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LETTER

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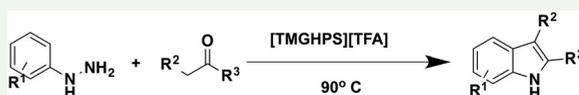
## Novel biodegradable protonic ionic liquid for the Fischer indole synthesis reaction

William C. Neuhaus<sup>a</sup>, Ian J. Bakanas<sup>a</sup>, Joseph R. Lizza<sup>a</sup>, Charles T. Boon, Jr.<sup>b</sup> and Gustavo Moura-Letts<sup>a</sup> 

<sup>a</sup>Department of Chemistry and Biochemistry, Rowan University, Glassboro, NJ, USA; <sup>b</sup>Department of Chemical Engineering, Rowan University, Glassboro, NJ, USA

### ABSTRACT

Novel eco-friendly tetramethylguanidinium propanesulfonic acid trifluoromethylacetate ([TMGHPS][TFA]) ionic liquid was developed as catalyst and medium for the Fischer indole synthesis of a wide variety of hydrazines and ketones. The indole products were isolated in high yields and with minimal amounts of organic solvent. This reaction showed that [TMGHPS][TFA] can be regenerated and reused with reproducible yields without eroding the integrity of the ionic liquid.



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Ionic liquids; indole; Fischer indole synthesis; tetramethylguanidinium; biodegradable

### Introduction

Acid-promoted organic reactions are among the most important transformations in the chemical industry (1). Brønsted acid catalyst has recently taken a more relevant role with the introduction of organocatalysis (2). However, the use of these conventional methods suffers from low solubility, waste production, corrosiveness, recycling, and high volatility (3). Ionic liquids (ILs) have been widely utilized as solvents for a range of organic reactions with the potential of improving product distribution, recycling, reaction rates, and reaction chemo-, regio-, and stereoselectivities (4, 5). Moreover, reactions in ILs remove the risks of fugitive emissions and combustion of conventional small organic molecules widely used as solvents in organic reactions (6, 7).

Biodegradable ILs offer a greener alternative to traditional Brønsted–Lewis acid catalyst with the potential to further increase the efficiencies of organic transformation (8). Protonic ILs have been reported as a new class of promising compounds for the development of environmentally friendly acidic catalysts owing to their combined advantages as both liquid acids and ILs. Pd-promoted coupling reactions with guanidine and amino acid-based ILs are among the most successful examples (9–11).

The indole molecular framework is among the most recurrent heterocyclic structure in natural and synthetic

molecules with pharmacological properties (12). Their synthesis has been a major focus in the field of organic chemistry for over 100 years, and a variety of methods are available for their synthesis (13–15). The reaction of hydrazines and ketones to make indoles (Fischer indole synthesis) still remains one of the most reliable approaches for the synthesis of these scaffolds (16–18). Despite being largely investigated, Lewis acids (ZnCl<sub>2</sub>, TiCl<sub>4</sub>), Brønsted acid catalysts (H<sub>2</sub>SO<sub>4</sub>, HCl, PPA, AcOH, TsOH), and solid acids (zeolite, rutile) have proven to be the simplest and most effective promoters for this transformation (19,20).

However, the development of innovative, environmentally benign and cost-efficient catalysts and catalytic systems remains a main objective in the field of organic chemistry.

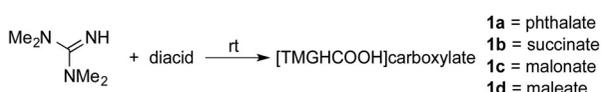
ILs have been previously used to promote the Fischer indole synthesis with a variety of results and efficiencies (21). Pyridinium and choline ILs have been shown to promote the reaction with good efficiencies, but the catalysts' lack of stability limited their application (22). Similar efforts have shown that highly stable Brønsted acid imidazolium IL ([bmim][HSO<sub>4</sub>]) promote this reaction with good conversions but with limited scope (23). Xu et al. demonstrated that increasing the acidity of the IL by introducing an alkyl-SO<sub>3</sub>H group, largely increased the scope and efficiencies of the reaction (24).

**CONTACT** Gustavo Moura-Letts  [moura-letts@rowan.edu](mailto:moura-letts@rowan.edu)

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**Scheme 1.** Synthesis of novel protonic TMG ILs.

**Table 1.** Indole synthesis with 2-trifluoromethylhydrazine and cyclohexanone with different protonic ILs.

Entry	IL	Conversion <sup>a</sup>	Yield <b>3</b> <sup>b</sup>	Yield <b>4</b>
1	[TMGH]lactate	90%	90%	0%
2	[TMGH]phthalate	>95%	88%	8%
3	[TMGH]succinate	>95%	78%	20%
4	[TMGH]malonate	>95%	95%	3%
5	[TMGH]maleate	>95%	93%	3%
6	CF <sub>3</sub> CO <sub>2</sub> H	>99%	99%	0%
7	TMG	0%	0%	0%
8	Sultone	0%	0%	0%
9	[TMGHPS]NO <sub>3</sub>	>99%	50%	50%
10	[TMGHPS]OAc	>99%	35%	62%
11	[TMGHPS]Cl	>99%	15%	82%
12	[TMGHPS]HSO <sub>4</sub>	>99%	16%	84%
13	[TMGHPS]TFA	>99%	3%	97%
14	[TMGHPS]OTf	>99%	20%	60%

Note: Reaction conditions: Hydrazine (1 mmol), ketone (1 mmol), and IL (1 mmol) were mixed and heated to 90°C.

<sup>a</sup>Reaction conversion measured by <sup>1</sup>H-NMR.

<sup>b</sup>Isolated yield.

Tetramethylguanidine (TMG) ILs have been utilized to promote a variety of organic reactions (25). Among these, [TMGH][lactate] has received considerable attention for its green and biodegradable properties, and for its efficient promotion of important organic transformations (26). We propose a novel class of eco-friendly TMG-based ILs with an alkyl acid substituent for the efficient Fischer indole synthesis. To the best of our knowledge, this is the first time TMG-based ILs have been applied to the synthesis of complex heterocyclic scaffolds.

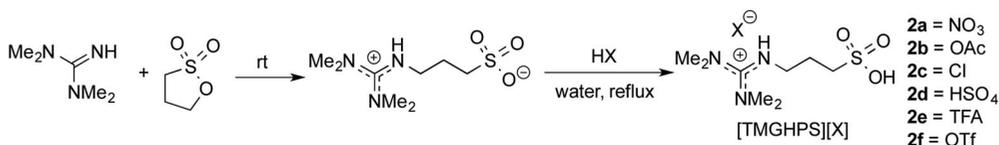
## Results and discussion

We hypothesized whether a greener [TMGHCOOH]carboxylate would efficiently promote the Fischer indole synthesis reaction. Thus, we reacted neat TMG with a series of organic dicarboxylic acids to furnish **1a-d** with

complete conversion (Scheme 1). Upon the successful synthesis of these ILs, we began to study their ability to promote the Fischer indole synthesis. The formation of indoles by reacting hydrazines and ketones goes through an initial formation of hydrazone intermediate **3**, which then undergoes a [3,3]-sigmatropic rearrangement followed by loss of ammonia to form indole **4** (Table 1). Based on the demonstrated promoting ability of similar ILs (27), deactivated hydrazine (2-trifluoromethylhydrazine) and cyclohexanone were used as the model reaction substrates for these ILs. [TMGH][lactate] was hypothesized as a potential promoter of this reaction (Table 1). Unfortunately, we were only able to obtain hydrazone **3** from the reaction crude (Entry 1). The key [3,3]-sigmatropic rearrangement requires strong acidic conditions; so we rationalized that ILs **1a-d** would be better candidates for this reaction. Unfortunately, we found that phthalate **1a** and succinate **1b** (Entries 2 and 3) did form indole **4**, but in poor yields 8% and 20%, respectively. Malonate **1c** and maleate **1d** only provided indole **4** in trace amounts (Entries 4 and 5).

It has been reported that imidazolium salts react at RT with sultones to provide the respective alkylated imidazolium sulfonic acid (28). Consequently, we reacted TMG with 1,3-propane sultone, and we were pleased to find that TMGH sulfonate was obtained with complete conversion (Scheme 2). This intermediate compound was then poised to react with a variety of inorganic and organic acids to form the respective ILs **2a-f**. These were water stable, non-volatile, and non-miscible with organic solvents and were all obtained with complete conversion.

With these in hand, we went ahead and test their ability to promote the indole reaction (Table 1). We found that the nitrate **1a** and acetate **1b** ILs (Entries 9 and 10) radically improved the formation of indole **4** (50% and 60% respectively). Furthermore, chloride **1c** and bisulfate **1d** provided the indole in synthetically useful yields (Entries 11 and 12, 82% and 84% yield, respectively). We then decided to use a stronger acid and we found that trifluoroacetate **1e** provided indole **4** in 97% yield (Entry 13). Conversely, triflate **1f** provided the indole **4** in considerably lower yield (Entry 14, 60% yield). We were enthusiastic to find that tetramethylguanidinium propanesulfonic acid trifluoromethylacetate ([TMGHPS][TFA]) was the ideal protonic IL for this reaction. We verified that the



**Scheme 2.** Synthesis of novel protonic TMG sulfonic acid ILs.

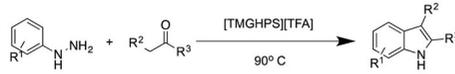
Fischer indole reaction was indeed being promoted in the presence of this IL by exposing the reaction to just trifluoroacetic acid and we found only complete conversion to hydrazone **3** (Entry 6, 99% yield). Moreover, TMG or sultone alone only provided the unreacted starting material (Entries 7 and 8).

Having established [TMGHPS][TFA] as the ideal IL for this transformation, we focused on assessing the scope of this reaction using this IL for a variety of ketones and hydrazines (Table 2). We assessed a variety of activated and deactivated hydrazines to establish the scope of [TMGHPS][TFA] **2e**. Activated hydrazines (4-methyl, 4-methoxy, and phenyl) with cyclohexanone in the presence of **2e** provided the respective indoles in very good yields (Entries 1, 2 and 3). Similarly, deactivated hydrazines (2-bromo, 4-chloro, 4-fluoro and 2-trifluoromethyl) provided the expected indoles in excellent yields (Entries 4, 5, 6 and 7).

These initial results demonstrated that **2e** was promoting this reaction with good generality. However, highly deactivated hydrazines (4-nitro, 2,4-dinitro and 4-cyano) provided mostly complex mixtures with predominant formation of the hydrazone intermediate. We then focused on the indole synthesis of other ketones. 4-Methylcyclohexanone successfully provided the indoles in similar yields as in the cyclohexanone series (Entries 8–12). Deactivated 2-Trifluoromethylhydrazine and 4-methylcyclohexanone reacted with high conversion, but the isolated yield was slightly lower than expected (Entry 13, 68% yield).

Encouraged by these results, we tried the reaction with unsymmetrical ketones. We found that 2-octanone with 4-chloro and 2-trifluoro hydrazines selectively provided the respective indoles in good yields (Entries 14 and 15, 71% and 66% yield, respectively). The regioselectivity of the indole synthesis with 2-octanone was shown to have complete selectivity for the 2-methyl indole isomer. Moreover, the reactions with methyl ethyl ketone with 4-methoxy and 4-chloro hydrazines were also successful at providing the thermodynamically favored indole in good yields (Entries 16 and 17 with 93% and 71% yield, respectively). We were also interested in assessing the reactivity with 3-pentanone and we found that when reacting with 4-methoxy, 4-chloro and 2-bromo hydrazines, the indoles were obtained in very high yields as well (Entries 18, 19 and 20 with 91%, 93% and 95% yield, respectively). Analogously to 2-octanone, the 2-methyl indole regioisomer was made selectively. We further investigated the scope of **2e**, and found that sterically demanding ketones (acetophenone, 1-tetralone) do not form the desired indole.

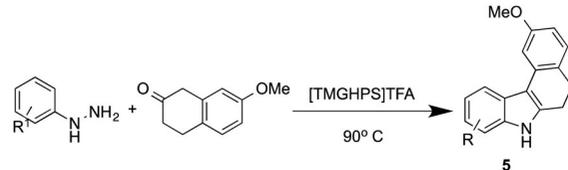
**Table 2.** Fischer indole synthesis scope for activated and deactivated hydrazines, and symmetric and nonsymmetrical ketones.

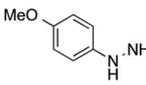
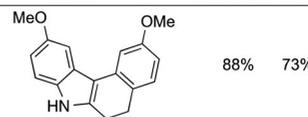
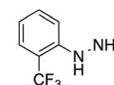
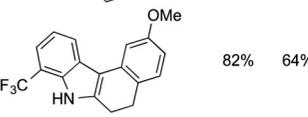
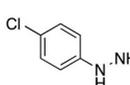
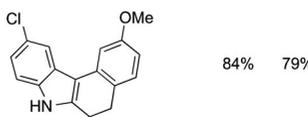
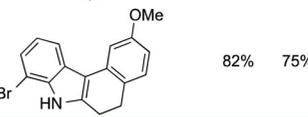


Entry	Hydrazine	Ketone	Indole	Conversion <sup>a</sup>	Yield <sup>b</sup>
1				93%	88%
2				95%	90%
3				99%	99%
4				95%	88%
5				98%	90%
6				99%	95%
7				95%	75%
8				84%	78%
9				88%	75%
10				95%	90%
11				95%	90%
12				94%	88%
13				88%	68%
14				75%	71%
15				81%	66%
16				95%	93%
17				80%	71%
18				95%	91%
19				97%	93%
20				98%	95%

<sup>a</sup>Reaction conversion was measured by <sup>1</sup>H-NMR.

<sup>b</sup>Isolated yields.

**Table 3.** Indoles from 7-methoxy-2-tetralones toward alkaloid core.


Entry	Hydrazine	Indole	Conversion <sup>a</sup>	Yield <sup>b</sup>
1			88%	73%
2			82%	64%
3			84%	79%
4			82%	75%

<sup>a</sup>Reaction conversion was measured by <sup>1</sup>H-NMR.<sup>b</sup>Isolated yields.

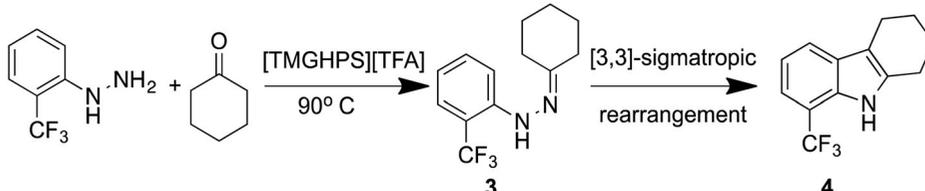
Biologically relevant alkaloids share the indole **5** molecular scaffold as their pharmacophore core (Table 3). We believe we could access these important synthons by the Fischer indole synthesis of hydrazines and substituted 2-tetralones. We reacted 7-methoxy-2-tetralone with activated 4-methoxyhydrazine and we found that we were able to reach almost complete conversion after 12 h (Entry 1). Moreover, we were able to isolate the desired indole in 73% yield. We then reacted 2-trifluoromethyl and found that we were also able to obtain the desired indole (Entry 2, 64% yield). Similarly,

4-chloro and 2-bromo reacted to provide the expected indole in good yields (Entries 3 and 4, 79% and 75% yield).

We then focused our efforts on determining the recyclability of our protonic IL **2e** (Table 4). Due to the fact that the reaction was performed in the presence of water, IL **2e** had the potential to be recycled by simple extraction of the organic product. Moreover, exposing the aqueous solution to trifluoroacetic acid acidified the recovered IL. We decided to use 2-trifluoromethylhydrazine and cyclohexanone as our model example. We were able to use IL **2e** through eight Fischer indole synthesis reaction cycles with complete conversion to indole **4** in each cycle. After cycle 4 we began to see erosion of **2e**, and by cycle 9 the reaction conversion dropped to 40% yield of **4**. The IL could be further purified by multiple extractions with EtOAc/CHCl<sub>3</sub> mixtures to regenerate its activity. However, the overall recovery of **2e** was limited to 50% yield.

## Conclusions

We have demonstrated that [TMGHPS][TFA] **2e** can efficiently promote Fischer indole synthesis reactions for a wide variety of activated and deactivated hydrazines and symmetrical and nonsymmetrical ketones. We established that **2e** was the optimal promoter for the indole synthesis of activated and deactivated hydrazines. Moreover, we were able to apply this protocol to the synthesis of alkaloids indole core by reacting hydrazines with 7-methoxy-2-tetralone. We were also able to demonstrate that [TMGHPS][TFA] can be recycled and reused for up to 8 cycles with reproducible conversions and yields.

**Table 4.** Fischer indole synthesis reaction with [TMGHPS][TFA] recycling study.


	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10
Conversion <sup>a</sup>	100%	100%	100%	100%	100%	100%	95%	95%	65%	50%
Yield of <b>4</b> <sup>b</sup>	97%	96%	97%	98%	95%	96%	92%	91%	40%	20%
Purity of IL <sup>c</sup>	100%	100%	100%	100%	95%	90%	89%	86%	75%	50%
Time <sup>d</sup>	60 min	60 min	60 min	60 min	80 min	90 min	90 min	120 min	180 min	240 min

<sup>a</sup>Reaction conversion was measured by <sup>1</sup>H-NMR.<sup>b</sup>Isolated yields.<sup>c</sup>IL purity was measured by <sup>1</sup>H-NMR.<sup>d</sup>Reaction was monitored by TLC.

## Experimental

**Synthesis of [TMGHPS][TFA] 2e:** In a 30 mL round-bottomed flask 1,1,3,3-tetramethylguanidine (1.50 mL, 12 mmol, 1 equiv.) was cooled to 0°C and 1,3-propanesultone (1.05 mL, 12 mmol, 1 equiv.) was then added. The resulting mixture was stirred at 0°C for 30 min and then 5 mL of DI water were added. The resulting mixture was then treated with trifluoroacetic acid (918 µL, 12 mmol, 1 equiv.) and then heated to 90°C for 12 h. The resulting mixture was then diluted with DI water to make a 1 M solution. IL was fully characterized after removal of excess water under vacuum to afford neat **2e** as a clear liquid (3.41 mL, 99% yield). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) δ 3.54 (t, *J* = 6.6 Hz, 2H), 2.82 (s, 12H), 2.79 (t, *J* = 6.4 Hz, 2H), 1.81 (quintet, *J* = 6.6 Hz, 2H). <sup>13</sup>C-NMR (125 MHz, D<sub>2</sub>O): δ 163.5, 161.4, 118, 60.2, 48.2, 38.5 (4C), 27.3 ppm. ESI-MS *m/z* (rel int): (pos) 238.11 ([M-TFA]<sup>+</sup>, 100).

**General protocol for the Fischer indole synthesis:** In a 4 mL vial 0.5 mL of a 1M [TMGHPS][TFA] in H<sub>2</sub>O was mixed with hydrazine (0.1 mmol, 1 equiv.) and ketone (0.1 mmol, 1 equiv.). The resulting mixture was heated at 90°C for 30 min or until the reaction was completed by thin layer chromatography (TLC). The mixture was then extracted with Diethyl Ether and the combined organic layers were concentrated under reduced pressure. The resulting crude was then quickly purified by automated silica gel chromatography using combinations of heptanes and EtOAc.

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## Disclosure statement

No potential conflict of interest was reported by the authors.

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## ORCID

Gustavo Moura-Letts  <http://orcid.org/0000-0001-8156-151X>

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