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Contributed Paper

One-pot Three Components Synthesis of 3-(α-arylaminobenzylidene)indoles Catalysed by L-proline

Tahira Naqvi [a], Masood Ahmad Rizvi*[b] and Kamal K. Kapoor*[a]

[a] Department of Chemistry, Faculty of Science, University of Jammu, Jammu-180006, India.

[b] Department of Chemistry, Faculty of Physical and Material Science University of Kashmir, Srinagar, Kashmir, 190006, India.

*Author for correspondence; e-mail: k2kapoor@yahoo.com and masoodku2@gmail.com.

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ABSTRACT

The one-pot three-components synthesis of 3-(α-arylaminobenzyl)indoles is achieved from indole, aromatic aldehydes and anilines by using L-proline as a catalyst. The reaction produced 3-alkyl-indoles in dominance over the bisindolyl alkanes. The reported L-proline catalyzed synthetic methodology is an environmentally benign alternative for the synthesis of 3-alkyl-indoles with comparable catalytic efficiency to that of costly and toxic metal based catalysts.

Keywords: organocatalysis, one-pot synthesis, multi-component reaction

1. INTRODUCTION

Indoles have always been of huge interest to synthetic chemists owing to their presence in a large number of biologically active alkaloids and pharmaceutical agents.[1-3] Indole based compounds are also pharmacophores for the development of therapeutic agents.[4] Presence of indole moiety in indole acetic acid (a plant growth regulator hormone) in tryptophan (an amino acid) and a number of alkaloids has attracted attention to obtain biologically important molecules. Among various others, 3-substituted indolyl ketones are important building blocks for the synthesis of many natural products like indole alkaloids hapalindole D.[5] In light of the occurrence of this motif in natural and bioactive products, several methods for its synthesis have been reported [6] and several attempts are being made to introduce methodologies which are simpler, milder, selective and higher yielding. [7,8]

Addition of indoles to unsaturated systems, in presence of Lewis acids like KF/Al_2O_3,[9] lanthanide salts (Ln = La, Sm,Yb),[10] $InCl_3$, $InBr_3$,[11] Zirconium(IV) salts,[12,13] $Bi(NO_3)_3$,[14] $Bi(OTf)_3$,[15] copper salts,[16] acidic clays[17,18] is an efficient approach to synthesize indole derivatives. However, majority of these catalysts suffer from one or the other drawbacks such as requirement of anhydrous conditions, stoichiometric amount of catalyst, expensive reagents, strongly acidic conditions, side reactions etc. Utilizing small chiral organic compounds as catalysts for the

asymmetric synthesis of desired molecules has led to the interesting area of organocatalysis. [19]. An article in this area has also appeared in this journal recently [20] *L*-proline and its derivatives are readily available in high enantiomeric purity and have been reported as an effective, efficient and eco-friendly catalyst for the synthesis of several compounds and various transformations[21,22] such as enamine based direct catalytic asymmetric Aldol,[23] Mannich,[24,25] Michael,[26] Diels-Alder,[27] α-amination reactions and Knoevenagel type reaction[28] and unsymmetric Biginelli reaction. [29] Xie and co-workers[30] have reported the formation of bisindolyl alkanes as a major product in the reaction of imines with indole catalysed by Lanthanide triflates. In continuation of our work [31] and embracing green chemistry principles for newer and ecofriendly synthetic methodologies for organic synthesis [32-35]. We attempted to investigate L-proline as a ecofriendly (metal free) catalyst for the three component synthesis of 3-(α-arylaminobenzyl) indoles from indole, aromatic aldehydes and anilines. The reaction produced 3-alkyl-indoles in dominance over the bisindolyl alkanes. The reported L-proline catalyzed synthetic methodology is an environmentally benign alternative for the synthesis of 3-alkyl-indoles with comparable catalytic efficiency to that of toxic metal based catalysts.

2. Materials and methods

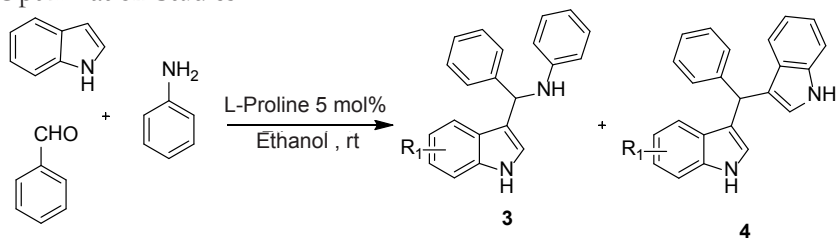
To a solution of benzaldehyde (0.61 g, 5 mmoL) and appropriate aryl amine (5 mmoL) in ethanol (10 ml) was added L-proline (0.01 g, 5 mol %) and indole (0.58 g, 5 mmoL). The reaction mixture was stirred at room temperature till the completion of reaction (TLC monitoring). The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (2 x 30 mL) and brine (1 x 30 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated on rotatory evaporator and the residue, after silica gel column chromatography using pet. ether-ethyl actetate mixture as eluent, gave the desired products in good yields [58-64%] along with bisindolyl alkanes as a minor product [yield: 9-15%].(Table 2).

Generally, imines being hygroscopic in nature tend to decompose during purification by distillation or column chromatography, so we contemplated to carry out the reaction in one pot in which in situ generated imine can be made to react with indole. Towards this course, imine formation was allowed between benzaldehyde and aniline in ethanol in presence of L-proline (5 mol %) followed by the addition of 1 eq. indole and similar results as described above were witnessed (Table 2).

3. Result and discussion

The behavior of the L-proline as organocatalyst for the one pot three component reaction of indole, aromatic aldehydes and aniline to 3-(α-arylaminobenzyl) indoles was explored. In order to optimize condition, we chose indole, benzaldehyde and aniline as model substrates with amino acids as organocatalysts, since these are inexpensive and recyclable. Various amino acids were screened for the Mannich type reaction using benzaldehyde, indole and aniline in EtOH; the obtained results are summarized in Table1. Basic amino acid *L*-lysine and *L*-histidine were found ineffective to form either of the products (**3**, **4**). Whereas, acidic amino acid *L*-glutamic acid was found to be a poor catalyst for the reaction. The desired product **3** was obtained as a major product, when *L*-proline was used as a catalyst. However, proline derivatives N-methyl proline was not found equally effective as proline and cause lower yields. In order to optimize the amount of *L*-proline used for the catalysis of the reaction to form the desired Mannich type product **3**, we analyzed the reaction by varying the loading amount to 5, 10, 20, 30 and 40 mol% of *L*-proline. The optimum

Table 1. Optimization Studies.

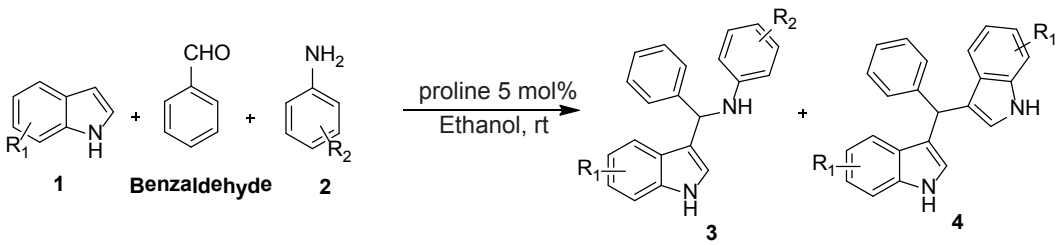


Entry	Catalyst	mol%	Solvent	Product Yield (%)	
				3	4
1	L-Lysine	5	EtOH	-	-
2	L-Histidine	5	EtOH	-	-
3	L-Glutamic acid	5	EtOH	12	-
4	N-Methyl proline	5	EtOH	-	-
5	L-Proline	5	EtOH	64	12
6	L-Proline	5	DMF	53	48
7	L-Proline	5	DMSO	48	68
8	L-Proline	5	MeOH	62	26
9	L-Proline	10	EtOH	64	-
10	L-Proline	15	EtOH	64	10
11	L-Proline	20	EtOH	64	<10
12	L-Proline	30	EtOH	64	<10
13	L-Proline	40	EtOH	64	<10

loading amount of L-proline turns out to be 5 mol% in order to obtain the best result, as no such significant improvement in the yield was observed on increasing the loading upto 40 mol%. The structures of compound **3** and **4** were established by ^{1}H and ^{13}C NMR spectroscopy. Compound **3** displayed resonance at δ 5.71 (1H, s), 6.52-6.80 (10H, m), 7.11-7.30 (3H, m), 7.41-7.50 (3H, m), 7.80 (1H, brs) in ^{1}H NMR. These features coupled with the ^{13}C NMR and mass spectra helped to identify **3** as 3-(α-phenylaminobenzyl)indole. ^{1}H NMR of **4** showed signals at δ 5.91 (1H, s), 6.70-6.92 (4H, m), 6.91-7.01 (5H, m), 7.10-7.41 (6H, m), 7.81 (2H, brs) which speak in support of the structure assigned as 3,3'-(phenylmethylene) bis(1H-indole). Further corroboration to the structures assigned to **3** and **4** came by the comparison of their analytical data with the samples prepared by a known method [25] using Lanthanide triflates catalyzed reaction in protic media. The usage of excess of imine (1.5 and 2.0 eq) in the reaction mixture did not lead to substantial change in mono/bis ratio.

Having conditions optimized we were intrigued to test the generality of the protocol, by extending the reaction to a variety of anilines with indoles (Table 2). The reaction of indole with substituted anilines like *p*-OCH_3, *p*-chloro, *p*-bromo and *p*-flouro resulted in the formation of desired product in 59, 64, 61 and 63% yields respectively. Under optimized conditions, the reaction of anilines with 5-methyl indole also occurred in acceptable yields, but with longer duration as compare to indole. The reaction of 5-methyl indole and benzaldehyde with *p*-OCH_3, *p*-chloro, *p*-methyl, 2-methyl and *p*-flouro anilines gave the desired product in 62, 60, 60, 62 and

Table 2. Synthesis of 3-(α-arylaminobenzyl)indole.



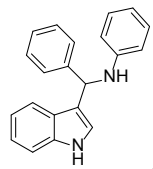
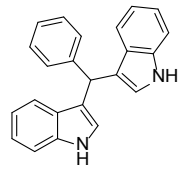
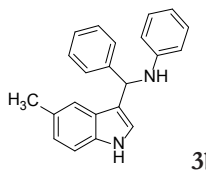
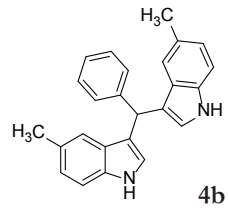
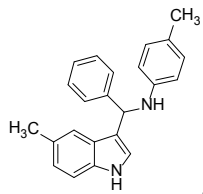
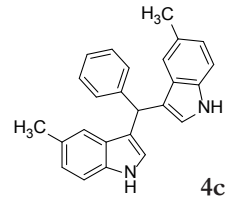
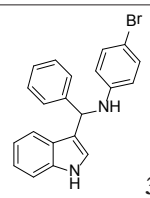
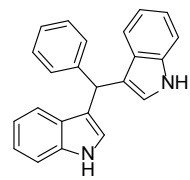
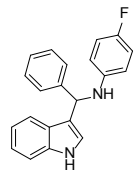
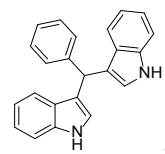
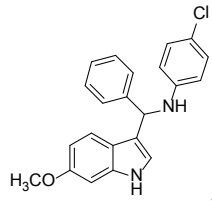
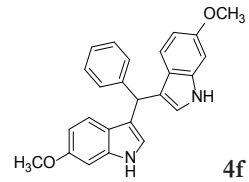
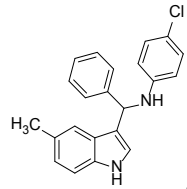
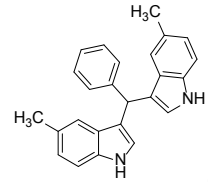
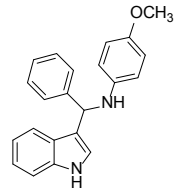
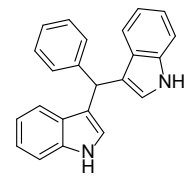
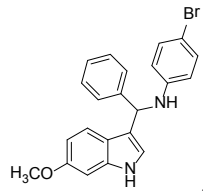
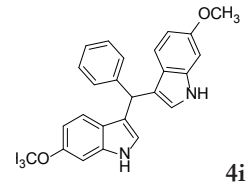
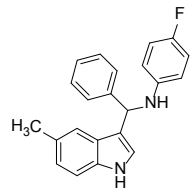
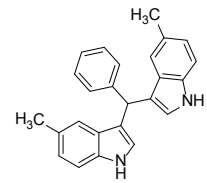
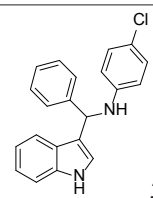
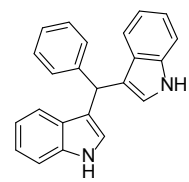
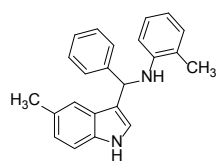
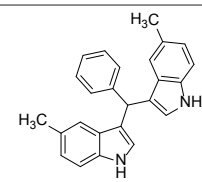
S.No.	R1	R2	Product		Time (h)	Yield (%)	
			3	4		3	4
1	H	H	 **3a**	 **4a**	3	64	12
2	5-CH_3	H	 **3b**	 **4b**	4	62	11
3	5-CH_3	4-CH_3	 **3c**	 **4c**	4	60	13
4	H	4-Br	 **3d**	 **4d**	3	61	12
5	H	4-F	 **3e**	 **4e**	3.5	63	11

Table 2. Continued.

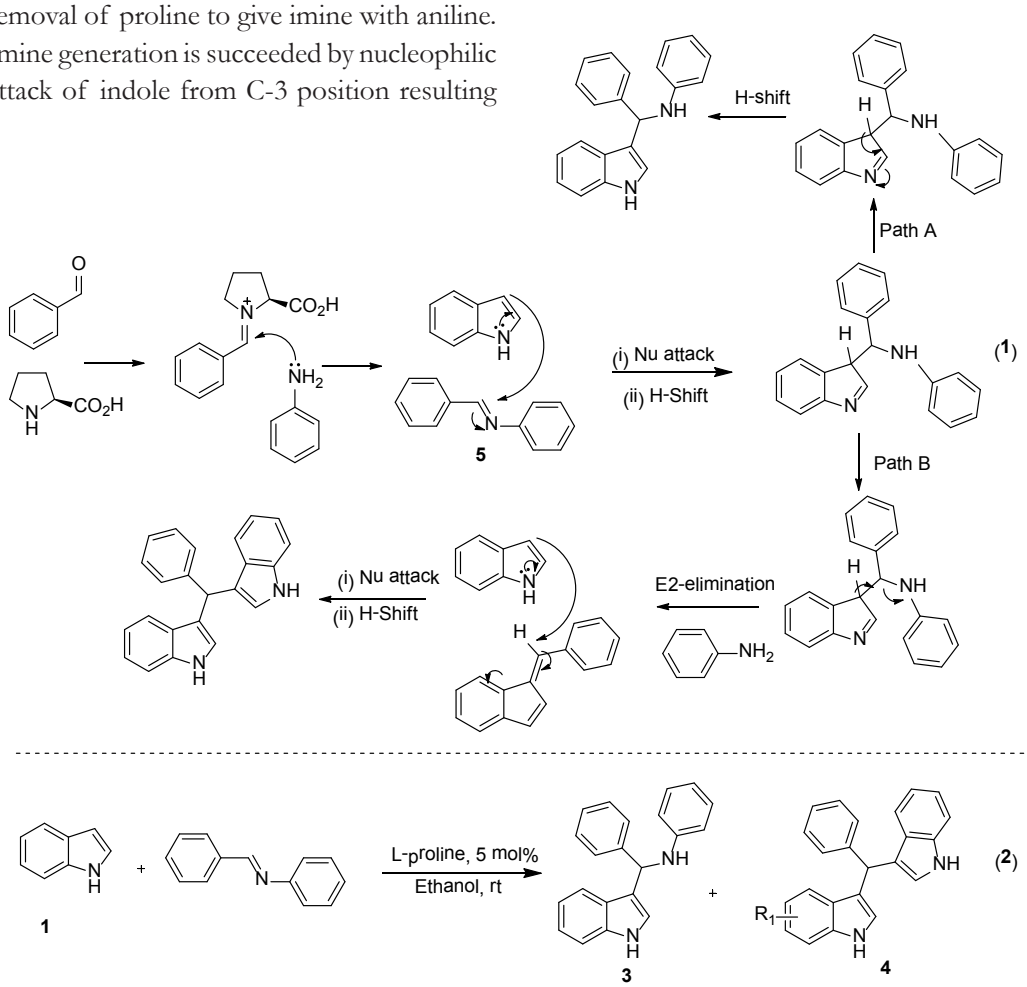
S.No.	R1	R2	Product		Time (h)	Yield (%)	
			3	4		3	4
6	6-OCH_3	4-Cl	 **3f**	 **4f**	3	59	10
7	5-CH_3	4-Cl	 **3g**	 **4g**	5	60	12
8	H	OCH_3	 **3h**	 **4h**	4	59	15
9	6-OCH_3	4-Br	 **3i**	 **4i**	5	60	12
10	5-CH_3	4-F	 **3j**	 **4j**	5	58	12
11	H	2-Cl	 **3k**	 **4k**	4	64	10
12	5-CH_3	2-CH_3	 **3l**	 **4l**	5	62	9

58% yields respectevely. Also, the reaction of 6-methoxy indole and with *p*-bromo and *p*-chloro anilines also resulted in formation of desired product in 60 and 40% respectively. The reported results depict product selectivity in terms of percent yield against the reaction time. In the synthesized library of 12 compounds the 3-(α-arylaminobenzyl) indoles derivatives were found in good excess to bisindolyl alkanes which indicate the selectivity of reaction.

The mechanism of formation of both the products is demonstrated in (Scheme 1, eq. 1). The reaction proceeds by preliminarily enamine formation between aldehyde and proline. This is followed by nucleophilic attack of aniline at electrophilic carbon resulting in auxiliary removal of proline to give imine with aniline. Imine generation is succeeded by nucleophilic attack of indole from C-3 position resulting in formation of 3-(α-arylaminobenzylidene) indoles. To substantiate the fact that reaction occurs via the enamine formation we carried out the reaction of indole under optimized conditions with pre-formed imine to get the desired product **3**, thereby validating our proposition (scheme 1, eq. 2).

The complete spectroscopic details of the representative compounds are as follows:

3-(α-phenylaminobenzyl) indole3a: δ_H(200 MHz, $CDCl_3$) 5.71 (1H, s), 6.50-6.82 (m, 10H), 7.11-7.30 (m, 3H), 7.41-7.50 (m, 3H), 7.80 (brs, 1H). δC(50 MHz, $CDCl_3$) 39.9, 111.2, 115.3, 119.8, 120.7, 120.9, 122.0, 124.2, 126.2, 127.5,



Scheme 1. Proposed mechanistic pathways for the formation of mono and bis indole derivatives.

128.8, 129.2, 129.8, 136.2, 144.6, 144.7. u_{max} (KBr) /cm^{-1} 3500, 2900, 1249. ESI-MS(*m/z*): 299 (M^++H). Calc. for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.70; H, 5.66; N, 8.71.

3-(α-Phenylaminobenzyl)-5-methylindole 3b: u_{max} (KBr) /cm^{-1}: 3347, 2976, 1300 δ_H(200 MHz, $CDCl_3$): δ 2.11 (3H, s), 5.70 (1H, s), 6.61-6.82 (10H, m), 7.01-7.31 (3H, m), 7.40-7.61 (2H, m), 7.80 (1H, brs); δ_C (50 MHz, $CDCl_3$): δ 21.4, 39.5, 110.9, 115.0, 118.9, 120.7, 120.9, 122.0, 124.2, 126.2, 127.5, 129.1, 129.6, 130.1, 136.2, 145.6, 147.7; ESI-MS(*m/z*): 335 $(M+Na)^+$; *Anal. Cacld.* for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97; Found: C, 84.59; H, 6.44; N, 8.99.

3-[α-(4-Methylphenyl) aminobenzyl]-5-methylindole 3c: δ_H(200 MHz, $CDCl_3$): δ 2.01 (3H, s), 2.11 (3H, s), 5.60 (1H, s), 6.50-6.70 (9H, m), 7.00-7.31 (3H, m), 7.42-7.57 (2H, m), 7.71 (1H, brs); δC (50 MHz, $CDCl_3$): 27.3, 27.7, 40.1, 111.2, 114.9, 120.1, 120.7, 121.3, 122.4, 124.2, 126.2, 127.5, 128.8, 129.2, 129.8, 136.2, 145.6, 146.1; ESI-MS(*m/z*): 349 $(M+Na)^+$; *Anal. Cacld.* for $C_{23}H_{22}N_2$: C, 84.63; H, 6.79; N, 8.58; Found: C, 84.64; H, 6.82; N, 8.60.

3-[α-(4-Bromophenyl) amino benzyl] indole 3d: δ_H(200 MHz, $CDCl_3$): 5.70 (1H, s), 6.50-6.80 (10H, m), 7.11-7.41 (5H, m), 7.61 (1H, brs, NH); δ_C (50 MHz, $CDCl_3$): 38.6, 111.2, 120.8, 121.4, 121.8, 122.6, 124.2, 126.2, 127.5, 128.5, 129.2, 130.2, 147.2, 148.7, 150.1;
u_{max} (KBr) /cm^{-1}: 3334, 3015, 1323; *Anal. Calcd.* for $C_{21}H_{17}BrN_2$: C, 66.85; H, 4.54; N, 7.43; Found: C, 66.87; H, 4.55; N, 7.44.

3-[α-(4-Fluorophenyl) amino benzyl] indole3e: δ_H(200 MHz, $CDCl_3$) 5.71 (1H, s), 6.51-6.81(10H, m), 7.22-7.51 (5H, m), 7.80 (1H, brs); δ_C (50 MHz, $CDCl_3$): 39.6, 110.2, 114.3, 116.8, 120.7, 120.9, 122.0, 124.2, 126.2, 127.5, 128.8, 129.2, 131.8, 139.6, 148.6, 150.1; u_{max} (KBr) /cm^{-1}: 3301, 3005, 1298; ESI-MS(*m/z*): 339 $(M+Na)^+$; *Anal. Calcd.* for $C_{21}H_{17}FN_2$: C, 79.72; H, 5.42; N, 8.85; Found: C, 79.71; H, 5.45; N, 8.86.

3-[α-(4-Chlorophenyl) aminobenzyl]-6-methoxyindole 3f: δ_H (200 MHz, $CDCl_3$): δ 3.71 (3H, s), 5.60 (1H, s), 6.52-6.81 (10H, m), 7.11-7.40 (4H, m), 7.70 (1H, brs); δ_C (50 MHz, $CDCl_3$): δ 38.6, 60.3, 111.3, 120.1, 120.7, 121.7, 122.1, 124.2, 125.2, 127.5, 128.2, 129.2, 130.6, 131.8, 136.2, 144.6, 146.9; u_{max} (KBr) /cm^{-1}: 3327, 3022, 1324; ESI-MS(*m/z*): 363 365 $(M+H)^+$; *Anal. Cacld.* for $C_{22}H_{19}ClN_2O$: C, 72.82; H, 5.28; N, 7.72; Found: C, 72.83; H, 5.25; N, 7.74.

3,3'-(Phenylmethylene) bis (6-methoxy-1*H*-indole) 4c: δ_H(200 MHz, $CDCl_3$): δ 2.10 (3H, s), 3.71 (6H, s), 5.71 (1H, s), 6.50-6.80 (8H, m), 7.11-7.31 (3H, m), 7.80 (1H, brs); δC (50 MHz, $CDCl_3$): δ 40.1, 60.3, 111.1, 119.2, 120.1, 121.6, 123.9, 125.1, 127.1, 127.9, 128.7, 135.9, 144.1; ESI-MS (*m/z*): 383 $(M+H)^+$; *Anal. Calcd.* for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32; Found: C, 78.52; H, 5.83; N, 7.54.

3-[α-(4-Chlorophenyl) aminobenzyl]-5-methylindole 3g: δ_H(200 MHz, $CDCl_3$): 2.11 (3H, s), 5.70 (1H, s), 6.51-6.83 (9H, m), 7.11-7.30 (3H, m), 7.80 (1H, brs); δ_C (50 MHz, $CDCl_3$): δ 39.9, 111.2, 115.3, 119.8, 120.7, 120.9, 122.0, 124.2, 126.2, 127.5, 128.8, 129.2, 129.8, 136.2, 144.6, 144.7; ESI-MS(*m/z*): 347, 349 $(M+H)^+$; *Anal. Cacld.* for $C_{22}H_{19}ClN_2$: C, 76.18; H, 5.52; N, 8.08; Found: C, 76.20; H, 5.54; N, 8.09.

3-[α-(4-Methoxyphenyl) aminobenzyl] indole 3h: δ_H(200 MHz, $CDCl_3$) 3.81 (3H, s), 5.61 (1H, s), 6.61- 6.92 (10H, m), 7.21-7.60 (5H, m), 7.81 (1H, brs); δ_C (50 MHz, $CDCl_3$): δ 38.9, 59.4, 112.2, 117.8, 120.7, 120.9, 122.0, 124.2, 126.2, 127.4, 128.8, 129.6, 130.2, 137.2, 144.9, 145.7; u_{max} (KBr) /cm^{-1}: 3322, 2993, 1343; ESI-MS(*m/z*): 329 $(M+H)^+$; *Anal. Cacld.* for

$C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53; Found: C, 80.45; H, 6.16; N, 8.55.

3-[α-(4-Bromophenyl) aminobenzyl]-6-methoxyindole 3i: δ_H(200 MHz, $CDCl_3$) 3.91 (3H, s), 5.70 (1H, s), 6.61-7.01 (10H, m), 7.11-7.30 (4H, m), 7.80 (1H, brs); δC (50 MHz, $CDCl_3$): δ 40.2, 111.9, 113.3, 119.8, 120.7, 120.9, 121.3, 124.2, 126.2, 127.5, 128.8, 129.2, 136.2, 144.6, 146.3; u_{max} (KBr) /cm^{-1}: 3334, 2973, 1332; ESI-MS(*m/z*): 378, 380 $(M+H)^+$; *Anal. Cacld.* for $C_{22}H_{19}BrN_2O$: C, 64.87; H, 4.70; N, 6.88; Found: C, 64.89; H, 4.72; N, 6.89.

3-[α-(4-Fluorophenyl) aminobenzyl]-5-methylindole 3j: δ_H(200 MHz, $CDCl_3$): δ 2.11 (3H, s), 5.70 (1H, s), 6.51-6.92 (10H, m), 7.21-7.52 (4H, m), 7.80 (1H, brs); δC (50 MHz, $CDCl_3$): δ 29.4, 40.1, 110.8, 116.3, 119.8, 120.7, 120.9, 122.4, 124.2, 126.2, 127.5, 128.8, 129.2, 129.8, 136.2, 143.4, 144.7, 147.2; ESI-MS(*m/z*): 331 $(M+H)^+$; *Anal. Cacld.* for $C_{22}H_{19}FN_2$: C, 79.97; H, 5.80; N, 8.48; Found: C, 79.98; H, 5.81; N, 8.46.

3-[α-(4-Chlorophenyl) aminobenzyl] indole 3k: δ_H (200 MHz, $CDCl_3$): δ 5.61 (1H, s), 6.51-6.93 (10H, m), 7.10-7.33 (5H, m), 7.80 (1H, brs); δ_C (50 MHz, $CDCl_3$): δ 40.3, 110.9, 116.3, 119.8, 120.7, 120.9, 122.0, 124.2, 126.2, 127.5, 128.8, 129.2, 129.8, 136.2, 144.6, 144.7, 149.4; ESI-MS(*m/z*): 333 335 $(M+H)^+$; *Anal. Cacld.* for $C_{21}H_{17}ClN_2$: C, 75.78; H, 5.15; N, 8.42; Found: C, 75.79; H, 5.12; N, 8.43.

3-[α-(2-Methylphenyl) aminobenzyl]-5-methylindole 3l: δ_H(200 MHz, $CDCl_3$): δ 2.11 (3H, s), 2.21 (3H, s), 5.71 (1H, s), 6.41-6.84 (10H, m), 7.01-7.32 (4H, m), 7.80 (1H, brs); δC (50 MHz, $CDCl_3$): δ 39.5, 111.2, 114.9, 118.8, 120.7, 120.9, 121.9, 124.2, 126.2, 127.5, 128.8, 129.2, 136.2, 143.6, 144.7, 144.9; ESI-MS(*m/z*): 327 $(M+H)^+$; *Anal. Calcd.* for $C_{23}H_{22}N_2$: C, 84.63; H, 6.79; N, 8.58; Found: C, 84.64; H, 6.78; N, 8.60.

3,3'-(phenylmethylene) bis (1*H*-indole) 4a: δ_H(200 MHz, $CDCl_3$) 5.91 (1H, s), 6.70-6.92 (4H, m), 6.91-7.01 (5H, m), 7.10-7.41 (6H, m), 7.81 (2H, brs). δC (50 MHz, CDCl3) 40.3, 111.1, 119.2, 120.1, 121.6, 123.6, 126.2, 127.1, 128.2, 128.7, 136.7, 143.9. u_{max} (KBr) /cm^{-1} 3321, 2879, 1249. ESI-MS(*m/z*): 323 (M^++H). Calc. for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.72; H, 5.64; N, 8.71.

3,3'-(Phenylmethylene) bis (5-methyl 1*H* indole) 4b: δ_H(200 MHz, $CDCl_3$): δ 2.01 (6H, s), 5.9 (1H, s), 6.61-6.80 (4H, m), 6.90-7.01 (3H, m), 7.11-7.31 (6H, m), 7.80 (2H, brs); δC (50 MHz, $CDCl_3$): 21.4, 40.3, 111.1, 119.2, 120.1, 121.6, 123.6, 126.2, 127.1, 128.2, 128.7, 136.7, 145.1; ESI-MS(*m/z*): 373 $(M+Na)^+$; *Anal. Cacld.* for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 7.99; Found: C, 85.66; H, 6.35; N, 7.98.

Conclusion

A newer environmentally benign methodology for the synthesis of 3-(α-arylaminobenzylidene) indole, using L-proline as a non toxic organocatalyst is reported. The present methodology is efficient and involves mild, non-toxic reaction conditions with the results comparable to catalytic efficiency of toxic and expensive metal based catalysts.

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