (eluent as indicated below). An analytically pure sample was obtained by recrystallization from an appropriate solvent.

*2-Phenyl-4*H-*thiochromen-4-one* (**4a**). Reaction time: 4 h. Eluent: CH_2Cl_2/EtOAc, 15:1 v/v. Yield: 131 mg, 54%; beige needles, mp 121–123 °C (MeOH) (lit. [18] mp 124–126 °C); ^{1}H= NMR (500 MHz): δ 8.54 (dd, 1H, H-5), 7.68 (m, 2H, Ph H-2,6), 7.65 (dd, 1H, H-8), 7.62 (dt, 1H, H-7), 7.54 (dt, 1H, H-6), 7.51 (m, 1H, Ph H-4), 7.50 (m, 2H, Ph H-3,5), 7.24 (s, 1H, H-3); ^{13}C-NMR (125 MHz): δ 180.8 (C-4), 153.0 (C-2), 137.6 (C-8a), 136.5 (Ph C-1), 131.6 (C-7), 130.8 (C-4a, Ph C-4), 129.2 (Ph C-3,5), 128.5 (C-5), 127.7 (C-6), 126.9 (Ph C-2,6), 126.4 (C-8), 123.4 (C-3, ^1J(C3,H3) = 163.6 Hz); IR: 1620 (C=O) cm^{-1}; MS *m/z* (%): 238 (M^+, 92), 210 ([M − C=O]$^+$, 100), 136 ([COC_6H_4S]$^+$, 53), 108 ([C_6H_4S]$^+$, 28).

*6-Phenyl-4*H-*thieno[2,3-*b*]thiopyran-4-one* (**4b**). Reaction time: 100 min. Eluent: CH_2Cl_2/EtOAc, 5:1 v/v. Yield: 20 mg, 50%; whitish powder, mp 115–117 °C (MeOH); ^{1}H-NMR (500 MHz): δ 7.78 (d, ^3J = 5.3 Hz, 1H, H-3), 7.62 (m, 2H, Ph H-2,6), 7.50 (m, 1H, Ph H-4), 7.49 (m, 2H, Ph H-3,5), 7.46 (d, ^3J = 5.3 Hz, 1H, H-2), 7.20 (s, 1H, H-5); ^{13}C-NMR (125 MHz): δ 177.1 (C-4, ^2J(C4,H5) = 1.2 Hz, ^3J(C4,H3) = 1.3 Hz), 151.5 (C-6, ^2J(C6,H5) = 3.4 Hz), 144.3 (C-7a, ^3J(C7a,H2) = 6.7 Hz, ^3J(C7a,H3) = 10.0 Hz), 137.5 (C-3a, ^2J(C3a,H3) = 4.7 Hz, ^3J(C3a,H2) = 9.9 Hz, ^3J(C3a,H5) = 3.7 Hz), 136.1 (Ph C-1, ^3J(Ph C1,H5) = 5.4 Hz), 130.7 (Ph C-4), 129.3 (Ph C-3,5), 127.0 (Ph C-2,6), 125.5 (C-3, ^1J(C3,H3) = 174.8 Hz, ^2J(C3,H2) = 4.4 Hz, ^4J(C3,H5) = 1.0 Hz), 125.3 (C-2, ^1J(C2,H2) = 189.6 Hz, ^2J(C2,H3) = 7.5 Hz), 125.0 (C-5, ^1J(C5,H5) = 163.3 Hz); IR: 1606 (C=O) cm^{-1}; MS *m/z* (%): 244 (M^+, 100), 216 ([M − C=O]$^+$, 31), 142 ([$COC_4H_2S_2$]$^+$, 97), 120 ([$COCH{=}CC_6H_5$]$^+$, 69), 114 ([$C_4H_2S_2$]$^+$, 38), 101 ([$C{=}CC_6H_5$]$^+$, 27). Calcd. for $C_{13}H_8OS_2$: C, 63.90; H, 3.30. Found: C, 63.57; H, 3.27.

*2-Phenyl-4*H-*thieno[3,4-*b*]thiopyran-4-one* (**4c**). Reaction time: 22.5 h. Eluent: CH_2Cl_2/EtOAc, 5:1 v/v. Yield: 28 mg, 34%; brownish needles, mp 160–162 °C (MeOH/H_2O); ^{1}H-NMR (500 MHz): δ 8.51 (d, ^4J = 3.4 Hz, 1H, H-5), 7.66 (m, 2H, Ph H-2,6), 7.52 (d, ^3J = 3.4 Hz, 1H, H-7), 7.49 (m, 1H, Ph H-4), 7.48 (m, 2H, Ph H-3,5), 6.99 (s, 1H, H-3); ^{13}C-NMR (125 MHz): δ 178.2 (C-4, ^2J(C4,H3) = 1.1 Hz, ^3J(C4,H5) = 2.2 Hz, ^4J(C4,H7) = 1.1 Hz), 153.3 (C-2, ^2J(C2,H3) = 3.1 Hz), 136.7 (Ph C-1, ^3J(Ph C1,H3) = 5.5 Hz), 134.7 (C-4a, ^2J(C4a,H5) = 3.2 Hz, ^3J(C4a,H3) = 3.8 Hz, ^3J(C4a,H7) = 7.8 Hz), 131.4 (C-7a, ^2J(C7a,H7) = 2.8 Hz, ^3J(C7a,H5) = 9.8 Hz), 130.8 (Ph C-4), 129.7 (C-5, ^1J(C5,H5) = 191.8 Hz, ^3J(C5,H7) = 4.9 Hz, ^4J(C5,H3) = 1.3 Hz), 129.2 (Ph C-3,5), 127.0 (Ph C-2,6), 122.1 (C-3, ^1J(C3,H3) = 163.6 Hz), 119.2 (C-7, ^1J(C7,H7) = 189.3 Hz, ^3J(C7,H5) = 5.7 Hz); IR: 1612 (C=O) cm^{-1}; MS *m/z* (%): 244 (M^+, 48), 216 ([M − C=O]$^+$, 16), 142 ([$COC_4H_2S_2$]$^+$, 100), 114 ([$C_4H_2S_2$]$^+$, 36), 82 ([C_4H_2S]$^+$, 22). Calcd. for $C_{13}H_8OS_2$: C, 63.90; H, 3.30. Found: C, 62.82; H 3.28. HRMS (ESI) Calcd. for $C_{13}H_9OS_2$ [M+H]: 245.0095. Found: 245.0100.

*5-Phenyl-7*H-*thieno[3,2-*b*]thiopyran-7-one* (**4d**). Reaction time: 1 h. Eluent: CH_2Cl_2/EtOAc, 5:1 v/v. Yield: 80 mg, 87%; brownish powder, mp 82–84 °C (EtOH/H_2O) (lit. [24] mp 80 °C); ^{1}H-NMR (500 MHz): δ 7.85 (d, ^3J = 5.3 Hz, 1H, H-2), 7.65 (m, 2H, Ph H-2,6), 7.51 (m, 3H, Ph H-3,4,5), 7.35 (d, ^3J = 5.3 Hz, 1H, H-3), 7.21 (s, 1H, H-6); ^{13}C-NMR (125 MHz): δ 176.2 (C-7, ^2J(C7,H6) = 1.1 Hz, ^4J(C7,H2) = 1.1 Hz, ^4J(C7,H3) = 1.1 Hz), 152.8 (C-5, ^2J(C5,H6) = 3.1 Hz), 139.0 (C-3a, ^2J(C3a,H3) = 4.4 Hz, ^3J(C3a,H2) = 11.2 Hz), 137.2 (C-7a, ^3J(C7a,H2) = 5.9 Hz, ^3J(C7a,H3) = 7.1 Hz, ^3J(C7a,H6) = 4.7 Hz), 136.4 (Ph C-1, ^3J(Ph C1,H6) = 5.4 Hz), 133.2 (C-2, ^1J(C2,H2) = 186.6 Hz, ^2J(C2,H3) = 6.0 Hz), 130.7 (Ph C-4), 129.3 (Ph C-3,5), 127.2 (Ph C-2,6), 125.3 (C-3, ^1J(C3,H3) = 173.4 Hz, ^2J(C3,H2)

= 4.8 Hz), 123.6 (C-6, ^1J(C6,H6) = 163.9 Hz); MS *m/z* (%): 244 (M^+, 46), 243 ($[M - H]^+$, 21), 216 ($[M - C{=}O]^+$, 16), 142 ($[COC_4H_2S_2]^+$, 94), 114 ($[C_4H_2S_2]^+$, 33), 102 ($[CH{=}CC_6H_5]^+$, 19), 82 ($[C_4H_2S]^+$, 20), 69 (100).

*2-Phenyl-4*H-*thiopyrano[3,2-*b*][1]benzothiophen-4-one* (**4e**). Reaction time: 70 min. Eluent: CH_2Cl_2/EtOAc, 15:1 v/v. Yield: 96 mg, 82%; colorless crystals, mp 166–167 °C (MeOH/EtOAc, 2:1 v/v) (lit. [25] mp 177 °C); ^{1}H-NMR (500 MHz): δ 8.00 (m, 1H, H-9), 7.99 (m, 1H, H-6), 7.71 (m, 2H, Ph H-2,6), 7.59 (m, 1H, H-7), 7.54 (m, 3H, Ph H-3,4,5), 7.53 (m, 1H, H-8), 7.32 (s, 1H, H-3); ^{13}C-NMR (125 MHz): δ 177.0 (C-4, ^2J(C4,H3) = 1.1 Hz), 152.1 (C-2, ^2J(C2,H3) = 3.1 Hz), 140.7 (C-5a), 137.3 (C-4a, ^3J(C4a,H3) = 4.6 Hz), 136.3 (Ph C-1, ^3J(Ph C1,H3) = 5.3 Hz), 136.2 (C-9a), 135.4 (C-9b, ^3J(C9b,H9) = 3.9 Hz), 130.8 (Ph C-4), 129.4 (Ph C-3,5), 128.6 (C-7, ^1J(C7,H7) = 162.0 Hz, ^3J(C7,H9) = 7.8 Hz), 127.2 (Ph C-2,6), 125.3 (C-8, ^1J(C8,H8) = 162.5 Hz, ^3J(C8,H6) = 7.6 Hz), 124.7 (C-3, ^1J(C3,H3) = 163.9 Hz), 123.8 (C-6, ^1J(C6,H6) = 164.8 Hz, ^2J(C6,H7) = 1.5 Hz, ^3J(C6,H8) = 8.0 Hz, ^4J(C6,H9) = 1.5 Hz), 122.5 (C-9, ^1J(C9,H9) = 161.1 Hz, ^2J(C9,H8) = 1.4 Hz, ^3J(C9,H7) = 8.1 Hz, ^4J(C9,H6) = 1.4 Hz); IR: 1618 (C=O) cm^{-1}; MS *m/z* (%): 294 (M^+, 32), 266 ($[M–C{=}O]^+$, 34), 164 ($[C_8H_4S_2]^+$, 25), 132 ($[C_8H_4S]^+$, 29), 120 (43), 68 (100). Calcd. for $C_{17}H_{10}OS_2$•0.1 H_2O: C, 68.94; H, 3.47; S, 21.65. Found: C, 68.91; H, 3.45; S, 21.26.

*2-Phenyl-4*H-*thiopyrano[2,3-*b*]pyridin-4-one* (**4f**). Reaction time: 1.5 h. Eluent: CH_2Cl_2/EtOAc, 15:1 v/v. Yield: 36 mg, 93%; luminous yellow needles, mp 114–117 °C (MeOH) (lit. [19] mp 113–116 °C); ^{1}H-NMR (300 MHz): δ 8.81 (dd, ^3J = 4.5 Hz, ^4J = 1.9 Hz, 1H, H-7), 8.77 (dd, ^3J = 8.1 Hz, ^4J = 1.9 Hz, 1H, H-5), 7.71 (m, 2H, Ph H-2,6), 7.53 (m, 3H, Ph H-3,4,5), 7.50 (dd, ^3J(H6,H7) = 4.5 Hz, ^3J(H6,H5) = 8.1 Hz, 1H, H-6), 7.26 (s, 1H, H-3); ^{13}C-NMR (75 MHz): δ 181.3 (C-4, ^3J(C4,H5) = 3.5 Hz), 159.1 (C-8a, ^3J(C8a,H5) = 6.5 Hz, ^3J(C8a,H7) = 14.0 Hz), 154.7 (C-2), 152.8 (C-7, ^1J(C7,H7) = 181.7 Hz, ^2J(C7,H6) = 3.8 Hz, ^3J(C7,H5) = 7.8 Hz), 136.7 (C-5, ^1J(C5,H5) = 168.2 Hz, ^2J(C5,H6) not resolved, ^3J(C5,H7) = 6.2 Hz), 136.3 (Ph C-1), 131.1 (Ph C-4), 129.4 (Ph C-3,5), 128.1 (C-4a), 127.0 (Ph C-2,6), 123.6 (C-3, ^1J(C3,H3) = 164.7 Hz), 122.9 (C-6, ^1J(C6,H6) = 167.0 Hz, ^2J(C6,H5) not resolved, ^2J(C6,H7) = 8.2 Hz); ^{15}N-NMR (50 MHz): δ −76.8 (N-8); IR: 1630 (C=O) cm^{-1}; MS *m/z* (%): 239 (M^+, 100), 211 ($[M - C{=}O]^+$, 99), 137 ($[COC_5H_3NS]^+$, 33), 109 ($[C_5H_3NS]^+$, 57), 105 ($[COC_5H_3N]^+$, 32), 102 ($[CH{=}CC_6H_5]^+$, 33). Calcd. for $C_{14}H_9NOS$: C, 70.27; H, 3.79; N, 5.85. Found: C, 70.26; H, 4.04; N, 5.75.

*2-Phenyl-4*H-*thiopyran[2,3-*c*]pyridin-4-one* (**4g**). Reaction time: 1.5 h. Eluent: CH_2Cl_2/EtOAc, 5:1 v/v. Yield: 21 mg, 44%; flat brownish prisms, mp 153–154 °C (EtOH/H_2O); ^{1}H-NMR (500 MHz): δ 9.02 (s, 1H, H-8), 8.73 (d, ^3J = 5.3 Hz, 1H, H-6), 8.27 (d, ^3J = 5.3 Hz, 1H, H-5), 7.69 (m, 2H, Ph H-2,6), 7.53 (m, 1H, Ph H-4), 7.52 (m, 2H, Ph H-3,5), 7.27 (s, 1H, H-3); ^{13}C-NMR (125 MHz): δ 179.5 (C-4, ^2J(C4,H3) = 1.0 Hz, ^3J(C4,H5) = 3.6 Hz, ^4J(C4,H8) = 1.6 Hz), 154.0 (C-2, ^2J(C2,H3) = 2.5 Hz), 148.8 (C-8, ^1J(C8,H8) = 183.4 Hz, ^3J(C8,H6) = 11.1 Hz, ^4J(C8,H5) = 0.8 Hz), 147.8 (C-6, ^1J(C6,H6) = 182.7 Hz, ^2J(C6,H5) = 3.2 Hz, ^3J(C6,H8) = 11.6 Hz), 136.1 (Ph C-1, ^3J(Ph C1,H3) = 5.5 Hz), 135.7 (C-4a, ^2J(C4a,H5) not resolved, ^3J(C4a,H3) = 3.7 Hz, ^3J(C4a,H6) = 6.7 Hz, ^3J(C4a,H8) = 5.1 Hz), 133.2 (C-8a, ^2J(C8a,H8) = 7.9 Hz, ^3J(C8a,H5) = 6.5 Hz, ^4J(C8a,H6) = 1.8 Hz), 131.3 (Ph C-4), 129.4 (Ph C-3,5), 127.0 (Ph C-2,6), 123.9 (C-3, ^1J(C3,H3) = 164.5 Hz), 120.6 (C-5, ^1J(C5,H5) = 168.9 Hz,

^{2}J(C5,H6) = 9.0 Hz, ^{4}J(C5,H3) = 0.8 Hz, ^{4}J(C5,H8) = 1.7 Hz); ^{15}N-NMR (50 MHz): δ −60.0 (N-7); IR: 1635 (C=O) cm^{-1}; MS *m/z* (%): 239 (M^+, 100), 211 ([M − C=O]$^+$, 77), 149 (49), 139 (28), 137 ([COC_5H_3NS]$^+$, 66), 109 ([C_5H_3NS]$^+$, 53), 105 ([COC_5H_3N]$^+$, 20), 102 ([$CH{=}CC_6H_5$]$^+$, 41), 81 (98). Calcd. for $C_{14}H_9NOS$: C, 70.27; H, 3.79; N, 5.85; S, 13.40. Found: C, 70.28; H, 4.02; N, 5.69; S, 13.21. HRMS Calcd. for $C_{14}H_9NOS$: 239.0405. Found: 239.0402.

*2-Phenyl-4*H-*thiopyrano[2,3*-b*]quinolin-4-one* (**4h**). Reaction time: 100 min. Eluent: CH_2Cl_2/EtOAc, 20:1 v/v. Yield: 77 mg, 67%; off-white needles, mp 208–210 °C (CH_2Cl_2/EtOAc, 5:1 v/v); ^{1}H-NMR (500 MHz): δ 9.30 (s, 1H, H-5), 8.09 (d, ^{3}J = 8.6 Hz, 1H, H-9), 8.04 (d, ^{3}J = 8.1 Hz, 1H, H-6), 7.88 (m, 1H, H-8), 7.74 (m, 2H, Ph H-2,6), 7.62 (m, 1H, H-7), 7.54 (m, 3H, Ph H-3,4,5), 7.23 (s, 1H, H-3); ^{13}C-NMR (125 MHz): δ 182.0 (C-4, ^{2}J(C4,H3) = 0.7 Hz, ^{3}J(C4,H5) = 4.1 Hz), 157.1 (C-10a, ^{3}J(C10a,H5) = 8.1 Hz), 155.1 (C-2), 149.2 (C-9a), 138.6 (C-5, ^{1}J(C5,H5) = 166.4 Hz, ^{3}J(C5,H6) = 4.7 Hz), 136.4 (Ph C-1), 133.1 (C-8), 131.2 (Ph C-4), 129.7 (C-6), 129.4 (Ph C-3,5), 128.1 (C-9), 127.2 (C-7), 127.0 (Ph C-2,6), 126.9 (C-5a), 125.1 (C-4a), 122.1 (C-3, ^{1}J(C3,H3) = 164.8 Hz); ^{15}N-NMR (50 MHz): δ −83.8 (N-10); IR: 1631 (C=O) cm^{-1}; MS *m/z* (%): 289 (M^+, 91), 261 ([M − C=O]$^+$, 88), 181 (46), 159 ([C_9H_5NS]$^+$, 39), 130 ([$COCH{=}CC_6H_5$]$^+$, 77), 101 ([$C{=}CC_6H_5$]$^+$, 44), 75 (82), 68 (100). Calcd. for $C_{18}H_{11}NOS$•0.2 H_2O: C, 73.80; H, 3.92; N, 4.78. Found: C, 73.85; H, 3.71; N, 4.77.

4.2.4. Preparation of *N,N*-diethyl-3-fluoropyridine-2-carboxamide (**5**)

Under the conditions given for the synthesis of compounds **2**, reaction of **1i** (2 mmol, 319 mg) with phenylacetylene (1 mmol, 102 mg), Et_3N (2 mL) and Pd(II) acetate (10 μmol, 2 mg) for 26 h resulted in formation of compound **5** after purification by column chromatography (eluent: EtOAc). Yield: 131 mg, 33%; brown oil; ^{1}H-NMR (500 MHz): δ 8.42 (dd, ^{3}J = 4.6 Hz, ^{4}J = 1.1 Hz, ^{5}J(H6,F3) = 1.4 Hz, 1H, H-6), 7.47 (dd, ^{3}J(H4,H5*)* = 8.5 Hz, ^{3}J(H4,F3) = 8.9 Hz, ^{4}J = 1.1 Hz, 1H, H-4), 7.35 (m, ^{3}J(H5,H6) = 4.6 Hz, ^{3}J(H5,H4) = 8.5 Hz, ^{4}J(H5,F3) = 4.2 Hz, 1H, H-5), 3.58 (q, ^{3}J = 7.1 Hz, 2H, N-CH_2 cis), 3.20 (q, ^{3}J = 7.1 Hz, 2H, N-CH_2 trans), 1.27 (t, ^{3}J = 7.1 Hz, 3H, CH_3 cis), 1.10 (t, ^{3}J = 7.1 Hz, 3H, CH_3 trans); ^{13}C-NMR (125 MHz): δ 164.7 (C=O, ^{3}J(CO,F3) = 3.1 Hz), 155.8 (C-3, ^{1}J(C3,F3) = 259.1 Hz, ^{2}J(C3,H4) = 4.8 Hz, ^{3}J(C3,H5) = 9.6 Hz, ^{4}J(C3,H6) = 1.9 Hz), 145.2 (C-6, ^{1}J(C6,H6) = 182.3 Hz, ^{2}J(C6,H5) = 2.7 Hz, ^{3}J(C6,H4) = 7.3 Hz, ^{4}J(C6,F3) = 5.0 Hz), 144.0 (C-2, ^{2}J(C2,F3) = 18.0 Hz, ^{3}J(C2,H4) = 3.8 Hz, ^{3}J(C2,H6) = 12.2 Hz, ^{4}J(C2,H5) = 1.5 Hz), 125.1 (C-5, ^{1}J(C5,H5) = 167.2 Hz, ^{2}J(C5,H4) = 2.0 Hz, ^{2}J(C5,H6) = 9.4 Hz, ^{3}J(C5,F3) = 3.8 Hz), 123.9 (C-4, ^{1}J(C4,H4) = 167.4 Hz, ^{2}J(C4,F3) = 18.4 Hz, ^{3}J(C4,H6) = 7.2 Hz), 42.8 (N-CH_2 trans, ^{1}J = 135.2 Hz, ^{2}J($\underline{C}H_2$,$C\underline{H}_3$) = 4.2 Hz), 39.4 (N-CH_2 cis, ^{1}J = 136.5 Hz, ^{2}J($\underline{C}H_2$,$C\underline{H}_3$) = 4.2 Hz), 14.0 (CH_3 trans, ^{1}J = 127.1 Hz, ^{2}J($\underline{C}H_3$,$C\underline{H}_2$) = 3.1 Hz), 12.8 (CH_3 cis, ^{1}J = 127.2 Hz, ^{2}J($\underline{C}H_3$,$C\underline{H}_2$) = 3.4 Hz); ^{15}N-NMR (50 MHz): δ −65.8 (N-1), −248.9 ($CONR_2$); ^{19}F-NMR (470 MHz): δ −124.3 (F-3, ^{3}J(F3,H4) = 8.9 Hz, ^{4}J(F3,H5) = 4.2 Hz, ^{5}J(F3,H6) = 1.4 Hz); IR: 1643 (C=O) cm^{-1}; MS *m/z* (%): 196 (M^+, 7), 124 ([M − $N(Et)_2$]$^+$, 65), 97 ([C_5H_3NF]$^+$, 55), 72 ([$N(Et)_2$]$^+$, 100), 44 (63). Calcd. for $C_{10}H_{13}FN_2O$•0.2 H_2O: C, 60.11; H, 6.76; N, 14.02. Found: C, 60.28; H, 6.59; N, 13.90.

4.2.5. Preparation of 3-chloro-*N,N*-diethylquinoxaline-2-carboxamide (**6**)

Under the conditions given for synthesis of compounds **2**, reaction of **1j** (2 mmol, 455 mg) with phenylacetylene (1 mmol, 102 mg), Et_3N (2 mL) and Pd(II) acetate (10 μmol, 2 mg) for 20 h resulted in formation of compound **6** after purification by column chromatography (eluent: CH_2Cl_2/EtOAc, 5:1 v/v.). Yield: 256 mg, 49%; brownish needles, mp 91–93 °C (MeOH); ^{1}H-NMR (500 MHz): δ 8.10 (m, 1H, H-8), 8.03 (m, 1H, H-5), 7.83 (m, 1H, H-6), 7.80 (m, 1H, H-7), 3.65 (q, ^3J = 7.2 Hz, 2H, N-CH_2 cis), 3.20 (q, ^3J = 7.1 Hz, 2H, N-CH_2 trans), 1.34 (t, ^3J = 7.2 Hz, 3H, CH_3 cis), 1.16 (t, ^3J = 7.1 Hz, 3H, CH_3 trans); ^{13}C-NMR (125 MHz): δ 164.8 (C=O), 149.1 (C-3), 143.8 (C-2), 141.6 (C-4a), 140.0 (C-8a), 131.6 (C-6), 130.8 (C-7), 129.2 (C-8), 128.3 (C-5), 42.9 (N-CH_2 trans), 39.5 (N-CH_2 cis), 13.8 (CH_3 trans), 12.5 (CH_3 cis); ^{15}N-NMR (50 MHz): δ –52.1 (N-1), −63.0 (N-4), −249.2 ($CONR_2$); IR: 1635 (C=O) cm^{-1}; MS *m/z* (%): 265/263 (M^+, 0.5/1.5), 191 ($[M - N(Et)_2]^+$, 3), 165/163 ($[C_8H_4N_2Cl]^+$, 7/18), 128 ($[C_8H_4N_2]^+$, 5), 72 ($[N(Et)_2]^+$, 100). Calcd. for $C_{13}H_{14}ClN_3O$: C, 59.21; H, 5.35; N, 15.93. Found: C, 59.43; H, 5.42; N, 15.99.

4.2.6. Preparation of (2*Z*,2'*Z*)-3,3'-sulfanediylbis[1-(2-chlorophenyl)-3-phenylprop-2-en-1-one] (**7**)

Ynone **2a1** (0.5 mmol, 120 mg) in EtOH (2 mL) was added to a suspension of NaSH hydrate (~60%, 1.3 mmol, 121 mg) in EtOH (20 mL). The resulting solution was stirred at room temperature for 30 min, and then processed as described in the preparation of compounds **4**. The residue was purified by column chromatography through silica gel (eluent: CH_2Cl_2). Yield: 48 mg, 19%; yellow powder, mp 161–164 °C (EtOH); ^{1}H-NMR (300 MHz): δ 7.65 (m, 2H, H-6), 7.43 (m, 2H, H-3), 7.42 (m, 2H, H-4), 7.38 (m, 2H, H-5), 7.18 (m, 2H, Ph H-4), 7.05 (m, 4H, Ph H-3,5), 6.97 (m, 4H, Ph H-2,6), 6.92 (s, 2H, COC<u>H</u>=C); ^{13}C-NMR (75 MHz): δ 189.7 (C=O), 155.4 (COCH=<u>C</u>), 140.6 (Ph C-1), 139.7 (C-1), 131.9 (C-4), 131.4 (C-2), 130.5 (C-6), 130.2 (C-3), 128.9 (Ph C-4), 128.3 (Ph C-2,6), 128.0 (Ph C-3,5), 127.7 (CO<u>C</u>H=C, ^1J = 161.5 Hz), 127.1 (C-5); IR: 1638 (C=O) cm^{-1}; MS *m/z* (%): 516/514 (M^+, 0.3/0.4), 275/273 ($[M - C_{15}H_{10}ClO]^+$, 13/33), 238 (19), 149 ($[COC(S)C_6H_5]^+$, 80), 141/139 ($[COC_6H_4Cl]^+$, 37/100), 113/111 ($[C_6H_4Cl]^+$, 29/49), 105 (38), 85 ($[COCH=CS]^+$, 32), 77 ($[C_6H_5]^+$, 33), 57 (83). HRMS (ESI) Calcd. for $C_{30}H_{21}Cl_2O_2S$ [M + H]: 515.0639. Found: 515.0642.

4.2.7. Preparation of (2*Z*)-1-(2-chlorophenyl)-3-(methylamino)-3-phenylprop-2-en-1-one (**10**)

Ethanolic methylamine-solution (33 wt%, 6 mL, 48 mmol) was added to a solution of ynone **2a1** (0.5 mmol, 120 mg) in pyridine (0.4 mL) and H_2O (3 drops). The solution was refluxed for 1 h. The solvent was then removed under reduced pressure and water (20 mL) was added to the residue. The resulting solution was adjusted to pH 5 with 5% HCl and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution and a saturated NaCl solution and then dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography through silica gel (eluent: CH_2Cl_2/EtOAc, 20:1 v/v.), which produced **10** as a slowly crystallizing oil. Yield: 99 mg, 73%; pale orange solid, mp 77–80 °C; ^{1}H-NMR (500 MHz): δ 11.18 (broad, 1H, N-H), 7.49 (m, 1H, H-6), 7.44 (m, 3H, Ph H-3,4,5), 7.42 (m, 2H, Ph H-2,6), 7.37 (m, 1H, H-3), 7.27 (m, 1H, H-4), 7.26 (m, 1H, H-5), 5.44 (s, 1H, COC<u>H</u>=C), 2.96 (d, ^3J = 5.4 Hz, 3H, N-CH_3);^{13}C-NMR (125 MHz): δ 189.2 (C=O), 167.6 (COCH=<u>C</u>), 141.3 (C-1), 134.8 (Ph C-1), 130.8 (C-

2), 130.1 (C-3), 129.9 (C-4), 129.7 (Ph C-4), 129.2 (C-6), 128.5 (Ph C-3,5), 127.7 (Ph C-2,6), 126.5 (C-5), 97.3 (CO<u>C</u>H=C, ^{1}J = 164.5 Hz, ^{3}J(C,NH) = 3.6 Hz), 31.6 (N-CH_3, ^{1}J = 138.5 Hz, ^{2}J(N<u>C</u>H_3,N<u>H</u>) = 3.4 Hz, ^{4}J(N<u>C</u>H_3,COC<u>H</u>=C) = 1.1 Hz); ^{15}N-NMR (50 MHz): δ −281.5 (N-CH_3); IR: 1595 (C=O) cm^{-1}; MS *m/z* (%): 273/271 (M^+, 12/43), 256/254 (22/45), 236 ($[M - Cl]^+$, 100), 160 ($[M–C_6H_4Cl]^+$, 57), 141/139 ($[COC_6H_4Cl]^+$, 14/33), 117 ($[CH=C(NH)C_6H_5]^+$, 66), 113/111 ($[C_6H_4Cl]^+$, 13/38), 104 ($[HNCC_6H_5]^+$, 25), 102 ($[CH=CC_6H_5]^+$, 97), 77 ($[C_6H_5]^+$, 74). Calcd. for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.15. Found: C, 70.32; H, 5.22; N, 5.32.

4.2.8. Preparation of 1-methyl-2-phenylquinolin-4(1*H*)-one (**11**)

Potassium carbonate (2 mmol, 277 mg) was added to a solution of **10** (220 μmol, 60 mg) in DMF (5 mL). The resulting mixture was refluxed for 52 h under a N_2 atmosphere (N_2 balloon). The solvent was then removed under reduced pressure and water (20 mL) was added to the residue. The resulting solution was adjusted to a slightly basic pH with 5% HCl and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution and a saturated NaCl solution and then dried over anhydrous Na_2SO_4. After removal of the solvent, the oily residue was purified by column chromatography through silica gel (eluent: EtOAc/NEt_3, 20:1 v/v.) to generate **11**. Yield: 37 mg, 72%; yellowish crystals, mp 137–140 °C (EtOH/H_2O) (lit. [53] mp 142–145 °C); ^{1}H-NMR (500 MHz): δ 8.50 (dd, ^{3}J = 8.1 Hz, ^{4}J = 1.7 Hz, 1H, H-5), 7.71 (ddd, ^{3}J(H7,H6) = 7.0 Hz, ^{3}J(H7,H8) = 8.6 Hz, ^{4}J = 1.7 Hz, 1H, H-7), 7.55 (d, ^{3}J = 8.6 Hz, 1H, H-8), 7.50 (m, 3H, Ph H-3,4,5), 7.42 (m, ^{3}J(H6,H7) = 7.0 Hz, ^{3}J(H6,H5) = 8.1 Hz, ^{4}J = 1.0 Hz, 1H, H-6), 7.41 (m, 2H, Ph H-2,6), 6.29 (s, 1H, H-3), 3.60 (s, 3H, N-CH_3); ^{13}C-NMR (125 MHz): δ 177.6 (C-4, ^{2}J(C4,H3) = 1.4 Hz, ^{3}J(C4,H5) = 3.9 Hz), 154.7 (C-2, ^{2}J(C2,H3) = 3.7 Hz, ^{3}J(C2,NCH_3) = 3.1 Hz), 141.9 (C-8a, ^{3}J(C8a,H5) = 7.6 Hz, ^{3}J(C8a,H7) = 9.5 Hz, ^{3}J(C8a,NCH_3) = 2.9 Hz), 135.9 (Ph C-1, ^{3}J(Ph C1,H3) = 3.9 Hz), 132.3 (C-7), 129.6 (Ph C-4), 128.8 (Ph C-3,5), 128.5 (Ph C-2,6), 126.8 (C-4a, ^{3}J(C4a,H3) = 4.8 Hz), 126.7 (C-5, ^{3}J(C5,H7) = 7.8 Hz), 123.6 (C-6), 115.9 (C-8), 112.7 (C-3, ^{1}J(C3,H3) = 165.8 Hz), 37.2 (N-CH_3, ^{1}J = 140.1 Hz); ^{15}N-NMR (50 MHz): δ −262.1 (N-1); MS *m/z* (%): 235 (M^+, 100), 207 ($[M–C=O]^+$, 100), 206 ($[M–H,–C=O]^+$, 55), 102 (40), 77 ($[C_6H_5]^+$, 47).

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