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$SnCl_2$/RSH: a versatile catalytic system for the synthesis of 4-alkylsulfanyl-indazole derivatives

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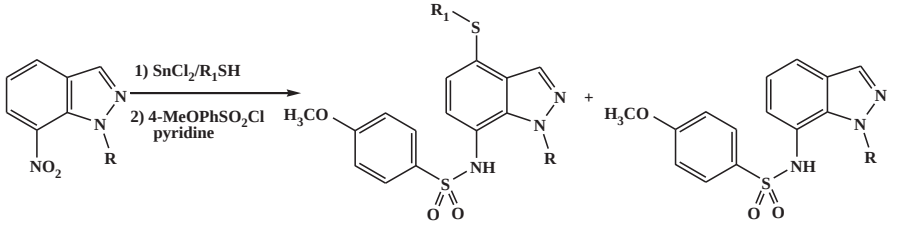
The treatment of alkylated nitro derivatives of indazole with stannous chloride in alkanethiol gave after coupling of the obtained amines with 4-methoxybenzenesulfonyl chloride in pyridine the new *N*-(4-alkylsulfanylindazol-7-yl)-4-methoxybenzene sulfonamides via the nucleophilic substitution of hydrogen in position 4 of indazole, together with the expected 4-methoxy-*N*-(indazol-7-yl)-benzenesulfonamides. All the newly synthesized compounds have been characterized by elemental analysis and spectroscopic data.



Keywords: *N*-alkyl-7-nitroindazole; stannous chloride; alkanethiol; reduction; *N*-(4-alkyl sulfanylindazol-7-yl)arylsulfonamide

1. Introduction

Recently, stannous chloride dihydrate has gained special attention as a mild and highly chemoselective reducing agent for various organic transformations.[1–5] In view of its inherent properties such as reusability, greater selectivity, operational simplicity, non-corrosiveness, low cost and ease of isolation, several groups have accomplished the facile synthesis of different heterocyclic compounds employing the catalytic reduction of nitro derivatives with stannous chloride. For example, Kurth and co-workers reported a one-step synthesis of 2,3-dihydro-1*H*-quinazolin-4-ones from 2-nitrobenzamides with stannous chloride in different alcohols.[6] In 2002, Bates and Li [7] described cyclization products produced for nitroarene reduction to ami-noarene using

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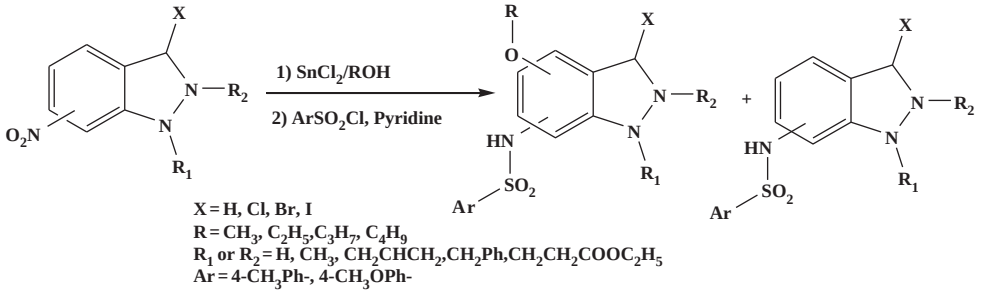
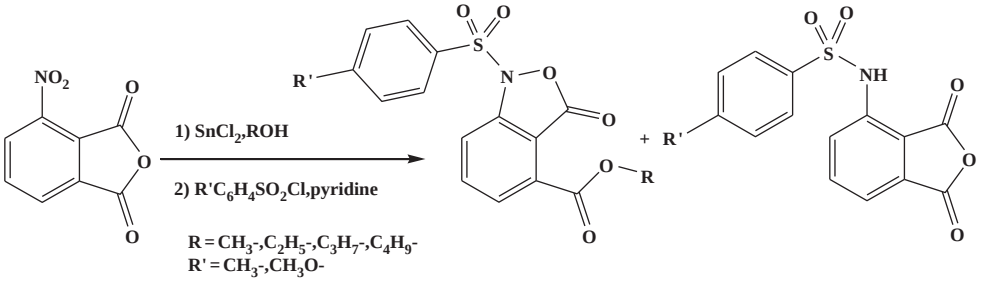
$SnCl_2,2H_2O$. In 2006, Roy and co-workers reported that a one-step reductive transformation of 2-(2-nitro-phenyl)-3H-quinazolin-4-one in various alcohols furnished the desired tetracyclic product with $SnCl_2,2H_2O$.[8] The method of reductive cyclization of 2-nitrobenzamides with haloketones or keto acids mediated by $SnCl_2,2H_2O$ was reported recently by Shi.[9] Previously our group has reported the reduction of some nitroindazoles with anhydrous $SnCl_2$ in various alcohols, in the presence of arylsulfonyl chlorides and pyridine.[10–12] Thus, we observed a new kind of transformation: 4-, 6- and 7-nitroindazoles, by the action of $SnCl_2$/EtOH, gave 4- or 7-alkoxyaminoindazoles, probably via an oxidative nucleophilic substitution of hydrogen, together with the expected 4-, 6- and 7-aminoindazoles (Scheme 1).



Scheme 1. Reduction of nitroindazoles with $SnCl_2$ in various alcohols.

More recently, we have described an efficient synthesis of some new alkyl 1-aryl-sulfonyl-1,3-dihydro-3-oxo-2,1-benzisoxazole-4-carboxylates and 4-arylsulfonamido-1,3-iso-benzofurandiones by simple reduction of 3-nitrophthalic anhydride with anhydrous $SnCl_2$ in different alcohols, and protection with arylsulfonyl chloride (Scheme 2).[13]



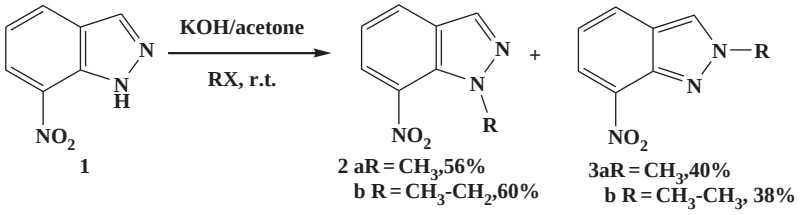
Scheme 2. Reduction of 3-nitrophtalic anhydride with $SnCl_2$ in various alcohols.

Based on our experience on the conversion of the nitro group of nitroindazole derivatives into the corresponding amino group with $SnCl_2$, in alcoholic solution, we decided to extend this original method, on the reduction of *N*-alkyl-7-nitroindazole **2a,b** and **3a,b** with $SnCl_2$ by using alkanethiol as the solvent.

2. Results and discussion

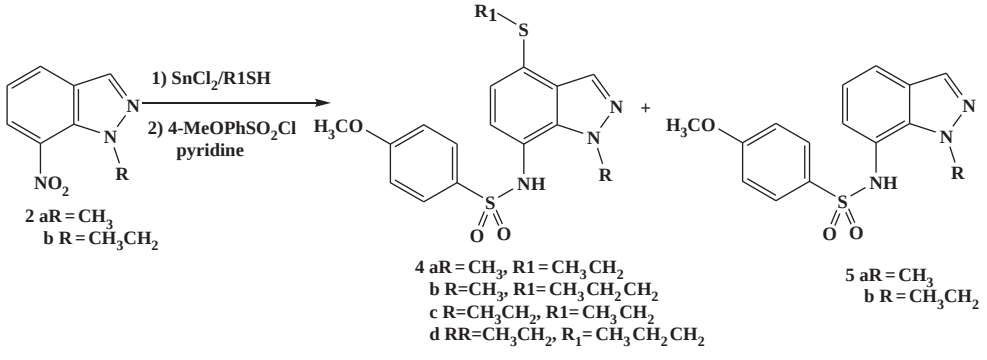
Our substrate compounds **2a,b** and **3a,b** were prepared as follows (Scheme 3). The alkylation of 7-nitroindazole with RX (methyl iodide, ethyl iodide) as the alkylating agent in dry acetone

and hydroxide potassium provided an expected mixture of N1 and N2 alkylation products with a poor selectivity in favor of the N1 product.



Scheme 3. Synthesis of 1-alkyl- and 2-alkyl-7-nitroindazole derivatives.

After chromatographic separation and isolation of each isomer, we studied the reduction of the nitro group of *N*-alkyl-7-nitroindazoles. Thus, we observed that reduction of 1-alkyl-7-nitroindazoles **2a,b** with $SnCl_2$ in RSH as the solvent gave two different compounds, that is, the desired amine and the amine substituted with alkylsulfanyl group in the 4-position. It is noteworthy that significant degradation of aromatic primary amine was observed. Consequently, we immediately protected this amine by using 4-methoxybenzenesulfonyl chloride in pyridine. This reaction afforded a mixture of *N*-(7-indazolyl)-4-methoxybenzenesulfonamide **5a,b** with the corresponding 4-alkylsulfanylsubstituted indazole **4a–d** (Scheme 4). In this case, we observed that *N*-alkylation of 7-nitroindazole at N-1 position provided **4a–d** functionalized in position 4 by the alkylsulfanyl group with a moderate selectivity (Table 1).



Scheme 4. Reduction of **2a,b** with $SnCl_2$ in RSH and protection with 4-MeOPhSO_2Cl.

We chose the protection of 7-aminoindazole by arylsulfonyl chlorides because in our previous studies we have found that indazoles bearing a sulfonamide moiety possess an important antiproliferative activity against some human and murine cell lines.[14,15]

Table 1. Reduction of **2a,b** with $SnCl_2$ in RSH and protection with 4-MeOPhSO_2Cl.

R	R_1	Time of reduction	Yield of **4a–d**	Yield of **5a,b**
CH_3	CH_3CH_2	3 h 30 min	**4a** (45%)	**5a** (32%)
CH_3	$CH_3CH_2CH_2$	4 h	**4b** (43%)	**5a** (29%)
CH_3CH_2	CH_3CH_2	5 h	**4c** (48%)	**5b** (34%)
CH_3CH_2	$CH_3CH_2CH_2$	6 h	**4d** (52%)	**5b** (31%)

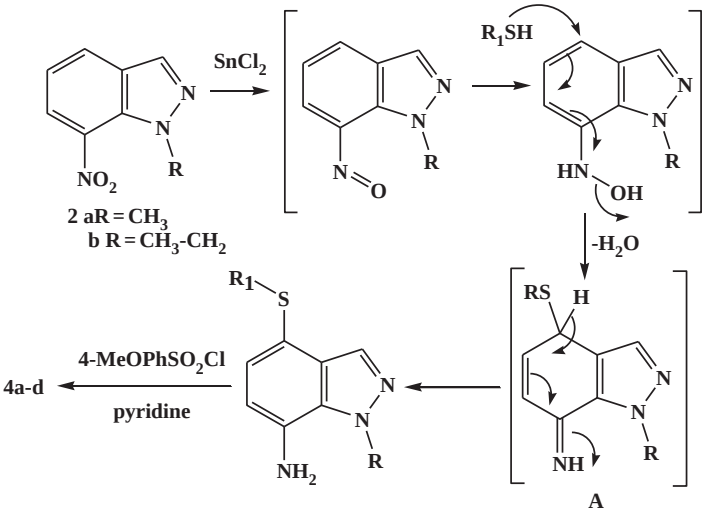
Note: Isolated yields over the two steps after separation by flash chromatography.

The structures of products **4a–d** and **5a,b** were deduced from their ^{1}H NMR, ^{13}C NMR and mass spectra (MS) and by elemental analysis.

The assignment of the structure of compounds **4a–d** was unambiguously supported by the ^{1}H and ^{13}C NMR spectra, in particular by the evaluation of the multiplet pattern of the C-ring proton signals: two doublets were observed at δ 6.36–6.50 ppm and 6.64–6.81 ppm due to 6-H and 5-H protons of indazole.

It is noteworthy that when using indium or iron dust as the catalytic system for the reduction of nitroindazole derivatives, we obtained only the compounds **5a,b**.

A plausible mechanism was proposed to explain the introduction of alkylsulfanyl group at position 4 of indazole **4a–d**. First, the usual partial reduction of the nitro group generates the corresponding hydroxylamine. Hence, we assume that the nucleophilic attack of alkylthiolate anion present in the reaction mixture occurs via the lone sulfur pair and leads to the intermediate **A**. Aromatization and coupling of the corresponding amine give the product **4a–d** (Scheme 5). The nucleophilic attack of alkylthiolate anion takes place not directly on the nitroindazole derivatives because we performed reaction between 7-nitroindazole **2a** and alkylthiolate in RSH at 60°C. Unfortunately, no reaction was observed, and we isolated only the starting substance **2a**.

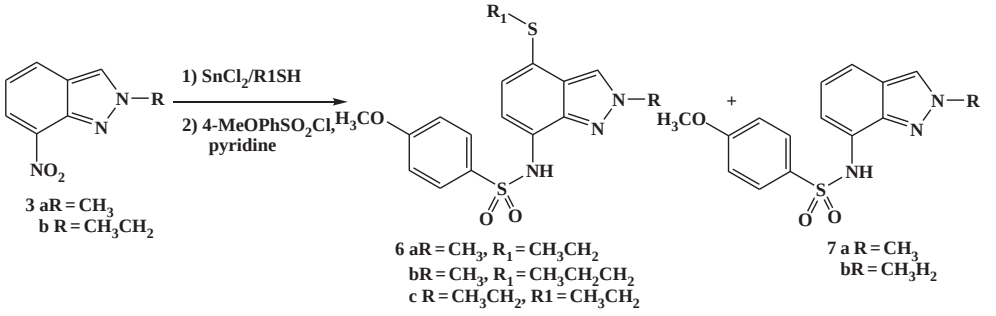


Scheme 5. Proposed mechanism for the formation of **4a–d**.

It is noteworthy that reduction of aromatic nitro compounds with metals in protic solvents such as alcohols is usually presumed to proceed by way of hydroxylamine-like intermediates.[16–19]

When we applied the same reduction conditions as previously described for 2-alkyl-7-nitroindazole **3a,b**, we obtained a mixture of two products, *N*-(4-ethyl(propyl) sulfanyl-2-alkyl-2*H*-indazol-7-yl)-4-methoxybenzenesulfonamides **6a–c** and 4-methoxy-*N*-(2-alkyl-2*H*-indazol-7-yl)-benzenesulfonamides **7a,b** (Scheme 6). This result indicates that *N*-alkylation of 7-nitroindazole at N-2 position leads to a moderate selectity in favor of unsubstituted indazole derivatives **7a,b** (Table 2). These results show that *N*-alkylation of 7-nitroindazole at position 1 plays an important role in the introduction of the group RS in 4-position of indazole.

The structures of all newly synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR and mass spectral data.



Scheme 6. Reduction of **3a,b** with $SnCl_2$ in RSH and protection with 4-MeOPhSO_2Cl.

Table 2. Reduction of **3a,b** with $SnCl_2$ in RSH and protection with 4-MeOPhSO_2Cl.

R	R_1	Time of reduction	Yield of **6a–c**	Yield of **7a,b**
CH_3	CH_3CH_2	3 h	**6a** (35%)	**7a** (48%)
CH_3	$CH_3CH_2CH_2$	4 h 30 min	**6b** (30%)	**7a** (45%)
CH_3CH_2	CH_3CH_2	5 h	**6c** (43%)	**7b** (45%)

Note: Isolated yields over the two steps after separation by flash chromatography.

3. Conclusions

We have developed an efficient approach to generate diversified functionalized indazoles by using anhydrous stannous chloride in alkanethiol as a method for the reduction of *N*-alkyl-7 nitroindazole. We investigated the *N*-alkylation effect of 7-nitroindazole to generate selectively 7-alkylsulfanyl-7-aminoprotected-indazoles. A selective way to *N*-(4-alkylsulfanyl indazol-7-yl)-4-methoxybenzene sulfonamides was developed through *N*-alkylation of N-1 position. Further biological evaluations of these compounds are currently under way in our laboratory.

4. Experimental

Melting points were determined using a Büchi–Tottoli apparatus. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6 and solution (unless otherwise specified) with TMS as an internal reference using a Bruker AC 300 (^{1}H) or 75 MHz (^{13}C) instruments. Chemical shifts are given in d parts per million (ppm) downfield from TMS. Multiplicities of ^{13}C NMR resources were assigned by distortionless enhancement by polarization transfer experiments. Low-resolution MS were recorded on a Perkin-Elmer Sciex API 3000 spectrometer. Column chromatography was carried out on SiO_2 (silica gel 60 Merck 0.063–0.200 mm). Thin-layer chromatography was carried out on SiO_2 (silica gel 60, F 254 Merck 0.063–0.200 mm), and the spots were located with UV light. Commercial reagents were used without further purification unless stated.

4.1. *General procedure for the synthesis of N-alkyl-7-nitroindazoles 2a–c and 3a–c*

To a solution of 7-nitroindazole **1** (6.13 mmol) in acetone (25 mL), KOH (6.8 mmol) was added. After 15 min at room temperature, alkyl halide (12.26 mmol) was added dropwise. The solution was stirred for 24 h. The resulting mixture was evaporated. The crude material was dissolved with EtOAc (50 mL), washed with water and brine, dried over MgSO4 and the

solvent was evaporated in vacuo. The resulting residue was purified by column chromatography (EtOAc/hexane 3 : 7).

4.1.1. *1-Methyl-7-nitro-1H-indazole (**2a**)*

Yield: 56%, Mp: 98–100°C; ^{1}H NMR (DMSO-d_6): δ 4.10 (s, 3H, CH_3), 7.28 (dd, 1H, $J = 7.8$ Hz), 8.15 (dd, 1H, $J = 7.8$, 1.0 Hz), 8.21 (dd, 1H, $J = 7.8$, 1.0 Hz), 8.35 (s, 1H, H-3). ^{13}C NMR (DMSO-d_6): δ 40.9 (CH_3), 120.1 (CH-5), 124.5 (CH-6), 128.5 (C-3a), 128.9 (CH-4), 130.8 (C-7a), 134.6 (CH-3), 135.0 (C-7).

4.1.2. *2-Methyl-7-nitro-2H-indazole (3a)*

Yield: 40%, Mp: 132–134°C; ^{1}H NMR (DMSO-d_6): δ 4.25 (s, 3H, CH_3), 7.23(dd, 1H, $J = 7.8$ Hz), 8.20 (dd, 1H, $J = 7.8$, 1.2 Hz), 8.26 (dd, 1H, $J = 7.8$, 1.2 Hz), 8.68 (s, 1H, H-3). ^{13}C NMR (DMSO-d_6): δ 40.5 (CH_3), 119.5 (CH-5), 124.7 (CH-6), 125.6 (C-3a), 127.6 (CH-3), 129.5 (CH-4), 136.2 (C-7), 139.4 (C-7a).

4.1.3. *1-Ethyl-7-nitro-1H-indazole (2b)*

Yield: 60%, Mp: 53–55°C; ^{1}H NMR (DMSO-d_6): δ 1.31 (t, 3H, CH_3, $J = 7.0$ Hz), 4.48 (q, 2H, CH_2O, $J = 7.0$ Hz), 7.31 (t, 1H, $J = 7.8$ Hz), 8.16 (dd, 1H, $J = 7.8$, 0.9 Hz), 8.22 (dd, 1H, $J = 7.8$, 0.9 Hz), 8.40 (s, 1H, H-3). ^{13}C NMR (DMSO-d_6): δ 15.8 (CH_3), 47.8 (NCH_2), 120.6 (CH-5), 125.2 (CH-6), 129.0 (C), 129.2 (CH-4), 129.8 (C), 135.3 (C), 135.4 (CH-3).

4.1.4. *2-Ethyl-7-nitro-2H-indazole (3b)*

Yield: 38%, Mp: 56–58°C; ^{1}H NMR (DMSO-d_6): δ 1.52 (t, 3H, CH_3, $J = 7.5$ Hz), 4.55 (q, 2H, CH_2O, $J = 7.5$ Hz), 7.23 (t, 1H, $J = 8.1$ Hz), 8.24 (dd, 1H, $J = 8.1$, 0.9 Hz), 8.28 (dd, 1H, $J = 7.8$, 1.0 Hz), 8.78 (s, 1H, H-3). ^{13}C NMR (DMSO-d_6): δ 16.1 (CH_3), 48.9 (NCH_2), 120.1 (CH-5), 125.1 (CH-6), 125.7 (C), 126.8 (CH-3), 130.5 (CH-4), 137.0 (C), 139.9 (C).

4.2. *General procedure for the synthesis of N-(4-alkylsulfanylindazol-7-yl)arylsulfonamides and N-(indazol-7-yl)arylsulfonamides*

A mixture of N-alkyl-7-nitroindazole (1.22 mmol) and anhydrous $SnCl_2$ (1.1 g, 6.1 mmol) in 25 mL of RSH was heated at 60°C. After reduction, the starting material disappeared and the solution was allowed to cool down. The pH was made slightly basic (pH 7–8) by the addition of 5% aqueous potassium bicarbonate before being extracted with EtOAc. The organic phase was washed with brine and dried over magnesium sulfate. The solvent was removed to afford the amine, which was immediately dissolved in pyridine (5 mL) and then reacted with 4-methoxybenzenesulfonyl chloride (0.26 g, 1.25 mmol) at room temperature for 24 h. After the reaction mixture was concentrated in vacuo, the resulting residue was purified by flash chromatography (eluted with EtOAc/hexane 1:9).

4.2.1. *N-(4-Ethylsulfanyl-1-methyl-1H-indazol-7-yl)-4-methoxybenzenesulfonamide (**4a**)*

Yield: 45%, Mp: 96–98°C; ^{1}H NMR (DMSO-d_6): δ 1.21 (t, 3H, CH_3, $J = 7.2$ Hz), 3.02 (q, 2H, CH_2S, $J = 7.2$ Hz), 3.82 (s, 3H, OCH_3), 4.20 (s, 3H, NCH_3), 6.37 (d, 1H, $J = 7.8$ Hz), 6.81

(d, 1H, $J = 7.8$ Hz), 7.08 (d, 2H, $J = 9.0$ Hz), 7.58 (d, 2H, $J = 9.0$ Hz), 8.00 (s, 1H), 9.79 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 14.4 (CH_3), 25.8 (CH_2S), 38.9 (NCH_3), 56.1 (OCH_3), 114.8 (2CH), 118.0 (C), 118.2 (CH), 125.4 (C), 126.9 (CH), 129.7 (2CH), 129.8 (C), 131.4 (CH), 131.6 (C), 136.8 (C), 162.9 (C). EI-MS (*m/z*): 378 $(M + H)^+$. Anal. Calcd for $C_{17}H_{19}N_3O_3S_2$: C, 54.09; H, 5.07; N, 11.13; S, 16.99. Found: C, 53.94; H, 5.01; N, 11.25; S, 17.08.

4.2.2. *4-Methoxy-N-(1-methyl-4-propylsulfanyl-1H-indazol-7-yl)-benzenesulfonamide (**4b**)*

Yield: 43%, Mp: 118–120°C; ^{1}H NMR (DMSO-d_6): δ 0.94 (t, 3H, CH_3, $J = 7.2$ Hz), 1.53–1.61 (m, 2H, CH_2), 2.98 (t, 2H, CH_2S, $J = 7.2$ Hz), 3.82 (s, 3H, OCH_3), 4.20 (s, 3H, NCH_3), 6.36 (d, 1H, $J = 8.1$ Hz), 6.81 (d, 1H, $J = 8.1$ Hz), 7.08 (d, 2H, $J = 9.0$ Hz), 7.58 (d, 2H, $J = 9.0$ Hz), 8.00 (s, 1H), 9.81 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 13.6 (CH_3), 22.3 (CH_2), 33.6 (CH_2S), 38.9 (NCH_3), 56.1 (OCH_3), 114.8 (2CH), 118.4 (CH), 120.6 (C), 125.4 (C), 126.8 (CH), 129.7 (2CH), 129.8 (C), 131.4 (CH), 131.7 (C), 136.8 (C), 162.9 (C). EI-MS (*m/z*): 392 $(M + H)^+$. Anal. Calcd for $C_{18}H_{21}N_3O_3S_2$: C, 55.22; H, 5.41; N, 10.73; S, 16.38. Found: C, 55.08; H, 5.36; N, 10.85; S, 16.51.

4.2.3. *4-Methoxy-N-(1-methyl-1H-7-indazolyl)-benzenesulfonamide (**5a**)*

Yield: 32%, Mp: 163–165°C; ^{1}H NMR (DMSO-d_6): δ 3.82 (s, 3H, OCH_3), 4.22 (s, 3H, NCH_3), 6.42 (d, 1H, $J = 7.4$ Hz), 6.88 (dd, 1H, $J = 7.4$ Hz), 7.08 (d, 2H, $J = 9.0$ Hz), 7.58 (d, 2H, $J = 9.0$ Hz), 7.63 (dd, 1H, $J = 7.4$, 0.9 Hz), 8.05 (s, 1H), 9.83 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 38.9 (NCH_3), 56.1 (OCH_3), 114.7 (2CH), 120.4 (C), 120.8 (CH), 121.1 (CH), 126.4 (CH), 126.7(C), 129.7 (2CH), 131.6 (C), 133.0 (CH), 137.1 (C), 162.9 (C). EI-MS (*m/z*): 318 $(M + H)^+$. Anal. Calcd for $C_{15}H_{15}N_3O_3S$: C, 56.77; H, 4.76; N, 13.24; S, 10.10. Found: C, 56.68; H, 4.67; N, 13.35; S, 10.21.

4.2.4. *N-(1-Ethyl-4-ethylsulfanyl-1H-indazol-7-yl)-4-methoxybenzenesulfonamide (**4c**)*

Yield: 48%, Mp: 121–123°C; ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H, CH_3, $J = 7.2$ Hz), 1.51 (t, 3H, CH_3, $J = 7.0$ Hz), 3.02 (q, 2H, CH_2S, $J = 7.0$ Hz), 3.88 (s, 3H, OCH_3), 4.88 (q, 2H, CH_2N, $J = 7.2$ Hz), 6.49 (d, 1H, $J = 7.5$ Hz), 6.76 (d, 1H, $J = 7.5$ Hz), 6.80 (s, 1H, NH), 6.94 (d, 2H, $J = 8.7$ Hz), 7.64 (d, 2H, $J = 8.7$ Hz), 8.21 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 15.8 (CH_3), 26.7 (CH_2S), 46.1 (NCH_2), 55.7 (OCH_3), 114.3 (2CH), 116.7 (C), 118.8 (CH), 125.0 (C), 129.1 (C), 129.3 (CH), 130.1 (2CH), 130.7 (CH), 132.9 (C), 136.1 (C), 163.4 (C). EI-MS (*m/z*): 392 $(M + H)^+$. Anal. Calcd for $C_{18}H_{21}N_3O_3S_2$: C, 55.22; H, 5.41; N, 10.73; S, 16.38. Found: C, 55.10; H, 5.32; N, 10.88; S, 16.48.

4.2.5. *N-(1-Ethyl-4-propylsulfanyl-1H-indazol-7-yl)-4-methoxybenzenesulfonamide (**4d**)*

Yield: 52%, Mp: 128–130°C; ^{1}H NMR ($CDCl_3$): δ 1.21 (t, 3H, CH_3, $J = 7.0$ Hz), 1.45–1.56 (m, 5H, CH_2 and CH_3), 2.95 (q, 2H, CH_2S, $J = 7.5$ Hz), 3.88 (s, 3H, OCH_3), 4.88 (q, 2H, CH_2N, $J = 7.2$ Hz), 6.50 (d, 1H, $J = 7.8$ Hz), 6.64 (d, 1H, $J = 7.8$ Hz), 6.75 (s, 1H, NH), 6.92 (d, 2H, $J = 9.0$ Hz), 7.64 (d, 2H, $J = 9.0$ Hz), 8.21 (s, 1H). ^{13}C NMR ($CDCl_3$): ^{13}C NMR ($CDCl_3$): δ 14.1 (CH_3), 15.8 (CH_3), 24.5 (CH_2), 35.4 (CH_2S), 46.1 (NCH_2), 55.7 (OCH_3), 114.4 (2CH), 119.6 (CH), 120.4 (C), 123.4 (CH), 125.8 (C), 128.9 (C), 130.0 (2CH), 132.0 (CH), 131.8 (C), 137.2 (C), 161.5 (C). EI-MS (*m/z*): 406 $(M + H)^+$. Anal. Calcd for $C_{19}H_{23}N_3O_3S_2$: C, 56.27; H, 5.72; N, 10.36; S, 15.81. Found: C, 55.12; H, 5.80; N, 10.46; S, 16.90.

4.2.6. *N-(1-Ethyl-1H-indazol-7-yl)-4-methoxybenzenesulfonamide (**5b**)*

Yield: 34%, Mp: 114–116°C; ^{1}H NMR ($CDCl_3$): δ 1.41 (t, 3H, CH_3, $J = 7.2$ Hz), 3.88 (s, 3H, OCH_3), 4.78 (q, 2H, CH_2N, $J = 7.2$ Hz), 6.52 (d, 1H, $J = 7.2$ Hz), 6.89–7.04 (m, 3H), 7.60 (d, 2H, $J = 9.0$ Hz), 7.71 (d, 1H, $J = 7.4$ Hz), 8.10 (s, 1H), 8.18 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 15.8 (CH_3), 46.3 (NCH_2), 55.7 (OCH_3), 114.3 (2CH), 119.7 (C), 120.6 (CH), 122.3 (CH), 127.5(C), 128.1 (CH), 129.8 (C), 130.0 (2CH), 131.9 (CH), 136.5 (C), 163.5 (C). EI-MS (*m/z*): 332 $(M+H)^+$. Anal. Calcd for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68; S, 9.68. Found: C, 58.10; H, 5.09; N, 12.57; S, 9.57.

4.2.7. *N-(4-Ethylsulfanyl-2-methyl-2H-indazol-7-yl)-4-methoxybenzenesulfonamide (**6a**)*

Yield: 35%, Mp: 88–90°C; ^{1}H NMR (DMSO-d_6): δ 1.15 (t, 3H, CH_3, $J = 7.2$ Hz), 2.92 (q, 2H, CH_2S, $J = 7.2$ Hz), 3.75 (s, 3H, OCH_3), 4.10 (s, 3H, NCH_3), 6.82 (d, 1H, $J = 7.8$ Hz), 6.93 (d, 1H, $J = 7.8$ Hz), 6.99 (d, 2H, $J = 9.0$ Hz), 7.78 (d, 2H, $J = 9.0$ Hz), 8.32(s, 1H), 10.11 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 14.8 (CH_3), 26.7 (CH_2S), 40.5 (NCH_3), 56.0 (OCH_3), 114.6 (2CH), 115.2 (CH), 120.9 (C), 121.4 (CH), 123.0 (C), 125.2 (CH), 129.5 (2CH), 129.8 (C), 132.6 (C), 142.6 (C), 162.8 (C). EI-MS (*m/z*): 378 $(M+H)^+$. Anal. Calcd for $C_{17}H_{19}N_3O_3S_2$: C, 54.09; H, 5.07; N, 11.13; S, 16.99. Found: C, 54.20; H, 5.14; N, 11.18; S, 17.12.

4.2.8. *4-Methoxy-N-(2-methyl-4-propylsulfanyl-2H-indazol-7-yl)-benzenesulfonamide (**6b**)*

Yield: 30%, Mp: 58–60°C; ^{1}H NMR ($CDCl_3$): δ 0.99 (t, 3H, CH_3, $J = 7.5$ Hz), 1.58–1.65 (m, 2H, CH_2), 2.88 (t, 2H, CH_2S, $J = 7.5$ Hz), 3.77 (s, 3H, OCH_3), 4.14 (s, 3H, NCH_3), 7.83 (d, 2H, $J = 9.0$ Hz), 6.94 (d, 1H, $J = 7.8$ Hz), 6.96 (s, 1H, NH), 7.31 (d, 1H, $J = 7.8$ Hz), 7.86 (d, 2H, $J = 9.0$ Hz), 7.92 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.4 (CH_3), 22.5 (CH_2), 35.1 (CH_2S), 40.5 (NCH_3), 55.5 (OCH_3), 112.7 (CH), 114.1 (2CH), 121.4 (C), 121.4 (CH), 123.7 (CH), 124.3 (C), 129.5 (2CH), 130.0 (C), 131.0 (C), 141.6 (C), 163.1 (C). EI-MS (*m/z*): 392 $(M+H)^+$. Anal. Calcd for $C_{18}H_{21}N_3O_3S_2$: C, 55.22; H, 5.41; N, 10.73; S, 16.38. Found: C, 55.14; H, 5.50; N, 10.64; S, 16.48.

4.2.9. *4-Methoxy-N-(2-methyl-2H-7-indazolyl)-benzenesulfonamide (**7a**)*

Yield: 48%, Mp: 103–105°C; ^{1}H NMR (DMSO-d_6): δ 3.75 (s, 3H, OCH_3), 4.11 (s, 3H, NCH_3), 6.88 (t, 1H, $J = 7.8$ Hz), 6.95–7.01 (m, 3H), 7.32 (dd, 1H, $J = 7.8, 0.9$ Hz), 7.81 (d, 2H, $J = 9.0$ Hz), 8.25 (s, 1H), 10.07 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 40.4 (NCH_3), 56.0 (OCH_3), 114.1 (CH), 114.5 (2CH), 116.5 (CH), 121.5 (CH), 122.9 (C), 125.6 (CH), 126.9(C), 129.5 (2CH), 132.6 (C), 142.7 (C), 162.7 (C). EI-MS (*m/z*): 318 $(M+H)^+$. Anal. Calcd for $C_{15}H_{15}N_3O_3S$: C, 56.77; H, 4.76; N, 13.24; S, 10.10. Found: C, 56.64; H, 4.65; N, 13.32; S, 10.24.

4.2.10. *N-(2-Ethyl-4-ethylsulfanyl-2H-indazol-7-yl)-4-methoxybenzenesulfonamide (**6c**)*

Yield: 43%, Mp: 124–126°C; ^{1}H NMR ($CDCl_3$): δ 1.36 (t, 3H, CH_3, $J = 7.2$ Hz), 1.52 (t, 3H, CH_3, $J = 7.5$ Hz), 2.98 (q, 2H, CH_2S, $J = 7.2$ Hz), 3.77 (s, 3H, OCH_3), 4.61 (q, 2H, CH_2N, $J = 7.2$ Hz), 6.84 (d, 2H, $J = 9.0$ Hz), 6.89 (s, 1H, NH), 7.10 (d, 1H, $J = 8.1$ Hz), 6.65 (d, 1H, $J = 8.1$ Hz), 7.94 (d, 2H, $J = 9.0$ Hz), 8.16 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.4 (CH_3), 15.2 (CH_3), 28.0 (CH_2S), 49.1 (NCH_2), 55.5 (OCH_3), 114.0 (2CH), 118.5 (C), 119.3 (CH), 124.8 (CH), 125.3 (C), 126.5 (CH), 129.7 (C), 129.8 (2CH), 131.1 (C), 140.1 (C), 163.1 (C). EI-MS

(*m/z*): 392 $(M+H)^+$. Anal. Calcd for $C_{18}H_{21}N_3O_3S_2$: C, 55.22; H, 5.41; N, 10.73; S, 16.38. Found: C, 55.13; H, 5.35; N, 10.85; S, 16.50.

4.2.11. *N-(2-Ethyl-1H-indazol-7-yl)-4-methoxybenzenesulfonamide (**7b**)*

Yield: 45%, Mp: 146–148°C; ^{1}H NMR ($CDCl_3$): δ 1.52 (t, 3H, CH_3, $J = 7.2$ Hz), 3.82 (s, 3H, OCH_3), 4.37 (q, 2H, CH_2N, $J = 7.2$ Hz), 6.83–6.90 (m, 3H), 7.65 (d, 1H, $J = 8.0$ Hz), 7.76 (d, 1H, $J = 8.4$ Hz), 8.20 (s, 1H), 9.30 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 15.4 (CH_3), 48.8 (NCH_2), 55.6 (OCH_3), 113.6 (2CH), 119.6 (CH), 121.7 (CH), 124.7 (CH), 126.5 (CH), 123.6(C), 130.1 (2CH), 130.8 (C), 131.1 (C), 163.1 (C). EI-MS (*m/z*): 332 $(M+H)^+$. Anal. Calcd for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68; S, 9.68. Found: C, 58.09; H, 5.11; N, 12.60; S, 9.54.

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References

[1] Singh OM, Sushuma Devi N. Application of β-oxodithioesters in domino and multicomponent reactions: facile route to dihydropyrimidines and coumarins. J Org Chem. 2009;74:3141–3144.
[2] Suresh R, Muthusubramanian S, Senthilkumaran R, Manickam G. $SnCl_2$-catalyzed selective atom economic Imino Diels–Alder reaction: synthesis of 2-(1H-Pyrrolo[2,3-b]pyridin-3-yl)quinolines. J Org Chem. 2012;77:1468–1476.
[3] Selvam NP, Hari Babu T, Perumal PT. A simple and convenient approach to the Friedländer synthesis of pyrano[2,3-*b*]pyridines. Tetrahedron. 2009;65:8524–8530.
[4] Bez G, Gogoi D. A rapid and efficient method for 1,3-dithiolane synthesis. Tetrahedron Lett. 2006;47:5155–5157.
[5] Tang L, Ding L, Chang W-X, Li J. $SnCl_2$-mediated carbonyl allylation of aldehydes and ketones in ionic liquid. Tetrahedron Lett. 2006;47:303–306.
[6] Yoo CL, Fettinger JC, Kurth MJ. Stannous chloride in alcohol: a one-pot conversion of 2-nitro-*N*-arylbenzamides to 2,3-dihydro-1*H*-quinazoline-4-ones. J Org Chem. 2005;70:6941–6943.
[7] Bates DK, Li K. Stannous chloride-mediated reductive cyclization-rearrangement of nitroarenyl ketones. J Org Chem. 2002;24:8662–8665.
[8] Roy AD, Subramanian A, Roy RJ. Auto-redox reaction: tin(II) chloride-mediated one-step reductive cyclization leading to the synthesis of novel biheterocyclic 5,6-dihydro-quinazolino[4,3-b]quinazolin-8-ones with three-point diversity. Org Chem. 2006;71:382–385.
[9] Wang M, Dou G, Shi D. Efficient and convenient synthesis of pyrrolo[1,2-a]quinazoline derivatives with the aid of tin(II) chloride. J Comb Chem. 2010;12:582–586.
[10] Abbassi N, Rakib EM, Hannioui A, Alaoui M, Benchidmi M, Essassi EM, Geffken D. Alkylation and reduction of *N*-alkyl-4-nitroindazoles with anhydrous $SnCl_2$ in ethanol: synthesis of novel 7-ethoxy-*N*-alkylindazole derivatives. Heterocycles. 2011;83:891–900.
[11] Abbassi N, Rakib EM, Bouissane L, Hannioui A, Khouili M, El Malki A, Benchidmi M, Essassi EM. Studies on the reduction of the nitro group in 4-Nitroindazole by anhydrous $SnCl_2$ in different alcohols. Synth Commun. 2011;41:999–1005.
[12] Bouissane L, El Kazzouli S, Leger J-M, Jarry C, Rakib EM, Khouili M, Guillaumet G. New and efficient synthesis of bi- and trisubstituted indazoles. Tetrahedron. 2005;61:8218–8225.
[13] Chicha H, Abbassi N, Rakib EM, Khouili M, El Ammari L, Spinelli D. Reduction of 3-nitrophthalic anhydride by $SnCl_2$ in different alcohols: a simple synthesis of alkyl 3-oxo-1,3-dihydro-2,1-benzoxazole-4-carboxylates. Tetrahedron Lett. 2013;54:1569–1571.
[14] Abbassi N, Rakib EM, Chicha H, Bouissane L, Hannioui A, Aiello C, Gangemi R, Castagnola P, Rosano C, Viale M. Synthesis and antitumor activity of some substituted indazole derivatives. Arch Pharm Chem Life Sci. 2014;347:423–431.
[15] Abbassi N, Chicha H, Rakib, EM, Hannioui A, Alaoui M, Hajjaji A, Geffken D, Aiello C, Gangemi R, Rosano C, Viale M. Synthesis, antiproliferative and apoptotic activities of *N*-(6(4)-indazolyl)-benzenesulfonamide derivatives as potential anticancer agents. Eur J Med Chem. 2012;57:240–249.
[16] Chauhan J, Fletcher S. One-pot synthesis of 2,1-benzisoxazoles (anthranils) by a stannous chloride-mediated tandem reduction–heterocyclization of 2-nitroacylbenzenes under neutral conditions. Tetrahedron Lett. 2012;53:4951–4954.

[17] Uchuskin MG, Molodtsova NV, Abaev VT, Trushkov IV, Butin AV. Furan ring opening–indole ring closure: $SnCl_2$-induced reductive transformation of difuryl(2-nitroaryl)methanes into 2-(2-acylvinyl)indoles. Tetrahedron. 2012;68:4252–4258.
[18] Xing W-K, Ogata Y. Effet of meta- and para-substituents on the stannous chloride reduction of nitrobenzenes in aqueous ethanol. J Org Chem. 1983;48:2515–2520.
[19] McAllister LA, Bechle BM, Dounay AB, Evrard E, Gan X, Ghosh S, Kim J-Y, Parikh VD, Tuttle JB, Verhoest PR. A general strategy for the synthesis of cyclic N-aryl hydroxamic acids via partial nitro group reduction. J Org Chem. 2011;76:3484–3497.