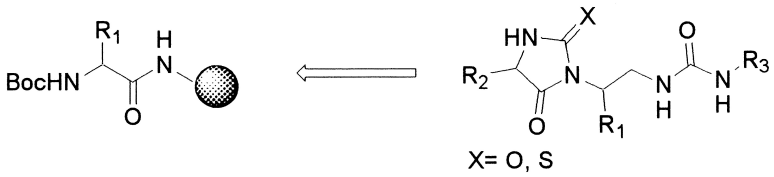
Article

# Solid-Phase Synthesis of Linear Ureas Tethered to Hydantoins and Thiohydantoins

Adel Nefzi, Marcello Giulianotti, Long Truong, Somkit Rattan, John M. Ostresh, and Richard A. Houghten

*J. Comb. Chem.*, **2002**, 4 (2), 175-178• DOI: 10.1021/cc010064l • Publication Date (Web): 17 January 2002






## More About This Article

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

- Supporting Information
- Links to the 2 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 Linear Ureas Tethered to Hydantoins and Thiohydantoins†

Adel Nefzi, Marcello Giulianotti, Long Truong, Somkit Rattan, John M. Ostresh, and Richard A. Houghten*

*Torrey Pines Institute for Molecular Studies, 3550 General Atomics Court, San Diego, California 92121*

*Received September 20, 2001*

An efficient method for the solid-phase synthesis of hydantoins and thiohydantoins tethered to ureas, starting from a resin-bound amino acid, is presented. Following reduction of the amide with borane−THF, a second amino acid was selectively coupled to the primary amine followed by treatment of the secondary amine by an isocyanate to generate the corresponding urea. Hydantoin and thiohydantoin formation was achieved through the use of carbonyldiimidazole and thiocarbonyldiimidazole, respectively. Cleavage from the solid support using hydrogen fluoride, followed by extraction and lyophilization, provided the desired urea-linked heterocyclic compounds in good yield and high purity.

Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents.[1] Continuing with our efforts directed toward the synthesis of combinatorial libraries of heterocyclic compounds starting from amino acids and short peptides,[2] we describe herein an efficient, practical solid-phase synthesis of compounds containing a urea functionality tethered to a hydantoin or thiohydantoin.

Hydantoins and ureas have long been the focus of considerable attention as a ubiquitous moiety incorporated into many drugs with numerous therapeutic applications and biological activities. Reported examples of pharmaceutical and medicinal applications of both pharmacophores are presented in Figure 1.

Starting from a resin-bound Boc amino acid, the Boc group was cleaved with a solution of trifluoroacetic acid (TFA) in dichloromethane (DCM). The amide bond was reduced using borane in THF to generate secondary amine **2**.[3] An Fmoc-amino acid was then selectively coupled to the primary amine using hydroxybenzotriazole (HOBt) and diisopropylcarbodiimide (DIPCDI) in dimethylformamide (DMF) to provide intermediate **3**. During the course of experimentations with different amino acids at the $R_2$ position, we observed that if compound **2** were treated with a Boc-amino acid and only DIPCDI in DMF with no HOBt, both the primary and secondary amines would be acylated with the incoming Boc-amino acid. It was also observed that if these same Boc-amino acids were coupled using both HOBt and DIPCDI, acylation of the secondary amine would be substantially reduced. Optimal conditions for selective acylation of the primary amine over the secondary amine were to use a 6-fold excess of the Fmoc-amino acid, DIPCDI, and HOBt in a 0.1 M solution of DMF. These conditions afforded 100% acylation of the primary amine by the amino acid and less than 1% acylation of the secondary amine for all compounds tested. Following coupling of the Fmoc-amino acid, the free secondary amine was treated with an isocyanate to form the linear urea **4**. Following Fmoc deprotection, the free amine was treated with carbonyldiimidazole or thiocarbonyldiimidazole at low concentrations, resulting in the formation of hydantoin or thiohydantoin heterocycles, respectively. The desired compounds **5** and **6** were obtained following cleavage from the solid support with HF.[4] These steps involving compounds **1**−**6** are shown in Scheme 1.

The structural characterization of compounds demonstrates the success of the major transformations described. LC−MS of cleaved compounds **4** showed >95% purity. The desired hydantoins **5** and thiohydantoins **6** were obtained with purities greater than 80% (Table 1). Yields of the crude products in all cases were greater than 90% and were calculated on the basis of the initial loading of the resin. From the NMR spectra, racemization was observed following formation of both hydantoins and thiohydantoins. In the case of thiohydantoins, the amount of racemization was significantly increased (in some cases, complete racemization was observed). We expect that following formation of the thioisocyanate and prior to cyclization, the Cα proton (of the second amino acid introduced) is much more acidic compared to the similar proton in the isocyanate analogue. The increased electron density around the sulfur atom allows a slight shift in the equilibrium toward a possible formation of the imine between the nitrogen and the Cα carbon. Further reactions involving the use of different reagents and cyclization conditions in order to study and minimize racemization are under investigation.

This synthetic approach has been expanded to include a wide range of different amino acids at the $R_1$ and $R_2$ positions as well as several different isocyanates at the $R_3$ position. More than 50 individual controls were synthesized for each heterocyclic compound type. For each potential building block tested, only those yielding final crude purities higher

† We dedicate this paper to the thousands of innocent people who tragically lost their lives on September 11th, 2001.

10.1021/cc010064l CCC: $22.00 
Published on Web 01/17/2002

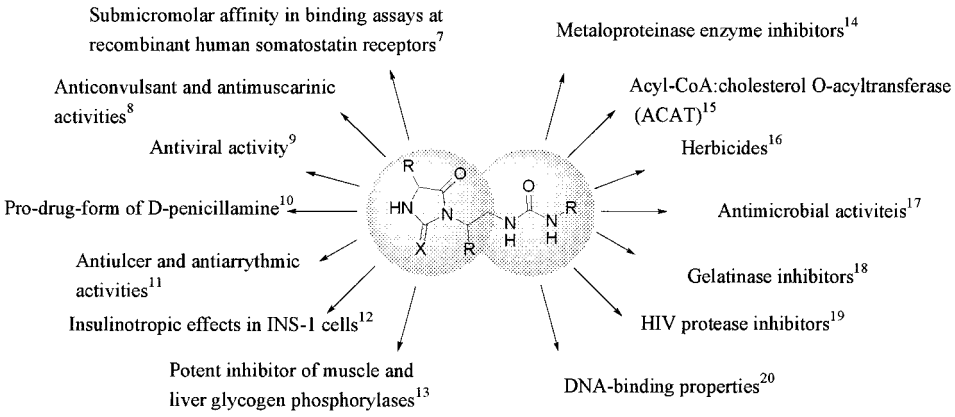
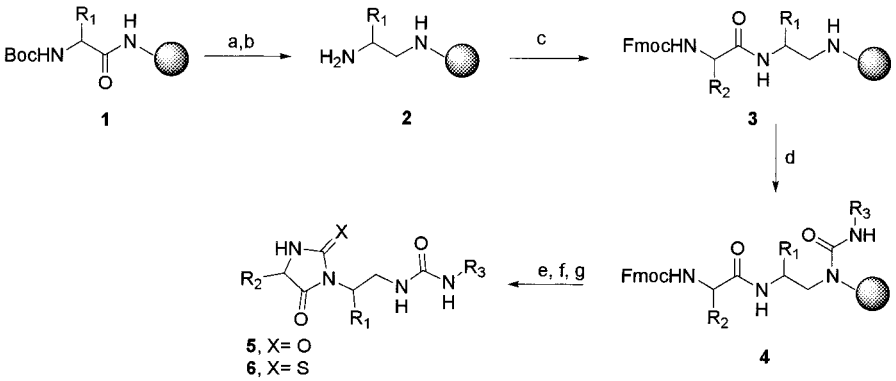


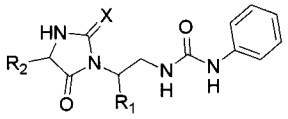

**Figure 1.** Some reported biological activities for urea and hydantoin/thiohydantoin scaffolds.

**Scheme 1**[a]




[a] (a) 55% TFA in DCM, neutralize; (b) $BH_3$−THF, 65 °C; (c) Fmoc Xaa−OH, DIPCDI, HOBt in DMF; (d) $R_3N{=}C{=}O$, DMF; (e) piperdine, DMF; (f) $CXIm_2$, DCM; (g) HF/anisole, 0 °C.

**Table 1.** Data for Compounds **5** and **6**[a]



| | | | **5** (X = O) | | **6** (X = S) | |
|---|---|---|---|---|---|---|
| entry | $R_1$ | $R_2$ | MW expected/MW found | purity, % | MW expected/MW found | purity, % |
| a | $-CH_3$ | $-CH_3$ | 290.3/291.0 ($MH^+$) | 91 | 306.1/307.0 ($MH^+$) | 95 |
| b | $-CH_2C_6H_5$ | $-CH_3$ | 366.4/367.1 ($MH^+$) | 92 | 382.1/383.1 ($MH^+$) | 95 |
| c | $-H$ | $-CH_3$ | 276.2/277.0 ($MH^+$) | 95 | 292.3/293.0 ($MH^+$) | 93 |
| d | $-CH(CH_3)CH_2CH_3$ | $-CH_3$ | 332.1/333.1 ($MH^+$) | 85 | 348.1/349.1 ($MH^+$) | >95 |
| e | $-CH_2OH$ | $-CH_3$ | 322.1/322.9 ($MH^+$) | 85 | 306.1/307.0 ($MH^+$) | 81 |
| f | $-CH(OH)CH_3$ | $-CH_3$ | 320.1/321.0 ($MH^+$) | 80 | 336.1/337.0 ($MH^+$) | 87 |
| g | $-(CH)_2-p-C_6H_4OH$ | $-CH_3$ | 382.1/383.1 ($MH^+$) | 80 | 398.1/399.1 ($MH^+$) | >95 |
| h | $-CH_2CH_2CH_2CH_3$ | $-CH_3$ | 332.1/333.1 ($MH^+$) | 85 | 348.1/349.0 ($MH^+$) | >95 |
| i | $-CH_2CH_2CH_3$ | $-CH_3$ | 318.1/319.0 ($MH^+$) | 84 | 334.1/335.0 ($MH^+$) | >95 |
| j | $-CH_2CH_2SCH_3$ | $-CH_3$ | 350.1/351.1 ($MH^+$) | 93 | 366.1/367.1 ($MH^+$) | >95 |
| k | $-CH_3$ | $-(CH_2)_4-NH_2$ | ND | ND | 363.1/363.9 ($MH^+$) | 86 |
| l | $-CH_3$ | $-CH_2C_6H_5$ | ND | ND | 382.1/382.8 ($MH^+$) | 85 |

[a] All compounds presented in the table are derived from L-amino acids, and the same purities were obtained for D-amino acids. The products were run on a Vydac column, gradient 5% to 95% with 0.05% TFA in ACN for 7 min. The purity was estimated on analytical traces at $\lambda$ = 214 nm. ND: not determined.

than 80% will be considered for inclusion in the synthesis of combinatorial libraries.

In summary, an efficient and general solid-phase synthesis of compounds containing both a urea and hydantoin or thiohydantoin functionality, from resin-bound amino acids, is presented. These transformations enable both individual compounds and mixture-based combinatorial libraries to be prepared with excellent yield and purity.

## Experimental Section

Solid-phase syntheses were carried out using the "tea-bag" method in which the resin is contained within sealed polypropylene mesh packets.[5] The completeness of amino acid couplings was verified using the ninhydrin test.[6]

**(1) Amino Acid Coupling.** A total of 100 mg of *p*-methylbenzydrylamine (MBHA) resin (0.1 mequiv/g, 100−200 mesh) was sealed within a polypropylene mesh packet.

Reactions were carried out in 10 mL polyethylene bottles. Following neutralization with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM), the resin was washed with DCM. Boc-amino acids were coupled (6 equiv) in the presence of diisopropylcarbodiimide (DIPCDI, 6 equiv) in dichloromethane (DCM) for 60 min. The Boc group was removed with 55% TFA in DCM (30 min).

**(2) Reduction of the Amide Group.** The reduction was performed in 50 mL Kimax tubes under nitrogen. The resin packet (100 mg, 0.1 mequiv of resin, 0.1 mequiv of carbonyl) and boric acid (15-fold excess for each amide bond) were added to each tube. Trimethyl borate (15-fold excess over each amide bond) was added, followed by 1 M $BH_3$−THF (40-fold excess over each amide bond). The tubes were heated at 65 °C for 72 h, decanted, and washed with THF, and any remaining borane was quenched with MeOH. The borane complexes were disproportionate by treatment with piperidine at 65 °C overnight. The resin was then washed with methanol (2×) and DMF (6×) and dried. Completeness of the reaction was verified by cleavage and analysis following reduction.

**(3) Amino Acid Coupling after Reduction.** Following reduction, an Fmoc-amino acid was coupled (6 equiv, 0.1 M) in the presence of hydroxybenzotriazole (HOBt, 6 equiv, 0.1 M) and diisopropylcarbodiimide (DIPCDI, 6 equiv, 0.1 M) in anhydrous DMF for 60 min.

**(4) Urea Formation.** Urea formation was accomplished by treatment of the resin-bound secondary amine with a 7-fold excess (0.1 M) of isocyanate in anhydrous DMF (12 h). Completeness of urea formation was verified by cleavage and analysis following the urea formation reaction.

**(5) Cyclization.** Cyclization occurred following treatment of the resin-bound *N*-urea amino acid compounds overnight with a 5-fold excess of either carbonyldiimidazole (0.05 M) in anhydrous DCM or thiocarbonyldiimidazole (0.05 M) in anhydrous DCM. The resin was then washed with DCM (3×) and DMF (3×). Following cleavage from the resin with anhydrous HF in the presence of anisole at 0 °C for 90 min, the desired product was extracted with acetonitrile/water (50:50) and lyophilized. The identities of all compounds were determined by LC−MS, and selected compounds were identified by $^1$H NMR.

**Acknowledgment.** This research was supported by National Cancer Institute, Grant CA 78040 (R. A. Houghten).

**Supporting Information Available.** LC−MS of selected compounds, LC−MS of an example of the selective primary amine acylation, and $^1$H NMR of a representative example. This material is available free of charge via the Internet at http://pubs.acs.org.

## References and Notes

(1) (a) Gallop, M. A.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233−1251. (b) Gordon, E. M.; Barret, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385−1401. (c) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600. (d) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17−42. (e) Balkenhohl, F.; Bussche-Hunnefeld, C. von dem.; Lansky, A.; Zechel, C. *Angew Chem., Int. Ed. Engl.* **1996**, *35*, 2288−2337. (f) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1996**, *52*, 4527−4554. (g) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449−472.

(2) Houghten, R. A.; Pinilla, C.; Appel, J. R.; Blondelle, S. E.; Dooley, C. T.; Eichler, J.; Nefzi, A.; Ostresh, J. M. *J. Med. Chem.* **1999**, *42*, 3743−3778.

(3) (a) Ostresh, J. M.; Schoner, C. C.; Hamashin, V. T.; Nefzi, A.; Meyer, J.-P.; Houghten, R. A. *J. Org. Chem.* **1998**, *63*, 8622−8623. (b) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron* **1999**, *55*, 335−344.

(4) Houghten, R. A.; Bray, M. K.; DeGraw, S. T.; Kirby, C. J. *Int. J. Pept. Protein Res.* **1986**, *27*, 6763−6768.

(5) Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 5131−5135.

(6) Kaiser, E. T.; Colescott, R. L.; Blossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595.

(7) Scicinski, J. J.; Barker, M. D.; Murray, P. J.; Jarvie, E. M. *Bioorg. Med. Chem. Lett.* **1998**, *24*, 3609−3614.

(8) (a) Hudkins, R. L.; DeHaven-Hudkins, D. L.; Doukas, P. *Bioorg. Med. Chem. Lett.* **1997**, *8*, 9979. (b) Rump, S.; Ilczuk, I.; Rabsztyn, T.; Walczyna, K. *Pharmazie* **1981**, *36*, 780−781.

(9) El-Barbarbary, A. A.; Khodair, A. I.; Pedersen, E. B. *Arch. Pharm. (Weinheim, Ger.)* **1994**, *327* (10), 653.

(10) Poupaert, J. H.; Mukarugambwa, S.; Dumont, P. *Eur. J. Med. Chem. Chim. Ther.* **1980**, *15* (6), 511−514.

(11) Lopez, C. A.; Trigo, G. G. *Adv. Heterocycl. Chem.* **1985**, *38*, 177.

(12) Bozdag, O.; Verspohl, E. J.; Ertan, R. *Arzneimittelforschung* **2000**, *50*, 626−630.

(13) Osz, E.; Somsak, L.; Szilagyi, L.; Kovacs, L.; Docsa, T.; Toth, B.; Gergely, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1385−1390.

(14) Jacobsoen, E. J.; Mitchell, M. A.; Hendges, S. K.; Belonga, K. L.; Skaletzky, L. L.; Stezer, L. S.; Lindberg, T. J.; Fritzen, E. L.; Schostarez, H. J.; O'Sullivan, T. J.; Maggiora, L. L.; Stuchly, C. W.; Laborde, A. L.; Kubicek, M. F.; Poorman, R. A.; Beck, J. M.; Miller, H. R.; Petzold, G. L.; Scott, P. S.; Truesdell, S. E.; Wallace, T. L.; Wilks, J. W.; Fischer, C.; Goodman, L. V.; Kaytes, P. S.; Ledbetter, S. R.; Powers, E. A.; Vogeli, G.; Mott, J. E.; Trepot, C. M.; Staples, D. J.; Baldwin, E. T.; Finzel, B. C. *J. Med. Chem.* **1999**, *42*, 1525−1536.

(15) Tanaka, A.; Terasawa, T.; Hagihara, H.; Sakuma, Y.; Ishibe, N.; Sawada, M.; Takasugi, H.; Tanaka, H. *Bioorg. Med. Chem.* **1998**, *6*, 15−30.

(16) Mizuno, T.; Kino, T.; Ito, T.; Miyata, T. *Synth. Commun.* **2000**, *30*, 1675−1688.

(17) Juelich, W.-D.; Ohme, R.; Alhitari, N.; Adrian, V.; von Woedtke, Th.; Kramer, A. *Pharmazie* **1999**, *54*, 171−178.

(18) Zhang, Y.; Li, D.; Houtman, J. C.; Witiak, D. T.; Seltzer, J.; Bertics, P. J.; Lauhon, C. T. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2823−2826.

(19) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Erickson-Viitanen, S.; Klabe, R. M.; Bacheler, L.; Cordova, B. C.; Chang, C. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 715−720.

(20) Fukutomi, R.; Kagechika, H.; Hashimoto, Y.; Shudo, K. *Chem. Pharm. Bull.* **1996**, *44*, 1983.

(21) *N*-[2-(4-Methyl-2,5-dioxoimidazolidin-1-yl)-3-(methylsulfunyl)propyl]-*N*′-phenylurea (**5j**). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.42 (s, 1H), 8.15 (s, 1H), 7.36 (d, $J$ = 7.9 Hz, 2H), 7.19 (t, $J$ = 7.8 Hz, 2H), 6.87 (t, $J$ = 7.2 Hz, 1H), 6.22 (t, $J$ = 5.9 Hz, 1H), 4.03 (m, 2H), 3.50 (m, 1H), 3.33 (m, 1H), 2.37 (m, 1H), 2.17 (m, 1H), 2.02 (s, 3H), 1.83 (m, 1H), 1.23

(d, $J = 6.9$ Hz, 3H). *N*-[2-(4-Methyl-2,5-dioxoimidazolidin-1-yl)-2-phenylethyl]-*N*′-phenylurea (**5b**). $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 8.49 (s, 1H), 8.29 (s, 1H), 6.88−7.36 (m, 10H), 6.32 (m, 1H), 5.15 (m, 1H), 3.99 (m, 1H), 4.09 (m, 1H), 3.79 (dd, $J = 9.6$ Hz, $J = 5.7$ Hz, 1H), 1.26 (d, $J = 6.8$ Hz, 3H).

CC010064L