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Optimized synthesis of tetrahydroisoquinoline-hydantoins

Julie Charton,* Amaury Cazenave Gassiot, Patricia Melnyk, Sophie Girault-Mizzi and Christian Sergheraert

UMR CNRS 8525, Université de Lille II, Institut de Biologie et Institut Pasteur de Lille, 1 rue du Professeur Calmette, B.P. 447, 59021 Lille cedex, France

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Abstract—Several methods have been developed and compared for the solution synthesis of tetrahydroisoquinoline-hydantoin (Tic-hydantoin) derivatives. Starting materials were Tic-OH and amines readily available from commercial sources. The best yields were observed when the imidazolidine-2,4-dione ring was synthesized in two steps: (1) reaction of Tic-OH with the appropriate amine and (2) cyclization with 1,1′-carbonyldiimidazole.

1. Introduction

One of the challenges of medicinal chemistry is the enhancement of the affinity of a given ligand for its target. A possible solution resides in decreasing its degrees of freedom and thereby reducing the entropy cost. Another difficult task is the promotion of structural diversity attached to such a rigidified molecule. Imidazolidine-2,4-diones, or hydantoins **1** (Fig. 1), common five-membered rings containing a reactive urea functionality, represent a good platform to apply this concept. This heterocycle is present in a wide range of biologically active compounds including antiarrhythmics, anticonvulsivant, antitumor, and anxiolytic agents.[1–5]

With the aim of combining bulky pharmacophoric moieties and hydantoins, we focused our efforts on compounds with the following structure **2** (Fig. 2). Indeed, the tetrahydroisoquinoline ring (Tic) was selected after screening different combinatorial libraries frequently containing such molecular structures.[6,7]

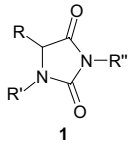

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Figure 1. Trisubstituted hydantoins **1**.

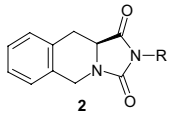

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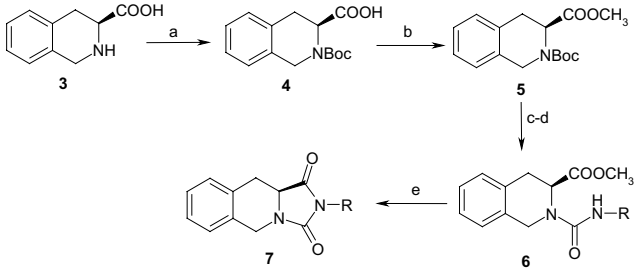
Figure 2. Tetrahydroisoquinoline-hydantoin derivatives **2**.

We have previously described a method for preparing Tic-hydantoins, which were inaccessible by solid phase synthesis under cyclization/cleavage conditions.[8]

Compounds were synthesized according to procedure described in Scheme 1, starting from (*S*)-(−)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **3** (L-Tic-OH).



Scheme 1. Reagents and conditions: (a) Boc_2O 1.1 equiv, NaOH 1 M 1.1 equiv, dioxane, rt, 12 h, 98%; (b) Cs_2CO_3 1 M 0.5 equiv, MeOH, rt, 10 min, then CH_3I 1.1 equiv, DMF, rt, 12 h, 98%; (c) TFA/DCM 1:1, rt, 1 h, then DIEA 4.5 equiv, DCM, rt, 15 min, 100%; (d) R-NCO 2.5 equiv, DCM, rt, 12 h; (e) NaOH 1.1 equiv, MeOH or DIEA, 1.1 equiv, DCM, rt, 1–24 h.

* Corresponding author. Tel.: +33 3 20 87 12 20; fax: +33 3 20 87 12 33; e-mail: julie.charton@ibl.fr

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For reasons of reactivity and solubility, two protection steps were necessary before reaction with the appropriate isocyanate. A final treatment with NaOH/MeOH or DIEA/DCM solution allowed to achieve cyclization as expected. This method was suitable for aliphatic and aromatic isocyanates, which were both tested.

However it remained limited in terms of diversity because a few isocyanates are commercially available and their synthesis is not always convenient.

2. Chemistry

Therefore, the use of other reagents leading to hydantoin cyclization was considered (Fig. 3). In particular, we investigated the use of 1,1′-carbonyldiimidazole (CDI) as a cyclizing agent. Three complementary strategies were designed around this reagent. They were applied to the synthesis of compounds of biological interest.

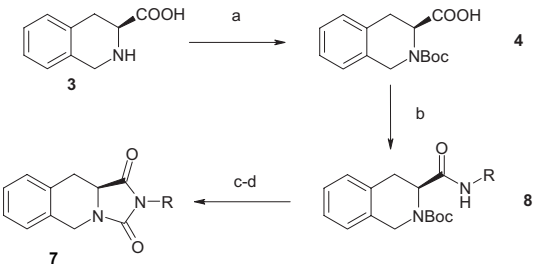
2.1. Strategy 1

Boc-protected L-Tic-OH **3** was coupled with a variety of amines using different coupling reagents (DCC, PyBroP, HOBt/EDCI). HOBt/EDCI activation using DIEA as a base was retained due to the good solubility of by-products in the aqueous phase.[9] After deprotection of the secondary amino group using TFA/DCM, the crude product was dissolved in THF and excess DIEA (4.5 equiv). CDI was added to yield the hydantoins **7** (Scheme 2).[10–12]

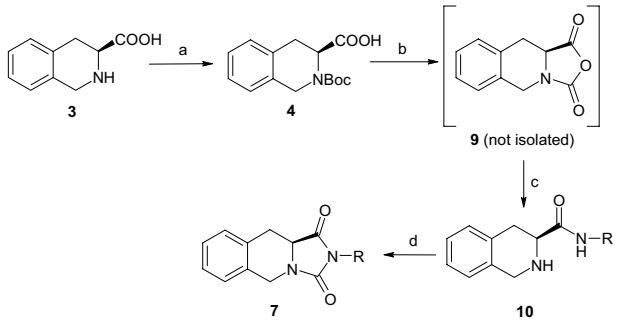
2.2. Strategy 2

This approach uses the α-amino acid *N*-carboxyanhydride of L-Tic-OH (10,10a-dihydro-5*H*-oxazolo-[3,4-*b*]isoquinoline-1,3-dione **9**),[13] which can be directly submitted to a coupling reaction with amines allowing the direct synthesis of compounds **10**. The hydantoins **7** were then synthesized using the conditions described above (Scheme 3).[14]

Unlike the first strategy, this approach eliminates the extra Boc-deprotection step and the use of coupling agent.



Scheme 2. Reagents and conditions: (a) Boc_2O 1.1 equiv, NaOH 1 M 1.1 equiv, dioxane, rt, 12 h, 98%; (b) R-NH_2 1.2 equiv, HOBt 1.1 equiv, EDCI 1.1 equiv, DIEA 2 equiv, DCM, rt, 2 h; (c) TFA/DCM 1:1, rt, 1 h; (d) CDI 1.5 equiv, DIEA 4.5 equiv, THF, reflux, 6–48 h.



Scheme 3. Reagents and conditions: (a) Boc_2O 1.1 equiv, NaOH 1 M 1.1 equiv, dioxane, rt, 12 h, 98%; (b) PCl_3 1.3 equiv, DCM, rt, 3 h; (c) R-NH_2 1.2 equiv, TEA 2 equiv, DCM, rt, 24 h; (d) CDI 1.5 equiv, DIEA, THF, reflux, 12 h.

2.3. Strategy 3

Another way to introduce diversity on the hydantoin ring at the 2-position is to synthesize the unsubstituted hydantoin **11** first and then to carry out nucleophilic substitutions. These substitutions could be achieved using an appropriate halide, in acetonitrile, in the presence of potassium carbonate (Scheme 4).

Use of potassium isocyanate followed by cyclization in acidic conditions was considered as a first method to obtain compound **11** (Scheme 5). Unfortunately the yield of the transformation was poor.

Consequently, an alternative method was used for the preparation of the unsubstituted hydantoin. After Boc

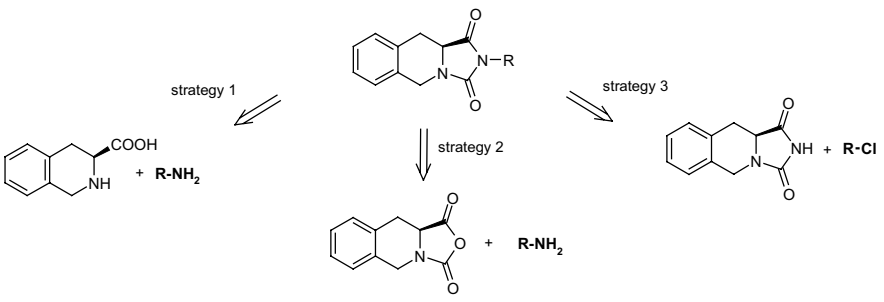
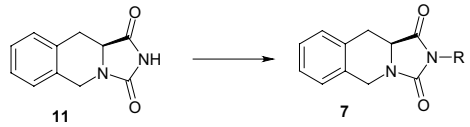
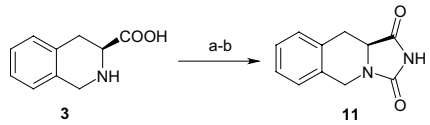


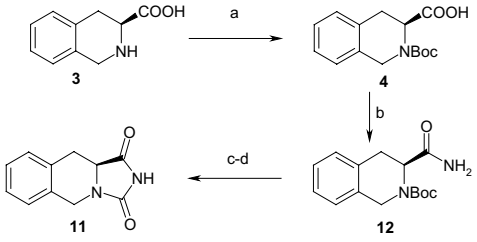
Figure 3. Starting materials used for the synthesis of target compounds.



Scheme 4. Reagents and conditions: R-Cl 1.1 equiv, K_2CO_3 1 equiv, CH_3CN, 60 °C, overnight.



Scheme 5. Reagents and conditions: (a) KNCO 2 equiv, H_2O, reflux, 18 h; (b) HCl, H_2O, reflux, 2 h, 25%.



Scheme 6. Reagents and conditions: (a) Boc_2O 1.1 equiv, NaOH 1 M 1.1 equiv, dioxane, rt, 12 h, 98%; (b) NH_4Cl 1.3 equiv, HOBt 1.1 equiv, EDCI 1.1 equiv, NMM 1.3 equiv, DMF, rt, overnight, 98%; (c) HCl (2 M in Et_2O), THF, rt, 12 h, 100%; (d) CDI 2 equiv, DIEA 2 equiv, THF, reflux, overnight, 45%.

protection of the starting material L-Tic-OH **3**, the primary amide **12** was obtained by reaction of compound **4** with ammonium chloride using HOBt/EDCI activation, in DMF, in presence of *N*-methylmorpholine (NMM).[15] After removal of the Boc-group by HCl/THF treatment, use of CDI and DIEA in THF led to a better overall yield of the unsubstituted hydantoin **11** (Scheme 6).

3. Results and discussion

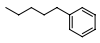
The efficiency of the different strategies is compared in Table 1, in the case of a phenyl or a phenylalkyl substituent.

As summed up in Table 1, the best yields were obtained using strategy 1. However, availability of the starting materials is a determining factor in the choice of one of the four routes.

As part of our program aimed at the design of biologically active compounds, we needed preparations of [(benzyl-methyl-amino)-alkyl]-10,10a-dihydro-5*H*-imidazo[1,5-*b*]isoquinoline-1,3-diones **17a–d** and [(1,3-dioxo-1,5,10,10a-tetrahydro-imidazo[1,5-*b*]isoquinolin-2-yl)-alkyl]carbamic acid *tert*-butyl esters **19a–c** (Fig. 4).

In order to obtain compounds **17a–d**, our original method (Scheme 1) was tried first, with chloroalkyl isocyanates, followed by substitution of the chloride by *N*-benzylmethylamine. Unfortunately overall yields were not satisfactory (respectively, 15% and 9% for $n = 2$ and 3). To improve efficiency, strategy 1 was thus investigated. The diversity of the side chain of hydantoin core was directly introduced on the amine before the coupling step. Protected amines **15a–d** were synthesized in a three step process from commercially available amino-alcohols.[16] After deprotection of the amines using TFA/DCM, the coupling and cyclization steps were performed according to strategy 1 to obtain desired

Table 1. Overall yields for hydantoins **7** by the different strategies

Product	R	Overall yield Scheme 1 (%)	Overall yield strategy 1 (%)	Overall yield strategy 2 (%)	Overall yield strategy 3 (%)
7a		22	80	26	—
7b		51	88	—	32
7c		16	54	56	30
7d		45	43	—	25
7e		70	58	30	—

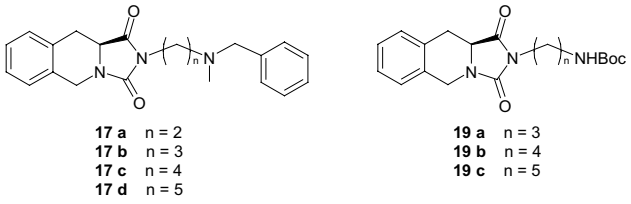
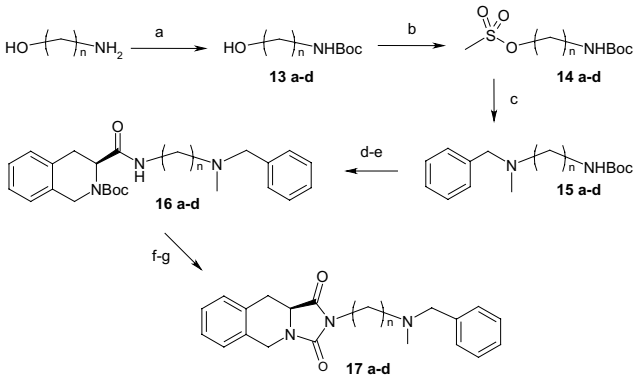


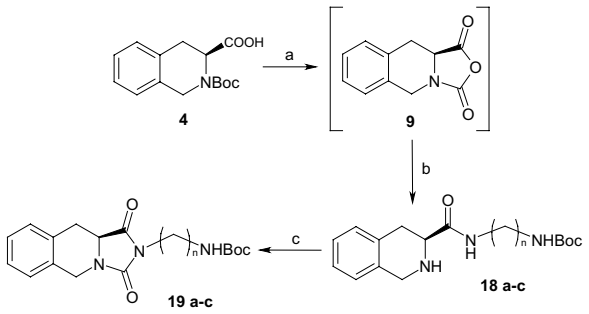
Figure 4. Compounds **17a–d** and **19a–c**.



Scheme 7. Reagents and conditions: (a) Boc_2O 1.1 equiv, DCM, rt, 12 h; (b) MsCl 1.3 equiv, TEA 2 equiv, DCM, 0 °C, 2 h; (c) *N*-benzylmethylamine 3 equiv, DIEA 10 equiv, CH_3CN, 35 °C, 24–72 h; (d) TFA/DCM 1:1, rt, 30 min; (e) *N*-Boc-L-Tic-OH **4** 1 equiv, HOBt 1.1 equiv, EDCI 1.1 equiv, DIEA 2 equiv, DCM, rt, 2 h; (f) TFA/DCM 1:1, rt, 30 min; (g) CDI 1.5 equiv, DIEA 4.5 equiv, THF, reflux, 6–24 h.

Table 2. Overall yield of steps d–g for compounds **17a–d**

Product	*n*	Overall yield (steps d–g) Scheme 7 (%)
17a	2	22
17b	3	26
17c	4	30
17d	5	10



Scheme 8. Reagents and conditions: (a) PCl_3 1.3 equiv, DCM, rt, 3 h; (b) Boc-NH-$(CH_2)_n$-NH_2 1.2 equiv, TEA 2 equiv, DCM, rt, 24 h; (c) CDI 1.5 equiv, DIEA 4.5 equiv, THF, rt, overnight.

Table 3. Overall yields for compounds **19a–c**

Product	*n*	Overall yield Scheme 8 (%)
19a	3	20
19b	4	40
19c	5	39

compounds **17a–d** (Scheme 7) with pretty good overall yields as shown in Table 2.[17]

To obtain compounds **19a–c**, a Boc aminoalkyl moiety was introduced using strategy 2. Strategy 1 was indeed inappropriate in this case because the Tic-deprotection (cf. Scheme 2, step c) was incompatible with the presence of the Boc protection on the side chain (Scheme 8). Commercially available mono-protected α–ω-diaminoalkanes were used as amines.

This method was found to be simple and efficient, with overall yields between 20% and 40% (Table 3).

4. Conclusion

In summary, we have described versatile and efficient methods to prepare tetrahydroisoquinoline-hydantoin derivatives using Tic-OH and amines or halides. These procedures will allow an easy access to further diversified hydantoin based products.

Acknowledgements

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17. (3*S*)-2-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (**4**): white solid; mp 110–112 °C; δ_H (300 MHz, DMSO-d_6): 12.6 (br s, 1H, COOH), 7.2–7.1 (m, 4H, Ar-H), 4.9–4.4 (m, 3H, CH, CH_2), 3.2—3.0 (m, 2H, CH_2), 1.4 (2 s, 9H, $C(CH_3)_3$); MALDI-TOF *m/z* 278 $[M+H]^+$.
(10a*S*)-2-Benzyl-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]-isoquinoline-1,3-dione (**7b**): white solid; mp 122–124 °C; δ_H (300 MHz, DMSO-d_6): 7.3–7.2 (m, 9H, Ar-H), 4.8 (d, J = 17 Hz, 1H, CH_2), 4.6 (s, 2H, CH_2-Ph), 4.4 (d, J = 17 Hz, 1H, CH_2), 4.3 (dd, J = 11 and 5 Hz, 1H, CH), 3.2 (dd, J = 15 and 5 Hz, 1H, CH_2 (*H trans*)), 2.8 (dd, J = 15 and 11 Hz, 1H, CH_2 (*H cis*)); δ_C (300 MHz, DMSO-d_6): 173, 155, 137, 132, 130, 129, 128.5, 128.1, 127.6, 127.5, 55, 42.1, 42.0, 30.6; MALDI-TOF *m/z* 293 $[M+H]^+$.
10,10a-Dihydro-5*H*-imidazo[1,5-*b*]isoquinoline-1,3-dione (**11**): white solid; mp 227–230 °C; δ_H (300 MHz, DMSO-d_6): 10.3 (br s, 1H, NH), 7.2–7.0 (m, 4H, Ar-H), 4.7 (d, J = 15 Hz, 1H, CH_2), 4.2 (d, J = 15 Hz, 1H, CH_2), 4.1 (dd,

J = 11 and 5 Hz, 1H, CH), 3.0 (dd, J = 15 and 5 Hz, 1H, CH_2 (*H trans*)), 2.8 (dd, J = 15 and 11 Hz, 1H, CH_2 (*H cis*)); δ_C (300 MHz, DMSO-d_6): 175, 133–127, 56, 42, 31; MALDI-TOF m/z 203 $[M+H]^+$.

2-[2-(Benzyl-methyl-amino)-ethyl]-10,10a-dihydro-5*H*-imidazo[1,5-*b*]isoquinoline-1,3-dione (**17a**): yellow oil; δ_H (300 MHz, DMSO-d_6): 7.3–7.1 (m, 9H, Ar-H), 4.8 (d, J = 17 Hz, 1H, CH_2), 4.4 (d, J = 17 Hz, 1H, CH_2), 4.3 (dd, J = 11 and 5 Hz, 1H, CH), 3.5 (t, J = 6 Hz, 2H, CH_2), 3.3 (s, 2H, CH_2-Ph), 3.1 (dd, J = 16 and 5 Hz, 1H, CH_2 (*H trans*)), 2.8 (dd, J = 16 and 11 Hz, 1H, CH_2 (*H cis*)), 2.5 (t, J = 6 Hz, 2H, CH_2), 2.1 (s, 3H, CH_3); δ_C (300 MHz, DMSO-d_6): 174, 156, 140–127, 62, 59, 55, 43, 42, 37, 31; MALDI-TOF m/z 350 $[M+H]^+$.