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Synthetic and structural studies on 1,2,4-dithiazolidine-3,5-dione derivatives

Mark E. Wood,*[a] Daniel J. Cane-Honeysett,[a] Michael D. Dowle,[b] Simon J. Coles[c] and Michael B. Hursthouse[c]

[a] *School of Chemistry, University of Exeter, Stocker Road, Exeter, UK EX4 4QD. E-mail: m.e.wood@exeter.ac.uk; Fax: 44 1392 263434; Tel: 44 1392 263450*

[b] *GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, UK SG1 2NY*

[c] *EPSRC X-ray Crystallography Service, Department of Chemistry, University of Southampton, Highfield, Southampton, UK SO17 1BJ*

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Methods have been developed for the *N*-alkylation of 1,2,4-dithiazolidine-3,5-dione **2** and the subsequent conversion of the *N*-alkylated derivatives into isocyanates **5**. An extension of this methodology onto a solid-support is also reported. X-ray crystallographic analysis has been carried out on potassium 1,2,4-dithiazolidine-3,5-dione **3** for structural comparison with the parent heterocycle **2**.

Introduction

Isocyanates have a multitude of important synthetic uses ranging from the industrial preparation of polyurethanes to the synthesis of complex, nitrogen-containing heterocycles. The reactivity of this functional group however, ensures that it is not compatible with many reaction conditions and the toxicity of organic isocyanates leads to potential hazards in their handling.

We have recently reported preliminary studies into direct methods for the preparation of *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **1** (Fig. 1) and have shown that they can be readily converted into isocyanates under mild conditions by treatment with triphenylphosphine.[1,2] Given that the principal use of this heterocyclic system to date has been as a protecting group (the dithiasuccinoyl, Dts group) for primary amines[3] in peptide[4] and aminoglycoside[5] synthesis, where it has been found to be stable to acidolytic, photolytic and mildly basic reaction conditions, the methodology developed represents a method for the straightforward introduction of a protected isocyanate group into organic molecules as well as a new method for producing Dts protected primary amines.

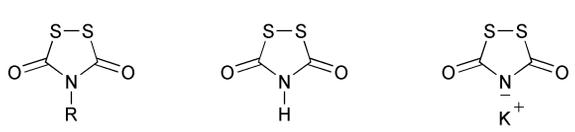


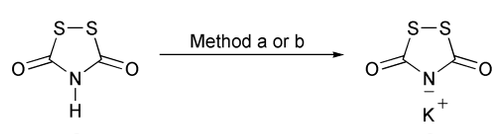
Fig. 1 1,2,4-Dithiazolidine-3,5-dione derivatives.

Herein, we report full details for the use of 1,2,4-dithiazolidine-3,5-dione **2** and its potassium salt **3** (Fig. 1) in nucleophilic substitution reactions with alkyl halides and the subsequent conversion of the resulting *N*-alkylated derivatives **1** into urethanes and ureas (*via* isocyanates) with X-ray crystallographic data also being presented for **3**.

Results and discussion

The traditional Gabriel synthesis, involving the *N*-alkylation of potassium phthalimide, has proved to be a popular and enduring method for the introduction of primary amines into organic molecules. The structural similarity between **2** and phthalimide suggested that **2** and **3** should be appropriate substrates for a similar alkylation procedure† and indeed, preliminary investigations showed that this could be feasible and that the resulting *N*-alkylated derivatives **1** could be converted into isocyanates by treatment with triphenylphosphine.[6]

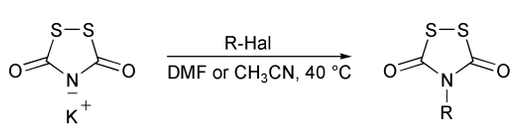
In order to fully develop this methodology, we firstly investigated methods for the generation of potassium salt **3**. 1,2,4-Dithiazolidine-3,5-dione **2**[7] was prepared in multigram quantities by the procedure reported by Barany[8] and treated with an ethanolic solution of potassium hydroxide in a similar procedure to that reported for the preparation of potassium phthalimide (Scheme 1).[9] This gave the potassium salt **3** as a white, crystalline precipitate which could generally be used successfully without any further purification, although recrystallisation from ethanol–diethyl ether gave an analytically pure sample (in 64% yield) which was used in the X-ray crystallographic studies described later.



Scheme 1 Method a: KOH, EtOH, −5 °C (64%); Method b: KH, CH_3CN, −20 °C (57%).

In a similar manner, the use of potassium hydride in acetonitrile gave **3** in a 57% yield after recrystallisation.

A general procedure for the *N*-alkylation of **3** was developed using either DMF or acetonitrile as solvent, with the reactions generally being carried out at 40 °C (Scheme 2 and Table 1).



Scheme 2 *N*-Alkylation of **3**.

† Barany has suggested that **2** "may be useful for mild homologation of the Gabriel synthesis"[8] although the authors are not aware of any such applications being developed prior to our work.

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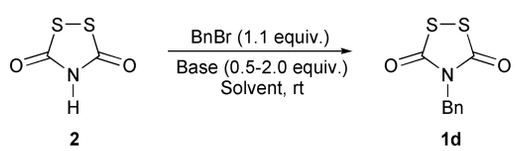
Table 1 Reactions of **3** with alkyl halides

Entry	R	Hal	Solvent	Yield (%)	Product
1	Me	I	DMF	44	**1a**
2	^{n}Hexyl	I	DMF	65	**1b**
3	^{i}Pr	I	CH_3CN	34	**1c**
4	Bn	Br	DMF	60	**1d**
5	(±)-$CH_3C(H)CO_2Me$	Br	DMF	27	**1e**

Simple primary alkyl iodides such as methyl and hexyl gave adequate yields of the corresponding *N*-alkylated 1,2,4-dithiazolidine-3,5-diones (**1a** and **1b** respectively) whereas a significant reduction in yield was observed with 2-iodopropane (entry 3, Table 1). As would be expected, benzyl bromide gave a reasonable yield of **1d**, suggesting that more reactive alkyl halides are better suited to this procedure. (±)-Methyl 2-bromopropionate gave a disappointing yield of the *N*-alkylated heterocycle **1e**, a reaction in which competing elimination could not be ruled out. In all of these experiments, 1.0–1.5 equiv. of the appropriate alkyl halide was used with yields being based on potassium salt **3**.

These reactions gave essentially identical results using either DMF or acetonitrile as solvent but interestingly, some unpurified batches of the potassium salt **3** gave rise to an intense blue colouration on dissolution in DMF with no reaction occurring on addition of the alkyl halide. This was found to occur when aqueous solutions of potassium hydroxide were used to prepare **3** and the solid thus prepared was stored for prolonged periods. Analysis of the products obtained from the attempted alkylation reactions suggested that extensive decomposition of the heterocycle had occurred and we were unable to identify the nature of this problem. Batches of **3** prepared using ethanolic potassium hydroxide however did not give rise to the same problem.

In order to simplify further the *N*-alkylation procedure, a range of bases were investigated for the *in situ* deprotonation of the parent heterocycle **2** in the presence of alkyl halides. For purposes of comparison of bases and solvents, benzyl bromide was chosen as the electrophile for initial studies (Scheme 3).



2 **1d**

Scheme 3 Direct *N*-alkylation of **2** with benzyl bromide.

The use of caesium carbonate (1.0 equiv.) gave a good (80%) yield of 4-benzyl-1,2,4-dithiazolidine-3,5-dione **1d** with acetonitrile as solvent and hence, the solvent dependency of the reaction was examined using this base. The results of these studies are summarised in Table 2.

Attempted alkylation in DMF gave no isolable products, with what appeared to be decomposition of **2**. A poor yield was also obtained using DMSO as solvent (entry 3) and this reaction was accompanied by significant colouration of the reaction mixture as occasionally seen in the reaction using the potassium salt **3** described earlier. THF gave a similarly disappointing result (entry 4) and hence, acetonitrile was chosen as the solvent for further studies.

Several inorganic bases were investigated and all gave acceptable results for the *N*-benzylation reaction (Scheme 3). Table 3 lists the bases used with the number of equiv. of each that gave the optimal yields. The use of amine bases was not investigated owing to the well-documented reactivity of 1,2,4-dithiazolidine-3,5-diones **1** towards such compounds.[10]

Two results in particular stand out from these studies. Firstly, the use of sodium bicarbonate (entry 4) gave an excellent (96%) yield of **1d** and secondly, sodium acetate proved to be an adequate base for the reaction (entry 5).

Table 2 Solvent effects on direct *N*-benzylation of **2** (Cs_2CO_3 as base)

Entry	Solvent	Yield (%)
1	CH_3CN	80
2	DMF	[a]
3	DMSO	24
4	THF	6

[a] Apparent decomposition of **2** observed.

Table 3 Base effects on direct *N*-benzylation of **2** (CH_3CN as solvent)

Entry	Base (equiv.)	Yield (%)
1	NaH (1.0)	77
2	KH (1.0)	74
3	^{t}BuOK (1.0)	60
4	$NaHCO_3$ (2.0)	96
5	NaOAc (2.0)	77

The latter result suggested that **2** must be considerably more acidic than a simple imide and hence, a pK_a determination was carried out. This gave the remarkable value of pK_a = 2.85 ± 0.002‡ which is considerably lower than quoted values for phthalimide (pK_a = 10.06[11]) and succinimide (pK_a = 9.56[12]).

The implication of this result is that there is considerable stabilisation in the conjugate base of **2** that is not present in the conjugate bases of other imides. In an attempt to investigate this further, crystals of the potassium salt **3** were prepared by slow crystallisation from ethanol–diethyl ether for X-ray crystallographic analysis. This was carried out with a view towards looking for significant structural changes compared with the equivalent data reported for the parent heterocycle **2**[8] in order to investigate the origin of the low pK_a. Fig. 2 shows the structure of the conjugate base of **2** in potassium salt **3** with bond lengths and angles being summarised in Table 4. The corresponding values obtained for **2** by Barany *et al.*[8] are also given for comparative purposes.

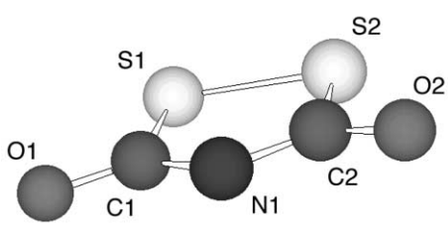


Fig. 2 X-ray crystal structure of the conjugate base of **2** in salt **3**.

The planar structure of the conjugate base is shown clearly in Fig. 2.

In forming the potassium salt **3** from **2**, there is a significant shortening of the C–N bonds with concomitant increase in length of the C–O bonds. This is consistent with the changes in bond order that would be expected to accompany the expected delocalisation of the negative charge in the conjugate base across the imide moiety (Fig. 3). No other significant

‡ The pK_a value for **2** was determined potentiometrically using a SIRIUS® PCA101 apparatus over a pH range of 2 to 12 in both directions at I = 0.163 and 25.6 °C. The value quoted is an average of 4 experiments.

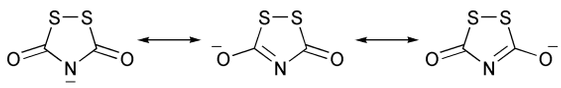


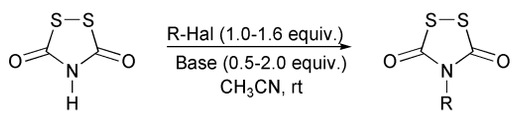
Fig. 3 Stabilisation of the conjugate base of **2**.

changes in bond length/angle were observed which could indicate stabilising other interactions in the conjugate base.

Interestingly, however, the C–S bonds are lengthened in the conjugate base, leading to the tentative suggestion that the sulfur atoms may not be involved in stabilisation. Minor changes to the C–N–C and S–C–N bond angles are also observed.

The origin of the unusually high acidity of **2** is therefore still unclear and is a current topic of investigation.

Further *N*-alkylation studies were then carried out using the *in situ* deprotonation method in order to investigate which alkyl halides are appropriate for this procedure (Scheme 4). A variety of bases were tried in varying stoichiometries and Table 5 summarises the optimised reaction conditions for a range of different alkyl halides. All of the reactions were carried out in acetonitrile at room temperature with 1.0–1.6 equiv. of the alkyl halide relative to **2**.



2 **1**

Scheme 4 Direct alkylation of **2** with alkyl halides.

Table 4 X-ray crystallographic data for **3** and **2**

Compound	**3**	**2**[8]
Bond lengths/Å		
N1–C1	1.339(8)	1.367(2)
C1–O1	1.234(8)	1.208(2)
C1–S1	1.796(7)	1.764(2)
S1–S2	2.046(2)	2.0584(8)
C2–S2	1.805(7)	1.761(2)
C2–O2	1.237(8)	1.208(2)
C2–N1	1.337(8)	1.369(2)
N1–K1	3.097(5)	
N1–K2	3.177(5)	
Bond angles/°		
N1–C1–S1	118.3(5)	113.5(1)
C1–S1–S2	93.6(2)	95.42(5)
C2–S2–S1	93.6(2)	95.45(6)
S2–C2–N1	118.0(5)	113.6(1)
C1–N1–C2	116.4(5)	121.96[a]
O1–C1–N1	125.8(6)	125.20[a]
O2–C2–N1	126.3(6)	124.86[a]
O1–C1–S1	115.9(5)	121.51[a]
O2–C2–S2	115.7(5)	121.30[a]
K1–N1–K2	79.74(13)	

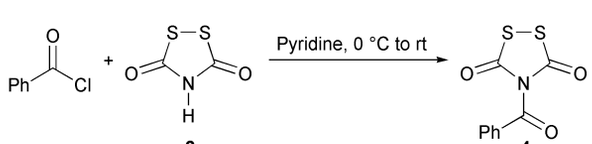
[a] Estimated errors not available for these bond angles.

Methyl iodide gave the corresponding *N*-methyl derivative **1a** in a very good (78%) yield with sodium bicarbonate as base (entry 1) but 1-iodohexane gave only a poor (12%) yield of **1b** (entry 2) in the presence of potassium hydride. Likewise, 2-iodopropane gave only a disappointing (11%) yield of the corresponding *N*-alkylated derivative **1c** (entry 3) with potassium hydride again proving to be the base of choice. The latter two results are poorer than those obtained from the same alkyl halides with the potassium salt **3** (Table 1). In the case of 1-iodohexane, this lower yield could be attributable to a temperature or solvent effect and for 2-iodopropane, a temperature effect seems most likely. (Note: Attempts to use the *in situ* deprotonation method at elevated temperatures led to what appeared to be decomposition of **2**.)

More reactive alkyl halides such as allyl and prenyl bromides (entries 4 and 5) however gave much better results and propargyl bromide gave the corresponding *N*-propargyl derivative **1h** (entry 6) with no evidence for formation of the allenyl derivative. As would be expected, ethyl bromoacetate proved to be an excellent alkylating agent in this procedure (entry 7) but (±)-methyl 2-bromopropionate gave a very low (13%) yield of the required product **1e** with potassium hydride as base (entry 8). Benzyl and 4-benzyloxybenzyl chlorides were essentially unreactive under these reaction conditions but the addition of 1 equiv. of either tetrabutylammonium bromide or potassium iodide (relative to the benzylic chloride) gave much-improved results (entries 9 and 10).

From these *in situ* deprotonation–alkylation studies, it can be concluded that a wide variety of bases can be successfully employed, with more reactive alkyl halides giving the best results.

N-Benzoylation of **2** was also attempted under the conditions reported for the preparation of *N*-benzoylphthalimide.[13] Treatment of **2** with benzoyl chloride (1 equiv.) in pyridine at 0 °C gave, after addition of ethanol, a white, crystalline solid (Scheme 5).



2 **4**

Scheme 5 *N*-Benzoylation of **2**.

This had infrared and $^{1}H/^{13}C$ NMR spectroscopic properties consistent with the desired product **4**. Electrospray mass spectrometry, however, gave data consistent with **4** fragmenting to *N*-benzoyl isocyanate **5** (R = PhC(O)) as the highest molecular weight fragment observed. (Note: Isocyanates appear to be fragmentation products in the mass spectra of *N*-alkylated derivatives **1**.) The product structure can therefore only be

Table 5 Direct alkylation of **2** with alkyl halides

Entry	R	Hal	Base (equiv.[a])	Yield (%)[d]	Product
1	Me	I	$NaHCO_3$ (1.9)	78	**1a**
2	^{n}Hexyl	I	KH (1.0)	12	**1b**
3	^{i}Pr	I	KH (1.0)	11	**1c**
4	Allyl	Br	$NaHCO_3$ (1.9)	90	**1f**
5	Prenyl	Br	$NaHCO_3$ (1.9)	77	**1g**
6	Propargyl	Br	$NaHCO_3$ (1.9)	47	**1h**
7	EtO_2CCH_2	Br	$NaHCO_3$ (1.9)	86	**1i**
8	(±)-$CH_3C(H)CO_2Me$	Br	KH (1.0)	13	**1e**
9	Bn	Cl[b]	Cs_2CO_3 (0.5)	42	**1d**
10	4-$BnOC_6H_4CH_2$	Cl[c]	$NaHCO_3$ (1.9)	75	**1j**

[a] Relative to **2**. [b] 1 equiv. of Bu_4NBr added. [c] 1 equiv. of KI added. [d] Yield based on quantity of **2** used.

Table 6 Urethane formation

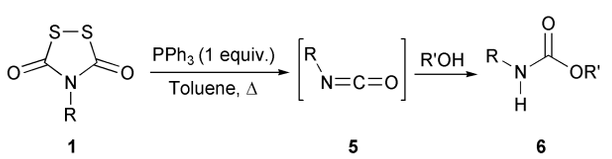
Entry	R	R′	Yield (%)	Product
1	Me	4-$NO_2C_6H_4CH_2$	45	**6a**
2	Bn	Et[a]	74	**6b**
3	Bn	Bn	77	**6c**
4	Bn	4-$BrC_6H_4CH_2$	60	**6d**
5	Bn	4-$MeOC_6H_4CH_2$	55	**6e**
6	Bn	4-$NO_2C_6H_4CH_2$	41	**6f**
7	EtO_2CCH_2	4-$NO_2C_6H_4CH_2$	50	**6g**

[a] A ten-fold excess of ethanol was used to circumvent problems with its volatility at the reaction temperature.

tentatively assigned as that of **4** with the yield of the reaction being 41%.

It is well-established that *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **1** can be deprotected to primary amines by mild thiolysis.[3,10] Preliminary studies, however, had also shown that isocyanates could be generated by the treatment of *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **1** with triphenylphosphine under anhydrous conditions[6] and indeed, isocyanates have been identified during the reductive decomposition of such heterocycles with phosphorus(III) reagents.[14] It was envisaged, therefore, that such a process could represent a viable method for the preparation of isocyanates and hence, investigations were carried out in this area.

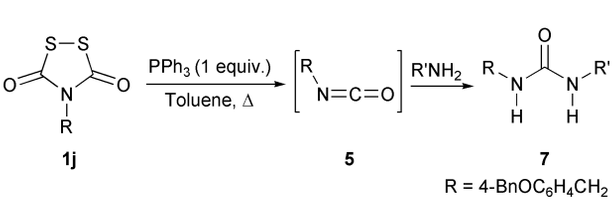
N-Alkylated 1,2,4-dithiazolidine-3,5-diones **1** were heated under reflux with 1 equiv. of triphenylphosphine in toluene. Although isocyanates **5** could be readily detected in this reaction by infrared spectrometry, they were not isolated and the heterocycle desulfurisations were generally carried out in the presence of an alcohol in order to produce the corresponding urethane **6** (Scheme 6). The results from these experiments are summarised in Table 6.



Scheme 6 Isocyanate/urethane formation.

4-Methyl-1,2,4-dithiazolidine-3,5-dione **1a** gave a 45% yield of urethane **6a** on treatment with triphenylphosphine in the presence of 4-nitrobenzyl alcohol (entry 1). This result is important, given that the procedure represents a safe method for the *in situ* generation of methyl isocyanate, a compound whose toxicity issues now preclude its general use. 4-Benzyl-1,2,4-dithiazolidine-3,5-dione **1d** gave reasonable to good yields of the expected urethanes **6b**–**f** under the same reaction conditions with ethanol (entry 2) and a range of substituted benzylic alcohols (entries 3–6). Protected glycine **6g** was also prepared from **1i**. In all cases, as would be expected,[14] triphenylphosphine sulfide was produced as a stoichiometric product in these reactions.

In an analogous manner, the intermediate isocyanates **5** could be trapped with primary amines to produce ureas **7** (Scheme 7), the results from three such experiments being summarised in Table 7.



Scheme 7 Urea formation.

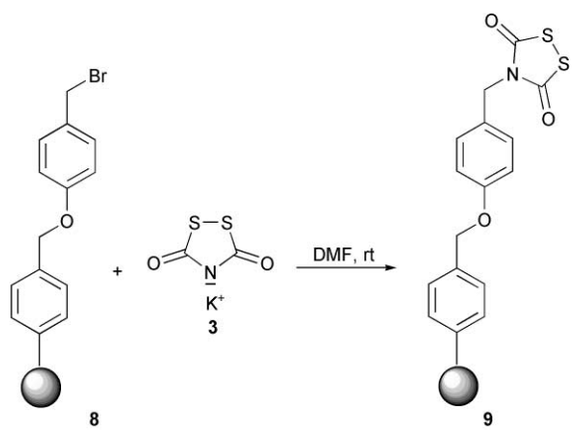
Table 7 Urea formation

Entry	R′	Yield (%)[a]	Yield (%)[b]	Product
1	^nBu	53	30	**7a**
2	^tBu	51	13	**7b**
3	Bn	71	64	**7c**

[a] PPh_3 (1 equiv.) present. [b] No PPh_3 present.

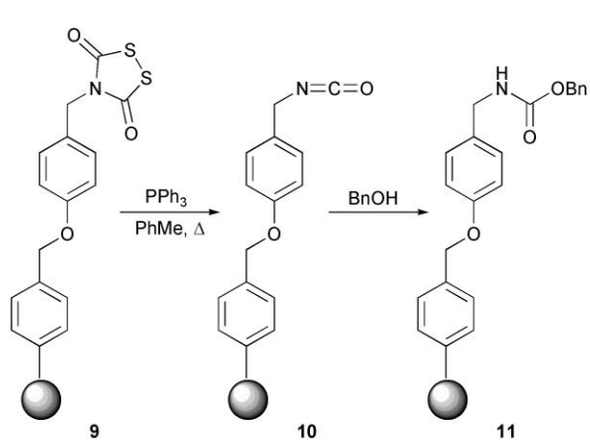
Barany *et al.* have found that ureas can be formed by the direct reaction of amines with peptidyl fragments, protected at the *N*-terminus with the dithiasuccinoyl group.[3] In this respect, we therefore repeated the urea preparations without the addition of triphenylphosphine. In all three cases, the expected ureas **7** were obtained but unfortunately, in significantly lower yields than with triphenylphosphine present (Table 7).

As a prelude to planned future studies, we investigated finally, the possibility of preparing a solid-supported derivative of **2**. (4-Bromomethylphenoxy)methyl polystyrene **8** was pre-swelled in DMF and treated with a solution containing 4.1 equiv. of the potassium 1,2,4-dithiazolidine-3,5-dione **3** (Scheme 8). After exhaustive washing, the dried resin was examined by infrared spectrometry. This clearly revealed strong, sharp absorbances at 1716 and 1647 cm^{-1}, consistent with the solid-supported derivative **9**. The bromide loading of the original resin was given as 1.4 mmol g^{-1} and the quantity of recovered potassium salt **3** suggested full loading of the heterocycle in **9**.



Scheme 8 Solid-supported 1,2,4-dithiazolidine-3,5-dione preparation.

9 was treated with triphenylphosphine (4 equiv.) in toluene (Scheme 9), under reflux and examination of the product by infrared spectrometry revealed a strong absorbance at 2256 cm^{-1}, consistent with the solid-supported isocyanate **10**. This absorbance disappeared on treatment with benzyl alcohol (4 equiv.) and it was replaced with one at 1716 cm^{-1}, consistent with the formation of urethane **11**.



Scheme 9 Solid-supported isocyanate/urethane preparation.

Solid-supported derivatives such as **9** and **10** have the potential to act simply as scavenging resins for nucleophiles such as amines and alcohols. In addition, isocyanate derivatives based on **11** will open up significant possibilities for solid-supported syntheses of a wide variety of nitrogen-containing heterocycles.

Conclusions

In summary, we have shown that the imide, 1,2,4-dithiazolidine-3,5-dione **2**, can be *N*-alkylated with reactive alkyl halides under mild reaction conditions. Potassium 1,2,4-dithiazolidine-3,5-dione **3** can be prepared in an analogous manner to potassium phthalimide and used in these alkylation reactions, although the unusually high acidity of **2** facilitates its *in situ* deprotonation with a variety of bases, simplifying the *N*-alkylation procedure.

X-ray crystallographic analysis of **3** revealed the expected planar structure of the conjugate base of **2** with the changes in bond lengths from **2** being consistent with straightforward delocalisation of the negative charge over the imide moiety. The reasons for the high acidity of **2** are still unclear.

The *N*-alkylated 1,2,4-dithiazolidine-3,5-diones **1** could be readily converted into isocyanates **5** by treatment with triphenylphosphine and to illustrate the synthetic utility of this procedure, these isocyanates **5** were trapped as a variety of urethanes **6** and ureas **7**.

Finally, we have shown that it is possible to carry out this sequence of transformations on a solid support, suggesting that such methodology could have a range of useful synthetic applications, particularly in the synthesis of nitrogen-containing heterocycles.

Experimental

General experimental

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

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.

X-ray crystallographic data were collected by means of combined phi and omega scans on a Brüker-Nonius KappaCCD area detector situated at the window of a rotating anode (λ(Mo-Kα) = 0.71073 Å). The structure was solved by direct methods, SHELXS-97 and refined using SHELXL-97.[15] Hydrogen atoms were included in the refinement but thermal parameters and geometry were constrained to ride on the atom to which they are bonded. The data were corrected for absorption effects using SORTAV.[16] Supplementary data in the form of a CIF file have been deposited with the Cambridge Crystallographic Data Centre.§

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 u.v. 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 described in *Purification of Laboratory Chemicals*, 3rd Edn., W. L. F. Armarego and D. D. Perrin, Pergamon Press, Oxford, 1988 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 or dry ice condenser as appropriate.

Potassium 1,2,4-dithiazolidine-3,5-dione (3)—Method a[6]

A solution of 1,2,4-dithiazolidine-3,5-dione **2**[8] (1.00 g, 7.41 mmol) in ethanol (8 cm^3) was added dropwise to a cooled (−5 °C), stirred, ethanolic solution of potassium hydroxide (1 M, 7.4 cm^3). After stirring the reaction mixture for a further 15 min and removal of the solvent under reduced pressure, the residue was recrystallised from ethanol–diethyl ether to give **3** (820 mg, 64%) as a white, crystalline solid (Found: C, 13.86; H, 0.00; N, 8.16; S, 36.74. $C_2KNO_2S_2$ requires C, 13.86; H, 0.00; N, 8.08; S, 37.02%); mp 170–180 °C (some decomposition observed at 140–142 °C); ν_{max}(Nujol mull)/cm^{-1} 1643 (s), 1545 (s), 1349 (w), 1256 (m), 1194, (s) and 672 (m).

Potassium 1,2,4-dithiazolidine-3,5-dione (3)—Method b

Potassium hydride (30 mg, 0.75 mmol) was added to a stirred, cooled (−20 °C) solution of 1,2,4-dithiazolidine-3,5-dione **2**[8] (100 mg, 0.74 mmol) in acetonitrile (1 cm^3). The reaction mixture was stirred at −20 °C for 2 h before warming to room temperature and removal of the solvent under reduced pressure. The resulting residue was recrystallised from ethanol–diethyl ether to give **3** (73 mg, 57%) as a white, crystalline solid; data as reported in Method a above.

Crystal structure determination of compound 3

Crystal data. $C_8K_4N_4O_8S_8$, M = 200.01, monoclinic, a = 7.3952(4), b = 22.4561(11), c = 13.6358(9) Å, U = 2192.4(2) Å^3, β = 104.494(3)°, T = 120(2) K, space group $P2_1/c$, Z = 4, μ(Mo-Kα) = 1.621 mm^{-1}, 3840 measured reflections, 2675 unique reflections ($I > 2\sigma I$), R_{int} = 0.0616, wR = 0.0593 (observed) and $wR2$ = 0.1847 (all data).

Alkylation of 3—General procedure

The alkyl halide (1.0–1.5 equiv.) was added to a stirred solution of potassium 1,2,4-dithiazolidine-3,5-dione **3** (100 mg, 0.58 mmol) in DMF or acetonitrile (2 cm^3) and the reaction mixture was stirred at 40 °C for 16 h. After evaporation of the solvent *in vacuo*, 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.

4-Methyl-1,2,4-dithiazolidine-3,5-dione (1a)

Using the general procedure above with iodomethane (50 μL, 0.80 mmol), potassium 1,2,4-dithiazolidine-3,5-dione **3** (100 mg,

§ CCDC reference number 210313. See http://www.rsc.org/suppdata/ob/b3/b305096c/ for crystallographic data in .cif or other electronic format.

0.58 mmol) and DMF (2 cm^3) gave **1a** (38 mg, 44%) as an off-white solid; mp 31–33 °C (lit.,[17] 33–35 °C). All other data in agreement with literature values.[17]

4-Hexyl-1,2,4-dithiazolidine-3,5-dione (1b)

Using the general procedure above with 1-iodohexane (130 μL, 0.58 mmol), potassium 1,2,4-dithiazolidine-3,5-dione **3** (100 mg, 0.58 mmol) and DMF (2 cm^3) gave **1b** (83 mg, 65%) as a brown oil (Found MH^+ (CI) 220.0475, $C_8H_{14}NO_2S_2$ requires 220.0466); ν_{max}(thin film)/cm^{-1} 2970–2780 (s) and 1654 (s); δ_H (300 MHz; $CDCl_3$) 0.88 (3H, t, J = 7, CH_3), 1.21–1.72 (8H, complex, $(CH_2)_4$) and 3.77 (2H, t, J = 7, CH_2N); δ_C (75 MHz; $CDCl_3$) 14.0 (CH_3), 22.45, 25.59, 27.31, 31.22 ($(CH_2)_4$), 46.5 (CH_2N) and 167.6 (C=O); *m*/*z* (CI) 220 (MH^+, 100%), 160 (18), 136 (12), 128 (94) and 85 (32).

4-Isopropyl-1,2,4-dithiazolidine-3,5-dione (1c)

Using the general procedure above with 2-iodopropane (85 μL, 0.85 mmol), potassium 1,2,4-dithiazolidine-3,5-dione **3** (100 mg, 0.58 mmol) and acetonitrile (2 cm^3) gave **1c** (35 mg, 34%) as a colourless oil (Found M^+ (EI) 176.9918, $C_5H_7NO_2S_2$ requires 176.9918); ν_{max}(thin film)/cm^{-1} 3060–2960 (m), 1720 (s), 1660 (m) and 1020 (m); δ_H (300 MHz; $CDCl_3$) 1.49 (6H, d, J = 7, $(CH_3)_2$), 3.73 (1H, septet, CH) and 3.77; δ_C (75 MHz; $CDCl_3$) 22.7 ($(CH_3)_2$), 43.1 (CH) and 167.2 (C=O); *m*/*z* (EI) 177 (M^+, 12%), 135 (8), 84 (23), 70 (37), 64 (28), 49 (47) and 43 (100).

4-Benzyl-1,2,4-dithiazolidine-3,5-dione (1d)

Using the general procedure above with benzyl bromide (100 μL, 0.84 mmol), potassium 1,2,4-dithiazolidine-3,5-dione **3** (100 mg, 0.58 mmol) and DMF (2 cm^3) gave **1d** (78 mg, 60%) as an off-white solid; mp 91–93 °C (lit.,[17] 90–92 °C). All other data in agreement with literature values.[17] Note: an identical reaction using acetonitrile (2 cm^3) as solvent gave **1d** in 57% yield.

(±)-2-(3,5-Dioxo-1,2,4-dithiazolidin-4-yl)propionic acid methyl ester (1e)

Using the general procedure above with (±)-methyl 2-bromopropionate (96 μL, 0.86 mmol), potassium 1,2,4-dithiazolidine-3,5-dione **3** (100 mg, 0.58 mmol) and DMF (2 cm^3) gave **1e** (34 mg, 27%) as a yellow oil (Found M^+ (EI) 220.9818, $C_5H_7NO_4S_2$ requires 220.9817); ν_{max}(thin film)/cm^{-1} 3060–2960 (m), 1732 (s), 1716 (s), 1370 (m), 1340 (w), 1290 (m), 1140 (w), 1020 (w) and 980 (w); δ_H (300 MHz; $CDCl_3$) 1.64 (3H, d, J = 7, CH_3), 3.77 (3H, s, CH_3O) and 5.04 (1H, q, J = 7, CH); δ_C (75 MHz; $CDCl_3$) 14.0 (CH_3), 53.1 (CH), 54.3 (CH_3O), 166.8 (C=O) and 168.4 (C=O); *m*/*z* (EI) 221 (M^+, 39%), 193 (12), 162 (45), 128 (37), 70 (100) and 64 (58).

Direct alkylation of 2—General procedure

The base (0.5–2.0 equiv.) was added to a stirred solution of 1,2,4-dithiazolidine-3,5-dione **2** (100 mg, 0.74 mmol) in acetonitrile (1.5 cm^3) at room temperature. The alkyl halide (1.0–1.6 equiv.) was added dropwise and after stirring at room temperature for 16 h, the solvent was evaporated *in vacuo* with adsorption of the residue onto silica gel for purification by flash chromatography on silica gel (typically eluting with 90% petroleum ether–10% ethyl acetate) to give the title compound.

4-Benzyl-1,2,4-dithiazolidine-3,5-dione (1d)

Using the general procedure above with 1,2,4-dithiazolidine-3,5-dione **2** (100 mg, 0.74 mmol), sodium bicarbonate (120 mg, 1.43 mmol), benzyl bromide (100 μL, 0.84 mmol) and acetonitrile (1.5 cm^3) gave **1d** (160 mg, 96%) as an off-white solid. Data as reported above.

4-Methyl-1,2,4-dithiazolidine-3,5-dione (1a)

Using the general procedure above with 1,2,4-dithiazolidine-3,5-dione **2** (100 mg, 0.74 mmol), sodium bicarbonate (120 mg, 1.43 mmol), iodomethane (50 μL, 0.80 mmol) and acetonitrile (1.5 cm^3) gave **1a** (86 mg, 78%) as an off-white solid. Data as reported above.

4-Hexyl-1,2,4-dithiazolidine-3,5-dione (1b)

Using the general procedure above with 1,2,4-dithiazolidine-3,5-dione **2** (100 mg, 0.74 mmol), potassium hydride (30 mg, 0.75 mmol), 1-iodohexane (130 μL, 0.88 mmol) and acetonitrile (1.5 cm^3) gave **1b** (19 mg, 12%) as a brown oil. Data as reported above.

4-Isopropyl-1,2,4-dithiazolidine-3,5-dione (1c)

Using the general procedure above with 1,2,4-dithiazolidine-3,5-dione **2** (100 mg, 0.74 mmol), potassium hydride (30 mg, 0.75 mmol), 2-iodopropane (85 μL, 0.87 mmol) and acetonitrile (1.5 cm^3) gave **1c** (14 mg, 11%) as a colourless oil. Data as reported above.

4-Allyl-1,2,4-dithiazolidine-3,5-dione (1f)

Using the general procedure above with 1,2,4-dithiazolidine-3,5-dione **2** (100 mg, 0.74 mmol), sodium bicarbonate (120 mg, 1.43 mmol), allyl bromide (100 μL, 1.16 mmol) and acetonitrile (1.5 cm^3) gave **1f** (117 mg, 90%) as an oil (Found M^+ (EI) 174.9760, $C_5H_5NO_2S_2$ requires 174.9762); ν_{max}(thin film)/cm^{-1} 3118–2813 (w), 1721 (s), 1660 (s), 1432 (m), 1414 (m), 1354 (m), 1301 (s), 1189 (w), 1153 (w), 1096 (w), 989 (w), 943 (w), 697 (m) and 650 (w); δ_H (300 MHz; $CDCl_3$) 3.35 (2H, d, J = 6, CH_2N), 5.28 (1H, d, J 11, CH_2=C), 5.33 (1H, dd, J 2.5 and 14, CH_2=C) and 5.82 (1H, m, CH); δ_C (75 MHz; $CDCl_3$) 48.0 (CH_2N), 120.2 (CH_2), 129.2 (CH) and 167.1 (C=O); *m*/*z* (EI) 175 (M^+, 19%), 82 (73), 70 (82), 64 (100), 60 (80), 56 (69) and 54 (71). This compound is reported in the patent literature as a solid; mp 80–81 °C.[18] All of our analytical data, however, are consistent with the structure as reported.

4-Prenyl-1,2,4-dithiazolidine-3,5-dione (1g)

Using the general procedure above with 1,2,4-dithiazolidine-3,5-dione **2** (100 mg, 0.74 mmol), sodium bicarbonate (120 mg, 1.43 mmol), prenyl bromide (100 μL, 0.87 mmol) and acetonitrile (1.5 cm^3) gave **1g** (116 mg, 77%) as an oil (Found: C, 41.37; H, 4.53; N, 6.66. $C_7H_9NO_2S_2$ requires C, 41.38; H, 4.43; N, 6.90%); (Found M^+ (EI) 203.0070, $C_7H_9NO_2S_2$ requires 203.0075); ν_{max}(thin film)/cm^{-1} 3147–2832 (m), 1724 (m), 1662 (s), 1429 (w), 1292 (m), 1215 (s), 1130 (w) and 667 (s); δ_H (300 MHz; $CDCl_3$) 1.73 (3H, s, CH_3), 1.79 (3H, s, CH_3), 4.35 (2H, d, J = 7, CH_2) and 5.22 (2H, br t, J = 7, CH); δ_C (75 MHz; $CDCl_3$) 18.1 (CH_3), 25.8 (CH_3), 44.2 (CH_2), 116.0 (CH), 140.0 (Me_2C) and 167.5 (C=O); *m*/*z* (EI) 203 (M^+, 70%), 143 (100), 128 (65), 110 (39), 101 (49), 96 (70), 82 (54), 69 (70), 68 (82) and 64 (98).

4-Propargyl-1,2,4-dithiazolidine-3,5-dione (1h)

Using the general procedure above with 1,2,4-dithiazolidine-3,5-dione **2** (100 mg, 0.74 mmol), sodium bicarbonate (120 mg, 1.43 mmol), propargyl bromide (100 μL, 1.12 mmol) and acetonitrile (1.5 cm^3) gave **1h** (60 mg, 47%) as an oil (Found M^+ (EI) 172.9597, $C_5H_3NO_2S_2$ requires 172.9605); ν_{max}(thin film)/cm^{-1} 3307 (w), 3160–2871 (m), 2121 (w), 1724 (m), 1668 (s), 1417 (w), 1348 (w), 1317 (w), 1306 (s), 1217 (s), 919 (w), 670 (s) and 592 (m); δ_H (300 MHz; $CDCl_3$) 3.35 (2H, d, J = 6, CH_2N), 5.28 (1H, d, J 11, CH_2=C), 2.31 (1H, t, J 2.5, CH) and 4.50 (2H, d, CH_2); δ_C (75 MHz; $CDCl_3$) 34.7 (CH_2), 73.1 (CH), 75.2 (C) and 166.5 (C=O); *m*/*z* (EI) 173 (M^+, 46%), 144 (42), 117 (46), 103 (100), 90 (29), 80 (56), 70 (63), 64 (61) and 52 (55).

(3,5-Dioxo-1,2,4-dithiazolidin-4-yl)acetic acid ethyl ester (1i)

Using the general procedure above with 1,2,4-dithiazolidine-3,5-dione **2** (300 mg, 2.22 mmol), sodium bicarbonate (360 mg, 4.29 mmol), ethyl bromoacetate (290 μL, 2.61 mmol) and acetonitrile (5 cm^3) gave **1i** (420 mg, 86%) as a yellow oil (Found MH^+ (CI) 221.9900, $C_6H_7NO_4S_2$ requires 221.9895); ν_{max}(thin film)/cm^{-1} 3060–2960 (m), 1734 (s), 1686 (m), 1360 (w), 1290 (s), 1140 (w), 1020 (w) and 980 (s); δ_H (300 MHz; $CDCl_3$) 1.29 (3H, t, J = 7, CH_3), 4.24 (2H, q, J = 7, CH_2O) and 4.46 (2H, s, CH_2N); δ_C (75 MHz; $CDCl_3$) 14.1 (CH_3), 45.6 (CH_2N), 62.4 (CH_2O), 165.5 (C=O) and 167.0 (C=O); *m*/*z* (CI) 222 (MH^+, 36%), 176 (100), 162 (7), 148 (6), 130 (8) and 102 (37).

(±)-2-(3,5-Dioxo-1,2,4-dithiazolidin-4-yl)propionic acid methyl ester (1e)

Using the general procedure above with 1,2,4-dithiazolidine-3,5-dione **2** (100 mg, 0.74 mmol), potassium hydride (30 mg, 0.75 mmol), (±)-methyl 2-bromopropionate (96 μL, 0.86 mmol) and acetonitrile (1.5 cm^3) gave **1e** (21 mg, 13%) as a yellow oil. Data as reported above.

4-(4-Benzyloxybenzyl)-1,2,4-dithiazolidine-3,5-dione (1j)

4-Benzyloxybenzyl chloride (170 mg, 0.73 mmol) was added to a stirred mixture of 1,2,4-dithiazolidine-3,5-dione **2** (100 mg, 0.74 mmol), sodium bicarbonate (120 mg, 1.43 mmol) and potassium iodide (123 mg, 0.74 mmol) in acetonitrile (1.5 cm^3). The reaction mixture was stirred at room temperature for 16 h and the solvent was evaporated *in vacuo* with adsorption of the residue onto silica gel for flash chromatography on silica gel (90% petroleum ether–10% ethyl acetate). This gave **1j** (182 mg, 75%) as a white solid (Found M^+ (EI) 331.0331, $C_{16}H_{13}NO_3S_2$ requires 331.0337); mp 52–53 °C; ν_{max}(thin film)/cm^{-1} 3034 (w), 2933–2829 (w), 1682 (s), 1608 (m), 1513 (s), 1450 (m), 1344 (s), 1242 (s), 1174 (m), 1128 (m), 1045 (s), 837 (m) and 729 (s); δ_H (400 MHz; $CDCl_3$) 4.81 (2H, s, CH_2N), 5.03 (2H, s, CH_2O), 6.92 (2H, part of AA′BB′, J = 9, aryl-H) and 7.28–7.42 (7H, complex, aryl-H and phenyl-H); δ_C (100 MHz; $CDCl_3$) 40.4 (CH_2N), 70.1 (CH_2O) and 127.3, 128.0, 129.6, 131.3, 134.4, 157.5, 158.1 (aryl and phenyl C); *m*/*z* (EI) 331 (M^+, 3%), 239 (5), 198 (10), 197 (100), 162 (7), 107 (7), 91 (22) and 61 (8).

4-Benzoyl-1,2,4-dithiazolidine-3,5-dione (4)

Benzoyl chloride (86 μL, 0.74 mmol) was added dropwise to a stirred solution of 1,2,4-dithiazolidine-3,5-dione **2** (100 mg, 0.74 mmol) in pyridine (150 μL, 1.86 mmol) at 0 °C. The reaction mixture was allowed to warm up to room temperature with stirring being continued for 72 h before the addition of ethanol (1 cm^3). This gave **4** (72 mg, 41%) as a white precipitate; mp 152–153 °C (sublimes); ν_{max}(thin film)/cm^{-1} 1716 (m), 1641 (s), 1620 (s), 1580 (w), 1540 (m), 1520 (m), 1430 (w), 1320 (m) and 1260 (m); δ_H (400 MHz; $CDCl_3$) 7.59 (2H, t, J = 8, phenyl-H), 7.72 (1H, t, J = 8, phenyl-H) and 8.33 (2H, d, J = 8, phenyl-H); δ_C (100 MHz; $CDCl_3$) 128.0 (phenyl *ipso* C), 129.1, 129.2 (phenyl C), 157.0 (PhC(O)) and 164.8 (imide C=O); *m*/*z* (ES^+) Fragments observed at 147 (43%), 105 (62) and 64 (100).

Isocyanate formation–trapping—General procedure

The alcohol (0.50 mmol or up to 10 fold excess if volatile) was added to a solution of the 4-alkylated-1,2,4-dithiazolidine-3,5-dione **1** (0.50 mmol) and triphenylphosphine (130 mg, 0.50 mmol) in toluene (2 cm^3) and the stirred mixture was heated at reflux for 48 h. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel (typically eluting with 90% petroleum ether–10% ethyl acetate) to give the title compound. For the preparation of ureas, an analogous procedure was followed using 4-(4-benzyloxybenzyl)-1,2,4-dithiazolidine-3,5-dione (50 mg, 0.15 mmol), triphenylphosphine (39 mg, 0.15 mmol) and the primary amine (0.15 mmol) in toluene (2 cm^3).

Methylcarbamic acid (4-nitrobenzyl) ester (6a)

Using the general procedure above with 4-methyl-1,2,4-dithiazolidine-3,5-dione **1a** (100 mg, 0.67 mmol), triphenylphosphine (184 mg, 0.70 mmol) and 4-nitrobenzyl alcohol (104 mg, 0.68 mmol) in toluene (2 cm^3) gave **6a** (63 mg, 45%) as a yellow, powdery solid; mp 124–126 °C (lit.,[19a] 125–127 °C). All other data in agreement with literature values.[19a,b]

Benzylcarbamic acid ethyl ester (6b)

Using the general procedure above with 4-benzyl-1,2,4-dithiazolidine-3,5-dione **1d** (110 mg, 0.49 mmol), triphenylphosphine (130 mg, 0.50 mmol) and ethanol (300 μL, 5.1 mmol) in toluene (2 cm^3) gave **6b** (66 mg, 74%) as a yellow oil. This compound is reported as a solid; mp 39 °C.[20] All other analytical data were, however, consistent with literature values.[20]

Benzylcarbamic acid benzyl ester (6c)

Using the general procedure above with 4-benzyl-1,2,4-dithiazolidine-3,5-dione **1d** (110 mg, 0.49 mmol), triphenylphosphine (130 mg, 0.50 mmol) and benzyl alcohol (52 μL, 0.50 mmol) in toluene (2 cm^3) gave **6c** (91 mg, 77%) as a solid; mp 58–59 °C (lit.,[21] 61–62 °C). All other data in agreement with literature values.[21]

Benzylcarbamic acid (4-bromobenzyl) ester (6d)

Using the general procedure above with 4-benzyl-1,2,4-dithiazolidine-3,5-dione **1d** (110 mg, 0.49 mmol), triphenylphosphine (130 mg, 0.50 mmol) and 4-bromobenzyl alcohol (94 mg, 0.50 mmol) in toluene (2 cm^3) gave **6d** (94 mg, 60%) as a white, powdery solid (Found MNH_4^+ (ES^+) 337.0548, $C_{15}H_{18}{}^{79}BrN_2O_2$ requires 337.0548); mp 95–96 °C; ν_{max}(thin film)/cm^{-1} 3340 (s), 2982–2807 (w), 1691 (s), 1535 (m), 1430 (w), 1410 (w), 1390 (w), 1270 (m), 1240 (w), 1090 (w), 1020 (w), 980 (w), 960 (w), 920 (w), 740 (m) and 720 (m); δ_H (300 MHz; $CDCl_3$) 4.39 (2H, d, J = 6, CH_2N), 5.08 (3H, br s, CH_2O and NH), 7.15–7.39 (7H, part of complex, aryl-H and phenyl-H) and 7.48 (2H, part of AA′BB′, aryl-H); δ_C (75 MHz; $CDCl_3$) 45.2 (CH_2N), 66.0 (CH_2O), 127.6, 128.7, 129.8, 131.7 (aryl and phenyl C), 135.5 (aromatic *ipso* C) and 138.3 (aromatic *ipso* C); *m*/*z* (CI) 339 (MNH_4^+ [^{81}Br], 13%), 337 (MNH_4^+ [^{79}Br], 13), 153 (10), 125 (55), 108 (100) and 106 (38).

Benzylcarbamic acid (4-methoxybenzyl) ester (6e)

Using the general procedure above with 4-benzyl-1,2,4-dithiazolidine-3,5-dione **1d** (110 mg, 0.49 mmol), triphenylphosphine (130 mg, 0.50 mmol) and 4-methoxybenzyl alcohol (62 μL, 0.50 mmol) in toluene (2 cm^3) gave **6e** (73 mg, 55%) as a white, powdery solid; mp 75–76 °C (lit.,[20] 77 °C). All other data in agreement with literature values.[20]

Benzylcarbamic acid (4-nitrobenzyl) ester (6f)

Using the general procedure above with 4-benzyl-1,2,4-dithiazolidine-3,5-dione **1d** (110 mg, 0.49 mmol), triphenylphosphine (130 mg, 0.50 mmol) and 4-nitrobenzyl alcohol (77 mg, 0.50 mmol) in toluene (2 cm^3) gave **6f** (57 mg, 41%) as a yellow, powdery solid; mp 109–110 °C (lit.,[22] 109–110 °C). All other data in agreement with literature values.[22]

***N*-(4-Nitrobenzyloxycarbonyl)glycine ethyl ester (6g)**

Using the general procedure above with (3,5-dioxo-1,2,4-dithiazolidin-4-yl)acetic acid ethyl ester **1i** (100 mg, 0.45 mmol), triphenylphosphine (120 mg, 0.46 mmol) and 4-nitrobenzyl alcohol (73 mg, 0.48 mmol) in toluene (2 cm^3) gave **6g** (63 mg,

50%) as a white, powdery solid; mp 104–106 °C (lit.,[23a] 107 °C). All other data in agreement with literature values.[23a,b]

1-(4-Benzyloxybenzyl)-3-*n*-butylurea (7a)

Using the general procedure above with 4-(4-benzyloxybenzyl)-1,2,4-dithiazolidine-3,5-dione **1j** (50 mg, 0.15 mmol), triphenylphosphine (39 mg, 0.15 mmol) and *n*-butylamine (15 μL, 0.16 mmol) in toluene (2 cm^3) gave **7a** (25 mg, 53%) as a white, powdery solid (Found MH^+ (CI) 313.1929, $C_{19}H_{25}N_2O_2$ requires 313.1916); mp 140–141 °C; ν_{max}(thin film)/cm^{-1} 3336 (w), 3017–2823 (w), 1653 (s), 1599 (s), 1560 (s), 1516 (m), 1451 (m), 1205 (w), 1140 (w) and 696 (m); δ_H (400 MHz; $CDCl_3$) 0.85 (3H, t, J = 7, CH_3), 1.23–1.53 (4H, complex, $(CH_2)_2$), 3.14 (2H, m, NCH_2Pr), 4.22 (2H, d, J = 5, NCH_2Ar), 4.32 (1H, br s, NH), 4.60 (1H, br s, NH), 5.05 (2H, s, OCH_2Ph), 6.94, 7.23 (2 × 2H, AA′BB′, J = 9, aryl-H) and 7.30–7.51 (5H, complex, phenyl-H); δ_C (100 MHz; $CDCl_3$) 13.8 (CH_3), 20.0 ($MeCH_2$), 32.2 ($EtCH_2$), 40.4 (CH_2N), 44.1 (CH_2N), 70.1 (CH_2O), 115.0, 127.5, 128.0, 128.6, 128.9 (aryl and phenyl C), 131.5 (aryl *ipso* C), 136.9 (aryl *ipso* C) and 157.7, 158.1 (BnOC and C=O); *m*/*z* (CI) 313 (MH^+, 62%), 312 (30), 198 (43), 197 (100), 100 (28) and 91 (52).

The preparation of **7a** was repeated in the absence of triphenylphosphine. A solution of 4-(4-benzyloxybenzyl)-1,2,4-dithiazolidine-3,5-dione **1j** (50 mg, 0.15 mmol) and *n*-butylamine (5 μL, 0.15 mmol) in toluene (2 cm^3) was heated under reflux for 48 h. Work-up as described in the general procedure above gave **7a** (14 mg, 30%) as a white, powdery solid. Data as reported above.

1-(4-Benzyloxybenzyl)-3-*tert*-butylurea (7b)

Using the general procedure above with 4-(4-benzyloxybenzyl)-1,2,4-dithiazolidine-3,5-dione **1j** (50 mg, 0.15 mmol), triphenylphosphine (39 mg, 0.15 mmol) and *tert*-butylamine (16 μL, 0.16 mmol) in toluene (2 cm^3) gave **7b** (24 mg, 51%) as a white, powdery solid (Found MH^+ (CI) 313.1935, $C_{19}H_{25}N_2O_2$ requires 313.1916); mp 155–157 °C; ν_{max}(thin film)/cm^{-1} 3332 (w), 3011–2826 (w), 1661 (s), 1606 (s), 1574 (s), 1523 (m), 1444 (m), 1210 (w), 1150 (w) and 706 (m); δ_H (400 MHz; $CDCl_3$) 1.49 (9H, s, $(CH_3)_3$), 4.12 (1H, br s, NH), 4.28 (3H, br complex, NCH_2 and NH), 5.08 (2H, s, $PhCH_2$), 6.98, 7.19 (2 × 2H, AA′BB′, J = 9, aryl-H) and 7.28–7.53 (5H, complex, phenyl-H); δ_C (100 MHz; $CDCl_3$) 28.6 (CH_3), 41.2 (Me_3C), 45.4 (NCH_2), 71.1 (CH_2O), 115.8, 127.4, 127.9, 128.3, 128.7 (aryl and phenyl C), 70.1 (CH_2O), 115.0, 127.5, 128.0, 128.6, 128.9 (aryl and phenyl C), 132.7, 136.6 (aryl *ipso* C), and 157.4, 158.0 (BnOC and C=O); *m*/*z* (CI) 313 (MH^+, 62%), 312 (27), 197 (100), 129 (15) and 91 (44).

The preparation of **7b** was repeated in the absence of triphenylphosphine. A solution of 4-(4-benzyloxybenzyl)-1,2,4-dithiazolidine-3,5-dione **1j** (50 mg, 0.15 mmol) and *tert*-butylamine (16 μL, 0.15 mmol) in toluene (2 cm^3) was heated under reflux for 48 h. Work-up as described in the general procedure above gave **7b** (6 mg, 13%) as a white, powdery solid. Data as reported above.

1-(4-Benzyloxybenzyl)-3-benzylurea (7c)

Using the general procedure above with 4-(4-benzyloxybenzyl)-1,2,4-dithiazolidine-3,5-dione **1j** (50 mg, 0.15 mmol), triphenylphosphine (39 mg, 0.15 mmol) and benzylamine (16 μL, 0.15 mmol) in toluene (2 cm^3) gave **7c** (37 mg, 71%) as a white, powdery solid (Found MH^+ (CI) 347.1767, $C_{19}H_{25}N_2O_2$ requires 313.1759); mp 146–177 °C; ν_{max}(thin film)/cm^{-1} 3063 (w), 2985–2823 (w), 1716 (m), 1700 (s), 1684 (s), 1558 (w), 1541 (w), 1508 (w), 1435 (s), 1308 (w), 1209 (m), 1182 (w), 1103 (m), 754 (m), 714 (s) and 690 (s); δ_H (400 MHz; $CDCl_3$) 4.33 (2H, d, J = 5, NCH_2), 4.38 (2H, d, J = 5, NCH_2), 4.60 (2H, br s, 2 × NH), 5.05 (2H, s, CH_2O), 6.92, 7.19 (2 × 2H, AA′BB′, J = 10, aryl-H) and 7.22–7.76 (10H, complex, phenyl-H); δ_C (100 MHz; $CDCl_3$) 44.2 (CH_2N), 44.7 (CH_2N), 70.0 (CH_2O), 115.0, 127.4, 128.0, 128.5, 128.7, 128.8 (aryl and phenyl C), 132.2, 132.3, 136.4 (aryl *ipso* C) and 157.7, 158.1 (BnOC and C=O); *m*/*z* (CI) 347 (MH^+, 44%), 197 (100), 107 (53) and 93 (17).

The preparation of **7c** was repeated in the absence of triphenylphosphine. A solution of 4-(4-benzyloxybenzyl)-1,2,4-dithiazolidine-3,5-dione **1j** (50 mg, 0.15 mmol) and benzylamine (16 μL, 0.15 mmol) in toluene (2 cm^3) was heated under reflux for 48 h. Work-up as described in the general procedure above gave **7c** (33 mg, 63%) as a white, powdery solid. Data as reported above.

Solid-supported 1,2,4-dithiazolidine-3,5-dione (9)

(4-Bromomethylphenoxy)methyl polystyrene **8** (1.4 mmol g^{-1} loading, 100 mg, 0.14 mmol Br) was swelled in DMF (3 × 5 cm^3) before treatment with a solution of potassium 1,2,4-dithiazolidine-3,5-dione (100 mg, 0.74 mmol) in DMF (5 cm^3). The mixture was agitated at room temperature for 12 h before washing the resin with DMF (2 × 5 cm^3), dichloromethane (2 × 5 cm^3) and methanol (2 × 5 cm^3). Drying *in vacuo* gave the solid-supported 1,2,4-dithiazolidine-3,5-dione **9**; ν_{max}(KBr disc)/cm^{-1} 1716 (s) and 1647 (s).

Solid-supported isocyanate (10)

Solid-supported 1,2,4-dithiazolidine-3,5-dione **9** (0.14 mmol) was swelled in toluene (3 × 5 cm^3) before the addition of a solution of triphenylphosphine (147 mg, 0.56 mmol) in toluene (5 cm^3). The mixture was heated under reflux for 48 h before washing the resin with toluene (3 × 5 cm^3). Drying *in vacuo* gave the solid-supported isocyanate **10**; ν_{max}(KBr disc)/cm^{-1} 2256 (br s).

Solid-supported urethane (11)

Solid-supported isocyanate **10** (0.14 mmol) was swelled in toluene (3 × 5 cm^3) before the addition of a solution of benzyl alcohol (58 μL, 0.56 mmol) in toluene (5 cm^3). The mixture was stirred at room temperature for 48 h before washing the resin with toluene (3 × 5 cm^3). Drying *in vacuo* gave the solid-supported urethane **11**; ν_{max}(KBr disc)/cm^{-1} 1716 (s).

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