$KAl(SO_4)_2.12H_2O$ as a recyclable Lewis acid catalyst for synthesis of some new oxindoles in aqueous media

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Potassium aluminum sulfate (Alum) efficiently catalyses the electrophilic substitution reaction of indole and isatin in aqueous solution at room temperature and under microwave irradiation to afford the new corresponding bis(indol-3-yl)methanes (DIM) and the new corresponding oxindoles.

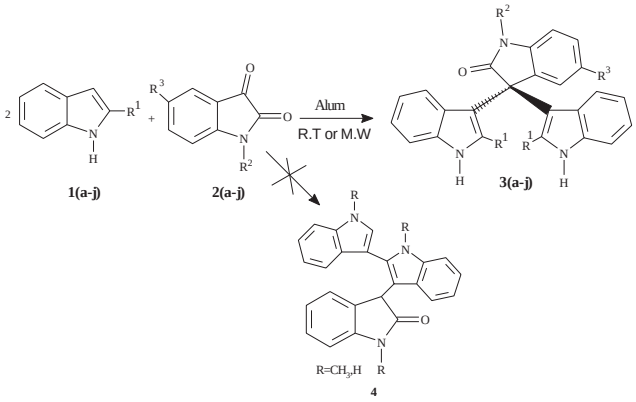
Keywords: alum, indole, isatin, oxindole, microwave irradiation

In connection with our ongoing work on isatin,[1] we now report a simple and efficient method for the synthesis of some bis(indol-3-yl)methanes (DIM) or oxindoles from isatin and indoles using alums as a catalyst. In addition, we wish to report the remarkable consequences of potassium aluminum sulfate ($KAlSO_4.12H_2O$) in a range of electrophilic substitution processes. These molecules may have enhanced biological activitiy because they incorporate both DIM and oxindole moieties. DIMs are useful because of antiestrogenic and antitumorigenic activities,[2] cytostatic effects,[3] as cancer chemopreventive agents,[4] as inducers of apoptosis of human cervical cancer cells,[5] and as aryl hydrocarbon receptor agonists and antagonists in T47D human breast cancer cells,[6] and oxindole derivatives have been shown to possess antibacterial and antiinflammatory activities[7] and are used as laxatives[8].

It is known[9] that the condensation of indole with a ketone or aldehyde proceeds via electrophilic substitution at the 3-position of the indole leading to the DIM derivatives. Activation of the carbonyl group has been accomplished by a broad range of acid catalysts, such as protic acid ,[10] Lewis acids,[11] lanthanide triflates [12] and montmorillonite K-10.[9a, 13]

Oxindole derivatives have been prepared by, the reaction of isatins with aromatics in triflic acid,[14] the reaction of isatins with diphenyl urea and $AlCl_3$,[15] the reaction of isatins with barbituric acid,[16] and other routes.[17]

Isatin and a number of its derivatives, possess a reactive keto-carbonyl group that readily undergoes condensation reactions under mild conditions.[18] Therefore it was speculated that isatin would be a suitable electrophilic component for the reaction with indole. Thus, it was found that when a mixture of indole **1a** (1 mmol) and isatin **2a** (0.5 mmol) in the presence of (0.25 mmol) alum, oxindole **3a** was isolated as the only product, in 92% yield. (Scheme 1). The reaction was carried out in ethanol/water at room temperature for 7 h (until the indole disappeared, as shown by TLC analysis).



Scheme 1

Although never previously tested, we found that alum acted as a reusable Lewis acid to catalyse the reaction of indole with isatin detivatives in ethanol/water or chloroform solvent systems.

In contrast, this reaction did not take place in the absence of alum. Furthermore, it was found that ethanol / water is a much better solvent for the catalytic reaction in terms of yield and product isolation, but the reaction of N–benzyl isatin **2e** and **2i** with indoles did not work in a mixture of ethanol/water. However, it took place in chloroform to produce **3e** and **3i** in high yield (Table 1).

To clarify the generality of this catalytic reaction, several isatin derivatives were treated with the indoles derivatives, the results being listed in Table 1. In all of the conversions electrophilic activation occurred only at the carbonyl on the 3- position. The carbonyl at the 2-position is unreactive and this may do due to stabilization by the indole nitrogen. All products were characterised by ^1H, ^{13}C NMR, IR and mass spectroscopic data.

Zhungietu and Sinyavskaya [19] reported the possible mechanism for the reaction of isatin with indole which yielded compound **4** rather than **3**. However, the assignment of the

Table 1 Alum-catalysed the reaction of indoles with isatins

Product	R^1	R^2	R^3	R.t time/h	Yield / %[a]	M.W time/min	Yield / %[a]	M.p. /°C	Lit. M. p. /°C
3a	H	H	H	7	92	10	94	311–313	312–314[20]
3b	H	H	Br	7	91	12	92	310–311	–
3c	H	H	NO_2	7.5	90	12	90	298–299	–
3d	H	Me	H	7.5	94	12	95	293–294	292–293[21]
3e	H	$PhCH_2$	H	7.5	91	12	91	288–289	–
3f	H	H	Me	7	92	12	93	321–322	–
3g	Me	H	H	7	94	10	95	300–301	–
3h	Me	Me	H	7	92	12	92	272–273	–
3i	Me	$PhCH_2$	H	7	90	12	90	212–214	–
3j	Me	H	Me	10	90	14	90	238–239	–

[a]Yields of pure isolated product based on indole.

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structure **3** to the product and exclusion of structure **4** was supported by the ^{1}H and ^{13}C NMR spectra.

Compounds of **3a–f** had symmetrical structures, because one signal appeared for the two NH·s of the indoles (IR, ^{1}H). But, for **3g–i**, two different signals appeared for the two NH·s (IR, ^{1}H), as well as for the two methyls (^{1}H, ^{13}C), which disclosed their unsymmetrical natures, presumably because the unfavourable methyl-methyl interaction restrained a symmetrical **3g–i**. Furthermore, the ^{1}H NMR spectra of **3e** at 25 °C showed resonances corresponding to the benzylic methylene as a singlet at δ 5.02 ppm, but, the benzylic methylene **3i** (at 25 °C, 60 °C and 100 °C) as an AB quartet at δ 5.03 ppm, these results are another reason to prove that compound of **3e** is symmetric and **3i** is unsymmetric. On the other hand, the ^{1}H, ^{13}C NMR and IR spectra for **3j**, showed that it is symmetrical, because R^3 was a bulky group and as a result caused a conformational change.

We then examined this reaction under microwave irradiation [20] and found that the process results in the rapid formation of oxindole **3a**. Prompted by this success, we extended the reaction of indole with a range of other isatins **2b–j**, under similar conditions, furnishing the respective oxindoles **3a–j** in good to excellent yields. The reactions were performed in open vessels in a microwave oven and in order to increase the energy input to the reaction mixture in a shorter time and also providing a uniform heating, an amount of ethanol (90%) was added to the reaction mixture. The results are summarised in Table 1.

This work is a further example of the utility of microwaves in organic synthesis. When conventional thermal procedures require a considerable reaction time, microwave irradiation can substitute classical methods allowing easy and rapid access to new heterocycles, reducing the reaction times from hours (24 h, using acetic acid as catalyst) [21] with improved yields.

In summary, we have described a novel and convenient method for the synthesis of oxindoles or of DIMs using the inexpensive, non-toxic and easily available alums as catalyst. The method offers several advantages including high yield of products, cleaner reaction profiles, short reaction times, simple experimental workup procedure, use of aqueous solvent and surprisingly, the catalyst was recovered from the aqueous layer during work-up and recycled in subsequent reactions without reduction in activity, which makes it a useful process for the synthesis of oxindole.

Exprimental

Melting points were measured on a Mettler FP5. IR spectra were recorded with KBr pellets on a Shimadzu IR-470 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker 500 DRX AVANCE instrument at 500 and 125 MHz. Mass spectra were recorded on a Shimadzu QP 1100 EX equipment. Elemental analyses were performed using a Heraeus CHN-O rapid analyzer.

*Typical experimental procedure at room temperature***:** A mixture of indoles 1 (1 mmol), corresponding isatin (0.5 mmol), alum (0,25 mmol) and EtOH/H_2O (4 ml/6 ml), (for **3e, i**, 6 ml $CHCl_3$), in a 20 ml flask was stirred at room temperature for the time period as indicated in Table 1. After completion of the reaction (monitored by TLC, ethyl acetate/hexane, 1/1), ethanol was removed under reduced pressure and then water (15 ml) was add to the reaction mixture and heated. The crude product obtained was filtered to yield a solid, which was washed with water and recrystallised from ethanol to afford a pure product.

*Typical experimental procedure under microwave irradiation***:** A mixture of indoles 1 (1 mmol), corresponding isatin (0.5 mmol), alum (0.25 mmol) and EtOH 90% (12 ml), in a Erlenmeyer flask was placed in the microwave oven. The Erlenmeyer was covered with a watch glass and irradiated at 150 W for an appropriate time (Table 1). Then the reaction mixture was allowed to cool to room temperature, the remainder of the ethanol was removed under reduced pressure and then water (15 ml) was add to the reaction mixture and heated. The crude product obtained was filtered and yielded a solid, which was washed with water and recrystallised from ethanol to afford a pure product.

*General procedure for recovered catalyst***:** The catalyst in the aqueous phase can be recovered by removing the water under vacuum then washing with acetone and ethanol (25 ml) and drying at room temperature.

3,3-Diindolyl oxindole (**3a**): IR (KBr): ν_{max}= 3415, 3150, 1709 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ_H: 6.79 (t, *J*=7.7 Hz, 2H), 6.85 (s, 2H), 6.93 (t, *J*=7.5 Hz, 1H), 6.68–7.03 (m, 1H), 7.21–7.24 (m, 4H), 7.36 (d, *J*=8.1 Hz, 2H), 10.59 (s, 1H, NH), 10.95 (s, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 53.41, 110.48, 112.47, 115.14, 119.01, 119.13, 121.62, 122.26, 125.05, 125.21, 126.55, 128.70, 135.45, 137.77, 142.17, 179.60 ppm. MS : *m/z*, (%)= 363 (M^+, 95), 334 (100), 247 (30), 219 (85), 190 (25), 117 (80), 90 (50), 63 (35), 39 (25). Anal. Calcd for $C_{26}H_{22}N_3O$: C, 79.57; H, 5.65; N, 10.71. Found: C, 79.49; H, 5.59; N, 10.63.

3,3-Diindolyl-5-bromooxindole (**3b**): IR (KBr): ν_{max}= 3340, 3120, 1699 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ_H: 6.81 (t, *J*=6.7 Hz, 2H), 6.88 (s, 2H), 6.96 (d, *J*=8.3 Hz, 1H), 7.03 (t, *J*=7.4 Hz, 2H), 7.21 (d, *J*=6.7 Hz, 2H), 7.30 (s, 1H), 7.38 (d, *J*=8.1 Hz, 2H), 7.43 (d, *J*=7.1 Hz, 1H), 10.77 (s, 1H, NH), 11.03 (s, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 53.64, 112.65, 114.00, 114.35, 119.23, 119.35, 121.35, 121.94, 125.21, 125.35, 126.34, 128.22, 137.79, 137.84, 141.53, 179.11 ppm. MS : *m/z*, (%)= 444 (M^++2, 75), 442 (M^+, 80), 412 (90), 332 (40), 297 (45), 218 (40), 190 (30), 166 (35), 117 (100), 90 (60), 39 (45). Anal. Calcd for $C_{26}H_{21}BrN_3O$: C, 66.25; H, 4.49; N, 8.91. Found: C, 66.15; H, 4.40; N, 8.82.

3,3-Diindolyl-5-nitrooxindole (**3c**): IR (KBr): δ_{max}=3365, 3115, 1703 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ_H: 6.83 (t, *J*=7.3 Hz, 2H), 6.96 (s, 2H), 7.04 (t, *J*=7.8 Hz, 2H), 7.20–7.22 (m, 3H), 7.39 (d, *J*=8.1 Hz, 2H), 7.90 (s, 1H), 8.25 (d, *J*=8.7 Hz, 1H), 11.09 (s, 2H, NH), 11.33 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 53.37, 110.79, 112.67, 113.65, 119.39, 119.42, 121.17, 122.07, 125.40, 125.52, 126.22, 136.11, 137.87, 143.06, 148.64, 179.76 ppm. MS : *m/z*, (%)= 408 (M^+, 100), 379 (95), 333 (40), 292 (20), 264 (35), 218 (30), 166 (15), 117 (95), 90 (20), 44 (60) Anal. Calcd for $C_{26}H_{21}N_4O_3$: C, 34.34; H, 2.33; N, 4.62. Found: C, 34.25; H, 2.27; N, 4.56.

3,3-Diindolyl-1-methyloxindole (**3d**): IR (KBr): ν_{max}= 3330, 1686 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ_H: 3.26 (s, 3H, Me), 6.79 (t, *J*=7.2 Hz, 2H), 6.85 (s, 2H), 6.99–7.03 (m, 3H), 7.18–7.24 (m, 3H), 7.29 (d, *J*=7.3 Hz, 1H), 7.33–7.36 (m, 3H), 10.98 (s, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 27.11, 53.00, 109.52, 112.75, 114.90, 119.10, 119.23, 121.56, 121.90, 125.10, 125.26, 126.46, 128.87, 134.53, 137.78, 143.59, 177.76 ppm. MS : *m/z*, (%)= 377 (M^+, 95), 348 (80), 261 (40), 233 (50), 190 (15), 117 (100), 90 (55), 63 (30), 39 (30). Anal. Calcd for $C_{27}H_{24}N_3O$: C, 79.78; H, 5.95; N, 10.34. Found: C, 79.67 H, 5.86; N, 10.23.

3,3-Diindolyl-1-benzyloxindole (**3e**): IR (KBr): ν_{max}= 3410, 1702 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ_H: 5.02 (s, 2H, CH_2), 6.74 (t, *J*=7.2 Hz, 2H), 6.87 (s, 2H), 6.98-7.03 (m, 3H), 7.10–7.13 (m, 3H), 7.24–7.33 (m, 5H), 7.35–7.37 (m, 4H), 11.01 (s, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 43.84, 53.12, 110.21, 112.54, 114.83, 119.05, 119.18, 121.66, 121.94, 123.12, 125.10, 125.26, 125.65, 126.44, 128.37, 128.47, 128.75, 129.44, 134.63, 137.41, 137.78, 142.57, 177.93 ppm. MS : *m/z*, (%)= 453 (M^+, 100), 424 (35), 362 (95), 336 (35), 247 (20), 190 (15), 117 (40), 91 (80), 65 (30), 39 (25). Anal. Calcd for $C_{33}H_{28}N_3O$: C, 82.13; H, 5.85; N, 8.71. Found: C, 82.04; H, 5.75; N, 8.63.

3,3-Diindolyl-5-methyloxindole (**3f**): IR (KBr): ν_{max}= 3340, 3150, 1696 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ_H: 2.19 (s, 3H, Me), 6.82 (t, *J*=7.3 Hz, 2H), 6.86 (s, 2H), 6.89 (d, *J*=8.0 Hz, 1H), 7.01-7.04 (m, 4H), 7.26 (d, *J*=8.0 Hz, 2H), 7.36 (d, *J*=8.1 Hz, 2H), 10.52 (s, 1H, NH), 10.79 (s, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 31.55, 53.49, 110.19, 112.46, 115.27, 119.08, 121.75, 121.80, 125.23, 126.33, 126.58, 128.99, 131.05, 135.50, 137.79, 139.75, 179.67 ppm. MS : *m/z*, (%)= 377 (M^+, 60), 348 (100), 260 (30), 232 (80), 217 (50), 165 (60), 116 (40), 90 (35), 39 (35). Anal. Calcd for $C_{27}H_{24}N_3O$: C, 79.78; H, 5.95; N, 10.34. Found: C, 79.77; H, 5.86; N, 10.23.

3,3-Bis(2-methylindolyl)oxindole (**3g**): IR (KBr): ν_{max}= 3400, 3250, 1700 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ_H: 1.95 (s, 3H, Me), 2.09 (s, 3H, Me), 6.61–6.66 (m, 2H), 6.71 (d, *J*=8.0 Hz, 1H), 6.85-6.92 (m, 3H), 6.96 (d, *J*=7.7 Hz, 1H), 7.16 (d, *J*=7.4 Hz, 1H), 7.21–7.24 (m, 3H), 10.57 (s, 1H, NH), 10.87 (s, 1H, NH), 10.90 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 13.87, 14.05, 53.28, 110.21, 110.29, 111.21, 111.27, 118.78, 118.84, 120.15, 120.21, 120.46, 120.63, 122.13, 126.32, 127.90, 128.54, 128.68, 132.84, 134.81, 135.76, 135.83, 136.44, 142.06, 180.21 ppm. MS : *m/z*, (%)= 391 (M^+, 50), 376 (55), 348 (100), 233 (20), 196 (30), 174 (35), 130 (40), 77 (30), 51 (20), 31 (25). Anal. Calcd for $C_{28}H_{26}N_3O$: C, 79.97; H, 6.23; N, 9.99. Found: C, 79.86; H, 6.15; N, 9.88.

3,3-Bis(2-methylindolyl)-1-methyloxindole (**3h**): IR (KBr): ν_{max}= 3405, 3290, 1697 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ_H: 1.92 (s, 3H,

Me), 2.00 (s, 3H, Me), 3.23 (s, 3H, Me-N), 6.35 (d, *J*=8.1 Hz, 1H), 6.58–6.64 (m, 3H), 6.84–6.91 (m, 2H), 6,95 (t, *J*=7.4 Hz, 1H), 7.13 (d, *J*=7.7 Hz, 1H), 7.19-7.22 (m, 3H), 7.33 (t, *J*=7.7 Hz, 1H), 10.54 (s, 1H, NH). 10.87 (s, 1H, NH), 10.91 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 13.80, 14.03, 27.07, 52.78, 109,40, 109.80, 111.04, 111.24, 118.83, 118.91, 119.99, 120.08, 120.47, 120.67, 122.86, 125.94, 127.74, 128.43, 128.81, 132.75, 134.96, 135.40, 135.71, 135.79, 143.41, 178.21 ppm. MS : *m/z*, (%)= 405 (M^+, 100), 391 (80), 362 (85), 348 (30), 274 (60), 246 (30), 203 (25), 174 (15), 130 (35), 77 (15). Anal. Calcd for C_{29} $H_{28}N_3O$: C, 80.15; H, 6.49; N, 9.67. Found: C, 80.06; H, 6.37; N, 9.58.

3,3-Bis(2-methylindolyl)-1-benzyloxindole (**3i**): IR (KBr): ν_{max}= 3405, 3300, 1694 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ_H: 1.92 (s, 3H, Me), 1.99 (s, 3H, Me), 5.03 (d.d, *J*=17.6 Hz, *J*=15.7 Hz, 2H, CH_2), 6.38 (d, *J*=8.0 Hz, 1H), 6.58 (t, *J*=7.4 Hz, 1H), 6.61–6.66 (m, 2H), 6.88–6.95 (m, 3H), 7.06 (d, *J*=7.8 Hz, 1H), 7.22–7.27 (m, 9H), 10.90 (s, 1H, NH). 10.94 (s, 1H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 13.89, 14.01, 43.74, 52.97, 110.02, 110.10, 110.96, 111.26, 118.77, 118.88, 120.18, 120.55, 120.71, 126.17, 127.78, 128.17, 128.38, 128.76, 129.28, 133.00, 134.81, 134.81, 135.55, 135.77, 135.85, 137.17, 142.65, 178.32 ppm. MS : *m/z*, (%)= 481 (M^+, 20), 466 (20), 392 (25), 351 (25), 260 (20), 159 (25), 130 (100), 90 (50). Anal. Calcd for C_{35} $H_{32}N_3O$: C, 82.32; H, 6.32; N, 8.23. Found: C, 82.21; H, 6.24; N, 8.15.

3,3-Bis(2-methylindolyl)-5-methyloxindole (**3j**): IR (KBr): ν_{max}= 3310, 3190, 1704 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ_H: 2.19 (s, 6H, 2*Me), 2.44 (s, 3H, Me), 6.76 (t, *J*=7.4 Hz, 2H), 6.80 (d, *J*=7.8 Hz, 2H), 6.92 (t, *J*=7.5 Hz, 2H), 7.00–7.05 (m, 3H), 7.20 (d, *J*=8.0 Hz, 2H), 10.30 (s, 1H, NH), 10.88 (s, 2H, NH) ppm. ^{13}C NMR (DMSO-d_6) δ_C: 14.19, 21.53, 76.89, 110.25, 110.41, 111.12, 119.07, 119.99, 120.67, 126.30, 127.47, 130.02, 131.37, 134.14, 135.09, 135.71, 139.91, 179.60 ppm. MS : *m/z*, (%)= 405 (M^+, 15), 362 (15), 329 (25), 292 (35), 263 (30), 247 (80), 129 (100), 76 (80). Anal. Calcd for C_{29} $H_{28}N_3O$: C, 80.15; H, 6.49; N, 9.67. Found: C, 80.07; H, 6.39; N, 9.56.

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