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Efficient and Simple Methods for the Introduction of the Sulfonyl, Acyl and Alkyl Protecting Groups on the Nitrogen of Indole and its Derivatives

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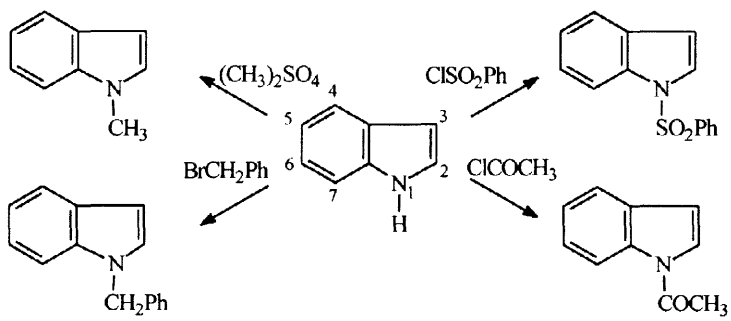
Abstract: The benzenesulfonylation, acetylation, methylation and benzylation at the 1 position of indole and its derivatives with bases such as NaOH, KOH and NEt_3 are presented. By using weaker bases than the traditional ones (BuLi, $NaNH_2$, etc.), the process is simpler, more general and leads to the products in 80-100% yields. The chemoselectivity in compounds bearing more than one nitrogen is also demonstrated.

Keywords: indoles, acylation, alkylation, sulfonation, protecting groups.

INTRODUCTION

The importance and the necessity of protecting the nitrogen of the indole ring is well established.[1-4] Two different kinds of protecting groups have been used on the nitrogen of indole: electron releasing groups and more commonly, electron withdrawing groups. Traditionally, most of the methodologies used to introduce these protecting groups require strong bases such as BuLi,[5-6] $NaNH_2$, [7] and NaH[8] in order to generate the indole anion, which reacts as a nucleophile with alkyl, acyl and sulfonyl halides (Scheme 1). The use of these strong bases may limit the processes to indoles containing certain functional groups, and the experimental work can be laborious and time consuming, requiring special care to avoid hydrolysis. Herein, we describe very simple methods to introduce protective groups on the nitrogen of the indole nucleus.

Scheme 1



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RESULTS AND DISCUSSION

Among the most common withdrawing groups used to protect the nitrogen of indole are the sulfonyl and acyl moieties, probably because the reagents to generate them are commercially available and cheap, and they are relatively easy to remove. The sulfonyl group presents an additional advantage since it almost always forms solid products easy to isolate and purify. Even though electron releasing groups are less used as protecting groups, the benzyl group is a good and important alternative.

The methodologies most commonly applied for the introduction of these protecting groups on indolic substrates are those involving very strong bases or phase-transference processes. However, both of these methods have limitations:

- The use of strong bases (BuLi, $NaNH_2$, NaH, etc.) is restricted to substrates that do not have functional groups bearing other acidic hydrogens or are themselves susceptible to nucleophilic attack.
- The phase-transference process, depending on the acidity of the substrate, does not work well for sulfonylation and acylation, due to the reversibility of the reaction.

Thus, searching for a simpler method of general application for introducing groups on the indole nitrogen, we have discovered that weaker bases such as KOH, NaOH and NEt_3 can be substituted for those strong bases and offer several advantages for alkylations, acylations and sulfonylations.

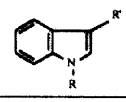
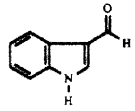
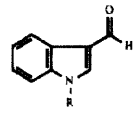
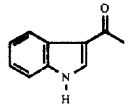
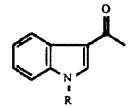
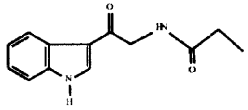
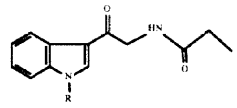
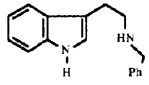
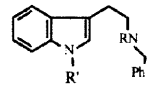
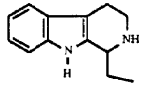
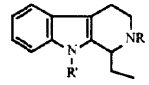
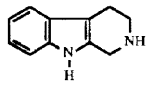
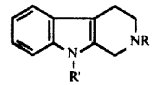
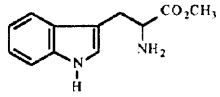
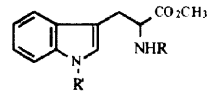
Withdrawing Groups

Electron withdrawing groups are attached to nitrogen of indoles to realize several goals: a) to avoid undesirable reactions at the nitrogen itself; b) to avoid the oligomerization that normally occurs under acidic conditions;[9] c) to avoid addition reactions at the 2,3 double bond of the indole system;[6,10] d) to make possible the generation of the anion at the 2 position.[11,12] Both, acyl and sulfonyl moieties are widely used as protecting groups and we studied acetylation and benzenesulfonylation as representatives of those classes.

Benzenesulfonylation. The substrates were chosen so that the N-H indole hydrogens have different pKa's values and varied steric requirements. In some cases, a second nitrogen with different basicity was present. The models examined were 3-acylindoles, tetrahydro-β-carbolines, tryptamine and tryptophan derivatives and indole itself. The results are shown on Table 1. Three methodologies for the introduction of the benzenesulfonyl group on nitrogen of indole and its derivatives were tested. The procedures employed were classified according to the base used: KOH method; NEt_3 method and NaOH method.

The method using KOH as a base consists in simply dissolving KOH pellets in an ethanolic solution of the indolic substrate, followed by the removal of the ethanol on a rotary evaporator and the addition of acetone and benzenesulfonyl chloride. One of the advantages of this method is that the experimental procedure takes approximately 20 minutes and does not require special purification of solvents. The method is very efficient for the 3-acylindoles (entries **3,4** and **5**), which have a more acidic hydrogen (pKa ~ 12 to 13) than indole (pKa ~ 17), and for pyrrole, even though it has a pKa of 17.5. For indole itself, the result was poor, similar to that obtained by Kikugawa,[18] the *N*-benzenesulfonylindole **2a**, being isolated in 40% yield along with the 1,3 disulfonylated product **2b** in 15% yield. The amidoketone (entry **5**) is particularly interesting because it contains a vinylogous amide[13,14] function as well as an amide. Compounds with two nitrogens such as

Table 1 - Benzenesulfonylation

Entry	Substrate	Product R=SO_2Ph	Methods			
			KOH	NaOH	NEt_3	Phase-transference
1			**1a**, 90%	*	*	*
2			**2a**, R'=H, 40% **2b**, R'=SO_2Ph, 15%	**2a**, 88%	**2a**, 30%	**2a**, 95%
3			**3a**, 95%	**3a**, 94%	**3a**, 90%	**3a**, 0%
4			**4a**, 95%	**4a**, 96%	**4a**, 89%	**4a**, 0%
5			**5a**, 85%	*	*	*
6			**6a**, R'= H, 83%	**6b**, R'= SO_2Ph, 76%	**6b**, 70%	*
7			**7a**, R'= SO_2Ph, 60% **7b**,R'=H, 30%	*	**7a**, 90%	**7a**, 95%
8			**8a**, R'= SO_2Ph, 35%	**8a**, 91%	**8a**, 90%	**8a**, 96%
9			*	**9a**, R'= SO_2Ph, 92%	**9a**, 89%	**9a**, 90%

**This experiment was not carried out.*

N- benzyltryptamine and tetrahydro-β-carbolines (entries **6**, **7** and **8**) were investigated in order to verify if any chemoselectivity could occur. For the *N*-benzyltryptamine only sulfonylation at the side chain amine (N_b) was observed and, for the tetrahydro-β-carboline system, a mixture of 2:1 disulfonylated/monosulfonylated (N_a and N_b) products was obtained. Attention is called to results when 3-acylindoles were used as substrates. These have several acidic hydrogens that can be abstracted by strong bases, and their functional groups are also susceptible to nucleophilic attacks, side reactions that have hampered the introduction of protecting groups under hasher conditions.

Another base employed was the triethylamine. Even though previously applied for preparation of amides,[15] we did not find any report about its use for introduction of substituents on the nitrogen of indole. Surprisingly, the use of triethylamine led to disulfonylated products when tetrahydro-β-carbolines and tryptophan derivatives were used as substrates, these products being isolated in excellent yields (Table 1). Following the reaction by TLC showed that the sulfonylation on the nitrogen (N_a) of the aromatic portion of the molecule occurred only after the N_b sulfonylation had gone to completion. This was expected, since the N_b nitrogen is much more basic (pKb ~ 3) than the indole nitrogen. Thus, it is also possible to obtain the N_b monosulfonylated products in excellent yields by controlling the reaction time and the amount of sulfonyl chloride.

The third method tested was using NaOH and CH_2Cl_2 as a solvent. Although the reagents used are the same employed in the phase-transfer process,[30] the methodology was completely different. In the NaOH method an excess of NaOH pellets is added to a solution or suspension of the substrate in CH_2Cl_2, and the mixture is stirred during 10 minutes. After adding the sulfonyl chloride, the mixture is stirred for another 10 to 40 minutes, depending on the nature of the substrate. This method presents several advantages and works very well for all substrates tested. Even for compounds that have a low pKa (entries **3**,**4** and **5**), no reversion of the reaction occurs as under phase-transfer conditions, in which excess water is present in the reaction medium. With the tetrahydro-β-carbolines, tryptamine and tryptophan derivatives, the disulfonylated products were obtained in excellent yields, and by controlling the reaction time (TLC) or the amount of sulfonyl chloride, the N_b monosulfonylated products can also be generated selectively. Even for indole the method also works well and the product was formed in 88% yield.

In order to compare the efficiencies of these methods, the benzenesufonylation of 3-acylindoles was performed by using published procedures with BuLi[5] or by a phase-transfer procedure similar to that reported by Illi[16] for the sulfonylation of indole, but using CH_2Cl_2 as solvent instead of benzene. Using BuLi as the base, **3a**, **4a** and **5a** were obtained in 70%, 75% and 50% yield, respectively. In the phase-transfer procedure (CH_2Cl_2/NaOH 50%/$ClSO_2Ph$/cat), for compounds such as 3-acylindoles with lower pKas, the sulfonylated products were initially detected by TLC, although hydrolysis occurred subsequently and only starting materials could be isolated. However, for the tetrahydro-β-carbolines, tryptophan and tryptamine derivatives (entries **6**, **7**, **8**, **9**), the disulfonylated products were obtained in high yields. The only exception was tryptamine, from which several compounds were formed as indicated by TLC.

By comparison of the data shown in Table 1 for sulfonylation, we can conclude that:

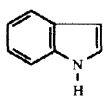
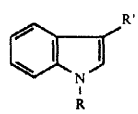
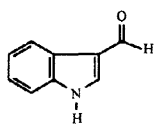
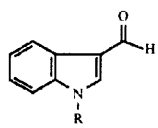
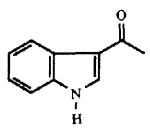
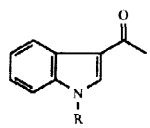
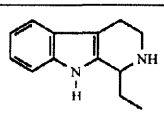
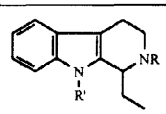
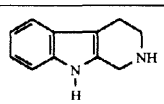
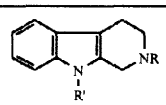
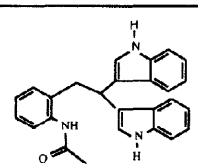
- The NaOH process is more general than the other methods, leading to products in very good yields.
- The KOH method works well for pyrrole and indole derivatives with low pKas.

- The NEt_3 method gives disulfonylated β-carbolines as well as N_a-sulfonylated 3-acylindoles in good yields, but the reaction times are longer and the purification of the products more laborious, compared to that of the KOH and NaOH methods.

Acetylation. Even though the acetyl group has been widely used to protect the 1 position of indole, it does not prevent addition reactions at the 2,3 double bond of the indole;[17] however, its presence avoids the other side reactions mentioned earlier.

The three procedures used for sulfonylation were then tested for the acetylation of indoles. The initial attempts using the KOH methodology failed. This was not a particular surprise since the hydrolysis of acetyl chloride is much faster than benzenesulfonyl chloride, and water is generated in the reaction medium. However, a very simple modification in the experimental procedure led to the acetylated products in high yields. The addition of anhydrous Na_2SO_4 to the acetone solution, prepared as before, permitted the removal of water from the reaction medium, thus avoiding the hydrolysis of the acid chloride and making *N*-acetylation possible (Table 2). The method worked very well for different kinds of substrates including those with low pKa's as 3-acylindoles as well as tetrahydro-β-carbolines where diacylated products were obtained in 95% yield. For indole itself the product was isolated in 85% yield, which represents an improvement when compared to the method described by Gribble[28] in which the 1-acylated product was obtained in 65% yield.

Table 2 - Acetylations

Entry	Substrate	Product R=$COCH_3$	Methods		
			NaOH	NEt_3	KOH/Na_2SO_4
10			**10a**, R'=H, 90%	**10a**, 50% +**10b**,R'=$COCH_3$, 18% +**10c**, *TRIMER, 6%	**10a**, 85%
11			**11a**, 75%	**11a**, 85%	**11a**, 68%
12			**12a**, 98%	**12a**, 85%	**12a**, 98%
13			**13a**, R'=Ac, 90%	**13b**, R'=H, 83%	**13a**, 95%
14			**14a**, R'=Ac, 91%	*	**14a**, 95%
10c	*TRIMER=				

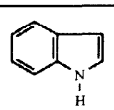
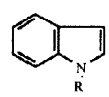
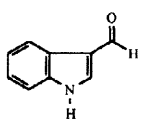
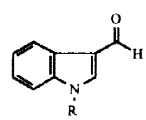
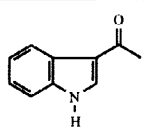
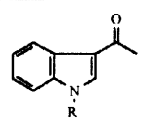
*This experiment was not carried out.

In the phase-transfer procedure, TLC indicated the initial formation of the desired products in very limited amounts for indole and 3-acylindoles. However, only starting materials could be isolated, showing that the reversion of the reaction as well as hydrolysis of acetyl chloride contributed to the poor results in this case. The results obtained by Illi[19] using phase-transfer catalyst/CH_2Cl_2 for the acylation of indole itself reinforces our hypothesis. On another hand, the NaOH method, in which the water is omitted, worked very well for all substrates shown on Table 2. The *N*-acetylated indole, 1,3-diacetylated indole and N_a,N_b-diacylated tetrahydro-β-carbolines were obtained in 90-98% yields. The process takes approximately 30 minutes and the work up is very simple. The triethylamine method was efficient only for indole systems that have low pKa values (entries **11** and **12**, the 3-acylindoles). For indole itself, a mixture of *N*-acetylated, 1,3 diacetylated indole and a trimer (**10c**) were obtained. For the β-carboline system, unlike the sulfonylation, acetylation occurred only at the N_b nitrogen. Thus, our results showed that for acetylation the most general methods were those that employed NaOH/CH_2Cl_2 and KOH/Na_2SO_4. For tryptophan methyl ester and tryptamine, none of the acetylation processes were efficient, giving mixtures of several compounds that were not characterized.

Electron Releasing Groups: Methyl and Benzyl

The presence of an electron releasing group instead of a withdrawing protective group on indole nucleus is sometimes necessary. The withdrawing groups can block reactions such as Pictet-Spengler, Bischler-Napieralski, DDQ oxidations, etc. Moreover several indole alkaloids have a methyl group as a substituent on the nitrogen of the indole nucleus. The electron releasing groups chosen for examination were benzyl and methyl. Through the treatment of indole with KOH, by the process described previously, and followed by the addition of dimethyl sulfate† or benzyl bromide, both *N*-methyl and *N*-benzylindole were obtained in 90% of yield. Using the same method, 3-acetyl *N*-methylindole and 3-acetyl *N*-benzylindole were prepared in 93 to 95% yields. Heaney[29] described similar results but using only indole as substrate.

Table 3 - Benzylations and Methylations

Entry	Substrate	Product	Method		
			KOH	NaOH	Phase-Transference
15			**15a**, R=CH_3, 93% **15b**, R=CH_2Ph, 95%	**15b**, R=CH_2Ph, 92%	**15a**, 90% **15b**, 90%
16			**16a**, R= CH_2Ph, 93%	*	**16a**, 95%
17			**17a**,R= CH_3, 95% **17b**,R= CH_2Ph, 95%	**17b**, 98%	**17a**, 95% **17b**, 96%

**This experiment was not carried out.*

† The use of methyl iodide gave poorer yields

Similar results were also reached by the employment of $NaOH/CH_2Cl_2$/R-X. Here too, the phase-transfer method[29a,29b] was used in order to compare the efficiency of the methods and proved that all three gave essentially the same yields of alkylated products. The similarity of the results were expected since the hydrolysis of the benzyl bromide or dimethylsulfate is much more difficult than the hydrolysis of acetyl or benzenesulfonyl chloride, the presence or absence of water in the reaction medium not influencing the results significantly.

CONCLUSION

New and simple methods for the introduction of protecting groups in indolic systems were developed. The advantage of these procedures relative to known ones are:

- The bases employed (KOH, NaOH, NEt_3) are milder compared to those traditionally used (BuLi, $NaNH_2$, NaH).
- No special purification of solvents and reagents is required.
- The experimental procedures are fast and the work up is not laborious.
- The yields are excellent.
- The methods are not restricted to indole itself having a widespread application involving a large number of different substrates.

The choice of one or another method depends on the nature of the substrate and protective group nature. The reactions using arylsulfonyl chlorides, and alkyl halides or dimethylsulfate, which do not hydrolyze easily, worked well under the majority of the conditions tested. However, the easily hydrolyzed acyl halides can not be used in aqueous medium.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. The ^1H NMR spectra were recorded on a Bruker 200-MHz or a Varian 90-MHz spectrometer. Infrared spectra were recorded on a Nicolet Dx FTIR DX spectrometer. All chemicals were purchased from Aldrich Chemical Co.

Representative Procedure for the *N*-Sulfonylation of Indole and Derivatives using the KOH Method.

1-[1-(Phenylsulfonyl-1*H*-3-indolyl)-1-ethanone] (4a). To a solution of 3-acetylindole **4** (2.4 mmol, 0.38 g) in ethanol (20 mL) at room temperature, KOH pellets were added (3 mmol, 0.17 g), and the mixture was stirred until total solubilization. The ethanol was completely removed in vacuum and acetone (20 mL) added followed by benzenesulfonyl chloride (2.4 mmol, 0.32 mL). A precipitate was formed instantly. The solid was filtered and the solution concentrated in vacuum. Crystals precipitated out and were filtered and washed with ethanol, yielding 0.68 g (95%) of **4a**: mp 154-157^{0}C (mp lit[11] 155-157^{0}C) ; IR (KBr) 1665 (C=O) cm^{-1};^1H NMR (DMSO-d_6) δ 2.5 (s, 3H) , 7.0-8.8 (m, 10H).

***N*-Phenylsulfonyl pyrrole (1a).** The same procedure described above but using 2.4 mmol of pyrrole **1** gave 0.42 g (90%) of **1a** as an yellow oil[21]; IR (film) 1449, 1379, 1177 (O=S=O); ^1H NMR ($CDCl_3$) δ 7.6-8.3 (m, 9H).

1-Phenylsulfonyl indole (2a). The same procedure described above but using 2.4 mmol of indole **2** gave a solution that was dried (Na_2SO_4) and evaporated. Dry flash chromatography of the residue and elution with 20:1 hexane- CH_2Cl_2 gave 0.25 g (40%) of **2a**, 0.14 g (15%) of **2b** and 0.19 g (45%) of starting material. **2a:** mp 75-78^{0}C (mp lit[12] 75.5-79^{0}C); ^{1}H NMR ($CDCl_3$) δ 6.53 (d, 1H, J = 4 Hz); 7.0-8.1 (m, 10H).**2b:** ^{1}H NMR δ ($CDCl_3$) 7.6-8.2 (m 15H).

1-(Phenylsulfonyl)-1*H*-3-indolecarbaldehyde (3a). The same procedure described above but using 2.4 mmol of indole-3-carbaldehyde **3** gave 0.65 g (95%) of **3a**; mp 156-158^{0}C (mp lit[20] 158-158.5^{0}C); IR (KBr) 1675 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.3-7.7 (m, 5H); 7.9-8.15 (m, 3H); 8.2 (s, 1H); 8.3 (m, 1H); 10.2 (s, 1H).

N-[2-(1-Phenylsulfonyl)-1*H*-3-indolyl]-2-oxoethyl-propanamide (5a). The same procedure described above but using 2.4 mmol of the indole-amide **5** gave 0.75 g (85%) of **5a**; mp 210-211^{0}C; IR (KBr) 1679(C=O), 1634 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 3H, J = 7,5 Hz); 2.4 (q, 2H, J = 7,5 Hz); 4.75 (d, 2H, J = 4,5 Hz); 6.7 (s broad, 1H); 7.3-8.5 (m, 10H). Anal. Calcd. for $C_{18}H_{18}N_2O_4S$: C, 61.62; H, 4.86; N, 7.56; S, 8.64. Found: C, 61.90; H, 4.87; N, 7.51; S, 8.15.

(3-{2-[Benzyl(phenyl)sulfonamido]ethyl}-1*H*-indole) (6a). The same procedure described above but using 2.4 mmol of *N*-benzyltryptamine **6** gave a dark solution that was dried with Na_2SO_4, filtered and evaporated. Dry flash chromatography of the residue and elution with $CHCl_3$ gave 0.75 g (83%) of **6a** as an brownish oil; IR (KBr) 1375, 1123, 968 cm^{-1}. ^{1} H NMR ($CDCl_3$) δ 2.8 (m, 2H); 3.45 (m, 2H); 4.55 (s, 2H); 7.13-8.2 (m, 11H).

1-Ethyl-2,9-di(phenylsulfonyl)-1,2,3,4-tetrahydro-1*H*-β-carboline (7a). The same procedure described above but using 2.4 mmol of ethylcarboline **7** gave a solution that was dried with Na_2SO_4 and evaporated. Dry flash chromatography of the residue and elution with CH_2Cl_2 gave 0.38 g (60%) of **7a** and 0,12 g (30%) of **7b**. For **7a**: mp 167-169^{0}C; IR (KBr) 1447, 1364, 1164; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, J = 6.0 Hz); 1.2-1,9 (m, 2H); 2,1-2.7 (m, 2H); 3.35 (m, 1H); 4.10 (m, 1H); 5.55 (dd, 1H, J_1 = 10.5 Hz, J_2 = 3.0 Hz); 6.9-8.3 (m, 14H). The methine proton in 5.55 δ as well as all methylene groups in the compound are diasterotopic and are split in multiplets. Anal. Calcd. for $C_{19}H_{20}N_2O_2S$: C, 67.05; H, 5.88; N, 8.02; S, 9.02. Found: C, 67.40; H, 5.87; N, 8.51; S, 9.15. For **7b**: mp 280-284^{0}C; ^{1}H NMR (DMSO-d_6) δ 1.08 (t, 3H); 2.1 (m, 2H); 2.95 (m, 2H); 3.5 (m, 2H); 4.7 (m, 1H); 6.9-7.8 (m, 7H); 8.3 (s, 1H); 9.0 (m, 1H); 10.0 (s broad, 1H). Anal. Calcd. for $C_{25}H_{24}N_2O_4S_2$: C, 61.50; H, 5.03; N, 5.82; S, 12.40. Found: C, 61.25; H, 4.89; N, 5.70; S, 12.10.

2,9-Di(phenylsulfonyl)-1,2,3,4-tetrahydro-1*H*-β-carboline (8a). The same procedure described above but using 2.4 mmol of tryptoline **8** gave 0.30 g (35%) of **8a**; mp 195-198^{0}C; ^{1}H NMR ($CDCl_3$) δ 2.9 (t broad, 2H,); 3.52 (t, 2H, J = 6,0Hz); 4.7 (s, 2H); 7.2-8.4 (m 14H). Anal. Calcd. for $C_{23}H_{20}N_2O_4S_2$: C, 60.53; H, 4.38; N,6.14; S, 14.05. Found: C, 59.02; H, 4.28; N, 5.92; S, 13.43.

Methyl-2-phenylsulfonamido-3-[1-(phenylsulfonyl)-1*H*-3-indolyl]propanoate (9a). The same procedure described above but using 2.4 mmol of tryptophan methyl esther **9** gave 1.0 g (90%) of **9a**. mp 92-94^{0}C; IR (KBr) 1736 (C=O), 1335, 1165, 1093 (O=S=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.2 (d, 2H, J = 1.5 Hz); 3.4 (s, 3H); 4.3 (m, 1H); 5.4 (d, 1H J = 1.5 Hz); 8.1-7.0 (m, 1H, 15H).

Representative Procedure for the *N*-Sulfonylation of Indole and Derivatives using Triethylamine Method.

1-Ethyl-2,9-di(phenylsulfonyl)-1,2,3,4-tetrahydro-1*H*-β-carboline (7a). A magnetically stirred solution of ethylcarboline **7** (2.3 mmol, 0.46 g), triethylamine (3.1 mmol, 0.43 mL), benzenesulfonyl chloride (3.1 mmol, 0.31mL) and 20 mL of ethanol was refluxed under N_2 for 2.5 h until no starting material was detected by TLC. The ethanol was evaporated in vacuum and the resultant residue poured onto 50 mL of 5% HCl solution. The aqueous emulsion was extracted with CH_2Cl_2. The organic extract was washed with brine, dried (K_2CO_3) filtered and concentrated in vacuum. Crystals precipitated out and were filtered, washed with CH_2Cl_2 yielding 1.0 g (90%) of **7a** as an yellow solid.

1-Phenylsulfonyl indole (2a). The same procedure described above but using 23 mmol of indole **2** gave a solution that was dried (Na_2SO_4) and evaporated. Dry flash chromatography of the residue and elution with 20:1 hexane- CH_2Cl_2 gave 0.20 g (30%) of **2a**, and 0.30 g (65%) of starting material.

1-Phenylsulfonyl-1*H*-3-indolecarbaldehyde (3a). The same procedure described above but using 2.3 mmol of indole-3-carbaldehyde **3** gave 0.65 g (90%) of **3a**.

1-[1-(Phenylsulfonyl)-1*H*-3-indolyl)-1-ethanone] (4a). The same procedure described above but using 2.3 mmol of 3-acetylindole **4** gave 0.6 g (89%) of **4a**.

(3-{2-[Benzyl(phenyl)sulfonamido]ethyl}-1*H*-indole) (6b). The same procedure described above but using 2.4 mmol of *N*-benzyltryptamine **6** gave a solution that was dried with Na_2SO_4, filtered and evaporated. Dry flash chromatography of the residue and elution with $CHCl_3$ gave 0.65 g (70%) of **6b** as an yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.9 (m, 2H); 3.6 (m, 2H); 4.7 (s, 2H); 7.2-8.7 (m, 10H).

2,9-Di(phenylsulfonyl)-1,2,3,4-tetrahydro-1*H*-β-carboline (8a). The same procedure described above but using 2.3 mmol of tryptoline **8** gave 0.94 g (90%) of **8a**.

Representative Procedure for the *N*-Sulfonylation of Indole and Derivatives using NaOH/CH_2Cl_2 Method.

1-Phenylsulfonyl indole (2a). A mixture of 1.17 g (10 mmol) of indole **2**, 10 mL of CH_2Cl_2 and 0.60 g (12 mmol) of NaOH was stirred for 15 min. 0.2 mL then (15 mmol) of benzenesulfonyl chloride was added and the mixture was stirred for 25 min until no indole was detected by TLC. The solution was washed exhaustively with water, dried with Na_2SO_4 and concentrated. Crystals precipitated out and were filtered, yielding 2.0 g (88%) of **2a** as a white solid.

1-(Phenylsulfonyl)-1*H*-3-indolecarbaldehyde (3a). The same procedure described above but using 2.4 mmol of indole-3-carbaldehyde **3** gave 0.60 g (94%) of **3a**.

1-[1-(Phenylsulfonyl)-1*H*-3-indolyl)-1-ethanone] (4a). The same procedure described above but using 2.4 mmol of 3-acetylindole **4** gave 0.75 g (96%) of **4a**.

(3-{2-[Benzyl(phenyl)sulfonamido]ethyl}-1*H*-indole) (6b). The same procedure described above but using 2.4 mmol of *N*-benzyltryptamine **6** gave a solution that was dried with Na_2SO_4, filtered and evaporated giving 0.70 g (76%) of **6b** as an yellow oil.

2,9-Di(phenylsulfonyl)-1,2,3,4-tetrahydro-1*H*-β-carboline (8a). The same procedure described above but using 2.3 mmol of tryptoline **8** gave 0.95 g (91%) of **8a**.

Methyl-2-phenylsulfonamido-3-[1-(phenylsulfonyl)-1*H*-3-indolyl]propanoate (9a). The same procedure described above but using 2,4 mmol of tryptophan methyl esther **9** gave 1.1 g (93%) of **9a**.

Representative Procedure for the *N*-Sulfonylation of Indole and Derivatives using Phase-Transfer Method.

1-Phenylsulfonyl indole (2a). A mixture of 1.17 g (10 mmol) of indole **2**, 65 mg of Aliquat 336^R, 0.2 mL (15 mmol) of benzenesulfonyl chloride in 10 mL of CH_2Cl_2 and 5 mL of 50% NaOH solution was stirred vigorously for 15 min until no indole was detected by TLC. The organic solution was separated, washed exhaustively with water, dried with Na_2SO_4 and evaporated giving 2.4 g (95%) of **2a** as a white solid.

Methyl-2-phenylsulfonamido-3-[1-(phenylsulfonyl)-1*H*-3-indolyl]propanoate (9a). The same procedure described above but using 10 mmol of tryptophan methyl esther **9** gave 4.5 g (90%) of **9a**.

1-Ethyl-2,9-diphenylsulfonyl-1,2,3,4-tetrahydro-1*H*-β-carboline (7a). The same procedure described above but using 10 mmol of ethylcarboline **7** gave 4.5 g (95%) of **7a**.

2,9-Diphenylsulfonyl-1,2,3,4-tetrahydro-1*H*-β-carboline (8a). The same procedure described above but using 10 mmol of tryptoline **8** gave 4.3 g (95%) of **8a**.

Representative Procedure for the *N*-Acetylation of Indole and Derivatives using NaOH/CH_2Cl_2 Method.

1-Acetylindole (10a). A solution of 1.17 g (10 mmol) of indole, 1.0 mL (15 mmol) of acetyl chloride, 440 mg (11mmol) NaOH in 10 mL of CH_2Cl_2 was stirred vigorously for 30 min until no indole was detected by TLC. The organic solution was washed exhaustively with water, dried with Na_2SO_4 and evaporated giving 1.4 g (90%) of **10a** as an yellow oil[19]. IR (film) 1707 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.65 (s, 3H, CH_3) ; 6.65 (d, 1H, J = 3.0 Hz) 7.2-8.4 (m, 5H).

1-(1-Acetyl-1*H*-3-indolecarbaldehyde] (11a). The same procedure described above but using 10 mmol of indolecarbaldehyde gave 1,5 g (85%) of **11a**; mp 162-163^{0}C (mp lit[22] 162-163^{0}C); IR (KBr) 1734 (C=O); 1675 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 3H); 7.5-7.7 (m, 2H); 8.4 (s, 1H); 8.5-8.6 (m, 2H); 10,2 (s, 1H).

1-[1-Acetyl-1*H*-3-indolyl)-1-ethanone] (12a). The same procedure described above but using 10 mmol of 3-acetylindole gave 2 g (98%) of **12a**; mp 92-94^{0}C (mp lit[23] 93-94^{0}C) ; IR (KBr) 1715 (C=O); 1661 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.5 (s, 3H); 2.73 (s, 3H); 7.4-7.65 (m 2H); 8.3-8.6 (m, 2H); 8.85 (s, 1H).

1-(2-Acetyl-1-ethyl-1,2,3,4-tetrahydro-1*H*-β-carbolin-9-yl)-1-ethanone (13a). The same procedure described above but using 10 mmol of ethylcarboline **13** gave 2.61 g (90%) of **13a** as an yellow oil; IR (film) 1715 (C=O), 1661 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.0 (t, 3H, J = 6,0 Hz); 2.25 (s, 3H); 2.35 (s, 3H); 2.8 (m, 2H) ; 3.5 (m, 2H) ; 4.00 (m, 2H) ; 5.75 (m, 1H) ; 7.0-7.6 (m, 4H). Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C, 71.80; H, 7.03; N, 9.86. Found: C, 71.94; H, 7.13; N, 9.91.

1-(2-Acetyl-1,2,3,4-tetrahydro-1*H*-β-carbolin-9-yl)-1-ethanone (14a). The same procedure described above but using 10 mmol of tryptoline gave **14** 1.5 g (91%) of **14a** as an yellow oil; IR (film) 1447, 1374, 1170 (O=S=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H); 2.25 (s, 3H); 3.4 (m, 2H); 3.9 (t, 2H, J =4,5 Hz); 4.95 (s, 2H); 7.0-7.8 (m, 4H). Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 72.87; H, 6.58; N, 13.07. Found: C, 73.01; H, 6.55; N, 13.48.

Representative Procedure for the *N*-Acetylation of Indole and Derivatives using Triethylamine Method.

1-[1-Acetyl-1*H*-3-indolyl)-1-ethanone] (12a). A magnetically stirred solution of 3-acetylindole **12** (2.3 mmol, 0.37 g), triethylamine (3.1 mmol, 0.43 mL), acetyl chloride (3.1 mmol, 0.25 mL) and 20 mL of CH_2Cl_2 was refluxed under N_2 for 1 h until no starting material was detected by TLC. The mixture was poured onto 50 mL of 5% HCl solution and the organic layer separeted. The aqueous layer was extract twice with CH_2Cl_2. The organic extract was washed with brine, dried (K_2CO_3) filtered and concentrated in vacuum to give 0.4 g (85%) of **12a** as white crystals.

1-Acetylindole (10a). The same procedure described above but using 2.3 mmol of indole gave an yellow solution that was dried with Na_2SO_4, filtered and evaporated. Dry flash chromatography of the residue and elution with 20:1 hexane- CH_2Cl_2 gave 0.18 g (50%) of **10a**, 0.06 g (18%) of **10b** and 0.05g (6%) of **10c**.

10c mp 209-211°C (mp lit[24] 210-211 °C); IR (KBr): 3610, 3340, 1655 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.85 (s, 3H); 3.6 (d, 2H, J = 7,5 Hz); 4.8 (t, 1H, J = 7,5 Hz) ; 6.8-7.8 (m, 16 H); 9.0 (s br, 1H).

1-(1-Acetyl-1*H*-3-indolecarbaldehyde] (11a). The same procedure described above but using 2,3 mmol of indolecarbaldehyde gave 0,42 g (98%) of **11a**.

1-(1-Ethyl-1,2,3,4,-tetrahydro-1*H*-β-carbolin-2-yl)-1-ethanone (13b). The same procedure described above but using 2.3 mmol of ethylcarboline **13** gave 0.46 g (83%) of **13b** as an yellow oil; IR (film) 1655 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.3 (t, 3H, J = 6,0 Hz); 2.1 (s, 3H); 2.8 (m, 2H); 3.55 (m, 2H); 4.00 (m, 2H); 5.8 (m, 1H); 7.0-8.8 (m, 5H). Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.48; N, 11.56. Found: C, 74.74; H, 7.43; N, 11.39.

Representative Procedure for the *N*-Acetylation of Indole and Derivatives using KOH/Na_2SO_4 Method.

1-[1-Acetyl-1*H*-3-indolyl)-1-ethanone] (12a). To a solution of 3-acetylindole (2.4 mmol, 0.38 g) in ethanol (20 mL) at room temperature, KOH pellets were added (3 mmol, 0.17 g), and the mixture was stirred until total solubilization. The ethanol was completely removed in vacuum and 1 g of Na_2SO_4 added followed by acetone (20 mL) and acetyl chloride (3.0 mmol, 0.24 mL). The mixture was stirred for 10 minutes, the solid was filtered and the solution concentrated in vacuum to give 0.41 g (98%) of **12a**.

1-Acetylindole (10a). The same procedure described above but using 2.4 mmol of indole gave 0.32 g (85%) of **10a** as an yellow oil.

1-(1-Acetyl-1*H*-3-indolecarbaldehyde] (11a). The same procedure described above but using 2,4 mmol of indolecarbaldehyde gave 0,40 g (95%) of **11a**.

1-(2-Acetyl-1-ethyl-1,2,3,4-tetrahydro-1*H*-β-carbolin-9-yl)-1-ethanone (13a). The same procedure described above but using 2.4 mmol of ethylcarboline gave 0.67 g (95%) of **13a** as an oil.

1-(2-Acetyl-1,2,3,4-tetrahydro-1*H*-β-carbolin-9-yl)-1-ethanone (14a). The same procedure described above but using 2.4 mmol of tryptoline gave 0.58 g (95%) of **14a** as an oil.

Representative Procedure for the *N*-Alkylation of Indole and Derivatives using KOH Method.

1-[1-Benzyl-1*H*-3-indolyl)-1-ethanone] (17b). To a solution of 3-acetylindole (2.4 mmol, 0.38 g) in ethanol (20 mL) at room temperature, KOH pellets were added (3 mmol, 0.17 g), and the mixture was stirred until total solubilization. The ethanol was completely removed in vacuum and acetone (20 mL) added followed by the benzyl bromide (2.4 mmol, 0,32 mL). A precipitate was formed instantly. The solid was filtered and the solution concentrated in vacuum to give 0.56 g (95%) of **17b**. mp 114-115°C; IR (KBr) 1635 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H); 5.35 (s, 2H); 7.0-8.7 (m, 10H). Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.10; N, 5.62. Found: C, 81.55; H, 6.41; N, 5.42.

1-(1-Methyl-1*H*-3-indolyl)-1-ethanone (17a). The same procedure described above (16) but using 2.4 mmol of dimethyl sulfate as alkylating agent, gave 0.39 g (95%) of **17a**. mp 106-107°C (mp lit[25] 107°C); IR (KBr) 1640 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H); 3.77 (s, 3H); 7.2-8.5 (m, 5H).

1-Benzyl-1*H*-3-indolecarbaldehyde (16a). The same procedure described above but using 2.4 mmol of indole-3-carbaldehyde gave 0.32 g (93%) of **16a**. mp 102-104^{0}C (mp lit[26] 102-104°C); IR (KBr) 1654 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.6 (s, 2H); 7.2-8.18 (m, 9H); 8.55 (s, 1H); 10.1 (s, 1H).

1-Benzyl-1*H*- indole (15b). The same procedure described above but using 2.4 mmol of indole gave 0.47 g (95%) of **15b**; mp 41-43^{0}C (mp lit[26] 44°C); ^{1}H NMR ($CDCl_3$); 5.25 (s, 2H); 6.5-7.8 (m, 11H).

1-Methyl-1*H*-indole (15a) - The same procedure described above (14) but using 2.4 mmol of dimethyl sulfate, as alkylating agent, gave 0.23 g (93%) of **15a**[27] as a liquid. ^{1}H NMR ($CDCl_3$); 3.5 (s, 3H); 6.3 (d, 1H, J = 3,0 Hz); 6.7 (d, 1H, J = 3 Hz); 7-7.5 (m, 4H).

Representative Procedure for the *N*-Alkylation of Indole and Derivatives using Phase-Transfer Method.

1-Benzyl-1*H*- indole (15b). A mixture of 1.17 g (10 mmol) of indole, 65 mg of Aliquat 336^R, 0.2 mL (15 mmol, 1.2 mL) of benzyl bromide in 10 mL of CH_2Cl_2 and 5 mL of 50% NaOH solution was stirred vigorously for 15 min until no indole was detected by TLC. The organic solution was separated, washed exhaustively with water, dried with Na_2SO_4 and evaporated giving 1.9 g (90%) of **15b**.

1-Methyl-1*H*-indole (15a). The same procedure described above (14) but using 10 mmol of dimethyl sulfate, as alkylating agent, gave 1.7 g (90%) of **15a**.

1-Benzyl-1*H*-3-indolecarbaldehyde (16a). The same procedure described above but using 10 mmol of 3-indolecarbaldehyde and benzyl bromide as alkylating agent gave 1.4 g (95%) of **16a** .

1-[1-Benzyl-1*H*-3-indolyl)-1-ethanone] (17b). The same procedure described above but using 10 mmol of 3-acetylindole gave 2.3 g (96%) of **17b**.

1-(1-Methyl-1*H*-3-indolyl)-1-ethanone (17a). The same procedure described above (16) but using 10 mmol of dimethyl sulfate as alkylating agent, gave 1.6 g (95%) of **17a**.

Representative Procedure for the *N*-Benzylation of Indole and Derivatives using NaOH/CH_2Cl_2 Method.

1-Benzyl-1*H*- indole(15b). A solution of 1.17 g (10 mmol) of indole, 1.0 mL (15 mmol) of benzyl bromide, 440 mg (11mmol) NaOH in 10 mL of CH_2Cl_2 was stirred vigorously for 30 min until no indole was detected by TLC. The organic solution was washed exhaustively with water, dried with Na_2SO_4 and evaporated giving 1.8 g (92%) of **15b**.

1-[1-Benzyl-1*H*-3-indolyl)-1-ethanone] (17b). The same procedure described above but using 10 mmol of 3-acetylindole gave 2.4 g (98%) of **17b**.

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