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

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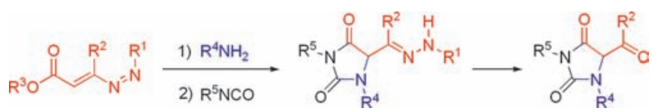
ABSTRACT



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

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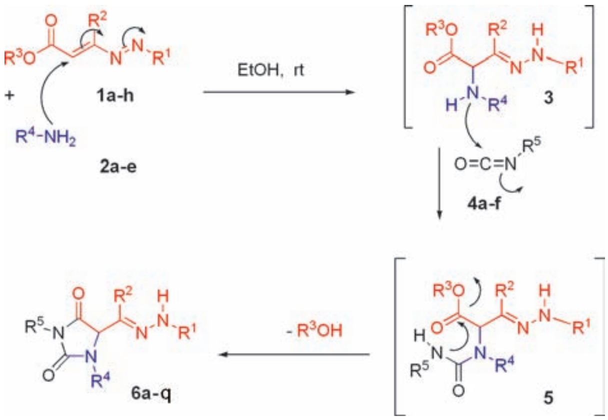
Scheme 1. One-Pot Synthesis of 1,3,5-Trisubstituted Hydantoins **6a−q**



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]

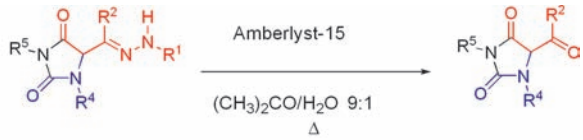
In summary, we have demonstrated the synthetic utility of 1,2-diaza-1,3-dienes in the construction of diversified trisubstituted 1,3,5-hydantoins with a controlled regioselectivity in the substitution at N-1 and N-3 of the heterocycle

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_2*t*-Bu	Me	Et	**2b**	*n*-Pr	**4a**	Ph	**6b**	76
3	**1b**	CO_2*t*-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_2*t*-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_2*t*-Bu	Ph	Et	**2a**	*n*-Bu	**4e**	4-Cl-Ph	**6n**	48
15	**1g**	CO_2*t*-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_2*t*-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_2*t*-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.

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

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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.

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