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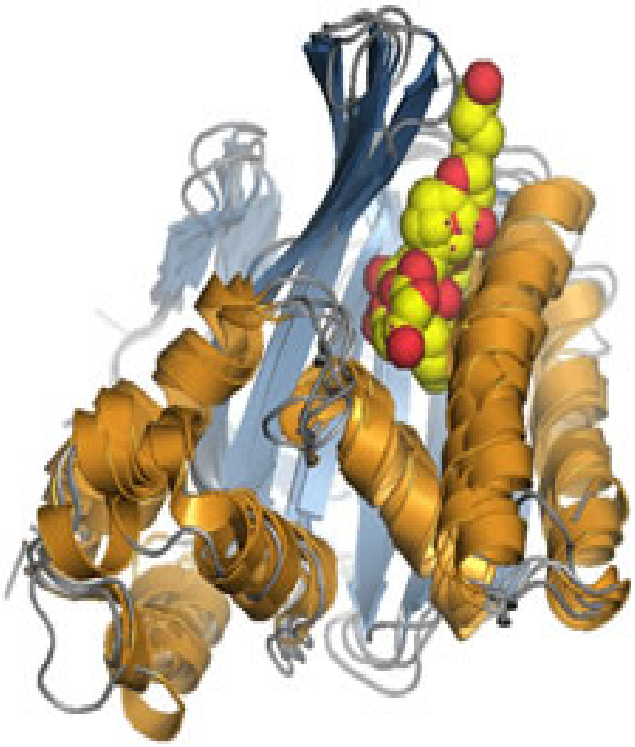

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Synthesis of a new series of sulfonamides containing isatin moiety

CHELOUFI Hadjer, BERREDJEM Malika* & AOUF Nour-Eddine

Laboratory of Applied Organic Chemistry (LAOC), Bioorganic Chemistry Group
Sciences Faculty, Badji Mokhtar; Annaba University, BP 12, Algeria

Received: December 23, 2013; Accepted: March 29, 2014
Corresponding author Email malika.berredjem@univ-annaba.org

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Abstract. *In the present work, a new series of sulfonamide derivatives containing isatin moiety were prepared. Our synthesis was carried out in two successive steps (acylation and condensation with different sulphonamide derivatives), using chlorosulfonyl isocyanate and isatin as starting materials. The structure of all compounds was elucidated by usual spectroscopic methods ^{1}H, ^{13}C NMR and IR.*

***Key Words*:** *Sulfonamide, Isatin, chloroacetyl chloride, chlorosulfonyl isocyanate, alkylation, acylation*

Introduction

The sulfonamide group is considered as a pharmacophore which is present in a number of biologically active molecules. In the last decade [1], they have long been used as precursors for the synthesis of biologically active molecules because of their wide spectrum of activity, it has found use in many applications in the field of medicinal chemistry [2-3]. A number of drug classes are characterized by the presence of the sulfonamide function, several derivatives have pronounced medicinal value as antibacterial, hypoglycemic, diuretic, anti-hypertensive, carbonic anhydrase inhibitors and antiviral drugs among others [4- 13].

Other potent sulfonamide derivatives were synthesized and found to be more effective therapeutically. For example, the celecoxib **1** used as an anti inflammatory [14], and recently, a series of anilino substituted pyrimidine sulfonamides were synthesized and considered as anticancer agents **2** [15] (**figure 1**).

Isatin (1H- indole-2,3-dione) is an endogenous compound, its synthetic derivatives at C-2, C-3, and *N* positions have led to a wide variety of pharmacological responses including cytotoxic, anticancer, antibacterial, antiviral, anti HIV, anticholinesterase, antiinflammatory, antihypertensive, antihypoxic, antiulcer, anticonvulsant, COX-2, and carboxylesterase inhibitor activities (**figure 1**) [16- 22].

In this context, the association of two significant moieties (Isatin and sulfonamide) enable to synthesis a new series of sulfonamides derivatives containing isatin moiety (**3a-d**). The chemical structures of the title compounds were confirmed by ^{1}H, ^{13}C NMR, and IR.

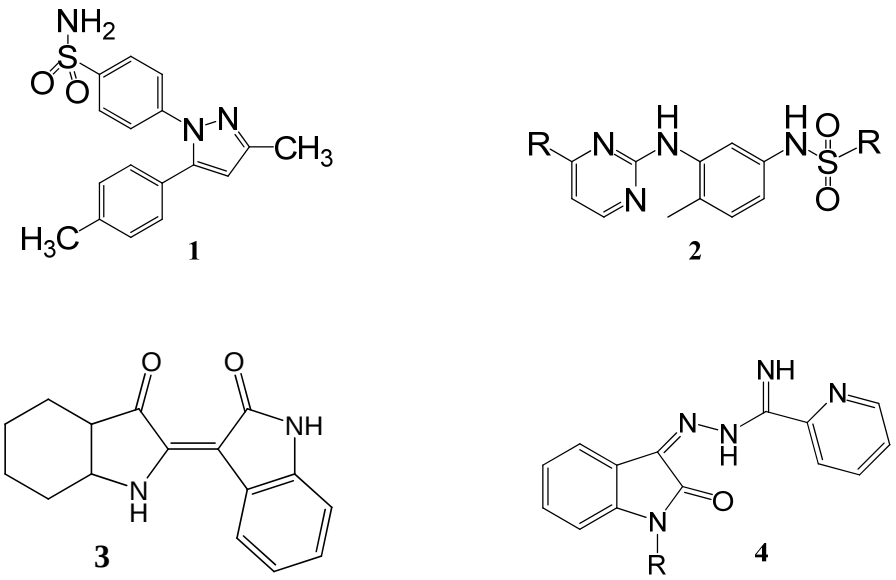


Figure 1. Exemples of sulfonamide and isatin derivatives

Results and discussion

The synthesis of the title compounds was realized in 2 steps. First, four derivatives of sulfonamides **(2a-d)** were prepared in two steps (carbamoylation, sulfamoylation), starting from chlorosulfonyl isocyanate as a suitable available reagent for allowing the introduction of a sulfonamide moiety [23-25] **(Scheme 1).**

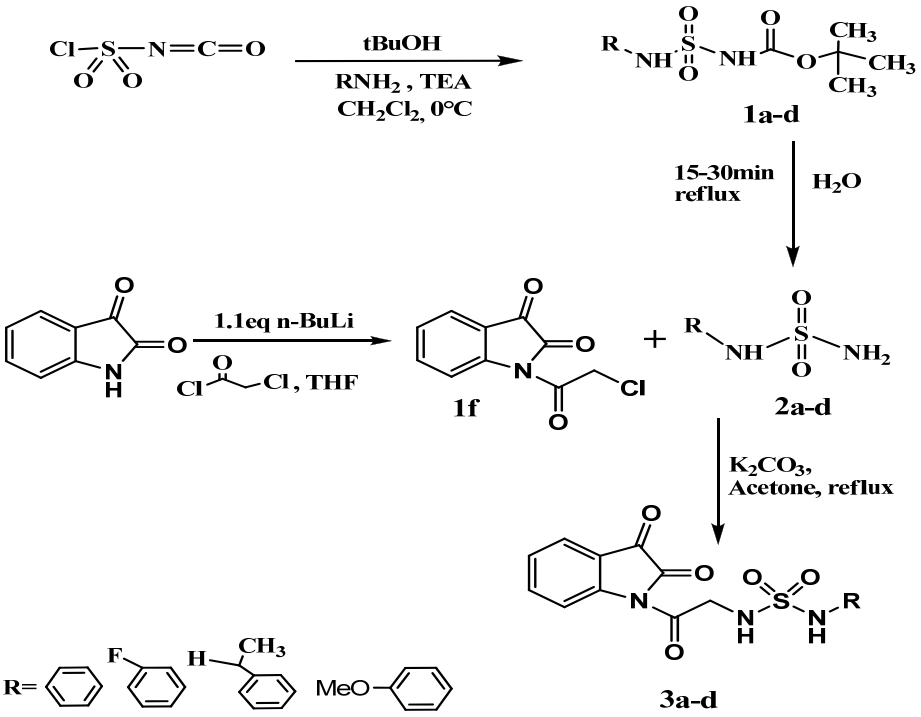
Carbamoylation: This step involves the addition of the tert-butanol and chlorosulfonyl isocyanate in anhydrous methylene chloride at 0°C for 30 min.

Sulfamoylation: the carbamate chlorosulfonyl formed in the first step is added to a solution of primary amine (1equiv.) in the same solvent in the presence of triethylamine (1.1 equiv.) at 0 °C. The reaction is left under magnetic stirring at room temperature for 2 h. After treatment, protected sulfonamides (**1a-d**) were obtained as a white powder with excellent yields.

Deprotection: the protected sulfonamides [26] (**1a-d**) were refluxed in water for 15-30 min to afford deprotected sulfonamides (**2a-d**) in good yields. The disappearance of C=O ester band in IR and $(CH3)_3$ signal in 1H NMR confirms the removal of the **BOC** fragment

Secondary, the synthesis of *N*-acylisatin under a variety of conditions has been described using acyl chlorides or anhydrides under reflux. The reaction may be performed without additives [27] or by using perchloric acid in benzene, triethylamine in benzene, [28] pyridine in benzene, [29] or triethylamine in chloroform [30- 31] as catalysts; or by conversion of isatin to sodium isatide using NaH in toluene under reflux and subsequent reaction with acyl chlorides [32].

In our case, *N*-acylisatin **1f** was formed by the reaction of isatin with chloroacetyl chloride (1.5 equiv) in the presence of a strong base n-BuLi (1.1 equiv) in anhydrous THF at 0°C. The reaction was monitored by TLC. This product was obtained and isolated in good yield.
The novel synthesized derivatives **3a-d** can be prepared easily in excellent yield (75-85%) by a simple condensation between sulfonamides derivatives **2a-d** and *N*-acylisatin **1f** in the presence of potassium carbonate (K_2CO_3) in a dry acetone. The reaction was refluxed for **12 h** and the residue was purified by column chromatography over silica gel using CH_2Cl_2 as eluent **(Scheme 1).**



Scheme 1. Synthesis of sulfonamides derivatives **3a-d.**

Experimental section

General procedure for the acylation of isatin:
To a stirred solution of isatin (0.5 g, 3.45 mmol) in anhydrous THF at -78° C and in argon atmosphere, n-BuLi (0.3 mL, 3.74 mmol) was added drop wise. The reaction was warmed at 0°C for 1 h. Then, 2-chloroacetyl chloride (0.4 mL, 5.10 mmol) was added and the reaction stirred at room temperature for **2**h. After confirming the end of the reaction by TLC, the acylated isatin was purified by column chromatography diluted with CH_2Cl_2 to give the product **1f**.

General procedure for the preparation of the title compounds (3a-e):
The N-alkylation reaction of sulfonamide (**2a-e)** (0.55 g, 3.20 mmol) with 1-(2-chloroacetyl) indoline-2,3-dione **1f** (0.71 g, 3.20 mmol) was carried out in acetone (5 mL) in the presence of K_2CO_3 (0.6 g, 1.5 equiv, 4.8 mmol). The reaction mixture was refluxed for

12h and monitored by TLC. The residue was evaporated and diluted with methylene chloride (30 mL) then washed with water. The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuo. The residue was purified by silica gel chromatography diluted with CH_2Cl_2 to give the product (**3a-e**).

***1-(2-chloroacetyl) indoline-2,3-dione 1f*:**
Yield: 80%. Yellow oil. R_f = 0.65 (CH_2Cl_2/MeOH: 9/1). ^{1}H NMR (DMSO, δppm): 7.10-7.60 (m, 4H, **H**-Ar); 4.30 (s, 2H, C**H$_2$**-Cl). ^{13}C NMR ($CDCl_3$, δ ppm): 184.4; 166.6; 155.5; 148.8; 136.0; 130.0; 129.5; 125.2; 117.7; 45.4. IR (KBr, γ cm^{-1}); 1770, 1740, 1730 cm^{-1} (**C=O**); 1658 (**C=C**); 730 cm^{-1} (**C-Cl**). MS-ESI+30ev m/z: 223.5 $[M+H]^+$100%.

N-(2-(2,3-dioxoindolin-1-yl)-2-oxoethyl) N'-(1-phenyl)sulfamide
Yield: 80%. mp: 170-173°C. R_f = 0.65 (CH_2Cl_2/MeOH: 9/1). ^{1}H NMR (DMSO, δppm): 7.80 -7.30 (m, 5H, **H**-Ar); 7.10- 7.60 (m, 4H, H-Ar$_{indole}$); 6.51 (s, 1H, N**H**); 5.26 (t, 1H, N**H**-CH_2); 4.55 (d, 2H, NH-C**H$_2$**). ^{13}C NMR ($CDCl_3$, δ ppm): 184.4; 166.6; 155.5; 148.8; 136.0; 130.0; 129.5; 125.2; 120.8; 117.7; 39.4. IR (KBr, γ cm^{-1}); 3085 and 2900 (**NH**); 1775, 1750, 1745 cm^{-1} (**C=O**); 1658 (**C=C**); 1364 and 1159 (**SO$_2$**). MS-ESI+30ev m/z: 360 $[M+H]^+$100%.

N-(2-(2,3-dioxoindolin-1-yl)-2-oxoethyl) N'-(3-fluorophenyl)sulfamide
Yield: 66%. mp:180-181 °C. R_f = 0.80 (CH_2Cl_2/MeOH: 9/1). ^{1}H NMR (DMSO, δ ppm): 7.40- 6.95 (m, 4H, H-Ar); 7.19- 7.69 (m, 4H, H-Ar$_{indole}$); 6.61 (s, 1H, N**H**); 5.30 (t, 1H, N**H**-CH_2); 4.45 (d, 2H, NH-C**H$_2$**). ^{13}C NMR ($CDCl_3$, δ ppm): 186.4; 168.6; 161.8; 150.5; 138.0; 129.7; 111.9; 110.0; 103.3; 40.1. IR (KBr, γ cm^{-1}): 3100 and 2990 (**NH**); 1765, 1740, 1720 cm^{-1} (**C=O**); 1652 (**C=C**); 1361 and 1155 (**SO$_2$**),. MS-ESI+30ev m/z: 378 $[M+H]^+$ 100%.

N-(2-(2,3-dioxoindolin-1-yl)-2-oxoethyl) N'-(1-methylbenzyl)sulfamide
Yield: 67%. mp: 173-175 °C. R_f = 0.70 (CH_2Cl_2/MeOH: 9/1). ^{1}H NMR (DMSO, δ ppm): 7.30-7.25 (m, 5H, **H**-Ar); 7.08- 7.70 (m, 4H, **H**-Ar$_{indole}$); 5.65 (s, 1H, N**H**-CH_2); 5.25 (s, 1H, NH-C**H***); 4.50 (m, 1H, C**H***); 4.57 (d, 2H, NH-C**H$_2$**); 1.40 (d, *J* = 6.93 Hz, 3H, C**H$_3$**). ^{13}C NMR ($CDCl_3$, δ ppm): 186.4; 166.6; 159.5; 148.8; 141.9; 128.2; 127.1; 125.6; 50.4; 38.9; 21.6. IR (KBr, γ cm^{-1}): 3011 and 2988 (**NH**); 1762, 1748, 1731 cm^{-1} (**C=O**); 1642 (**C=C**); 1305 and 1163 (**SO$_2$**). MS-ESI+30ev m/z: 388 [M+H]+ 100%.

N-(2-(2,3-dioxoindolin-1-yl)-2-oxoethyl) N'-(4-methoxy-phenyl)sulfamide
Yield: 74%. mp: 184-185°C. R_f = 0.62 (CH_2Cl_2/MeOH: 9/1). ^{1}H NMR (DMSO, δ ppm): 7.20-7.60 (m, 4H, **H**-Ar); 7.25- 7.65 (m, 4H, **H**-Ar$_{indole}$); 5.10 (s, 1H, N**H**); 6.20 (s, 1H, N**H**-CH_2); 3.90 (s, 3H, C**H$_3$**-O); 4.60 (d, 2H, NH-C**H$_2$**). ^{13}C NMR (DMSO, δ ppm): 188.4; 164.6; 151.5; 136.0; 129.58; 125.29; 120.82; 118.6; 55.2; 40.2. IR (KBr, γ cm^{-1}): 3368- 3257(**NH**); 1774, 1755, 1728 cm^{-1} (**C=O**); 1658 **(C=C**); 1364.8 and 1159 (**SO$_2$**). MS-ESI+ 30ev m/z: 390 [M+H] +100%.

Conclusion

In conclusion, a simple method for the preparation of new series of sulfonamides derivatives containing isatin moiety, using isatin as precursor and different sulfonamides derivatives. We have developed a general and mild two steps approach: acylation of isatin

and condensation with different sulfonamides which are previously prepared. The structure of all synthesized compounds was confirmed by spectroscopic methods ^{1}H, ^{13}C NMR and IR.

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