Convenient Synthesis of 3*H*-Indoles (Indolenines) by Reaction of 1*H*-Indoles with Corey–Kim Reagent

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A new preparation method for a variety of 3*H*-indoles by 3-methylthiomethylation is described. Reactions of 1*H*-indoles with *S,S*-dimethylsuccinimidosulfonium chloride (Corey–Kim reagent) in the presence of diisopropylethylamine afforded either 3,3-bis(methylthiomethyl)- or 3-methylthiomethyl-3*H*-indoles, depending upon the absence or the presence of a substituent at the C-3 position.

Keywords 3*H*-indole; dienophile; dipolarophile; *S,S*-dimethylsuccinimidosulfonium chloride; Corey–Kim reagent; methylthiomethylation; azasulfonium salt

3*H*-Indoles (indolenines) are interesting dienophile or dipolarophile synthons applicable to cycloaddition[1] or 1,3-dipolar cycloaddition.[2] Although 3-halo-3*H*-indoles have been obtained by halogenation of the corresponding 1*H*-indoles in good yields,[3] preparation of 3-alkyl-3*H*-indoles by 3-alkylation of 1*H*-indoles is not usually satisfactory in terms of yield owing to the competing 1-alkylation.[4] In addition, it has been reported that 1*H*-indole gave 3-methylthiomethyl-1*H*-indole upon reaction with the dimethyl sulfoxide–dicyclohexylcarbodiimide (DMSO–DCC) adduct in the presence of base in low yields,[5] and 3,3-dialkylsulfonium salts with *S,S*-dialkylsuccinimidosulfonium salt in the absence of base.[6]

On the other hand, it is well known that *S,S*-dimethylsuccinimidosulfonium chloride (Corey–Kim reagent) **1** reacts with nucleophiles such as alcohols and phenols in the presence of base to give the corresponding carbonyl compounds and *ortho*-methylthiomethylphenols *via* oxasulfonium salts, respectively.[7] We though that the reaction of **1** with 1*H*-indoles as nucleophiles in the presence of base would afford 3-methylthiomethyl-3*H*-indoles through formation of the azasulfonium salt followed by [2,3]-sigmatropic rearrangement (Sommelet Hauser rearrangement).[8] Herein we wish to report a convenient method for synthesis of 3,3-bis(methylthiomethyl)- or 3-methylthiomethyl-3*H*-indoles **3** by reaction of 1*H*-indoles **2** with an excess of the Corey–Kim reagent **1** in the presence of diisopropylethylamine (Hunnig base).

Results and Discussion

The reaction of the 1*H*-indoles (**2**) with an excess (*ca.* 4.0 eq) of the reagent (**1**) was carried out in dry methylene chloride at −78 °C under an atmosphere of argon in the presence of diisopropylethylamine to give, after the usual work-up, the 3*H*-indoles (**3**). The results are summarized in Tables I and II.

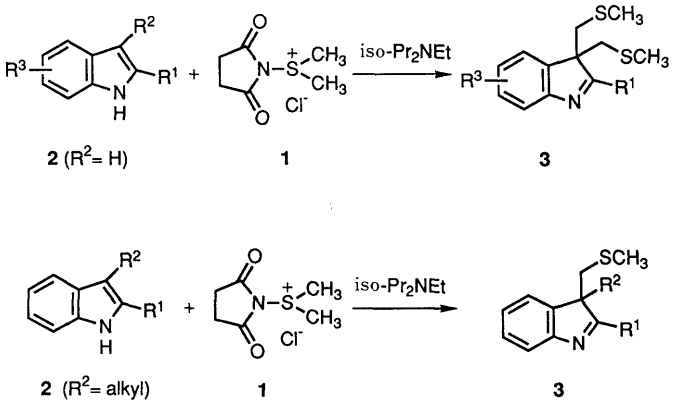

Chart 1

The reaction of 3-unsubstituted 1*H*-indoles **2a—e** with the reagent **1** gave 3,3-bis(methylthiomethyl)-3*H*-indoles **3a—e** in satisfactory yields compared with the known methods[5] except for the case of entry 2 where product **3b** is too unstable to isolate quantitatively by column chromatography (Table I). The reaction proceeded even in the presence of an acid-labile functional group such as methoxymethyl (MOM) ether (entry 3). But, in the case of a substrate having a strongly electron-withdrawing group such as a nitro group, the 3*H*-indole was not obtained and only an unidentified mixture was formed.

The reaction of 3-substituted 1*H*-indoles **2g—k** with the reagent **1** afforded 3-methylthiomethyl-3*H*-indoles **3g—k** in satisfactory yields except for the case of entry 1 where the product **3g** was very unstable on silica gel, like compound **3b** (Table II). In the reaction of the 1*H*-indole **2j**, use of 4 eq of the reagent **1** led to recovery of the starting material

TABLE I. Reactions of 3-Unsubstituted 1*H*-Indoles **2** with the Corey–Kim Reagent **1**

Entry	Mol ratio **1/2**	R^1	R^3	**3**[a]	Yield (%)
1	4	H	H	**a**	85
2	4	CH_3	H	**b**	30
3	4	H	4-MOM	**c**	66
4	8	H	5-Cl	**d**	70
5	4	H	5-OMe	**e**	69
6	4	H	5-NO_2	**f**	0

a) All products were obtained as colorless oils. MOM: methoxymethyl.

TABLE II. Reactions of 3-Substituted 1*H*-Indoles **2** with the Corey–Kim Reagent **1**

Entry	Mol ratio **1/2**	R^1	R^2	**3**[a]	Yield (%)
1	4	H	CH_3	**g**	43
2	4	H	$(CH_2)_2OMOM$	**h**	77
3	4	H	$(CH_2)_3OMOM$	**i**	74
4	8	CH_3	CH_3	**j**	82
5	4	$CH_2(CH_2)_2CH_2$		**k**	76
6	4	H	CH_2NMe_2	**l**	0[b]
7	4	H	$CH_2N(CH_2)_4$	**m**	0[c]

a) All products were obtained as colorless oils. *b*) Compound **3a** was isolated in 66% yield. *c*) Compound **3a** was isolated in 43% yield.

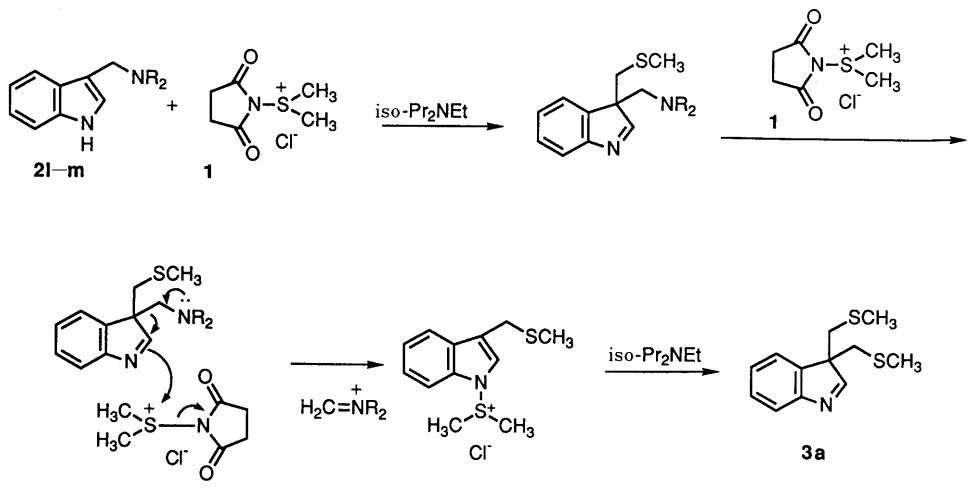

Chart 2

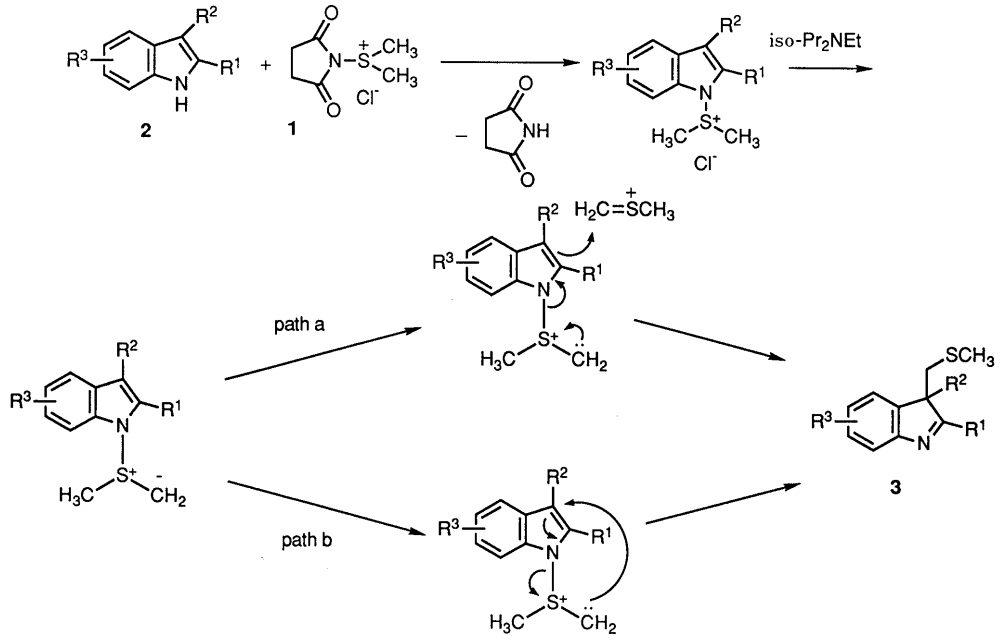

Chart 3

in 34% yield along with the 3*H*-indole **3j** in 52% yield.

In the reaction of 3-aminomethyl-1*H*-indoles **2l—m** with the reagent **1** the expected 3-aminomethyl-3-methylthiomethyl-3*H*-indoles were not obtained but only the 3,3-bis(dimethylthiomethyl)-3*H*-indole **3a** was generated. These reactions can be explained by the reaction mechanism shown in Chart 2 involving elimination of an immonium group followed by regeneration of the azasulfonium salt.

The structures of the 3*H*-indoles **3** were confirmed by the nuclear magnetic resonance (NMR) spectral data (the ^{13}C and ^{1}H signals at δ 173—187 and δ 8.01—8.17 of the imino group).

1-Methyl-1*H*-indole, in which NH proton is protected by the methyl group, was quite unreactive to the reagent **1**. This fact and the generation of **3a** by the reaction of **2l—m** with **1** suggest that the reaction of 1*H*-indoles **2** with the reagent **1** in the presence of base proceeded through formation of the azasulfonium salt, dissociation of the ylide, and then alkylation at the C-3 position by methylmethylene sulfonium ion (path a), or intramolecular rearrangement of the ylide in a [2,3]-sigmatropic manner (path b) (Chart 3).

In conclusion, we have demonstrated that the reactions of the Corey–Kim reagent with 1*H*-indoles in the presence of diisopropylethylamine afforded 3*H*-indoles in satisfactory yields. These reactions proceeded at low temperature and were applicable to compounds containing acid-labile functional groups. Therefore, this method should provide a useful means for the preparation of various 3*H*-indoles.

Experimental

Spectral data were obtained using the following apparatus: infrared (IR) spectra on a JASCO IR-810 spectrophotometer; ultraviolet (UV) spectra in ethanol on a Hitachi spectrophotometer U-3200; mass spectra (MS) on a JEOL JMS-DX300 mass spectrometer by direct insertion at 70 eV; ^{1}H- and ^{13}C-NMR spectra in chloroform-*d* ($CDCl_3$) at 270 MHz on a JEOL JMN-GX270 instrument with chemical shifts being reported in δ units from tetramethylsilane as an internal standard and coupling constants in hertz.

General Method for Preparation of 3*H*-Indoles (3) from 1*H*-indoles (2) Dimethylsulfide (2.3 ml, 30.8 mmol) was added dropwise to a suspension of *N*-chlorosuccinimide (3.738 g, 28.0 mmol) in anhydrous dichloro-

methane (90 ml) at −78 °C under argon and stirring was continued for 1 h at the same temperature. Then, a solution of 1*H*-indole **2a** (7.0 mmol) and diisopropylethylamine (5.3 ml, 30.4 mmol) in anhydrous dichloromethane (30 ml) was added to the above mixture at the same temperature. Stirring was continued until the reaction mixture changed from a colorless suspension to a clear yellow solution (generally requires reaction times of 3—5 h). The mixture was treated with cooled brine (40 ml) and extracted with ether (120 ml). The organic layer was washed three times with brine (60 ml) and dried over anhydrous magnesium sulfate. The solvent was evaporated, and the residue obtained with purified by column chromatography (100—200 mesh, Micro Bead 4B, Fuji-Davison Chemical Ltd., eluent; 20% ether in hexane) to afford the 3*H*-indole **3a**.

3,3-Bis(methylthiomethyl)-3*H*-indole (3a) IR (neat): 1615, 1600, 1550 cm^{-1}. UV nm (log ε): 225 (4.01), 253.6 (3.55), 281 (3.28). ^{1}H-NMR δ: 1.99 (6H, s, CH_3–S), 2.99 (4H, ABq, J=13.4 Hz, CH_2–S), 7.23 (1H, t, J=7.4 Hz, H-5 or H-6). 7.36 (1H, t, J=7.4 Hz, H-6 or H-5), 7.47 (1H, d, J=7.4 Hz, H-4 or H-7), 7.63 (1H, d, J=7.4 Hz, H-7 or H-4), 8.13 (1H, s, H-2). ^{13}C-NMR δ: 18.0 (CH_3–S), 38.7 (CH_2–S), 62.6 (C-3), 121.3 (C-4 or C-7), 122.6 (C-7 or C-4), 126.2 (C-5 or C-6), 128.6 (C-6 or C-5), 140.6, 155.4 (C-3a, C-7a), 175.7 (C-2). MS *m/z* (%): 237 (M^+, 6), 190 (41), 143 (72), 61 (base). HRMS *m/z*: M^+ Calcd for $C_{12}H_{15}NS_2$: 237.0645. Found: 237.0641.

3,3-Bis(methylthiomethyl)-2-methyl-3*H*-indole (3b) IR (neat): 1580 cm^{-1}. UV nm (log ε): 214 (4.11), 253 (3.90), 285 (3.64). ^{1}H-NMR δ; 1.83 (6H, s, CH_3–S), 2.29 (3H, s, C-2–CH_3), 2.97 (4H, ABq, J=13.3 Hz, CH_2–S), 7.17 (1H, t, J=7.4 Hz, H-5 or H-6), 7.33 (1H, t, J=7.4 Hz, H-6 or H-5), 7.46 (1H, d, J=7.4 Hz, H-4 or H-7), 7.54 (1H, d, J=7.4 Hz, H-7 or H-4). ^{13}C-NMR δ 16.5 (C-2–CH_3), 17.4 (CH_3–S), 39.8 (CH_2–S), 62.8 (C-2), 119.9 (C-4 or C-7), 122.7 (C-7 or C-4), 125.0 (C-5 or C-6), 128.6 (C-6 or C-5), 140.4 (C-4a or C-7a), 155.0 (C-7a or C-4a), 183.3 (C-2). MS *m/z* (%): 251 (M^+, 3), 204 (29), 143 (87), 61 (base). HRMS *m/z*: M^+ Calcd for $C_{13}H_{17}NS_2$: 251.0802. Found: 251.0799.

3,3-Bis(methylthiomethyl)-4-methoxy-3*H*-indole (3c) IR (neat): 1600 cm^{-1}. UV nm (log ε): 219 (4.15), 253 (3.48), 290 (3.38). ^{1}H-NMR δ: 1.96 (6H, s, CH_3–S), 3.24 (4H, ABq, J=13.4 Hz, CH_2–S), 3.49 (3H, s, CH_3–O), 5.25 (2H, s, CH_2–O), 6.96—6.99 (1H, m, aromatic protons), 7.32—7.34 (2H, m, aromatic protons), 8.14 (1H, s, H-2). ^{13}C-NMR δ: 18.0 (CH_3–S), 37.4 (CH_2–S), 56.2 (CH_3–O), 64.8 (C-3), 94.0 (O–CH_2–O), 111.8, 115.2, 130.2 (C-5, C-6, C-7), 126.8 (C-3a), 153.2, 157.3 (C-4, C-7a), 176.6 (C-2). MS *m/z* (%): 298 (M^++1, 3), 297 (M^+, 18), 250 (79), 61 (base). HRMS *m/z*: M^+ Calcd for $C_{14}H_{19}NO_2S_2$: 297.0857. Found: 297.0860.

3,3-Bis(methythiomethyl)-5-chloro-3*H*-indole (3d) IR (neat): 1570 cm^{-1}. UV nm (log ε): 219 (4.18), 259 (3.78). ^{1}H-NMR δ: 2.06 (6H, s, CH_3–S), 3.00 (4H, ABq, J=13.4 Hz, CH_2–S), 7.37 (1H, dd, J=2.0, 8.4 Hz, H-6), 7.49 (1H, d, J=2.0 Hz, H-4), 7.57 (1H, d, J=8.4 Hz, H-7), 8.14 (1H, s, H-2). ^{13}C-NMR δ: 18.2 (CH_3–S), 38.6 (CH_2–S), 63.2 (C-3), 122.3 (C-7), 123.3 (C-4), 129.0 (C-6), 132.3 (C-5), 142.5 (C-3a or C-7a), 154.0 (C-7a or C-3a), 176.0 (C-2). MS *m/z* (%): 273 (M^++2, 5), 272 (M^++1, 2), 271 (M^+, 12), 224 (59), 61 (base). HRMS *m/z*: M^+ Calcd for $C_{12}H_{14}ClNS_2$: 271.0256. Found: 271.0252.

3,3-Bis(methylthiomethyl)-5-methoxy-3*H*-indole (3e) IR (neat): 1770, 1610, 1595 cm^{-1}. UV nm (log ε): 224 (4.06), 280 (3.76), 288 (3.70). ^{1}H-NMR δ: 2.05 (6H, s, CH_3–S), 2.99 (4H, ABq, J=13.4 Hz, CH_2–S), 3.82 (3H, s, CH_3–O), 6.89 (1H, dd, J=2.5, 8.9 Hz, H-6), 7.06 (1H, d, J=2.5 Hz, H-4), 7.54 (1H, d, J=8.9 Hz, H-7), 8.01 (1H, s, H-2). ^{13}C-NMR δ: 17.6 (CH_3–S), 38.6 (CH_2–S), 55.7 (CH_3–O), 62.7 (C-3), 109.4 (C-4), 113.3 (C-6), 121.5 (C-7), 142.3, 149.0, 158.7 (C-3a, C-5, C-7a), 173.6 (C-2). MS *m/z* (%): 267 (M^+, 1), 220 (29), 61 (base). HRMS *m/z*: M^+ Calcd for $C_{13}H_{17}NOS_2$: 267.0751. Found: 267.0730.

3-Methyl-3-methylthiomethyl-3*H*-indole (6g) IR (neat): 1600 cm^{-1}. UV nm (log ε): 225 (3.52), 253 (3.40), 298 (2.76). ^{1}H-NMR δ 1.38 (3H, s, CH_3–C), 1.95 (3H, s, CH_3–S), 2.81 (2H, ABq, J=13.4 Hz, CH_2–S), 7.21—7.63 (4H, m, aromatic protons), 8.06 (1H, s, H-2). ^{13}C-NMR δ: 18.0 (CH_3–S), 19.4 (C-3–CH_3), 40.8 (CH_2–S), 58.11 (C-3), 121.1, 121.7, 126.1, 128.1 (C-4, C-5, C-6, C-7), 142.7 (C-3a), 154.8 (C-7a), 177.7 (C-2). MS *m/z* (%): 192 (M^++1, 2), 191 (M^+, 18), 144 (base), 61 (18). HRMS *m/z*: M^+ Calcd for $C_{11}H_{13}NS$: 191.0769. Found: 191.0774.

3-(2-Methoxymethoxyethyl)-3-methylthiomethyl-3*H*-indole (3h) IR (neat): 1680, 1565 cm^{-1}. UV nm (log ε): 215 (4.09), 254 (3.53), 294 (2.95). ^{1}H-NMR δ: 2.00 (3H, s, CH_3–S), 2.16—2.51 (2H, m, C-3–CH_2–C), 2.89 (2H, ABq, J=13.4 Hz, CH_2–S), 3.02—3.34 (2H, m, CH_2–O), 3.21 (3H, s, CH_3–O), 4.39 (2H, ABq, J=6.43 Hz, O–CH_2–O), 7.23—7.39 (3H, m, aromatic protons), 7.63 (1H, J=7.4 Hz, H-4 or H-7), 8.17 (1H, s, H-2). ^{13}C-NMR δ: 18.3 (CH_3–S), 34.3 (C-3–CH_2–C), 40.7 (CH_2–S), 55.2 (CH_3–O), 61.0 (C-3), 63.9 (C–CH_2–O), 96.5 (O–CH_2–O), 121.3, 122.3, 126.2, 128.5 (C-4, C-5, C-6, C-7), 140.5 (C-3a), 155.7 (C-7a), 177.2 (C-2). MS *m/z* (%); 266 (M^++1, 16), 265 (M^+, base), 218 (52), 158 (67). HRMS *m/z*: M^+ Calcd for $C_{14}H_{19}NO_2S$: 265.1137. Found: 265.1135.

3-(3-Methoxymethoxypropyl)-3-methylthiomethyl-3*H*-indole (3i) IR (neat): 1700 cm^{-1}. UV nm (log ε): 225.0 (3.81), 254.4 (3.28), 294.0 (2.69). ^{1}H-NMR δ: 1.02—1.34 (2H, m, C-3–C–CH_2), 1.87—2.22 (2H, m, C-3–CH_2–C), 2.00 (3H, s, CH_3–S), 2.91 (2H, ABq, J=13.3 Hz, CH_2–S), 3.30 (3H, s, CH_3–O), 3.37 (2H, t, J=6.2 Hz, C-3–C–C–CH_2), 4.53 (2H, s, O–CH_2–O), 7.24—7.39 (3H, m, aromatic protons), 7.63—7.66 (1H, m, aromatic proton), 8.11 (H-2). ^{13}C-NMR δ: 18.2 (CH_3–S), 24.6 (C-3–C–CH_2–C), 30.8 (C-3–CH_2), 40.4, (CH_2–S), 55.1 (CH_3–O), 62.3 (C-3), 67.4 (C–CH_2–O), 96.3 (O–CH_2–O), 121.4, 122.1, 126.3, 128.4 (C-4, C-5, C-6, C-7), 141.0, 155.7 (C-3a, C-7a), 177.2 (C-2). MS *m/z* (%): 280 (M^++1, 11), 279 (M^+, 58), 232 (74), 200 (base), 61 (87). HRMS *m/z*: M^+ Calcd for $C_{15}H_{21}NO_2S$: 279.1293. Found: 279.1281.

2,3-Dimethyl-3-methylthiomethyl-3*H*-indole (3j) IR (neat): 1575 cm^{-1}. UV nm (log ε): 220 (4.10), 254 (3.70). ^{1}H-NMR δ: 1.35 (3H, s, C-3–CH_3), 1.81 (3H, s, CH_3–S), 2.27 (3H, s, C-2–CH_3), 2.90 (2H, ABq, J=12.9 Hz, CH_2–S), 7.15—7.38 (3H, m, aromatic protons), 7.54 (1H, d, J=7.6 Hz, H-4 or H-7). ^{13}C-NMR δ: 15.9 (C-2–CH_3), 17.3 (CH_3–S), 21.8 (C-3–CH_3), 41.1 (CH_2–S), 58.2 (C-3), 119.9, 122.0, 125.1, 128.1 (C-4, C-5, C-6, C-7), 142.9 (C-3a), 154.4 (C-7a), 185.4 (C-2). MS *m/z* (%): 206 (M^++1, 2), 205 (M^+, 11), 158 (base), 61 (28). HRMS *m/z*: M^+ Calcd for $C_{12}H_{15}NS$: 205.0925. Found: 205.0922.

4a-Methylthiomethyl-2,3,4,4a-tetrahydro-1*H*-carbazole (6k) IR (neat): 1615, 1585 cm^{-1}. UV nm (log ε): 219 (4.20), 252 (3.74), 273 (3.59). ^{1}H-NMR δ: 1.15 (1H, dt, J=4.5, 12.9 Hz), 1.31—1.49 (1H, m), 1.67—1.77 (2H, m), 1.82 (3H, s, CH_3–S), 2.15—2.19 (1H, m), 2.44—2.60 (2H, m), 2.92—3.02 (1H, m), 2.97 (2H, ABq, J=13.2 Hz, CH_2–S), 7.16 (1H, t, J=7.4 Hz, H-6 or H-7), 7.29—7.35 (1H, m, H-7 or H-6), 7.43 (1H, d, J=6.4 Hz, H-5 or H-8), 7.59 (1H, d, J=7.4 Hz, H-8 or H-5). ^{13}C-NMR δ: 17.3 (CH_3–S), 21.2, 28.8, 30.1, 37.0 (C-1, C-2, C-3, C-4), 38.0 (CH_2–S), 58.2 (C-4a), 120.1 (C-5 or C-8), 122.1 (C-8 or C-5), 124.7 (C-6 or C-7), 128.0 (C-7 or C-6), 144.3 (C-5b or C-8a), 154.9 (C-8a or C-5b), 187.5 (C-9a). MS *m/z* (%): 232 (M^++1, 1), 231 (M^+, 6), 184 (base), 61 (7). HRMS: *m/z* M^+ Calcd for $C_{14}H_{17}NS$: 231.1082. Found: 231.1105.

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