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# Efficient synthesis of pyrano[4,3-*b*]indol-1(5*H*)-ones from $CO_2$ and alkynyl indoles promoted by a protic ionic liquid

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ABSTRACT

An efficient method was developed for the synthesis of pyrano[4,3-*b*]indol-1(5*H*)-ones, which uses a protic ionic liquid [$HTBD^+$][$TFE^-$] as both the solvent and reaction promoter. The reactions could be efficiently carried out at atmospheric pressures of $CO_2$, and various pyrano[4,3-*b*]indol-1(5*H*)-ones bearing versatile functionalities were obtained in moderate to high yields (71–99%).

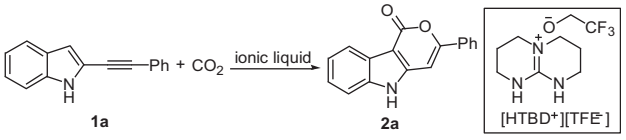


## Introduction

Functionalized indoles are useful structural motifs in heterocyclic chemistry [1] which have drawn significant attention due to their various biological and pharmaceutical activities [2]. In particular, pyranoindolones have gained increased interest due to the importance of the pyranone core which is widely present in pharmaceutical intermediates and natural products [3]. For example, pyrano[4,3-*b*]indol-1(5*H*)-ones were reported as tumor cell growth inhibitors against human cervix adenocarcinoma (HeLa) [4]. Pyrano[4,3-*b*]indol-1(5*H*)-ones have also been utilized for the synthesis of $\gamma$-carbolinone alkaloids with serotonin 5-HT3 receptor antagonist properties [5]. Typically, pyrano[4,3-*b*]indol-1(5*H*)-ones are synthesized *via* metal-catalyzed methods, using $AuCl_3$ [6], $[(Cp^*RhCl_2)_2]/Cu(OAc)_2$ [7], $Pd(OAc)_2/Ag_2O$ [8], and CuI [9]. However, these synthetic routes possess a negative environmental impact. Recently, the organocatalyzed $CO_2$ trapping of alkynyl indoles was reported as an atom-economical and green route to synthesise pyrano[4,3-*b*]indol-1(5*H*)-ones [10], since $CO_2$ is an abundant, non-toxic, inexpensive and renewable C1 resource [11]. Therefore, it is of interest to develop highly-efficient routes to transform $CO_2$ into pyrano[4,3-*b*]indol-1(5*H*)-ones using simple systems.

Protic ionic liquids (PILs) formed by an equimolar combination of a Brønsted base and Brønsted acid can be employed as reaction media for the synthesis of quinazoline-2,4(1*H*,3*H*)-diones utilising $CO_2$ under mild reaction conditions [12]. In addition, in our previ-

**Table 1**
Reaction of **1a** with $CO_2$ using different PIL systems.[a]




| Entry | PIL/Solvent | Time [h] | Yield **2a** [%] [b] |
|---|---|---|---|
| 1 | – | – | – |
| 2 | [$HDBU^+$][$TFA^-$] | 18 | 15 |
| 3 | [$HDBU^+$][$Ac^-$] | 18 | 28 |
| 4 | [$HDBU^+$][$TFE^-$] | 18 | 64 |
| 5 | [$HDBN^+$][$TFE^-$] | 18 | 68 |
| 6 | [$HTBD^+$][$TFE^-$] | 18 | 96 |
| 7 | [$HTBD^+$][$TFE^-$] | 7 | 95 |
| 8 | [$HTBD^+$][$TFE^-$] | 6 | 83 |
| 9 [c] | [$HTBD^+$][$TFE^-$] | 7 | 99 |
| 10 [d] | [$HTBD^+$][$TFE^-$] | 7 | 58 |
| 11 [e] | [$HTBD^+$][$TFE^-$] | 7 | 50 |
| 12 [f] | [$HTBD^+$][$TFE^-$] | 7 | – |

[a] Reagents and conditions: **1a** (1 mmol), PIL (6 mmol), $CO_2$ (balloon), 80 °C.
[b] Isolated yield.
[c] 100 °C.
[d] [$HTBD^+$][$TFE^-$] (4 mmol).
[e] [$HTBD^+$][$TFE^-$] (2 mmol).
[f] Room temperature.

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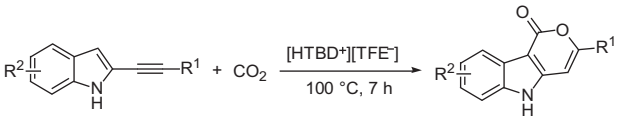
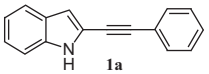
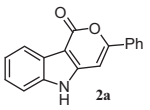
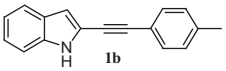
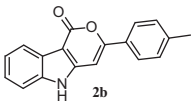
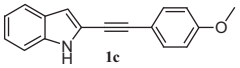
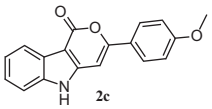
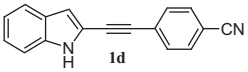
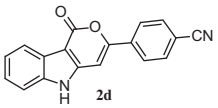
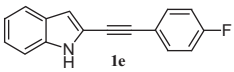
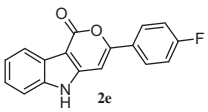
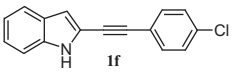
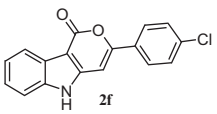
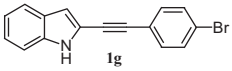
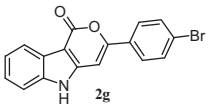
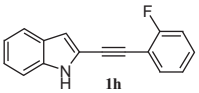
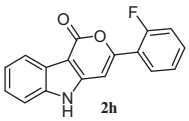
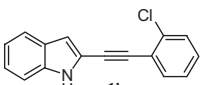
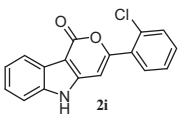
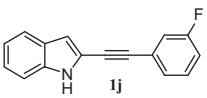
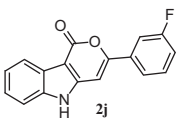
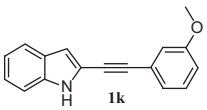
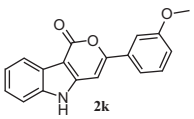
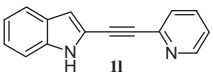
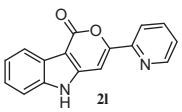
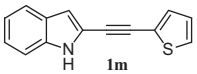
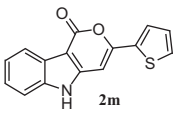
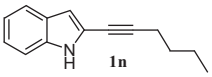
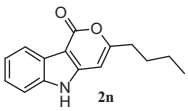
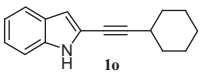
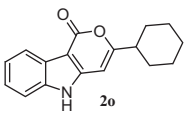
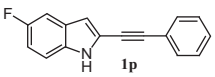
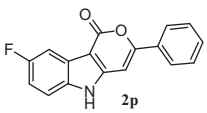
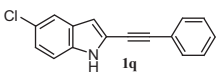
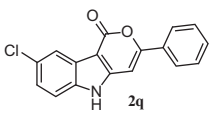
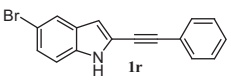
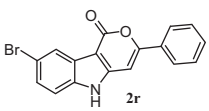
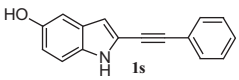
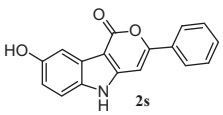
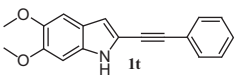
0040-4039/

**Table 2**
Scope of the aromatic 2-alkynyl indoles.[a]



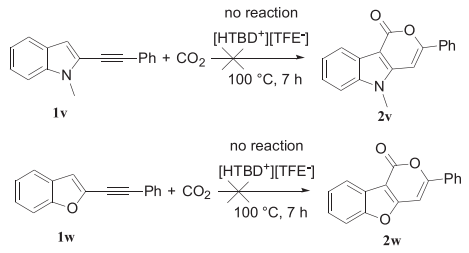

| Entry | Substrate | Product | Yield [%] [b] | Entry | Substrate | Product | Yield [%] [b] |
|---|---|---|---|---|---|---|---|
| 1 |  1a |  2a | 99 | 2 |  1b |  2b | 84 |
| 3 |  1c |  2c | 96 | 4 |  1d |  2d | 90 |
| 5 |  1e |  2e | 91 | 6 |  1f |  2f | 72 |
| 7 |  1g |  2g | 86 | 8 |  1h |  2h | 72 |
| 9 |  1i |  2i | 87 | 10 |  1j |  2j | 86 |
| 11 |  1k |  2k | 97 | 12 |  1l |  2l | 83 |
| 13 |  1m |  2m | 93 | 14 |  1n |  2n | 93 |
| 15 |  1o |  2o | 94 | 16 |  1p |  2p | 91 |
| 17 |  1q |  2q | 71 | 18 |  1r |  2r | 75 |
| 19 |  1s |  2s | 89 | 20 |  1t |  2t | 71 |
| 21 |  1u |  2u | 71 | | | | |

[a] Reagents and conditions: substrate **1** (1 mmol), [HTBD$^+$][TFE$^-$] (6 mmol), $CO_2$ (balloon), 100 °C, 7 h.
[b] Isolated yield.

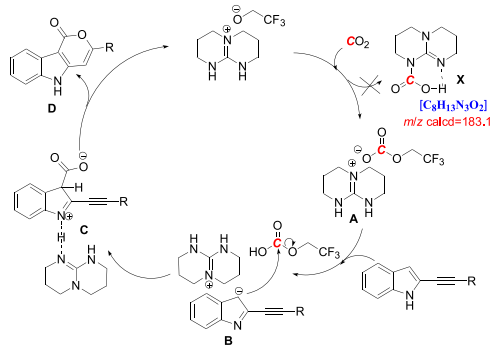
ous research regarding the preparation of various heterocycle-fused pyrimidine-2,4(1*H*,3*H*)-diones, PILs displayed superior performance for $CO_2$ capture and conversion under solvent-free conditions [13]. Thus, we postulated that pyrano[4,3-*b*]indol-1(5*H*)-ones could be obtained using $CO_2$ as a C1 resource under PILs-promoted conditions.

## Results and discussion

Initially, five PILs were synthesized according to literature procedures: [12] [HDBU$^+$][TFE$^-$], [HDBN$^+$][TFE$^-$], [HTBD$^+$][TFE$^-$], [HDBU$^+$][TFA$^-$], and [HDBU$^+$][Ac$^-$]. 2-Phenylethynyl-1*H*-indole **1a** was selected as a model substrate, and the reaction with $CO_2$




**Scheme 1.** Reaction of **1v** or **1w** with $CO_2$.




**Scheme 2.** Plausible reaction pathway.

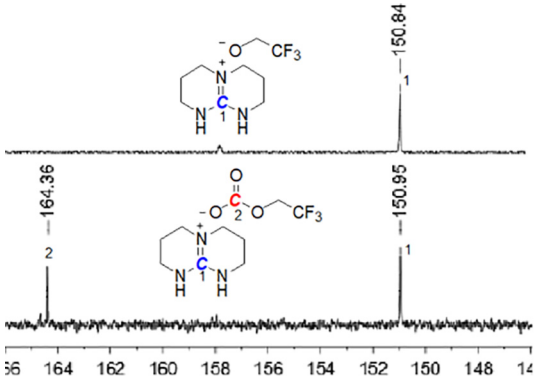



**Fig. 1.** $^{13}C$ NMR spectrum of [HTBD$^+$][TFE$^-$] and the intermediate derived from exposure of [HTBD$^+$][TFE$^-$] to $CO_2$.

was carried out in the absence and presence of the PILs, which acted as both the solvent and reaction promoter (Table 1). The reaction did not proceed in the absence of PILs (Entry 1). The PILs [HDBU$^+$][TFA$^-$] and [HDBU$^+$][Ac$^-$] afforded low yields of 3-phenyl-5*H*-pyrano[4,3-*b*]indol-1-one **2a** after 18 h (Entries 2, 3). However, when [HDBU$^+$][TFE$^-$] was used, **2a** was obtained in 64% yield (Entry 4), thus suggesting that the anion of the PILs affected the reactivity. Encouraged by these results, [HDBN$^+$][TFE$^-$] and [HTBD$^+$][TFE$^-$] which have the same anion as [HDBU$^+$][TFE$^-$] were tested, affording **2a** in 68% and 96% yield, respectively (Entries 5, 6). Furthermore, we found that **2a** was obtained in 95% yield after 7 h (Entry 7), but the yield decreased when the reaction time was reduced to 6 h (Entry 8). When the reaction was conducted at 100 °C for 7 h, the isolated yield was improved to 99% (Entry 9). However, the yield decreased significantly upon decreasing the amount of [HTBD$^+$][TFE$^-$] (Entries 10, 11). Finally, the [HTBD$^+$][TFE$^-$] promoted reaction was examined at room temperature, but only trace amounts of the product was obtained due to poor solubility (Entry 12).

With the optimal conditions in hand, we set out to explore the scope and limitations of the reaction using various alkynyl indoles derivatives (Table 2). Gratifyingly, substrates possessing either electron-donating or electron-withdrawing substituents on the phenyl ring readily reacted with $CO_2$ to give the corresponding pyrano[4,3-*b*]indol-1(5*H*)-ones **2a**-**g** (Entries 1–7). Moreover, substrates bearing *ortho*- and *meta*-positioned substituents on the phenyl ring were likewise tolerated, giving **2h**-**k** in good yields (Entries 8–11). Additionally, alkynyl indoles with heterocyclic substituents, such as pyridyl and thienyl, afforded **2l** and **2m** in 83% and 93% yield, respectively (Entries 12, 13). It was worth noting that aliphatic 2-alkynyl indoles were well tolerated, affording **2n** and **2o** in 93% and 94% yield, respectively (Entries 14, 15). The reaction was then extended to substrates containing substituted indole rings, and a range of pyrano[4,3-*b*]indol-1(5*H*)-ones **2p**-**u** were obtained in high yields (Entries 16–21). Notably, the incorporation of electron-withdrawing groups on the indole rings of these substrates improved the yields, while electron-donating groups gave reduced yields.

In previous studies, $CO_2$ was reported as being initially activated by TBD to form a zwitterionic adduct **X** (Scheme 2) [12,14]. Nevertheless, in this study, the peak at 183.1 *m*/*z* corresponding to **X** was not found by MS analysis of the mixture of [HTBD$^+$][TFE$^-$] with $CO_2$ at 100 °C for 7 h, which indicated that **X** was not the key intermediate of the reaction. However, a new $^{13}C$ NMR signal peak at $\delta$ = 164.36 ppm appeared, which may belong to the carbonyl carbon atom of the carbonate, suggesting $CO_2$ was activated by the anion [TFE$^-$] (Fig. 1). In the FTIR spectrum a new band appeared at 1637 cm$^{-1}$, which was assigned to the stretching vibration of the C=O bond of the carbonate, thus confirming its formation and the $^{13}C$ NMR data (ESI, Fig. S2).

On the other hand, when the reaction of **1v** or **1w** with $CO_2$ was carried out under the optimized reaction conditions, the desired product was not obtained. It can therefore be speculated that there was an interaction between the indole N—H and TBD (Scheme 1).

On the basis of these experimental results, a plausible mechanism is presented in Scheme 2. In [HTBD$^+$][TFE$^-$], $CO_2$ was activated by the anion [TFE$^-$] to form carbonate intermediate **A**. Then, the C—C bond is formed by nucleophilic attack of the indole C3-position onto the carbon atom of **A** to afford intermediate **C**. Finally, re-aromatization *via* deprotonation and cyclization produces the desired pyrano[4,3-*b*]indol-1(5*H*)-ones **D** and regenerates [HTBD$^+$][TFE$^-$].

## Conclusion

In summary, a new and highly efficient, solvent-free system was developed for the preparation of various pyrano[4,3-*b*]indol-1(5*H*)-ones using [HTBD$^+$][TFE$^-$] as a promoter and $CO_2$ as a C1 resource. The advantages of the present protocol are moderate to excellent yields, broad substrate scope and easy workup.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152449.

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