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Unusual Reactivity of Sulfahydantoins in the Mitsunobu Reaction

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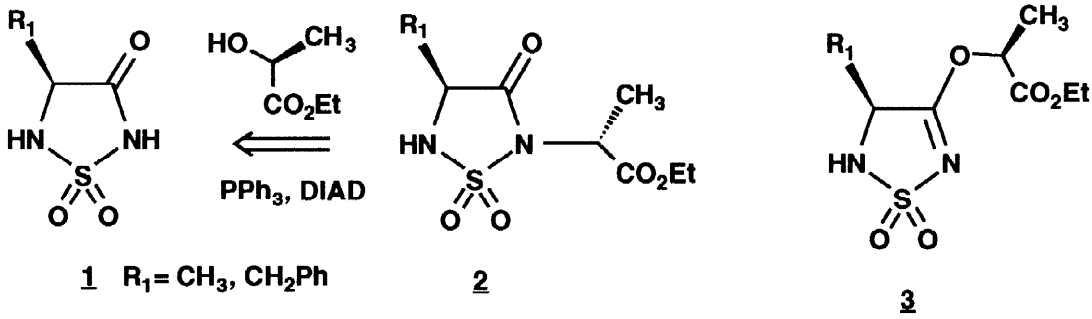
Abstract: *The use of sulfahydantoins in the Mitsunobu reaction with hydroxyacids lead to O-substituted compounds rather than the expected N-alkylated structures. Crystallographic analysis by X-ray diffraction confirmed the structure of unusual compounds and a mechanism for their formation is proposed.*

During the course of our investigation on novel modification of peptide backbones, we sought to use sulfahydantoins **1** as building blocks and nucleophiles in Mitsunobu reactions to obtain *N*-substituted sulfahydantoins **2** (Scheme 1).



1 $R_1 = CH_3, CH_2Ph$ **2** **3**

Scheme 1

The synthesis of *sulfa* analogues of hydantoins is easily realized starting from natural amino acids and chlorosulfonyl isocyanate under enantioconservative conditions using a procedure we have described recently.[1] In analogous linear structures, the greater nucleophilicity of the sulfocarbamate NH allows its selective functionalization by a Mitsunobu reaction. Indeed, alkylation by a hydroxyester such as lactate, malate, and glycolate on the carbamate site using the tandem triphenylphosphine: diisopropylazodicarboxylate (DIAD) lead to clean alkylated compounds with inversion of configuration.[2]

Herein, we report however that the use of cyclic sulfahydantoins in the same reaction yield unexpectedly *O*-alkylated lactim compounds **3**. Even though the lactim-lactam equilibrium is possible for this type of compounds, alkylation using diazomethane gives only the *N*-substituted derivative.[3] Moreover, it is well established that Mitsunobu reactions with nucleophiles such as cyclic imides (uraciles, hydantoins and related compounds) give selectively the *N*-alkylated derivatives following a S_N2 mechanism.[4]

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Sulfahydantoins **1**, derived from L-alanine and L-phenylalanine, were synthesized and characterized as previously described.[5] S_N-Redox reaction with ethyl (*S*)-lactate was carried out in THF to give the derivatives **3** in 55-75% yields (Table 1). The NMR data showed that the exocyclic C*H was more deshielded than the endocyclic C*H. The same reactivity was observed using benzyl alcohol and malate esters as hydroxyl component. The Schotten-Baumann acylation of compounds **3** with acetic anhydride 6 gave the corresponding *N*-acetyl derivatives. As expected, in these compounds, the endocyclic C*H undergoes a downfield shift from 0.8 to 1.0 ppm.

Table 1: Selected spectroscopic data for compounds **3** and the acetylated derivatives.

R_1	N-subs	mp °C	^{1}H NMR (300 MHz, $CDCl_3$)
Me	H		5.28 (q, 1H, CH exocyc); 4.75 (d, 1H, NH, Exch); 4.52 (quint, 1H, CH endocyc); 4.25 (q, 2H, CH_2 Et); 1.65 (d, 3H, Me exocyc); 1.55 (d, 3H, Me endocyc); 1.30 (t, 3H, CH_3 Et).
Bn	H		7.26 (m, 5H, ArH); 5.28 (q, 1H, CH exocyc); 5.0 (d, IH, NH, exch); 4.54 (m, 1H, CH endocyc); 4.20 (q, 2H, CH_2-O); 3.22, 2.92 (2dd, 2H, J=13.9, 9.6, 3.6, CH_2 Ph); 1.62 (d, 3H, Me-CH); 1.16 (t, 3H, Me est).
Me	Ac		5.35 (2q, 2H, CH exo+endocyc); 4.20 (m, 2H, CH_2 est); 2.35 (s, 3H, Me Ac); 1.55, 1.50 (2d, 6H, 2 Me-CH); 1.20 (t, 3H, Me est).
Bn	Ac	108-9	7.27 (s, 5H, ArH); 5.25 (q, 1H, CH exocyc); 5.17 (t, 1H, CH endocyc); 4.31 (q, 2H, CH_2 Et); 3.37 (d, 2H, CH_2 Ph), 2.45 (s, 3H, Ac); 1.57 (d, 3H, Me CH); 1.33 (t, 3H, CH_3 Et). ^{13}C NMR *: 173.7, 168.2, 167.0 (C=O); 133.9, 129.8, 128.5, 127.6 (Ar); 76.0 (C*H); 63.3, 62.4 (C-O); 35.9 (C-Ph); 23.1, 17.0, 14.1 (Me).

It is noteworthy that the spectroscopic data for **3** look quite close at first to the ones that would be expected for the usual *N*-alkylated compounds. However, the crystallographic analysis (Figure 1) of compound **3** (*N*-acetyl, R_1= CH_2-Ph)[7] confirms the *O*-alkylation. Surprisingly, the crystal structure shows that the lactate chiral center preserved its configuration in **3**.[8] Also interestingly, the *N*-acetyl bond (in E conformation similarly of Oppolzer's acylsultams 9) and the exocyclic C*H were coplanar with the heterocycle. The ester part of the molecule appears as disordered between two positions (a and b, about 1/1 ratio).

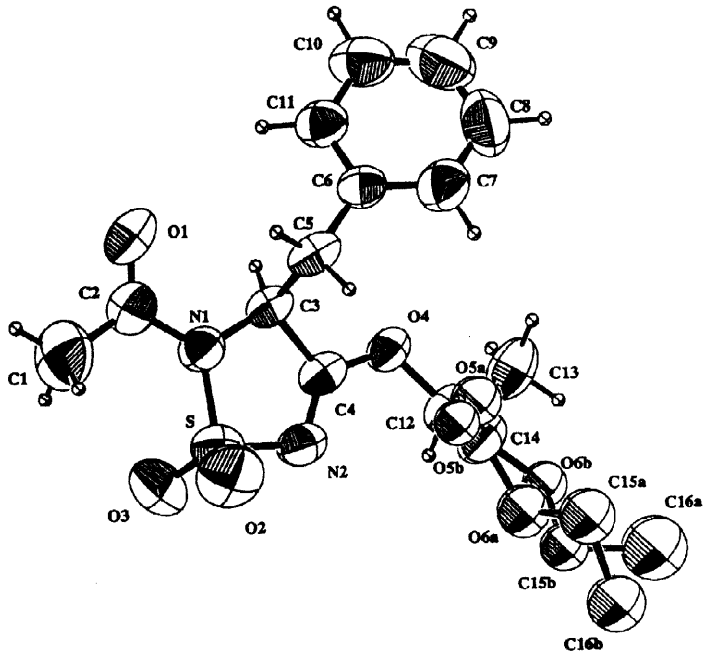
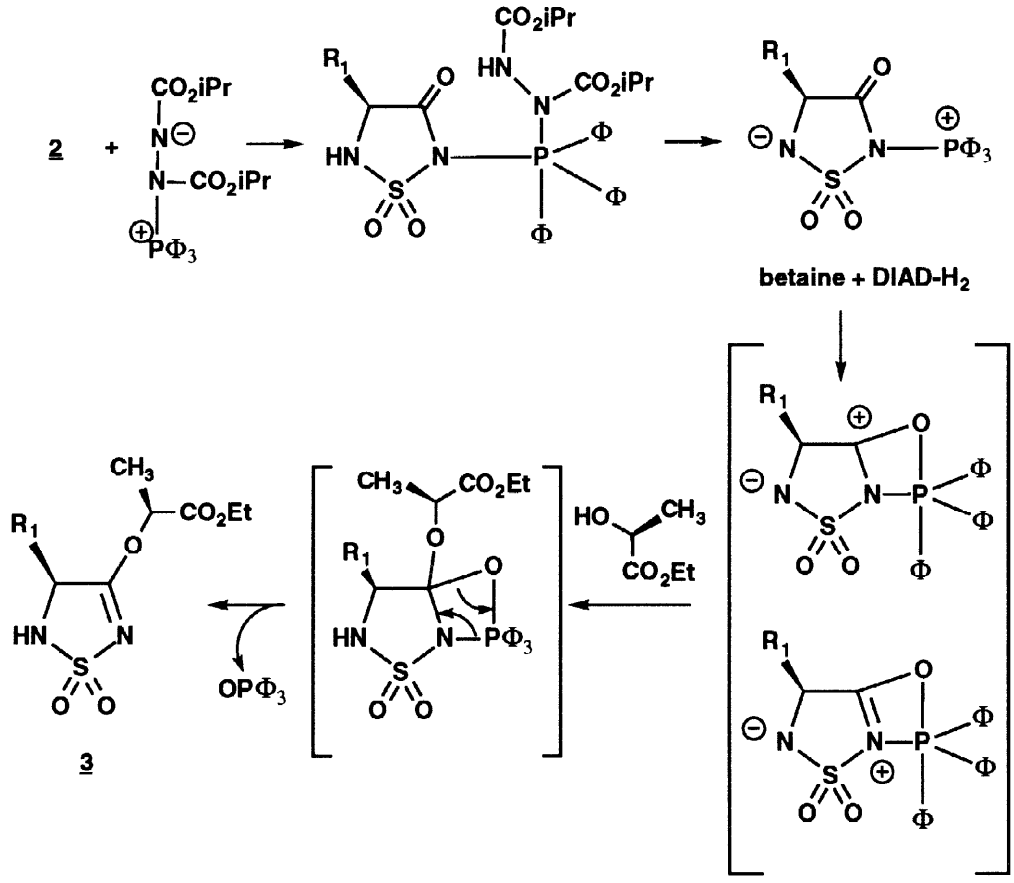


Figure 1. Ortep view of the *N*- acetyl derivative of sulfonyllactim **3** (R_1= CH_2Ph).[7]

To explain the formation of **3**, we propose a "*pseudo*-Mitsunobu" mechanism (Scheme 2) involving the initial formation of a phosphonium betaine10, which can equilibrate between the carbonium and iminium species11 in the bicyclic form. The latter could undergo a nucleophilic attack by the oxanion of the hydroxyl component, concurrent with the Wittig-like formation of triphenylphosphine oxide, to give the *O*-alkylated structures with retention of configuration. On the other hand, the reaction with malate diester with sulfahydantoins confirms that the proposed mechanism is plausible. Indeed, contrarily to usual Mitsunobu reactions with malate, the formation fumarate resulting from elimination was not observed. This fact suggests the cleavage of the O-H bond of the alcohol rather than the normal C-O cleavage.12 Also, the hypothesis of a N->O transposition with double-inversion can be dismissed, because of the thermodynamic stability of the *N*-alkylated regioisomers versus the *O*-alkylated analogs.13



Scheme 2

In conclusion, the sulfahydantoin heterocycles under Mitsunobu reaction conditions lead to unusual lactim *O*-alkylated compounds. The key step involves the nucleophilic attack of the oxygen from the hydroxyl component on the lactam carbon resulting in retention of configuration. Work is actually in progress to explore the applicability of the unusual reactivity of sulfahydantoins.

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7- After Lorenz and polarization corrections, the structure was solved by a direct method with the program SHELX-86 (Scheldrick, G.M., *Crystallographic computing 3: Data Collection, Structure Determination, Proteins and Databases.* Sheldrick, Kruger and Goddard Edt., Clarendon Press, Oxford, 1985) which reveals all the non-hydrogen atoms of the compound. Crystallographic data of compound **3** (*N*-Ac, R_1= CH_2Ph):

Formula	$C_{16}H_{20}N_2O_6S$	Scan	ω/2θ = 1
Mol.Wt	354.40	t max (for one measure), s	60
Cryst. Syst	Orthorhombic	Variance of standards 0.3%	
Space Group	P212121	Range of HKL	0,10 ; 0,15; 0,19
a	8.885(8)	Reflections measured 1928	
b	12.994(4)	Reflections observed (I> s(I)): 1224 (2.0s)	
c	16.321(3)	R (isotropic)	0.105
V	1884(6)	R (anisotropic)	0.082
Z	4	Fourier Difference	0.45 - 0.29
ρ calc g.cm^{-3}	1.249	N(obs)/N(var)	1224/223
F(000)	748	Final R	0.052
μ (MoKα) cm^{-1}	1.904	Rw	0.047
T (° K)	294	w = 1/s (Fo)2=[s^2(I) + (0.04Fo^2)^2]-1/2	
Crystal size (mm)	0.45*0.45*0.55	Sw	0.998
Radiation	Mo Kα	Max residual e.Å^{-3}, D/s	0.25, 0.29
Max 2Θ (°)	50°		

8- Only one diastereoisomer was detected in the crude reaction mixture by NMR ruling out the possiblility of a selective enrichment during crystallization.

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12- Another possible mechanism would be the phosphorylation of the lactim form of **1** followed by an addition-elimination process by the alcohol.

13- We have synthesized by a different strategy the following *N*-benzyl compound and showed that it does not interconvert to the *O*-alkylated analog.