

Efficient, rapid synthesis of bis(indolyl)methane using ethyl ammonium nitrate as an ionic liquid

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A simple and rapid protocol has been developed for an efficient synthesis of bis(indolyl)methane in excellent yields using ethyl ammonium nitrate (EAN) as reusable ionic liquid at room temperature. The protocol involves an electrophilic substitution reaction of indoles with several aldehydes.

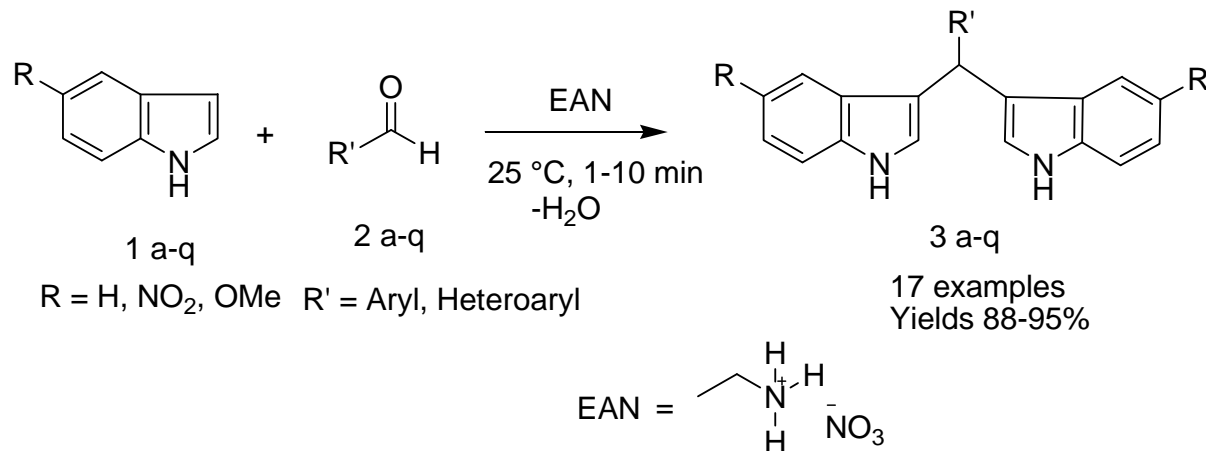
Introduction

Several bis(indolyl)alkanes and their derivatives have been isolated from plant and marine sources.¹ Among the various derivatives of indoles, bis(indolyl)methanes have wide medicinal applications such as to induce apoptosis in human cancer cell and normalize abnormal cell growth associated with cervical dysplasia,² to promote beneficial estrogen metabolism in both women and men, to prevent the breast cancer³ and also to increase the natural metabolism of body's hormones.⁴ Due to vast biological activity of bis(indolyl)methanes and their wide medicinal applications, various methods of their synthesis have been reported in the literature. However, almost all the methods have employed conventional Lewis acids as well as protic acids as catalysts to promote electrophilic substitution reaction of indoles with various aldehydes or carbonyl compounds.⁵ A variety of other catalysts such as H-Y zeolite,⁶ sulphamic acid,⁷ In(OTf)₃,⁸ LiClO₄,⁹ bis(cyclopentadienyl)ZrCl₂,¹⁰ CuBr₂,¹¹ ZrCl₄,¹² Zn(HSO₄)₂,¹³ polyindole salt,¹⁴ CAN,¹⁵ N-tert-butanefulfinyl aldimines,¹⁶ ion exchange resin,¹⁷ acetic acid,¹⁸ InCl₃,¹⁹ InF₃,²⁰ Dy(OTf)₃,²¹ Ln(OTf)₃,²² FeCl₃·6H₂O,²³ V(HSO₄)₃,²⁴ SBA-15/SO₃H,²⁵ oxalic acid,²⁶

TBBDA,²⁷ silica bonded S-sulfonic acid,²⁸ Bi(NO₃)₃,²⁹ Cu(BF₄)₂.SiO₂,³⁰ vanadomolybdophosphoric acid,³¹ Ph-PMO-SO₃H,³² glycerin and CeCl₃,³³ B(C₆F₅)₃,³⁴ H₆P₂W₁₈O₆₂,³⁵ phosphated zirconia,³⁶ Ph₃CCl,³⁷ have been reported for synthesis of bis(indolyl)methanes. However, these methods suffer from drawbacks, such as toxic metal ions, expensive solvents, long reaction times, tedious work-up, low product yields, higher catalyst loading and formation of large amounts of wastes.³⁸⁻⁴⁰

Recently, use of ionic liquids (IL) attracted an increasing interest in the area of organic synthesis due to their unique properties such as hydrophobicities and/ or hydrophilicities as well as good solvating capability, easy recoverability, reusability and non-flammability with almost no vapour pressure. A significant progress has been made in the application of ionic liquids in catalytic processes for the synthesis of heterocyclic compounds.⁴¹⁻⁴⁴ And also the ionic liquid catalyzed synthesis of bis(indolyl)methane using [bmim]BF₄,⁴⁵ [bmim]PF₆,⁴⁵ [acmim]Cl, [hmim]HSO₄⁴⁶ and TMGT,⁴⁷ at room temperature have been reported so far in the literature. However, these methods suffer from certain disadvantages such as very long reaction times and lower product yields. Hence, there has been considerable interest in the development of an elegant, rapid and efficient method for the synthesis of bis(indolyl)methanes using ionic liquids as a recyclable, eco-friendly reaction medium. Ethyl ammonium nitrate (EAN) is an ionic liquid with acidic properties (pH=5),⁴⁸ cheap and easily recoverable, reusable at room temperature, when compared to other ionic liquids. Recently, EAN has been used in various organic reactions such as Kabachnik-Field reaction, Knoevenagel condensation, nitration of phenol and also in the synthesis of 2-amino-4,6-diphenylpyridine-3-carbonitrile and flavones.⁴⁹ Herein, we report the use of ethyl ammonium nitrate [C₂H₅NH₃]NO₃ as a media as well as catalyst in the electrophilic substitution of indoles

with a variety of aldehydes to provide bis(indolyl)methanes at ambient conditions (Scheme 1).



Scheme 1 Ethyl ammonium nitrate (EAN) mediated synthesis of bis(indolyl) methane.

Results and Discussion

Using indole and benzaldehyde as test substrates, the reaction parameters were optimized to determine the optimal condition for the synthesis of bis(indolyl)methanes (Table 1). When Indole (2 mmol) was treated with benzaldehyde (1 mmol) for 5 h in ethylammonium nitrate (EAN) (0.2 mmol) as an ionic liquid without solvent at 25 °C, the corresponding bis(indolyl)methane (3a) was obtained in 30% yield. When we carried out the same reaction in absence of EAN no reaction took place even at higher temperature (85 °C); however the yield and reaction time could be significantly improved to 60% yield in 1.5 h. when 0.8 mmol of EAN was used. Interestingly, increasing the molar ratio of EAN (2 mmol) resulted in a dramatic improvement in the yield of 3a (95%) in 3 min. In general, higher EAN concentration (2 mmol) gave better yields in shorter time. These results clearly indicate that the ENA acts as catalyst as well as a

Table 1 Influence of ethyl ammonium nitrate for the reaction of benzaldehyde and indole^a

Entry	Ethyl ammonium Nitrate (mmol)	Reaction Time (min)	Yield (%) ^b
1	0	300	0
2	0.2	300	30
3	0.4	300	45
4	0.6	210	50
5	0.8	90	60
6	1.0	10	90
7	2.0	03	95

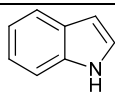
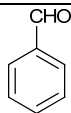
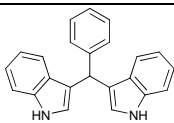
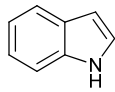
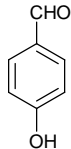
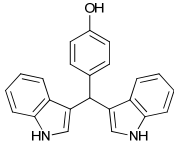
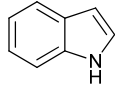
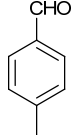
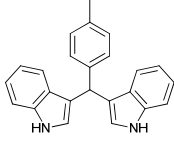
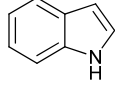
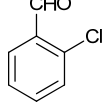
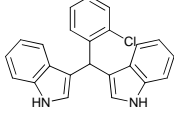
^a Reaction conditions: Indole (2 mmol), Benzaldehyde (1 mmol), Ethylammonium nitrate at 25 °C. ^bIsolated yields after chromatographic purification.

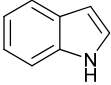
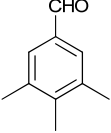
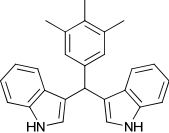
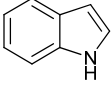
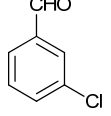
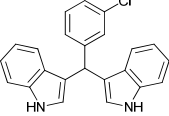
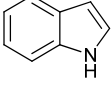
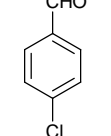
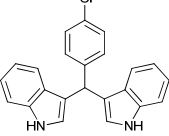
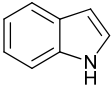
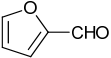
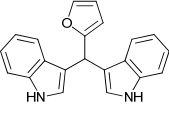
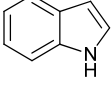
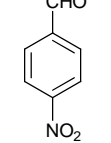
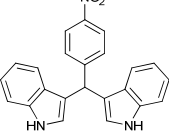
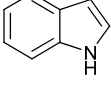
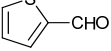
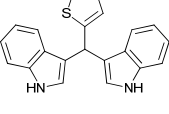
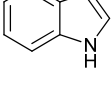
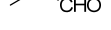
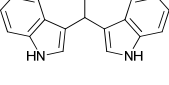
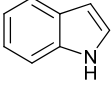
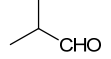
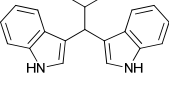
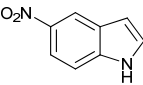
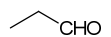
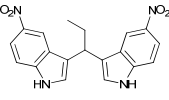
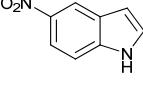
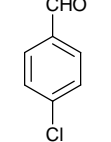
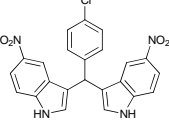
green reaction media. To gauge the scope of this methodology, a variety of substituted aldehydes (2a-q) were reacted with indoles (1a-q) in the presence of 2 mmol of EAN at 25 °C to produce the corresponding bis(indolyl)methanes (3a-q, Table 2). The nature of substitution on the aromatic ring showed some effect on product yields and reactions times. Aromatic aldehydes with electron-withdrawing groups at *o*- and *p*- positions, provided products in excellent yields with shorter reactions time (Table 2, entry d, g & i), the reaction is extremely fast often completing in < 3 min. However, in case of the 3-chlorobenzaldehyde, a low yield of the corresponding product was obtained in longer reaction time (Table 2, entry f). Substrates with electron-donating groups took longer time with moderate yields (Table 2, entry b, c & e). In the case of 3,4,5-trimethylbenzaldehyde, rate of reaction is found to be very slow, due to presence of three electron donating methyl groups (Table 2, entry e). Also, similar effect is observed in case of 5-methoxy indole with 4-methyl and 4-methoxy benzaldehyde (Table 2, entry p and q). This clearly indicates that the position and nature of the substitutions on aromatic ring play a key role on the rate of reaction. Heterocyclic aldehydes reacted smoothly with indole to give the corresponding product in excellent yield (Table 2, entry h & j). Furthermore aliphatic aldehydes also react smoothly with the indole to give the corresponding products in good yields (Table 2, entry k and l).

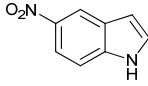
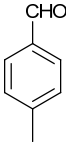
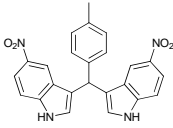
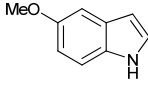
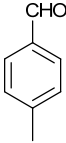
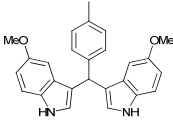
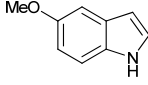
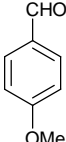
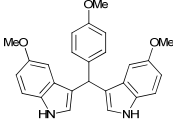
To further elaborate the scope of this protocol with substituted indole, a reaction of 5-nitro indole and 5-methoxy indole was carried out with different aromatics as well as aliphatic aldehyde, which provided the corresponding bis(indolyl)methanes in good to moderate yields (Table 2, entries m, n, o, p and q).

A probable mechanism is shown in Scheme 2 for synthesis of bis(indolyl) methanes. The mechanism involves activation of the carbonyl group by EAN followed by nucleophilic addition of indole to aldehyde proceeds to afford the intermediate A. The subsequent dehydration of A gave B which on nucleophilic addition of another mole of indole gave C followed by aromatization gave the product 3a-q (Scheme 2).

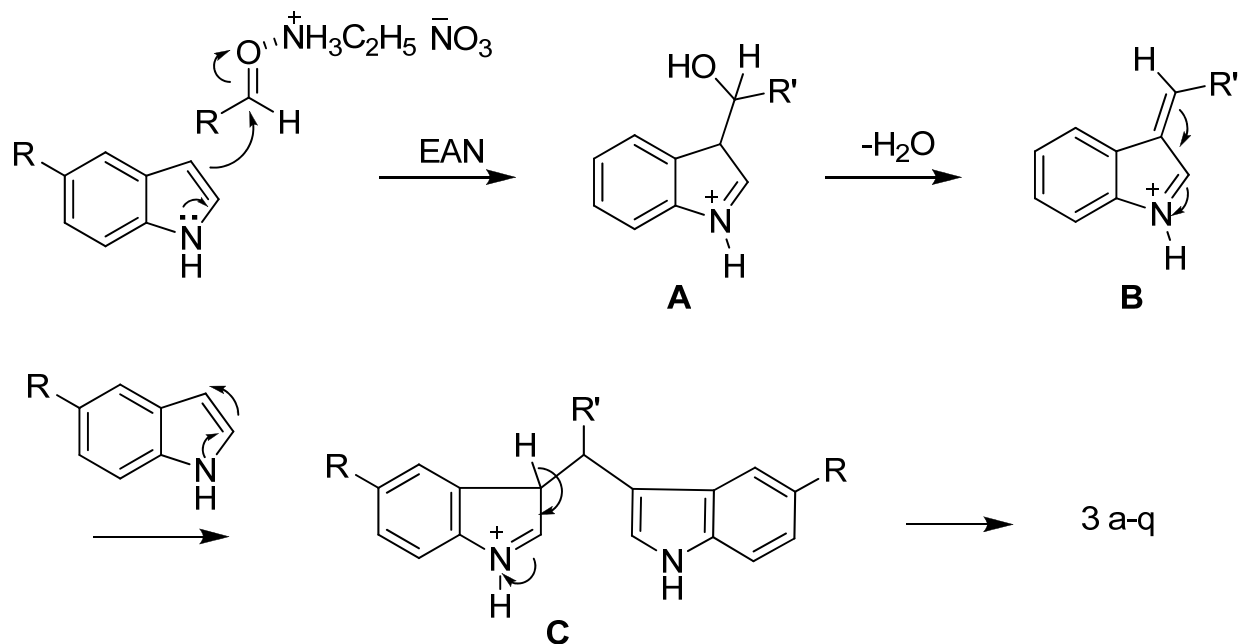
Table 2 EAN mediated synthesis of bis(indole) methane at 25 °C ^a

Entry	Indole (1)	Aldehyde (2)	Product (3)	Time (min)	%Yield ^{b[ref]}
a				03	93 ^[11]
b				05	92 ^[11]
c				08	91 ^[11]
d				03	92 ^[11]

e				10	90 ^[4]
f				10	88 ^[4]
g				01	95 ^[11]
h				03	92 ^[11]
i				01	95 ^[11]
j				04	93 ^[8]
k				02	93 ^[8]
l				02	89 ^[5]
m				08	87 ^[14]
n				08	86 ^[12]

o				05	94 ^[6]
p				11	87
q				12	83

^a Reaction conditions: Indole (2 mmol), Aldehyde (1 mmol), Ethylammonium nitrate (2 mmol) at 25 °C. ^b Isolated yields after chromatographic purification.



Scheme 2 Plausible reaction mechanism for synthesis of bis(indolyl) methane over EAN

Recyclability of Ethyl ammoniumnitrate

The EAN was recovered from aqueous layer by removal of water at 70 °C under reduced pressure and recycled several times with almost no loss of activity (Table 3, Run1-4).

The efficacy of EAN for the synthesis of bis(indolyl)methanes as compared to other acid catalysts and ionic liquids (ILs) reported in the literature can be understood from the results shown in Table 4. The high rate can be rationalized due to high acidity associated with it (pH=5) coupled with its ability to absorb water formed during the reaction in the synthesis bis(indolyl)methanes.

Table 3 Recoverability and reusability of ethyl ammonium nitrate^a

No. of cycles	Fresh	Run 1	Run 2	Run 3	Run 4
Yield (%) ^b	95	95	94	94	93
EAN (%)Recovery	>98	>97	>96	>96	>95

^a Reaction conditions: Indole (2 mmol), Benzaldehyde (1 mmol), Ethylammonium nitrate (2 mmol) at 25 °C. ^bIsolated yields after chromatographic purification.

Table 4 Comparison between EAN and acid catalysts/ionic liquid used in synthesis of bis(indolyl)methanes

Sr. No.	Reaction Condition	Time	Catalyst	Yield (%) ^[Reff.]
1	EAN, rt	03 min	EAN	93
2	Ionic liquid , 1 ml , rt	15 min	TMGT	93 ^[47]
3	Microwave oven, 450 W	05 min	[bmim] [HSO ₄]	93 ^[46]
4	Acetonitrile 3 ml, rt	5.5 hr	Acidic Ionic Liquid Immobilized on Silica (ILIS)	97 ^[50]
5	Ionic liquid 1ml, rt	1.5 hr	FeCl ₃ ·6H ₂ O	98 ^[23]

6	[bmim]BF ₄ or [bmim]PF ₆ 2 ml, rt	4.5 hr		87 ^[45]
7	Ionic liquid 1 ml, rt	15 min	In(OTf) ₃	90 ^[8]

Conclusions

In conclusion, this communication describes EAN mediated an efficient, rapid synthesis of bis(indolyl) methane from indoles and aldehydes in excellent yields at room temperature in shorter reaction time. Novel EAN acts as catalyst and green media for the reaction, making this method cheaper, simple, convenient, and environmentally friendly process for the synthesis of substituted bis(indolyl)methanes.

Experimental Section

All chemicals and reagents required for the reactions were procured from Sigma-Aldrich with purity >98% and used without further purification. The products were characterized using ¹H NMR, ¹³C NMR spectra. NMR spectrums of product were obtained using Bruker AC-200 and AC-400 MHz spectrometer with TMS as the internal standard. Column chromatography was performed on silica gel, Merck grade 60-120 mesh size. TLC was performed on 0.25 mm E. Merck precoated silica gel plates (60 F₂₅₄). The compounds are already well known in the literature.⁶⁻¹⁰

Typical procedure for the synthesis of EAN ionic liquid

Ethylammonium nitrate used were synthesized according to the procedures reported in the literature.⁴⁹ The aqueous solution of ethylamine (70%, 100 ml) was taken in 1 lit. round bottom flask, which maintained below 10 °C using ice water bath. To this cold solution, nitric acid (30%,

330 ml) was added slowly drop-wise with vigorous stirring to attain the pH of the mixture 7.3, the addition was stopped and the mixture was stirred further for 0.5 h. The water from a mixture was removed in a rotary evaporator in a boiling water bath at a pressure of 200 mmHg. The traces of water were removed at 100 °C and 1 mmHg pressure to afford the ethylammonium nitrate in quantitative yield (170 g). The ethylammonium nitrate obtained was used as catalyst in this reaction.

A typical experimental procedure for synthesis of bis(indolyl)methane

A mixture of indole (2 mmol), benzaldehyde (1 mmol) and EAN (2 mmol) was stirred at room temperature. The completion of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was diluted by water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuum to get crude product. The crude product was purified by column chromatography. All the isolated reaction products were characterized and confirmed by NMR, IR and Mass Spectroscopy.

Characterization of selected compounds

3,3'-(phenylmethylene)bis(1H-indole) (Table 2. Entry a):

Colourless solid ¹HNMR (200 MHz, CDCl₃): δ 5.60 (1H, s, Ar-CH), 6.67 (2H, s), 7.04 (2H, t), 7.18-7.27 (3H, m), 7.29-7.32 (2H, m), 7.35-7.46 (6H, m).

3,3'-((2-chlorophenyl)methylene)bis(1H-indole) (Table 2. Entry d):

Pink solid ¹HNMR (200MHz, CDCl₃): δ 6.32 (1H, s, ArCH), 6.67 (2H, s), 7.02 (2H, t, *J* = 7.8 Hz), 7.10-7.22 (6H, m), 7.38-7.43 (4H, m), 7.98 (2H, br, NH).

3,3'-(p-tolylmethylene)bis(1H-indole) (Table 3. Entry c):

Colourless solid ¹HNMR (200MHz, CDCl₃): δ 2.31(3H, s), 5.84(1H, s), 6.64(2H, s), 6.85-7.40(12H, m), 7.94(2H, bs, NH) **(3,3'-((4-chlorophenyl)methylene)bis(1H-indole) (Table 2.**

Entry g):

Pinck solid ¹HNMR (200MHz, CDCl₃): δ 5.88 (1H, s), 6.63 (2H, brs), 7.00-7.70(12H, m), 7.92(2H, bs, NH)

3,3'-(furan-2-ylmethylene)bis(1H-indole) (Table 2. Entry h):

Brown solid ¹HNMR (200 MHz, CDCl₃): δ 5.94

(1H, s), 6.06 (1H, d), 6.30(1H, d), 6.87(1H, d), 7.08(2H, t), 7.17(2H, t), 7.29 -7.48(5H, m), 7.95(2H, bs, NH).

3,3'-(thiophen-2-ylmethylene)bis(indole) (Table 2. Entry j):

Brown solid ¹HNMR (200MHz, CDCl₃): δ 6.08 (1H, s, ArCH), 6.86 (2H, s), 6.97-7.45 (11H, m), 7.94 (2H, br, NH)

3,3'-(propane-1,1-diyl)bis(5-nitro-1H-indole) (Table 2. Entry m): Colorless liquid ¹HNMR (200MHz, CDCl₃): δ 1.05 (3H, t), 2.31-2.25 (2H, m), 4.36-4.39 (1H, m), 7.31-7.38 (4H, m), 7.90 (2H, d), 8.34 (2H, s), 10.97 (2H, brs).

3,3'-(p-tolylmethylene)bis(5-methoxy-1H-indole) (Table 2. Entry p): Brown solid, mp 215–216 °C ¹HNMR (400MHz, DMSO-D₆): δ 2.27 (3H, s), 3.6 (6H, s), 5.7 (1H, s), 6.64-6.77 (6H, m), 7.03-7.09 (2H, m), 7.19-7.25 (4H, m), 10.6 (2H, brs).

3,3'-((4-methoxyphenyl)methylene)bis(5-methoxy-1H-indole) (Table 2. Entry q): Brown solid, mp 198–200°C ¹HNMR (200MHz, CDCl₃+DMSO-d₆): δ 3.62 (6H, s), 3.73 (3H, s), 5.61 (1H, s), 6.64-6.77 (8H, m), 7.15-7.21 (4H, m), 10.03 (2H, brs).

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