Alum Catalyzed Simple and Efficient Synthesis of Bis(indolyl)methanes by Ultrasound Approach

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Alum ($KAl(SO_4)_2{\cdot}12H_2O$) is an inexpensive, efficient, non-toxic and mild catalyst for the synthesis of bis(indolyl)methanes by the reaction of 1*H*-indole with various aldehydes/ketones under the influence of ultrasound irradiation in solvent-free condition. The remarkable advantages of this method are the simple experimental procedures, shorter reaction times, high yields of product and green aspects by avoiding toxic catalysts and solvents.

Key Words: Bis(indolyl)methanes, Alum, 1*H*-indole, Aldehydes/ketones, Ultrasound irradiation

Introduction

Indole and its derivatives are known as an important class of heterocyclic compounds in the pharmaceutical as well as synthetic chemistry.[1] The most ubiquitous of the known bioactive alkaloids are based on the indole moiety.[2] Medicinal chemists repeatedly turn to indole based compounds as a target pharmacophore for the development of therapeutic agents.[3] Bis(indolyl)alkanes have attracted considerable attention due to its diverse pharmacological and biological importance. The bioactive substrate including bis(indolyl)-alkanes moiety are widely occurs in various natural products isolated from marine sponge alkaloids.[4] Also, it shows potent antibacterial activity.[5] In particular, bis(indolyl)methanes are the most active cruciferous substances for promoting beneficial estrogen metabolism and including apoptosis in human cancer cells.[6]

Numerous methods have been reported for the synthesis of bis(indolyl)methanes using variety of reagents such as, AcOH,[7a] $InCl_3$,[7b] $LiClO_4$,[7c] NBS,[7d] PPh_3HClO_4,[7e] $NaHSO_4{\cdot}SiO_2$,[7f] CAN,[7g] InF_3,[7h] $KHSO_4$,[7i] $ZrCl_4$,[7j] $ZrOCl_2$,[7k] $Zr(DS)_4$,[7l] P_2O_5/SiO_2,[7m] $Sb_2(SO_4)_3$,[7n] PPh_3CCl.[7o] A part from this, synthesis of bis(indolyl)methanes also have been achieved using Zeolites,[8] Clays,[9] ionic liquids,[10] metal triflates,[11] ion exchange resin[12] and rare earth metal.[13]

At present, with the raid development in the fields of synthetic and catalytic chemistry, researchers have started to develop environmentally benign processes to avoid or minimize the harmful effects. The application of solvent-free reaction conditions in organic chemistry has been explored extensively within the last decade. It has been demonstrated to be an efficient technique for various organic reactions. Solvent-free conditions often lead to a remarkable decrease in reaction time, increased yields, easier workup, enhancement of regio and stereo selectivity of reaction matches with the green chemistry protocol.[14]

Ultrasound irradiation has been established as an important technique in synthetic organic chemistry. It has been used as an efficient heating source for the organic reactions. Shorter reaction time is the main advantage of ultrasound-assisted reactions. Simple experimental procedure, very high yields, increased selectivities and clean reaction of many ultrasound induced organic transformations offers additional convenience in the field of synthetic organic chemistry.[15]

Alum ($KAl(SO_4)_2{\cdot}12H_2O$) were found to be effective in the synthesis of *cis*-isoquinolic acids,[16a] mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones,[16b] dihydropyrimidines *via* Biginelli reaction,[16c] coumarins,[16d] 1,3,4-oxadiazoles,[16e] dibenzoxanthenes,[16f] 1,5-benzodiazepines,[16g] trisubstituted imidazoles[16h] 2-arylbenzothiazoles and 2-arylbenzoxazoles.[16i] However, there are no any reports of the use of alum as a catalyst for the synthesis of bis(indolyl)methanes.

Experimental

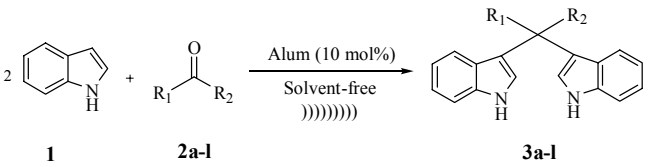
Bandelin Sonorex (35 kHz) ultrasonic bath was used for ultrasonic irradiation. ^{1}H NMR spectra were recorded on Mercury Plus Varian in $CDCl_3$ at 400 MHz using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer FTIR using KBr discs. Mass spectra were recorded on Micromass Quattro II using electrospray Ionization technique, showing (m+1) peak as a base peak. The progress of the reactions was monitored by TLC.

General Procedure

A mixture of 1*H*-indole (5 mmol), aldehyde (2.5 mmol) and powdered alum (10 mol%) was irradiated under ultrasound irradiation at ambient temperature for appropriate time (Table 4). The progress of reaction was monitored by TLC. After the completion of reaction 20 mL ice cold water was added to the reaction mixture. The solid obtained was filtered and recry-stallized from ethanol to get the pure product.

Result and Discussion

In continuation of our interest in synthesis of bis(indolyl)-methanes[10d] and the development of novel synthetic metho-



1 **2a-l** **3a-l**

Scheme 1

dologies[16i,17] herein, we would like to report a simple, efficient and rapid method for the synthesis of bis(indolyl)methanes (Scheme 1). It was found that alum is an effective promoter in the synthesis of bis(indolyl)methanes by the reaction of 1*H*-indole with aryl and heteroaryl aldehydes under ultrasound irradiation.

In order to get the best experimental reaction condition, the reaction of 1*H*-indole **1** and benzaldehyde **2a** (in 2:1 molar ratio) in the presence of 20 mol% of alum under solvent-free condition has been considered as a standard model reaction. We have investigated the model reaction by grinding at ambient temperature, 60 °C or 100 °C and by ultrasound irradiation method. When the reaction was carried out by grinding method, the product obtained in low yield (Table 1, Entry 1). In the next step, we carried out the reaction at 60 °C and 100 °C which provided the product in almost similar yields after 60 min (Table1, Entry 2-3). However, the best result was obtained by ultrasound irradiation at ambient temperature and the product was obtained within 10 min in 92 % yield (Table 1, Entry 4).

To determine the appropriate concentration of the catalyst alum, we investigated the model reaction at different concentrations of catalyst like 2.5, 5, 7.5, 10 and 12.5 mol% under ultrasound irradiation. The product formed in 74, 80, 85, 92 and 92 % yield respectively. This indicates that 10 mol% of alum is sufficient for the best result (Table 2, Entry 4).

To establish the generality with respect to the carbonyl compounds; 1*H*-indole were treated with various aldehydes and ketones in the presence of alum under the influence of ultrasound irradiation. It was observed that aryl aldehydes were reacted faster (5-15 min) and providing excellent yields 85-95 % (Table 3, Entry 1-10). In case of α-β unsaturated

Table 1. Effect of Catalysts on the synthesis of Bis(indolyl)methanes **3a**[a]

Entry	Condition	Time (min)	Yield[b] (%)
1	Grinding/rt	60	14
2	60 °C	60	71
3	100 °C	60	73
4	Ultrasound/rt	10	92

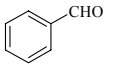
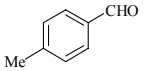
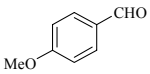
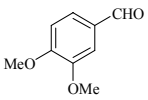
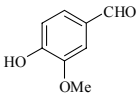
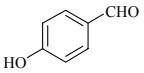
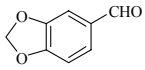
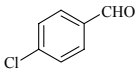
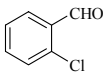
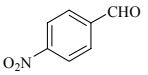
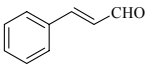
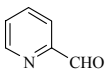
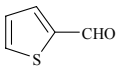
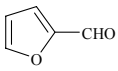
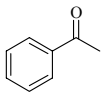
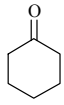
[a]**1** (5 mmol), **2a** (2.5 mmol), alum (20 mol%). [b]Isolated yields.

Table 2. Effect of Concentrations of Alum for synthesis of Bis(indolyl)methanes **3a**[a]

Entry	Alum (mol%)	Time (min)	Yield[b] (%)
1	2.5	10	74
2	5	10	80
3	7.5	10	85
4	10	10	92
5	12.5	10	92

[a]**1** (5 mmol), **2a** (2.5 mmol), under the influence of ultrasound irradiation. [b]Isolated yields.

Table 3. Synthesis of Bis(indolyl)methanes **3a**[a]

Entry	Compound	Aldehyde/Ketone	Time (min)	Yield[b] (%)	M.P. (°C)[c] Found	M.P. (°C)[c] Lit
1	**3a**		10	92	121-123	123-125
2	**3b**		10	87	95-97	96-98
3	**3c**		12	87	191-193	190-192
4	**3d**		15	85	221-222	220-222
5	**3e**		15	84	111-112	111-112
6	**3f**		12	87	125-126	124-125
7	**3g**		15	86	100-101	100-102
8	**3h**		7	92	77-78	76-77
9	**3i**		10	92	75-76	74-76
10	**3j**		5	95	222-223	221-223
11	**3k**		15	83	100-102	100-102
12	**3l**		17	88	138-140	137-139
13	**3m**		20	88	277-279	278-280
14	**3n**		20	90	321-322	320-323
15	**3o**		30	53	190-191	189-190
16	**3p**		30	42	120-121	118-120

[a]**1** (5 mmol), **2a** (2.5 mmol), alum (20 mol%) under ultrasound irradiation. [b]Isolated yields. [c]All the melting points were matched with the reported data.

Table 4. Comparison of result with reported procedure for synthesis of Bis(indolyl)methanes **3a**[a]

Entry	Catalyst	Catalyst (mol%)	Solvent/Medium	Time (min)	Yield[b] (%)
1	$Ln(OTf)_3$	10	$EtOH{\cdot}H_2O$	12 h	95[11a]
2	$LiClO_4$	10	CH_3CN	5 h	90[7c]
3	$Sb_2(SO_4)_3$	5	CH_3OH	90	96[7n]
4	$Dy(OTf)_3$	2	Ionic liquid	60	98[11c]
5	HY-Zeolite	0.2g	CH_2Cl_2	60	85[8a]
6	$ZrCl_4$	1	CH_3CN	35	91[7j]
7	$ZrOCl_2$	1	CH_3CN	35	89[7k]
8	$La(PFO)_3$	5	EtOH	30	90[13]
9	$In(OTf)_3$	5	CH_3CN	25	71[11b]
10	$Zr(DS)_4$	10	H_2O	25	94[7l]
11	Alum	10	-	10	92

[a]**1** was treated with **2a**. [b]Isolated yields.

aldehyde the product formed in 83 % yield. (Table 3, Entry 11). In comparison with these results, heteroaryl aldehydes forms their respective bis(indolyl)methanes in longer times (17-20 min) with 88-90 % yields (Table 3, Entry 12-14). Unfortunately ketones were afforded the desired product in lower yield (Table 3, Entry 15-16).

Various substituted aryl aldehydes were used for the synthesis of bis(indolyl)methanes having different substituents such as -Cl, -OH, $-NO_2$, -Me, -OMe. It was found that; electron donating substituent requires longer time where as electron withdrawing substituent requires shorter time for the completion of reaction (Table 3, Entry 4 and 8).

With these optimized reaction conditions; we have carried out the reaction of 1*H*-indole (**1**) with various aryl or heteroaryl aldehydes/ketones (**2a-l**) in the presence of alum (10 mol%) under the influence of ultrasound irradiation at ambient temperature. The corresponding bis(indolyl)methanes (**3a-l**) were formed within short reaction times in excellent yields and confirmed by IR, ^{1}H NMR, Mass spectroscopic analysis.[18] The results are summarized in Table 3.

In order to show the merit of alum in comparison with other catalysts used for the similar reaction, we have tabulated some of the results in Table 4. As it is evidence from the results, alum found to be effective catalyst for the synthesis of bis(indolyl)methanes.

Conclusion

In conclusion, alum is an easily available, inexpensive, efficient and safe catalyst for the synthesis of bis(indolyl)-methane derivatives from various aryl or heteroaryl aldehydes by ultrasound irradiation. The remarkable advantages offered by this method are simple experimental procedure, solvent-free reaction conditions, short reaction times, high yields, and easiness of product isolations.

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Jiang, Z. Q.; Loh, T. P. *Eur. J. Org. Chem.* **2004**, 1584. (d) Sadaphal, S. A.; Sonar, S. S.; Shingare, M. S. *Central Euro. J. Chem.* **2008**, *6*, 622.
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18. 3,3'-Bis(indolyl) phenylmethane (**3a**): IR (KBr, cm^{-1}): 3478, 1601, 1522. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89 (1H, s), 6.67 (2H, s), 7.09-7.58 (13H, m), 7.94 (2H, bs, NH). ES-MS: *m/z* 322 (M+1).