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A novel NH_4OAc and $CuBr(PPh_3)_3$-induced intermolecular Pummerer-type reaction between free (NH)-indoles and dimethylsulfoxide: facile synthesis of 3-methylthiomethyl substituted indoles

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ABSTRACT

A novel $NH_4OAc/CuBr(PPh_3)_3$-induced intermolecular Pummerer-type reaction between free (NH)-indoles and dimethylsulfoxide is first reported, which offers the 3-methylthiomethyl substituted indoles conveniently and efficiently.

1. Introduction

3-Alkyl substituted indoles have potentially high biological activities.[1] They have also been used to synthesis complex indole derivatives that can be used as pharmaceuticals and agrochemicals.[2] Among all the 3-alkyl substituted indoles, 3-methylthiomethyl substituted indoles have attracted most interest because they are naturally presented in some indole alkaloids and they show excellent anti-insect activity.[3] For instance, dithyreanitrile, which had been isolated from the seeds of *Dithyrea widizenii* (Cruciferae), was a useful insect antifeedant.[3f–h] However, very few methods of the synthesis of these 3-methylthiomethyl substituted indoles had been reported. One of the practicable approaches towards 3-methylthiomethyl substituted indoles is through the reaction of gramine with methanethiol or sodium thiomethoxide,[4] which is limited by the not readily available substrates as well as the narrow reaction scope. Thus our efforts to explore facile and new routes to the 3-methylthiomethyl substituted indoles is significant.

The Pummerer reaction,[5] which situ-generates thionium ion intermediates through the reaction of alkyl sulfoxides with electrophilic reagents, has been studied extensively and has established itself as a very useful method for C–C bond construction in the valuable synthetic processes.[6] Since the first report in the year of 1909, chemists have reported numerous Pummerer reaction examples using different nucleophiles, such as arenes, alkenes, amides and phenols attacking the thionium ions either intra-[7,9] or intermolecularly.[8] In addition, as a synthetic strategy to the natural and complex heterocyclic compounds, the intramolecular Pummerer reactions of electron-rich heterocycles have been widely studied and reported.[9] However, to the best of our knowledge, using indoles as nucleophiles to trap the thionium ion intermediates by intermolecular strategy have remained yet to be reported. This perhaps because classical Pummerer reactions have to use harsh acidic initiators, in which indoles usually can hardly tolerate and it may induces side reactions. Another reason is the thionium ion intermediates are more difficult to be trapped intermolecularly. Therefore, it is of great importance to find novel routes to generate thionium ions to expand the Pummerer reaction's scope and develop methodologies to achieve the intermolecular Pummerer reactions between indoles and alkyl sulfoxides.

In our previous studies on the synthesis and functionalization of bioactive heterocycles,[10] we developed a simple and mild reaction for the synthesis of 1*H*-indol-3-yl acetate.[10e] As the extension of this reaction, we further examined whether NH_4OAc could be used as an acetoxylation reagent in this process. The reaction was performed in DMSO in the presence of $Pd(OAc)_2$ and base at 120 °C. Unexpectedly, we got the 3-(methylthiomethyl)-1*H*-indole other than the desired 1*H*-indol-3-yl acetate product (Scheme 1). Given

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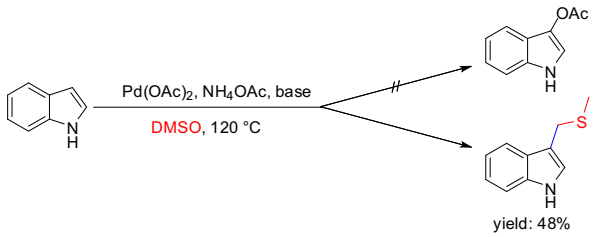
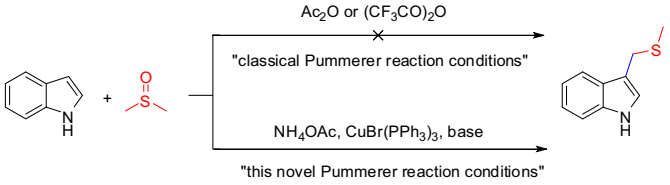
the importance of 3-methylthiomethyl substituted indoles in synthetic organic chemistry and biological chemistry, it is valuable to develop a new synthetic strategy for these useful compounds. Herein, we report a novel $NH_4OAc/CuBr(PPh_3)_3$-induced intermolecular Pummerer-type reaction between free (NH)-indoles and dimethylsulfoxide to efficiently give 3-methylthiomethyl substituted indoles under simple conditions (Scheme 2).



Scheme 1. Unexpected intermolecular Pummerer-type reaction between indole and dimethylsulfoxide.



Scheme 2. A novel NH_4OAc and $CuBr(PPh_3)_3$-induced intermolecular Pummerer-type reaction between indole and dimethylsulfoxide.

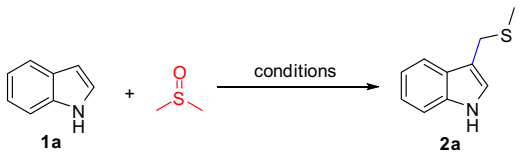
2. Results and discussion

On the outset of this investigation, we used indole (**1a**) as a model reactant to screen suitable reaction conditions. The impact of the catalyst, base, additives, and temperature was investigated in detail for the reaction (Table 1). It was found that no reaction was observed in the absence of NH_4OAc (Table 1, entries 1, 3) and no products were detected while we used other ammonium salts ($HCOONH_4$, NH_4HCO_3) or organic amine, such as benzylamine, urea as additives (Table 1, entries 22–25). On the other hand, it was shown that some metal catalysts could promote the reaction. Among the examined metal catalysts including copper, palladium and aluminium salts, $CuBr(PPh_3)_3$ gave the best result, which 3-(methylthiomethyl)-1*H*-indole could be afforded in 71% yield (Table 1, entry 8). Additionally, we found that trace reaction could also occur only in the presence of NH_4OAc (7% yield, Table 1, entry 2), catalysts and bases made the reaction work better. Several bases were screened in the experiments, with CH_3ONa proving to be the base of choice. In addition, to optimize the reaction conditions further, we carried out the same reaction at temperatures ranging from 90 to 130 °C (Table 1, entries 26–28). At last, 120 °C was chosen to be the reaction temperature.

For the optimal reaction conditions, **1** was reacted with dry dimethylsulfoxide in the presence of $CuBr(PPh_3)_3$ (15 mol %), NH_4OAc (4 equiv) and CH_3ONa (1 equiv) at 120 °C for 12 h and these conditions were subsequently employed when we examined the substrate scope of the reaction (Table 2). Gratifyingly, a variety of free (NH)-indoles **1a**–**s** successfully reacted under the aforesaid conditions to afford the desired 3-methylthiomethyl substituted indoles **2a**–**s** in moderate to good yields.

In general, a majority of free (NH)-indoles with electron-rich substituents were superior to those with electron-deficient substituents. Notably, 2-phenyl-1*H*-indoles (**1r** and **1s**) were very reactive to afford the corresponding 3-methylthiomethyl substituted indoles in good yields (88% and 90% yields, respectively).

Table 1
Screening the conditions for the intermolecular Pummerer-type reaction between indole and dimethylsulfoxide[a]



Entry	catalyst	Additive	Base	Temp (°C)	Yield[b] (%)
1	—	—	—	120	n.r.
2	—	NH_4OAc	—	120	7
3	$CuBr(PPh_3)_3$	—	CH_3ONa	120	n.r.
4	$CuBr(PPh_3)_3$	NH_4OAc	—	120	48
5	$CuBr(PPh_3)_3$	NH_4OAc	Bu^tOK	120	68
6	$CuBr(PPh_3)_3$	NH_4OAc	Cs_2CO_3	120	60
7	$CuBr(PPh_3)_3$	NH_4OAc	K_2CO_3	120	64
8	**$CuBr(PPh_3)_3$**	**NH_4OAc**	**CH_3ONa**	**120**	**71**
9	$CuBr(PPh_3)_3$	NH_4OAc	Bu^tOLi	120	58
10	—	NH_4OAc	CH_3ONa	120	20
11	CuBr	NH_4OAc	CH_3ONa	120	48
12	CuI	NH_4OAc	CH_3ONa	120	46
13	CuCl	NH_4OAc	CH_3ONa	120	46
14	$AlCl_3$	NH_4OAc	CH_3ONa	120	28
15	$PdCl_2(PPh_3)_3$	NH_4OAc	CH_3ONa	120	57
16	$Pd(OAc)_2$	NH_4OAc	CH_3ONa	120	48
17	$CuCl(PPh_3)_3$	NH_4OAc	CH_3ONa	120	56
18	Cu(phen)(PPh_3)Br	NH_4OAc	CH_3ONa	120	63
19[c]	$CuBr(PPh_3)_3$	NH_4OAc	CH_3ONa	120	56
20[d]	$CuBr(PPh_3)_3$	NH_4OAc	CH_3ONa	120	64
21[e]	$CuBr(PPh_3)_3$	NH_4OAc	CH_3ONa	120	71
22	$CuBr(PPh_3)_3$	$HCOONH_4$	CH_3ONa	120	n.r.
23	$CuBr(PPh_3)_3$	$CO(NH_2)_2$	CH_3ONa	120	n.r.
24	$CuBr(PPh_3)_3$	NH_4HCO_3	CH_3ONa	120	n.r.
25	$CuBr(PPh_3)_3$	$BnNH_2$	CH_3ONa	120	n.r.
26	$CuBr(PPh_3)_3$	NH_4OAc	CH_3ONa	90	n.r.
27	$CuBr(PPh_3)_3$	NH_4OAc	CH_3ONa	110	68
28	$CuBr(PPh_3)_3$	NH_4OAc	CH_3ONa	130	71

The bold values protrudes the optimal results of screening the conditions for the reaction.

[a] Reaction conditions: **1a** (0.4 mmol), dry DMSO (1.2 mL), catalyst (15 mol %), additive (4 equiv), base (1 equiv), 90–130 °C for 12 h.

[b] Isolated yield after column chromatography.

[c] $CuBr(PPh_3)_3$ (5 mol %).

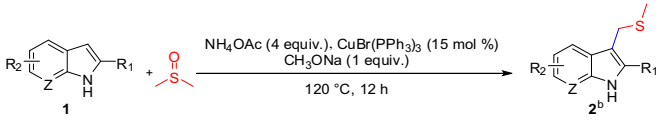
[d] $CuBr(PPh_3)_3$ (10 mol %).

[e] $CuBr(PPh_3)_3$ (20 mol %).

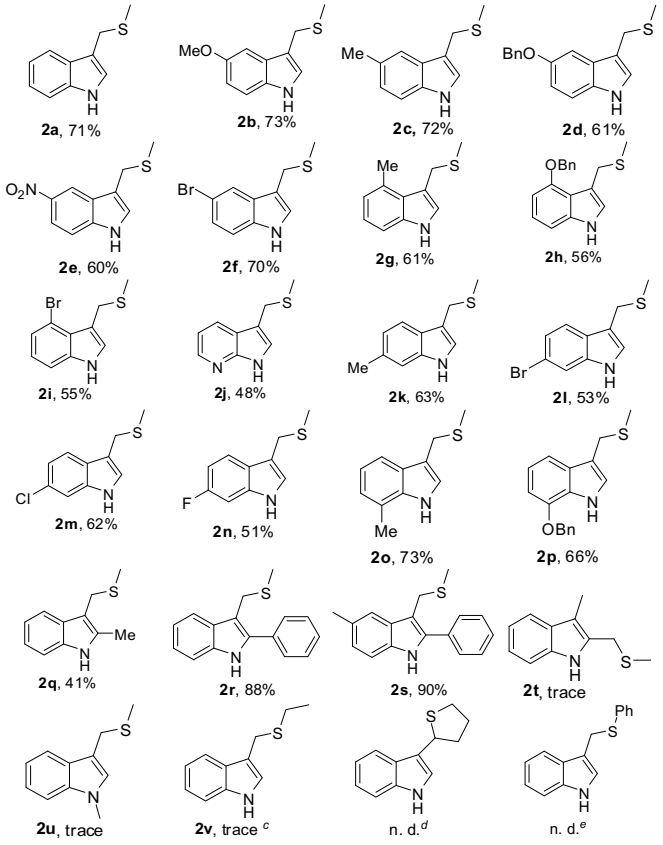
Conversely, indole with C2 having an alkyl substituent (**1q**) was not very suitable in the reaction, giving the product only in 41% yield. Unfortunately, because of their less reactivity, when 1-methyl-1*H*-indole (**1u**), 3-methyl-1*H*-indole (**1t**) and ethyl methyl sulfoxide were employed, there were almost a trace of product, respectively. In addition, when other sulfoxides, such as methyl phenyl sulfoxide and tetramethylene sulfoxide were examined in the reaction, there were no desired products detected. The structure of these 3-methylthiomethyl substituted indoles products were further confirmed by single-crystal X-ray analysis of **2f** (Fig. 1).[11]

Trying to have an insight into this unusual Pummerer-type reaction pathway, we carried out some experiments subsequently. When methylthiomethyl acetate (**I**), the product of the Pummerer rearrangement of dimethylsulfoxide in the presence of acetic anhydride,[5] was loaded instead of DMSO and NH_4OAc in the reaction, the desired product **2a** was not observed (Scheme 3, the left equation). However, to our delight, we got the desired 3-(methylthiomethyl)-1*H*-indole product **2a** in 73% yield when putting ammonia gas through the reaction mixture for 3 h (Scheme 3, the right equation). In addition, methylthiomethyl acetate (**I**) was observed when we heated the mixture of DMSO, AcOH and AcONa (AcOH/AcONa=3:1, molar ratio, in 1.2 mL DMSO) at 120 °C for 12 h. A plausible reaction pathway is proposed in Scheme 4, that is, based on previous reports[6g,h,12] and combined with our experiments results. As is shown in Scheme 4,

Table 2
Synthesis of 3-methylthiomethyl substituted indoles **2** from free (NH)-indoles **1**[a]



1 → **2**[b]



[a]Reaction conditions: **1** (0.4 mmol), NH_4OAc (4 equiv), $CuBr(PPh_3)_3$ (15 mol %), CH_3ONa (1 equiv), dry DMSO (1.2 mL), 120 °C for 12 h.
[b]Isolated yields after column chromatography.
[c]Ethyl methyl sulfoxide was used instead of DMSO.
[d]Tetramethylene sulfoxide was used instead of DMSO, n.d.=not detected.
[e]Methyl phenyl sulfoxide was used instead of DMSO.

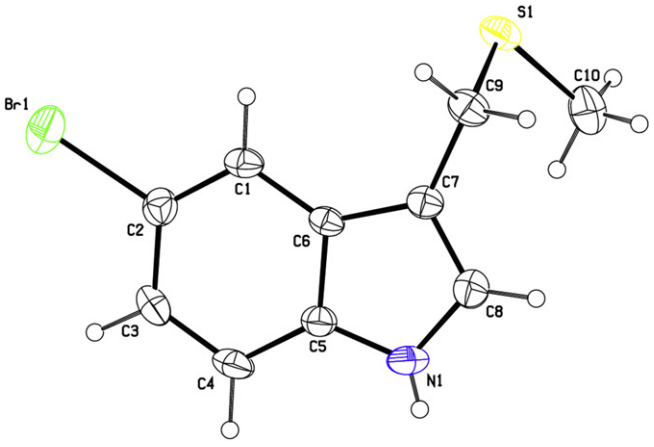
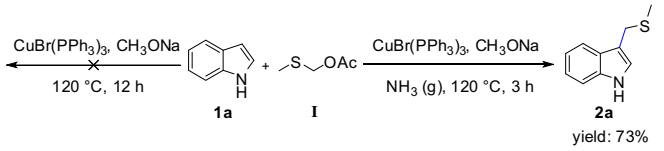
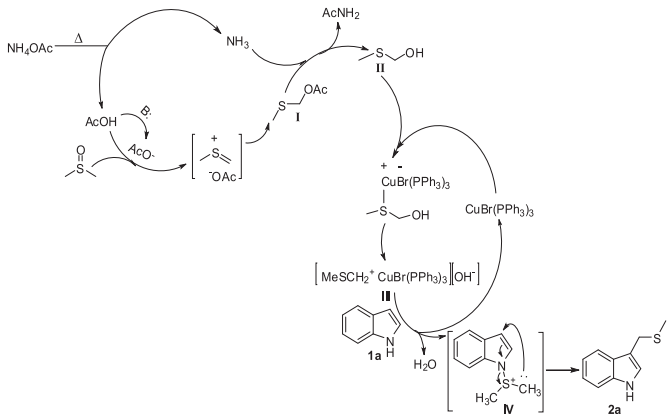


Fig. 1. X-ray crystallography structure of compound **2f**.

NH_4OAc, which releases AcOH and NH_3 in the reaction, plays a very important part in the whole reaction pathway. Initially, dimethylsulfoxide was activated by AcOH in the presence of AcO^- giving the product of methylthiomethyl acetate (**I**), which was then rapidly ammonolyzed by NH_3 yielding methylthiomethanol (**II**). Methylthiomethanol (**II**) attacked $CuBr(PPh_3)_3$ leading to the reactive intermediate (**III**), which was then trapped by indole (**1a**) affording the indole 1-sulfonium ylide intermediate (**IV**). Then 3-(methylthiomethyl)-1*H*-indole product (**2a**) was formed after the [2,3]-sigmatropic rearrangement of the indole 1-sulfonium ylide intermediate (**IV**).[13]

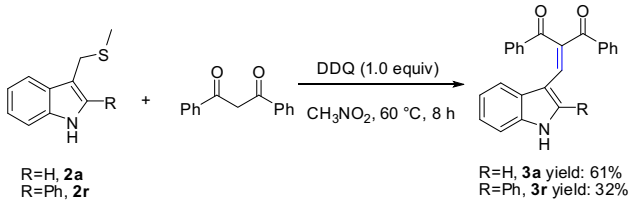


Scheme 3. The reaction between indole **1a** and methylthiomethyl acetate **I** in the absence and in the presence of NH_3 (g).



Scheme 4. A plausible pathway of this intermolecular Pummerer-type reaction.

Next, we investigated the Knoevenagel-type reaction of 3-(methylthiomethyl)-1*H*-indoles with 1,3-diphenylpropane-1,3-dione as shown in Scheme 5 referring to the previous report.[14] Satisfactorily, the corresponding useful 2-((1*H*-indol-3-yl)methylene)-1,3-diphenylpropane-1,3-dione products[15] **3a** and **3r** were successfully prepared in a mild condition with 61% and 32% yields, respectively.



Scheme 5. The Knoevenagel-type reaction between 3-(methylthiomethyl)-1*H*-indoles and 1,3-diphenylpropane-1,3-dione.

3. Conclusions

In conclusion, we have developed a novel and facile NH_4OAc/$CuBr(PPh_3)_3$-induced intermolecular Pummerer-type reaction between free (NH)-indoles and dimethylsulfoxide, which can not be achieved through the classical Pummerer conditions. This is the first example of the intermolecular Pummerer reaction between free (NH)-indoles and dimethylsulfoxide. It provides a new and efficient approach to the synthesis of 3-methylthiomethyl substituted indoles of both biological and synthetic interest. The present method may find some value in organic synthesis because of simple manipulations as well as the ready availability of the

starting materials. Moreover, we believe that our new Pummerer-type reaction system may be utilized in the intermolecular Pummerer reactions between other electron-rich aromatic cycles and alkyl sulfoxides, which are ongoingly under investigation in our laboratory.

4. Experimental section

4.1. General

Melting points were determined using an XT-4 melting point apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ and acetone-d_6 on a Varian-Inova 400 MHz with TMS as an internal standard. IR spectra were obtained on Nicolet NEXUS 670 FT-IR instrument and only major peaks were reported in cm^{-1}. Elemental analyses were performed on Elementar vario EL. HRMS data were performed on Bruker Apex II mass instrument (ESI). Mass spectra were performed on Thermo DSQ mass instrument (EI at 70 eV). Copies of their ^{1}H NMR and ^{13}C NMR spectra were provided. Column chromatography was performed with 200–300 mesh silica gel using flash column techniques. DMSO was distilled over calcium hydride (CaH_2). CuBr(PPh_3)$_3$, 2-phenyl-1*H*-indoles (**1r** and **1s**) and methylthiomethyl acetate (**I**) were prepared according to the literature methods, respectively.[16–18] Other materials were purchased from common commercial sources and used without additional purification.

4.2. General procedure for the synthesis of 3-methylthiomethyl substituted indoles by using dimethylsulfoxide

All reactions were performed on a 0.40 mmol scale relative to **1a**. To a solution of ammonium acetate in dry DMSO (NH_4OAc, 1.6 mmol in 1.2 mL DMSO) in a 10 mL general branch reaction vial was added indole **1a** (0.40 mmol), CuBr(PPh_3)$_3$ (0.06 mmol) and CH_3ONa (0.40 mmol). The reaction vial was strictly sealed with the air in it drived away. Then the reaction vial was heated in an oil bath at 120 °C for 12 h with stirring. Following, to the reaction mixture was added H_2O (2 mL) and it was extracted with methylene dichloride (3×10 mL). The combined organic phases were washed with saturated brine (2×3 mL), dried over anhydrous $NaSO_4$ and concentrated in vacuo. The residue was subjected to flash column chromatography on silica gel with petroleum ether/EtOAc (v/v 8/1) as eluent to obtain the pure 3-(methylthiomethyl)-1*H*-indole product **2a** as a white solid (50 mg, 71% yield).[19]

*4.2.1. 3-(Methylthiomethyl)-1H-indole (**2a**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2a** (71% yield) as a white solid; mp: 86–88 °C; IR (KBr): 3406, 2915, 2245, 1619, 1458, 908, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.92 (s, 1H), 7.72 (d, *J*=8 Hz, 1H), 7.31 (d, *J*=8 Hz, 1H), 7.20 (t, *J*=7.4 Hz, 1H), 7.13 (t, *J*=7.4 Hz, 1H), 7.05 (d, *J*=2 Hz, 1H), 3.89 (s, 2H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.4, 126.8, 122.8, 122.2, 119.5, 119.1, 112.3, 111.2, 28.9, 15.2; MS (ESI): *m*/*z* [M+H]$^+$=178, 130; Anal. Calcd for $C_{10}H_{11}NS$: C, 67.76; H, 6.25; N, 7.90. Found: C, 67.81; H, 6.29; N, 7.86.

*4.2.2. 5-Methoxy-3-(methylthiomethyl)-1H-indole (**2b**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2b** (73% yield) as a white solid; mp: 56–58 °C. IR (KBr): 3415, 2918, 2250, 1585, 1485, 1216, 909, 734 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.95 (s, 1H), 7.20 (d, *J*=8.8 Hz, 1H), 7.15 (d, *J*=2.4 Hz, 1H), 7.05 (d, *J*=2.4 Hz, 1H), 6.85–6.87 (dd, *J*=8.4 Hz, 2.4 Hz, 1H), 3.87 (s, 2H), 3.86 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.0, 131.6, 127.2, 123.7, 112.5, 111.9, 111.9, 100.9, 55.8, 29.0, 15.2. MS (ESI): *m*/*z* [M+H]$^+$=208, 160. Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76. Found: C, 63.78; H, 6.40; N, 6.69.

*4.2.3. 5-Methyl-3-(methylthiomethyl)-1H-indole (**2c**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2c** (72% yield) as a white solid; mp: 80–82 °C. IR (KBr): 3395, 2915, 2244, 1586, 1456, 1308, 908, 797, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.83 (s, 1H), 7.50 (s, 1H), 7.20 (d, *J*=8.4 Hz, 1H), 7.03 (s, 1H), 7.01 (s, 1H), 3.87 (s, 2H), 2.45 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=134.7, 128.8, 126.8, 123.9, 123.0, 118.7, 111.6, 110.8, 28.9, 21.5, 15.2. MS (ESI): *m*/*z* [M+H]$^+$=192, 144. Anal. Calcd for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32. Found: C, 69.16; H, 6.90; N, 7.25.

*4.2.4. 5-(Benzyloxy)-3-(methylthiomethyl)-1H-indole (**2d**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2d** (61% yield) as a white solid; mp: 106–108 °C. IR (KBr): 3290, 2913, 1582, 1482, 1203, 1013, 734 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.96 (s, 1H), 7.53 (d, *J*=7.2 Hz, 2H), 7.44 (t, *J*=7.2 Hz, 2H), 7.37 (t, *J*=7.2 Hz, 1H), 7.31 (s, 1H), 7.24 (d, *J*=8.8 Hz, 1H), 7.07 (d, *J*=2.4 Hz, 1H), 6.99 (d, *J*=8 Hz, 1H), 5.16 (s, 2H), 3.91 (s, 2H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.1, 137.5, 131.7, 128.5, 127.8, 127.7, 127.1, 123.7, 131.1, 111.9, 111.9, 102.4, 70.8, 28.9, 15.2. MS (ESI): *m*/*z* [M+H]$^+$=284, 236. Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 72.18; H, 6.25; N, 4.89.

*4.2.5. 3-(Methylthiomethyl)-5-nitro-1H-indole (**2e**).* Purified by flash chromatography (PE/EtOAc, v/v 5/1) to give **2e** (60% yield) as a yellow solid; mp: 100–102 °C. IR (KBr): 3367, 2915, 1516, 1330, 1091, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.70 (d, *J*=2 Hz, 2H), 8.10–8.12 (dd, *J*=8.8, 2.2 Hz, 1H), 7.41 (d, *J*=9.2 Hz, 1H), 7.31 (d, *J*=2 Hz, 1H), 3.92 (s, 2H), 2.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=141.6, 139.5, 126.3, 125.9, 117.9, 116.7, 115.2, 111.3, 28.5, 15.4. MS (ESI): *m*/*z* [M+H]$^+$=223, 175. Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 54.10; H, 4.61; N, 12.56.

*4.2.6. 5-Bromo-3-(methylthiomethyl)-1H-indole (**2f**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2f** (70% yield) as a white solid; mp: 118–120 °C. IR (KBr): 3310, 2915, 1655, 1450, 1096, 796 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.06 (s, 1H), 7.85 (d, *J*=1.6 Hz, 1H), 7.26–7.29 (dd, *J*=8.4, 1.8 Hz, 1H), 7.20 (d, *J*=8.4 Hz, 1H), 7.10 (d, *J*=2 Hz, 1H), 3.84 (s, 2H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=135.0, 128.5, 125.1, 124.0, 121.8, 112.9, 112.6, 112.1, 28.7, 15.2. MS (ESI): *m*/*z* [M+H]$^+$=256, 208. Anal. Calcd for $C_{10}H_{10}BrNS$: C, 46.89; H, 3.93; N, 5.47. Found: C, 46.92; H, 3.96; N, 5.39.

*4.2.7. 4-Methyl-3-(methylthiomethyl)-1H-indole (**2g**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2g** (61% yield) as a white solid; mp: 92–94 °C. IR (KBr): 3318, 2915, 1435, 1116, 1060, 752 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.950 (s, 1H), 7.19 (d, *J*=8 Hz, 1H), 7.11 (t, *J*=7.6 Hz, 1H), 7.05 (d, *J*=2.4 Hz, 1H), 6.90 (d, *J*=7.2 Hz, 1H), 4.02 (s, 2H), 2.83 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=137.0, 131.1, 125.2, 123.4, 122.4, 121.3, 112.8, 109.0, 30.9, 20.1, 14.9. MS (ESI): *m*/*z* [M+H]$^+$=192, 144. Anal. Calcd for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32. Found: C, 69.15; H, 6.94; N, 7.23.

*4.2.8. 4-(Benzyloxy)-3-(methylthiomethyl)-1H-indole (**2h**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2h** (56% yield) as a white solid; mp: 92–94 °C. IR (KBr): 3417, 2913, 2244, 1504, 1256, 1093, 733 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.00 (s, 1H), 7.60 (d, *J*=7.6 Hz, 2H), 7.46 (t, *J*=7.6 Hz, 2H), 7.38 (t, *J*=7.6 Hz, 1H), 7.13 (t, *J*=8 Hz, 1H), 6.98 (d, *J*=3.2 Hz, 1H), 6.96 (s, 1H), 6.62 (d, *J*=8 Hz, 1H), 5.33 (s, 2H), 4.10 (s, 2H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.7, 138.1, 137.4, 128.4, 127.7, 127.4, 116.7, 113.0, 104.7, 101.0, 69.8, 30.2, 15.0. MS (ESI): *m*/*z* [M+H]$^+$=284, 236.

Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 72.09; H, 6.11; N, 4.89.

*4.2.9. 4-Bromo-3-(methylthiomethyl)-1H-indole (**2i**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2i** (55% yield) as a white solid; mp: 92–94 °C. IR (KBr): 3415, 2914, 2241, 1556, 1422, 1335, 910, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.13 (s, 1H), 7.27 (d, J=7.6 Hz, 1H), 7.23 (d, J=8 Hz, 1H), 7.09–7.12 (m, 1H), 6.98 (t, J=8 Hz, 1H), 4.13 (s, 2H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=137.7, 124.7, 124.5, 124.3, 123.1, 114.1, 113.2, 110.6, 29.7, 15.0. MS (ESI): m/z $[M+H]^+$=256, 208. Anal. Calcd for $C_{10}H_{10}BrNS$: C, 46.89; H, 3.93; N, 5.47. Found: C, 46.96; H, 3.98; N, 5.40.

*4.2.10. 3-(Methylthiomethyl)-1H-pyrrolo[2,3-b]pyridine (**2j**).* Purified by flash chromatography (PE/EtOAc, v/v 6/1) to give **2j** (48% yield) as a white solid; mp: 118–120 °C. IR (KBr): 3394, 2907, 1580, 1416, 1118, 769 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=11.52 (s, 1H), 8.36 (d, J=4.8 Hz, 1H), 8.10–8.12 (dd, J=8 Hz, 0.8 Hz, 1H), 7.33 (s, 1H), 7.11–7.14 (dd, J=8 Hz, 4.8 Hz, 1H), 3.91 (s, 2H), 2.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.3, 142.6, 128.0, 123.8, 119.7, 115.4, 110.5, 29.1, 15.1. MS (ESI): m/z $[M+H]^+$=179, 131. Anal. Calcd for $C_9H_{10}N_2S$: C, 60.64; H, 5.65; N, 15.72. Found: C, 60.68; H, 5.69; N, 15.66.

*4.2.11. 6-Methyl-3-(methylthiomethyl)-1H-indole (**2k**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2k** (63% yield) as a white solid; mp: 64–66 °C. IR (KBr): 3386, 2912, 1623, 1455, 1092, 802, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.86 (s, 1H), 7.65 (d, J=8 Hz, 1H), 7.15 (s, 1H), 7.04 (s, 1H), 7.03 (d, J=8 Hz, 2H), 3.93 (s, 2H), 2.50 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.8, 132.1, 124.6, 122.2, 121.3, 118.8, 112.1, 111.1, 29.0, 21.7, 15.1. MS (ESI): m/z $[M+H]^+$=192, 144. Anal. Calcd for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32. Found: C, 69.10; H, 6.89; N, 7.30.

*4.2.12. 6-Bromo-3-(methylthiomethyl)-1H-indole (**2l**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2l** (53% yield) as a white solid; mp: 68–70 °C. IR (KBr): 3290, 2916, 2248, 1612, 1452, 909, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.99 (s, 1H), 7.58 (d, J=8 Hz, 1H), 7.48 (d, J=1.2 Hz, 1H), 7.22–7.25 (dd, J=8.8 Hz, 1.8 Hz, 1H), 7.08 (d, J=2 Hz, 1H), 3.86 (s, 2H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=137.2, 125.7, 123.4, 122.9, 120.5, 115.9, 114.1, 112.7, 28.7, 15.2. MS (ESI): m/z $[M+H]^+$=256, 208. Anal. Calcd for $C_{10}H_{10}BrNS$: C, 46.89; H, 3.93; N, 5.47. Found: C, 46.92; H, 3.96; N, 5.41.

*4.2.13. 6-Chloro-3-(methylthiomethyl)-1H-indole (**2m**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2m** (62% yield) as a white solid; mp: 38–40 °C. IR (KBr): 3285, 2953, 1646, 1455, 1334, 1059, 800, 657 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.01 (s, 1H), 7.65 (d, J=8.4 Hz, 1H), 7.32 (d, J=1.2 Hz, 1H), 7.12–7.14 (dd, J=8.6 Hz, 1.8 Hz, 1H), 7.09 (d, J=2 Hz, 1H), 3.88 (s, 2H), 2.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.7, 128.2, 125.3, 123.4, 120.3, 120.1, 112.5, 111.1, 28.7, 15.2. MS (ESI): m/z $[M+H]^+$=212, 164. Anal. Calcd for $C_{10}H_{10}ClNS$: C, 56.73; H, 4.76; N, 6.62. Found: C, 56.78; H, 4.80; N, 6.56.

*4.2.14. 6-Fluoro-3-(methylthiomethyl)-1H-indole (**2n**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2n** (51% yield) as a white solid; mp: 74–76 °C. IR (KBr): 3281, 2915, 1871, 1623, 1453, 1090, 808, 646 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.00 (s, 1H), 7.63–7.66 (dd, J=8.6, 5.4 Hz, 1H), 7.09 (d, J=2.4 Hz, 1H), 702–7.05 (dd, J=9.6, 2.4 Hz, 1H), 6.92 (tt, J=8.8, 2 Hz, 1H), 3.88 (s, 2H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.1 (d, $^1J_{C-F}$=236 Hz), 136.3 (d, $^3J_{C-F}$=12 Hz), 123.3, 123.0 (d, $^4J_{C-F}$=3 Hz), 120.0 (d, $^3J_{C-F}$=11 Hz), 112.5, 108.3 (d, $^2J_{C-F}$=25 Hz), 97.5 (d, $^2J_{C-F}$=26 Hz), 28.9, 15.2. MS (ESI): m/z $[M+H]^+$=196, 148. Anal. Calcd for $C_{10}H_{10}FNS$: C, 61.51; H, 5.16; N, 7.17. Found: C, 61.56; H, 5.20; N, 7.09.

*4.2.15. 7-Methyl-3-(methylthiomethyl)-1H-indole (**2o**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2o** (73% yield) as a white solid; mp: 110–112 °C. IR (KBr): 3399, 2916, 2250, 1895, 1432, 908, 733 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ=7.95 (s, 1H), 7.63 (d, J=8 Hz, 1H), 7.11–7.15 (m, 2H), 7.07 (d, J=6.8 Hz, 1H), 3.95 (s, 2H), 2.51 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=136.0, 126.3, 122.8, 122.5, 120.3, 119.8, 116.8, 112.8, 29.0, 16.5, 15.2. MS (ESI): m/z $[M+H]^+$=192, 144. Anal. Calcd for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32. Found: C, 69.12; H, 6.93; N, 7.28.

*4.2.16. 7-(Benzyloxy)-3-(methylthiomethyl)-1H-indole (**2p**).* Purified by flash chromatography (PE/EtOAc, v/v 8/1) to give **2p** (66% yield) as a white solid; mp: 90–92 °C. IR (KBr): 3431, 3033, 2913, 2873, 2244, 1577, 1260, 1028, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.28 (s, 1H), 7.51 (d, J=6.8 Hz, 2H), 7.38–7.47 (m, 4H), 7.10 (d, J=8 Hz, 1H), 7.07 (d, J=2.4 Hz, 1H), 6.77 (d, J=8 Hz, 1H), 5.22 (s, 2H), 3.92 (s, 2H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=145.3, 137.0, 128.5, 128.3, 128.1, 127.8, 127.1, 122.4, 119.9, 112.7, 112.1, 103.3, 70.1, 29.0, 15.2. MS (ESI): m/z $[M+H]^+$=284, 236. Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 72.02; H, 6.08; N, 4.86.

*4.2.17. 2-Methyl-3-(methylthiomethyl)-1H-indole (**2q**).* Purified by flash chromatography (PE/EtOAc, v/v 6/1) to give **2q** (41% yield) as a yellow oil. IR (neat): 3399, 2913, 1619, 1461, 1227, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.74 (s, 1H), 7.60 (d, J=8.8 Hz, 1H), 7.21–7.23 (dd, J=6.2, 2.6 Hz, 1H), 7.08–7.11 (m, 2H), 3.86 (s, 2H), 2.36 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=135.1, 132.6, 128.2, 121.2, 119.4, 118.2, 110.2, 107.8, 27.6, 15.1, 11.6. MS (ESI): m/z $[M+H]^+$=192, 144. Anal. Calcd for $C_{11}H_{13}NS$: C, 69.07; H, 6.85; N, 7.32. Found: C, 69.01; H, 6.95; N, 7.25.

*4.2.18. 3-(Methylthiomethyl)-2-phenyl-1H-indole (**2r**).* Purified by flash chromatography (PE/EtOAc, v/v 10/1) to give **2r** (88% yield) as a yellow oil. IR (neat): 3407, 3058, 2915, 2245, 1706, 1604, 1454, 1238, 908, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.01 (s, 1H), 7.73 (d, J=7.6 Hz, 1H), 7.59 (d, J=7.6 Hz, 2H), 7.43 (t, J=7.6 Hz, 2H), 7.34 (t, J=7.4 Hz, 1H), 7.27 (d, J=7.6 Hz, 1H), 7.16 (qn, J=8.2, 6.8 Hz, 2H), 4.00 (s, 2H), 2.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=135.7, 135.6, 132.4, 128.9, 128.7, 128.0, 127.9, 122.5, 119.9, 119.3, 110.8, 109.0, 28.4, 15.7. MS (ESI): m/z $[M+H]^+$=254, 206. Anal. Calcd for $C_{16}H_{15}NS$: C, 75.85; H, 5.97; N, 5.53. Found: C, 75.90; H, 5.93; N, 5.46.

*4.2.19. 5-Methyl-3-(methylthiomethyl)-2-phenyl-1H-indole (**2s**).* Purified by flash chromatography (PE/EtOAc, v/v 10/1) to give **2s** (90% yield) as a yellow solid; mp: 98–100 °C. IR (KBr): 3400, 2915, 1603, 1450, 1309, 1239, 764, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.94 (s, 1H), 7.62 (d, J=7.2 Hz, 2H), 7.52 (s, 1H), 7.45 (t, J=7.6 Hz, 2H), 7.35 (t, J=7.4 Hz, 1H), 7.21 (d, J=6.4 Hz, 1H), 7.02 (d, J=8 Hz, 1H), 4.00 (s, 2H), 2.46 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=135.9, 134.0, 132.6, 129.2, 129.0, 128.9, 128.0, 127.8, 124.2, 118.9, 110.5, 108.5, 28.6, 21.6, 15.7. MS (ESI): m/z $[M+H]^+$=268, 220. Anal. Calcd for $C_{17}H_{17}NS$: C, 76.36; H, 6.41; N, 5.24. Found: C, 76.40; H, 6.36; N, 5.16.

4.3. General procedure for the Knoevenagel-type reactions of 3-(methylthiomethyl)-1*H*-indole 2a with 1,3-diphenylpropane-1,3-dione-synthesis of 2-((1*H*-indol-3-yl) methylene)-1,3-diphenylpropane-1,3-dione 3a[14]

To a mixture of 1,3-diphenylpropane-1,3-dione (0.1 mmol), 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ) (0.1 mmol) and 3-(methylthiomethyl)-1*H*-indole **2a** (0.2 mmol),

nitromethane (0.8 mL) was added. The resulting mixture was stirred at 60 °C for 8 h. The resulting mixture was diluted with diethyl ether and purified by flash column chromatography on silica gel with petroleum ether/EtOAc (v/v 5/1) as eluent to obtain the desired product **3a** as a yellow solid (21 mg, 61% yield). **3r** was synthesized according to the same procedure.

*4.3.1. 2-((1H-Indol-3-yl)methylene)-1,3-diphenylpropane-1,3-dione (**3a**).* Purified by flash chromatography (PE/EtOAc, v/v 5/1) to give **3a** (61% yield) as a yellow solid; mp: 206–208 °C. IR (KBr): 3300, 2924, 1664, 1594, 1330, 1246, 1124, 741 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ=10.98 (s, 1H), 8.06 (s, 1H), 8.04 (d, J=4.8 Hz, 2H), 7.89 (d, J=8.4 Hz, 2H), 7.63–7.67 (m, 1H), 7.57–7.61 (m, 5H), 7.46–7.50 (m, 3H), 7.20 (t, J=7.2 Hz, 1H), 7.15 (t, J=7.2 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ=199.3, 195.9, 140.2, 138.3, 138.2, 137.8, 134.9, 133.1, 130.5, 130.5, 130.4, 130.2, 129.8, 129.0, 124.3, 122.5, 119.3, 113.6, 111.4. HRMS (ESI): m/z $[M+Na]^+$ Calcd for $C_{24}H_{17}NO_2Na$: 374.1151; found: 374.1152.

*4.3.2. 1,3-Diphenyl-2-((2-phenyl-1H-indol-3-yl)methylene)propane-1,3-dione (**3r**).* Purified by flash chromatography (PE/EtOAc, v/v 5/1) to give **3r** (32% yield) as a yellow solid; mp: 198–200 °C. IR (KBr): 3288, 2923, 1656, 1564, 1452, 1244, 1108, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.62 (s, 1H), 7.92 (s, 1H), 7.82–7.86 (m, 4H), 7.33–7.47 (m, 10H), 7.25–7.29 (m, 2H), 7.15 (t, J=7.2 Hz, 1H), 7.02 (t, J=7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.6, 195.5, 142.3, 140.9, 138.3, 137.7, 136.2, 136.1, 132.9, 132.1, 131.1, 129.4, 129.2, 129.2, 129.0, 128.9, 128.3, 128.2, 126.3, 123.4, 121.4, 121.3, 111.2, 109.7. HRMS (ESI): m/z $[M+Na]^+$ Calcd for $C_{30}H_{21}NO_2Na$: 450.1466; found: 450.1468.

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Supplementary data

Supplementary data related to this article can be found online version, at doi:10.1016/j.tet.2011.12.002. These data include MOL files and InChiKeys of the most important compounds described in this article.

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19. All new compounds give satisfied analytical and spectral data, which is available via the Internet at http://www.sciencedirect.com/.