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Traceless Synthesis of Hydantoin Fused Tetrahydro-β-carboline on Ionic Liquid Support in Green Media

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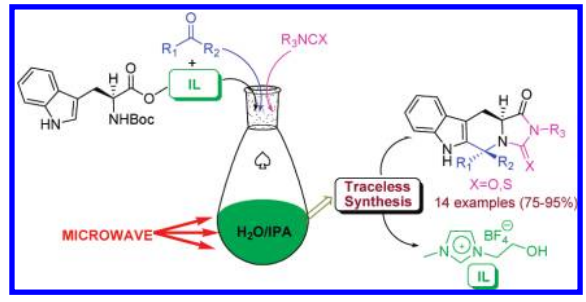
ABSTRACT



A novel ionic liquid (IL) supported, green synthetic protocol has been developed toward the synthesis of oxo and thio hydantoin analogues tethered with tetrahydro-β-carboline by the use of focused microwave irradiation. IL-bound tryptophan underwent a Pictet−Spengler reaction with various carbonyl compounds to generate the IL- immobilized tetrahydro-β-carbolines in aqueous isopropanol media. Subsequent reaction of substituted tetrahydro-β-carboline derivatives with various isocyanates and isothiocyanate provided a three-dimensional combinatorial library in a traceless fashion.

Tetrahydro-β-carbolines (**1a**), a key constituent of most naturally occurring indole alkaloids, have received considerable attention by medicinal chemists owing to their important bioproperties including antiaggregation, in vitro trypanocidal activity, antimalarial, and anticonvulsant activity.[1] Recently, it has been found that hydantoin and thio hydantoin derivatives (**1b**) also possess several pharmacological properties including dual action for anticonvulsant and antimuscarinic activity, insulinotropic properties, and antifungal activity.[2] However, the ring system **2** as the conceptual derivation of a new scaffold, which represents the amalgamation of two important pharmacophores, is much less known (Figure 1). The generation of tetracyclic skeletons with tetrahydro-β-carboline and hydantoin thus has a substantial intellectual appeal due to their resemblance to drug-like molecules. This type of compound has been documented for the inhibition of cGMP-phosphodiesterase (**2a**, **2b**), a chemical messenger in the body that activates cGMP kinase, and as a novel antimitotic agent (**2c**) and a novel Eg5 inhibitor (**2d**).[3,6] Because of their diverse array of biological activities, these

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novel drug-like molecules are interesting to explore in early screening (Figure 2). The advent of combinatorial chemistry for the rapid generation of numerous collections of small molecules has greatly helped in the design and choice of lead structures in the drug discovery process.[7]

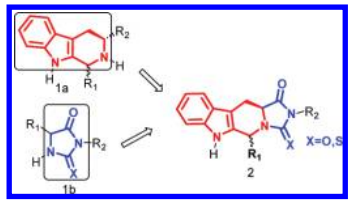

Figure 1. Conceptual derivation of a new scaffold.

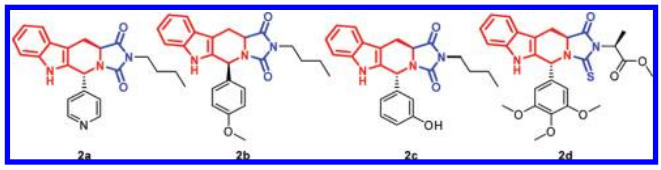

Figure 2. Representative examples of biologically active hydantoin analogues tethered with tetrahydro-β-carbolines.

Ionic liquids are used as ecofriendly solvents as well as catalysts in organic synthesis because of their unique chemical and physical properties.[8,9] On the basis of the choice of cations and anions, ionic liquids can be reused, and the solubility can be adjusted readily for phase separation from organic as well as aqueous media.[10] When the hydroxyl group is on the cation of an ionic liquid, these ionic liquid have been used as synthetic equivalents of classical low molecular weight soluble polymer supports in combinatorial synthesis of structurally diverse small molecules. There are some literature reports regarding the employment of alcohol-functionalized ILPs as a soluble support in liquid-phase combinatorial synthesis.[11] Significant interest has recently been garnered in the development of organic reactions in aqueous medium.[12,14] Water, a profuse and non-toxic solvent, could be a greener option because of its nonflammable, nonhazardous properties. Due to numerous favorable properties, isopropyl alcohol (IPA) was preferred as the cosolvent by lessening the polarity of the reaction medium and thus enhancing the solubility of organic substrates. It is cheap, safe, and easily biodegradable via the acetone pathway and a predominantly favorable organic cosolvent.[15] Higher yields and shorter reaction times are the two features that make microwave irradiation superior to meet the increased demands of high-throughput synthesis.[16] Ionic liquid support in aqueous systems increases the power of microwave irradiation and makes the reaction sequences more attractive in terms of aqueous chemistry perspective. Herein, we describe a simple and efficient synthetic protocol for the fast synthesis of substituted indole alkaloids under microwave irradiation in aqueous IPA media.

To attain the target compound on ionic liquid support, the most essential reaction involves the coupling of Boc-protected L-tryptophan **4** to hydroxyl ethyl methyl imidazolium tetrafluoroborate **3c**[17] (Scheme 1). For comparison purposes, this coupling reaction was carried out under a set of different conditions, involving (i) room temperature for 48 h; (ii) thermal heating at refluxing temperature for 12 h; and (iii) microwave irradiation in a closed vessel system under pressure (80 °C, 2 bar) which reduced the time to 12 min. After completion of the reaction, the dicyclohexyl urea (DCU) was filtered off and IL-conjugates **5** were precipitated with addition of cold ether, which was then filtered to obtain the IL-conjugates **5**. Unlike other solid supports, the main advantage of using ionic liquid soluble support was its direct monitoring capacity by standard analytical technique such as ^{1}H and ^{13}C NMR and mass spectroscopy. For the first time, we have demonstrated here that the product conversion was quantitative, monitored by regular proton NMR spectroscopy in each intermediate step with an attached IL-tag.

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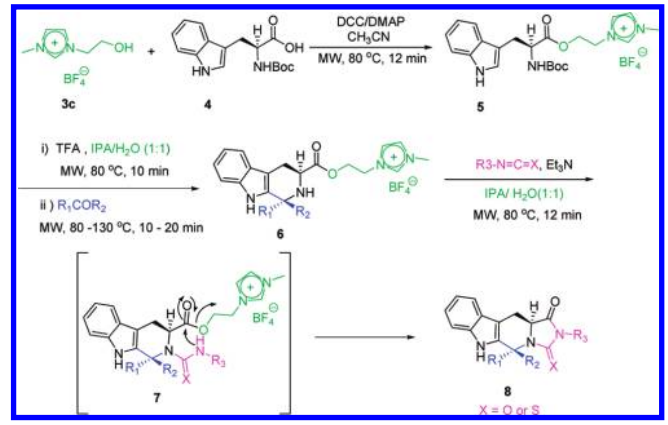
It has been found that protons of the -CH_2CH_2OH group of the free IL appeared at 3.94 ppm in proton NMR spectra A (Figure 3), whereas the same protons were shifted to 4.48 ppm after attachment to the Boc-protected L-tryptophan **4** as a result of the electron-withdrawing nature of the ester linkage to the IL-tag in spectra B. The generation of β-carbolines by [5 + 1] approach could be realized by the NHBoc deprotection and subsequent Pictet−Spengler cyclization with carbonyl compounds in aqueous acidic medium.[18,19] It is noteworthy that NHBoc deprotection and subsequent cyclization were carried out in one pot manner using 20% TFA in H_2O−IPA (1:1) under microwave irradiation (80 °C, 2 bar) for 20−30 min. The NHBoc deprotection was achieved in 10 min under microwave irradiation, which was further confirmed from the disappearance of *tert*-butyl group around 1.44 ppm in spectra C. The in situ generated amine was subsequently reacted with various carbonyl compounds in the same reaction media to generate imines that subsequently underwent intramolecular cyclization to achieve the tetrahydro-β-carbolines **6** with the IL-tag remaining intact. When ketones were used in the Pictet−Spengler cyclization, more harsh reaction conditions (130 °C, 9 bar, 20 min) were required to complete cyclization owing to the deactivating nature of the ketone functionality. Moreover, the same set of reactions was finished in 18 h under refluxing condition. After the reaction was finished, the water and IPA were removed from the reaction mixtures under reduced pressure, and the residue remaining was redissolved in CH_3CN, further precipitated with ether, and filtered through a fritted funnel to remove unreacted carbonyl compounds and other side products to obtain the IL-conjugates **6**.

The formation of the IL-immobilized tetrahydro-β-carboline was evident from ^{1}H NMR spectra, which indicates the appearance of a NH proton of β-carboline moiety at 10.5 ppm and two methyl group absorbances manifested at 2.0 ppm in spectra D. The formation of *cis* and *trans* diastereomers in various ratios of IL-bound β-carboline **6** is determined through proton NMR analysis.

To create the second diversity point in target structures, the terminal hydantoin moiety is constructed across IL-immobilized β-carbolines by the reaction with various isocyanates and thioisocyanates under microwave irradiation to form urea intermediate **7**. Simultaneous intramolecular cyclization of IL-conjugated urea **7** in water/IPA cosolvents followed by cleavage of the ionic liquid support led to a traceless synthesis of tetracyclic scaffold **8** in high yield and high purity. The cyclization of the hydantoin ring and subsequent traceless cleavage of the ionic liquid support was performed in one step under mild basic conditions in triethylamine. The reaction was eventually completed in 12 min (80 °C, 2 bar) as compared to requiring 10 h in refluxing conditions. Reaction progress was directly monitored by TLC, which indicated the complete release of the desired compound **8** from the IL support to confirm the traceless nature of the reaction. The solvents were removed, and the residue remaining was redissolved in CH_3CN and further purified by precipitation in ether to obtain the targeted compounds **8**. The formation was achieved from proton NMR spectra, which clearly indicated the nullifying of the signal at 10.5 ppm and the disappearance of the characteristic signal of the IL-tag at 4.8−4.7 ppm (-CH_2CH_2-). Moreover, all intermediates of IL-supported products could be confirmed

Scheme 1. Ionic Liquid Supported Synthesis of Hydantoin Fused Tetrahydro-β-carbolines



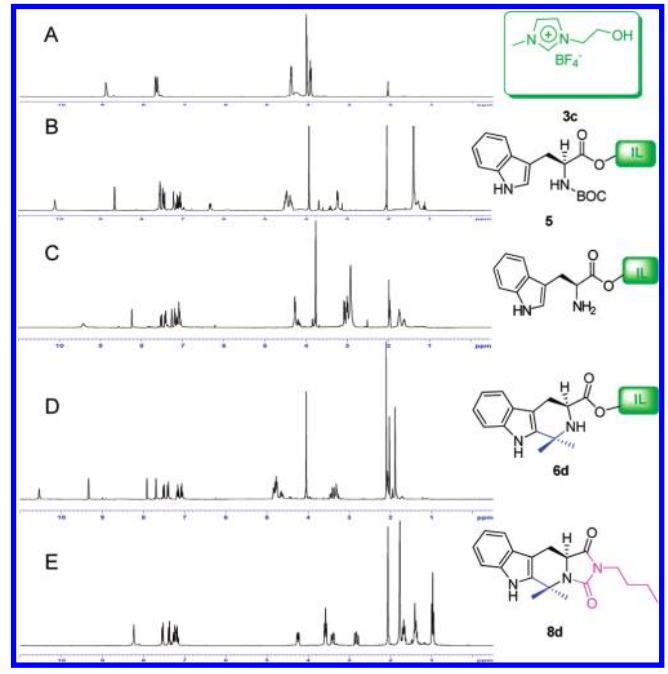


Figure 3. Stepwise monitoring toward the formation of tetrahydro-β-carboline fused oxo and thio hydantoin analogues on ionic liquid support.

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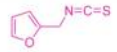
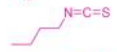
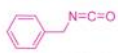
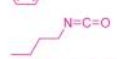
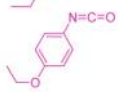
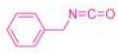
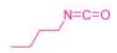
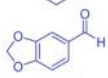
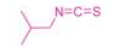
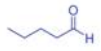
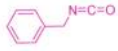
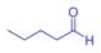
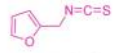
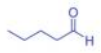
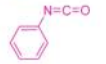
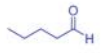
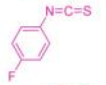
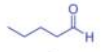
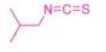
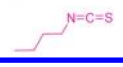
with mass spectra (MS). The analytical data including crude yield and purity are reported in Table 1.

Table 1. Microwave-Assisted, IL-Supported Synthesis of Tetrahydro-β-carboline Hydantoin and Thio Hydantoins (**8a**−**8n**)

entry	R_1COR_2	R_3NCX	LRMS[a]	isolated yield[b] (%)	crude purity[c] (%)
8a			366	82	94
8b			342	80	76
8c			359	82	81
8d			326	85	89
8e			430	76	79
8f			400	95	98
8g			366	90	86
8h			433	77[d]	92
8i			388	75[d]	77
8j			394	82[d]	72
8k			374	80[d]	78
8l			408	83[d]	73
8m			370	83[d]	87
8n			368	75	79

[a] LRMS were detected with ESI ionization source. [b] Yields are based on loading of ionic liquid soluble support. [c] Determined by HPLC analysis at UV 254 nm of the crude product. [d] Isolated as only the *trans* isomer.

The predominantly *trans* stereochemistry of tetrahydro-β-carboline hydantoins **8h**−**8m** is based on spectral data through comparison with earlier works by Cook's research group.[20] To further confirm the obtained results, we undertook the 1D NOE analysis of compound **8l**, which showed that there is no correlation between C_2-Ha and C_{12}-Hb protons, which demonstrates clearly the *trans* stereochemistry (Figure 4). Moreover, the irradiation of Hf caused the enhancement of He and Hb by 9.00% and 2.03% respectively which further enhanced the Hd by 2.70%. Similarly, the irradiation of Hd caused the enhancement of Ha and Hc by 4.86% and 23.48%. In the same way, the irradiation of He caused the enhancement of Hb and Hf signals by 1.81 and 12.4% respectively. We also obtained the signal enhancement of Hc by 3.18% followed by irradiation of Ha.

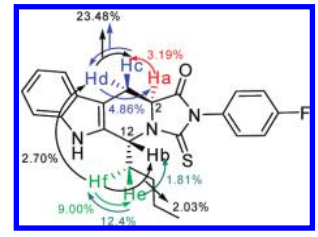


Figure 4. Some important NOE interactions in the **8l** *trans* isomer.

In this study, an efficient and green methodology for the gram-scale synthesis of pharmacologically interesting trisubstituted indole alkaloids through the use of commercially available building blocks has been demonstrated. Final libraries are usually obtained in high purity and yield just by simple precipitation and washings of each IL-attached intermediate with minimum column purification. In contrast to the solid-phase synthesis, the reaction progress of IL-bound support was successfully monitored by a conventional analytical technique without the "cleave-&-analyze" method. Moreover, the aqueous chemistry provides a practical prospect for the sustainable development of future science and technologies in drug discovery.

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