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Revisiting the Urech Synthesis of Hydantoins: Direct Access to Enantiopure 1,5-Substituted Hydantoins Using Cyanobenziodoxolone

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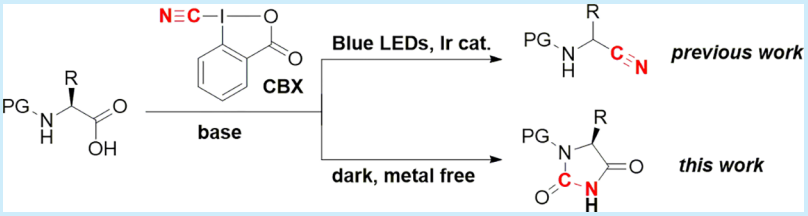
Supporting Information



ABSTRACT: A method for the synthesis of enantiopure 1,5-substituted hydantoins was developed using a hypervalent iodine cyanation reagent (cyanobenziodoxolone, CBX) as a source of electrophilic carbon. Starting from inexpensive commercially available enantiopure protected amino acids, the method allowed the synthesis of various hydantoins without epimerization. Formation of hydantoins from dipeptides was also possible, but partial epimerization was observed in this case. This synthetic strategy is user friendly as CBX is a bench-stable easy-to-handle crystalline reagent and avoids conventional multistep protocols, thus allowing the facile synthesis of a library of chiral hydantoins.

Hydantoins (2,4-imidazolidinediones) are important heterocycles in organic chemistry. The most simple hydantoin has been isolated in 1861 by Adolf von Bayer through reduction of allantoin (**1**) (Figure 1).[1] Since then,

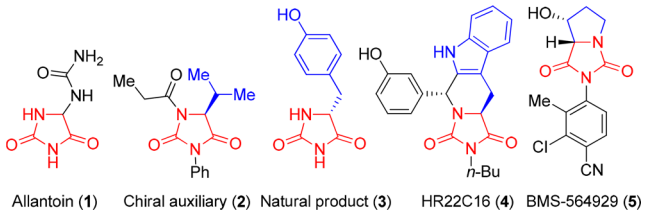


Figure 1. Important chiral 5-substituted hydantoins derived from α-amino acids.

tremendous efforts have been invested to synthesize and study this important family of five-membered heterocycles.[2] Among them, chiral 5-substituted hydantoins are broadly used as chiral ligands[3] or auxiliaries, such as hydantoin **2** for enolate functionalization.[4] Many of them are bioactive compounds, either natural, such as **3** isolated from the Red Sea sponge *Hemimycale arabica*,[5] or synthetic, such as the clinical candidates HR22C16 (**4**) (antimitotic)[6] and BMS-564929 (**5**) (orally active and selective androgen receptor modulator).[7] Compounds **1**−**5** are all derivatives of natural amino acids.

The synthesis of hydantoins is well-established.[2] Classical methods are the Bucherer−Bergs,[8] the Biltz,[9] the Read,[10] and the Urech[11] syntheses. The two firsts are based on carbonyl or dicarbonyl condensation, affording racemic hydantoins, whereas the Read and Urech's conditions involve a two-step enantioconservative condensation−cyclization of amino acid derivatives in the presence of isocyanates under harsh conditions (Scheme 1). These isocyanates are often not commercially available, and their synthesis requires extra steps with often toxic reagents. Since then, efforts toward more environmental and user-friendly approaches have been made, especially based on amino acid derivatives.[12] Using amino amides, Cuny and co-workers were able to obtain enantiopure hydantoins in the presence of triphosgene.[13] Amino amides were also used by Pan and co-workers using triflic anhydride,[14] while Fang and co-workers described a method using amino acid ureas under similar conditions of the Read/Urech cyclization step.[15] The reaction of α-amino methyl ester hydrochlorides with carbamates to produce substituted hydantoins was recently developed by Gill and co-workers.[16] However, these syntheses still required highly reactive reagents and prefunctionalization of the amino acids. Earlier this year, Gong and co-workers developed an elegant asymmetric synthesis of 5-substituted hydantoins using chiral Lewis base and copper cooperative catalysis.[17]

Recently, our group has been interested in transformations of amino acids using hypervalent iodine reagents.[18] We reported a room-temperature decarboxylative cyanation of carboxylic acids using photoredox catalysis and cyanobenzio-

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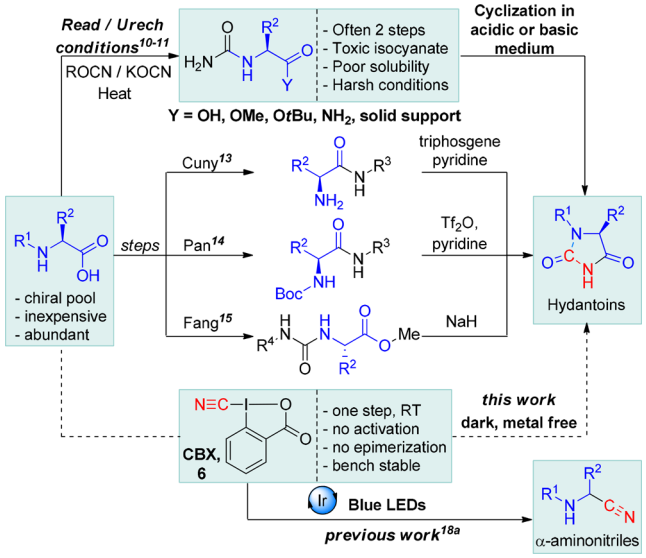
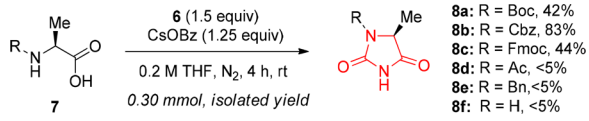
Scheme 1. Reported Syntheses of Chiral Hydantoins Starting from the Chiral Pool and Our Previous Work on Decarboxylative Cyanation of Amino Acids



doxolone (CBX, **6**, Scheme 1).[19] The synthesis of CBX (**6**) had been first described by Zhdankin, who developed the cyanation of dialkylanilines.[20] Since then, several electrophilic cyanations using CBX reagents have been described.[21,22] Herein, we report a new method for the one-step synthesis of 1,5-substituted enantiopure hydantoins, starting from chiral protected amino acids and CBX (**6**).

During our previous work on decarboxylative cyanation, screening of different amino acids was performed, but the reaction was not always efficient. In fact, the desired transformation did not occur for tryptophan and cysteine. Instead, a hydantoin was formed, as confirmed by X-ray analysis.[23] A control experiment on Boc-protected L-alanine **7a** in the absence of light and photocatalyst led also to the formation of hydantoin **8a** (Scheme 2, 42% in the dark with

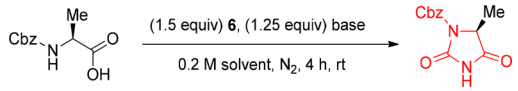
Scheme 2. Screening of N-Substituents for the Synthesis of Hydantoins Using CBX (6)



1.25 equiv of CsObz). This background reaction had not been observed before, as the photoredox-mediated process was faster. Based on this unexpected result, different protecting groups on the nitrogen were first examined. Carbamate protecting groups were successful (products **8a**–**c**), and the best results were obtained for Cbz (**8c**). In contrast, acetyl- and benzyl-protected as well as unprotected amino acids **7** could not be used.

We continued our investigation with optimization of the synthesis of hydantoin **8b** from L-Cbz-Ala (**7b**) (Table 1). Even though conversion, yield, and retention of enantiomeric excess were excellent (95% conversion, 83% isolated yield, 95% ee after 4 h, entry 1), we had solubility issues leading to lack of reproducibility. Two chromatography columns were required to separate the desired hydantoin from 2-iodobenzoic acid and benzoic acid. Both CBX and CsOBz are poorly soluble in

Table 1. Optimization of the Synthesis of Hydantoin 8b[a]



entry	base	solvent	concentration (M)	NMR yield (%)
1	CsOBz	THF	0.2	>95, 83[b]
2	CsOBz	dioxane	0.2	60
3	CsOBz	EtOAc	0.2	20
4	CsOBz	DCM	0.2	45
5	CsOBz	DMF	0.2	55
6	NaOBz	THF	0.2	50
7	KOBz	THF	0.2	60
8	Cs_2CO_3	THF	0.2	<10
9	CsOAc	THF	0.2	<10
10	pyridine	THF	0.2	60
11	Et_3N	THF	0.2	60
12	DMAP	THF	0.2	>95, 75[b]
13	DMAP	THF	0.05	90
14	DMAP	THF	0.1	90
15	DMAP	THF	0.3	80

[a]Reaction conditions: **7b** (67 mg, 0.30 mmol, 1 equiv), CBX **6** (123 mg, 0.450 mmol, 1.5 equiv), and base (0.375 mmol, 1.25 equiv) in the corresponding solvent (1.5 mL) for 4 h at rt under N_2. The NMR yield of **8b** is given. [b]Isolated yield (%) after two-column chromatography.

THF, thus making a white slurry. Therefore, different solvents were tested to improve the solubility of the reaction mixture. Dioxane and ethyl acetate (entries 2 and 3) did not allow us to enhance the solubility, while a slightly better solubility was observed with DCM and DMF (entries 4 and 5), albeit the yields obtained were lower than in THF. We then decided to screen the base. Neither sodium nor potassium benzoate was superior to cesium benzoate (50 and 60% yield, entries 6 and 7). Surprisingly cesium carbonate and cesium acetate did not promote the formation of hydantoin (entries 8 and 9). Organic bases such as pyridine and triethylamine gave moderate yields (60%, entries 10 and 11), while DMAP allowed a clean conversion, better reproducibility, and excellent isolated yield (entry 12). When lowering concentration in THF to 0.05 and 0.1 M (entries 13 and 14), the yield was slightly lower than at 0.2 M. The yield dropped to 80% when increasing the concentration to 0.3 M (entry 15). Screening of CBX derivatives and other cyanation reagents under optimized conditions has also been performed (results not shown, see SI). However, none of the examined reagents allowed us to improve neither reactivity nor purification efficiency. Control experiments were performed with other cyanation reagents such as BrCN, ICN, and 1-cyano-4-dimethylaminopyridinium tetrafluoroborate (CDAP) instead of CBX (**6**). Using BrCN and ICN, hydantoin formation could be observed, albeit in lower yield (35% NMR yield compared to quantitative yield with CBX), while CDAP gave much lower yield (<20%).

We then studied the scope of amino acids, running the reaction overnight at room temperature to ensure complete conversion for all substrates (Scheme 3). Under these conditions, Cbz-protected L-alanine (**7b**) is fully converted to hydantoin **8b** with 85% isolated yield and 96% ee. Boc- and Fmoc-protected hydantoins **8a** and **8c** were obtained in better yields. 30% NMR yield could be observed for acetyl-protected hydantoin **8d** and the benzyl-protected hydantoin **8e**. Less

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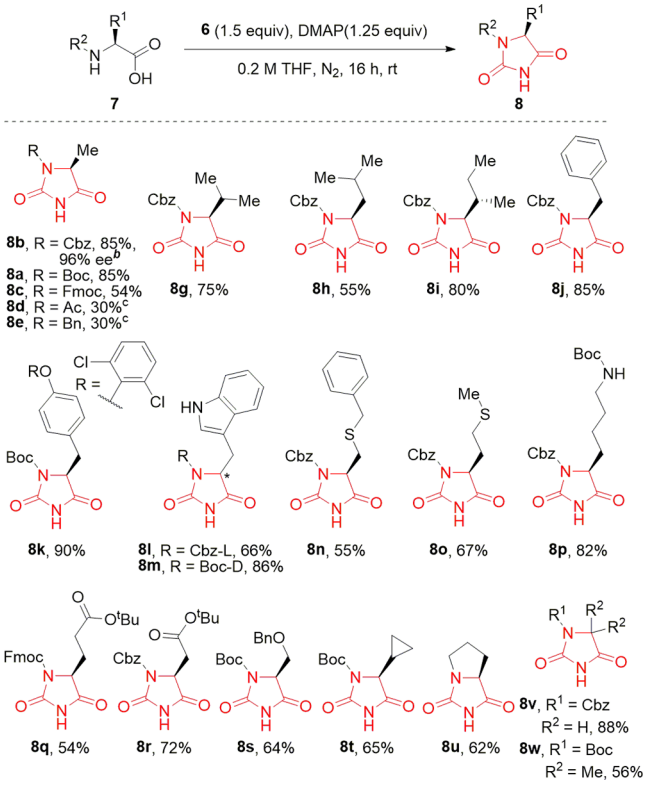
Scheme 3. Scope of Amino Acids[a]

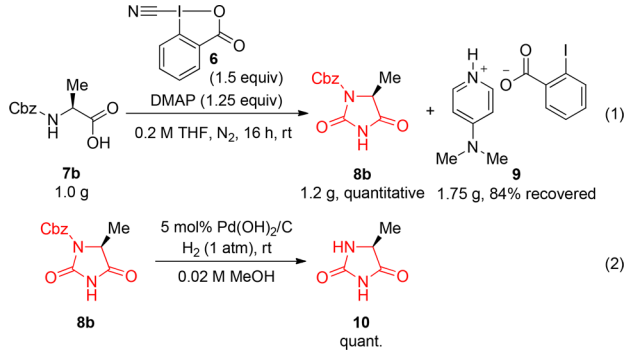


[a]Reaction conditions: **7** (0.15 mmol, 1.0 equiv), CBX (**6**) (61 mg, 0.23 mmol, 1.5 equiv), and DMAP (23 mg, 0.19 mmol, 1.25 equiv) in THF (0.75 mL) for 16 h at rt under N_2. Isolated yield of **8** after purification by preparative TLC (heptane/Et_2O) is given. [b]ee was measured by chiral HPLC. [c]NMR yield.

than 5% NMR yield was observed when using benzamide as a protecting group (result not shown). Amino acids bearing apolar side chains (valine, leucine, *iso*-leucine, and phenylalanine) gave the corresponding hydantoins in good to excellent yields (55−85%, **8g−j**). Tyrosine is suitable for this transformation, but protection of the phenol moiety is required for efficient purification. Protected hydantoin **8k** was further crystallized and allowed unambiguous confirmation of the hydantoin core, with full retention of the stereochemistry of the amino acid.[23] Both L-Cbz-tryptophan- and D-Boc-tryptophan-based hydantoins **8l** and **8m** were obtained in good yields. L-Methionin, L-S(Bn)-cysteine, L-N(Boc)-lysine, L-O(*t*Bu)-glutamatic acid, L-O(*t*Bu)-asparagic acid, and L-O(Bn)-serine were successfully converted to the corresponding hydantoins **8n−s** in good to excellent yields (54−82%). It is also possible to use unnatural amino acids. For example, hydantoin **8t** with a cyclopropyl side chain was obtained in 65% yield. Surprisingly, although the nitrogen of L-proline is electron-rich, 62% of bicyclic hydantoin **8u** was isolated. Hydantoin **8v** was obtained from glycine in 88% yield. Hydantoin **8v** can be condensed with benzaldehyde derivatives to afford bioactive methylenehydantoins.[5,24] Sterically hindered hydantoin **8w** was obtained in 56% yield. Side chain unprotected asparagine, glutamine, threonine, histidine, and cysteine were unsuccessful.

To highlight the efficiency of this transformation, a gram-scale synthesis was undertaken, and 1.2 g of optically pure hydantoin **8b** was obtained (Scheme 4, eq 1), along with the recovery of 1.75 g of the precipitated salt **9**. Cbz deprotection of **8b** to give **10** was quantitative using 5 mol % of $Pd(OH)_2/C$ in methanol (eq 2).

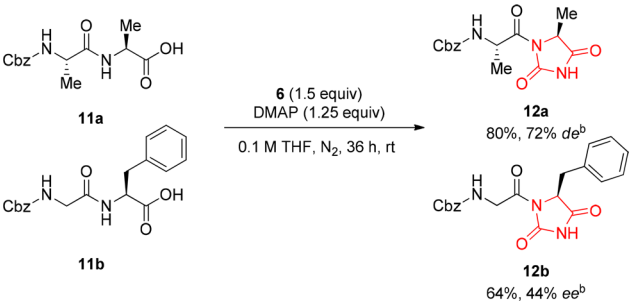
Scheme 4. Gram-Scale Synthesis and Cbz Deprotection of Hydantoin 8b[a]



[a]Reaction conditions: (1) **7b** (1.0 g, 4.5 mmol, 1.0 equiv), CBX (**6**) (1.84 g, 6.72 mmol, 1.5 equiv), and DMAP (0.68 g, 5.6 mmol, 1.25 equiv) for 16 h at rt. Isolated yield of **8b** after filtration and column chromatography. (2) **8b** (30 mg, 0.12 mmol, 1.00 equiv) and $Pd(OH)_2/C$ (6.1 μmol, 5 mol %) in MeOH (6.0 mL) for 4 h at rt under H_2. Isolated yield of **10** after filtration over HPLC filter.

We then wondered if the reaction could be applied on peptides to access more complex hydantoins. Indeed, the formation of the hydantoin was feasible on Cbz-protected Ala-Ala-OH and Gly-Phe-OH dipeptides **11a** and **11b** (Scheme 5),

Scheme 5. C-Terminal Hydantoin Formation on Dipeptides 11[a]



[a]Reaction conditions: **11** (0.15 mmol, 1.0 equiv), CBX (**6**) (61 mg, 0.23 mmol, 1.5 equiv), and DMAP (23 mg, 0.19 mmol, 1.25 equiv) in THF (0.75 mL) for 16 h at rt under N_2. Isolated yield of **12** after purification by preparative TLC (heptane/Et_2O) is given. [b]Measured by chiral HPLC.

even though the reaction was slower. After 36 h at room temperature, hydantoins **12a** and **12b** were obtained in 80% and 64% isolated yield, respectively. In contrast to amino acids, some epimerization occurred, leading to a decrease of diastereomeric/enantiomeric excess (**12a**, 72% de; **12b**, 44% ee). This may be due to the prolonged reaction time under basic conditions.

A speculative mechanism is outlined in Scheme 6. We envisioned that deprotonation of amino acid **7** by DMAP will lead to carboxylate **7′**. Cyanation with CBX **6** gives then mixed anhydride intermediate **I** and salt **9**, which was indeed isolated at the end of the reaction. Cyclization of intermediate **I**,

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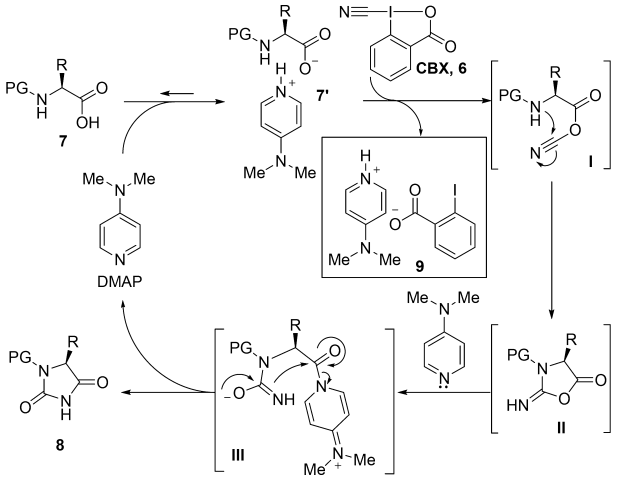
Scheme 6. Speculative Mechanism for Hydantoin Formation



affording the corresponding 2-iminooxazolidin-5-one **II**, appears highly probable.

Subsequent rearrangement of **II** to more stable hydantoin **8** may be accelerated by DMAP as a nucleophilic catalyst, via intermediate **III**. A possible alternative inspired from Urech synthesis is a nucleophilic attack of DMAP on the activated carbonyl of **I** releasing in situ a cyanate anion, which after condensation on the amine would also give intermediate **III**. Concerning transfer of the cyanide group, several pathways can be proposed (see SI details). Based on our previous work on thiocyanation with CBX,[22b] a concerted mechanism via a three-atom transition state could be considered, but a stepwise process cannot be excluded. Mechanisms involving a single electron transfer and subsequent formation of radical intermediates also constitute an alternative when considering the strong oxidizing properties of hypervalent iodine reagents.[19,25]

In conclusion, we have developed an efficient and practical method for the synthesis of 1,5-substituted enantiopure hydantoins. Starting from chiral amino acids, the reaction proceeds at room temperature, using cyanobenziodoxolone (CBX, **6**) and DMAP. A broad range of hydantoins could be synthesized without epimerization starting from protected amino acids, whereas partial epimerization was observed in the case of dipeptides. The method is expected to be highly useful in synthetic and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03843.

Experimental procedures and analytical data for all new compounds. (PDF)

Accession Codes

CCDC 1869712 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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