Expedient Syntheses of Sulfonylhydantoins and Two Six-Membered Analogues

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Abstract: A range of α-amino esters can be turned into sulfonylhydantoins **2** in a single, atom-economic step using sulfamide and DBU. This procedure obviates the need for a three- or four-step sequence utilised by traditional procedures. Two new six-membered analogues **3** and **4** have also been prepared utilising novel synthetic protocols.

Key words: amino acids, sulfonamides, heterocycles, medicinal chemistry, phosphates

The first report of the 1,2,5-thiadiazolidin-3-one 1,1-dioxide moiety ('sulfonylhydantoin', **1**) was in 1965 by the group of Ziegler.[1] Since then, this heterocycle has received a lot of attention amongst the synthetic and medicinal chemistry community particularly in relation to serine protease inhibitors,[2] crop protection agents,[3] antihypertensives,[4] artificial sweetners[5] and others.[6] More recently, they have been described as PTB-1b inhibitors which may have a role in controlling blood sugar in diabetes[7a] and as anti-cancer compounds.[7b] We became interested in sulfonylhydantoins such as **2** and their closely related but previously unknown analogues **3** (5-aryl-1,2,6-thiadiazinan-3-one 1,1-dioxide) and **4** (5-aryl-1,2-thiazinan-3-one 1,1-dioxide) as phosphate mimics (Figure 1). N-substituted sulfonylhydantoins are usually prepared by one of two general methods starting from N-substituted α-aminoesters.[2b,5] Reaction of an alcohol with chlorosulfonyl isocyanate generates the N-protected sulfonyl chloride (Scheme 1), which is then reacted with the amine to form the sulfamoyl group. Protecting group removal followed by basic cyclisation forms the desired sulfonylhydantoin. Alternatively, the isocyanate is reacted with formic acid[8] or water[9] to generate 'NH_2SO_2Cl' which is subsequently reacted with the amine and cyclised to form the same products. Although this route works, we believed this three- or four-step sequence could be improved and avoid the use of the highly reactive chlorosulfonyl isocyanate.

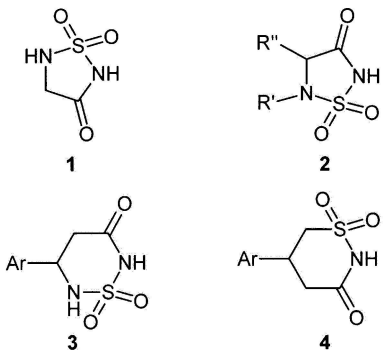
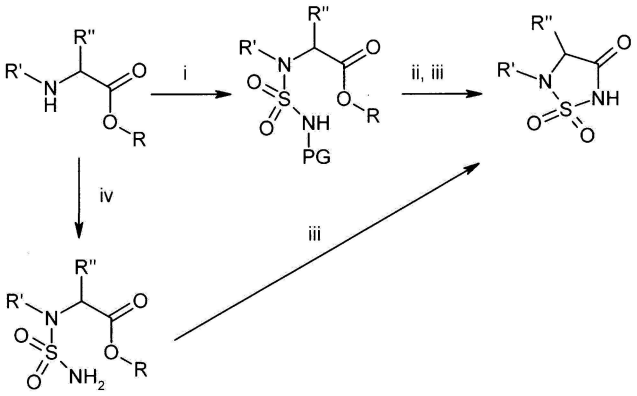


Figure 1 Examples of sulfonylhydantoins and analogues required.



Scheme 1 Standard methods for synthesising sulfonylhydantoins. *Reagents and conditions*: i) $ClSO_2NCO$, ROH then α-amino ester, base; ii) deprotection of protecting group (PG); iii) NaH or NaOMe; iv) $ClSO_2NCO$, HCOOH or H_2O then α-amino ester/base.

We hoped to react our amino esters with sulfamide ($NH_2SO_2NH_2$) in the presence of a base to effect a sulfamoylation and cyclisation in one pot. There is one literature example of this transformation being achieved directly without the use of base,[4] although the substrate scope was not examined. The amino esters were either commercially available or prepared by standard amine-monoalkylation of methyl bromoacetate or reductive amination with glycine methylester hydrochloride with the corresponding aldehyde according to the procedure of Groutas and co-workers.[2b] The reaction of amines with sulfamide is well documented[10] so we initially attempted heating *N*-benzyl glycine ethyl ester with sulfamide at 160 °C in the absence of solvent for 15 minutes. Following purification, we were pleased to isolate the desired sulfamoylated product (addition of SO_2NH_2 to the amine) in 65% yield. The same reaction was attempted with the addition of one equivalent of DBU, and the required sulfonylhydantoin was isolated after acid/base work up in good yield without the need for chromatography.[11] This procedure was then applied to a range of substituted glycine derivatives (Table 1). Although the unoptimised

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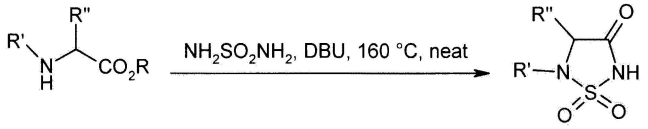
yields are moderate in most cases, the one-step protocol allowed for a large range of sulfonylhydantoins to be prepared in a time efficient manner without the need for chromatography in any example. The procedure tolerates substitution at the α-carbon (entries 10, 13–15) and substitution α to the amine (entry 6) although the yield drops considerably with *gem*-dimethyl substitution (entry 11). The reaction also tolerates thiophene (entry 5), nitrile (entry 8) and ester functionalities (entry 9). The reaction with *N*-phenyl glycine methyl ester failed to give any product (entry 16) while dilution with solvent (entry 3) and heating under microwave conditions also failed to give clean product formation.

Table 1 Results for the Reaction of α-Amino Esters with Sulfamide and DBU[11]



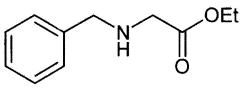
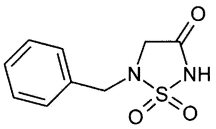
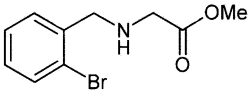
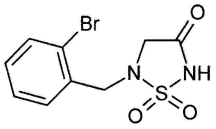
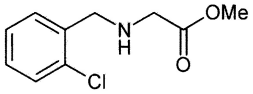
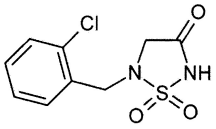
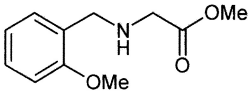
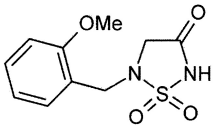
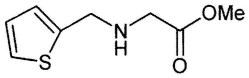
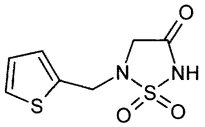
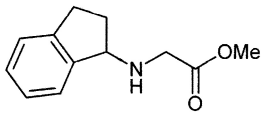
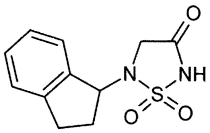
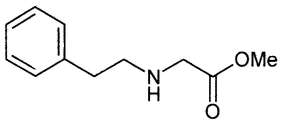
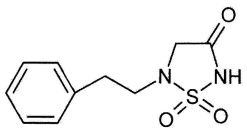
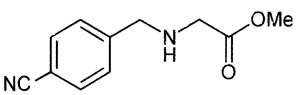
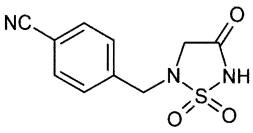
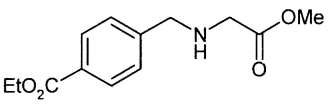
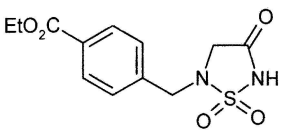
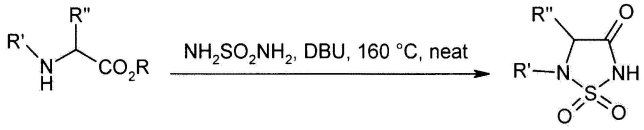
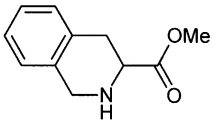
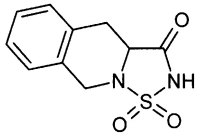
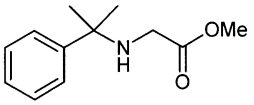
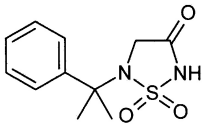
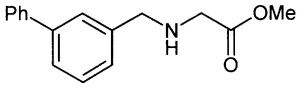
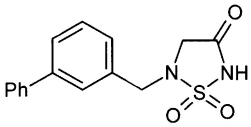
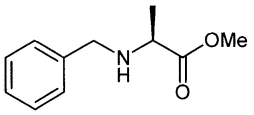
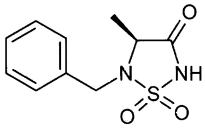
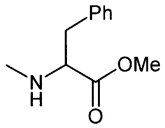
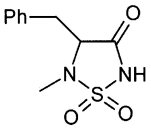
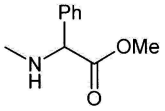
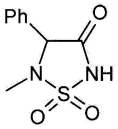
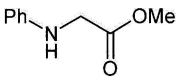
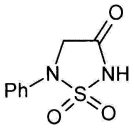
Entry	α-Amino ester	Product	Yield (%)[a,b]
1			65[a,b]
2			35
3			29[c]
4			45
5			43
6			26
7			47
8			36
9			55

Table 1 Results for the Reaction of α-Amino Esters with Sulfamide and DBU[11] (continued)

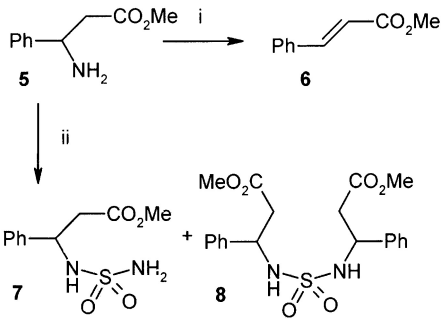


Entry	α-Amino ester	Product	Yield (%)[a,b]
10			23
11			2
12			40
13			38
14			57
15			39
16			0

[a] Reaction without DBU gave uncyclised material in 65% isolated yield.
[b] If a salt is used in this reaction, a second equivalent of DBU was added. The yield was 65%.
[c] Heating at 160 °C in THF–H_2O for 15 min gave an impure reaction mixture.

We next turned our attention to the hitherto unknown 5-aryl-1,2,6-thiadiazinan-3-one 1,1-dioxide system **3** which we hoped to make by the same method. Unfortunately, when β-amino acid **5** was heated with sulfamide and DBU, the only isolated product was methyl cinnamate **6** presumably formed by elimination in the basic conditions. Heating with sulfamide in the absence of DBU did form the desired product in low yield, however, by-products **6** and **8** were isolated as the major products (Scheme 2).

We therefore reverted to homologation using NH_2SO_2Cl. The required starting β-amino esters were prepared by Rodionow reaction[12] of 3-bromobenzaldehyde and 5-bromo-2-methoxybenzaldehyde with ethyl hydrogen malonate in the presence ammonium chloride (Scheme 3). Although the yields were relatively low, the starting



Scheme 2 Reaction of β-amino ester with sulfamide with and without added DBU. *Reagents and conditions*: i) $NH_2SO_2NH_2$, DBU, 160 °C, 15 min, 55%; ii) $NH_2SO_2NH_2$, 160 °C, 20 min, **7**, 15%, **8**, 22%, **6**, 42%.

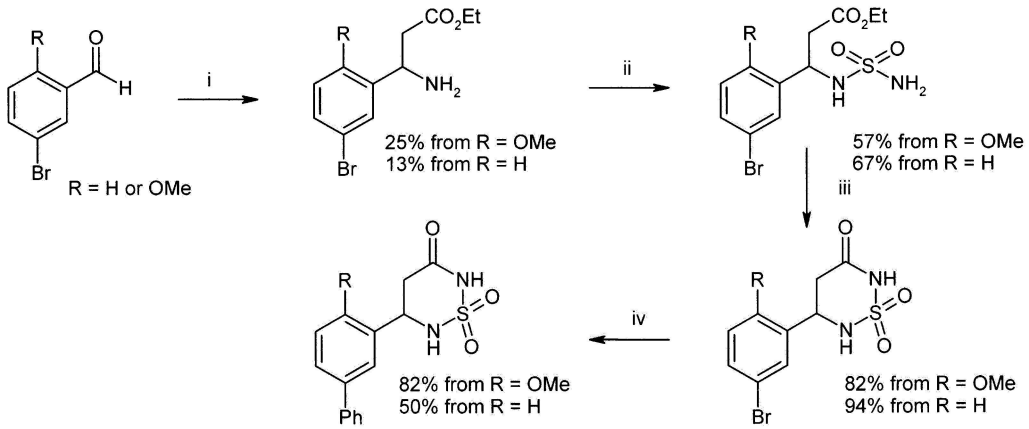
materials were cheap, readily available and the amine products easily purified. These amines were then reacted with sulfamoyl chloride prepared from chlorosulfonyl isocyanate and water in THF. This revised procedure gave much improved yields compared to the formic acid procedure.[8] The sulfamoylated products underwent smooth cyclisation with NaOMe in MeOH to afford the novel substituted ring system. Both compounds were coupled smoothly with phenyl boronic acid under Suzuki conditions to give homologated products and to exemplify that these structures are amenable to palladium-catalyzed coupling protocols.

The final ring system (5-aryl-1,2-thiazinan-3-one 1,1-dioxide) **4** had not been prepared previously although the work by Morris and Wishka[13] gave us an insight into preparing a regioisomeric aryl-substituted product. Our initial plan relied heavily on the preparation of vinyl sulfonate ester **12** (Scheme 4) and a Michael addition of the malonate anion to it.[14] The phenyl sulfonate ester was chosen due its lability to sulfur-oxygen cleavage compared to an alkyl sulfonate ester, which may be prone to alkyl-oxy fission. Thus, phenyl methylsulfonate was treated with two equivalents of LiHMDS at –78 °C followed by addition of one equivalent of diethyl chlorophosphate to generate the Wadsworth–Emmons reagent in situ. Aldehyde **9** was added and warmed to room temperature. Unfortunately, no product was isolated from the reaction. In order to ascertain why the reaction had failed, we attempted the same reaction using ethyl methanesulfonate and were pleased to isolate the alkenyl product **11** in 85% yield solely as the *E*-isomer (J = 15.6 Hz). Hence, we assumed that during the generation of the anion of phenyl methylsulfonate, elimination to sulfene and phenoxide was occurring[15] prior to addition to diethyl chlorophosphate. Therefore, we decided to carry out an in situ quench at low temperature, which might circumvent sulfene formation. We were delighted to find that this rationale was substantiated by obtaining a 36% yield of product **11** as the *E*-isomer (J = 15.6 Hz). Unfortunately, on scale-up (8 mmol) the yield dropped to 23%.

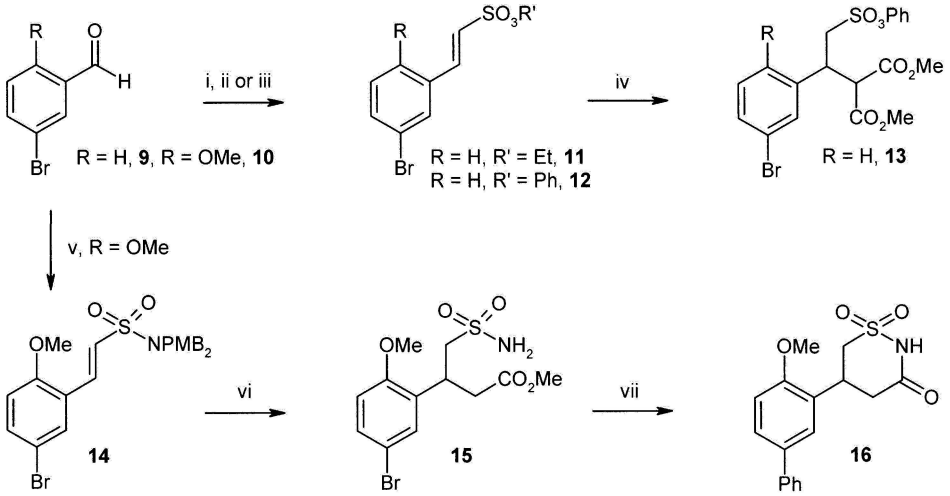
Another strategy utilising a cross-metathesis between phenyl vinylsulfonate and 3-bromo styrene using Grubbs second generation ruthenium catalyst failed to give any cross-metathesis product despite good precedent with vinyl phosphates and styrenes.[16] Although alkenyl sulfonate **12** could be prepared and indeed reacted with dimethyl malonate, the low yielding initial step meant that an alternative strategy had to be followed.

Our second option was to go via a Michael reaction of a malonate anion to a β-substituted vinyl sulfonamide as the key step (Scheme 4), a process that is not documented in the literature. Thus *N*,*N*-bis(4-methoxybenzyl)methanesulfonamide was easily prepared by reaction of methanesulfonyl chloride with *bis*(4-methoxybenzyl)amine. Alternatively, the same material could be prepared by alkylation of methanesulfonamide with 4-methoxybenzyl chloride albeit in lower yield. The sulfonamide was then treated with LiHMDS (2 equiv) followed by the addition of diethyl chlorophosphate and quenched with 5-bromo-2-methoxybenzaldehyde to form alkenyl sulfonamide **14** in 80% yield. We were delighted to find that Michael addition proceeded smoothly with dimethyl malonate to form the diester in 85% yield. Krapcho decarboxylation carried out in DMF and sulfonamide deprotection in 1:1 TFA–CH_2Cl_2[13] formed the sulfonamide **15** in 46% yield over two steps. Cyclisation using standard NaOMe in MeOH conditions smoothly formed the novel 5-aryl-1,2-thiazinan-3-one dioxide system in excellent yield. Suzuki coupling with phenyl boronic acid formed the biaryl product **16** in 74% yield.

In conclusion, we have developed a novel one-step protocol for the synthesis of sulfonylhydantoins from N-substituted α-amino esters. The products are formed in high



Scheme 3 Generation of the 5-aryl-1,2,6-thiadiazinan-3-one 1,1-dioxide ring system. *Reagents and conditions*: i) NH_4Cl, ethyl hydrogen malonate, EtOH, reflux 16 h, R = OMe, 25%; R = H, 13%; ii) $ClSO_2NCO$, THF, H_2O (1 equiv), 0 °C, 1 h, β-amino ester then Et_3N, R = OMe, 57%; R = H, 67%; iii) NaOMe–MeOH, r.t., 1 h, R = OMe, 82%; R = H, 94%; iv) $PhB(OH)_2$, DME–H_2O (2:1), $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (4 equiv), R = OMe, 82%; R = H, 50%.



Scheme 4 Generation of the 5-aryl-1,2-thiazinan-3-one 1,1-dioxide ring system. *Reagents and conditions*: i) ethyl methanesulfonate, LiHMDS (2 equiv), –78 °C, 30 min then $ClPO(OEt)_2$, 1 h then RCHO **9**, –78 °C to r.t., 1 h, 85%; ii) phenyl methanesulfonate, LiHMDS (2 equiv), –78 °C, 30 min then $ClPO(OEt)_2$, 1 h then RCHO **9**, –78 °C to r.t., 1 h, 0%; iii) phenyl methanesulfonate, $ClPO(OEt)_2$, LiHMDS (2 equiv), –78 °C, 1 h then RCHO **9**, –78 °C to r.t. 1 h, 23–36%; iv) dimethyl malonate, NaOMe–MeOH, MeCN, 48 h, r.t., 85%; v) *N*,*N*-bis(4-methoxybenzyl)methanesulfonamide, LiHMDS (2 equiv), –20 °C, 30 min then $ClPO(OEt)_2$, 1 h then RCHO **10**, –20 °C to r.t., 1 h, 80%; vi) a) dimethyl malonate, NaOMe–MeOH, MeCN, 18 h, reflux, 85%; b) DMF, NaCl, H_2O, reflux, 5h; c) TFA–CH_2Cl_2 (1:1), 18 h, r.t., 46% (2 steps); vii) a) NaOMe–MeOH, r.t., 1 h, 93%; b) $PhB(OH)_2$, DME–H_2O (2:1), $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (4 equiv), 74%.

purity, quickly and without the need for chromatography. The procedure should be readily applicable to the synthesis of other sulfonylhydantoins. Two previously undescribed six-membered analogues have also been prepared using novel chemistry and have proved compatible to further functionalisation.

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(11) Sulfamide (159 mg, 1.65 mmol) was added to methyl *N*-(2-methoxybenzyl)glycinate (345 mg, 1.65 mmol) followed by addition of DBU (0.25 mL, 1.65 mmol) in a 10 mL pyrex tube under an argon stream. The reaction was then heated to 160 °C at which point the reaction became homogeneous and bubbling was observed. After 15 min, the reaction was cooled to r.t. and diluted with 1 M NaOH (40 mL) and Et_2O (20 mL) and shaken until all the gum dissolved. The aqueous layer was separated, acidified with 6 M HCl until pH 1 and then extracted with EtOAc (2 × 20 mL). The combined EtOAc layers were dried ($MgSO_4$), filtered and evaporated to form a beige solid. Trituration with Et_2O–hexanes (1:5, 5 mL) followed by filtration afforded the sulfonylhydantoin product (Table 1 entry 4, 190 mg, 0.742 mmol, 45%) as an off-white solid. ^1H NMR (300 MHz, DMSO): δ = 3.80 (s, 3 H), 4.00 (s, 2 H), 4.24 (s, 2 H), 6.93 (t, *J* = 7.5 Hz, 1 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 7.29–7.37 (m, 2 H), 8.60 (br s, 1 H). ^{13}C NMR (75 MHz, DMSO): δ = 45.1, 55.3, 55.8, 111.3, 120.7, 123.7, 129.7, 129.9, 157.5, 168.6. HRMS (TOF MS EI^+): *m*/*z* calcd for $C_{10}H_{12}N_2O_4S$: 256.0518; found: 256.0521.

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