Synthesis of pyrimidine annulated furothiopyrans — An efficient sequential and tandem catalyzed Claisen rearrangement – intramolecular hydroaryloxylation

K.C. Majumdar and S.K. Chattopadhyay

Abstract: Regioselective synthesis of a hitherto unreported furothiopyran moiety fused at the C-5 and C-6 positions of a pyrimidine heterocycle was achieved by the application of sequential Claisen rearrangement in which a second aromatic Claisen rearrangement and intramolecular hydroaryloxylation were catalyzed by aluminum chloride. The second aromatic Claisen rearrangement step was also studied under thermal conditions to give mostly isomerized exocyclic compounds. The precursor endocyclic compounds were synthesized by thermal [3,3] sigmatropic rearrangement of the corresponding sulfide.

Key words: aluminum chloride, sequential Claisen rearrangement, hydroaryloxylation, furothiopyran, pyrimidine.

Résumé : Faisant appel à une séquence des réarrangements de Claisen dans laquelle le deuxième réarrangement aromatique de Claisen et l'hydroaryloxylation sont catalysées par du chlorure d'aluminium, on a effectué la synthèse régiosélective qui n'avait pas été réalisée jusqu'à maintenant de la portion furothiopyrane condensée aux positions C-5 et C-6 de l'hétérocycle pyrimidine. On a aussi étudié le deuxième réarrangement de Claisen dans des conditions thermiques et il conduit principalement à des composés isomérisés exocycliques. On a réalisé la synthèse des composés endocycliques précurseurs en procédant à un réarrangement thermique [3,3] du sulfure correspondant.

Mots clés : chlorure d'aluminium, séquence de réarrangements de Claisen, hydroaryloxylation, furothiopyrane, pyrimidine.

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Introduction

Claisen rearrangement, since its discovery in 1912, has been proven to be one of the preeminent methodologies for the construction of carbon–carbon bonds in synthetic organic chemistry (1). A high level of stereocontrol, securing its widespread use in the synthesis of natural products and medicinal agents, can be achieved by this concerted [3,3] sigmatropic rearrangement (1). The traditional methodologies for accomplishing the rearrangement are based on thermally controlled procedure; however, the development of new methodologies employing a catalyst in the Claisen rearrangement have been the focus of many recent investigations in organic synthesis (2). Over the past few years we embarked on the development of new synthetic methodologies for the synthesis of novel heterocycles based on sequential Claisen rearrangement (3). During the investigation of the synthetic perspectives of the aforementioned thermally controlled rearrangement, we observed interesting results in the second Claisen rearrangement (3*a*, 3*b*). We sought to extend this chemistry to encompass a new synthetic route leading to a [6,5]-furothiopyran moiety.

The incorporation of the pyrimidine moiety in the present investigation is due to its wide biological and pharmacological activities (4). Numerous pyrimidine- and uracil-based molecules, e.g., AZT, DDC, and BVDU, have been known to be active agents against cancer and the AIDS virus (5). Some pyrido-[2,3-*d*]-pyrimidines exhibit antibacterial activity and antitumor activities (6). Extensive investigations have been carried out with these heterocyclic systems (7). In contrast, a few examples dealing with the chemistry of an 8-sulfurisostere, thiopyrano-[2,3-*d*]-pyrimidine system, which may have potential biological activity, are reported in the literature (8). This has prompted us to undertake a study of sequential Claisen rearrangement with the development of broadly useful new routes to a [6,5]-furothiopyran system fused at the C-5 and C-6 positions of the pyrimidine moiety. Herein we report the results of our investigation.

Results and discussion

The requisite sulfides (**3a**–**3g**) for the present investigation were synthesized in 75%–92% yields by phase-transfer-catalyzed alkylation of 6-mercaptouracil (**2**) with different 1-chloro-4-aryloxybut-2-ynes. Compound **2** was in turn prepared by the reaction of 6-chlorouracil (**1**) with NaSH in dry ethanol at 0 °C. Compounds **3a**–**3g** were all solid and were

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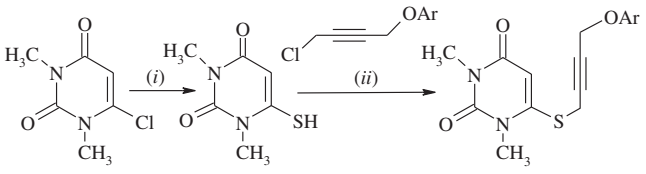
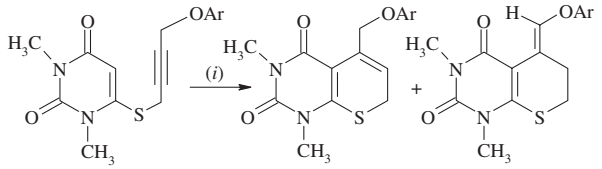
Scheme 1. Reagents and conditions: (*i*) NaSH, EtOH, 0 °C, stirring, 7 h; (*ii*) CH_2Cl_2, 1% aq. NaOH sol. BTEAC, rt, stirring, 12 h.



3a) Ar = 4-$MeOC_6H_4$ 3d) Ar = 2,3-$Me_2C_6H_4$ g) Ar = 2,4-$Me_2C_6H_3$
3b) Ar = 3,5-Me_2-4-ClC_6H_2 3e) Ar = 3,5-$Me_2C_6H_4$
3c) Ar = 2-ClC_6H_4 3f) Ar = 2,4-$Cl_2C_6H_3$

Scheme 2. Reagents and conditions: (*i*) chlorobenzene, reflux, 4 h.



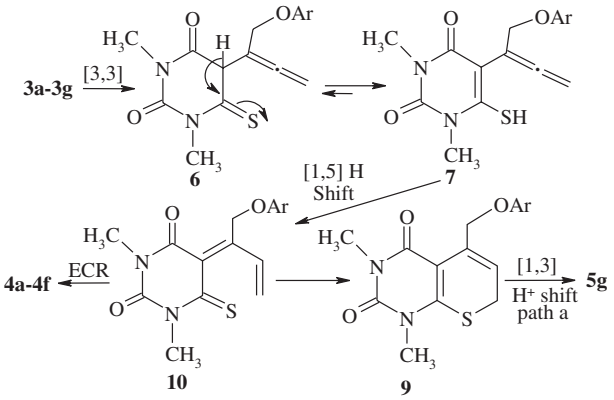
	Ar	Yield (%)
4a	4-$MeOC_6H_4$	94
4b	3,5Me_2-4-ClC_6H_2	88
4c	2-ClC_6H_4	92
4d	2,3-$Me_2C_6H_4$	88
4e	3,5-$Me_2C_6H_4$	85
4f	2,4-$Cl_2C_6H_3$	95
5g	2,4-$Me_2C_6H_3$	88

characterized from their elemental analyses and spectral data (Scheme 1).

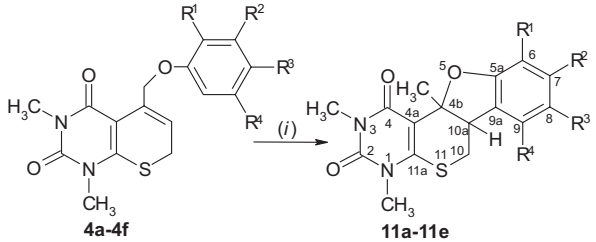
The substrates **3a**–**3g** possess two potential sites for [3,3] sigmatropic rearrangement: a vinyl propargyl sulfide moiety and an aryl propargyl ether moiety. Compounds with this structural feature offer an excellent scope for the study on the competition between oxy- and thio-Claisen rearrangement along with the synthesis of new heterocycles through [3,3] sigmatropic rearrangement. To accomplish the thio-Claisen rearrangement, the substrate **3a** was first subjected to thermal rearrangement by refluxing in the lower boiling solvent chlorobenzene (132 °C) for 4 h to give crystalline solid **4a** in 94% yield (Scheme 2). Elemental analysis and spectral data of compound **4a** established its endocyclic nature, which is necessary for further Claisen rearrangement. Encouraged by the initial accomplishment, the remaining substrates (**3b**–**3g**) were similarly treated to afford **4b**–**4f** (84%–95% yield) and **5g** (88% yield) (Scheme 2). The exocyclic nature of the product **5g** was established from the high field (300 MHz) ^{1}H NMR spectrum. The ^{13}C NMR chemical shift values of compound **5g** and multiplicities were assigned from the DEPT experiment. The DEPT spectrum obtained showed 10 protonated carbons, four -CH_3, two >CH_2, and four >CH-.

The mechanistic rationalization (Scheme 3) for the formation of compounds **4a**–**4f** and **5g** can be explained by assuming initial [3,3] sigmatropic rearrangement of **3a**–**3g**, followed by rapid enolization to form the allenylene–thiol intermediate **7**, which then undergoes a [1,5]-hydrogen shift, followed by 6π electrocyclic ring closure to give the products **4a**–**4f**. The product **5g** may also be formed because of the [1,3] protropic rearrangement of the thermally unstable endocyclic compound **9** to afford **5g** (Scheme 3). It is noteworthy that all the substrates **3a**–**3f**, except **3g**, regioselectively afforded exclusive products **4a**–**4f** in excellent yield. A lesser energy requirement for the sigmatropic rearrangement in vinyl propargyl sulfide systems (9) compared with that in aryl propargyl ether moieties (10) might be responsible for this excellent regioselectivity.

Scheme 3.



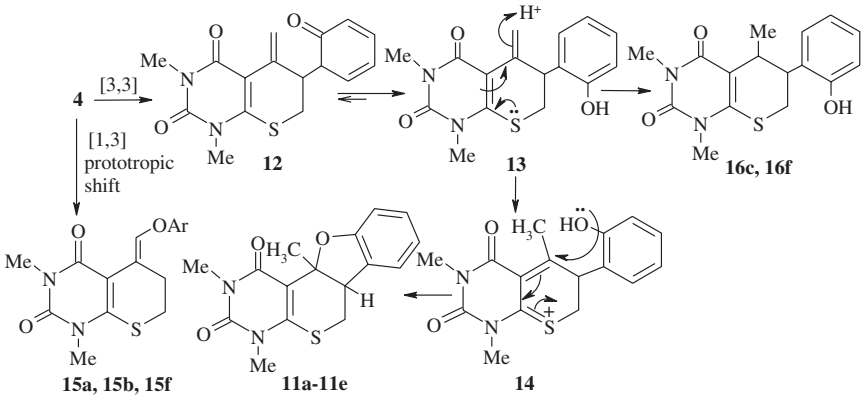
Scheme 4. Reagents and conditions: (*i*) $AlCl_3$, CH_2Cl_2, rt, 1 h.



	R^1	R^2	R^3	R^4	Yield (%)
11a	H	H	OMe	H	96
11b	H	Me	Cl	Me	90
11c	Cl	H	H	H	92
11d	Me	Me	H	H	94
11e	H	Me	Me	H	90
11f	Cl	H	Cl	H	—

Compound **4** still posses an allyl aryl ether segment requisite for further study on the [3,3] sigmatropic rearrangement. In our earlier efforts, we found different regioselectivity with different substrates in the thermal second aromatic Claisen rearrangement (3). In some cases, [1,3] prototropic rearrangement was an important side reaction along with [3,3] sigmatropic rearrangement (11). To circumvent this unwanted problem in thermal second Claisen rearrangement, we turned our attention to the Lewis acid catalyzed Claisen rearrangement approach (2). Among the different Lewis acid catalysts available for the aromatic oxy-Claisen rearrangement, aluminum chloride and its different derivatives have received the most attention (1*d*, 2*a*). So we subjected compound **4a** to catalyzed Claisen rearrangement using aluminum chloride as the catalyst in dry dichloromethane at room temperature to afford the cyclized product **11a** (96% yield), which was characterized by its elemental analysis and spectral data. To test the generality of the reaction, other substrates (**4b**–**4f**) were similarly treated to afford the cyclized

Scheme 5.

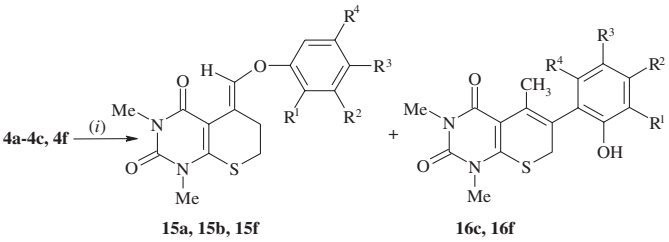


products **11b–11e** (90%–96% yield) (Scheme 4). No cyclized product corresponding to **11** was obtained in the case of compound **4f**, as several other unwanted products (TLC observation) were formed during the reaction that were not characterized. We have tried the reaction with other Lewis acids, e.g., $BF_3{\cdot}Et_2O$ and Cp_2TiCl_2. In the case of Cp_2TiCl_2, no reaction occurred. The reaction is quite sluggish with $BF_3{\cdot}Et_2O$ with the formation of undesired products, which were not characterized.

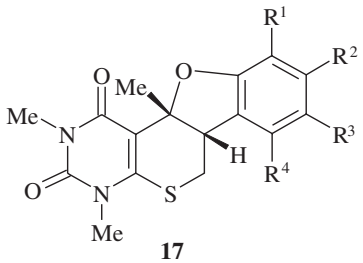
The conversion of **4** into **11** may take a pathway similar to that observed in thermal Claisen rearrangement via the 2-allylphenol intermediate **13** (Scheme 5). From the literature it may be assumed that this transformation may be a charge-induced Claisen rearrangement similar in mechanism to the process reported for BCl_3 by Schmid and co-workers (12). The reaction may be facilitated by the coordination of the oxygen atom, which itself is a strong Lewis base, to the hard Lewis acid, aluminum chloride. The hydroaryloxylation step leading to the formation of the benzofuran moiety may occur by the addition of H^+ to the position of the homothioenol ether followed by simultaneous conjugate addition of a phenolic OH group to the resulting thionium ion. To isolate the 2-allylphenol intermediate **13**, we tried the reaction in the presence of additives such as PPh_3 or amine base, e.g., morpholine and triethylamine. There too no reaction was observed. It is noteworthy that in the present investigation aluminium chloride promotes both Claisen rearrangement and hydroaryloxylation and the unusual ring contraction pertinent to the $AlCl_3$-catalyzed oxy-Claisen rearrangement (13) was unobserved, mainly owing to the soft basic character of sulfur being unable to form a complex with aluminum chloride. The overall regioselectivity of the catalyzed reaction leading to the formation of tetracyclic heterocycles **11** is excellent.

We have also examined the thermal second Claisen rearrangement of the same substrates. For compounds **4a**–**4c** and **4f**, when subjected to thermal rearrangement in refluxing dichlorobenzene in the presence of *N*,*N*-diethylaniline for 8 h (Scheme 6), the observed results were quite interesting as compounds **4a** and **4b** exclusively gave the exocyclic compounds **15a** and **15b** in 40% and 45% yield, respectively, and from compound **4c** the endocyclic phenolic compound **16c** was obtained in 10% yield. Both products **15f** and **16f** were isolated; in the case of substrate **4f**, in almost 38% and 25% yield, respectively. In each case, an appreciable amount of starting material was recovered. We have also attempted the reaction in dichlorobenzene and *N*,*N*-diethylaniline separately. There too the same products were obtained in very poor yield. All the compounds were solid and were characterized from their elemental analysis and spectral data.

Scheme 6. Reagents and conditions: (*i*) dichlorobenzene, *N*,*N*-diethylaniline, reflux, 8 h.



The formation of products **15a**, **15b**, **15f**, **16c**, and **16f** can be mechanistically interpreted as follows (Scheme 5). Compounds **15a**, **15b**, and **15f** can be obtained by [1,3] prototropic rearrangement in compounds **4a**, **4b**, and **4f**. Initial [3,3] sigmatropic rearrangement followed by rapid tautomerization may result in the formation of **16c** and **16f** from **4c** and **4f** via the 2-allyl phenol intermediate **13**. In the present investigation, the [1,3] prototropic rearrangement with the formation of an exocyclic compound as the major product is quite unusual. In two cases we were successful in isolating the endocyclic phenolic product, but in very poor yield. The presence of different substituents in the benzene nuclei of compounds **4a**, **4b**, and **4f** thus results in a change in the mode of rearrangement. However, the role of the substituent in the formation of products **15** and **16** is not clear. It may be conceivable that the thermal stability of the resulting compounds might be responsible for their formation.



From a molecular modelling (Dreiding model) study and comparison with the stereochemistry of natural pterocarpin (14), the stereochemistry of the ring fusion in the tetracyclic system may be assumed to be cis and is represented as **17**.

In conclusion, we have demonstrated a broadly useful new route based on a sequential thermal plus tandem-catalyzed Claisen rearrangement – intramolecular hydroaryloxylation approach that we expect to provide an expedient avenue for the synthesis of a furothiopyran system, quite similar to the petrocarpin system. This protocol is complementary to our preliminary thermal methodology. The mild reaction conditions and compatibility with various substituents on the aromatic ring make this route a significant addition to the existing methodologies for the synthesis of a synthetically challenging furothiopyran moiety fused with other heterocycles.

Experimental

General remarks

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a PerkinElmer L120-000A spectrometer (γ_{max} in cm^{-1}) using samples as neat liquids, solid samples were recorded in KBr disks, and UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401PC spectrophotometer (λ_{max} in nm). ^1H NMR (300 MHz, 500 MHz) spectra were recorded on Bruker DPX-300 and Bruker DRX-500 spectrometers in $CDCl_3$ (chemical shifts in δ) with TMS as the internal standard. Elemental analyses and mass spectra were recorded on a JEOL JMS600 instrument. Silica gel (60–120 mesh, Spectrochem, India) was used for chromatographic separation. Silica gel G (E-Merck, India) was used for TLC. Petroleum ether refers to the fraction boiling between 60 and 80 °C.

The 1-aryloxy-4-chlorobut-2-ynes were prepared according to the published procedure (15).

General procedure for the preparation of 6-mercaptouracil (2)

To a magnetically stirred solution of NaSH (1.2 g, 20.8 mmol) in dry ethanol (50 mL), a solution of 6-chlorouracil (**1**) (1.5 g, 8.6 mmol) in dry ethanol (50 mL) was added dropwise for a period of 2 h. After the addition was complete, the stirring was continued for an additional 4 h. Ethanol was removed under vacuum at room temperature. The residue was acidified with concd. HCl (25 mL). This was then extracted with CH_2Cl_2 (4 × 20 mL). The dichloromethane solution was washed with water (2 × 10 mL) and dried (Na_2SO_4). Attempts to evaporate dichloromethane led to considerable decomposition of compound **2**. Therefore, this dichloromethane solution was directly used in the next phase-transfer-catalyzed alkylation step.

General procedure for the preparation of sulfides (3a–3g)

To a stirred solution of 6-mercaptouracil (**2**) (obtained from 1.5 g, 8.6 mmol of compound **1**) and 1-aryloxy-4-chlorobut-2-yne (8.6 mmol) in dichloromethane (100 mL), a solution of benzyltriethylammonium chloride (BTEAC) (0.5 g, 1.8 mmol) in 1% aq. NaOH solution (100 mL) was added, and the mixture was stirred for 12 h at room temperature. It was then diluted with water (25 mL). The dichloromethane layer was then separated and washed with 2 N HCl (25 mL), brine (25 mL), and water (25 mL), and dried (Na_2SO_4). The crude mass obtained upon evaporation of CH_2Cl_2 was subjected to column chromatography. Elution with petroleum ether – ethyl acetate (7:3) afforded the products **3a**–**3g**.

Compound 3a

Yield: 84%; brown solid, mp 70 °C. IR (KBr, cm^{-1}) ν_{max}: 1645, 1702, 2963. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 3.34 (s, 3H, -*N*CH_3), 3.45 (s, 3H, -*N*CH_3), 3.69 (s, 2H, -SCH_2), 3.77 (s, 2H, -OCH_3), 4.63 (s, 2H, -OCH_2), 5.66 (s, 1H, =CH), 6.81–6.88 (m, 4H, ArH). MS *m*/*z*: 346 (M^+). Anal. calcd. for $C_{17}H_{18}N_2O_4S$ (%): C 58.95, H 5.20, N 8.09; found: C 59.15, H 5.44, N 8.25.

Compound 3b

Yield: 78%; brown solid, mp 130 °C. IR (KBr, cm^{-1}) ν_{max}: 1644, 1706, 2930. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 2.33 (s, 6H, Ar$(CH_3)_2$), 3.33 (s, 3H, -*N*CH_3), 3.45 (s, 3H, -*N*CH_3), 3.70 (s, 2H, -SCH_2), 4.65 (s, 2H, -OCH_2), 5.65 (s, 1H, =CH), 6.66 (s, 2H, ArH). MS *m*/*z*: 378, 380 (M^+). Anal. calcd. for $C_{18}H_{19}N_2O_3SCl$ (%): C 56.99, H 5.01, N 7.38; found: C 57.23, H 5.18, N 7.59.

Compound 3c

Yield: 85%; brown solid, mp 116 °C. IR (KBr, cm^{-1}) ν_{max}: 1651, 1693, 2942. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 3.34 (s, 3H, -*N*CH_3), 3.44 (s, 3H, -*N*CH_3), 3.70 (s, 2H, -SCH_2), 4.79 (s, 2H, -OCH_2), 5.65 (s, 1H, =CH), 6.92–7.37 (m, 4H, ArH). MS *m*/*z*: 350, 352 (M^+). Anal. calcd. for $C_{16}H_{15}N_2O_3SCl$ (%): C 54.70, H 4.27, N 7.97; found: C 54.89, H 4.49, N 8.14.

Compound 3d

Yield: 78%; brown solid, mp 92 °C. IR (KBr, cm^{-1}) ν_{max}: 1630, 1691, 2949. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 2.14 (s, 3H, -ArCH_3), 2.26 (s, 3H, -ArCH_3), 3.34 (s, 3H, -*N*CH_3), 3.44 (s, 3H, -*N*CH_3), 3.70 (s, 2H, -SCH_2), 4.69 (s, 2H, -OCH_2), 5.66 (s, 1H, =CH), 6.74–7.04 (m, 4H, ArH). MS *m*/*z*: 344 (M^+). Anal. calcd. for $C_{18}H_{20}N_2O_3S$ (%): C 62.79, H 5.81, N 8.13; found: C 62.97, H 6.03, N 8.36.

Compound 3e

Yield: 82%; brown solid, mp 94 °C. IR (KBr, cm^{-1}) ν_{max}: 1634, 1697, 2953. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 2.28 (s, 6H, -Ar$(CH_3)_2$), 3.34 (s, 3H, -*N*CH_3), 3.45 (s, 3H, -*N*CH_3), 3.71 (s, 2H, -SCH_2), 4.66 (s, 2H, -OCH_2), 5.66 (s, 1H, =CH), 6.55 (s, 2H, ArH), 6.63 (s, 1H, ArH). MS *m*/*z*: 344 (M^+). Anal. calcd. for $C_{18}H_{20}N_2O_3S$ (%): C 62.79, H 5.81, N 8.13; found: C 63.01, H 5.97, N 8.30.

Compound 3f

Yield: 92%; brown solid, mp 126 °C. IR (KBr, cm^{-1}) ν_{max}: 1645, 1702, 2964. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 3.35 (s, 3H, -*N*CH_3), 3.45 (s, 3H, -*N*CH_3), 3.70 (s, 2H, -SCH_2), 4.77 (s, 2H, -OCH_2), 5.64 (s, 1H, =CH), 6.92–7.37 (m, 3H, ArH). MS *m*/*z*: 384, 386, 388 (M^+). Anal. calcd. for $C_{16}H_{14}N_2O_3SCl_2$ (%): C 49.87, H 3.63, N 7.27; found: C 50.09, H 3.81, N 7.46.

Compound 3g

Yield: 84%; brown solid, mp 92 °C. IR (KBr, cm^{-1}) ν_{max}: 1656, 1696, 2917. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 2.18 (s, 3H, -ArCH_3), 2.25 (s, 3H, -ArCH_3), 3.34 (s, 3H, -*N*CH_3), 3.44 (s, 3H, -*N*CH_3), 3.68 (s, 2H, -SCH_2), 4.67 (s, 2H, -OCH_2), 5.66 (s, 1H, =CH), 6.75–6.94 (m, 3H, ArH). MS *m/z*: 344 (M^+). Anal. calcd. for $C_{18}H_{20}N_2O_3S$ (%): C 62.79, H 5.81, N 8.13; found: C 62.99, H 6.01, N 8.32.

General procedure for the preparation of 4a–4f and 5g

Compounds **3a**–**3h** (250 mg, 0.72 mmol) were refluxed in chlorobenzene (10 mL) for 5 h. The reaction mixture was then cooled and directly subjected to column chromatography over silica gel. Chlorobenzene was eluted out with petroleum ether. On eluting the column with petroleum ether – ethyl acetate (4:1), compounds **4a**–**4g** and **5h** were obtained. All compounds were recrystalized from dichloromethane – petroleum ether.

Compound 4a

Yield: 94%; white solid, mp 102 °C. IR (KBr, cm^{-1}) ν_{max}: 1633, 1705, 2928. ^1H NMR ($CDCl_3$, 500 MHz) δ_H: 3.36 (s, 3H, -*N*CH_3), 3.39 (d, 2H, *J* = 6 Hz, -SCH_2), 3.56 (s, 3H, -*N*CH_3), 3.75 (s, 3H, -OCH_3), 5.04 (s, 2H, -OCH_2), 5.86 (t, 1H, *J* = 6 Hz, =CH), 6.78–6.88 (m, 4H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C: 26.60, 28.62, 33.76, 56.11, 69.71, 107.74, 111.45, 114.45, 116.51, 136.53, 151.16, 153.18, 154.34, 155.19, 159.78. MS *m/z*: 346 (M^+). Anal. calcd. for $C_{17}H_{18}N_2O_4S$ (%): C 58.95, H 5.20, N 8.09; found: C 59.13, H 5.42, N 8.32.

Compound 4b

Yield: 88%; white solid, mp 148 °C. IR (KBr, cm^{-1}) ν_{max}: 1664, 1702, 2948. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 2.32 (s, 6H, -Ar(CH_3)$_2$), 3.36 (s, 3H, -*N*CH_3), 3.40 (d, 2H, *J* = 6 Hz, -SCH_2), 3.56 (s, 3H, -*N*CH_3), 5.03 (s, 2H, -OCH_2), 5.84 (t, 1H, *J* = 6 Hz, =CH), 6.66 (s, 2H, ArH). MS *m/z*: 378, 380 (M^+). Anal. calcd. for $C_{18}H_{19}N_2O_3SCl$ (%): C 56.99, H 5.01, N 7.38; found: C 57.17, H 5.23, N 7.62.

Compound 4c

Yield: 92%; white solid, mp 152 °C. IR (KBr, cm^{-1}) ν_{max}: 1647, 1696, 2892. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 3.37 (s, 3H, -*N*CH_3), 3.43 (d, 2H, *J* = 6 Hz, -SCH_2), 3.56 (s, 3H, -*N*CH_3), 5.16 (s, 2H, -OCH_2), 5.99 (t, 1H, *J* = 6 Hz, =CH), 6.88–7.35 (m, 4H, ArH). MS *m/z*: 350, 352 (M^+). Anal. calcd. for $C_{16}H_{15}N_2O_3SCl$ (%): C 54.70, H 4.27, N 7.97; found: C 54.92, H 4.45, N 8.18.

Compound 4d

Yield: 88%; white solid, mp 152 °C. IR (KBr, cm^{-1}) ν_{max}: 1646, 1696, 2917. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 2.15 (s, 3H, -ArCH_3), 2.26 (s, 3H, -ArCH_3), 3.37 (s, 3H, -*N*CH_3), 3.41 (d, 2H, *J* = 6 Hz, -SCH_2), 3.56 (s, 3H, -NCH_3), 5.07 (s, 2H, -OCH_2), 5.91 (t, 1H, *J* = 6 Hz, =CH), 6.73–7.03 (m, 3H, ArH). MS *m/z*: 344 (M^+). Anal. calcd. for $C_{18}H_{20}N_2O_3S$ (%): C 62.79, H 5.81, N 8.13; found: C 63.03, H 6.01, N 8.31.

Compound 4e

Yield: 85%; white solid, mp 134 °C. IR (KBr, cm^{-1}) ν_{max}: 1655, 1706, 2911. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 2.27 (s, 3H, -CH_3), 3.37 (s, 3H, -*N*CH_3), 3.40 (d, 2H, *J* = 6 Hz, -SCH_2), 3.56 (s, 3H, -*N*CH_3), 5.05 (s, 2H, -OCH_2), 5.88 (t, 1H, *J* = 6 Hz, =CH), 6.56 (s, 2H, ArH), 6.58 (s, 1H, ArH). MS *m/z*: 344 (M^+). Anal. calcd. for $C_{18}H_{20}N_2O_3S$ (%): C 62.79, H 5.81, N 8.13; found: C 62.95, H 6.05, N 8.32.

Compound 4f

Yield: 95%; white solid, mp 108 °C. IR (KBr, cm^{-1}) ν_{max}: 1647, 1702, 2944. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 3.36 (s, 3H, -*N*CH_3), 3.42 (d, 2H, *J* = 6 Hz, -SCH_2), 3.57 (s, 3H, -*N*CH_3), 5.13 (s, 2H, -OCH_2), 5.93 (t, 1H, *J* = 6 Hz, =CH), 6.89–7.35 (m, 3H, ArH). MS *m/z*: 384, 386, 388 (M^+). Anal. calcd. for $C_{16}H_{14}N_2O_3SCl_2$ (%): C 49.87, H 3.63, N 7.27; found: C 50.07, H 3.85, N 7.44.

Compound 5g

Yield: 88%; white solid, mp 128 °C. IR (KBr, cm^{-1}) ν_{max}: 1657, 1708, 2921. ^1H NMR ($CDCl_3$, 300 MHz) δ_H: 2.24 (s, 3H, -ArCH_3), 2.27 (s, 3H, -ArCH_3), 2.96–2.99 (m, 2H, =C-CH_2), 3.11–3.14 (m, 2H, -SCH_2), 3.37 (s, 3H, -*N*CH_3), 3.56 (s, 3H, -*N*CH_3), 6.94–6.97 (m, 3H, ArH), 8.03 (s, 1H, =CH). MS *m/z*: 344 (M^+). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C: 16.65, 20.84, 26.64, 33.77, 68.86, 107.87, 110.63, 112.37, 126.87, 127.37, 130.03, 131.78, 136.65, 151.76, 154.90, 155.13, 159.82. Anal. calcd. for $C_{18}H_{20}N_2O_3S$ (%): C 62.79, H 5.81, N 8.13; found: C 63.00, H 5.99, N 8.34.

General procedure for the aluminum chloride catalyzed reaction

To a stirred solution of the compounds **4a**–**4f** (0.28 mmol) in dry dichloromethane (10 mL), anhydrous aluminium chloride (36 mg, 0.28 mmol) was added at room temperature. The stirring was continued for about 1 h. After completion of the reaction, 1% HCl solution (5 mL) was added. The reaction mixture was then extracted with dichloromethane (2 × 10 mL). The organic layer was washed with water (2 × 10 mL) and brine (10 mL) and dried (Na_2SO_4). Dichloromethane was distilled off and the residue obtained was subjected to flash chromatography. On eluting the column with ethyl acetate – petroleum ether (1:10), compounds **11a**–**11e** were obtained as white solids. All compounds were recrystalized from dichloromethane.

Compound 11a

Yield: 96%; white solid, mp 132 °C. IR (KBr, cm^{-1}) ν_{max}: 1646, 1701, 2927. ^1H NMR ($CDCl_3$, 500 MHz) δ_H: 1.78 (s, 3H, C_{4b}-CH_3), 2.80 (dd, 1H, *J* = 11, 13 Hz, C_{10}-H), 3.02 (dd, 1H, *J* = 3, 13 Hz, C_{10}-H), 3.29 (dd, 1H, *J* = 3, 11 Hz, C_{10a}-H), 3.39 (s, 3H, -*N*CH_3), 3.51 (s, 3H, -*N*CH_3), 3.77 (s, 3H, -OCH_3), 6.72–6.86 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C: 25.05, 28.57, 30.20, 32.89, 51.26, 56.41, 86.30, 108.54, 111.04, 111.69, 111.53, 129.13, 151.19, 151.77, 153.09, 154.67, 160.39. MS *m/z*: 346 (M^+). Anal. calcd. for $C_{17}H_{18}N_2O_4S$ (%): C 58.95, H 5.20, N 8.09; found: C 59.18, H 5.34, N 8.27.

Compound 11b

Yield: 90%; white solid, mp 102 °C. IR (KBr, cm^{-1}) ν_{max}: 1640, 1700, 2924, 2976. ^1H NMR ($CDCl_3$, 500 MHz) δ_H: 1.71 (s, 3H, C_{4b}-CH_3), 2.32 (s, 3H, Ar-CH_3), 2.37 (s, 3H, Ar-CH_3), 2.62 (dd, 1H, *J* = 11, 13 Hz, C_{10}-H), 2.93 (dd, 1H,

J = 3, 13 Hz, C_{10}-H), 3.22 (dd, 1H, J = 3, 11 Hz, C_{10a}-H), 3.40 (s, 3H, -NCH_3), 3.54 (s, 3H, -NCH_3), 6.71 (s, 1H, ArH). MS *m*/*z*: 378, 380 (M^+). Anal. calcd. for $C_{18}H_{19}N_2O_3SCl$ (%): C 56.99, H 5.01, N 7.38; found: C 57.19, H 5.29, N 7.62.

Compound 11c

Yield: 92%; white solid, mp 198 °C. IR (KBr, cm^{-1}) ν_{max}: 1629, 1692, 2895. ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 1.83 (s, 3H, C_{4b}-CH_3), 2.82 (dd, 1H, J = 11, 13 Hz, C_{10}-H), 3.02 (dd, 1H, J = 3, 13 Hz, C_{10}-H), 3.39 (s, 3H, -NCH_3), 3.40 (dd, 1H, J = 3, 11 Hz, C_{10a}-H), 3.51 (s, 3H, -NCH_3), 6.83–6.86 (m, 1H, ArH), 7.12 (d, 1H, J = 7 Hz, Ar-H), 7.19 (d, 1H, J = 7 Hz, Ar-H). MS *m*/*z*: 350, 352 (M^+). Anal. calcd. for $C_{16}H_{15}N_2O_3SCl$ (%): C 54.70, H 4.27, N 7.97; found: C 54.92, H 4.46, N 8.21.

Compound 11d

Yield: 94%; white solid, mp 216 °C. IR (KBr, cm^{-1}) ν_{max}: 1651, 1702, 2926. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H: 1.76 (s, 3H, C_{4b}-CH_3), 2.16 (s, 3H, Ar-CH_3), 2.24 (s, 3H, Ar-CH_3), 2.76 (dd, 1H, J = 11, 13 Hz, C_{10}-H), 2.99 (dd, 1H, J = 3, 13 Hz, C_{10a}-H), 3.28 (dd, 1H, J = 3, 11 Hz, C_{10a}-H), 3.39 (s, 3H, -NCH_3), 3.51 (s, 3H, -NCH_3), 6.70 (d, 1H, J = 7 Hz, ArH), 6.95 (d, 1H, J = 7 Hz, ArH). ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C: 12.35, 19.93, 25.18, 28.55, 30.29, 32.85, 51.16, 85.79, 108.72, 120.33, 121.07, 122.38, 125.15, 138.71, 151.31, 153.03, 156.46, 160.23. MS *m*/*z*: 344 (M^+). Anal. calcd. for $C_{18}H_{20}N_2O_3S$ (%): C 62.79, H 5.81, N 8.13; found: C 62.95, H 6.03, N 8.32.

Compound 11e

Yield: 90%; white solid, mp 188 °C. IR (KBr, cm^{-1}) ν_{max}: 1643, 1700, 2923. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H: 1.71 (s, 3H, C_{4b}-CH_3), 2.27 (s, 3H, Ar-CH_3), 2.31 (s, 3H, Ar-CH_3), 2.63 (dd, 1H, J = 11, 13 Hz, C_{10}-H), 2.96 (dd, 1H, J = 3, 13 Hz, C_{10}-H), 3.21 (dd, 1H, J = 3, 11 Hz, C_{10a}-H), 3.40 (s, 3H, -NCH_3), 3.53 (s, 3H, -NCH_3), 6.54 (s, 1H, Ar-H), 6.61 (s, 1H, Ar-H). MS *m*/*z*: 344 (M^+). Anal. calcd. for $C_{18}H_{20}N_2O_3S$ (%): C 62.79, H 5.81, N 8.13; found: C 63.00, H 5.98, N 8.33.

General procedure for the preparation of 15a, 15b, 15f, 16c, and 16f

Compounds **4a**–**4c** and **4f** (100 mg, 0.28 mmol) were refluxed in dichlorobenzene (10 mL) in the presence of *N*,*N*-diethylaniline (2 mL) for 8 h. The reaction mixture was then cooled and directly subjected to column chromatography over silica gel. Dichlorobenzene along with *N*,*N*-diethylaniline was eluted out with petroleum ether. On eluting the column with petroleum ether – ethyl acetate (4:1), compounds **15a**, **15b**, **15f**, **16c**, and **16f** were obtained. All compounds were solid and were recrystalized from dichloromethane – petroleum ether.

Compound 15a

Yield: 40%; white solid, mp 148 °C. IR (KBr, cm^{-1}) ν_{max}: 1647, 1707, 2932. ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 2.93–2.96 (m, 2H, =C-CH_2), 3.11–3.13 (m, 2H, -SCH_2), 3.39 (s, 3H, -NCH_3), 3.55 (s, 3H, -NCH_3), 3.78 (s, 3H, -OCH_3), 6.83–7.25 (m, 4H, ArH), 8.02 (s, 1H, =CH). MS *m*/*z*: 346 (M^+). Anal. calcd. for $C_{17}H_{18}N_2O_4S$ (%): C 58.95, H 5.20, N 8.09; found: C 59.17, H 5.39, N 8.31.

Compound 15b

Yield: 45%; white solid, mp 168 °C. IR (KBr, cm^{-1}) ν_{max}: 1629, 1697, 2934. ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H: 2.36 (s, 6H, -Ar$(CH_3)_2$), 2.91–2.95 (m, 2H, =C-CH_2), 3.09–3.11 (m, 2H, SCH_2), 3.40 (s, 3H, -NCH_3), 3.54 (s, 3H, -NCH_3), 6.81 (S, 2H, ArH), 8.05 (s, 1H, =CH). MS *m*/*z*: 378, 380 (M^+). Anal. calcd. for $C_{18}H_{19}N_2O_3SCl$ (%): C 56.99, H 5.01, N 7.38; found: C 57.17, H 5.22, N 7.64.

Compound 15f

Yield: 38%; white solid, mp 174 °C. IR (KBr, cm^{-1}) ν_{max}: 1632, 1699, 2917. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H: 2.97–3.01 (m, 2H, =C-CH_2), 3.13–3.16 (m, 2H, -SCH_2), 3.39 (s, 3H, -NCH_3), 3.55 (s, 3H, -NCH_3), 7.11–7.39 (m, 3H, ArH), 8.07 (s, 1H, =CH). MS *m*/*z*: 384, 386, 388 (M^+). Anal. calcd. for $C_{16}H_{14}N_2O_3SCl_2$ (%): C 49.87, H 3.64, N 7.27; found: C 50.11, H 3.83, N 7.48.

Compound 16c

Yield: 10%; white solid, mp 186 °C. IR (KBr, cm^{-1}) ν_{max}: 1648, 1698, 2927, 3322. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H: 2.06 (s, 3H, =C-CH_3), 3.40 (s, 3H, -NCH_3), 3.51 (s, 2H, -SCH_2), 3.57 (s, 3H, -NCH_3), 5.77 (s, 1H, -OH, D_2O exchangeable), 6.89–7.12 (m, 3H, ArH). MS *m*/*z*: 350, 352 (M^+). Anal. calcd. for $C_{16}H_{15}N_2O_3SCl$ (%): C 54.70, H 4.27, N 7.97; found: C 54.94, H 4.50, N 8.21.

Compound 16f

Yield: 25%; white solid, mp 208 °C. IR (KBr, cm^{-1}) ν_{max}: 1640, 1683, 2938, 3444. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H: 2.06 (s, 3H, =C-CH_3), 3.40 (s, 3H, -NCH_3), 3.48 (s, 2H, SCH_2), 3.57 (s, 3H, -NCH_3), 5.76 (s, 1H, -OH, D_2O exchangeable), 7.10 (d, 1H, J = 2 Hz, ArH), 7.31 (d, 1H, J = 2 Hz, ArH). MS *m*/*z*: 384, 386, 388 (M^+). Anal. calcd. for $C_{16}H_{14}N_2O_3SCl_2$ (%): C 49.87, H 3.64, N 7.27; found: C 50.03, H 3.87, N 7.49.

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