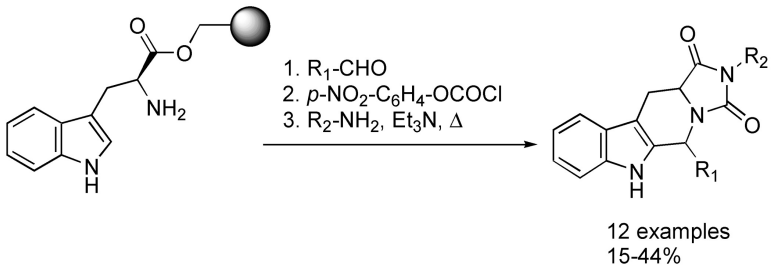
JOURNAL OF combinatorial CHEMISTRY

Report

Solid-Phase Synthesis of Tetrahydro-β-carbolinehydantoins via the *N*-Acyliminium Pictet–Spengler Reaction and Cyclative Cleavage

Dominique Bonnet, and A. Ganesan

J. Comb. Chem., **2002**, 4 (6), 546-548• DOI: 10.1021/cc020026h • Publication Date (Web): 21 September 2002



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 3 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Solid-Phase Synthesis of Tetrahydro-*β*-carbolinehydantoins via the *N*-Acyliminium Pictet−Spengler Reaction and Cyclative Cleavage

Dominique Bonnet and A. Ganesan*

Department of Chemistry, University of Southampton, Southampton SO17 1BJ, U.K.

Received April 11, 2002

The hydantoin and tetrahydro-*β*-carboline scaffolds appear in a diverse array of biologically active compounds of both natural and synthetic origin. Consequently, both these ring systems are popular choices for combinatorial libraries[1] targeted at drug discovery. The ring system **1** (Figure 1), which represents the *union* of these two pharmacophores, is less well-known, although documented for therapeutic areas such as CNS activity,[2] CCK receptor antagonists,[3] and the inhibition[4] of cGMP-phosphodiesterase. In these cases, the ring skeleton was constructed by the classical hydantoin synthesis whereby urea **2** undergoes intramolecular cyclization. The intermediate urea **2** was in turn derived from the reaction of **3** (the product of an acid-catalyzed Pictet−Spengler reaction) with an isocyanate. As part of our program on the combinatorial synthesis of hydantoins[5] and indoles,[6] we were interested in a new route to scaffold **1** that avoids the reliance on isocyanates in favor of more accessible building blocks and is adaptable to parallel solid-phase synthesis.

Our premise was that urea **2** would be obtained by an alternative disconnection involving displacement of an activated carbamate. In a model study, the cis and trans diastereomers of the known[7] tetrahydro-*β*-carboline **4** (Scheme 1) were individually treated with *p*-nitrophenyl chloroformate to give the carbamate **5**. **5** proved to be quite stable to reaction with benzylamine under several conditions, but successful cyclization to the hydantoin **6** was achieved upon heating with triethylamine. We are unaware of previous examples of hydantoin synthesis proceeding via *p*-nitrophenyl carbamates such as **5**. In this new method, the second nitrogen is derived from primary amines, which as a functional group are commercially available with higher diversity than isocyanates.

In our present application, both *cis*- and *trans*-**5** produced *trans*-**6** but with optical rotations of opposite value. This is presumably due to epimerization of the cis compound adjacent to the carbonyl center to the thermodynamically more stable *trans*-tetrahydro-*β*-carboline. Similar isomerizations were reported[2c] in previous syntheses of scaffold **1** proceeding by the cyclization of urea **2**. Carbamate **5** was also obtained more directly from L-tryptophan methyl ester (Scheme 2) by an *N*-acyliminium Pictet−Spengler process in which the tryptophan imine was reacted with *p*-nitrophenyl chloroformate under basic conditions.

After the feasibility of our approach for tetrahydro-*β*-carbolinehydantoin synthesis was established, the method was adapted for solid-phase conditions (Scheme 3) with L-Trp immobilized on the polystyrene−Wang resin. In the

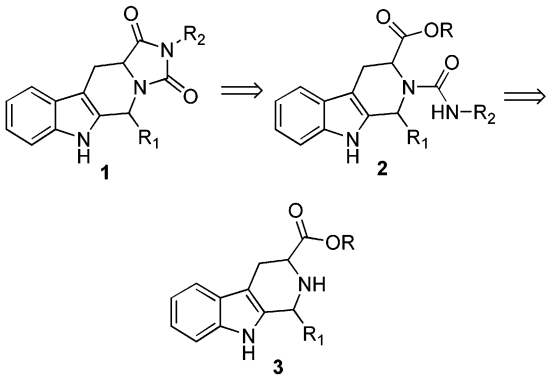
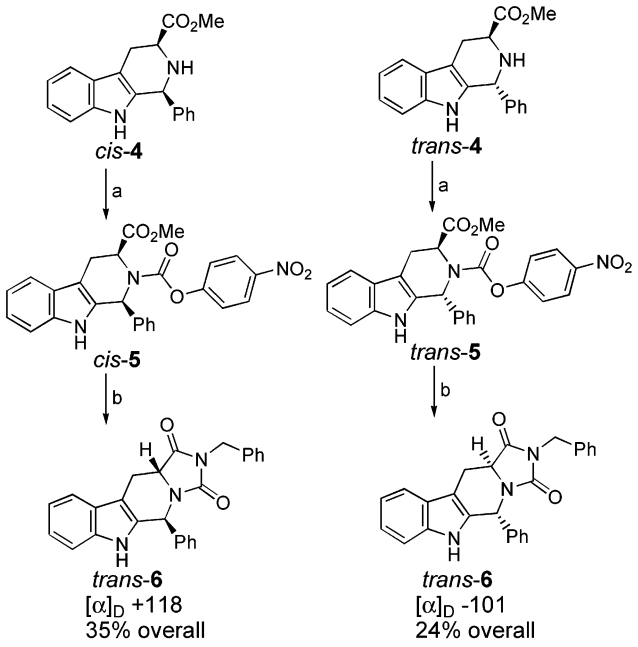


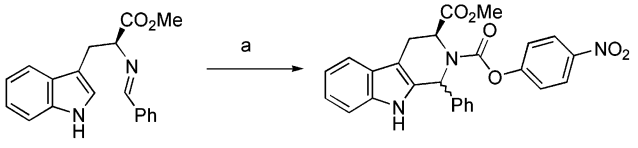
Figure 1. Traditional retrosynthesis of tetrahdydro-*β*-carboline-hydantoins.

Scheme 1. Synthesis of Tetrahydro-*β*-carbolinehydantoins via an Activated Carbamate[a]



[a] Reagents and conditions: (a) 3 equiv of *p*-NO_2−C_6H_4−OCOCl, 5 equiv of Et_3N, 1:1 CH_2Cl_2/THF, room temp, 3 h; (b) 4 equiv of $PhCH_2NH_2$, 4 equiv of Et_3N, DMF, 90 °C, 16 h.

Scheme 2. Synthesis of Carbamate **5** by *N*-Acyliminium Pictet−Spengler Reaction[a]

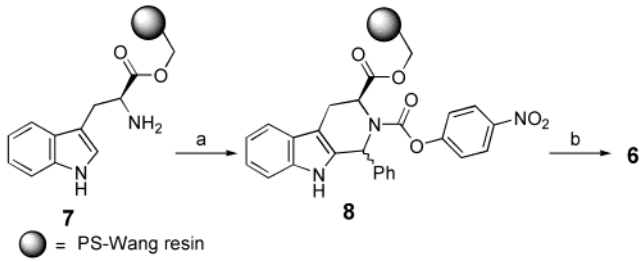


[a] Reagents and conditions: (a) 4 equiv of *p*-NO_2−C_6H_4−OCOCl, 8 equiv of py, 1 equiv of DMAP, CH_2Cl_2, inverse addition of imine, room temp, 15 h, 40% isolated yield.

* To whom correspondence should be addressed. E-mail: ganesan@soton.ac.uk.

10.1021/cc020026h CCC: $22.00
Published on Web 09/21/2002

Scheme 3. Solid-Phase Synthesis of Tetrahydro-β-carbolinehydantoins by Acid-Catalyzed or *N*-Acyliminium Pictet−Spengler Reaction[a]



[a] Reagents and conditions: (a) acid-catalyzed Pictet−Spengler, (i) 10 equiv of PhCHO, 1% TFA, CH_2Cl_2, room temp, 3 h; (ii) 10 equiv of *p*-NO_2−C_6H_4−OCOCl, 12 equiv of Et_3N, 1:1 CH_2Cl_2/THF, room temp, 18 h or (a) *N*-acyliminium Pictet−Spengler, (i) 10 equiv of PhCHO, 1:1 CH_2Cl_2/$CH(OMe)_3$, room temp, 18 h; (ii) 10 equiv of *p*-NO_2−C_6H_4−OCOCl, 14 equiv of py, 1 equiv of DMAP, CH_2Cl_2, room temp, 18 h; (b) 8 equiv of $PhCH_2NH_2$, 8 equiv of Et_3N, DMF, 90 °C, 18 h.

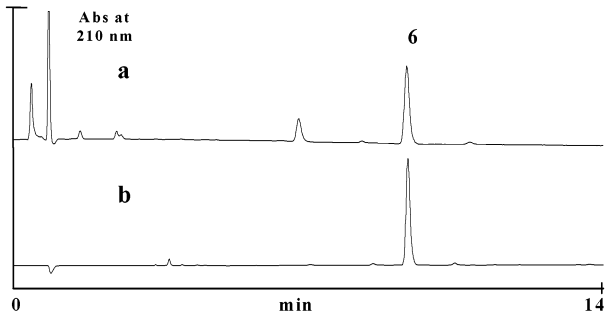


Figure 2. Reverse-phase HPLC profile (C8 column, linear gradient 40−70% MeCN/H_2O in 14 min, flow rate of 2 mL/min) of **6** from solid-phase synthesis: (a) crude material after cyclative cleavage; (b) product after rapid purification (aqueous Na_2CO_3 wash, silica plug).

solid-phase version, the carbamate analogous to **5** was generated by either protic Pictet−Spengler reaction[8] followed by reaction with *p*-nitrophenyl carbonate or the *N*-acyliminium Pictet−Spengler reaction in Scheme 2. In both cases, parallel experiments were run with an Argonaut Quest 210 instrument in order to optimize solvent, reagent equivalents, and reaction time.

The best overall yield of hydantoin **6** obtained with the *N*-acyliminium Pictet−Spengler route was 31%, significantly higher than the 11% isolated with the acid-catalyzed process. Since the protic Pictet−Spengler reaction of **7** is reported to proceed efficiently, we believe the poor yield is due to difficulties in the subsequent acylation step. This problem has also been encountered by others[8,9] when attempting to acylate the free secondary amine of tetrahydro-β-carbolines on solid phase.

Although the yield from the *N*-acyliminium Pictet−Spengler reaction was modest, the cyclative nature of the final cleavage ensured that other tryptophan derivatives were not released. The only significant impurities were the reagent benzylamine and the byproduct *p*-nitrophenol, which were readily removed (Figure 2) by a wash with aqueous Na_2CO_3 and filtration through a short silica plug. Tetrahydro-β-carbolinehydantoin **6** from the solid-phase synthesis was nearly racemic ($[\alpha]_D$ −14°). This is consistent with our previous results[6a] indicating ~1:1 cis/trans ratios during the solid-phase *N*-acyliminium Pictet−Spengler reactions, followed by epimerization of the cis diastereomer.

Table 1. Solid-Phase Synthesis of Tetrahydro-β-carbolinehydantoins **1**

	R_1	R_2	yield,[a] %
1a	Ph−	Bn−	31
1b	Ph−	*c*-$C_6H_{11}CH_2$−	38
1c	Ph−	Me_2CHCH_2−	32
1d	3,4,5-$(MeO)_3C_6H_2$−	Bn−	20
1e	3,4,5-$(MeO)_3C_6H_2$−	*c*-$C_6H_{11}CH_2$−	33
1f	3,4,5-$(MeO)_3C_6H_2$−	Me_2CHCH_2−	44
1g	*p*-$NO_2C_6H_4$−	Bn−	15
1h	*p*-$NO_2C_6H_4$−	*c*-$C_6H_{11}CH_2$−	35
1i	*p*-$NO_2C_6H_4$−	Me_2CHCH_2−	30
1j	Me_2CHCH_2−	Bn−	17[b]
1k	Me_2CHCH_2−	*c*-$C_6H_{11}CH_2$−	22[b]
1l	Me_2CHCH_2−	Me_2CHCH_2−	20[b]

[a] Isolated yield based on manufacturer's loading of Fmoc-L-Trp resin. All compounds were fully characterized spectroscopically (IR, ^1H and ^{13}C NMR, MS). [b] Obtained as two diastereomers with the following ratios: **1j**, 64:36; **1k**, 63:37; **1l**, 51:49.

The scope of our methodology was demonstrated by the synthesis of a small library on solid phase (Table 1). Resin **7** was reacted with benzaldehyde, 3,4,5-trimethoxybenzaldehyde, 4-nitrobenzaldehyde, and isovaleraldehyde to form the corresponding imines. After the *N*-acyliminium reaction with *p*-nitrophenyl chloroformate, cleavage was initiated with benzylamine, cyclohexanemethylamine, or isobutylamine. In all cases, the tetrahydro-β-carbolinehydantoin was isolated in >85% purity (HPLC analysis, UV detection at 210 nm) after the aqueous wash and silica filtration. While hydantoins **1a**−**i** were obtained as a single diastereomer, those arising from isovaleraldehyde were cis and trans mixtures.

In summary, we have demonstrated a solid-phase route to the tetrahydro-β-carbolinehydantoin scaffold. The route features a new approach to hydantoins that proceeds via amine addition to an activated carbamate and avoids the need for isocyanate building blocks. Interestingly, attempted solid-phase synthesis of a similar tetrahydroisoquinolinehydantoin by the isocyanate method was recently reported[10] to be unsuccessful. The preparation of a larger tetrahydro-β-carbolinehydantoin library and its biological evaluation is currently underway.

Acknowledgment. We thank the Association pour la Recherche sur le Cancer (ARC) for a postdoctoral fellowship, the Combinatorial Centre of Excellence, University of Southampton for the use of equipment (HPLC, Argonaut Quest), and Alexander Yurek-George for the acquisition of some NMR spectra.

Supporting Information Available. Experimental procedure for solid-phase synthesis, ^1H NMR spectra, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) For a recent review, see the following. Ganesan, A. Recent Developments in Combinatorial Organic Synthesis. *Drug Discovery Today* **2002**, *7*, 47−55.

(2) (a) Braña, M. F.; Garrido, M.; López Rodríguez, M. L. L.; Miguel, P.; Morcillo, M. J.; Riaño, A. Synthesis of New Derivatives of β-Carboline-hydantoin. *J. Heterocycl. Chem*. **1990**, *27*, 703−706. (b) Braña, M. F.; Garrido, M.; López, M. L.; de Miguel, P.; Riaño, A. Synthesis and Reactivity of β-Carboline-hydantoin systems. *Synth. Commun.* **1990**, *20*, 1793−1810. (c) Garrido, M.; López-Rodríguez, M. L.; Morcillo, M. J.; Garrido, M.; Benhamú, B.; Pérez, V.; de la Campa, J. G. Stereospecificity in the Reaction of Tetrahydro-β-carboline-3-carboxylic Acids with Isocyanates and Isothiocyanates. Kinetic vs Thermodynamic Control. *J. Org. Chem*. **1994**, *59*, 1583−1585.

(3) De la Figuera, N.; Garcîa-López, M. T.; Herranz, R.; González-Muñiz, R. New Scaffolds for Peptidomimetics. Synthetic Approaches towards 2,4-Dioxooctahydropyrimido-[1′,6′:1,2]pyrido[3,4-*b*]indole-6-carboxylic Acid Derivatives. *Heterocycles* **1999**, *51*, 265−280.

(4) Daugan, A. C. M.; Labaudiniere, R. F. 5,6,11,11a-Tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-diones as Medicinal Agents. U.S. Patent 6143757, 2000.

(5) Sim, M. M.; Ganesan, A. Solution-Phase Synthesis of a Combinatorial Thiohydantoin Library. *J. Org. Chem*. **1997**, *62*, 3230−3235.

(6) (a) Wang, H.; Ganesan, A. The *N*-Acyliminium Pictet−Spengler Condensation as a Multicomponent Combinatorial Reaction on Solid Phase and Its Application to the Synthesis of Demethoxyfumitremorgin C Analogues. *Org. Lett.* **1999**, *1*, 1647−1649. (b) Wang, H.; Usui, T.; Osada, H.; Ganesan, A. Synthesis and Evaluation of Tryprostatin B and Demethoxyfumitremorgin C Analogues. *J. Med. Chem*. **2000**, *43*, 1577−1585.

(7) Bailey, P. D.; Hollinshead, S. P. The Use of Carbon-13 NMR in the Determination of Stereochemistry of 1,2,3-Trisubstituted Tetrahydro-β-carbolines. *Heterocycles* **1987**, *26*, 389−399.

(8) Mayer, J. P.; Bankaitis-Davis, D.; Zhang, J.; Beaton, G.; Bjergarde, K.; Andersen, C. M.; Goodman, B. A.; Herrera, C. J. Application of the Pictet−Spengler Reaction in Combinatorial Chemistry. *Tetrahedron Lett.* **1996**, *37*, 5633−5636.

(9) (a) Kaljuste, K.; Unden, A. Solid-Phase Synthesis of 1,2,3,4-Tetrahydro-β-carbolines. Implications for Combinatorial Chemistry. *Tetrahedron Lett*. **1995**, *36*, 9211−9214. (b) van Loevezijn, A.; van Maarseeven, J. H.; Stegman, K.; Visser, G. M.; Koomen, G.-J. Solid-Phase Synthesis of Fumitremorgin, Verruculogen and Tryprostatin Analogs Based on a Cyclization/Cleavage Strategy. *Tetrahedron Lett*. **1998**, *39*, 4737−4740. (c) Li, X.; Zhang, L.; Zhang, W.; Hall, S. E.; Tam, J. P. Solid-Phase Synthesis of 1,2,3,4-Tetrahydro-β-carboline-containing Peptidomimetics. *Org. Lett*. **2000**, *2*, 3075−3078.

(10) Charton, J.; Delarue, S.; Vendeville, S.; Debreu-Fontaine, M.-A.; Girault-Mizzi, S.; Sergheraert, C. Convenient Synthesis of Tetrahydroisoquinoline-hydantoins. *Tetrahedron Lett*. **2001**, *42*, 7559−7561.

CC020026H