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Manganese(III) Acetate Mediated Synthesis of 3-arylsulfenylindoles and Evaluation of Their Antibacterial Activity

RAVI KUMAR G.M.V.N.A.R. and THANGAMANI ARUMUGAM*

Department of Chemistry, Karpagam University, Karpagam Academy of Higher Education, Coimbatore- 641021, Tamil Nadu, India.
*corresponding author: Email: thangabell2003@gmail.com

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ABSTRACT

The present work reports a simple and efficient method for the sulfenylation of a wide variety of indoles with aryl, benzothiazolethiols using manganese(III) acetate promoted free radical reaction. This method is selective at the C3 position of indoles and offers several advantages such as broad substrate scope, functional group tolerance (bromo, carboxylic acid, methoxy, difluoromethoxy, ester groups) and gives the required products in good to excellent yields. The experimental simplicity makes it a useful and attractive approach for the synthesis of 3-arylsulfenylindoles. The compounds 1-12 are evaluated for the anti-bacterial agents. Most of them exhibited promising activities.

Keywords: Sulfenylation of indoles, Regioselectivity, Manganese(III) acetate, C-S bond formation, Antibacterial activity.

INTRODUCTION

Among the most important heterocyclic units indole nucleus has received major attention as a key structural building block due to their medicinal and pharmaceutical applications.[1] Further 3-thioindole motifs are very common in various drugs for the treatment of heart disease,[2] allergies,[3] these are also utilized in the field of organic nonlinear optical materials.[4] The following compounds such as MK-886 (III) is having antitumor activity,[5] L-737,126 (VII) is identified as a potent anti-HIV agent,[6] the 3-(arylsulfenyl)indole is able to inhibit human breast cancer cell growth,[7] vasoconstrictor tinazoline (I) is 4,5-dihydro-2-(3-indolyl) mercaptoimidazole known as a nasal decongestant[8] and acting as an alpha-adrenergic blocking drug (Figure 1).

It is planned to synthesize analogues of tinazoline by replacing the imidazole moiety with benzimidazole because compounds containing benzimidazole have numerous biological activities, for example antitumor[9] and antiparasitic[10]. Although compounds containing both indole-benzimidazoles are known to show diuretic acitivity[11] but their complete study is unexplored and hence this work targets to synthesize compounds containing both indole-benzimidazoles (or benzothiazole) through C-S bond.

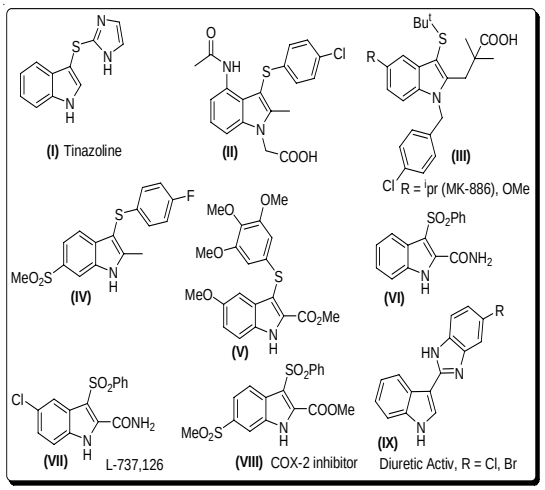
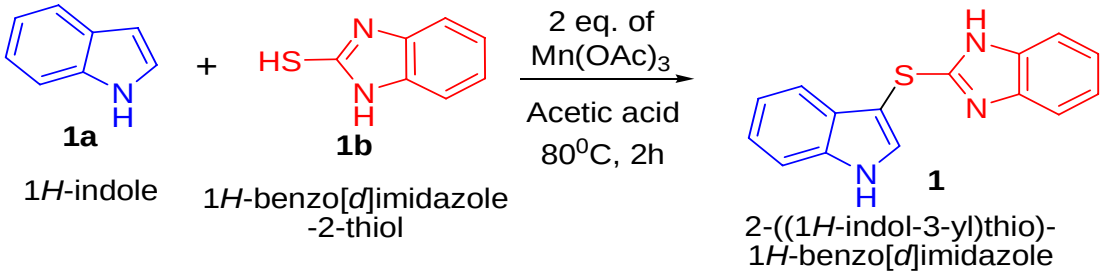


Fig.1. Biologically active thioindole derivatives and indole-benzimidazoles

Recently, various methods are reported for the 3-arylthiolation of indoles using the various sulfenylating agents such as buntesalts,[12] disulfides,[13] sulfenyl halides,[14] and N-thioarylphthalimides.[15] Reagents such as Vanadium oxyacetylacetonate,[16] $AlCl_3$[17], Selectfluor[18], NCS[19], oxone[20], FeF_3[21], (bis(trifluoroacetoxy)iodo benzene)[22], Cu[23] and Iodine[24], and $CeCl_3$[30] have been reported under different conditions. Particularly substrates substituted benzimidazolethiol and benzothiazolethiol were unexplored in the 3-arylthiolation. Therefore, the development of a simple, convenient and general methodology for the sulfenylation of indoles utilizing a stable and readily available reagent would extend the scope of this reaction and further applications of 3-arylsulfenyl indole products.

Although $Mn(OAc)_3$ is a good single-electron oxidant, selective, mild oxidant and commercially available. Use of Mn(III)acetate in C-C bond construction between carbon centered radical with olefins[25] and arenes[26] was well investigated. But its applications are limited mostly in the field of sulfur-centered free radicals generating from thiols.[27] The main advantage in the selection of this reagent is its moderate reactivity thereby is envisioned higher selectivity in the thioarylation.

Table 1: Screening of the Optimal Conditions [a]



Entry	Solvent	Temperature (°C)	Yield (%)[b]
1.	DMF	100	30
2.	Acetic acid	80	90
3.	H_2O	80	n.r.[c]
4.	EtOH	80	n.r.[c]

[a] Reaction conditions unless specified otherwise: 1H-Indole (1mmol), benzothiazole (1mmol) Solvent (10mL), under N2 atmosphere, 2 h.;

[b] Isolated yield.; [c] n.r. = no reaction.

MATERIAL AND METHODS

Initially we conducted reaction between 1H-indole and 1H-benzoimidazole thiol using $Mn(OAc)_3$and tried to optimize the reaction conditions (Table 1). In the beginning, this reaction is conducted under solvent free conditions followed by preferred solvents such as water and ethanol. But good results were not observed in the reaction. Then reaction is examined with toluene, acetonitrile, THF, DMF and acetic acid[28]. Among the different solvents surveyed, better yield was observed with acetic acid and moderate yield in DMF. Acetic acid is the solvent of choice, because it has a good solubility for $Mn(OAc)_3$ and also giving higher yields in addition to that it degrades rapidly to harmless substances in the environment.

RESULTS AND DISCUSSION

The optimized condition for regeo selective sulfenylation reaction of indoles consists of using Indole (1.0equiv.), thiol (1.0 equiv.), reagent (2 equiv.) in acetic acid at 80 ˚C for 2 h (Table-1, entry 2).With this optimized reaction condition, the scope of the reaction is extended by taking into account various thiols with indole derivatives. As shown in the Table. 2, unsubstituted indole with thiol yielded with the required products (85- 90%, entries 1-3), indoles with electron-donating methyl group (88-92%; Table entries 4,5,6,13 & 14) resulted higher yields in comparison to those having electron-withdrawing groups(72-76%; Table. 2, entries 10-12). The reaction is tolerant to bromo substituent on the aromatic ring of indole, and the corresponding target products were obtained in good yields (80-84%; Table 2, entries 7-9). Compounds 2a, 3a,5a, 6a,8a, 9a, 11a and 12a, are existing as a mixture of tautomers.[29]

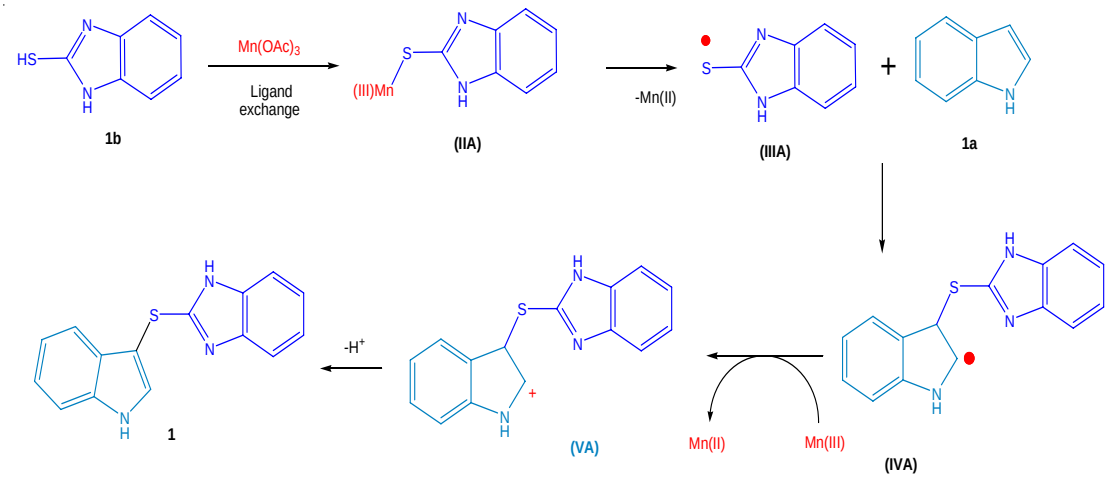
Plausible mechanism

A plausible mechanism[27c] is proposed involving ligand-exchange pathway for the reaction of indole with 1H-benzo[d]imidazole-2-thiol (1b) shown in the scheme-2. The ligand exchange between $Mn(OAc)^3$ and 1H-benzo[d]imidazole-2-thiol produces the intermediate (IIA), which gets oxidized to the sulphur centered free radical (IIIA), and then attacks the electron-rich site of indole i.e. the 3′-position to yield radical (IVA). Subsequently, $Mn(OAc)^3$ oxidizes radical (IVA) to cation (VA) , and finally loses a proton affording 3-arylthiol product (1).

EXPERIMENTAL

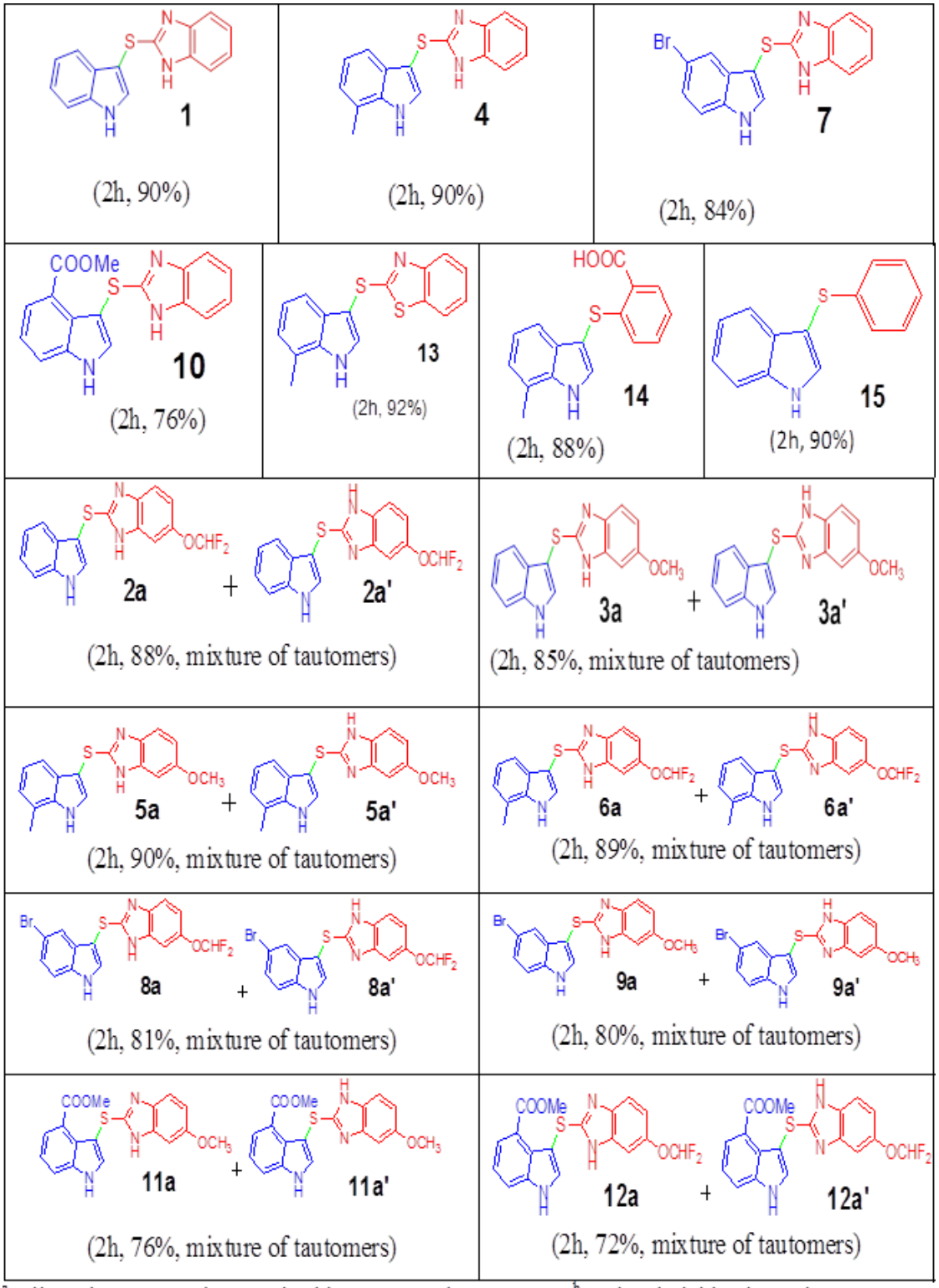
Chemistry

Melting points were determined in open capillaries and are uncorrected. IR spectra (KBr) were recorded on a Jasco, FT/IR–4100 spectrophotometer. Mass spectras were recorded on Shimadzu, LC-2010EV. ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL 400MHz and Brukar Avance 300 MHz spectrometer. TMS was used as internal reference. All the analysis data obtained at Sapala Organics Private Limited, Hyderabad.



Scheme-2: Mechanism involved in the arythiolation of Indoles

Table. 2: Reaction of various indoles with different thiols using $Mn(OAc)_3$



[a] All products were characterized by NMR and MS spectra.[b] Isolated yield using coloumn

MATERIALS AND METHODS

Manganese(III) acetate mono hydrate used for these reactions was purchased from Aldrich & Company. All the other solvents and raw materials were purchased from common suppliers. Reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (60A°; Aldrich & Company), visualized under 254 nm ultraviolet Light. Column chromatography separations were performed using silica gel (70–230 mesh) obtained from the Aldrich Company. The solvents used for elution varied depending on the compound and included either one or a combination of hexane and ethylacetate. All reactions were conducted under a nitrogen atmosphere unless otherwise noted.

Typical experimental procedure for the synthesis of Compounds 1-14.

Manganese triacetate (2 mmol) is added portion wise to a pre dissolved solution of Indole (1mmol) and benzimidazolethiol (1mmol) in acetic acid (10mL) at room temperature under Nitrogen atmosphere. The reaction mixture is stirred at 80 °C for 2 hours. After completion of reaction, as monitored by T.L.C analysis, the reaction mixture was quenched by the addition of water 20 ml. The organic compounds are extracted with ethyl acetate (3x20ml). The combined layers are dried over anh.Na_2SO_4. The required product is purified by column chromatography, eluted with 8% methanol in DCM to get the product. The product is confirmed by ^{1}H, ^{13}C, NMR, IR and mass.

2-(1H-indol-3-ylthio)-1H-benzo[d]imidazole (Compound 1):

90% Yield; m.p. 221°C; R_f= 0.750 (hexane:ethyl acetate, 60:40, v/v);^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ ppm 8.32 - 8.43 (3 H, m), 8.52 (1 H, t, *J*=7.44 Hz), 8.66 (2 H, br s), 8.79 (1 H, d, *J*=8.1 Hz), 8.83 - 8.86 (1 H, m), 9.21 (1 H, d, *J*=3.1 Hz), 13.13 (2 H, br s); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 95.6, 112.3, 118.1, 120.2, 121.2, 121.2, 122.1, 128.8, 133.0, 136.6, 150.9; IR: 3381 cm^{-1} (N-H); ESI-mass: m/z 266[M$^{\cdot+}$+1 peak]; Mol. Formula:$C_{15}H_{11}N_3S$;

2-(1H-indol-3-ylthio)-6-(difluoromethoxy)-1H-benzo[d]imidazole & 2-(1H-indol-3-ylthio)-5-(difluoromethoxy)-1H-benzo[d]imidazole (Compound 2 as tautomeric mixture of 2a and 2a'):

Yield 88%; m.p. 209-211 ^{0}C ^{0}C; R_f= 0.77 (hexane: ethyl acetate, 60:40, v/v); ^{1}H NMR (400MHz, DMSO-d_6,25°C) δ 6.90-6.93 (m, 1H), 7.05-7.36(m , 4H), 7.45 -7.52 (d, *J* = 7.8 Hz, 4H), 7.91 (1 H, d, *J* = 2.3 Hz), 11.82 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 95.2, 112.3, 113.6, 116.8, 118.0, 120.3, 122.2, 128.7, 133.2, 136.6, 145.7, 202.3; IR: 3411cm^{-1} (N-H); ESI-mass: m/z 332 [M$^{\cdot+}$+1 peak]. Mol. Formula: $C_{16}H_{11}F_2N_3OS$

2-(1H-indol-3-ylthio)-6-methoxy-1H-benzo[d] imidazole & 2-(1H-indol-3-ylthio)-5-methoxy-1H-benzo[d]imidazole (compound 3 as tautomeric mixture of 3a and 3a')

85% Yield; m.p. 219-221 ^{0}C ^{0}C; R_f= 0.77 (Hexane: Ethyl acetate, 60:40, v/v);^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ ppm 3.71 (s, 3H), 6.68 (dd, *J*= 8.6, 2.3 Hz, 1H), 6.86 (br s, 1H), 7.07 - 7.11(m, 1H), 7.15 - 7.29 (m, 2H), 7.47 (br d, *J* = 7.82 Hz, 1H), 7.51 (d, *J* = 7.83 Hz, 1H), 7.87 (d, *J* = 2.35 Hz, 1H), 11.78 (br s, 2H); ^{13}C NMR(100 MHz, DMSO-d_6) δ ppm 55.3, 96.1, 110.3, 112.2, 118.1, 120.1, 122.1, 128.8, 132.8, 136.6, 155.1; IR: 3363 cm^{-1} (N-H); ESI-Mass: m/z 296[M$^{\cdot+}$+1 peak]; Mol. Formula: $C_{16}H_{13}N_3OS$

2-(7-methyl-1H-indol-3-ylthio)-1H-benzo [d] imidazole (compound 4)

83% yield; m.p. 183 ^{0}C; Rf= 0.49 (Hexane: Ethyl acetate, 70:30, v/v); ^{1}H NMR(300 MHz, DMSO-d_6, 27°C) δ ppm 2.55 (3 H, s), 6.98–7.06 (4 H, m), 7.22 - 7.29 (2 H, m), 7.40–7.43 (1 H, m), 7.90 (1 H, d, *J*=2.7 Hz), 11.77 (1H, s), - 11.83 (1 H, s); ^{1}H NMR (300 MHz, CDCl3, 27°C) δ ppm 2.56 (3 H, s), 7.03 –7.19 (6 H, m), 7.47 - 7.52 (2 H, m), 8.38 (1 H, bs); ^{13}C NMR (500 MHz, DMSO-d_6) δ ppm 97.5, 115.5, 118.0, 118.0, 121.5, 121.9, 123.0, 123.9, 126.1, 127.7, 133.5, 154.0, 171.4; ESI-Mass: m/z 280 [M$^{\cdot+}$+1 peak]; Mol. Formula: $C_{16}H_{13}N_3S$

2-(7-methyl-1H-indol-3-ylthio)-6-methoxy-1H-benzo[d]imidazole & 2-(7-methyl-1H-indol-3-ylthio)-5-methoxy-1H-benzo[d]imidazole (compound 5 as tautomeric mixture of 5a and 5a')

Yield 90% ; m.p. 183 ^{0}C; Rf= 0.6 (hexane: ethyl acetate, 70:30, v/v);^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ ppm 2.45 (6 H, s), 3.30(6 H, s), 3.66(6 H, s), 3.77(6 H, s), 6.45(1 H, d, *J*=2 Hz), 6.57(1 H, d, *J*=2 Hz), 6.57(1 H, d, *J*=2 Hz), 6.74-6.79 (2H, m),6.83-6.87 (2H, m), 6.97-7.01 (5H, m), 7.16 (1H, d, J=8.8Hz), 7.42-7.47 (2H, m); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 16.7, 55.6, 55.6, 94.7, 94.7, 99.5, 99.7, 109.9, 110.2, 110.3, 110.9, 118.0, 118.1,

119.6, 120.8, 120.9, 122.5, 122.5, 124.9, 126.4, 126.4, 128.2, 128.4, 128.5, 131.6, 134.0, 134.1, 135.1, 156.1, 156.6, 170.1; IR: 3410 cm^{-1} (N-H); ESI-mass: m/z 310 [$M^{\cdot+}$+1 peak]; Mol. Formula: $C_{17}H_{15}N_3OS$

2-(7-methyl-1H-indol-3-ylthio)-6-(difluoromethoxy)-1Hbenzo[d]imidazole & 2-(7-methyl-1H-indol-3-ylthio)-5-(difluoromethoxy)-1H-benzo[d]imidazole (compound 6 as tautomeric mixture of 6a and 6a')

Yield 89%, m.p. 110^{0}C, R_f= 0.77 (hexane: ethyl acetate, 60:40, v/v); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ ppm 2.53 - 2.54 (4 H, m), 6.89 - 6.93 (2 H, m), 6.98 - 7.04 (3 H, m), 7.10 (2 H, s), 7.90 (1 H, d, *J*=3.1 Hz), 11.67 - 12.07 (2 H, m) ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 16.5, 58.2, 95.5, 113.6, 114.3, 115.6, 116.8, 120.5, 121.6, 122.7, 128.5, 132.9, 136.1, 145.7, 152.7; IR: 3402 cm^{-1} (N-H); ESI mass: m/z 346 [M.++1 peak]; Mol. Formula: $C_{17}H_{13}F_2N_3OS$

2-(5-bromo-1H-indol-3-ylthio)-1H-benzo[d] imidazole (compound 7)

Yield 84% , m.p. 268-270 ^{0}C, Rf Value 0.86 (10% methanol in DCM); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ ppm 7.06 -7.08 (2 H, m), 7.30 - 7.35 (3 H, m), 7.47 – 7.49 (1 H, d , J=8.4), 7.57 (1H, d, J=1.6), 7.93 (1H, d, J=2.8), 11.99 (2H, bs); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 95.2, 113.0, 113.7, 116.8, 114.5, 120.2, 124.8, 130.7, 134.8, 135.4, 145.8; IR: 3392cm^{-1} (N-H); ESI-mass: m/z 344 [$M^{\cdot+}$+1 peak]; Mol. Formula: $C_{15}H_{10}BrN_3S$

2-(5-bromo-1H-indol-3-ylthio)-5-(difluoromethoxy)-1H-benzo[d]imidazole & 2-(5-bromo-1H-indol-3-ylthio)-6-(difluoromethoxy)-1H-benzo[d] imidazole (compound 8 as tautomeric mixture of 8a and 8a')

Yield 81% , m.p. 240 ^{0}C, Rf =0.51 (in 10% methanol in DCM); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.97(1 H, dt, *J*=5.8, 2.5 Hz), 7.16 (1 H, s), 7.22(1 H, br s), 7.30 - 7.48(3 H, m), 7.55(1 H, d, *J*=8.6 Hz), 7.63(1 H, d, *J*=1.5Hz), 8.02(1 H, d, *J*=2.3Hz), 11.96 - 12.21(2 H, m); ^{1}H NMR (400 MHz, CD_3OD) δ ppm 6.69(1H, t, 74.4 Hz), 6.91 (1H, d, J=8.8Hz), 6.93 (5H , d , J= 8.8)^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 95.6, 112.9, 114.4, 120.2, 121.3, 124.7, 130.8, 134.6, 135.3, 150.38; IR: 3398 cm^{-1} (N-H); ESI-mass: m/z 411 [M^{+}+1 peak]; Mol. Formula: $C_{16}H_{10}BrF_2N_3OS$

2-(5-bromo-1H-indol-3-ylthio)-5-methoxy-1H-benzo[d]imidazole & 2-(5-bromo-1H-indol-3-ylthio)-6-methoxy-1H-benzo[d]imidazole (compound 9 as tautomeric mixture of 9a and 9a')

Yield 80% , m.p. 190^{0}C, Rf Value 0.47 (in 10% methanol in DCM), ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ ppm 3.70(3H, s), 6.69(1H, dd, J= 8.8Hz, J=2.4Hz), 6.86 (1H, bs), 7.23(1H, d, J=7.2 Hz), 7.3(1H, dd, J=8.4, J=3.2 Hz), 7.47(1H, d, J=7.2 Hz), 7.57 (1H, s), 7.91 (1H, d, J=2.8Hz), 11.82 (1H, s), 11.95(1H, s); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 55.3, 95.2, 96.0, 106.0, 110.4, 112.9, 114.4, 120.2, 124.7, 130.7, 134.4, 135.3, 155.1; IR: 3389 cm^{-1} (N-H); ESI mass: m/z 373[M.$^{+}$+1 peak]; Mol. Formula: $C_{16}H_{12}BrN_3OS$

methyl 3-(1H-benzo[d]imidazol-2-ylthio)-1H-indole-4-carboxylate (compound 10)

Yield 76%, m.p. 240 ^{0}C, Rf Value 0.54(in 10% methanol in DCM); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 - 1.27 (m, 1 H), 3.67-3.95 (m, 4 H), 7.01 - 7.13 (m, 2 H), 7.23 - 7.34 (m, 1 H), 7.40 - 7.50 (m, 1 H), 7.63 (d, *J*=8.6Hz, 1H), 7.84 (dd, *J*=8.6, 1.5 Hz, 1H), 8.04 - 8.16 (m, 2H), 11.97 (s, 1H), 12.19 (br s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 51.7, 97.4, 110.5, 112.5, 117.4, 120.4, 121.1, 121.5, 121.7, 123.1, 128.5, 135.2, 139.3, 143.9, 150.4, 166.8; IR: 1688 cm^{-1} (ester, C=O stretching), 1618 (ester, C=O asym. Str.);ESI Mass: m/z 324 [$M^{\cdot+}$+1 peak]; Mol. Formula: $C_{17}H_{13}N_3O_2S$

methyl 3-(5-methoxy-1H-benzo[d]imidazol-2-ylthio)-1H-indole-4-carboxylate & methyl 3-(6-methoxy-1H-benzo[d]imidazol-2-ylthio)-1H-indole-4-carboxylate (compound 11 as tautomeric mixture of 11a and 11a')

76% Yield, m.p. 220 ^{0}C, Rf Value 0.60(in 10% methanol in DCM); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ ppm 1.15 - 1.35 (1 H, m), 3.29 (1 H, br s), 3.36 (3 H, br s), 3.70 - 3.90 (7 H, m), 6.71 (1 H, d, *J*=8.8Hz), 6.87 (1 H, br s), 7.24 (1 H, br d, *J*=8.6 Hz), 7.62 (1 H, d, *J*=8.6Hz), 7.84 (1 H, dd, *J*=8.6, 1.5Hz), 8.04 (1 H, d, *J*=2.3Hz), 8.16 (1H, s), 12.17 (1H, br s); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 51.7, 55.3, 97.8, 110.4, 112.4, 120.4, 121.7, 123.0, 128.5, 135.0, 139.3, 155.2, 166.8; IR: 1685 cm^{-1} (ester, C=O symm. str.), 1619 (ester, C=O asym. Str.) ESI mass: m/z 354 [$M^{\cdot+}$+1 peak]; Mol. Formula: $C_{18}H_{15}N_3O_3S$

Table.3: Anti-bacterial activity *(Cup-plate Method)*

Compound	Conc of test sample (µg/mL)	Zone of inhibition in mm (mean ± SD) n=3 S.A.	P.A.	B.S.	S. typhi	E. coli
2	800	18 ± 0.2	20 ± 0.1	24 ± 0.1	18 ± 0.2	28 ± 0.1
	400	15 ± 0.1	20 ± 0.3	20 ± 0.1	15 ± 0.1	26 ± 0.2
	200	11 ± 0.1	19 ± 0.1	19 ± 0.1	14 ± 0.2	23 ± 0.1
3	800	26 ± 0.2	14 ± 0.1	18 ± 0.2	14 ± 0.1	20 ± 0.2
	400	24 ± 0.1	12 ± 0.1	14 ± 0.1	13 ± 0.2	20 ± 0.1
	200	17 ± 0.1	11 ± 0.2	-	11 ± 0.1	17 ± 0.1
1	800	26 ± 0.1	22 ± 0.2	22 ± 0.2	27 ± 0.2	29 ± 0.1
	400	22 ± 0.2	20 ± 0.1	20 ± 0.1	22 ± 0.2	27 ± 0.3
	200	18 ± 0.1	18 ± 0.2	20 ± 0.2	18 ± 0.1	22 ± 0.1
4	800	18 ± 0.3	20± 0.1	22 ± 0.2	13 ± 0.2	28 ± 0.2
	400	13 ± 0.2	18 ± 0.2	18 ± 0.1	11 ± 0.3	26 ± 0.1
	200	-	14± 0.1	15 ± 0.1	-	22 ± 0.2
8	800	26 ± 0.2	23 ± 0.1	20 ± 0.1	22 ± 0.3	28 ± 0.2
	400	24 ± 0.3	21 ± 0.3	20 ± 0.3	19 ± 0.2	22 ± 0.1
	200	20 ± 0.1	20 ± 0.2	18 ± 0.2	12 ± 0.2	16 ± 0.1
7	800	22 ± 0.2	16 ± 0.1	20 ± 0.1	12 ± 0.3	16 ± 0.1
	400	17 ± 0.3	15 ± 0.3	19 ± 0.3	-	14 ± 0.3
	200	11 ± 0.1	15 ± 0.2	13 ± 0.2	-	13 ± 0.2
9	800	24 ± 0.2	26 ± 0.1	16 ± 0.1	20 ± 0.3	24 ± 0.3
	400	22 ± 0.3	22 ± 0.3	15 ± 0.3	19 ± 0.2	22 ± 0.2
	200	15 ± 0.1	18 ± 0.2	12 ± 0.2	19 ± 0.1	-
5	800	13 ± 0.2	22 ± 0.1	26 ± 0.1	13 ± 0.3	17 ± 0.1
	400	12 ± 0.3	20 ± 0.3	22 ± 0.1	11 ± 0.2	13 ± 0.3
	200	-	17 ± 0.2	18 ± 0.2	-	11 ± 0.2
6	800	24 ± 0.2	23 ± 0.1	24 ± 0.1	19 ± 0.1	28 ± 0.1
	400	20 ± 0.2	22 ± 0.3	18 ± 0.3	15 ± 0.2	25 ± 0.1
	200	19 ± 0.1	20 ± 0.2	13 ± 0.2	11 ± 0.2	18 ± 0.2
10	800	14 ± 0.2	26 ± 0.1	28 ± 0.1	19 ± 0.3	30 ± 0.1
	400	13 ± 0.1	18 ± 0.1	16 ± 0.1	12 ± 0.1	29 ± 0.2
	200	-	13 ± 0.2	11 ± 0.2	-	22 ± 0.2
11	800	24 ± 0.1	26 ± 0.1	27 ± 0.2	24 ± 0.1	28 ± 0.1
	400	18 ± 0.3	23 ± 0.1	23 ± 0.1	18 ± 0.1	22 ± 0.3
	200	12 ± 0.2	19 ± 0.2	19 ± 0.2	13 ± 0.2	19 ± 0.1
12	800	24 ± 0.1	25 ± 0.1	23 ± 0.2	18 ± 0.1	29 ± 0.1
	400	22 ± 0.3	20 ± 0.1	20 ± 0.1	16 ± 0.1	24 ± 0.3
	200	16 ± 0.2	18 ± 0.2	17 ± 0.2	15 ± 0.2	24 ± 0.1
Standard (Amoxicillin)	1mg/ml	36 ± 0.2	36 ± 0.2	34 ± 0.1	32 ± 0.2	31 ± 0.2

S.A.- Staphylococcus aureus; P.A. - pseudomonas aeruginosa;
B.S. - Bacillus subtilius; S.T. - Salmonella typhi; E Coli- Escherichia coli
Note: Bore size: 8 mm; Standard: Amoxcillin; Control: DMF (Dimethyl Formamide)

methyl3-(5-(difluoromethoxy)-1H-benzo[d]imidazol-2-ylthio)-1H-indole-4-carboxylate & methyl 3-(6-(difluoromethoxy)-1H-benzo[d]imidazol-2-ylthio)-1H-indole-4-carboxylate (compound 12 as tautomeric mixture of 12a and 12a')

Yield 72% , m.p. 205-207^{0}C, Rf Value 0.45(in 10% methanol in DCM); ^{1}H NMR (400 MHz, DMSO-d_6, 25°C) δ ppm 3.74 (1 H, s), 3.78 - 3.86 (3 H, m), 6.93 (1H, br d, *J*=6.2Hz), 7.11 (1H, s), 7.17 (1H, br s), 7.24 - 7.44 (1H, m), 7.64 (1H, br d, *J*=8.6Hz), 7.85 (1H, br d, *J*=7.8Hz), 8.04 - 8.11 (1H, m), 8.11 - 8.17 (1 H, m), 11.99 - 12.27 (2 H, m); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 51.5, 51.7, 97.0, 112.5, 113.7, 120.3, 121.8, 123.1, 124.8, 128.5, 135.3, 139.3, 145.8, 166.8; IR: 3312 cm^{-1} (N-H), 1698 (ester, C=O symm. Str.), 1619 (ester, C=O asymm. Str.); ESI mass: m/z 390 [M$^{\cdot+}$+1 peak]; Mol. Formula: $C_{18}H_{13}F_2N_3O_3S$

2-(7-methyl-1H-indol-3-ylthio)benzo[d]thiazole (Compound 13)

Yield 92% , m.p. 210 ^{0}C, Rf Value 0.80 (10% methanol in DCM) ^{1}H NMR (300 MHz, DMSO-d_6, 27°C) δ ppm 2.54 (3 H, s), 7.03 (2 H, m), 7.22-7.28 (1H, m), 7.35-7.43 (2H, m), 7.8 (2H, d, J= 8.7Hz), 12.04 (1H, bs); ^{1}H NMR (300 MHz, CD_3OD-d_6, 27°C) δ ppm 2.58 (3 H, s), 7.06 –7.11 (2 H, m), 7.23-7.28 (1H, t, J=7.2Hz), 7.39-7.44 (2H, m), 7.65-7.68 (1H,d, J=8.1Hz), 7.75 -7.78 (2H, m); C^{13}NMR (500 MHz, DMSO-d_6, 27 °C) 16.5, 97.5, 115.5, 121.02, 121.0, 121.5, 121.9, 123.0, 123.9, 126.1, 127.7, 133.5, 154.0, 173.4; ; IR: 3418 cm^{-1} (N-H); ESI mass: m/z 297 [M$^{\cdot+}$+1 peak]; Mol. Formula: $C_{16}H_{12}N_2S_2$

2-(7-methyl-1H-indol-3-ylthio)benzoic acid (compound 14)

Yield 88% , m.p.143 ^{0}C, Rf Value 0.61(10% methanol in DCM); H^1 NMR (300 MHz, CD3OD, 27 °C) δ ppm 2.58 (3H, s), 7.73 –7.76 (1H, dd, J=0.9Hz, J=6Hz), 6.92-6.98 (2H, m), 7.04 (1H,t, J=6.3), 7.10 (1H, t, J=5.7), 7.98 (1H, d, J=5.7), 7.48 (1H, m), 7.96 (1H, dd, J=6, J=1.2), 11.09 (1H, bs) ESI mass: m/z 284[M$^{\cdot+}$+1 peak]; Mol. Formula: $C_{16}H_{13}NO_2S$

Anti-bacterial activity

The newly synthesized compounds 1 to 12 are screened for antibacterial activity against *gram-positive* bacterium (*B. subtilis and S. aureus)* and *Gram-negativ*e bacteria (*P. aeruginosa*, *E. coli* and *S. typhi).* Dimethyl formamide is used as solvent control. The bacterial culture was inoculated on nutrient agar (Merck & Co.) (20 mL) and poured into sterilized Petri dishes (99 mm). Media plates were inoculated with liquid cultures homogeneously by spread plate method. All the test compounds were dissolved in dimethyl formamide(DMF) to get different concentration of 100 µL and loaded into the wells of agar plates directly. Plates inoculated with the bacteria were incubated at 37 °C for 24 hours. All determinations were done in triplicates. Amoxicillin (1mg/mL) were used as standard drugs for antibacterial.

The results for antibacterial activities depicted in Table 3. It reveals most of the compounds (1, 2, 4, 6, 8, 10, 11, and 12) showing good anti-bacterial activity against *E.coli.* Incorporation of the ester group in the fourth position of the indole nucleus is favorable to anti-bacterial activity. Whereas the incorporation of Bromo or Methyl group on the indole nucleus is unfavorable to anti-bacterial activity.

CONCLUSION

A simple, convenient and inventive protocol for the sulfenylation of indoles using $Mn(OAc)_3$ reagent was developed. This method offers several advantages such as broad substrate scope, high yields and regioselectivity. The experimental simplicity makes it a valuable and elegant strategy for the synthesis of 3-sulfenyl indoles.

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