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Convenient synthesis of tetrahydroisoquinoline-hydantoins

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Abstract—NaOH/MeOH or DIEA/CH_2Cl_2 were convenient conditions for the synthesis in solution phase of hydantoins derived from Tic-OH and isocyanates.

One of the challenges of medicinal chemistry is the enhancement of the affinity of a given ligand for its target by decreasing its degrees of freedom and thereby reducing the cost in entropy. Another difficult task is the promotion of the structural diversity which can be achieved by the attachment of pharmacophoric groups to the rigidified molecule. An example of such a process includes di- and trisubstituted hydantoins **1** (Fig. 1), which have been widely used in biological screenings resulting in numerous pharmaceutical applications.[1–3]

As part of our strategy towards the preparation and biological evaluation of hydantoin-containing heterocycles, we elected to fuse the hydantoin ring by its C-5 and N-1 positions to another ring in order to design a new series of more constrained derivatives **2** (Fig. 1). The tetrahydroisoquinoline ring was selected as a pharmacophoric moiety frequently found in our screenings of combinatorial libraries.[4,5] The subsequent absence of variation in the C-5 and N-1 positions could be counter-balanced by the presence of substituents on the tetrahydroisoquinoline ring and the introduction of a side chain to the N-3 position capable of generating a broad structural diversity.

All previous efforts to prepare di- or trisubstituted hydantoins in solid phase have focused upon the ring synthesis from acyclic precursors. According to the literature, strongly acidic (or basic) conditions, extended reaction times or elevated temperatures have been required for formation of the hydantoins.[6–8] However, recent reports have described efficient mild cyclization/cleavage conditions for various linear urea compounds, employing triethylamine or diisopropylamine at room temperature.[9,10] These conditions were thus applied to the benzyl urea, prepared by reacting benzyl isocyanate and (*S*)-(−)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (L-Tic-OH) fixed either to a Tentagel S-OH or to a Wang resin (Scheme 1).[11]

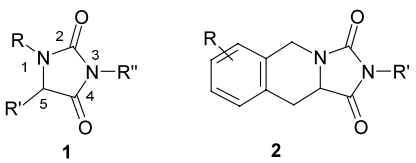
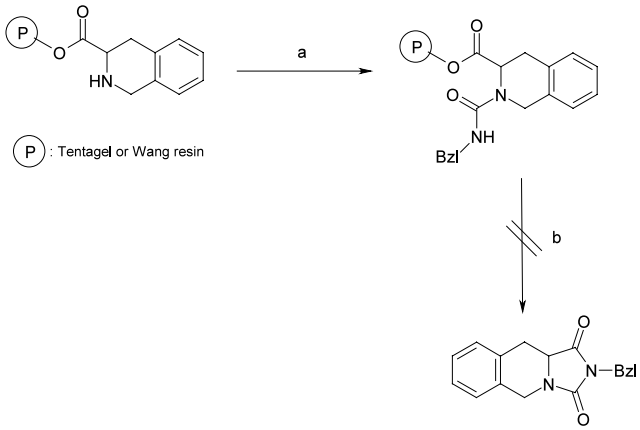


Figure 1. Di- and trisubstituted hydantoins **1** and more constrained Tic derivatives **2**.



Scheme 1. *Reagents and conditions*: (a) Bzl-NCO, TEA, rt; (b) TEA, MeOH, rt or TEA, CH_2Cl_2, rt.

Keywords: hydantoins; cyclization.

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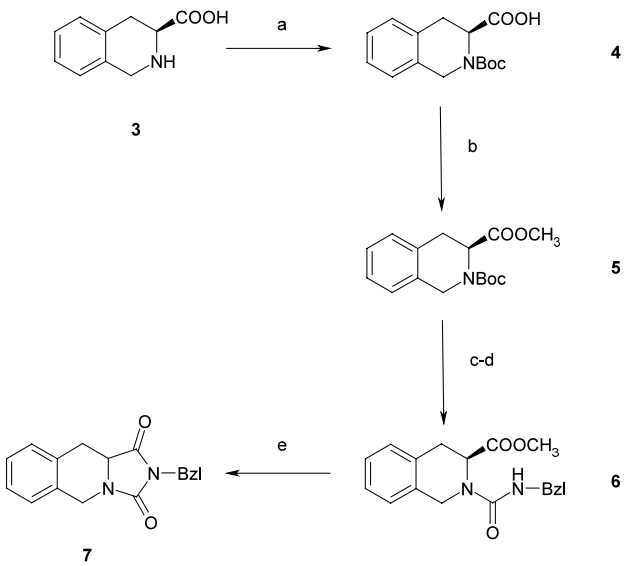
The final treatment (TEA/MeOH with Tentagel resin or TEA/CH_2Cl_2 with Wang resin) led to a very low yield of the free cyclized derivative or, as in the second case, to the total absence of the desired compound. Since we had obtained, under the same conditions, the high yields reported for the hydantoin derived from phenylalanine and benzyl isocyanate, we concluded that the Tic residue was responsible for these disappointing results and carried out the subsequent synthesis of our Tic-hydantoin derivatives in solution phase.



Scheme 2. *Reagents and conditions*: (a) Boc_2O 1.1 equiv., dioxane, NaOH 1 M 1.1 equiv., 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/CH_2Cl_2 1:1, rt, 1 h then DIEA 4.5 equiv., CH_2Cl_2, rt, 15 min, 100%; (d) Bzl-NCO 2.5 equiv., CH_2Cl_2, rt, 12 h, 68%; (e) base 1.1 equiv., solvent, rt, 1–24 h.

Table 1. Optimization of synthesis of hydantoin **7** by cyclization of urea **6**

Entry	Solvent	Base[a] 1.1 equiv.	Reaction time (h)	Conversion rate in HPLC (%)
1	CH_2Cl_2	TEA	1	15
2	CH_2Cl_2	TEA	2	20
3	CH_2Cl_2	TEA	24	50
4	CH_2Cl_2	DIPA	1	40
5	CH_2Cl_2	DIPA	2	65
6	CH_2Cl_2	DIPA	24	85
7	THF	DIPA	2	75
8	THF	DIPA	24	75
9	DMF	DIPA	2	75
10	DMF	DIPA	24	75
11	MeOH	DIPA	1	100
12	MeOH	TEA	1	100
13	MeOH	DIEA	1	30
14	MeOH	DIEA	12	100
15	MeOH	DBU	1	100
16	MeOH	Pyridine	24	30
17	MeOH	NaOH[b]	1	100
18	MeOH	Na_2CO_3	1	100
19	MeOH	AcOK	1	100

[a] DIPA: diisopropylamine.
[b] 1 M aqueous solution NaOH was used.

The starting material was commercial L-Tic-OH **3** whose secondary amine function was protected by a Boc group, using Boc_2O in aqueous dioxane, before its transformation into methyl ester **5** by reacting the cesium salt of Boc-L-Tic-OH **4** with methyl iodide (Scheme 2). After deprotection of the secondary amino group by treatment with a 1:1 mixture of TFA/CH_2Cl_2, evaporation followed by addition of dry dichloromethane and an excess of DIEA (4.5 equiv.), benzyl isocyanate was introduced to the solution of crude L-Tic-OMe to yield the urea **6** (Scheme 2). This latter, assessed by HPLC, was obtained as a very pure sample following a simple brine washing.[12]

Several bases (TEA, diisopropylamine, DIEA, DBU, pyridine, NaOH, Na_2CO_3 and AcOK,) in a variety of solvents (CH_2Cl_2, THF, DMF and MeOH) were compared for the cyclization step of the benzyl urea **6** (Scheme 2, Table 1). First, the two bases (triethylamine or diisopropylamine) and the solvent (CH_2Cl_2), used in solid phase, were tested. Then, the nature of the solvent was optimized in the presence of diisopropylamine and finally the nature of the base in the solvent selected.

The hydantoin derived from L-Tic-OH was obtained quantitatively and quickest from the use of an organic or mineral base (except DIEA and pyridine) in methanol.

Using sodium hydroxide in methanol, the final compound **7** was isolated with a high level of purity following evaporation of methanol, dichloromethane extraction and simple brine washing. A sample for analysis was obtained by thick layer chromatography.[12] This method of cyclization was applied to other ureas obtained from aliphatic (ethyl, *tert*-butyl, allyl) and phenyl isocyanates with similar results (data not shown). The same behavior was also observed in each step of Scheme 2 when D-Tic-OH was used, while no cyclization occurred from urea derived from L-Pro-OH and benzyl isocyanate.

With the aim of decreasing the number of steps without changing the conditions of synthesis for urea **6**, we have demonstrated that the isolation of this latter compound was unnecessary. Indeed, the addition of benzyl isocyanate to a solution of intermediate L-Tic-OMe in dry dichloromethane and in the presence of a large excess of DIEA (15 equiv.), led directly to the formation of hydantoin **7**. With a reaction time of 14 h, despite the use of CH_2Cl_2 as solvent and DIEA as base, the yield of this 'one-pot' reaction was found to be similar (60%) to that observed via isolation of the intermediate urea **6** and cyclization of this latter in an NaOH/MeOH mixture (65%). Similar results were obtained with other aliphatic and aromatic isocyanates. Application of the optimum conditions for the 'one-pot' reaction (DIEA 15 equiv. in CH_2Cl_2), in solid phase (Tentagel or Wang resin), did not enable us to obtain hydantoin **7**.

In conclusion, we have described a convenient and efficient method to prepare Tic-hydantoins not otherwise accessible using cyclization/cleavage conditions in solid-phase synthesis. This 'one-pot' method is suitable for both aliphatic and aromatic isocyanates and will be extended to L-Tic-OH derivatives substituted on the tetrahydroisoquinoline ring in order to introduce another site of structural diversity.

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References

1. Karolacawojciechowska, J.; Kwiatkowski, W.; Kieckononо, K. *Pharmazie* **1995**, *50*, 114.
2. Brouillette, W. J.; Brown, G. B.; Deloreg, T. M.; Liang, G. *J. Pharm. Sci.* **1990**, *79*, 871.
3. Brouillette, W. J.; Jestkov, V. P.; Brown, M. L.; Akhtar, M. S. *J. Med. Chem.* **1994**, *37*, 3289.
4. Vendeville, S.; Buisine, E.; Williard, X.; Schrevel, J.; Grellier, P.; Santana, J.; Sergheraert, C. *Chem. Pharm. Bull.* **1999**, *47*, 194.
5. Deprez, B.; Williard, X.; Bourel, L.; Coste, H.; Hyafil, F.; Tartar, A. *J. Am. Chem. Soc.* **1995**, *117*, 5405.
6. De Witt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Reynolds Cody, D. M.; Pavia, M. R. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6909.
7. Dressmann, B. A.; Sprangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937.
8. Hanessian, S.; Yang, R. Y. *Tetrahedron Lett.* **1996**, *37*, 5835.
9. Kim, S. W.; Ahn, S. Y.; Koh, J. S.; Lee, J. H.; Ro, S.; Cho, H. Y. *Tetrahedron Lett.* **1997**, *38*, 4603.
10. Boeijen, A.; Kruijtzer, J. A. W.; Liskamp, R. M. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2375.
11. Tentagel resin was from Rapp Polymere (initial loading: 0.27 mmol/g). Wang resin was from Novabiochem (initial loading: 0.63 mmol/g).
12. Thick-layer chromatography (TLC) was performed using silica gel from Merck, the compounds were extracted from silica gel using the following solvent system: CH_2Cl_2/MeOH, 80:20. All melting points were determined on a Büchi melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained using a Brucker 300 MHz spectrometer, chemical shifts (δ) were expressed in ppm relative to TMS used as an internal standard. Mass spectra were recorded on a 'time-of-flight' plasma mass desorption spectrometer (TOF-PDMS) using a Californium source. The purity of final compounds was checked by high-pressure liquid chromatography (HPLC) with a C18 Vydac column. Analytical HPLC was performed on a Shimadzu system equipped with a UV detector set at 254 nm. Compounds were dissolved in MeOH and injected through a 50 μL loop. The following eluent systems were used: A (H_2O/TFA, 100:0.05) and B (CH_3CN/H_2O/TFA, 80:20:0.05). HPLC retention times (HPLC t_R) were obtained, at flow rates of 0.5 mL/min, using the following conditions: a gradient run from 100% eluent A during 1 min, then to 100% eluent B over the next 29 min.
(3*S*)-2-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid (4): white solid (98% yield); mp 110–112°C; R_f 0.8 (CH_2Cl_2/MeOH, 9:1); HPLC t_R 20.81 min, purity 100%; δ_H (DMSO-d_6): 12.60 (bs, 1H, COOH), 7.19–7.16 (m, 4H, Ar-H), 4.90–4.80 (m, 1H, CH *cis* or *trans*), 4.64–4.41 (m, 3H, CH *cis* or *trans* and CH_2), 3.20–3.00 (m, 2H, CH_2), 1.46 (s)+1.38 (s) (9H, $C(CH_3)_3$); TOF-PDMS m/z 177 (M^+–Boc).
Methyl (3*S*)-2-(*tert*-butoxycarbonyl)-1,2,3,4-tetra-hydro-3-isoquinolinecarboxylate (5): colorless oil (98% yield); R_f 0.7 (CH_2Cl_2); HPLC t_R 23.54 min, purity 100%; δ_H (DMSO-d_6): 7.23–7.17 (m, 4H, Ar-H), 4.94 (t, $J=4.6$ Hz, 1H, CH *cis* or *trans*), 4.67 (t, $J=5.4$ Hz, 1H, CH *trans* or *cis*), 4.63–4.34 (m, 2H, CH_2), 3.55 (d, $J=12.1$ Hz, 3H, $COOCH_3$), 3.21–2.99 (m, 2H, CH_2), 1.45 (s)+1.37 (s) (9H, $C(CH_3)_3$); TOF-PDMS m/z 191 (M^+–Boc).
Methyl (3*S*)-2-[(benzylamino)carbonyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylate (6): colorless oil (68% yield); R_f 0.60 (CH_2Cl_2/MeOH, 9.5:0.5); HPLC t_R 20.97 min, purity 98%; δ_H (DMSO-d_6): 7.37–7.35 (m, 5H, Ar-H), 7.21–7.16 (m, 4H, Ar-H), 5.41 (dd, $J=5.9$, 2.9 Hz, 1H, CH), 4.64–4.41 (m, 4H, CH_2 and C$\underline{H}_2$-Ph), 3.60 (s, 3H, $COOCH_3$), 3.30 (dd, $J=15.9$, 2.8 Hz, 1H, CH_2), 3.17 (dd, $J=16.3$, 6.1 Hz, 1H, CH_2); TOF-PDMS m/z 325 (M^+).
(10a*S*)-2-Benzyl-1,2,3,5,10,10a-hexahydroimidazo[1,5-*b*]-isoquinoline-1,3-dione (7): white solid (85% yield); mp 122–124°C; R_f 0.40 (CH_2Cl_2); HPLC t_R 21.62 min, purity 100%; δ_H (DMSO-d_6): 7.34–7.17 (m, 9H, Ar-H), 4.84 (d, $J=16.8$ Hz, 1H, CH_2), 4.59 (s, 2H, C$\underline{H}_2$-Ph), 4.40–4.31 (m, 2H, CH_2), 3.16 (dd, $J=15.5$, 4.8 Hz, 1H, CH_2), 2.84 (dd, $J=15.3$, 11.6 Hz, 1H, CH); δ_C (300 MHz, DMSO-d_6): 173.65, 155.63, 137.48, 132.39, 130.18, 129.39, 128.26, 128.19, 127.62, 127.52, 54.99, 42.15, 42.07, 30.65; TOF-PDMS m/z 292 (M^+).