Indian Journal of Chemistry
Vol. 48B, April 2009, pp. 585-589

Note

A practical, clean and green synthesis of vibrindole and bis(indolyl)methanes catalyzed by alum [$KAl(SO_4)_2.12H_2O$] in water

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Received 13 May 2008; accepted (revised) 10 November 2008

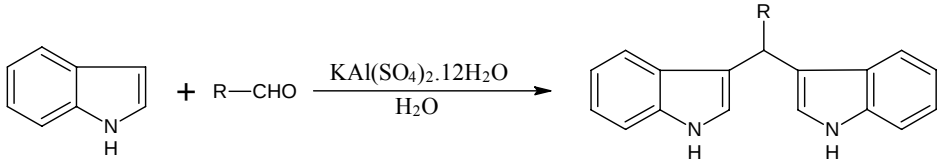
Facile and efficient electrophilic substitution reactions of indoles with various carbonyl compounds are carried out using alum [$KAl(SO_4)_2.12H_2O$], an in-expensive and reusable catalyst, to afford vibrindole and other bis(indolyl)methanes in excellent yields.

Keywords: Alum [$KAl(SO_4)_2.12H_2O$], vibrindole, indole, carbonyl compounds, bis(indolyl)methanes

Indole is one of the privileged molecules of organic chemistry and several its derivatives are established pharmaceuticals[1]. In the past one decade or so several bis(indolyl)methanes have been isolated from natural sources[2]. A few members from this class like, vibrindole A have shown promising biological activity[3]. Particularly bis(indolyl)methanes are known to enhance estrogen metabolism in humans and is likely to be drug of choice for breast cancer. Because of these interesting biological activities and other uses, development of protocols for the synthesis of bis(indolyl)methanes is of current interest. To achieve facile and efficient production of this group of indoles several Brönsted acids (e.g., HCl, H_2SO_4, Ref. 4) or Lewis acids like $AlCl_3$, $BF_3.Et_2O$, Ref. 5) and others[6-8] have been used. Generally, traditional Lewis acid catalysts are moisture sensitive and are easily decomposed or deactivated in the presence of water. While in some cases more than stoichiometric amounts of Lewis acids are necessitated because these acids are trapped by nitrogen containing reactants. Therefore, to provide efficient synthesis, recently $NaHSO_4$-SiO_2, I_2, NBS, montmorillonite K-10, ionic liquids and rare earth triflates have also been used in this reaction[9-12]. Even though various procedures are reported, disadvantages including low yield, prolonged reaction times, use of an excess of reagent/catalyst and formation of hazardous by-products during aqueous work-up, and at the top of every thing majority of them are expensive rare chemicals or needs special preparation, this necessitate further development of an environment benign, economical alternative for the synthesis of *bis*-indolylmethanes.

In recent years emphasis is on the use of environmentally benign procedures and reagents in the prominent reactions of the organic chemistry. Recently alum [$KAl(SO_4)_2.12H_2O$], which is relatively nontoxic and inexpensive catalyst, has emerged as an efficient alternative catalyst for a variety of prominent organic reactions such as Biginelli[13], Pechmann reaction[14] and also used for the synthesis of isoquinolonic acids[15], 2,3-dihydroquinazolin-4(1H)-ones[16], 1,3,4-oxadiazoles[17-19] and very recently alum is used for the synthesis of 1,5-benzodiazepines[20]. In continuation of our work on indole chemistry[21] and use of metal sulphates[22], herein, this paper reports the alum, [$KAl(SO_4)_2.12H_2O$], as a mild efficient, economical and green catalyst, for the condensation of indole with carbonyl compounds in water for the one pot efficient synthesis of *bis*-(indolyl)methanes (**Scheme I**).

In course of optimization of reaction conditions, benzaldehyde (1 mmole), indole (2 mmole) and alum (0.5 mmole) in water (5 mL) were stirred at RT and afforded the 3,3'-bis(1*H*-indolyl)phenylmethane **3a** in 62% yields even after 24 hr. The optimum temperature is found to be 80°C for efficient conversion as



1 **2** **3**

Scheme I

Table I —- Effect of temperature for the synthesis of bisindolyl(phenyl)methanes

S.No.	Reaction temperature	Yields (%)
1	RT	62
2	40°C	67
3	50°C	77
4	80°C	95
5	100°C	92

Table II — Synthesis of **3a** with varied amount of catalyst

S. No.	Catalyst (equiv.)	Time (min.)	Yield (%)
1	0.1	120	71
2	0.2	75	84
3	0.3	50	94
4	0.5	45	95
5	1.0	45	95

Table III — Catalyst recyclables

Run	R	Time (min)	Yield (%)
1st	Ph	50	94
2nd	Ph	50	93
3rd	Ph	50	89
4th	Ph	50	88
5th	Ph	50	83

indicated in **Table I**, which afforded the desired product in 95% yield in 45 minutes.

Further it is investigated that the efficacy of the catalyst and 0.3 equivalents of catalyst were enough to obtain the optimum yield of bis(indolyl)methanes. Decrease in amount of catalyst affected the reaction inversely both in terms of yields as well as reaction time (**Scheme II**, **Table II**). Increase in amount of catalyst to 0.5 equivalents found to be equieffective, while further higher amount of catalyst did not provide any fruitful results (**Table II**).

The catalyst efficacy is fairly general and catalyst can be recycled with any considerable loss of reactivity to afford the desired products (**Table III**). Products are obtained by simple filtration of the reaction-mixture in almost pure form. After removal of the reaction product by filtration, water was removed under reduced pressure to recover the catalyst and the recovered catalyst is used without any further purification.

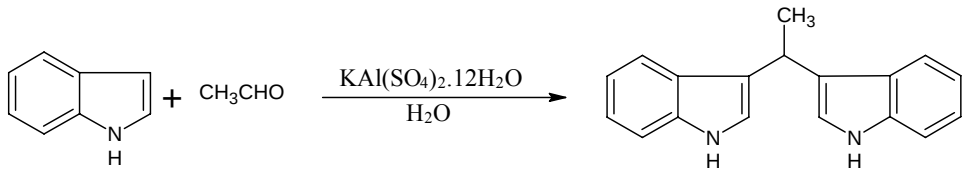
To generalize this protocol various substituted indoles and a variety of aldehydes were employed and good to excellent yields (83-94%) of bis(indolyl)-methanes have been obtained (**Scheme I, Table IV**). The present protocol could successfully be extended to alipahatic aldehydes (entry 8, **Table IV**) as well as heterocyclic aldehydes (entry 9-10, **Table IV**) without the formation of any side products. In particular much needed vibrindole **3h** can be synthesized in 84% yield (entry 8, **Table IV**) following this procedure. It is worth mentioning that stronger acidic conditions earlier used would certainly cannot be extended to aliphatic aldehydes because of side product formation due to acid catalyzed unwanted self-condensation.

It is worth mentioning here in present procedure when equimolar quantities of **1** and **2** are used, yields clearly bis(indolyl)methane **3** is obtained; contrary to earlier reports there is no formation of indolo[2,3-*b*]carbazoles **5** (**Scheme III**, Ref. 20).

In conclusion, this present protocol affords vibrindole and other bis(indolyl)methanes in excellent yields employing mild, efficient, environmentally benign, reusable and inexpensive catalyst, alum, in water. In contrast several of the earlier used catalysts are expensive, moisture sensitive and are not environment friendly, which is present day concern. Furthermore, this process is wider in scope and is devoid of formation of any by-product like **5**.

Experimental Section

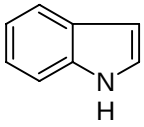
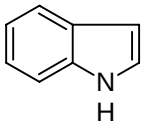
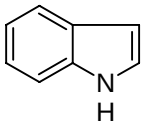
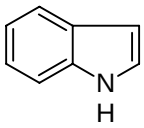
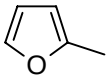
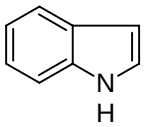
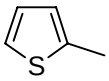
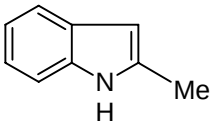
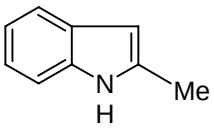
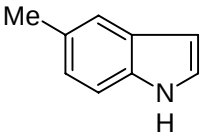
Melting points were determined in open capillary and compared with those of authentic samples. IR spectra were obtained by using Perkin-Elmer 237B infrared spectrometer in KBr discs. ^{1}H NMR spectra were recorded in Varian Gemini 300 spectrometer (300 MHz) using tetramethylsilane (TMS) as internal standard. Alum used was of commercial grade and procured from SD Fine Chem Ltd. All other chemicals were purified by distillation or crystallization prior to use.



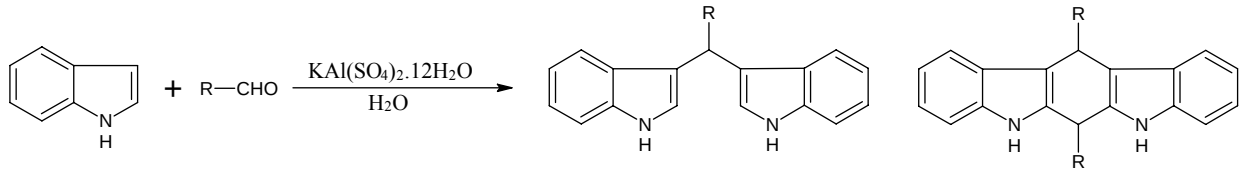
1 **4** **3h**
Vibrindole

Scheme II

Table IV —- Alum [$KAl(SO_4)_2.12H_2O$] mediated synthesis of bis-(indolyl)methanes

Entry	Product	Indole	R	Time (min)	Yield (%)[b]	m.p. (°C) (Lit. m.p.)
6	**3f**		4-NO_2-C_6H_4	45	93	223-25 (221-23,Ref. 6e)
7	**3g**		4-OH-C_6H_4	60	86	122-23 (124-25,Ref. 6e)
8	**3h**		CH_3	60	84	148-49 (148-50, Ref.12c)
9	**3i**			65	87	321-23 (320-22, Ref. 6e)
10	**3j**			65	86	151-52 (149-56, Ref. 9a)
11	**3k**		Ph	55	91	245-47 (247-48, Ref.12c)
12	**3l**		4-Me-C_6H_4	55	92	176-78 (174-75, Ref. 12c)
13	**3m**		Ph	50	90	194-96 (195-96, Ref.12c)

[a]Reaction conditions: aldehydes (1 equiv.), indole (2 equiv.) and alum (0.3 equiv.) in H_2O, 80°C
[b]Yields refers to pure isolated products



1 (Molar ratio 1:1) **2** **3** **5**

Scheme III

Typical experimental procedure for the synthesis of 3,3′-bis(indolyl)phenylmethane: To a solution of alum (142 mg, 0.3 mmole) was added indole (234 mg, 2 mmole) and benzaldehyde (106 mg, 1 mmole). The reaction-mixture was stirred at 80°C for the 50 min. After the completion of reaction (TLC, hexane:ethyl acetate, 3:1 v/v), reaction-mixture was cooled to RT and solid thus obtained was filtered and washed thoroughly with cold water. Recrystallised with EtOH to afford pure *bis*(indolyl)phenylmethane, **3a** in 94% yield, m.p. 124-25°C. (Lit. 123-25 °C, Ref. 6c); IR (KBr): 3482, 3012, 1598, 1532, 1465, 1427, 1218, 1091 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.89 (1H, s), 6.67 (2H, s), 7.09-7.58 (13H, m), 7.94 (2H, br, s, NH); ^{13}C NMR ($CDCl_3$): δ 143.7 136.4, 128.1, 126.9, 123.4, 122.1, 120.1, 119.1, 118.8, 110.9, 39.8; EIMS: *m/z* 322 (M+); Anal. Calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.62; N, 8.68. Found: C, 85.71; H, 5.59; N, 8.63%.

General experimental procedure for the synthesis of bis(indolyl)methanes: To a solution of alum (142 mg, 0.3 mmole) was added indole (2 mmole, 2 equiv.) and aldehyde (1 mmole, 1 equiv.) and reaction-mixture was stirred at 80°C for the specified time (**Table IV**). After the completion of reaction, reaction-mixture was cooled to RT and solid thus obtained was filtered and washed thoroughly with cold water and recrystallised with ethanol to afford the bis(indolyl)methanes.

3,3'-Bis(indolyl)-4-methoxyphenylmethane (Entry 2). IR (KBr): 3485, 3021, 2848, 1616, 1517, 1465, 1411, 1326, 1221, 1094, cm-1; ^1H NMR (CDCl3): δ 3.79(3H, s), 5.83(1H, s), 6.67(2H, d), 6.81(2H d), 7.01(2H, t, *J* = 7.2 Hz), 7.24(2H, t, *J* = 7.2 Hz); 7.28-7.46(6H, m), 7.92(2H, bs, NH); ^{13}C NMR (CDCl3): δ 136.9, 135.8, 127.0, 123.2, 122.1, 119.7, 119.4, 119.1, 118.7, 113.2, 111.1, 55.3, 38.6. EIMS: *m/z* 352 (M+); Anal. Calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.67; H, 5.62; N, 7.82%.

3,3′-Bis(indolyl)-4-chlorophenylmethane (Entry 4): IR (KBr): 3481, 3023, 2917, 1612, 1533, 1461, 1425, 1231, 1026 cm^{-1}; ^1H NMR (CDCl3): δ 5.89 (1H, s), 6.67 (2H, d, *J* = 8.2 Hz), 7.11-7.87 (12H, m), 7.91(2H, bs, NH); ^{13}CNMR (CDCl3): δ 136.7, 130.3, 128.4, 126.5, 123.9, 122.2, 120.1, 119.5, 119.2, 111.2, 39.7. EIMS: *m/z* 356 (M+); Anal. Calcd for $C_{23}H_{17}ClN_2$: C, 77.41; H, 4.80; N, 7.85%. Found: C, 77.36; H, 4.69; N, 7.78%.

Vibrindole or 3,3′-bis(indolyl)ethane (Entry 8): IR (KBr): 3387, 2956, 1541, 1427, 1223 cm^{-1}; ^1H NMR: □ 1.92 (d, 3H, *J* = 6.8 Hz), 4.53 (m, 1H), 6.81 (t, 2H, *J* = 6.8 Hz), 7.08 (m, 2H), 7.11 (t, 2H, *J* = 8.2 Hz), 7.29 (d, 2H, *J* = 8.1 Hz), 7.43 (d, 2H, *J* = 8.1 Hz), 7.89 (br s, 2H); EIMS: *m/z* 260 (M+); Anal. Calcd for C18H16N2: C, 83.04; H, 6.19; N, 10.75. Found: C, 83.16; H, 6.17; N, 10.69%.

3,3′-Bisindolyl(2-furfuryl)methane (Entry 9): IR (KBr): 3481, 3014, 2387, 1604, 1466, 1421, 1218, 1097 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.95 (1H, s), 6.03 (1H, d, *J* = 7.3 Hz), 6.31 (1H, d, *J* = 7.2 Hz), 6.86 (1H, d), 7.09 (2H, t), 7.17(2H, t), 7.31 -7.52 (5H, m), 7.96 (2H, bs, NH). EIMS: *m/z* 264 (M+); Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.24; H, 6.10; N, 10.59. Found: C, 77.31; H, 6.16; N, 10.53%.

Acknowledgements

Authors thank CSIR, New Delhi, India and Indian National Science Academy, New Delhi, India for financial support.

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