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$ZnCl_2$ promoted efficient, one-pot synthesis of 3-arylmethyl and diarylmethyl indoles

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ABSTRACT

Anhydrous $ZnCl_2$ mediated convenient, one-pot synthesis of 3-arylmethyl and diarylmethyl indoles was accomplished in good yields. Under reaction condition, in situ formation of kinetically stable bis(indolyl)methane product was identified. Its subsequent conversion to the thermodynamically stable 3-diarylmethyl indole at elevated temperature and pressure was confirmed by carrying out pressure tube reaction with bis(indolyl)methane.

Multicomponent reactions offer a tangible way to access both chemically and structurally diverse class of molecules.[1] Moreover, multicomponent organic transformations accomplished by readily available, inexpensive catalysts/reagents are invariably attractive. In continuation of our efforts to devise efficient multicomponent reaction,[2] herein we report anhydrous $ZnCl_2$ mediated one-pot synthesis of 3-arylmethyl and diarylmethyl indoles. Indole frame work is present in plethora of bioactive molecules such as etodolac,[3] indometacin,[4] and reserpine[5] used for treating inflammation, hypertension, and psychiatric disorders. The presence of indole skeleton plays a vital role in determining anticancer activity of tryprostatin A, an antimitotic agent used in the treatment of multidrug resistant tumours.[6] 3-Alkyl substituted indoles are useful in the total synthesis of paraherquamide A,[7] an anthelmintic agent; clavicipitic acid,[8] a derailment product of ergot alkaloid biosynthesis; indolmycin,[9] a novel antibiotic; veiutamine,[10] a marine alkaloid etc. Excellent reviews are available which provide significant insight into the synthesis and applications of indole derivatives.[1a,11] Synthesis of 3-arylmethyl/diarylmethyl indole from indole and aldehyde/ketone is difficult due to the high nucleophilicity of indole toward azafulven intermediate leading to the formation of bis(indolyl)methane.[12] Steele and co-workers utilized triethylsilane/trifluoroacetic acid reagent system to rapidly donate hydride ion to the azafulven intermediate to form 3-arylmethyl indole. Campbell et al., employed TMSOTf/Et_3SiH to synthesize 3-arylmethyl indoles as selective COX-2 inhibitors.[13] Trifluoroacetic acid,[14a] $HClO_4$-SiO_2,[14b] and ferric chloride[15] were useful in the synthesis of 3-arylmethyl/diarylmethyl indoles. Enantioselective synthesis of 3-arylmethyl indoles using $Zn(OTf)_2$-axially chiral BINAM derived catalyst was reported by Shi and co-workers.[16] Jana et al., reported $FeCl_3$ catalyzed C3-selective Friedel–Crafts alkylation of indoles with allylic, benzylic, and propargylic alcohols.[17] Pei et al., reported chiral Brønsted acid catalyzed enantioselective 3-arylmethyl indole synthesis.[18] Damu et al., synthesized 3-arylmethyl indole by DDQ mediated oxidative coupling between indole and 1,3-diarylpropyne.[19] Periasamy et al., successfully employed diimine-copper complexes[20] and iron(III) oxide/potassium *tert*-butoxide[21] for the N-arylation of indole.

N,*N*-Dimethylaniline, bezaldehyde, and indole were chosen as model substrates to find optimized reaction condition for $ZnCl_2$ promoted 3-diarylmethyl indole **2** synthesis. Both methanesulfonic acid and montmorillonite K10 in toluene solvent at 100 °C did not yield the corresponding product **2**, while anhydrous $MgSO_4$ under neat condition gave the product in 30% yield (Table 1, entries 1–3). Interestingly, reaction with anhydrous $ZnCl_2$ in ethanol gave product **2** in 60% yield (entry 4). Encouraged by this result, anhydrous $ZnCl_2$ mediated Friedel–Crafts reaction was screened with different solvents and reaction condition. The reaction carried out with one equivalent of anhydrous $ZnCl_2$ in methanol at room temperature gave a marginal improvement in the yield to 64%, while in glycerol indeed reduced the yield to 55% (Entries 5 and 6). By keeping the reaction in methanol at 60 °C did not improve the yield (Footnote *f*). Friedel–Crafts reaction in MeOH–H_2O mixture (2 mL, 1:1 v/v)

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Table 1
Screening of reaction condition for 3-diarylmethyl indole synthesis[a]. Entry 9 gives the optimized condition for the reaction.

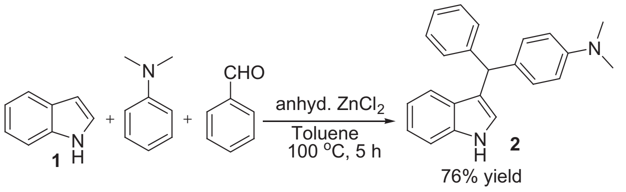
Entry	Catalyst/reagent (mmol)	Additive	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	CH_3SO_3H (0.4)	–	Toluene	100	5	Traces
2	Montmorillonite-K10[c]	–	Toluene	100	7	NR
3[d]	$MgSO_4$ (1)	–	Neat	100	3	30
4[e]	$ZnCl_2$ (1)	–	C_2H_5OH	rt	12	60
5[e]	$ZnCl_2$ (1)	–	CH_3OH	rt[f]	12	64
6[e]	$ZnCl_2$ (1)	–	Glycerol	rt	12	55
7[g]	$ZnCl_2$ (1)	–	$CH_3OH:H_2O$[h]	rt	12	68 (46)[i]
8	$ZnCl_2$ (1)	–	Neat	rt	12	40
9[j]	**$ZnCl_2$ (1)**	**–**	**Toluene**[k]	**100**	**5**	**76**
10	$ZnCl_2$ (0.5)	–	Toluene	100	10	61
11	$ZnCl_2$ (0.2)	–	Toluene	100	12	57
12	$ZnSO_4$ (1)	–	Toluene	100	5	NR
13	$Zn(OAc)_2$ (1)	–	Toluene	100	5	Traces
14	$Zn(NO_3)_2$ (1)	–	Toluene	100	5	21
15	ZnO (1)	–	Toluene	100	5	12
16	$ZnCl_2$ (1)	K10 (250 mg)	Toluene	rt	10	65
17	$ZnCl_2$ (1)	Silica (100 mg)[l]	Toluene	100	7	67
18	$ZnCl_2$ (1)	HCl (1 mL)	Toluene	100	5	40
19	CH_3SO_3H (0.4)	–	Toluene	100	5	Traces

[a] All the reactions were carried out with 1 mmol of indole, 1.2 mmol of *N*,*N*-dimethylaniline and 1.2 mmol of benzaldehyde.
[b] Yields are for the isolated products.
[c] 500 mg of catalyst was used.
[d] Reaction carried out at room temperature for 12 h did not give the product.
[e] 2 mL of solvent was used.
[f] Reaction carried out at 60 °C for 5 h gave 40% yield of the product.
[g] Reaction carried out with only water (2 mL) did not give the product.
[h] 2 mL (1:1 v/v) of methanol and water was taken.
[i] $MeOH:H_2O$ (2:2 mL v/v) at reflux for 12 h gave 46% yield.
[j] Reaction carried out at room temperature for 12 h gave 60% yield of the product.
[k] In toluene:MeOH (3.5:0.5 mL v/v) at 100 °C for 12 h gave 54% yield. In toluene: MeOH (3.5 mL:100 μL v/v) at 100 °C for 12 h gave 49% yield.
[l] In the absence of $ZnCl_2$, only trace quantity of product was formed.

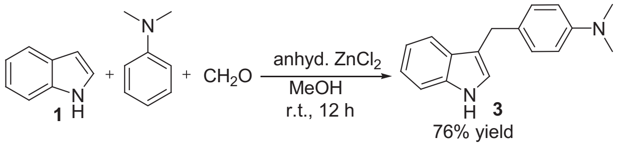
gave 68% yield (Entry 7). Efforts to increase the yield by carrying out the reaction in (a) $MeOH–H_2O$ mixture at reflux condition (b) under neat condition (c) and in water medium were not successful (Footnote *i*, Entry 8). Later, toluene was identified as suitable solvent to carry out anhydrous $ZnCl_2$ mediated 3-diarylmethyl indole synthesis. Reaction carried out in toluene at room temperature for 12 h gave product **2** in 60% yield. The yield was increased to 76% by carrying out the reaction at 100 °C for 5 h (Entry 9, Scheme 1).

One equivalent of anhydrous $ZnCl_2$ was necessary to obtain optimum yields. Reduction in the quantity of anhydrous $ZnCl_2$ to 0.5 or 0.2 equiv increased the reaction time and reduced the product yield to 61% or 57%, respectively (Entries 10 and 11). Addition of methanol as co-solvent increased the solubility of $ZnCl_2$ in toluene but did not improve the yield (Footnote *k*). We have also examined $Zn(OAc)_2$, $Zn(NO_3)_2$, ZnO, and $ZnSO_4$ promoted Friedel–Crafts reaction of indole (Entries 12–15). However, none of the aforementioned reagents gave better yield than $ZnCl_2$. It was previously reported that the presence of additives substantially improved the catalytic activity of $ZnCl_2$.[22] The role of montmorillonite K10, silica, and HCl as additives was examined (Entries 16–18). However, none of the additives enhanced the reaction yield. Anhydrous $ZnCl_2$ mediated Friedel–Crafts reaction of indole, *N*,*N*-dimethylaniline, and 37% formaldehyde solution in methanol gave product **3** in 76% yield (Scheme 2). Interestingly, in toluene solvent, formation of product **3** was not observed.

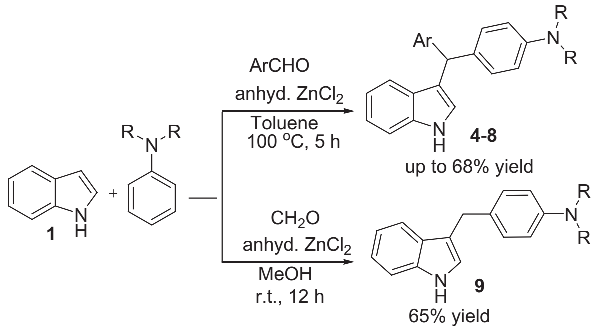
This could be due to the poor solubility of aqueous formaldehyde (37%) solution in toluene. After optimization, 3-diarylmethyl indole synthesis was screened for various aromatic aldehydes and *N*,*N*-dialkylanilines (Scheme 3, Fig. 1). Anhydrous $ZnCl_2$ mediated Friedel–Crafts reaction was found to be general for both electron donating and electron withdrawing aldehydes (Fig. 1, compounds **7** and **5**).



Scheme 1. Synthesis of 3-diarylmethyl indole.



Scheme 2. Synthesis of 3-arylmethyl indole.



Scheme 3. Synthesis of 3-diarylmethyl and 3-arylmethyl indole.

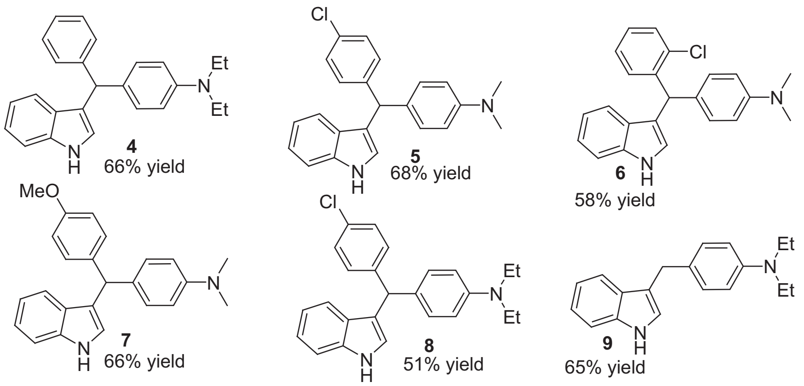


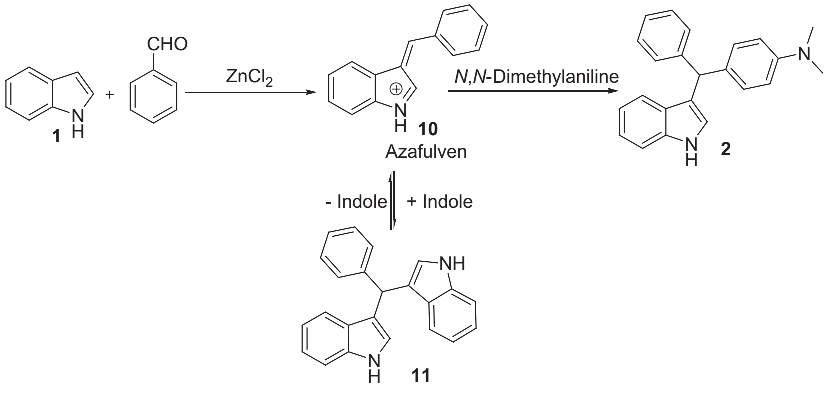
Figure 1. 3-Diarylmethyl and 3-arylmethyl indole.

During the course of investigation on $ZnCl_2$ mediated 3-diarylmethyl indole synthesis in toluene at room temperature, formation of bis(indolyl)methane **11** was observed in the reaction medium which was later converted to the corresponding product (Table 1, Footnote *j*). Initial formation of both 3-diarylmethyl indole **2** and bis(indolyl)methane **11** in the reaction medium was further confirmed by quenching the reaction within one hour at room temperature. Due to the inhomogenity of the reaction medium, efforts to periodically monitor the progress of reaction was unsuccessful. Bhuyan and co-workers reported the formation of bis(indolyl)methane as minor product along with 3-alkylated indoles.[23] Recently, Lubell and co-workers reported the in situ formation of kinetically stable bis(indolyl)methane in the reaction medium and its subsequent conversion to the 3-vinylindole in trifluoroacetic acid mediated, microwave assisted 3-vinylindoles synthesis.[24] Based on this, we have proposed a plausible mechanism for the formation of 3-diarylmethyl indole **2** from indole/bis(indolyl)methane (**1/11**) (Scheme 4).

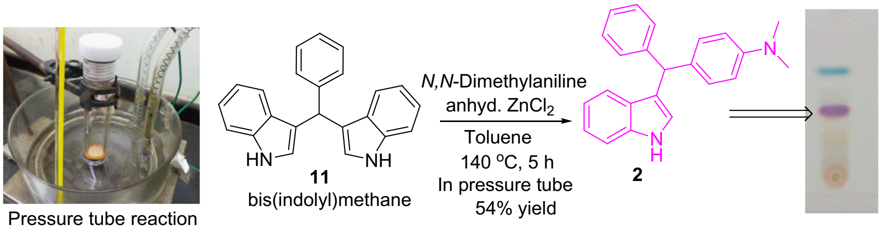
Reaction of indole **1** with benzaldehyde in the presence of $ZnCl_2$ could result in the formation of azafulven **10**.[1a] Addition of indole **1** to azafulven **10** may lead to the formation of kinetically stable bis(indolyl)methane **11**. In the presence of *N*,*N*-dimethylanilines at higher temperature/elongated reaction time, bis(indolyl)methane could convert to the corresponding 3-diarylmethyl indole **2**. Moreover, bis(indolyl)methane **11** was completely soluble in toluene while 3-diarylmethyl indole **2** was sparingly soluble. This could further facilitate the gradual transformation of bis(indolyl)methane to 3-diarylmethyl indole **2** in toluene.

To further confirm this transformation, we have synthesized bis(indolyl)methane **11** by closely following a literature report[25] and subjected to test reaction condition (Table 1, Entry 9). However, only partial conversion of **11** to the corresponding product **2** was observed. Successful conversion of the bis(indolyl)methane to the product **2** in 54% yield was achieved by carrying out the reaction in a pressure tube (Scheme 5). Reactions carried out in toluene at 60 °C and in DMF at 100 °C did not yield the desired product. In benzene, product **2** was obtained in 52% yield. In addition to appropriate solvent, both high temperature and pressure are vital for this transformation. Previously, Mahadevan et al., employed trifluoroacetic acid/Et_3SiH to synthesize 3-arylmethyl indoles from bis(indolyl)methane in 60% yield.[26] To the best of our knowledge, substitution of indole moiety in bis(indolyl)methane by *N*,*N*-dimethylaniline in Friedel–Crafts reaction has not been reported yet.

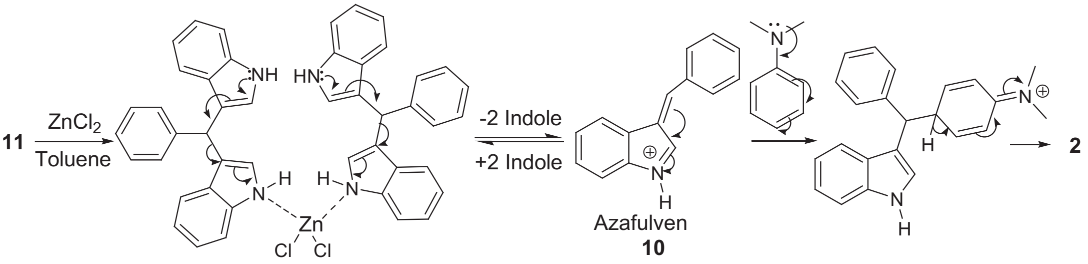
It was previously reported that bis(indolyl)methane derivatives[27a] and dipyrromethane derivatives[27b] displayed good affinity towards Zn^{2+} ions. Moreover, Zn^{2+} ions prefer to coordinate with nitrogen atom of bis(tetrazole) ligands in a intermolecular fashion.[27c] Bhuyan and co-workers reported the addition of indole nucleophile to 3-alkylated indole to form diindolylmethane proceed via elimination-addition mechanism.[28] Based on this, a plausible mechanism for the formation of 3-diarylmethyl indole is given in Scheme 6. Coordination of zinc chloride to nitrogen atom of bis(indolyl)methane **11** could result in the elimination of indole from **11** to form azafulven **10** intermediate. Subsequent addition of *N*,*N*-dialkylaniline to azafulven followed by deprotonation may result in the formation of product **2**. N-methyl derivative of bis(indolyl)methane (1-methyl-3-[(1-methyl-1H-indol-3-yl)(phenyl)methyl]-1H-indole) was also synthesized and subjected to pressure tube reaction condition. However, formation of corresponding 3-diarylmethyl indole product was not observed. It shows the presence of unsubstituted –NH in **11** is essential for



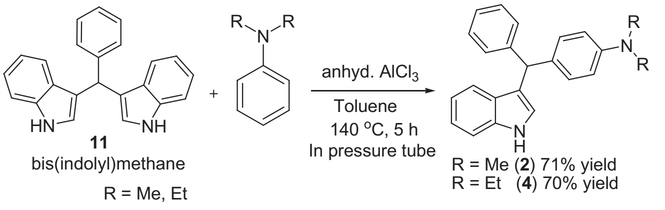
Scheme 4. Mechanism for the formation of 3-diarylmethyl indole.



Scheme 5. Synthesis of 3-diarylmethyl indole from bis(indolyl)methane.



Scheme 6. Mechanism of formation of **2** from bis(indolyl)methane.



Scheme 7. Anhydrous $AlCl_3$ mediated synthesis of 3-diarylmethyl indole

the $ZnCl_2$ mediated conversion of bis(indolyl)methane to 3-diarylmethyl indole. Moreover, changing zinc chloride:bis(indolyl)methane mole ratio to 0.5:1 did not affect the product **2** yield. Further reducing zinc chloride to 0.1:1 reduced the product **2** yield to 43%.

To improve the reaction yield, we have screened several Lewis acids and anhydrous $AlCl_3$ was found to be the suitable reagent than anhydrous $ZnCl_2$ for the efficient conversion of **11** to **2**. In presence of anhydrous $AlCl_3$, reaction yield increased from 54% to 71% (Scheme 7). Anhydrous $AlCl_3$ mediated Friedel–Crafts reaction of unsymmetrical bis(indolyl)methane is underway in our laboratory.

In summary, a convenient, one-pot methodology has been established for 3-arylmethyl and diarylmethyl indole synthesis.[29] The in situ formation of kinetically stable bis(indolyl)methane during the reaction was identified and its conversion to the 3-diarylmethyl indole was confirmed by carrying out the reaction under high temperature and pressure.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.11.115. These data include MOL files and InChiKeys of the most important compounds described in this article.

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29. *Representative procedure for 3-diarylmethyl indole synthesis:* To a stirred homogeneous solution of indole (117 mg, 1 mmol), *N*,*N*-dimethylaniline (152 μL, 1.2 mmol) and benzaldehyde (122 μL, 1.2 mmol) in 10 mL of toluene, anhydrous $ZnCl_2$ (136 mg, 1 mmol) was added and heated in an oil bath at 100 °C for 5 h. The reaction mixture was quenched with 5 mL of cold water and extracted with ethyl acetate (2 × 10 mL). The organic extract was separated, washed with brine, dried over anhydrous sodium sulphate and solvents were evaporated under reduced pressure. The products were purified by column chromatography on silica gel, using hexanes/EtOAc (95:5) as eluent. 4-((1*H*-Indol-3-yl) (phenyl)methyl)-*N*,*N*-dimethyl aniline (**2**): White Color solid; Yield = 248 mg (76%); m.p. 161–162 °C (161–162 °C);[15] IR (KBr): 3391, 3090, 1615, 1451, 1358, 1336, 1517, 799, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.91 (6H, s, $N(CH_3)_2$), 5.59 (1H, s, Ar-$\underline{CH}$), 6.58–6.59 (1H, m, ArH), 6.68 (2H, d, J = 8.7 Hz, ArH), 6.98 (1H, t, J = 7.8 Hz, ArH), 7.10 (2H, d, J = 8.7 Hz, ArH), 7.13–7.21(2H, m, ArH), 7.23–7.27 (5H, m, ArH), 7.35 (1H, d, J = 8.4 Hz, ArH), 7.94 (1H, s, NH). *Representative procedure for 3-arylmethyl indole synthesis:* To a stirred homogeneous solution of indole (117 mg, 1 mmol), *N*,*N*-dimethylaniline (152 μL, 1.2 mmol) and formaldehyde (37%) solution (160 μL, 2 mmol) in 10 mL of methanol, anhydrous zinc chloride (136 mg, 1 mmol) was added and the mixture was further stirred at room temperature for 12 h. The reaction mixture was concentrated, quenched with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and the products were purified by column chromatography on silica gel, using hexanes/EtOAc (95:5) as eluent. 4-(1*H*-Indol-3-ylmethyl)-*N*,*N*-dimethylaniline (**3**): Off-white solid; Yield = 190 mg (76%); m.p. 143 °C (143 °C);[14b] IR (KBr): 3408, 1610, 1517, 1463, 1216, 1134, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.91 (6H, s, $N(CH_3)_2$), 4.03 (2H, s, Ar-$\underline{CH2}$), 6.70 (2H, d, J = 8.4 Hz, ArH), 6.89–6.90 (1H, m, ArH), 7.08 (1H, t, J = 7.2 Hz, ArH), 7.17 (3H, d, J = 8.4 Hz, ArH), 7.35 (1H, d, J = 8.1 Hz, Ph), 7.55 (1H, d, J = 7.8 Hz, ArH), 7.93 (1H, s, NH); *Procedure for the synthesis of 4-((1H-Indol-3-yl) (phenyl)methyl)-N,N-dimethyl aniline (**2**) from bis(indolyl)methane (**11**):* To a homogeneous solution of bis(indolyl)methane (322 mg, 1 mmol) in 3 mL toluene in a pressure reaction vessel, *N*,*N*-dimethylaniline (254 μL, 2 mmol) and (a) anhydrous $ZnCl_2$ (136 mg, 1 mmol) or (b) anhydrous aluminum chloride (133 mg, 1 mmol) were successively added and heated in the oil bath at 140 °C for 5 h. The product was isolated from the reaction mixture as stated in 3-diarylmethyl indole synthesis above. (a) Yield = 176 mg (54%) (b) Yield = 232 mg (71%).