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UNUSUAL ACETYLATION OF 2-METHYL-1-PHENYLSULFONYLINDOLE

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Abstract: Acetylation of 2-methyl-1-phenylsulfonylindole with an excess of aluminium chloride and acetic anhydride afforded exclusively 6-acetyl-3-chloro-2-methylindole and 6-acetyl-3-chloro-2-methyl-1-phenylsulfonylindole .

Regioselective electrophilic substitution of indolic derivatives is a crucial problem in the indole chemistry since a mixture of isomers are formed. Acylation of indoles has been widely used[1] and Friedel-Crafts acylation is one of the best method for introducing acyl group at the position 3 of 1-acetyl or 1-tosylindole. The 3-position of the indole ring is generally the normal site of attack.[1] However, ethoxycarbonyl substituent in 2-position directed the acetylation towards the 3, 5, 7-positions of the indole ring.[2,3] A mixture of 5 and 6-acetyl derivatives were obtained from 3-ethoxycarbonylindole.[4] The acetylation of 3-acetylindole afforded a mixture of 3,5, 3,6 and 3,7-diacetylindoles.[5]

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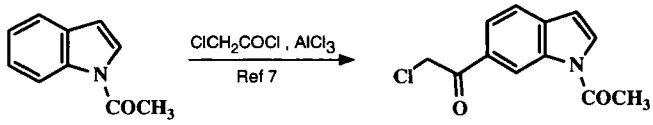
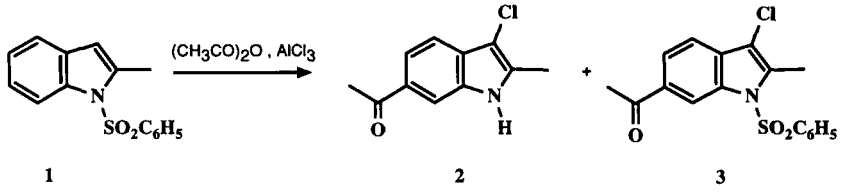


FIG 1

The acylation of 1-acylindole under Friedel-Crafts conditions is more intricate than a simple reaction with acetyl choride in the presence of aluminium chloride. Nakatsuka has reported that either 6 or 3-acylated products can be exclusively obtained depending on the nature of the 1-acyl group and the acyl chloride used[6,7] (Figure 1).

As part of a programme aimed at Baeyer-Villiger oxidation of 3-acetylindoles derivatives[8,9] we needed to prepare 3-acetyl-2-methyl-1-phenylsulfonylindole. The experimental conditions reported by Gribble for the acetylation of 1-phenylsulfonylindole[10] (6 eq. of $AlCl_3$ and 3 eq. of acetic anhydride at room temperature) failed to give the expected 3-acetyl-2-methyl-1-phenylsulfonylindole (**4**) and as a result the chloro derivatives, the 6-acetyl-3-chloro-2-methylindole (**2**) (30%) and the 6-acetyl-3-chloro-2-methyl-1-phenylsulfonylindole (**3**) (32%) were obtained (Figure 2). Nevertheless using the adequate conditions of acetylation, also reported by Gribble[11] for the 2-methyl-1-sulfonylindole (1 eq. of $AlCl_3$ and 1 eq. of acetic anhydride), gave the expected compound **4**. It may be noted that chloroindoles are scarcely described in the literature.[12,13] Using $AlBr_3$ instead of $AlCl_3$ in this acetylation procedure afforded a complex mixture of products.

Compound **3** can be easily transformed into compound **2** by debenzenesulfonylation in basic media (sodium carbonate/ methanol/water/ 60°C).



1 2 3

FIG 2

The ^1H NMR (500 MHz) spectrum of compound **2** indicated the presence of a methyl in 2-position, an acetyl group and a monosubstitution in 5- or 6-position on the benzene ring. The mass spectra showed the presence of a chlorine atom.

The 5-acetyl-3-chloro-2-methylindole (**9**) and the 3-acetyl-5-chloro-2-methylindole (**11**) were prepared to exclude their possible formation in the above reaction, figure 2. 5-Bromo-2-methylindole (**6**)[16] (obtained from 2-methylindoline (**5**)) was treated with benzenesulfonylchloride in dichloromethane in the presence of sodium hydroxide and a catalytic amount of benzyltriethylammonium chloride to give 5-bromo-2-methyl-1-benzenesulfonylindole (**7**) in 80% yield. A Stille coupling was performed in the presence of palladium tetrakis triphenylphosphine and ethoxyvinyltributylstannane to afford 5-acetyl-2-methyl-1-sulfonylindole (**8**) directly in 61% yield. The sulfonyl group was then cleaved in basic media to give the 5-acetyl-2-methylindole (76%), and the 3-chloro substituent was introduced by using *N*-chlorosuccinimide[14] in methanol to obtain (**9**) (81%) (Figure 3).

5-Chloroindole (**10**) was benzenesulfonylated in 90% yield. It was then methylated in 2-position to afford the 1-phenylsulfonyl-5-chloro-2-methylindole (98%). The acetyl group in 3-position was introduced, after the cleavage of the benzenesulfonyl group (K_2CO_3/ CH_3OH), using phosphorus oxychloride in dimethylacetamide to give **11** (27%) (Figure 4).

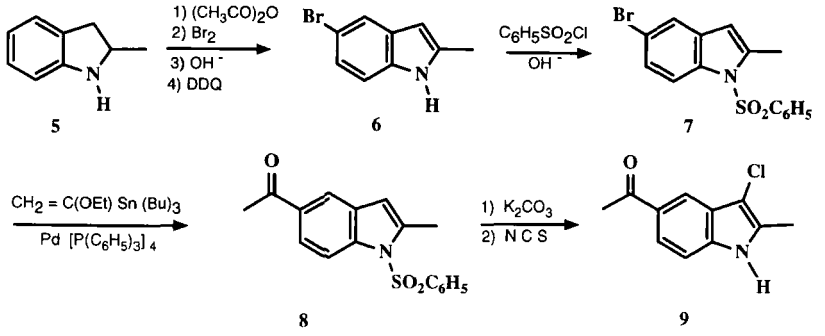


FIG 3

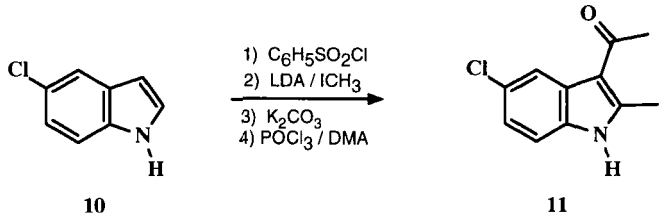


FIG 4

^1H NMR spectra and physical data of compounds **9** and **11** were different to those of **2**. The examination of the chemical shifts of the aromatic protons indicated the presence of a substitutent in 6-position in compound **2**. The debenzenesulfonylation of compound **3** implies an important shielding of 0.89 ppm for the H_7 in the resulting compound **2**. The H_7 for 6-acetylindole[15] has a chemical shift of 8.04 ppm which is higher than the chemical shift of the H_7 in the 6-chloroindole, 7.45 ppm. This therefore indicates the presence of the acetyl substituent at the position 6 in compound **2**. In addition a NOESY spectrum for compound **2** showed Nuclear Overhauser interactions between aromatic hydrogens, C_7H and C_5H and CH_3CO confirming the proposed structure

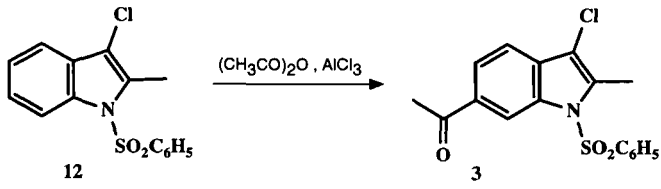


FIG 5

In order to have more information about the outcome of the reaction (Figure 2) we have prepared 3-chloro-2-methyl-1-phenylsulfonylindole[12] (**12**) and then we submitted it to the same acetylation conditions as described for compound **1**. As a result compound **3** was exclusively obtained (68%), unambiguously indicating the presence of the acetyl group on the benzene part of the indole ring for compound **3** (Figure 5).

The formation of compounds **2** and **3** can therefore result from a chlorination in 3-position (which is faster than the acetylation in 3-position in the presence of a large excess of $AlCl_3$) followed by acetylation in 6-position of compound **1**.

In summary, acetylation and chlorination under suitable conditions thus provide a convenient route to functionnalize the 3 and 6-positions in a single regioselectif step. We are currently investigating this reaction to other indoles derivatives.

Experimental

Melting points are uncorrected and were taken on a Kofler hot stage apparatus. The ^1H NMR spectra were determined on a Bruker instrument (AM 300WB, 300 MHz or ARX 500 MHz) in $CDCl_3$ with TMS as internal standard; IR spectra were

recorded on a Perkin Elmer 1310 spectrophotometer on a KBr matrix; mass spectra were obtained using a Nermag 10-10C instrument using chemical ionization with ammonia. Reactions were monitored by thin layer chromatography using Merck silica gel $60F_{254}$.; Column chromatography were performed using Merck silica gel 60 (0.063-0.200 mm).

6-Acetyl-3-choro-2-methylindole (2) and 6-acetyl-3-chloro-2-methyl-1-phenyl sulfonylindole (3).

To a suspension of aluminium trichloride (2.4g, 18 mmol) in dichloromethane (20 ml) were added acetic anhydride (0.83 ml, 9 mmol) and then 2-methyl-1-phenylsulfonylindole **1** (0.713 g, 3 mmol) in dichloromethane (5 ml) dropwise at 0°C. The mixture was allowed to stir for 2.5 h at 25°C. It was then cooled at 0°C and ice was carefully added. The aqueous layer was treated with solid $NaHCO_3$ till pH 7 and was then extracted with dichoromethane (3 x 30 ml). The combined organic extracts were dried ($MgSO_4$), evaporated *in vacuo* and the remaining residue was chromatographed on a silica gel column (eluent : CH_2Cl_2) giving compound **3** (30%) and then compound **2** (32%).

Compound **2**: mp 180-182°C (ethanol). IR (KBr): 3260(NH), 1660(CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.48(s, 3H, CH_3); 2.65(s, 3H, $COCH_3$); 7.44(d, J=8.2, 1H, H_4); 7.69(d, J=8.2, 1H, H_5); 7.97(s, 1H, H_7); 11.72(s, 1H, NH); ^{13}C NMR (Acetone-d_6) : δ 11.3(CH_3); 26.7($COCH_3$); 103.0(C3); 112.9(C7); 117.0(C4); 120.8(C5); 130.0(C6); 132.3(C); 134.7(C); 136.5(C2); 197.3(CO). MS (CI): 208 ($M^+ + 1$); 210 ($M^+ + 3$).

Compound **3**: mp 146-148°C (ethanol). IR (KBr): 1670(CO), 1380, 1180(SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.68(s, 3H, CH_3); 2.73(s, 3H, CH_3); 7.40-7.60(m, 4H, Harom); 7.83(m, 2H, Harom); 7.96(d, J=8.4, 1H, H_5); 8.86(s, 1H, H_7). MS (CI) : 348 ($M^+ +1$), 350 ($M^+ + 3$).

Debenzenesulfonylation of compound (3):

To a solution of compound **3** (40mg, 0.13 mmol) in methanol/water (3ml/1ml) was added K_2CO_3 (54 mg, 0.39 mmol). The mixture was heated at reflux for 24 h. It was then cooled and water (3 ml) was added. The mixture was neutralized and extracted with CH_2Cl_2 (3 x 5 ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give a residue which was chromatographed on a silica gel column (eluent: CH_2Cl_2) affording **2** (76%).

5-Acetyl-2-methyl-1-phenylsulfonylindole (8):

5-Bromo-2-methyl-1-phenylsulfonylindole[16] **7** (100mg, 0.285 mmol) and 1-ethoxyvinyltributylstannane (0.065ml, 0.313 mmol) were dissolved in THF (2 ml) under argon. Lithium chloride (38 mg, 0.855 mmol) and $Pd[P(C_6H_5)_3]_4$ (33 mg, 0.028 mmol) were then added and the mixture was refluxed for 24 h. The resulting mixture was then cooled and water was added (4 ml). The mixture was acidified with HCl 10% and stirred for 0.5 h at room temperature and then neutralized. Extraction with CH_2Cl_2 (3x 5 ml), drying ($MgSO_4$) and evaporation afforded a residue which was chromatographed on a silica gel column (eluent CH_2Cl_2) to give compound **8** (61%) as a solid; mp 144-146°C (ethanol). IR (KBr): 1665 (CO), 1365, 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.61(s, 3H, CH_3); 2.62(s, 3H, CH_3); 6.43(s, 1H, H_3); 7.40-7.60(m, 3H, Harom); 7.78(d, J=8.1, 2H, Harom); 7.89(d, J= 8.8, 1H, H_6); 8.03(s, 1H, H_4); 8.21(d, J=8.8, 1H, H_7).

5-Acetyl-3-chloro-2-methylindole (9):

The deprotection of the nitrogen atom of compound **8** was performed according to the same procedure as described for compound **3** to give 5-acetyl-2-methylindole; (76)%; mp 140-142°C (ethanol). IR (KBr): 3240 (NH), 1650 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, D_2O): δ = 2.45(s, 3H, CH_3); 2.63(s, 3H, CH_3); 6.31(s, 1H, H_3); 7.28(d, J= 8.8, 1H, H_7); 7.78(dd, J=1.5, 8.8, 1H, H_6); 8.16(d, J=1,5, 1H, H_4). A mixture of

5-acetyl-2-methylindole (13 mg, 0.075 mmol) and *N*-chlorosuccinimide (10 mg, 0.075 mmol) in methanol (1 ml) was stirred for 10 min at room temperature. The solvent was evaporated *in vacuo*. Water (1 ml) was then added and the residue was extracted with CH_2Cl_2 (3 x 2 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give a crude which was chromatographed on a silica gel column (eluent: CH_2Cl_2) affording **9** (70%); mp 178-180°C. IR (KBr): 3220 (NH), 1640 (CO) cm^{-1}; ^1H NMR ($CDCl_3$, D_2O): δ = 2.46(s, 3H, CH_3); 2.69(s, 3H, CH_3); 7.29(d, J= 8.7, 1H, H_7); 7.86(dd, J=1.5, 8.7, 1H, H_6); 8.17(d, J=1.5, 1H, H_4). MS (CI): 218 (M^+ +1), 210 (M^+ +3).

3-Acetyl-5-chloro-2-methylindole (11):

5-Chloro-1-phenylsulfonylindole (291 mg, 1 mmol) in THF (5 ml) was added to a solution of LDA (1.3 eq.) in THF (1 ml) at -78°C. The mixture was allowed to stir for 1 h at this temperature. Iodomethane (0.070 ml, 1.1 mmol) in THF (1 ml) was then added dropwise and the mixture was stirred for another 0.5 h. The mixture was allowed to warm to room temperature overnight and water (10 ml) was then added. The resulting mixture was neutralized and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated to give a residue which was chromatographed on a silica gel column (eluent: Petroleum ether/ CH_2Cl_2, 75/25, v/v) to afford the 5-chloro-2-methyl-1-phenylsulfonylindole (98%); mp 82-84°C (ethanol). IR (KBr): 1360, 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.61(s, 3H, CH_3); 6.29(s, 1H, H_3); 7.21(dd, J=1.5, 8.7, 1H, H_6); 7.37(d, J=1.5, 1H, H_4); 7.40-7.65(m, 3H, Harom); 7.74(m, 2H, Harom); 8.09(d, J=8.7, 1H, H_7). 5-Chloro-2-methylindole was obtained from 5-chloro-2-methyl-1-phenylsulfonylindole according to the same procedure as described for compound **3**; yield 62%; mp 116-118°C (ethanol). IR (KBr): 3400(NH); ^1H NMR ($CDCl_3$): δ = 2.45(s, 3H, CH_3); 6.14(s, 1H, H_3); 7.04(dd,

J=1.5, 8.7, 1H, H_7); 7.18(d, J=8.7, 1H, H_7); 7.46(d, J=1.5, 1H, H_4). $POCl_3$ (0.020ml, 0.22 mmol) was added to dimethylacetamide (0.5 ml) at 0°C. To this mixture was then added 5-chloro-2-methylindole (30 mg, 0.18 mmol) in dimethylacetamide (0.5 ml). The mixture was stirred for 5 min at 0°C and then heated to 90°C for 0.5 h. After cooling, water (1 ml) and then NaOH 10% were added till pH 7. Extraction with CH_2Cl_2 (3 x 2 ml), drying ($MgSO_4$) and evaporation afforded compound **11** which was pure; mp 172-174°C (ethanol). IR (KBr): 3420 (NH), 1620(CO) cm^{-1}; ^1H NMR ($CDCl_3$): δ= 2.64 (s, 3H, CH_3); 2.76(s, 3H, CH_3); 7.17(dd, J= 1.4, 8.6, 1H, H_6); 7.25(d, J= 8.6, 1H, H_7); 8.03(d, J= 1.4, 1H, H_4).

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