COMMUNICATION

# 1,2,4-Dithiazolidine-3,5-dione as an isocyanate equivalent in the Mitsunobu reaction

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**1,2,4-Dithiazolidine-3,5-dione 1 can be used as a nitrogen nucleophile in a modified Mitsunobu procedure to give *N*-alkylated products 2 which can be converted *via* isocyanates, into amine derivatives, under very mild conditions.**

The Mitsunobu procedure is now a well established method for the preparation of amines from alcohols, using acidic imide derivatives as the nitrogen nucleophile.[1] Phthalimide is perhaps the most common nucleophile that has been used in such reactions, but the well known problems associated with the deprotection of phthalimides to amines have led to the development of some alternative imides for this process.[2]

The remarkably high acidity of 1,2,4-dithiazolidine-3,5-dione **1** ($pK_a = 2.85$)[3] suggested that it should be a synthetically useful nucleophile in this procedure (Fig. 1). Most importantly,

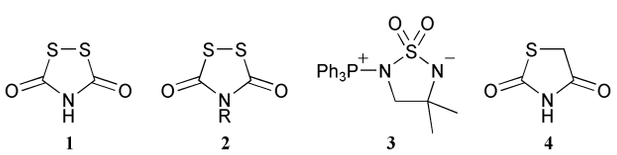



**Fig. 1**

*N*-alkylated derivatives **2** can be readily transformed into either amines[4] or isocyanates[3] (by very mild thiolysis or treatment with triphenylphosphine under anhydrous conditions respectively), whilst being stable towards commonly encountered acidic, mildly basic and photolytic deprotection conditions. The sensitivity of the heterocycle to phosphines does preclude the use of traditional phosphine–azodicarboxylate Mitsunobu conditions, but the observation that triphenylphosphine cyclic sulfamide betaine **3** can be used to couple alcohols and nitrogen acids,[5] including thiazolidine-2,4-dione **4**,[6] led us to examine the compatibility of this reagent with **1**.

A suitable range of alcohol substrates **5**–**15** (Fig. 2) was

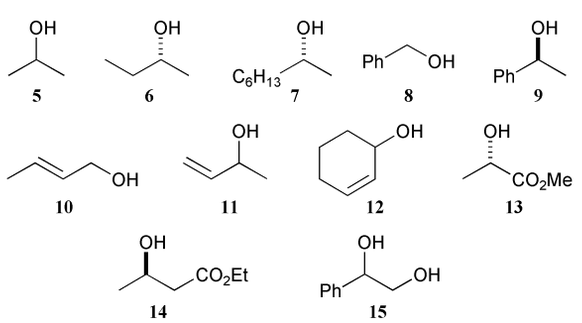


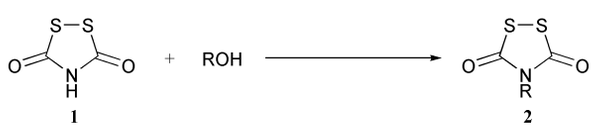

**Fig. 2** Alcohol substrates.

chosen in order to obtain results which could be compared with known phthalimide Mitsunobu (and closely related[7]) reactions. Treatment of these alcohols with 1,2,4-dithiazolidine-3,5-dione **1** (1–1.5 equiv.) and betaine **3** (1–1.5 equiv.) in dichloromethane at room temperature (Scheme 1) gave the corresponding *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **2** (Table 1).†

**Table 1** Mitsunobu-type reaction of alcohols with **1**

| | Alcohol | Yield (%) | Ee (%) |
|---|---|---|---|
| **5** | | 51 | — |
| **6** | | 51 | 71 |
| **7** | | 78 | [a] |
| **8** | | 80 | — |
| **9** | | 51 | 70 |
| **10** | | 54 | [b] |
| **11** | | 42 | [c,d] |
| **12** | | 38 | [c] |
| **13** | | 52 | 92 |
| **14** | | 37 | 71 |
| **15** | | 38 | [c,e] |

[a] Product enantiomers were inseparable by chiral HPLC. [b] A trace of the product resulting from allylic transposition was present. [c] Racemic alcohol used. [d] 2 : 1 ratio of direct displacement : allylic transposition products. [e] 2 products obtained in a 3 : 1 ratio (tentatively assigned as being from primary : secondary hydroxy group displacement).




**Scheme 1** *Reagents and conditions*: **3** (1–1.5 equiv.), $CH_2Cl_2$, RT (see Table 1).

Very good yields were obtained using more reactive alcohols such as benzyl alcohol (alcohol **8**, Table 1) whereas secondary alcohols gave lower, but still reasonable, yields. As expected, crotyl alcohol gave a trace of the product resulting from allylic transposition (alcohol **10**, Table 1) and racemic but-3-en-2-ol produced a 2 : 1 ratio of products, in favour of that resulting from direct displacement (alcohol **11**, Table 1).

Most importantly, the 52% yield obtained using (*S*)-methyl lactate (alcohol **13**, Table 1) correlates well with that achieved in "traditional" Mitsunobu reactions between phthalimide and both racemic[8] and (*S*)-ethyl lactate.[9] The enantiomeric excess for this reaction was found to be 92%.‡ In spite of the likelihood of competing dehydration of (*R*)-ethyl 2-hydroxybutyrate under the reaction conditions, an acceptable yield of 37% of the corresponding *N*-alkylated 1,2,4-dithiazolidine-3,5-dione with an enantiomeric excess of 71% was obtained (alcohol **14**, Table 1).

A number of *N*-alkylated derivatives **2** were converted into urethanes **16** (Scheme 2) *via* the *in situ* trapping of the intermediate, triphenylphosphine generated isocyanates **17**[3] with either benzyl or 4-nitrobenzyl alcohol. The results thus obtained are summarised in Table 2.

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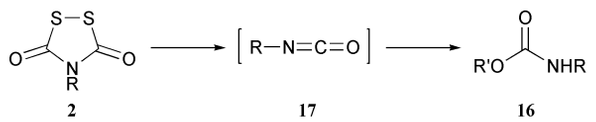
**Table 2** Formation of urethanes *via* isocyanates

| R | R′OH | Yield (%) | Ee (%) |
|---|---|---|---|
| (*S*)-Et(Me)CH | 4-$NO_2C_6H_4CH_2OH$ | 65 | 67 |
| (*S*)-$C_6H_{13}$(Me)CH | 4-$NO_2C_6H_4CH_2OH$ | 90 | 97 |
| (*R*)-Ph(Me)CH | 4-$NO_2C_6H_4CH_2OH$ | 79 | 68 |
| (*R*)-$MeO_2C$(Me)CH | $C_6H_5CH_2OH$ | 57 | 90 |
| (*R*)-$MeO_2C$(Me)CH | 4-$NO_2C_6H_4CH_2OH$ | 75 | 91 |
| (*S*)-$EtO_2CCH_2$(Me)CH | 4-$NO_2C_6H_4CH_2OH$ | 92 | 70 |




**2** **17** **16**

**Scheme 2** *Reagents and conditions*: **2** (1.25 equiv.), $PPh_3$ (1.25 equiv.), R′OH (1 equiv.), PhMe, 110 °C (see Table 2).

Confirmation of the expected inversion of configuration in the earlier Mitsunobu-type reactions was obtained by the preparation of *N*-benzyloxycarbonyl-D-alanine methyl ester (R = (*R*)-$MeO_2C$(Me)CH, R′OH = $C_6H_5CH_2OH$, Table 2), which in turn, originated from (*S*)-methyl lactate (alcohol **13**, Table 1). This protected amino acid was obtained with an enantiomeric excess of 90%, with analytical data corresponding to those of authentic samples. This result confirmed that within experimental error, no appreciable racemisation had occurred during the isocyanate generation process, a problem which can accompany the deprotection of *N*-phthaloyl amino acids with hydrazine.[10]

In summary, we have demonstrated that 1,2,4-dithiazolidine-3,5-dione **1** can be used as an effective substitute for phthalimide in Mitsunobu-type amination reactions. Moreover, the resulting alkylated derivatives **2** can be transformed, *via* isocyanates, into useful derivatives, under very mild conditions, with no appreciable loss of stereochemical integrity. 1,2,4-Dithiazolidine-3,5-dione **1** can therefore be used as an isocyanate equivalent in the Mitsunobu reaction.

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## Notes and references

† In a typical procedure (alcohol **13**, Table 1): betaine **3** (345 mg, 0.87 mmol) was added to a stirred solution of 1,2,4-dithiazolidine-3,5-dione **1**[11] (110 mg, 0.81 mmol) and (*S*)-methyl lactate (75 μl, 0.79 mmol) in dichloromethane (1.5 $cm^3$) under a nitrogen atmosphere at room temperature. After stirring for 16 h, the solvent was evaporated *in vacuo* with adsorption of the crude product onto silica gel. Flash chromatography on silica gel (eluting with 9 : 1 v/v light petroleum–ethyl acetate) gave (*R*)-2-(3,5-dioxo-1,2,4-dithiazolidin-4-yl)propionic acid methyl ester (91 mg, 52%, ee 92%) as an oil; $R_f$ 0.7 (9 : 1 v/v light petroleum–ethyl acetate) $[\alpha]_D^{21}$; +44 (*c* = 1, $CHCl_3$); $\nu_{max}/cm^{-1}$ ($CHCl_3$) 1732 and 1716 (C=O); $\delta_H$ (300 MHz; $CDCl_3$) 1.63 (3H, d, *J* 7, $CH_3$CH), 3.76 (3H, s, $CO_2CH_3$) and 5.03 (1H, q, *J* 7, $CH_3CH$); $\delta_C$ (75.5 MHz; $CDCl_3$) 14.0 ($CH_3$CH), 53.1, 54.3 ($CH_3CH$ and $CO_2CH_3$) and 166.8, 168.4 (*C*=O); *m/z* (EI) 221 ($M^+$, 38%) and 70 (100) [Found, $MH^+$ (EI) 220.9823, $C_6H_7NO_4S_2$ requires 220.9817].

‡ 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.

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