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PAPER

Trifluoroacetic acid catalyzed thiophenylmethylation and thioalkylmethylation of lactams and phenols via domino three-component reaction in water #¤

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An efficient one-pot trifluoroacetic acid catalyzed thiophenylmethylation and thioalkylmethylation of lactams, isatins and phenols via domino three-component coupling (3CC) with thiols and formaldehyde in water has been described. The developed protocol has wide substrate-scope for variety of thiols, lactams and isatins. Utility of the protocol for *ortho*-/*para*-thiophenylmethylation of phenols indicated that reaction proceeds through in-situ formation of thiophenylmethylium cation intermediate. LC-ESIMS-based mechanistic investigation further confirmed formation of this intermediate. For isatins, the *N*- versus *O*-thiophenylmethylation was confirmed by recording X-ray crystal structure of compound 4e. Thionaphthyl analog 3e exhibited significant antiproliferative activity in MCF-7 cells (IC_{50} 8 µM) via apoptosis-induction.

Introduction

Thiols are common building blocks in organic chemistry,[1] and plays important role in biological processes and also used in cell imaging and protein labelling.[2] The thiophenylmethylation reaction finds wide utility in organic chemistry and in the total synthesis of natural products.[3] Available protocols[3-4] involve use of organic solvents, and also the substrate-scope for these protocols has not been established.

The three-component coupling (3CC) of phenols with formaldehyde and styrene produced flavans **1** via [4+2]-Diels-Alder cycloaddition of in situ generated *ortho*-quinone methide with styrene.[5] Further, the 3CC of phenols with formaldehyde and lactam gave amidoalkyl products **2** through Mannich-type condensation.[6] As a continuation of these results, herein we investigated the reactivity of thiophenols in these 3CC reactions. This resulted in development of simple and efficient trifluoroacetic acid catalyzed one-pot protocol for thiophenylmethylation and thioalkylmethylation of lactams, isatins and phenols (Figure 1). With the advances in green chemistry, development of reactions in aqueous media is gaining tremendous importance.[7] The present protocol involves use of water as a reaction medium containing 0.1% TFA as a catalyst.

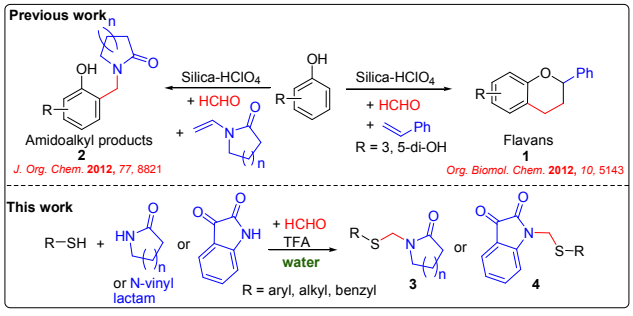

Figure 1. Our previous work on phenols (reaction of phenols with formaldehyde and styrene/ vinyl lactams) and the present work on thiols

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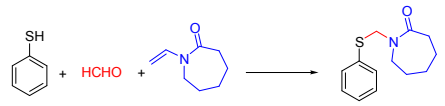
Results and discussion

The present study was initiated with the reaction of thiophenol **5a** with formaldehyde **6** and *N*-vinyl caprolactam **7** in presence of 50% w/w silica-$HClO_4$ (Table 1, entry 1). In this reaction, thiophenylmethylated lactam **3a** was formed and not the *ortho*-amidoalkyl product, as it was formed with phenols.[6] Similar to our earlier reports,[6, 8] it was noticed that the formation of product **3a** proceeds via acid and heat mediated devinylation of *N*-vinyl lactam **7**, which is followed by the 3CC of lactam with thiol **5a** and formaldehyde **6**. The preference of 3CC on SH-functionality over ortho-CH demonstrates higher nucleophilicity of SH- group than ortho-CH position in this reaction.

Next, the catalyst and solvent optimization study was carried out. The silica-$HClO_4$ catalyst produced 60% yield of product **3a** in ACN; however no improvements in reaction yield was observed when further solvent optimization was carried out using other solvents such as DCM, MeOH and DMF. Next, the reaction in acetic acid and formic acid was investigated, which produced poor yields (10 and 30%, respectively) of product **3a** (entries 2 and 3). In the presence of 10 mol% TFA in water, reaction moved efficiently producing 80% of the product (entry 4). Next,we attempted to use water as a reaction medium for this reaction. The use of 10% TFA in water produced **3a** in excellent yield (entry 5). Further optimization of the TFA amount and reaction time (entries 5-11) indicated that 0.1% TFA in water at 80 ºC for 30 min was able to produce desired product in good yield (entry 11). Continuation of reaction for additional time (entries 9 and 10) does not let to significant improvement in product yield. Thus, entry 11 was considered as optimized reaction condition. When the reaction was performed only in water, no product was formed (entry 12). As reported by Abdel-Ghany and coworkers,[4a] we attempted this 3CC reaction in dioxane as a solvent without addition of any catalyst; however no product was formed (entry 13). When this reaction was carried out using lactam instead of *N*-vinyl lactam using optimized reaction conditions (entry 11), similar results were obtained. Since *N*-vinyl lactam undergoes acid and heat-mediated devinylation to produce lactam, which participates in thiophenylmethylation reaction, all further investigations were performed using lactams.

As the reaction also proceeded without water as a medium, it is clear that water only acts a reaction medium and do not participate in reaction mechanism.

Table 1. Solvent and catalyst optimization studies[a]



Entry	Reaction medium	Temp. (ºC)	Time (h)	%Yield[b] of **3a**
1.	50 mol% w/w silica-$HClO_4$ in ACN	80	8	60
2.	10 mol% AcOH	80	6	10
3.	10 mol% HCOOH	80	6	30
4.	10 mol% TFA	80	2	80
5.	10% TFA in water	80	2	80
6.	10% TFA in water	rt	1	0
7.	10% TFA in water	rt	12	0
8.	1% TFA in water	80	2	80
9.	0.1% TFA in water	80	2	80
10.	0.1% TFA in water	80	1	78
11.[c]	**0.1% TFA in** water	**80**	**0.5**	**76**
12.	Water	80	24	0
13	Dioxane	80	12	0

[a] Reagents and conditions: thiol **5a** (1.0 mmol), *N*-vinyl lactam **7** (1.2 mmol), formaldehyde **6** (3.0 mmol); [b] isolated yield; [c] optimized reaction condition.

The scope of this 3CC protocol was investigated for variety of aromatic and aliphatic thiols and various lactams. Results are shown in Figure 2. The reaction proceeded smoothly with both aromatic as well as aliphatic thiols, producing 64-90% yields of thiophenyl / thioalkyl methylated products.

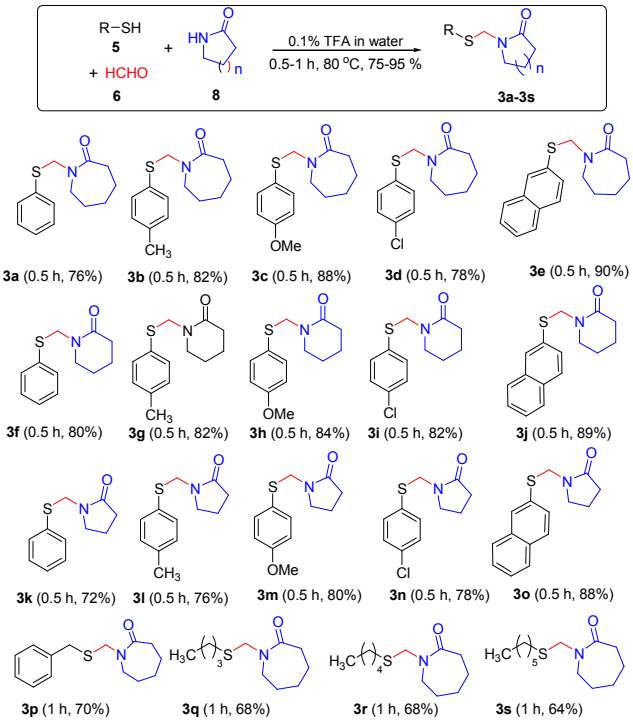


Figure 2. Thiophenylmethylation and thioalkylmethylation of lactams (reaction time and yields are mentioned in the parentheses). Reagents and conditions: thiol **5** (1.0 mmol), lactam **8** (1.2 mmol), formaldehyde **6** (3.0 mmol), 0.1% TFA in water, 80 ºC, 0.5-1 h.

The substitution of various electron-donating (**3b**, **3c**, **3g**, and **3h**) as well as electron-withdrawing groups (**3d**, **3i**, and **3n**) on thiophenol was also well tolerated. Furthermore, the thionaphthol also participated well in this reaction producing corresponding thiophenylmethylated products in excellent yields (products **3e**, **3j** and **3o**).

In case of lactams as well as isatins, there are two possible positions for alkylation. For lactams, it was possible to differentiate *N*- versus *O*-alkylation simply by checking the presence or absence of amidic carbonyl (–N-CO-) stretching frequency in IR spectrum. All alkylated products of lactams showed presence of stretching frequency of ~1650 cm^{-1} in IR

spectrum indicating *N*-alkylation. Further, this observation was supported by ^{1}H and ^{13}C NMR data.

Next we investigated the 3CC reaction of thiophenols **5** and formaldehyde **6** with isatins **9** as nucleophiles. Like lactams and N-vinyl lactams, the thiophenylmethylated isatins **4a-e** were formed in excellent yields (Figure 3). In this case, two possible positions for alkylation cannot be differentiated only with IR data as products contain additional –C=O group. Further, both possible products have similar expected NMR values. Thus, in order to confirm the structure of the obtained products, X-ray crystallography study for one of the analog **4e** was carried out The ORTEP diagram showing the molecular conformation of **4e** in crystals is shown in Figure 4.

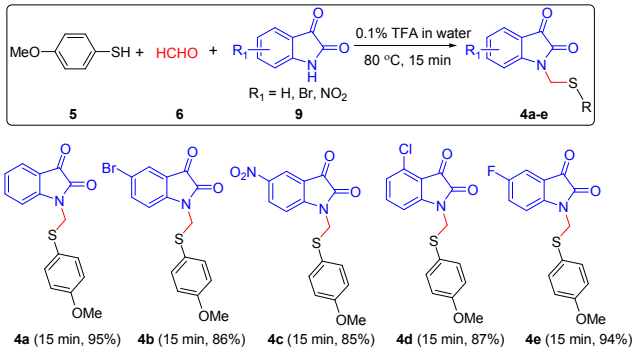


Figure 3. Thiophenylmethylation of isatins. Reagents and conditions: Thiol **5** (1.0 mmol), formaldehyde **6** (3.0 mmol), isatin **9** (1.2 mmol), 0.1% TFA in water, 80 °C, 15 min.

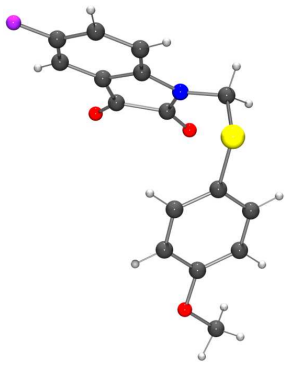


Figure 4. ORTEP diagram showing the molecular conformation of **4e** in crystals.

Next, the reactivity of thiophenol **5c** with formaldehyde **6** and styrene **10** in presence of 50 mol% silica-$HClO_4$ was investigated. The silica- $HClO_4$ catalyst was chosen for this reaction, in order to follow the exactly same protocol as we reported earlier for phenols.[5] The expected styrene-linked product **12** was not formed; instead a thiophenol dimer **11** was produced. The formation of thiophenol dimer **11** occurred presumably via formation of thiophenylmethylium cation intermediate **I**. The styrene **10** has not participated and not played any role in this reaction, which was further confirmed by performing control reaction (reaction in the absence of styrene **10**). When this 3CC reaction was performed in presence of 0.1% TFA in water, it also led to formation of product **11** and not the thioflavan **12** (Figure 5). This finding further suggested that nucleophilicity of SH is higher than ortho-CH .

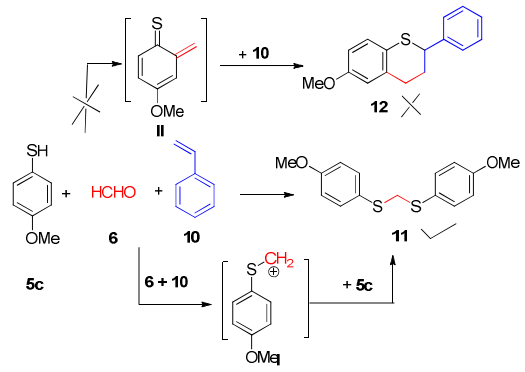


Figure 5. The 3CC reaction of thiophenol with formaldehyde and styrene. Reagents and conditions: thiophenol **5c** (1.0 mmol), formaldehyde **6** (3.0 mmol), styrene **10** (1.2 mmol) and 50 mol% silica-$HClO_4$ in ACN was heated at 80 °C for 4 h. Similar results were observed when 0.1% TFA in water was used instead of silica-$HClO_4$ in ACN.

Further, in order to support the formation of intermediate **I**, and also to investigate the scope of this protocol for thiophenylmethylation of –CH activated phenols, the reaction of thiophenols with formaldehyde **6** and *o*-cresol **13** was studied. In this reaction, a pair of two products were formed, one with *para*-substituted *o*-cresols **14aa-14ba** and other with *ortho*-/*para*-disubstituted *o*-cresols **14ab-14bb**, the former being a major product. The occurrence of thiophenylmethylation at 4, 6-positions of *o*-cresol, indicates that the reaction sequence should be involving formation of thiophenylmethylium cation **I**, followed by subsequent electrophilic substitution on *o*-cresol at 4, 6-positions (Figure 6).

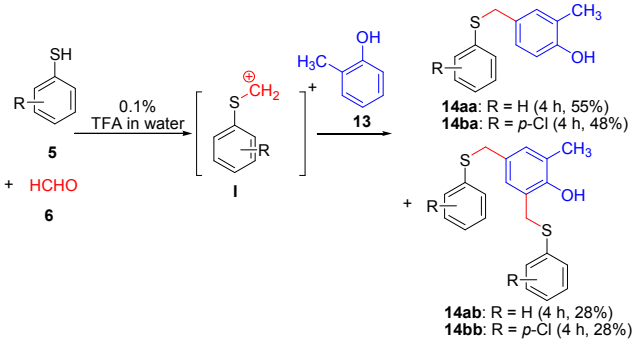


Figure 6. Thiophenylmethylation of phenols. Reagents and conditions: Thiophenol **5** (1.0 mmol) and formaldehyde **6** (3.0 mmol), *o*-cresol **13** (1.2 mmol), 0.1% TFA in water, 80 °C, 4 h.

Next, in order to confirm the formation of thiophenylmethylium cation **I** intermediate, the reaction between 4-methoxy thiophenol, formaldehyde and caprolactam was monitored by LC-ESIMS. The proposed mechanism for formation of N-thiophenylmethylated product **3c** is depicted in Figure 7b. The LCMS spectra depicted in Figure 7a showed formation of thiophenylmethylium cation **I** with *m/z* 153 $[M]^+$ at t_R 13.3 min, which eventually led to formation of product **3c** (*m/z* 265 $[M]^+$ at t_R 21.5 min). Apart from these peaks, LCMS analysis also indicated formation of lactam dimer **16** (*m/z* 238), and

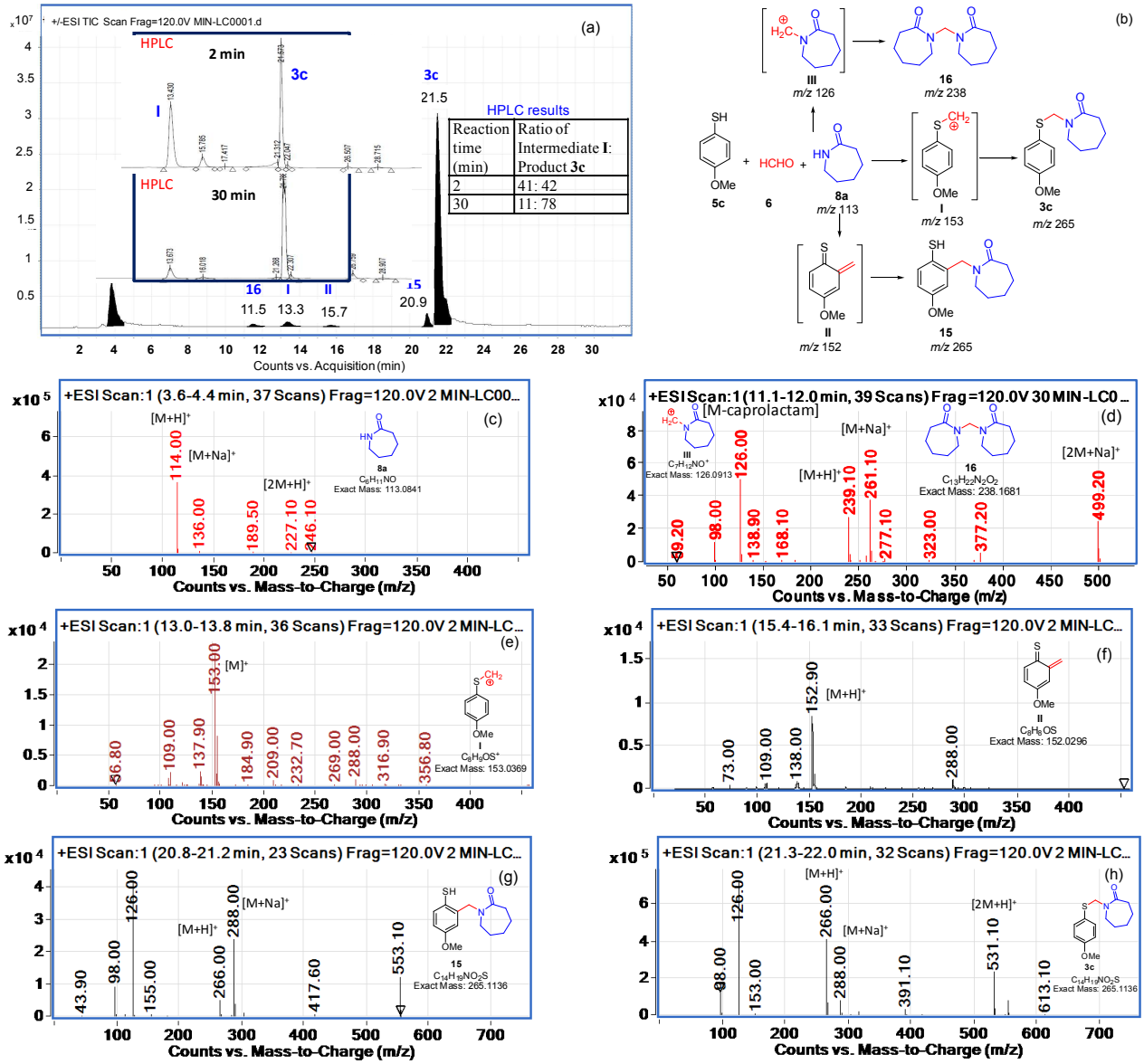


Figure 7. LC-ESIMS analysis to investigate the mechanism for thiophenylmethylation of lactam. (a) TIC chromatogram of crude reaction mixture recorded after 2 min of reaction time (insets: HPLC chromatogram of reaction mixture recorded at 2 and 30 min, respectively; UV 240 nm). (b) Scheme depicting various formation of various intermediates and products (c-h) MS spectrum of peaks eluted at t_R 3.8, 11.5, 13.3, 15.7, 20.9 and 21.5 min.

interestingly an *ortho*-thioquinone methide **II** (*m/z* 152), which further produced *ortho*-amidoalkyated product **15** (*m/z* 265). The product **15** was formed in very minor amount, and thus could not be isolated. In order to rule out the possibility of formation of **I** through hydrolysis of product **3c**, the HPLC analysis of the reaction mixture at different time intervals was carried out. The HPLC analysis (Figure 7a insets) performed at 2 min, showed 41: 42 ratio of **I**: **3m**, which was further changed to 11: 78 ratio at 30 min, indicating that the thiophenylmethylium cation **I** has been formed immediately after mixing reactants as an intermediate and not through the hydrolysis of product **3c**. Further, we checked the stability[9] of representative products **3h** and **4a** in LCMS mobile phase (0.1% formic acid in water; and acetonitrile) as well as in biological fluids (PBS, SGF and SIF) and both compounds were found to be stable after incubation at 37 °C for 30 min (See section S8 of Supporting information).

Based on the literature precedence on anticancer potential for this class of compounds,[4b] all synthesized compounds were screened for cytotoxicity against a panel of cancer cell lines (results shown in supporting information: Table S1). Analog **3e** displayed cytotoxicity against MCF-7 cells with IC_{50} value of 8 μM. The mechanistic investigation of compound **3e** for cell cycle phase distribution, mitochondrial membrane potential (MMP) loss, and effect on apoptotic body formation in MCF-7 cells, revealed that the compound exhibits antiproliferative activity via MMP loss and induction of apoptosis in MCF-7 cells (see, supporting information: Section S5).

Conclusion

In summary, results presented here indicated that phenols and thiophenols react differently via different intermediates and gives different types of products. The simple and efficient TFA-catalyzed protocol for thiophenylmethylation and thioalkylmethylation of lactams and phenols in aqueous medium has been described. The developed protocol has several advantages such as metal-free conditions, aqueous medium and broad substrate scope. Further, the LCMS-based mechanistic studies suggested that reaction proceeds through thiophenylmethylium cation intermediate. The naphthyl analog **3e** displayed promising cytotoxic activity and induced apoptosis in breast cancer MCF-7 cells.

Experimental section

General information

All chemicals were obtained from Sigma-Aldrich Company and used as received. ^{1}H, ^{13}C and DEPT NMR spectra were recorded on Brucker-Avance DPX FT-NMR 500 and 400 MHz instruments. Chemical data for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$, 7.26 ppm). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz or 100 MHz: chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the solvent ($CDCl_3$, 77 ppm). ESIMS and HRMS spectra were recorded on Agilent 1100 LC-Q-TOF and HRMS-6540-UHD machines. IR spectra were recorded on Perkin-Elmer IR spectrophotometer. Melting points were recorded on digital melting point apparatus. LC-ESIMS analysis was carried out on Triple-Quad LC-MS/MS system (model 6410).

General procedure for thiophenyl/thioalkyl methylation of lactams and isatins.

To the solution of substituted thiol (**5a**, 300 mg) in water (5 mL) were added formaldehyde (**6**, 3 equiv.), lactam (**8**, 1.2 mmol) / *N*-vinyl lactam (**7**, 1.2 mmol)/ isatins (**9**, 1.2 mmol) and 0.1% TFA in water. The resulting reaction mixture was then refluxed at 80 °C for 15-60 min. Completion of the reaction was monitored by TLC (20% EtOAc in n-hexane). Reaction mixture was cooled to room temperature and was neutralized with saturated $NaHCO_3$ solution and extracted with with EtOAc (50 mL × 2). Combined organic layers were dried over anhydrous sodium sulphate and evaporated on vacuo rotavapor to get crude product. Crude products were purified by silica gel column chromatography using EtOAc: hexane to get amido alkylated products.

1-((Phenylthio)methyl)azepan-2-one (3a). yield: 80%; light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.32 (dd, *J* = 8.8 Hz, 2H), 7.24 (dd , *J* =4, 4Hz, 1H), 4.93 (s , 2H), 3.40 (t, *J* = 4.0 Hz, 2H), 2.49 (t, *J* = 4.0 Hz, 2H), 1.66-1.56 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 176.0, 134.0, 130.8, 128.9, 126.9, 51.6, 48.7, 37.2, 29.8, 28.3, 23.2; IR ($CHCl_3$): ν_{max} 3308, 2927, 2854, 1726, 1648, 1478, 1439, 1419, 1257, 1083, 1025 cm^{-1}; ESIMS: *m/z* 236.1 [M+H]; HR-ESIMS: *m/z* 236.1102 calcd for $C_{13}H_{17}NOS+H^+$ (236.1103).

1-((p-Tolylthio)methyl)azepan-2-one (3b). yield: 82%; light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.33 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 4.83 (s, 2H), 3.34 (t, *J* = 8.0 Hz, 2H), 2.44 (t, *J* = 4.0 Hz, 2H), 2.28 (s, 3H), 1.62-1.53 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 175.8, 137.0, 131.5, 130.3, 129.7, 52.3, 48.8, 37.1, 29.8, 28.4, 23.2, 21.0; IR ($CHCl_3$): ν_{max} 3435, 2927, 2855, 1649, 1492, 1476, 1442, 1419, 1351, 1336, 1256, 1228, 1191, 1138, 1089, 1042 cm^{-1}; ESI-MS: *m/z* 249.0 [M-H]$^-$; HR-ESIMS: *m/z* 250.1264 calcd for $C_{14}H_{19}NOS+H^+$ (250.1260).

1-((4-Methoxyphenylthio)methyl)azepan-2-one (3c). yield: 88%; colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.41 (d, *J* = 8.0 Hz, 2H), 6.84 (d, *J* = 12.0 Hz, 2H), 4.79 (s, 2H), 3.77 (s, 3H), 3.35 (t, *J* = 4.0 Hz, 2H), 2.45 (t, *J* = 4.0 Hz, 2H), 1.65-1.56 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 175.9, 159.4, 134.3, 124.2, 114.6, 55.2, 53.4, 49.1, 37.1, 29.8, 28.4, 23.3 ; IR ($CHCl_3$): ν_{max} 3849, 3740, 3684, 3665, 3308, 2927, 2854, 1726, 1648, 1591, 1493, 1442, 1419, 1284, 1244, 1191, 1029 cm^{-1}; ESI-MS: *m/z* 266.0 [M+H]$^+$, 288.0 [M+Na]$^+$; HR-ESIMS: *m/z* 266.1209 calcd for $C_{14}H_{19}NO_2S+H^+$ (266.1209).

1-((4-Chlorophenylthio)methyl)azepan-2-one (3d). yield: 78%; light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.32 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.82 (s, 2H), 3.32 (t, *J* = 4.0 Hz, 2H), 2.41 (t, *J* = 4.0 Hz, 2H), 1.58-1.48 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 176.0, 133.0, 132.5, 132.0, 129.3, 51.6, 48.7, 37.2, 29.8, 28.4, 23.3; IR ($CHCl_3$): ν_{max} 3434, 2929, 2854, 1649, 1477, 1442, 1419, 1352, 1256, 1229, 1191, 1138, 1094, 1042, 1011 cm^{-1}; ESI-MS: *m/z* 270.0 [M+H]$^+$; HR-ESIMS: *m/z* 270.071 calcd for $C_{13}H_{16}ClNOS+H^+$ (270.0713).

1-((Naphthalen-6-ylthio)methyl)azepan-2-one (3e). yield: 90%; brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.91 (s, 1H), 7.79 (m, 3H), 7.53-7.43 (m, 3H), 5.01 (s, 2H), 3.40 (t, *J* = 4.0 Hz, 2H), 2.48 (t, *J* = 4.0 Hz, 2H), 1.61-1.52 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 176.0, 133.7, 132.1, 131.6, 129.1, 128.5, 128.1, 127.7, 127.4, 126.5, 126.0, 51.5, 48.8, 37.2, 29.8, 28.4, 23.2; IR ($CHCl_3$): ν_{max} 3308, 3049, 2927, 2853, 1726, 1647, 1500, 1478, 1442, 1418, 1351, 1257, 1132, 1073, 1041 cm^{-1}; ESI-MS: *m/z* 286.1 [M+H]$^+$, 308.1 [M+Na]$^+$; HR-ESIMS: *m/z* 286.1248 calcd for $C_{17}H_{19}NOS+H^+$ (286.1260).

1-((Phenylthio)methyl)piperidin-2-one (3f). yield: 80%; brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.47 (d, *J* = 8.0 Hz, 2H), 7.28-7.20 (m, 3H), 4.86 (s, 2H), 3.29 (t, *J* = 4.0 Hz, 2H), 2.28 (t, *J* = 4.0 Hz, 2H), 1.70-1.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 169.6, 134.0, 131.3, 128.7, 127.0, 50.7, 46.7, 32.1, 22.7, 20.9; IR ($CHCl_3$): ν_{max} 3793, 3700, 3308, 2945, 2865, 1726, 1644, 1485, 1463, 1439, 1414, 1348, 1330, 1245, 1172, 1087, 1024 cm^{-1}; ESI-MS: *m/z* 222.0 [M+H]$^+$; HR-ESIMS: *m/z* 222.0948 calcd for $C_{12}H_{15}NOS+H^+$ (222.0947).

1-((p-Tolylthio)methyl)piperidin-2-one (3g). yield: 82%; light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.37 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.82 (s, 2H), 3.33 (t, *J* = 4.0 Hz, 2h), 2.30 (m, 5H), 1.73 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 176.0, 137.5, 132.2, 130.2, 129.7, 51.6, 46.9, 32.2, 22.9, 21.14, 21.10; IR ($CHCl_3$): ν_{max} 3435, 2944, 2866, 1647, 1488, 1462, 1443, 1415, 1348, 1330, 1282, 1245, 1171, 1089, 1043 cm^{-1}; ESI-MS: *m/z* 236.1 [M+H]$^+$; HR-ESIMS: *m/z* 236.1109 calcd for $C_{13}H_{17}NOS+H^+$ (236.1103).

1-((4-Methoxyphenylthio)methyl)piperidin-2-one (3h). yield: 84%; light brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 4.75 (s, 2H), 3.78 (s, 3H), 3.33 (t, J = 4.0 Hz, 2H), 2.29 (t, J = 4.0 Hz, 2H), 1.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.8, 159.6, 135.0, 124.1, 114.5, 55.2, 52.4, 47.0, 32.2, 22.9, 21.1; IR ($CHCl_3$): ν_{max} 3790, 3435, 2943, 2868, 1726, 1644, 1591, 1570, 1493, 1463, 1443, 1415, 1349, 1331, 1285, 1244, 1171, 1092, 1028 cm^{-1}; ESI-MS: m/z 252.1 $[M+H]^+$; HR-ESIMS: *m/z* 252.1057 calcd for $C_{13}H_{17}NO_2S+H^+$ (252.1052).

1-((4-Chlorophenylthio)methyl)piperidin-2-one (3i). yield: 82%; light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 4.78 (s, 2H), 3.26 (t, J = 4.0 Hz, 2H), 2.22 (t, J = 4.0 Hz, 2H), 1.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 179.8, 133.1, 132.8, 132.5, 128.9, 50.8, 46.8, 32.2, 22.8, 21.1; IR ($CHCl_3$): ν_{max} 3435, 2946, 2867, 2345, 1729, 1646, 1572, 1477, 1463, 1443, 1414, 1388, 1348, 1331, 1283, 1245, 1172, 1157, 1093, 1011 cm^{-1}; ESI-MS: *m/z* 256.0 $[M+H]^+$; HR-ESIMS: *m/z* 256.0557 calcd for $C_{12}H_{15}ClNOS+H^+$ (256.0557).

1-((Naphthalen-3-ylthio)methyl)piperidin-2-one (3j). yield: 89%; brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (s, 1H), 7.76 (m, 3H), 7.53-7.41 (m, 3H), 4.95 (s, 2H), 3.28 (t, J = 4.0 Hz, 2H), 2.27 (t, J = 4.0 Hz, 2H), 1.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.0, 133.6, 132.2, 131.5, 130.0, 128.8, 128.5, 127.7, 127.4, 126.6, 126.1, 50.8, 47.0, 32.3, 22.9, 21.1; IR ($CHCl_3$): ν_{max} 3435, 3051, 2945, 2866, 1644, 1588, 1485, 1462, 1414, 1348, 1330, 1281, 1246, 1172, 1132, 1090, 1071 cm^{-1}; ESI-MS: *m/z* 272.1 $[M+H]^+$; HRMS: *m/z* 272.1110 calcd for $C_{16}H_{17}NOS+H^+$ (272.1103).

1-((Phenylthio)methyl)pyrrolidin-2-one (3k). yield: 72%; light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.44 (d, J = 8.0 Hz, 2H), 7.29-7.21 (m, 3H), 4.74 (s, 2H), 3.42 (t, J = 4.0 Hz, 2H), 2.28 (t, J = 4.0 Hz, 2H), 1.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.8, 133.6, 130.8, 129.0, 127.1, 46.6, 45.8, 30.7, 17.5; IR ($CHCl_3$): ν_{max} 3435, 3055, 2920, 1686, 1582, 1482, 1460, 1437, 1419, 1289, 1252, 1157, 1024 cm^{-1}; ESI-MS: *m/z* 208.0 $[M+H]^+$, 230.0 $[M+Na]^+$; HR-ESIMS: *m/z* 208.0791 calcd for $C_{11}H_{13}NOS+H^+$ (208.0790).

1-((p-Tolylthio)methyl)pyrrolidin-2-one (3l). yield: 76%; light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 4.70 (s, 2H), 3.44 (t, J = 4.0 Hz, 2H), 2.32 (s, 3H), 2.31-2.25 (m, 2H), 1.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.8, 137.5, 131.7, 129.8, 47.3, 45.9, 30.8, 29.7, 21.1, 17.6; IR ($CHCl_3$): ν_{max} 3308, 2920, 2851, 1690, 1492, 1460, 1418, 1289, 1252, 1157, 1090, 1040 cm^{-1}; ESI-MS: *m/z* 222.0 $[M+H]^+$; HR-ESIMS: *m/z* 222.0948 calcd for $C_{12}H_{15}NOS+H^+$ (222.0947).

1-((4-Methoxyphenylthio)methyl)pyrrolidin-2-one (3m). yield: 80%; brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 4.63 (s, 2H), 3.78 (s, 3H), 3.45 (t, J = 4.0 Hz, 2H), 2.28 (t, J = 4.0 Hz, 2H), 1.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.8, 159.6, 134.5, 123.6, 114.6, 55.2, 48.2, 45.9, 30.8, 17.6; IR ($CHCl_3$): ν_{max} 3435, 2924, 2837, 1688, 1591, 1570, 1494, 1460, 1420, 1325, 1286, 1245, 1174, 1104, 1028 cm^{-1}; ESI-MS: *m/z* 238.0 $[M+H]^+$; HR-ESIMS: *m/z* 238.0892 calcd for $C_{12}H_{15}NO_2S+H^+$ (238.0896).

1-((4-Chlorophenylthio)methyl)pyrrolidin-2-one (3n). yield: 78%; light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 4.73 (s, 2H), 3.44 (t, J = 4.0 Hz, 2H), 2.31 (t, J = 4.0 Hz, 2H), 1.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.0, 133.1, 132.15, 132.1, 129.1, 46.7, 46.6, 30.7, 17.5; IR ($CHCl_3$): ν_{max} 3434, 2920, 1687, 1477, 1460, 1419, 1289, 1251, 1158, 1094, 1011 cm^{-1}; ESI-MS: *m/z* 264.0 $[M+Na]^+$; HR-ESIMS: *m/z* 264.0217 calcd for $C_{11}H_{12}ClNOS+Na^+$ (264.0220).

1-((Naphthalen-3-ylthio)methyl)pyrrolidin-2-one(3o). yield: 88%; light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (s, 1H), 7.77 (m, 3H), 7.50-7.42 (m, 3H), 4.85 (s, 2H), 3.42 (t, J = 4.0 Hz, 2H), 2.26 (t, J = 4.0 Hz, 2H), 1.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.0, 133.7, 132.2, 131.1, 129.2, 128.6, 128.0, 127.7, 127.4, 126.6, 126.1, 46.5, 46.0, 30.8, 17.5; IR ($CHCl_3$): ν_{max} 3860, 3789, 3308, 3052, 2920, 1726, 1687, 1624, 1588, 1490, 1459, 1418, 1289, 1253, 1157, 1132, 1071, 1042 cm^{-1}; ESI-MS: *m/z* 258.0 $[M+H]^+$, 280.0 $[M+Na]^+$; HR-ESIMS: *m/z* 258.0941 calcd for $C_{15}H_{15}NOS+H^+$ (258.0947) .

1-((Benzylthio)methyl)azepan-2-one (3p). *yield: 70%;* light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.23 (m, 5H), 4.57 (s, 2H), 3.78 (s, 2H), 3.34 (t, J = 4.0 Hz, 2H), 2.48 (t, J = 4.0 Hz, 2H), 1.70-1.6 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.4, 137.8, 127.9, 127.5, 126.0, 48.7, 47.5, 36.3, 34.6, 28.9, 27.5, 22.4; IR ($CHCl_3$): ν_{max} 3435, 3060, 3027, 2926, 2853, 1645, 1494, 1478, 1453, 1442, 1420, 1352, 1337, 1229, 1190, 1137, 1082, 1071, 1029 cm^{-1}; ESI-MS: *m/z* 250.1 $[M+H]^+$, 272.1 $[M+Na]^+$; HR-ESIMS: *m/z* 250.1259 calcd for $C_{14}H_{19}NOS+H^+$ (250.1260).

1-((Butylthio)methyl)azepan-2-one (3q). yield: 68%; light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.55 (s, 2H), 3.45 (t, J = 4.0 Hz, 2H), 2.56 (m, 4H), 1.73-1.67 (m, 6H), 1.61-1.57 (m, 2H), 1.42-1.38 (m, 2H), 0.92 (t, 4.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.1, 49.0, 48.3, 37.3, 31.7, 30.3, 29.9, 28.6, 23.5, 21.9, 13.7; IR ($CHCl_3$): ν_{max} 3789, 3682, 3435, 2928, 2856, 1648, 1442, 1420, 1352, 1257, 1228, 1190, 1138, 1082 cm^{-1}; ESI-MS: *m/z* 216.14 $[M+H]^+$, 238.12 $[M+Na]^+$; HR-ESIMS: *m/z* 216.1421 calcd for $C_{11}H_{21}NOS+H^+$ (216.1417).

1-((Pentylthio)methyl)azepan-2-one (3r). yield: 68%; light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.55 (s, 2H), 3.45 (t, J = 4.0 Hz, 2H), 2.56-2.52 (m, 4H), 1.73-1.61 (m, 8H), 1.35 (m, 2H), 0.91 (t, J = 4.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.3, 49.2, 48.4, 37.3, 31.0, 30.7, 29.9, 29.4, 28.5, 23.5, 22.3, 14.0 ; IR ($CHCl_3$): ν_{max} 3435, 2927, 2855, 1648, 1476, 1442, 1420, 1383, 1352, 1256, 1228, 1190, 1138, 1082, 1041 cm^{-1}; ESI-MS: *m/z* 230.15 $[M+H]^+$; HR-ESIMS: *m/z* 230.1578 calcd for $C_{12}H_{23}NOS+H^+$ (230.1573).

1-((Hexylthio)methyl)azepan-2-one (3s). yield: 64%; light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.55 (s, 2H), 3.45 (t, J = 4.0 Hz, 2H), 2.56 (m, 4H), 1.73-1.60 (m, 8H), 1.29-1.26 (m, 8H), 0.90 (t, J = 4.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.2, 49.1, 48.3, 37.2, 31.3, 30.7, 29.9, 29.6, 28.5, 23.5, 22.5, 14.0; IR ($CHCl_3$): ν_{max} 3435, 2926, 2855, 1648, 1468, 1442,

1420, 1352, 1256, 1228, 1190, 1138, 1082, 1040 cm^{-1}; ESI-MS: *m/z* 230.15 $[M+H]^+$, 266.15 $[M+Na]^+$; HR-ESIMS: *m/z* 244.1723 calcd for $C_{13}H_{25}NOS+H^+$ (244.1730).

1-(((4-Methoxyphenyl)thio)methyl)indoline-2,3-dione (4a). yield: 95%; orange red solid; m.p. 109-111 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.63 (m, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.13 (m, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 2H), 4.98 (s, 2H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.6, 160.6, 157.2, 149.4, 138.3, 136.2, 125.3, 124.1, 121.6, 117.7, 115.0, 112.0, 55.4, 45.8; IR ($CHCl_3$): ν_{max} 3447, 2921, 1738, 1611, 1590, 1493, 1469, 1363, 1339, 1286, 1267, 1171, 1094, 1022 cm^{-1}; ESI-MS: *m/z* 300 $[M+H]^+$, 322 $[M+Na]^+$; HR-ESIMS: *m/z* 300.0661 calcd for $C_{16}H_{13}NO_3S+H^+$ (300.0689) and *m/z* 322.0478 calcd for $C_{16}H_{13}NO_3S+Na^+$ (322.0508).

5-Bromo-1-(((4-methoxyphenyl)thio)methyl)indoline-2,3-dione (4b). yield: 86%; orange red solid; m.p. 135-137 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.72 (M, 2H), 7.31 (d, J = 8 Hz, 2H), 6.92 (d, J = 12.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 2H), 4.96 (s, 2H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 181.4, 160.7, 156.5, 148.1, 140.4, 136.2, 128.0, 121.3, 118.8, 117.1, 115.1, 113.8, 55.3, 45.9; IR ($CHCl_3$): ν_{max} 3436, 2055, 1742, 1638, 1493, 1467, 1439, 1247, 1158, 1019 cm^{-1}; ESI-MS: *m/z* 377.9 $[M+H]^+$, 399.9 $[M+Na]^+$; HR-ESIMS: *m/z* 377.9782 calcd for $C_{16}H_{12}BrNO_3S+H^+$ (377.9794).

1-(((4-Methoxyphenyl)thio)methyl)-5-nitroindoline-2,3-dione (4c). yield: 85%; orange red solid; m.p. 180-181 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.54 (d, J = 8.0 Hz, 1H), 8.48 (s, 1H), 7.30-7.28 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 2H), 5.04 (s, 2H), 3.80 (s, 3H); IR ($CHCl_3$): ν_{max} 3436, 2920, 2064, 1749, 1615, 1531, 1494, 1475, 1340, 1247, 1163, 1018 cm^{-1}; ESI-MS: *m/z* 345.0 $[M+H]^+$, 367.0 $[M+Na]^+$; HR-ESIMS: *m/z* 345.0535 calcd for $C_{16}H_{12}N_2O_5S+H^+$ (345.0540) and *m/z* 367.0359 calcd for $C_{16}H_{12}N_2O_5S+Na^+$ (367.0359).

4-Chloro-1-(((4-methoxyphenyl)thio)methyl)indoline-2,3-dione (4d). yield: 87%; orange red solid; m.p. 116-118 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.54 (d, J = 4.0 Hz, 1H), 7.40-7.30 (m, 2H), 7.13 (d, J = 8.0 Hz, 1H), 6.86-6.77 (m, 3H), 4.94 (s, 2H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 181.1, 160.8, 157.1 150.4, 144.7, 136.3, 132.6, 126.2, 124.3, 115.1, 114.6, 112.7, 55.3, 46.1; IR ($CHCl_3$): ν_{max} 3436, 2067, 1636, 1493, 1361, 1287, 1247, 1171, 1020 cm^{-1}; ESI-MS: *m/z* 334.0 $[M+H]^+$, 355.9 $[M+Na]^+$; HR-ESIMS: *m/z* 356.0101 calcd for $C_{16}H_{12}ClNO_3S+Na^+$ (356.0110).

5-Fluoro-1-(((4-methoxyphenyl)thio)methyl)indoline-2,3-dione (4e). yield: 94%; orange red solid; m.p. 103-104 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.29 (m, 4H), 6.99 (d, J = 4.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 2H), 4.98 (s, 2H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 182.0, 160.6, 158.5, 157.0, 145.4, 136.2, 124.8, 121.3, 118.3, 115.0, 113.4, 112.3, 55.3, 45.9; IR ($CHCl_3$): ν_{max} 3436, 2918, 1745, 1621, 1484, 1247, 1019 cm^{-1}; ESI-MS: *m/z* 318.0 $[M+H]^+$, 340.0 $[M+Na]^+$; HR-ESIMS: *m/z* 340.0429 calcd for $C_{16}H_{12}FNO_3S+Na$ (340.0414).

Preparation of bis((4-methoxyphenyl)thio)methane (11).[4a]

To the solution of thiophenol (**5a**, 1.0 mmol) in water (5 mL) was added formaldehyde (**6**, 3 equiv.) and 0.1% TFA in water. The resulting reaction mixture was then refluxed at 80 °C for 6 h. The crude reaction mixture was purified by silica gel column chromatography using EtOAc: hexane as mobile phase to yield product **11**. yield: 72%; white solid; m.p. 67-68 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30 (d, J = 8.0 Hz, 2H), 6.76 (d, J = 8.0 Hz, 2H), 4.05 (s, 2H), 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.6, 134.5, 125.3, 114.6, 55.4, 44.5; IR ($CHCl_3$): ν_{max} 3436, 2920, 2833, 2040, 1633, 1590, 1492, 1461, 1438, 1284, 1244, 1196, 1094, 1026 cm^{-1}; ESI-MS: *m/z* 293.0 $[M+H]^+$.

General procedure for thiophenylmethylation of phenols.

To the solution of substituted thiophenol (**5a-b**, 1.0 mmol) in 0.1% TFA in water (5 mL) was added formaldehyde (**6**, 3 equiv.). The resulting reaction mixture was then refluxed at 80 °C for 30 min. The *ortho*-cresol (**13**, 2.0 mmol) was then added and reaction mixture was further stirred at 80 °C for 4 h. The reaction mixture was purified by silica gel column chromatography using EtOAc: hexane as mobile phase to yield pair of products, one with *para*-substituted *o*-cresols **14aa-14ba** and other with *ortho*-/*para*-disubstituted *o*-cresols **14ab-14bb**.

2-Methyl-4-((phenylthio)methyl)phenol (14aa). yield: 55%; white solid; m.p. 68-70 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.29 (m, 2H), 7.26-7.22 (m, 2H), 7.18-7.14 (m, 1H), 7.04 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 5.0 (s, 1H), 4.03 (s, 2H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.1, 136.7, 131.7, 129.6, 129.3, 128.9, 127.6, 126.3, 124.2, 115.1, 38.5, 15.9; IR ($CHCl_3$): ν_{max} 3847, 3350, 3058, 2921, 2850, 2351, 2284, 1600, 1585, 1501, 1479, 1436, 1384, 1368, 1298, 1265, 1245, 1201, 1151, 1114, 1089, 1070, 1042, 1024 cm^{-1}.

2-Methyl-4,6-bis((phenylthio)methyl)phenol (14ab). yield: 28%; light brown solid; m.p. 97-99 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.31 (m, 2H), 7.27-7.17 (m, 8H), 6.97 (s, 1H), 6.84 (s, 1H), 5.95 (s, 1H), 4.11 (s, 2H), 3.96 (s, 2H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$ 100 MHz): δ 152.2, 136.7, 134.5, 131.0, 130.7, 129.6, 129.0, 128.9, 128.8, 128.7, 127.1, 126.2, 125.4, 122.0, 38.4, 36.0, 15.9 ; IR ($CHCl_3$): ν_{max} 3445, 2921, 2852, 1619, 1480, 1438, 1019 cm^{-1}.

4-(((4-Chlorophenyl)thio)methyl)-2-methylphenol (14ba). yield: 48%; light brown solid; m.p. 92-94 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.20 (m, 4H), 7.03 (s, J = 8.0 Hz, 1H), 6.95 (m, 1H), 6.66 (d, J = 8.0 Hz, 1H), 5.04 (s, 2H), 3.99 (s, 2H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.3, 134.1, 131.4, 130.7, 130.3, 128.0, 126.7, 123.2, 114.1, 37.9, 14.9; IR ($CHCl_3$): ν_{max} 3745, 3324, 3024, 2927, 2854, 1601, 1506, 1474, 1442, 1426, 1387, 1366, 1298, 1270, 1260, 1249, 1208, 1179, 1151, 1112, 1095, 1007 cm^{-1}; ESI-MS: *m/z* 263.02 $[M-H]^-$; HR-ESIMS: *m/z* 263.0298 calcd for $C_{14}H_{13}ClOS-H^-$ (263.0303).

2,4-Bis(((4-chlorophenyl)thio)methyl)-6-methylphenol (14bb). yield: 28%; light yellow sticky solid; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.24-7.14 (m, 8H), 6.95 (s, 1H), 6.78 (s, 1H), 5.77 (s, 1H), 4.07 (s, 2H), 3.92 (s, 2H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.1, 135.0, 133.3, 132.9, 132.3, 132.28, 131.1, 131.0, 129.1, 128.9, 128.7, 128.6, 38.6, 35.9, 15.8; IR ($CHCl_3$): ν_{max} 3446, 2922, 1619, 1476, 1387, 1219, 1095, 1016 cm^{-1}.

X-ray crystallography of 5-fluoro-1-(((4-methoxyphenyl)thio)methyl)indoline-2,3-dione (4e): Single crystals of 5-fluoro-1-(((4-methoxyphenyl)thio)methyl)indoline-2,3-dione **4e** were obtained by slow evaporation at room temperature, from a mixture of methanol/water. The X-ray data was collected from a dry crystal mounted on an 'Xcalibur, Sapphire3', Oxford diffractometer. The crystal structure was solved by direct method using SHELXS-97 followed by Full matrix anisotropic least square refinement using SHELXL-97.[10] All the hydrogen atoms were located from difference Fourier map and refined isotropically. All the relevant crystallographic data collection parameters and structure refinement details for **4e** is summarized in Table S4. Bond lengths and bond angles are given in Table S5.

Crystal data for **4e**: C_{16} $H_{12}F1N_1O_3S_1$, M = 317.33, monoclinic, space group: $P2_1/c$, a = 21.243 (5), b = 5.558(5), c = 13.288(5) Å , α= 90°, β= 107.615 (5)°, γ = 90°; V = 1495.3(15) Å^3, Z = 4, D_c = 1.410 mg/m^3, μ = 0.239 mm^{-1}, θ range: 3.65 to 26.0°., 5636 reflections measured, 2926 independent (R_{int} = 0.0492), 248 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2; final R indices for 1337 observed reflections [I >2σ (I)]: R_1 = 0.0652, wR_2 = 0.1593; maximal / minimum residual electron density: 0.199 and -0.176e.Å^{-3}. CCDC reference number 975544. For crystallographic data in CIF or other electronic format, see ESI.

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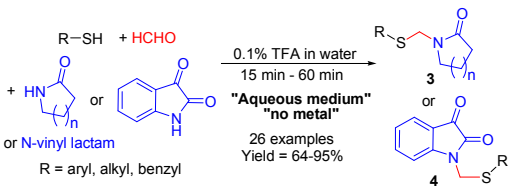
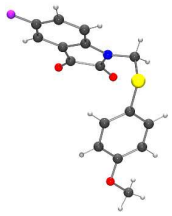
Graphical Abstract

Trifluoroacetic acid catalyzed one-pot thiophenylmethylation and thioalkylmethylation of lactams, isatins and phenols via domino three-component coupling reaction in water has been described.





4e