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### **Graphical Abstract**





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# [TBA][Gly] ionic liquid promoted multi-component synthesis of 3-substituted indoles and indolyl-4*H*-chromenes

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#### Introduction

Multi-component reactions (MCRs) played a pivotal role in the field of modern medicinal and combinatorial chemistry,<sup>1</sup> however, metals/hazardous reagents catalyzed MCR causes a serious problem of metal contamination in the products/waste disposal in the environment.<sup>2</sup> Still, there is a need of bringing general awareness among synthetic chemists to design methodologies for MCR in eco-friendly and sustainable manner with metal free/less waste generation and greater economic benefits at industrial scale production.<sup>3</sup> Green chemistry metrics have been introduced to overcome the aforementioned problems and to achieve the advantages including both transmaterialization and dematerialization strategies in the academic and industrial research.<sup>4</sup> Moreover, it is well known that the solvents are a major concern and can have significant impact on the amount of waste generated from a multi-step synthetic pathway.<sup>5</sup> In the past decade, green solvents such as water, polyethylene glycol, glycerol and ionic liquids have been known to promote few multi-component reactions with low E-factor and high atom economy.<sup>6</sup> The E-factor of organic conversion can be calculated as the ratio of mass of waste per unit of product i.e the total mass of raw materials (m<sub>1</sub>) minus the total mass of product (m<sub>2</sub>), divided by the total mass of the product (m)  $[E = m_1 - m_2/m]$ . Biodegradable ionic liquids generated from natural amino acids (AAIL) have attracted the attention of scientists working in various fields, which mainly deals with the green and sustainability factors.<sup>7</sup> Especially, tetraalkylammonium cations containing amino acid based ionic liquids [TBA][AA] ILs were found to be an efficient medium for the absorption of CO<sub>2</sub> and for

## ABSTRACT

Tetrabutylammonium glycinate [TBA][Gly] ionic liquid was found to be an efficient recyclable and biodegradable organocatalyst for selective synthesis of 3-substituted indoles and indolyl-4H-chromenes. The reaction between substituted aliphatic/aromatic aldehydes, malononitrile and indoles in the presence of [TBA][Gly] IL at 60 °C under solvent free condition afforded 3-substituted indoles in excellent yields. Indolyl-4H-chromenes were achieved in excellent yields by replacing the benzaldehydes with salicylaldehyde under optimized reaction conditions.

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stabilization of metal NPs and efficient chiral additive for various reactions including Heck arylation, cycloaddition of  $CO_2$  to epoxides,  $\alpha$ -amination of aldehydes and intramolecular aldolization.<sup>8-10</sup>

Indole nucleus has been found as an essential element in medicinal and agricultural chemistry with significant biological activities.<sup>11</sup> 3-Substituted indoles are prominent structural motif found in numerous natural products or therapeutic agents with diverse pharmaceutical activities.<sup>12</sup> 2-Amino-4*H*-chromenes are found to be potent pharmacological scaffolds with wide range of biologically activies.<sup>13</sup> Indolyl-4*H*-chromenes are hybrid scaffolds of vital importance in the field of medicinal chemistry.

Multi-component synthesis of 3-substituted indoles and indolyl-4H-chromenes have been achieved using few catalysts such as Zn(salphen) complex,<sup>14</sup> N,N1-dioxide Zn(II) complex,<sup>15</sup> copper (II) sulfonato salen complex,<sup>16</sup> and tetrabutylammonium fluoride.<sup>17</sup> These methods have disadvantages including usage of metal based catalysts, which results either metal contamination in the products or more waste generation from the reaction mixture or usage of organic solvents and toxic reagents with complicated work up procedures. In order to overcome these limitations, and in continuation of our studies toward development of green methods for organic synthesis,<sup>18</sup> we reported recyclable nanocatalysts such as functionalized Fe<sub>3</sub>O<sub>4</sub> NPs<sup>19</sup> and RGO/ZnO nanocomposites<sup>20</sup> for the synthesis of indolyl-4H-chromenes and 3-substituted indoles. Still, there is need of developing metal free catalytic system, in this context, we developed an efficient metal free, [TBA][Gly] ionic liquid promoted synthesis of 3-substituted

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indoles and indolyl-4*H*-chromenes under green conditions (Figure 1).



Figure 1: [TBA][Gly] promoted synthesis of 3-substituted indoles (4a-4u) and indolyl-4H-chromenes (6a-6i)

#### **Results and discussion**

Initially, a model reaction between benzaldehyde (1a), malononitrile (2a) and indole (3a) was performed using 10 mol% of [TBA][Gly] ionic liquid in the presence of various solvents and solvent free condition at 60 °C (Table 1, Entries 1-9). The results revealed that solvent free condition was the best to afford the product 4a in 93% yield in 30 min (Table 1, Entry 9). However, the reaction proceeded smoothly even in the presence of water as a solvent to afford the product 4a in 85% yield in 60 min (Entry 1). In case of organic solvents, the progress of reaction was very slow to afford the product 4a in poor to moderate yields (Table 1, Entries 2-8). Moreover, other amino acid based ionic liquids including [TBA][Ala], [TBA][His], [TBA][Ser], [TBA][Val] and [TBA][Pro] gave product 4a in 80-88% yields in 60 min (Entries 12-16). The product formation was not observed in the absence of ionic liquid under optimized reaction conditions (Table 1, Entry 17). Thus, the model reaction was optimized using 10 mol% of [TBA][Gly] under solvent free condition for 30 min at 60 °C.

 Table 1: Optimization study for one-pot synthesis of 3-substituted indole (4a).<sup>a</sup>

					CN
CHO + CN + Inic Liquids Solvents, Temp.				CN	
1a	2a	3a		4a	
Entry	Ionic liquids	Solvents	Temp.	Time	Yield of
			(°C)	(min)	$4a (\%)^{b}$
1	[TBA][Gly]	Water	60	60	85
2	[TBA][Gly]	EtOH	60	180	30
3	[TBA][Gly]	Acetone	60	120	55
4	[TBA][Gly]	MeOH	60	180	48
5	[TBA][Gly]	THF	60	180	40
6	[TBA][Gly]	CH <sub>3</sub> CN	60	180	60
7	[TBA][Gly]	Toluene	60	180	50
8	[TBA][Gly]	DMSO	60	180	60
9	[TBA][Gly]	neat	60	30	93
10	[TBA][Gly]	neat	100	30	89
11	[TBA][Gly]	neat	rt	180	55
12	[TBA][Ala]	neat	60	60	80
13	[TBA][His]	neat	60	60	83
14	[TBA][Ser]	neat	60	60	80
15	[TBA][Val]	neat	60	60	85
16	[TBA][Pro]	neat	60	60	88
17	Blank	neat	60	240	

<sup>a</sup>Reaction condition: aldehyde (1 mmol), malononitrile (1 mmol), indole (1 mmol) and ionic liquid (10 mol%). <sup>b</sup>Isolated yield.

With these interesting results in our hand, the generality of method was investigated for a wide range of aromatic and aliphatic aldehydes (**1a-1k**) and substituted indoles (**3a-3c**) under optimized reaction conditions to afford the various 3-substituted indoles (**4a-4u**) as shown in Scheme 1. The results showed that almost all substrates gave best results to afford the products (**4a-4u**) in good to excellent yields (65-93%) as shown in Table 2 (Entries 1-21). However, the progress of reaction was slow in case of isopropyl aldehyde and afforded product **4u** in 65% yield in 120 min (Entry 21, Table 2). Whereas, Wan *et al.* reported the synthesis of **4u** using KH<sub>2</sub>PO<sub>4</sub>/PEG-200/H<sub>2</sub>O catalytic system in prolonged reaction time 12 days.<sup>21</sup> (see ESI for experimental procedures and characterization data of selected compounds).



Scheme 1: One-pot synthesis of 3-substituted indoles (4a-4u)

Next, the model reaction was performed at 10 mmol scale under optimized conditions afforded the 3-substituted indole **4a** in 92% yield (Table 2, Entry 1). It is important to mention here that the purification of these compounds is very simple which requires addition of water followed by filtration and recrystalization of crude solid compounds. Moreover, [TBA][Gly] ionic liquid is biodegradable, non-toxic, recyclable and greener catalyst. Thus the green chemistry metric calculations for model reaction revealed that the method is environmentally benign with the smaller E-factor (0.13) and high atom economy (AE = 93.8%) (see ESI for calculations).

The versatility of [TBA][Gly] catalyst was studied for the synthesis of indol-3-yl-4*H*-chromene derivatives **6a-6i** from the reaction between salicylaldehyde (5), active methylene compounds (2) and substituted indoles (3) as shown in Scheme 2.



Scheme 2: One-pot synthesis of indol-3-yl-4H-chromenes (6a-6i)

The model reaction between salicylaldehyde (5), malononitrile (2a) and 2-methylindole (3c) was performed under optimized condition using 10 mol% of [TBA][Gly] IL to afford the product **6a** in 89% yield (Table 3, Entry 1). The scope of [TBA][Gly] catalyst was studied for various substrates as shown in Scheme 2 and the results are depicted in Table 3. To our delight, the reactions with all substrates proceeded smoothly to afford the products **6a-6i** in good to excellent yields 73-95% (Table 3, Entries 1-9). Whereas, in the case of 1,3-cyclohexanedione (**2c**) and dimedone (**2d**), the expected products **6g, 6h** and **6i** were formed in moderate yields (72%, 70% and 69%) along with the minor products as 2-(1-oxo-2,3,4,9-

tetrahydro-1*H*-xanthen-9-yl)cyclohexane-1,3-diones **7a** and **7b** respectively (Table 3, Entries 7-9) (see ESI for experimental procedures and characterization data of selected compounds).

**Table 2:** [TBA][Gly] promoted one-pot synthesis of 3-substituted indole derivatives.<sup>a</sup>

Entry	Aldehydes	Indoles	Products	Time	Yield
-	(1)	(3)	(4)	(min)	$(\%)^{b}$
1	C <sub>6</sub> H <sub>5</sub>	3a	4a	30	93, 92 <sup>°</sup>
2	2-ClC <sub>6</sub> H <sub>4</sub>	3a	4b	40	89
3	3-ClC <sub>6</sub> H <sub>4</sub>	3a	4c	40	85
4	$4-FC_6H_4$	3a	<b>4d</b>	35	88
5	$4-NO_2C_6H_4$	3a	<b>4e</b>	45	83
6	$2-NO_2C_6H_4$	3a	<b>4f</b>	45	79
7	4-MeC <sub>6</sub> H <sub>4</sub>	3a	4g	30	86
8	4-MeOC <sub>6</sub> H <sub>4</sub>	3a	<b>4h</b>	30	84
9	3-MeOC <sub>6</sub> H <sub>4</sub>	3a	4i	35	89
10	$C_6H_5$	3b	4j	50	80
11	3-ClC <sub>6</sub> H <sub>4</sub>	3b	4k	40	85
12	2-ClC <sub>6</sub> H <sub>4</sub>	3b	41	30	83
13	$2-FC_6H_4$	3b	4m	60	81
14	$3-FC_6H_4$	3b	4n	30	85
15	$4-FC_6H_4$	3b	<b>4o</b>	30	80
16	2-BrC <sub>6</sub> H <sub>4</sub>	3b	4p	40	77
17	C <sub>6</sub> H <sub>5</sub>	3c	$4\mathbf{q}$	30	86
18	$4-ClC_6H_4$	3c	4 <b>r</b>	30	90
19	4- <sup>t</sup> BuC <sub>6</sub> H <sub>4</sub>	3c	<b>4</b> s	30	82
20	$C_6H_{11}$	3a	4t	40	85
21	C <sub>2</sub> H <sub>7</sub>	3a	<b>4</b> 11	120	65

<sup>a</sup>Reaction condition: aldehydes (1 mmol), malononitrile (1 mmol), indoles (1 mmol) and [TBA][Gly] catalyst (10 mol%) at 60 °C under solvent free condition. <sup>b</sup>Isolated yield. <sup>c</sup>Reaction at 10 mmol scale.

**Table 3**: [TBA][Gly] promoted one-pot synthesis of indol-3-yl-4*H*-chromenes.<sup>a</sup>

Entry	Compound	Indoles	Product	Time (min)	Yield (%) <sup>b</sup>
-	2	3	6		
1	2a	3c	6a	30	94
2	2a	3b	6b	40	91
3	2b	3b	6c	60	82
4	2b	3c	6d	40	89
5	2a	3a	6e	30	92
6	2b	3a	6f	45	83
7	2c	3a	6g	45	72 <sup>c</sup>
8	2c	3d	6h	45	70 <sup>c</sup>
9	2d	3a	6i	45	69 <sup>°</sup>

<sup>a</sup>Reaction condition: salicylaldehydes (1 mmol), active methylene compounds (1 mmol) and indoles (1 mmol), [TBA][Gly] (10 mol%) were stirred at 60 °C under solvent free condition, <sup>b</sup>Isolated yield. <sup>c</sup> Side product formation was observed (25-27%) (see ESI for details on minor products).

The green chemistry metrics calculation for a model reaction to afford the indol-3-yl-4*H*-chromene (**6a**) revealed that the present protocol is an environmentally benign with high atom economy (AE) = 90% and small E-factor (0.21) (see ESI for calculations).

The plausible mechanism for [TBA][Gly] IL promoted synthesis of 3-substituted indole **4a** and indol-3-yl 4*H*-chromene **6e** is depicted in Figure 2. The uniqueness of [TBA][Gly] IL is the presence of electrophilic bulky quaternary ammonium cation as a conjugate acid and nucleophilic naked carboxylate anion as a conjugate base. The carbonyl carbon of aldehydes **1a** or **5** can be activated by ammonium ion of IL and the carboxylate anion of IL abstract the proton from malononitrile **2a** to generate carbanion which attacks on activated aldehydes **1a** or **5** to form olefinated products **8** or **9** respectively *via* Knoevenagel condensation. In path 1, [TBA][Gly] initiated the Michael addition of indole **3a** on preformed olefinated product **8** to form an intermediate **II** which further can rearrange into 3-substituted indole **4a** (Figure 2). In path II, [TBA][Gly] promoted the Pinner cyclization of preformed Knoevenagel product **9** to obtain the iminochromene intermediate (V) followed by Friedel-Crafts alkylation with indole 3a to afford the indol-3-yl-4*H*-chromene **6e** (Figure 2).



Figure 2: Plausible mechanism for [TBA][Gly] promoted synthesis of 3-substituted indoles 4a and 6e.

The re-usability of [TBA][Gly] ionic liquid was investigated for a model reaction between benzaldehyde **1a** (10 mmol), malononitrile **2a** (10 mmol) and indole **3a** (10 mmol) in the presence of 10 mol% (356 mg) of [TBA][Gly] catalyst under optimized condition (Table 2, Entry 1) as shown in Figure 3. After completion of the reaction (monitored by TLC), water was added to the reaction mixture to afford the organic compound as a precipitated solid in aqueous medium. The [TBA][Gly] ionic liquid from aqueous layer was recovered and re-used for six times by repeating the similar procedure. The results revealed that there was no change in its catalytic activity to afford the product **4a** as depicted in Figure 2.



Figure 3: Recylability of [TBA][Gly] promoted synthesis of 3-substituted indole 4a.

#### Conclusions

Tetrabutylammonium glycinate [TBA][Gly] ionic liquid was explored as a novel recyclable and biodegradable organocatalyst for the selective synthesis of 3-substituted indoles and indolyl-4*H*-chromenes. The present method is metal free and highly efficient, biodegradable, and afforded products in excellent yields in short reaction time. [TBA][Gly] IL was recyclable for six times without loss in its catalytic activity. The present method follows green chemistry metrics such as low E-factor and high atom economy (AE). The further work on applications of chiral amino acid based ILs as recyclable catalysts for asymmetric organic conversions are underway.

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Notes and references

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Electronic Supplementary Information (ESI) available:

[Green chemistry metrics calculation, <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of selected compounds]

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#### Highlights of present work

- 1. Metal free approach for 3-substituted indoles and indolyl-4H-chromenes.
- 2. [TBA][Gly] ionic liquid is a novel biodegradable and recyclable catalyst.
- 3. All substrates afforded products in excellent yields in short reaction time.
- 4. This method shows low E-factor and high atom economy (AE).