ORGANIC LETTERS

2011
Vol. 13, No. 3
353−355

# 1,3,5-Trisubstituted and 5-Acyl-1,3-Disubstituted Hydantoin Derivatives via Novel Sequential Three-Component Reaction

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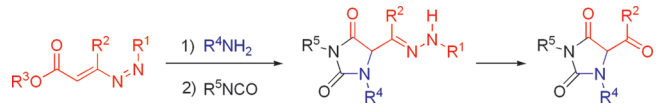
**Received November 3, 2010**

## ABSTRACT




**1,2-Diaza-1,3-dienes (DDs) react as Michael acceptors with primary amines to afford α-aminohydrazone derivatives that were in situ coupled with isocyanates. Intramolecular ring closure of the asymmetric urea derivatives so formed allows for a selectively substituted hydantoin ring to be obtained. The hydrazone side chain introduced by the conjugated heterodiene system at the 5-position of the heterocycle represents a valuable functionality for accessing novel 5-acyl derivatives difficult to obtain by other methods.**

Hydantoin-based scaffolds have been found to possess significant pharmacological activities. In fact, many derivatives have been identified as anticonvulsant,[1] antimuscarinics,[2] antiulcers and antiarrhythmics,[3] antivirals, antidiabetics,[4] and serotonin and fibrinogen receptor antagonists.[5] Moreover, substituted hydantoins are important building blocks for the synthesis of nonnatural amino acids by alkaline degradation.[6] Therefore, many methods for the rapid acquisition of structurally varied and functionalized hydantoins are desirable. The synthesis of 1,3,5-trisubstituted hydantoins is usually accomplished by reacting *N*-substituted α-amino acids or their esters with isocyanates, either in solution[7] or in solid phase.[8] Other strategies for the synthesis of 1,3,5-hydantoins have been recently reported in the literature and are based on the reaction of *N*,*N*′-disubstituted ureas with carbon monoxide and aldehydes,[9] on a Ugi four-component condensation[10] and on the reaction between activated α,*β*-unsaturated carboxylic acids and asymmetric carbodiimides.[11] To the best of our knowledge, there is no report on the synthesis of 1,3,5-trisubstituted hydantoins having hydrazone or acyl function at the 5-position of the ring neither

(1) Thenmozhiyal, J. C.; Wong, P. T. H.; Chui, W. K. *J. Med. Chem.* **2004**, *47*, 1527.

(2) (a) Brazil, C. W.; Pedley, T. A. *Annu. Rev. Med.* **1998**, *49*, 135. (b) Luer, M. S. *Neurol. Res.* **1998**, *20*, 178.

(3) (a) Matzukura, M.; Daiku, Y.; Ueda, K.; Tanaka, S.; Igarashi, T.; Minami, N. *Chem. Pharm. Bull.* **1992**, *40*, 1823. (b) Knabe, J.; Baldauf, J.; Ahlhelm, A. *Pharmazie* **1997**, *52*, 912.

(4) Somsák, L.; Kovács, L.; Tóth, M.; Ösz, E.; Szilágyi, L.; Györgydeak, Z.; Dinya, Z.; Docsa, T.; Tóth, B.; Gergely, P. *J. Med. Chem.* **2001**, *44*, 2843.

(5) (a) Moloney, G. P.; Robertson, A. D.; Martin, G. R.; MacLennan, S.; Mathews, N.; Dosworth, S.; Sang, P. Y.; Knight, C.; Glen, R. *J. Med. Chem.* **2001**, *44*, 2843. (b) Moloney, G. P.; Martin, G. R.; Mathews, N.; Milne, A.; Hobbs, H.; Dosworth, S.; Sang, P. Y.; Knight, C.; Maxwell, M.; Glen, R. *J. Med. Chem.* **1999**, *42*, 2504.

(6) Sutherland, J. C.; Hess, G. P. *Nat. Prod. Rep.* **2000**, *17*, 621.

(7) (a) Martin, D. J. *J. Prakt. Chem.* **1991**, *333*, 261. (b) Atay, E.; Blogoeva, I. B.; Jirby, A. J.; Pojarieff, I. G. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2289. (c) Blogoeva, I. B.; Toteva, M. M.; Ouarti, N.; Ruasse, M.-F. *J. Org. Chem.* **2001**, *66*, 2123.

(8) (a) Matthews, J.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 6090. (b) Kim, S. W.; Ahn, S. Y.; Koh, J. S.; Lee, J. H.; Ro, S.; Cho, H. Y. *Tetrahedron Lett.* **1997**, *38*, 4603. (c) Boeijen, A.; Kruijtzer, J. A. W.; Liskamp, R. M. J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 47.

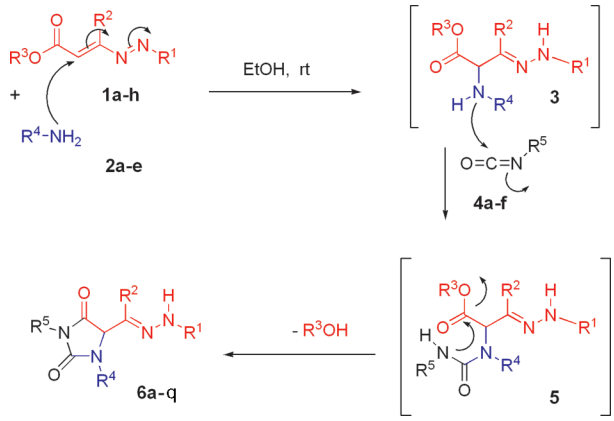
(9) Beller, M.; Eckert, M.; Moradi, W. A.; Neumann, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1454.

(10) Ignacio, J. M.; Macho, S.; Marcaccini, S.; Pepino, R.; Torroba, T. *Synlett* **2005**, 3051.

(11) Volonterio, A.; de Arellano, C. R.; Zanda, M. *J. Org. Chem.* **2005**, *70*, 2161.

10.1021/ol102664n 
**Published on Web 12/27/2010**

**Scheme 1.** One-Pot Synthesis of 1,3,5-Trisubstituted Hydantoins **6a−q**




from amino acid derivatives nor from *N*,*N*′-disubstituted ureidomalonate building blocks.[12] Indeed, by continuing our investigations designed to develop the usefulness of the conjugated azo-ene system of 1,2-diaza-1,3-dienes (DDs) as building blocks in heterocyclic chemistry, the present paper reports a synthetic strategy for regioselective trisubstituted hydantoin derivatives bearing novel and valuable functionality at the C-5 position of the hydantoin ring as a general procedure to achieve 5-acyl derivatives.

The versatility of DDs **1** in the synthesis of useful heterocyclic scaffolds is well documented[13] and relies on their ability to undergo 1,4-Michael additions. Our approach, for acquiring the title compounds in a one-pot procedure, involves the construction of *N*,*N*′-disubstituted asymmetric urea moieties linked to suitable DD substrates. Since the conjugated heterodiene system exalts the electrophilic character of the terminal carbon of **1** making it capable to undergo nucleophilic attack, primary amines **2** constitute useful reagents to perform an aza-Michael addition producing the corresponding α-aminohydrazone derivatives **3**.[14] Subsequent acylation of secondary amines **3** with isocyanates **4** generates the requisite asymmetric ureas **5** to be directed to a ring closure. Indeed, compounds **5** provide spontaneous regioselective heteroring closure owing to the nucleophilic attack of the amidic NH at the terminal ester function of the azo-ene system, affording the hydantoin derivative **6** (Scheme 1) by loss of an alcohol molecule. This one-pot reaction sequence represents a valuable route to variously 1,3,5-trisubstituted hydantoins **6a−q** containing an electron-withdrawing hydrazone function at C-5 derived from the conjugated azo-ene system of DDs. It can be easily accomplished in EtOH at room temperature, with satisfactory yields (47−76%, Table 1) overcoming the drawback of regiocontrol (i.e., **6c,d,i,p**) especially when weakly asymmetric carbodiimides are used.[11]

Although aromatic amines (i.e., 4-methoxyaniline) worked well in the Michael addition producing α-aminohydrazones **3**, unfortunately the subsequent coupling with isocyanates (i.e., butylisocyanate) failed probably because of the poor nucleophilicity of the amine nitrogen atom of **3** (only traces of **5** were observed even upon prolonged reaction times).

Since the hydrazone side chain represents a protected carbonyl function, the hydrolytic cleavage of the hydrazide moiety under heterogeneous conditions (Scheme 2) introduces a point of diversity leading to novel 5-acyl disubstituted 1,3-hydantoin scaffolds difficult to obtain from amino acid ester building blocks[8a] or by other methods.[9,11,12]

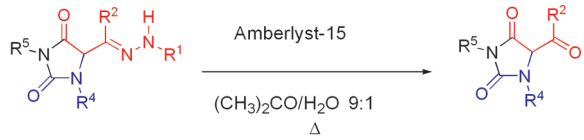
In summary, we have demonstrated the synthetic utility of 1,2-diaza-1,3-dienes in the construction of diversified trisubstituted 1,3,5-hydantoins with a controlled regioselectivity in the substitution at N-1 and N-3 of the heterocycle

**Table 1.** Results of the Synthesis of Hydantoin Derivatives **6a−q**

| | DD **1** | | | | amine **2** | | isocyanate **4** | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| entry | | $R^1$ | $R^2$ | $R^3$ | | $R^4$ | | $R^5$ | hydantoin **6** | yield[a] (%) |
| 1 | **1a** | $CO_2Et$ | Me | Et | **2a** | *n*-Bu | **4a** | Ph | **6a** | 67 |
| 2 | **1b** | $CO_2t$-Bu | Me | Et | **2b** | *n*-Pr | **4a** | Ph | **6b** | 76 |
| 3 | **1b** | $CO_2t$-Bu | Me | Et | **2b** | *n*-Pr | **4b** | Cyclohexyl | **6c** | 65 |
| 4 | **1c** | $CO_2Me$ | Me | Et | **2b** | *n*-Pr | **4c** | $CH_2CO_2Et$ | **6d** | 68 |
| 5 | **1d** | $CO_2Bn$ | Me | Et | **2a** | *n*-Bu | **4a** | Ph | **6e** | 62 |
| 6 | **1a** | $CO_2Et$ | Me | Et | **2b** | *n*-Pr | **4a** | Ph | **6f** | 66 |
| 7 | **1c** | $CO_2Me$ | Me | Et | **2c** | Allyl | **4a** | Ph | **6g** | 65 |
| 8 | **1a** | $CO_2Et$ | Me | Et | **2d** | Propargyl | **4d** | 3-Cl-Ph | **6h** | 63 |
| 9 | **1a** | $CO_2Et$ | Me | Et | **2e** | Benzyl | **4b** | Cyclohexyl | **6i** | 63 |
| 10 | **1e** | $CO_2t$-Bu | Et | Et | **2b** | *n*-Pr | **4a** | Ph | **6j** | 66 |
| 11 | **1a** | $CO_2Et$ | Me | Et | **2b** | *n*-Pr | **4d** | 3-Cl-Ph | **6k** | 63 |
| 12 | **1c** | $CO_2Me$ | Me | Et | **2d** | Propargyl | **4a** | Ph | **6l** | 63 |
| 13 | **1c** | $CO_2Me$ | Me | Et | **2e** | Benzyl | **4e** | 4-Cl-Ph | **6m** | 73 |
| 14 | **1f** | $CO_2t$-Bu | Ph | Et | **2a** | *n*-Bu | **4e** | 4-Cl-Ph | **6n** | 48 |
| 15 | **1g** | $CO_2t$-Bu | $CH_2CO_2Et$ | Et | **2b** | *n*-Pr | **4a** | Ph | **6o** | 65 |
| 16 | **1c** | $CO_2Me$ | Me | Et | **2e** | Benzyl | **4f** | *n*-Bu | **6p** | 69 |
| 17 | **1h** | $CO_2Me$ | $CO_2Et$ | Et | **2e** | Benzyl | **4e** | 4-Cl-Ph | **6q** | 47[b] |

[a] Yield of pure isolated product. [b] Yield referred to isolated α-aminohydrazone derivative.

**Scheme 2**




**6a** $R^1 = CO_2Et$; $R^2 = Me$; $R^4 = n$-Butyl; $R^5 = Ph$ — **7a** (80%)

**6d** $R^1 = CO_2Me$; $R^2 = Me$; $R^4 = n$-Propyl; $R^5 = CH_2CO_2Et$ — **7b** (77%)

**6j** $R^1 = CO_2t$-Bu; $R^2 = Et$; $R^4 = n$-Propyl; $R^5 = Ph$ — **7c** (87%)

**6m** $R^1 = CO_2Me$; $R^2 = Me$; $R^4 = Benzyl$; $R^5 = 4$-Cl-Ph — **7d** (83%)

**6n** $R^1 = CO_2t$-Bu; $R^2 = Ph$; $R^4 = n$-Butyl ; $R^5 = 4$-Cl-Ph — **7e** (74%)

with respect to that obtained when weakly asymmetric carbodiimides are coupling with α,β-unsaturated carboxylic acids. The one-pot procedure described here is based on sequential aza-Michael addition/condensation reactions and introduces a valuable hydrazone functionality at the 5-position of the heteroring that allows access to 5-acyl hydantoins. Noteworthily, the acyl residue directly bonded at the C-5 of the hydantoin nucleus is not easily achievable from amino acid esters or with ureidomalonate building blocks.

Further extension of this sequential three-component pathway is currently being pursued in our laboratories and will be reported in due course.

**Acknowledgment.** Financial support from the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR)-Roma and from the University of Urbino "Carlo Bo" is gratefully acknowledged.

**Supporting Information Available:** Detailed experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102664N

(12) Li, J. P. *J. Org. Chem.* **1975**, *40*, 3414.

(13) (a) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Perrulli, F. R.; Santeusanio, S. *Eur. J. Org. Chem.* **2009**, 3109. and the references cited therein. (b) Attanasi, O. A.; Baccolini, G.; Boga, C.; De Crescentini, L.; Filippone, P.; Mantellini, F. *J. Org. Chem.* **2005**, *70*, 4033. (c) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Lillini, S.; Mantellini, F.; Santeusanio, S. *Synlett* **2005**, 1474. (d) Attanasi, O. A.; Abbiati, G.; Rizzato, S.; Rossi, E.; Santeusanio, S. *Tetrahedron* **2007**, *63*, 11055. (e) Attanasi, O. A.; Cotarca, L.; Favi, G.; Filippone, P.; Perrulli, F. R.; Santeusanio, S. *Synlett* **2009**, 1583. (f) Attanasi, O. A.; Favi, G.; Filippone, P.; Perrulli, F. R.; Santeusanio, S. *Org. Lett.* **2009**, *11*, 309. (g) Attanasi, O. A.; Caselli, E.; Davoli, P.; Favi, G.; Mantellini, F.; Ori, C.; Prati, F. *Org. Lett.* **2009**, *11*, 2840. (h) Attanasi, O. A.; Favi, G.; Giorgi, G.; Mantellini, F.; Kaarapetyan, V.; Langer, P. *Tetrahedron* **2009**, *65*, 5456. (i) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Mantellini, F.; Moscatelli, G.; Perrulli, F. R. *Org. Lett.* **2010**, *12*, 468. (j) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Felluga, F.; Forzato, C.; Mantellini, F.; Nitti, P.; Pitacco, G.; Valentin, E. *Tetrahedron: Asymmetry* **2010**, *21*, 617. (k) Attanasi, O. A.; Bartoccini, S.; Giorgi, G.; Mantellini, F.; Perrulli, F. R.; Santeusanio, S. *Tetrahedron* **2010**, *66*, 5121.

(14) Attanasi, A.; Berretta, S.; De Crescentini, L.; Favi, G.; Giorgi, G.; Mantellini, F. *Adv. Synth. Catal.* **2009**, *351*, 715.