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A stereocontrolled route to protected isocyanates from alcohols

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Abstract—Full details are given for a modified Mitsunobu approach to the formation of *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **2** from a wide range of alcohols **10** with predominantly, inversion of configuration. The resulting products **2** can be regarded as protected isocyanates **6**.

1. Introduction

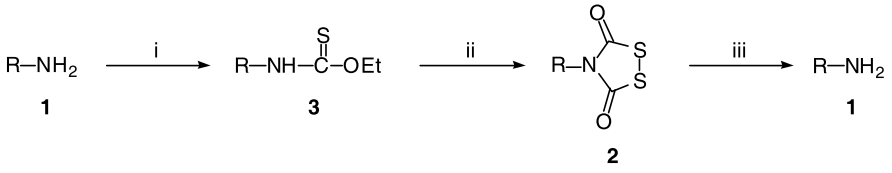
Amongst the plethora of protecting groups that have been developed for primary amines **1**,[1] the dithiasuccinoyl imide or 1,2,4-dithiazolidine-3,5-dione **2** (abbreviated to RNDts) stands out in that it can be cleaved under unusual conditions. For example, such imides **2** can be converted back into primary amines **1** using mild thiolysis, under basic conditions[2] or using phosphorus(III) reagents under partly aqueous conditions[3] (Scheme 1).

The 1,2,4-dithiazolidine-3,5-dione heterocycle is, however, stable under strongly acidic, mildly basic and photochemical cleavage conditions and hence, this group has been used in orthogonal protection strategies in peptide[4] and aminoglycoside[5] synthesis. *N*-Alkylated 1,2,4-dithiazolidine-3,5-diones **2** can be prepared from primary amines **1** via the treatment of their corresponding alkoxythiocarbamates **3** with chlorocarbonylsulfenyl chloride (Scheme 1).[6]

As an alternative, straightforward route to *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **2**, we have recently shown that it is possible to use the parent heterocycle, 1,2,4-dithiazolidine-3,5-dione **4** and its corresponding potassium salt **5** as the nucleophile in substitution reactions with reactive alkyl halides. These studies have also highlighted the fact that such imides **2** can also be regarded as a masked form of an isocyanate **6**, which can be released on treatment with triphenylphosphine, under anhydrous conditions (Scheme 2).[7,8] In addition to representing a protected form of a primary amine therefore, alkylated 1,2,4-dithiazolidine-3,5-diones **2** are also versatile and potentially very useful, synthetic intermediates.

Our findings on the use of **4** in Mitsunobu-type alkylations of alcohols have also been reported (in preliminary form).[9] Herein, we give full experimental details and a discussion of the methods used in this synthetic procedure.

Imide derivatives and phthalimide in particular, have seen wide usage as nitrogen nucleophiles in Mitsunobu amination reactions.[10] In order to circumvent the problems that are sometimes encountered in the cleavage of *N*-alkylated phthalimides, a variety of other imide and related



Scheme 1. Reagents and conditions: (i) $EtOCS_2CH_2CO_2H$ or $EtOCS_2CSOEt$; (ii) ClCOSCl; (iii) $HOCH_2CH_2SH$, Et_3N or Ph_3P, H_2O.

Keywords: 1,2,4-Dithiazolidine-3,5-diones; Mitsunobu amination; Isocyanates; Urethanes; Amino acids.
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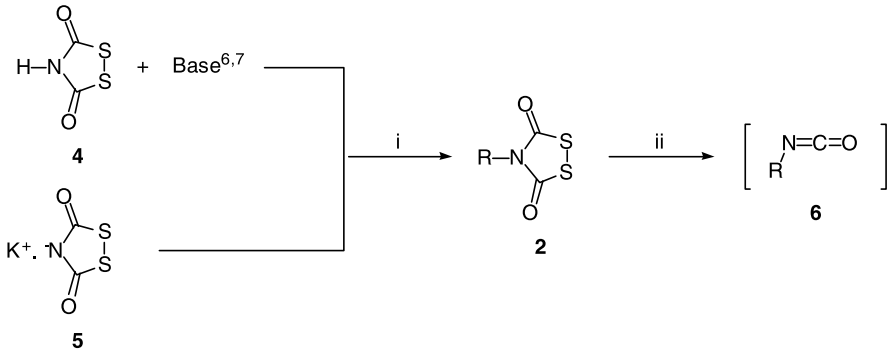
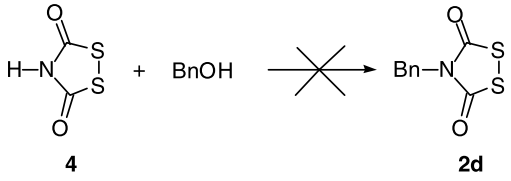


Scheme 2. Reagents and conditions: (i) R-Hal; (ii) Ph_3P, $PhCH_3$, $\triangle$.

derivatives have also been developed for use as protected amine nucleophiles.[11] The ability of *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **2** to act as protected amines or isocyanates, coupled with the remarkably high acidity of the parent heterocycle **4** ($pK_a = 2.85$),[7–9] suggested that conducting investigations into the behaviour of **4** under Mitsunobu amination conditions would be worthwhile.

2. Results and discussion

Initial experiments were carried out using benzyl alcohol, **4**, triphenylphosphine and diethyl azodicarboxylate (DEAD) (Scheme 3). As expected, these reaction conditions appeared only to result in degradation of **4**, presumably by reaction with triphenylphosphine and none of the desired product **2d** could be detected. An attempt to avoid this degradation by pre-mixing the triphenylphosphine and DEAD, followed by sequential addition of benzyl alcohol **10d** and **4**, also failed.



Scheme 3. Reagents and conditions: Ph_3P, $EtO_2C–N{=}N–CO_2Et$.

Castro et al. had reported the unexpected formation of betaine **7** in attempted Mitsunobu reactions with sulfamide **8** as the nucleophile (Fig. 1)[12] and showed that it could be used effectively to promote stereoselective Mitsunobu-type reactions between carboxylic and nitrogen acids and alcohols. Most importantly, Brummond and Lu showed that **7** could be used to mediate a Mitsunobu-type reaction with the phosphine-sensitive thiazolidinedione **9** (Fig. 1).[13]

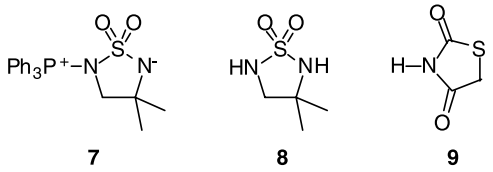
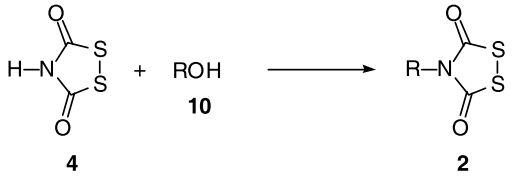


Figure 1.

We therefore carried out a systematic study of the use of **7** in reactions between **4** and a range of alcohols **10** (Scheme 4). These were chosen in order to compare results with those obtained in traditional and modified[14] Mitsunobu reactions with phthalimide.



Scheme 4. Reagents and conditions: **7**, CH_2Cl_2.

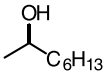
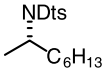
Initial experiments were carried out with three simple secondary alcohols. The results obtained are detailed in Table 1 with comparative yields and enantiomeric excesses, where available, being given for similar reactions of these alcohols with phthalimide under standard Mitsunobu conditions (Scheme 5) and using Barrett's imidate ester method (Scheme 6).

Isopropyl **10a** and *R*-*sec*-butyl **10b** alcohols gave an acceptable (51%) isolated yield of the corresponding *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **2a** and **2b**, respectively. In the latter case, the ee of the product was found to be 71% and this is consistent with the observation that incomplete inversion is sometimes observed with betaine reagent **7**.[12] Whilst *R*-2-octanol **10c** gave a good yield of the desired product **2c**, we were unable to determine the enantiomeric excess by chiral HPLC, although further reactions of this product (see later) suggested that **2c** had an ee of 97%.

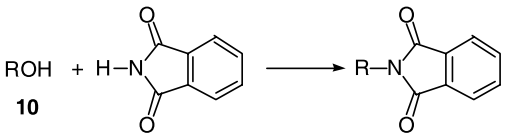
Analogous reactions of a number of allylic and benzylic alcohols were also investigated (Table 2).

Benzyl alcohol **10d** gave a very good (80%) yield of the desired *N*-alkylated 1,2,4-dithiazolidine-3,5-dione **2d**. A higher yield was expected from this reactive alcohol and indeed, this result is directly comparable with the 75% yield obtained in a standard Mitsunobu reaction between benzyl alcohol **10d** and phthalimide.[17] *R*-α-Methylbenzyl alcohol **10e** gave a lower yield (50%) of **2e** than that obtained for the corresponding phthalimide derivative (73%) produced using Barrett's imidate ester method.[14a] Interestingly however, both processes resulted in some racemisation, the products

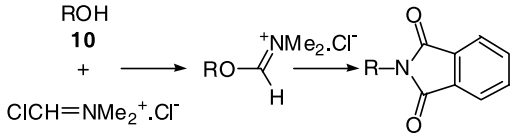
Table 1. Mitsunobu-type reactions with secondary alcohols

Alcohol **10** (equiv)[a]	Product **2**	Yield[b] (%)	ee (%)	Comparable reactions with phthalimide	
				Yield (%)	ee (%)
 **10a** (0.21)	 **2a**	51	—	[c]75[15] —[d]	— —
 **10b** (0.89)	 **2b**	51	71	[c]75 (±)[14] —[d]	— 92
 **10c** (0.93)	 **2c**	76	97[e]	[c]75[14] —[d]	>99 96

[a] Equivalent of **10** relative to **4**.
[b] Based on **10**.
[c] Using typical Mitsunobu conditions.
[d] Using Barrett's imidate ester method.
[e] Determined from urethane **11a** (see text).



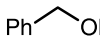
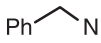
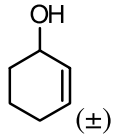
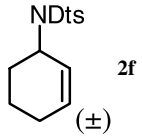
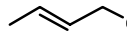
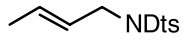
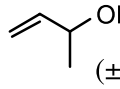
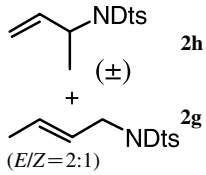
Scheme 5. Reagents and conditions: $R'O_2C–N{=}N–CO_2R'$, Ph_3P, solvent.



Scheme 6. Reagents and conditions: (i) CH_3CN, 0 °C; (ii) KPhth, 60–70 °C.

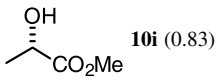
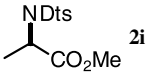
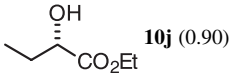
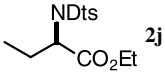
having similar ee's (70 and 72%, respectively), suggesting that Mitsunobu-type reactions of **10e** probably involve significant S_N1 character. Racemic 2-cyclohexen-1-ol **10f** gave a lower yield (38%) of the desired product **2f** although this is comparable with the imidate ester result obtained by Barrett et al. with potassium phthalimide (34%). In comparison, Sammes et al. have reported a 57% yield for the preparation of *N*-cyclohex-2-enyl phthalimide under standard Mitsunobu conditions.[18] Crotyl alcohol **10g** gave an acceptable yield of the desired product **2g** in an *E*/*Z* ratio which remained unchanged from the starting alcohol **10g**. For this alcohol, no products arising from allylic transposition could be detected. In contrast, racemic 3-buten-l **10h** gave a mixture of products in a relatively low (39%) yield. Here, the ratio of direct alcohol displacement/allylic transposition was found to be 2:1 with **2g** being obtained in

Table 2. Mitsunobu-type reactions with benzylic and allylic alcohols

Alcohol **10** (equiv)[a]	Product(s) **2**	Yield[b] (%)	ee (%)	Comparable reactions with phthalimide	
				Yield (%)	ee (%)
 **10d** (0.83)	 **2d**	80	—	[c]75[16] —[d]	— —
 **10e** (0.92)	 **2e**	50	71	—[c] [d]73[13a]	— 72
 **10f** (0.83)	 **2f**	38	—	[c]57 (±)[17] [d]34 (±)[13a]	— —
 **10g** (0.84)	 (*E*/*Z*=12:1) **2g**	57	—	—[c] —[d]	— —
 **10h** (1.00)	 (*E*/*Z*=2:1)	39 (overall)	—	—[c] [d]98 (±)[13a]	— —

[a] Equivalent of **10** relative to **4**.
[b] Based on **10**.
[c] Using typical Mitsunobu conditions.
[d] Using Barrett's imidate ester method.

Table 3. Mitsunobu-type reactions with hydroxyesters

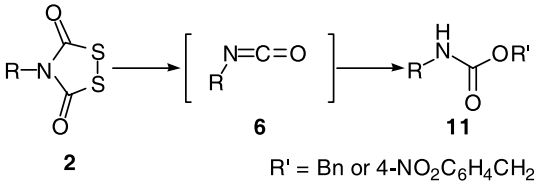
Alcohol 10 (equiv)[a]	Product 2	Yield[b] (%)	ee (%)	Comparable reactions with phthalimide	
				Yield %	ee %
 **10i** (0.83)	 **2i**	52	92	[c,d]45[18] [e]25[13b]	>99% —
 **10j** (0.90)	 **2j**	37	71	—[c] —[e]	— —

[a] Equiv. of **10** relative to **4**.
[b] Based on **10**.
[c] Using typical Mitsunobu conditions.
[d] Yield for reaction with *S*-ethyl lactate.
[e] Using Barrett's imidate ester method.

an *E*/*Z* ratio of 2:1. Interestingly, in comparison, Barrett et al. reported a very high (98%) yield in the imidate ester reaction of **10h** with potassium phthalimide, with no allylic transposition being observed.[14b]

In order to investigate our methodology in the context of the preparation of protected α- and β-amino acids, reactions between *S*-methyl lactate **10i** and *S*-ethyl 3-hydroxybutyrate **10j** and 1,2,4-dithiazolidine-3,5-dione **4** and betaine **7** were also carried out (Table 3).

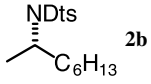
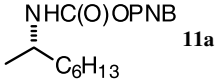
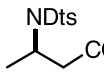
S-Methyl lactate **10i** gave a 52% yield of **2i**, with an enantiomeric excess of 92%. This result compares favourably with the analogous preparation of *S*-*N*-phthaloyl alanine ethyl ester under Mitsunobu conditions, using a solid-supported azodicarboxylate, where a 45% yield and > 99% ee have been reported for the reaction between *S*-ethyl lactate and phthalimide.[19] (Note: a 58% yield was originally reported for the standard Mitsunobu reaction between racemic ethyl lactate and phthalimide.[17]) In comparison, the reaction between *S*-methyl lactate **2i** and potassium phthalimide under imidate ester conditions, has been reported to give a low (25%) yield of *N*-phthaloyl alanine methyl ester with complete racemisation.[14b]



Scheme 7. Reagents and conditions: Ph_3P (1.00 equiv), R′OH (0.80–1.07 equiv), $PhCH_3$, reflux.

S-Ethyl 3-hydroxybutyrate **10j** gave a disappointing (37%) yield of the corresponding protected β-amino acid **2j** with some racemisation having occurred. The low yield, in this instance, is however, perhaps not surprising, given the propensity of such β-hydroxy esters to undergo elimination under Mitsunobu reaction conditions.[10a] Unfortunately, comparative literature data for reactions between phthalimide and 3-hydroxybutyrates are not available.

Table 4. Urethane preparation

Imide **2**	Alcohol (equiv)	Product **11**	Yield (%)	ee (%)	Imide **2** ee (%)
 **2b**	PNB–OH (0.80)	 **11a**	[a]92	97	[b]
 **2e**	Bn–OH (0.85)	 **11b**	[a]25	69	70
 **2e**	PNB–OH (0.85)	 **11c**	[a]79	69	70
 **2i**	Bn–OH (1.07)	 **11d**	[c]59	90	92
 **2j**	PNB–OH (1.05)	 **11e**	[c]89	71	71

[a] Based on benzylic alcohol.
[b] Could not be determined by chiral HPLC.
[c] Based on *N*-alkyl-1,2,4-dithiazolidine-3,5-dione **2**.

A number of the *N*-alkylated 1,2,4-dithiazolidine-3,5-dione products **2** were converted, through the intermediate (detectable but not isolated/characterised) isocyanates **6**, into urethane-protected amines **11** (Scheme 7).

Our previously reported procedure[8] was employed, in which a mixture of the *N*-alkylated 1,2,4-dithiazolidine-3,5-dione **2** was heated with an equimolar quantity of triphenylphosphine and a benzylic alcohol (0.80–1.07 equiv) in toluene, under reflux. Table 4 summarises the results of these studies, with yields being calculated, in all cases, from the minor component in the reaction.

As mentioned earlier, we had been unable to determine the enantiomeric excess in **2c**, which was derived from *R*-2-octanol but the enantiomers of the 4-nitrobenzyl urethane **11a** proved to be separable by chiral HPLC, indicating a 97% ee Importantly, for all of the urethanes **11** isolated, the enantiomeric excess was determined to be the same as the starting alcohol **10**, within experimental error, suggesting that the intermediate isocyanates **6** were configurationally stable under the reaction conditions employed.

The preparation of the urethane-protected alanine methyl ester derivative **11d** from the *S*-methyl lactate-derived 1,2,4-dithiazolidine-3,5-dione **2i** allowed us to confirm that inversion of configuration was the predominant pathway in the original Mitsunobu-type reaction. The formation of protected β-amino ester **11f** illustrates the potential use of the overall methodology in the synthesis of β-amino acids.

3. Conclusions

Overall, we have shown that the structurally simple heterocycle, 1,2,4-dithiazolidine-3,5-dione **4** provides an excellent isocyanate synthetic equivalent in Mitsunobu-type reactions using a wide variety of alcohols. The methodology developed has, therefore, significant potential to be of use in the synthesis of amines, ureas and also many nitrogen-containing heterocycles. The stability of this heterocyclic system to strongly acidic, mildly basic and photochemical conditions provides the possibility of carrying an isocyanate through a series of synthetic steps in a protected form, greatly expanding the number of possibilities for using this highly reactive functional group in synthesis.

4. Experimental

4.1. General

Enantiomeric excesses were determined by chiral HPLC, using a Chiralcel® OD™ column, eluting with 9:1 v/v hexane-propan-2-ol. Detection was carried out at a wavelength of 254 nm.

Melting points were determined using a Gallenkamp MPD350 apparatus and are uncorrected.

Specific rotations were determined using an Optical Activity AA-1000 automatic polarimeter in a 1dm path length cell.

Infrared spectra were recorded using a Nicolet Magna 550 spectrometer with only major absorbances being quoted, using the abbreviations: w, weak; m, medium; s, strong and br, broad. Thin film samples were prepared by evaporation of a dilute chloroform sample of the compound on a sodium chloride plate.

^{1}H NMR spectra were obtained using Brücker AM300, ACF300 and Advance DRX400 spectrometers at operating frequencies of 300 and 400 MHz. Chemical shifts are quoted in ppm relative to tetramethylsilane with referencing to the residual protonated solvent peak. Coupling constants are given to the nearest 0.5 Hz. The abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad are used.

^{13}C NMR spectra were obtained using either a Brücker ACF300 or Brücker Advance DRX400 spectrometer at operating frequencies of 75 and 100 MHz, respectively. Chemical shifts are quoted in ppm relative to tetramethylsilane, with referencing to the solvent peak. Assignments are derived from DEPT editing.

Mass spectra were determined using Thermoquest Finnigan TRACE 2000 GC–MS and Micromass GCT instruments or by the EPSRC National Mass Spectrometry Service Centre, Swansea, UK in electron impact (EI), ammonia chemical ionisation (CI) and positive ion electrospray (ES^{+}) modes.

Analytical thin layer chromatography was carried out using glass or aluminium-backed plates coated with Merck Kieselgel 60 F_{254}, with plates being visualised by quenching of UV fluorescence or by staining with iodine or potassium permanganate as appropriate. Flash chromatography was carried out using BDH silica gel with particle size 40–63 μm.

Solvents and reagents were used as supplied commercially or purified using standard procedures as appropriate. Petroleum ether refers to the fraction of light petroleum ether boiling between 40 and 60 °C.

Solvents were removed under reduced pressure using a Büchi R110 Rotovapor, equipped with a water and/or dry ice condenser as appropriate.

4.2. Mitsunobu-type *N*-alkylation of 1,2,4-dithiazolidine-3,5-dione 4—general procedure

The alcohol **10** (typically *ca* 0.74 mmol) was added to a stirred solution of 1,2,4-dithiazolidine-3,5-dione **4** (typically 0.82 mmol) and betaine reagent **7**[12] in dichloromethane (2 cm^3) at room temperature. After stirring at this temperature for 18 h, the solvent was evaporated in vacuo and the resulting residue was purified by flash chromatography on silica gel (typically eluting with 90% petroleum ether–10% ethyl acetate) to give the *title compound* **2**.

4.2.1. 4-Isopropyl-1,2,4-dithiazolidine-3,5-dione 2a. Using

the general procedure above with isopropyl alcohol **10a** (300 μL, 3.93 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2a** (74 mg, 51%). as a colourless oil. Data as reported previously.[8]

4.2.2. *S*-4-*sec*-Butyl-1,2,4-dithiazolidine-3,5-dione 2b. Using the general procedure above with *R*-*sec*-butyl alcohol **10b** (67 μL, 0.73 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2b** (74 mg, 51%) as a colourless oil, 71% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ +24 ($c=1$, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3044–2883 (w), 1736 (s), 1646 (s), 1454 (m), 1311 (w), 1223 (m), 1189 (w), 1034 (w), 949 (m) and 692 (s); δ_H (300 MHz; $CDCl_3$) 0.86 (3H, t, $J=8$ Hz, CH_3CH_2), 1.42 (3H, d, $J=8$ Hz, CH_3CH), 1.72–1.84 (1H, m, CH_AH_B), 1.94–2.06 (1H, m, CH_AH_B) and 4.39–4.49 (1H, m, C*H*); δ_C (100.6 MHz; $CDCl_3$) 14.2, 17.4 (*C*H_3), 32.3 (*C*H_2) and 56.6 (*C*H); *m*/*z* (EI) 191 (M^+, 12%), 135 (14), 99 (21), 73 (100) and 64 (33).

4.2.3. *S*-4-(1-Methylheptyl)-1,2,4-dithiazolidine-3,5-dione 2c. Using the general procedure above with *R*-2-octanol **10c** (120 μL, 0.76 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2c** (142 mg, 76%) as a brown oil, enantiomers inseparable by chiral HPLC; $[\alpha]_D^{21}$ +14 ($c=1$, $CHCl_3$); (Found M^+ (EI) 247.3810, $C_{10}H_{17}NO_2S_2$ requires 247.3795); ν_{max} (thin film)/cm^{-1} 3030–2834 (w), 1734 (s), 1685 (s), 1516 (w), 1375 (w), 1221 (m), 1136 (w) and 1059 (w); δ_H (300 MHz; $CDCl_3$) 0.87 (3H, t, $J=8$ Hz, CH_3CH_2), 1.11–1.36 (8H, complex, $(CH_2)_4$) 1.45 (3H, d, $J=8$ Hz, CH_3CH), 1.55–1.79 (1H, m, CH_AH_BCH), 1.94–2.12 (1H, m, CH_AH_BCH) and 4.42–4.58 (1H, m, C*H*); δ_C (75.1 MHz; $CDCl_3$) 14.0, 17.3 (*C*H_3), 22.5, 26.5, 28.8, 31.6, 32.2 ($(CH_2)_5$), 56.6 (*C*H) and 167.7 (*C*=O); *m*/*z* (EI) 247 (M^+, 7%), 155 (13), 135 (11), 129 (44) and 64 (100).

4.2.4. 4-Benzyl-1,2,4-dithiazolidine-3,5-dione 2d. Using the general procedure above with benzyl alcohol **10d** (70 μL, 0.68 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2d** (74 mg, 80%) as an off-white solid. Data as reported previously.[20]

4.2.5. *S*-4-(1-Phenylethyl)-1,2,4-dithiazolidine-3,5-dione 2e. Using the general procedure above with *R*-α-methylbenzyl alcohol **10e** (90 μL, 0.75 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2e** (90 mg, 50%), as a brown oil, 70% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ −32 ($c=1$, $CHCl_3$); (Found MH^+ (CI) 240.0168, $C_{10}H_{10}NO_2S_2$ requires 240.0153); ν_{max} (thin film)/cm^{-1} 3033–2844 (w), 1732 (s), 1630 (m), 1595 (m), 1554 (m), 1505 (w), 1426 (w), 1297 (m), 1190 (w), 1024 (w) and 723 (m); δ_H (400 MHz; $CDCl_3$) 1.78 (3H, d, $J=7$ Hz, CH_3), 5.73 (1H, q, $J=7$ Hz, C*H*) and 7.24–7.44 (5H, complex, phenyl-*H*); δ_C (100.6 MHz; $CDCl_3$) 16.0 (*C*H_3), 57.6 (*C*H), 128.3, 128.7, 128.9 (phenyl *C*H), 137.9 (phenyl *ipso*-*C*) and 167.8 (*C*=O); *m*/*z* (CI) 240 (MH^+, 9%), 192 (9), 164 (18), 151 (100) and 47 (87).

4.2.6. (±)-4-Cyclohex-2-enyl-1,2,4-dithiazolidine-3,5-dione 2f. Using the general procedure above with (±)-2-cyclohexen-1-ol **10f** (67 μL, 0.68 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2f** (56 mg, 38%), as a white solid; (Found MH^+ (CI) 216.0158, $C_8H_{10}NO_2S_2$ requires 216.0153); mp 89–91 °C; ν_{max} (thin film)/cm^{-1} 2980–2740 (w), 1646 (s), 1296 (m), 1167 (m) and 1134 (m); δ_H (400 MHz; $CDCl_3$) 1.62–2.25 (6H, complex, $(CH_2)_3$), 4.98–5.11 (1H, m, alkene C*H*), 5.46 (1H, dd, $J=2$, 12 Hz, NC*H*) and 5.89–6.01 (1H, m, alkene C*H*); δ_C (100.6 MHz; $CDCl_3$) 21.8, 24.0, 25.5 ($(CH_2)_3$), 56.3 (NCH), 124.4, 131.4 (alkene *C*H) and 167.3 (*C*=O); *m*/*z* (CI) 216 (MH^+, 16%), 164 (36), 136 (100) and 123 (24).

4.2.7. *E*-4-But-2-enyl-1,2,4-dithiazolidine-3,5-dione 2g. Using the general procedure above with crotyl alcohol **10g** (commercial *E*/*Z* mixture, 59 μL, 0.69 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2g** (74 mg, 57%), as a yellow oil; (Found MH^+ (CI) 189.9998, $C_6H_8NO_2S_2$ requires 189.9996); ν_{max} (thin film)/cm^{-1} 3060–2960 (m), 1718 (s), 1656 (m), 1420 (w), 1360 (w), 1340 (w), 1290 (m), 1140 (w), 1020 (w), and 980 (w); δ_H (400 MHz; $CDCl_3$) 1.70 (3H, dd, $J=1$, 6 Hz, CH_3), 4.28 (2H, dd, $J=1$, 7 Hz, CH_2), 5.38–5.55 (1H, m, alkene C*H*) and 5.76–5.89 (1H, m, alkene C*H*); δ_C (100.6 MHz; $CDCl_3$) 17.7 (*C*H_3), 47.7 (*C*H_2), 122.1, 132.9 (2×alkene *C*H) and 167.3 (*C*=O); *m*/*z* (CI) 190 (MH^+, 16%), 164 (18), 136 (100) and 98 (8). ^1H NMR indicated that the product contained a small quantity of *Z*-4-but-2-enyl-1,2,4-dithiazolidine-3,5-dione (*E*/*Z* ratio=12:1). The only ^1H NMR signals for this stereoisomer which could be positively identified were: δ_H (400 MHz; $CDCl_3$) 1.74 (3H, d, $J=$ 6 Hz, CH_3) and 4.40 (2H, d, $J=7$ Hz, CH_2).

4.2.8. (±)-4-(1-Methylallyl)-1,2,4-dithiazolidine-3,5-dione 2h and *E*/*Z*-4-but-2-enyl-1,2,4-dithiazolidine-3,5-dione 2g. Using the general procedure above with (±)-3-buten-2-ol **10h** (64 μL, 0.74 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.74 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave a 2:1 mixture of **2h** and **2g** (55 mg, 39%), as an oil; (Found MH^+ (CI) 189.9998, $C_6H_8NO_2S_2$ requires 189.9996); ν_{max} (thin film)/cm^{-1} 2926 (w), 1734 (m), 1686 (s), 1516 (w), 1311 (w), and 1059 (w); For **2h**: δ_H (400 MHz; $CDCl_3$) 1.56 (3H, d, $J=$ 6.8 Hz, CH_3), 5.00–5.08 (1H, m, NC*H*), 5.25–5.31 (2H, complex, CH=CH_2) and 6.07–6.18 (1H, m, C*H*=CH_2); δ_C (100.6 MHz; $CDCl_3$) 16.8 (*C*H_3), 57.4 (*C*H), 118.6 (CH=*C*H_2), 134.5 (*C*H=CH_2) and 167.2 (*C*=O); Data for **2g** as described above with the *E*/*Z* ratio being 1:2.

4.2.9. *R*-Methyl 2-(3,5-dioxo-1,2,4-dithiazolidin-4-yl)propionate 2i. Using the general procedure above with *S*-methyl lactate **10i** (65 μL, 0.68 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2i** (78 mg, 52%), as an oil, 92% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ +44 ($c=1$, $CHCl_3$). All other data as described previously for racemic **2i**.[8]

4.2.10. *R*-Ethyl 3-(3,5-dioxo-1,2,4-dithiazolidin-4-yl)-butyrate 2j. Using the general procedure above with

S-ethyl 3-hydroxybutyrate **10j** (98 μL, 0.74 mmol), 1,2,4-dithiazolidine-3,5-dione **4** (110 mg, 0.82 mmol) and betaine **7** (345 mg, 0.84 mmol) in dichloromethane (2 cm^3) gave **2j** (68 mg, 37%), as a yellow oil, 71% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ −7 ($c=1$, $CHCl_3$); (Found MH^+ (CI) 250.0210, $C_8H_{12}NO_4S_2$ requires 250.0208); ν_{max} (thin film)/cm^{-1} 1733 (m), 1635 (s), 1456 (w), 1375 (w), 1275 (m), 1173 (m), 1144 (m), 1068 (w), 804 (w) and 698 (m); δ_H (300 MHz; $CDCl_3$) 1.23 (3H, t, $J=7$ Hz, CH_3CH_2), 1.48 (3H, d, $J=7$ Hz, CH_3CH), 2.70 (1H, dd, $J=6$, 17 Hz, $CH_AH_BCO_2Et$), 3.18 (1H, dd, $J=9$, 17 Hz, $CH_AH_BCO_2Et$), 4.11 (2H, dq, $J=1$, 7 Hz, CH_2CH_3) and 4.88–4.96 (1H, m, CHN); δ_C (75.1 MHz; $CDCl_3$) 14.1, 17.4 (2×CH_3), 36.5 (CH_2CO_2Et), 51.7 (CHN), 61.0 (CH_2O) and 167.5, 170.2 (2×C=O); *m/z* (CI) 250 (MH^+, 7%), 206 (10), 204 (100), 156 (13), 116 (53) and 112 (27).

4.3. Urethane 11 formation from 4-alkylated 1,2,4-dithiazolidine-3,5-diones 2

A general procedure for urethane formation has been reported.[8]

4.3.1. *S*-(4-Nitrobenzyl)-1-methylheptyl carbamate 11a. Using the general procedure[8] with *S*-4-(1-methylheptyl)-1,2,4-dithiazolidine-3,5-dione **2b** (120 mg, 0.49 mmol), triphenylphosphine (130 mg, 0.50 mmol) and 4-nitrobenzyl alcohol (60 mg, 0.39 mmol) in toluene (2 cm^3) gave **11a** (111 mg, 92% based on 4-nitrobenzyl alcohol) as an oil, 97% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ +23 ($c=1$, $CHCl_3$); (Found MH^+ (CI) 309.1816, $C_{16}H_{25}N_2O_4$ requires 309.1814); ν_{max} (thin film)/cm^{-1} 3031–2856 (w), 1732 (s), 1611 (w), 1532 (s), 1452 (w), 1355 (s), 1243 (m), 1201 (m), 1111 (w), 1060 (w), 1024 (w), 740 (w) and 659 (s); δ_H (400 MHz; $CDCl_3$) 0.86 (3H, d, $J=7$ Hz, CH_3CH), 1.14 (3H, d, $J=7$ Hz, CH_3CH), 1.18–1.49 (10H, complex, $(CH_2)_5$), 3.63–3.74 (1H, m, CHN), 4.66 (1H, br d, $J=8$ Hz, NH), 5.17 (2H, s, CH_2Ar) and 7.49, 8.20 (2×2H, AA′BB′, $J=9$ Hz, aryl-*H*); δ_C (100.6 MHz; $CDCl_3$) 14.1, 21.2 (2×CH_3), 22.6, 25.9, 29.1, 31.8, 37.1 ($(CH_2)_5$), 47.4 (CHN), 64.9 (CH_2Ar), 123.7, 128.0 (aryl *C*–H), 144.3, 147.5 (2×aryl *ipso C*) and 155.2 (C=O); *m/z* (CI) 309 (MH^+, 17%), 296 (19), 295 (100), 185 (8), 154 (60), 113 (13) and 106 (28).

4.3.2. *S*-Benzyl-1-phenylethylcarbamate 11b. Using the general procedure8 with *S*-4-(1-phenylethyl)-1,2,4-dithiazolidine-3,5-dione **2e** (140 mg, 0.59 mmol), triphenylphosphine (155 mg, 0.59 mmol) and benzyl alcohol (60 μL, 0.50 mmol) in toluene (2 cm^3) gave **11c** (32 mg, 25% based on benzyl alcohol) as an oily solid, 69% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ −34 ($c=1$, $CHCl_3$) (literature $[\alpha]_D^{21}$ +44 ($c=0.59$, $CHCl_3$) for *R*-enantiomer[21]). All other data in agreement with literature values.[22]

4.3.3. *S*-(4-Nitrobenzyl)-1-phenylethyl carbamate 11c. Using the general procedure[8] with *S*-4-(1-phenylethyl)-1,2,4-dithiazolidine-3,5-dione **2e** (140 mg, 0.59 mmol), triphenylphosphine (155 mg, 0.59 mmol) and 4-nitrobenzyl alcohol (76 mg, 0.50 mmol) in toluene (2 cm^3) gave **11c** (118 mg, 79% based on 4-nitrobenzyl alcohol) as a brown oil, 69% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ −41 ($c=1$, $CHCl_3$); (Found MH^+ (CI) 301.1174, $C_{16}H_{17}N_2O_4$ requires 301.1188); ν_{max} (thin film)/cm^{-1} 3158–2839 (w), 1705 (s), 1606 (w), 1522 (s), 1450 (w), 1348 (s), 1240 (m), 1061 (m), 1014 (w), 852 (w), 739 (w) and 700 (m); δ_H (400 MHz; $CDCl_3$) 1.51 (3H, d, $J=7$ Hz, CH_3CH), 4.79–4.91 (1H, br m, CH), 5.08 (1H, br s, NH), 5.15, 5.17 (2×1H, AB, $J=14$ Hz, $ArCH_2$), 7.21–7.41 (5H, complex, phenyl-*H*) and 7.49, 8.20 (2×2H, AA′BB′, $J=8$ Hz, aryl-*H*); δ_C (100.6 MHz; $CDCl_3$) 22.4 (CH_3), 50.9 (CH), 65.2 (CH_2), 123.7, 125.9, 127.5, 128.2, 128.4 (aryl *C*–H), 143.1, 144.0 (2×aryl *ipso C*) and 155.0 (C=O); *m/z* (CI) 301 (MH^+, 5%), 295 (13), 280 (16), 279 (100), 201 (10) and 105 (37).

4.3.4. *R*-Benzyloxycarbonyl alanine methyl ester 11d. Using the general procedure[7] with *R*-methyl 2-(3,5-dioxo-1,2,4-dithiazolidin-4-yl) propionate **2i** (100 mg, 0.45 mmol), triphenylphosphine (120 mg, 0.46 mmol) and benzyl alcohol (50 μL, 0.48 mmol) in toluene (2 cm^3) gave **11d** (63 mg, 59% based on *R*-methyl 2-(3,5-dioxo-1,2,4-dithiazolidin-4-yl) propionate **2i**) as a white, powdery solid, 90% ee (determined by chiral HPLC); mp 45–46 °C (lit.[23] 47–48.5 °C); All other data in agreement with literature values.[23]

4.3.5. *R*-Ethyl 3-(4-nitrobenzyloxycarbonylamino) butyrate 11e. Using the general procedure[7] with *R*-ethyl 3-(3,5-dioxo-1,2,4-dithiazolidin-4-yl) butyrate **2j** (150 mg, 0.60 mmol), triphenylphosphine (164 mg, 0.63 mmol) and 4-nitrobenzyl alcohol (96 mg, 0.63 mmol) in toluene (2 cm^3) gave **11e** (166 mg, 89% based on *R*-ethyl 3-(3,5-dioxo-1,2,4-dithiazolidin-4-yl) butyrate **2j**) as a brown oil, 71% ee (determined by chiral HPLC); $[\alpha]_D^{21}$ +5 ($c=1$, $CHCl_3$); (Found MH^+ (CI) 311.1235, $C_{14}H_{19}N_2O_6$ requires 311.1243); ν_{max} (thin film)/cm^{-1} 3050–2836 (w), 1734 (br s), 1608 (w), 1536 (s), 1456 (w), 1348 (s), 1247 (m), 1194 (w), 1109 (w), 1066 (m), 1028 (w), 852 (w) and 739 (w); δ_H (300 MHz; $CDCl_3$) 1.18 (3H, t, $J=7$ Hz, CH_3CH_2), 1.19 (3H, d, $J=7$ Hz, CH_3CH), 2.46 (2H, d, $J=6$ Hz, CH_2CH), 3.96–4.06 (1H, m, $CHCH_3$), 4.07 (2H, q, $J=7$ Hz, CH_2CH_3), 5.11 (2H, s, $ArCH_2$), 5.36 (1H, br d, $J=7$ Hz, NH) and 7.43, 8.14 (2×2H, AA′BB′, $J=9$ Hz, aryl-*H*); δ_C (75.1 MHz; $CDCl_3$) 14.6 (CH_3), 20.7 (CH_3), 40.7 ($CHCH_2$), 44.6 (NCH), 61.1 (CH_3CH_2), 64.3 $ArCH_2$), 124.1, 128.4 (aryl *C*–H), 144.5, 147.9 (2×aryl *ipso C*), 155.4 (urethane C=O) and 171.9 (ester C=O); *m/z* (CI) 311 (MH^+, 86%), 295 (23), 265 (100), 223 (12), 158 (24), 132 (18), 116 (77) and 112 (33).

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