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Novel synthesis of 1-aryl-3-chloro-3-phenylazetidin-2-one-4-spiro-5′-4′-chloro-5′*H*-1′,2′,3′-dithiazoles and bis(2-oxo-azetidin-4-yl) trisulfides†

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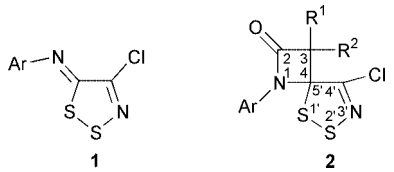
Treatment of 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles with *in situ* generated (chloro)phenylketene in CH_2Cl_2 at rt gave azetidin-2-one-4-spiro-5′-(1′,2′,3′-dithiazoles) as major products, which reacted with primary and secondary alkylamines in CH_2Cl_2 at rt to afford bis(2-oxo-azetidin-4-yl) trisulfides in good to excellent yields.

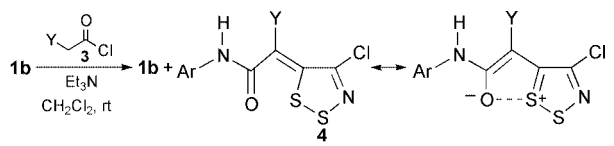
Azetidin-2-ones have been one of the most attractive classes of organic compounds due to their potential biological applications.[1] Numerous methods for the synthesis of azetidin-2-ones are known and these are well-documented in the literature.[1] In connection with our ongoing project for exploring the potential synthetic utility of 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles **1**,[2] we are interested in investigating the reactivity of the N=C-5 imine bond of **1** toward cycloaddition reactions with a ketene because a [2 + 2] cycloaddition with a ketene would give azetidin-2-one-4-spiro-5′-(1′,2′,3′-dithiazoles) **2**, which, to the best of our knowledge, has never been reported. Compound **2** is



1 **2**

of interest with respect to the stereochemistry at C-3 and C-4. In addition, it may be utilized as a precursor for the synthesis of hitherto unknown azetidin-2-ones created by cleaving the bond between S-1′ and S-2′ with nucleophiles, as shown in the ready conversion of **1** to diverse products.[3] With this in mind, **1** was treated with various ketenes which were generated *in situ*. This paper describes the preliminary results we have obtained.

For the generation of a ketene, a method involving acid chlorides and Et_3N[4] in CH_2Cl_2 at rt was employed since neither reagent reacts with **1** under conditions for the generation of ketenes. When Et_3N (1.22–2.87 mmol) in CH_2Cl_2 (30 ml) was added dropwise to a mixture of **1b** (Ar = 4-$MeOC_6H_4$) (0.773–0.935 mmol) and acid chlorides **3** (1.20–2.89 mmol) in CH_2Cl_2 (20 ml) at rt, followed by stirring for 0.5–1 h, only a small amount of **4a** (Y = Cl), **4c** (Y = MeO), and **4e** (Y = AcO), which comprised a single isomer in view of the ^1H and ^{13}C NMR spectroscopic data, and most of the unreacted **1b** were isolated (Scheme 1).



Ar = 4-$MeOC_6H_4$ **a**, Y = Cl, 26% **d**, Y = PhO, 0%
b, Y = Ph, 0% **e**, Y = AcO, 17%
c, Y = MeO, 2%

Scheme 1

Compounds **4a**, **4c**, and **4e**, derivatives of 5-(phenylcarbamoyl)methylidene-5*H*-1,2,3-dithiazole,[5] are all new. The (*E*)-stereochemistry of **4** was assigned based on the IR absorptions of the carbonyl group at 1603, 1613, and 1619 cm^{-1}, respectively, which suggests the possible interaction of the carbonyl oxygen with electron deficient S-1.[2] Surprisingly, the reactions of **1** with 2-chloro-2-phenylacetyl chloride (**3f**) under the foregoing conditions gave the desired compound **2** (R^1 = Cl, R^2 = Ph) in good to excellent yields (Scheme 2). Yields and mps of **2** are summarized in Table 1.

The structures of **2** were determined based on spectroscopic (^1H and ^{13}C NMR, IR, MS) and analytical data. The X-ray single crystal structure of **2d**‡ (Fig. 1) clearly shows *cis*-stereochemistry with *S* and *R* configurations at C-3 and C-4, respectively. The *cis*-stereochemistry of **2** may be ascribed to the avoidance of severe electronic repulsions between lone pair electrons on the two chlorine atoms at C-3 and C-4′.

Treatment of **2** (0.23–0.38 mmol) in CH_2Cl_2 (10 ml) with a slightly excessive molar amount of primary and secondary alkylamines at rt gave bis(2-oxo-azetidin-4-yl) trisulfides **5** along with alkylamino 2-oxo-azetidin-4-yl disulfides **6** and a considerable amount of unreacted **2** (Scheme 2). However, by employing 4 molar equivalents of alkylamines, **5** were obtained as major products along with **6** and a small amount of isothiazol-3-ones **7**, which were obtained only from the reactions of **2c** and

Table 1 Yields and mps of **2**[a]

Compound	Ar	Yield[b] (%)	Mp[c]/°C
2a	4-MeO-2-$MeOC_6H_3$	97	142–146 (dec.)
2b	4-$MeOC_6H_4$	96	122–124
2c	4-MeC_6H_4	95	73–76
2d	4-ClC_6H_4	86	147–149
2e	4-$MeCOC_6H_4$	74	156–160 (dec.)
2f	4-$O_2NC_6H_4$	44	139–144 (dec.)

[a] Time for dropwise addition of Et_3N: 2–3 h; time stirred: 0.5–1 h. [b] Isolated yields. [c] Recrystallized from a mixture of *n*-hexane and CH_2Cl_2.

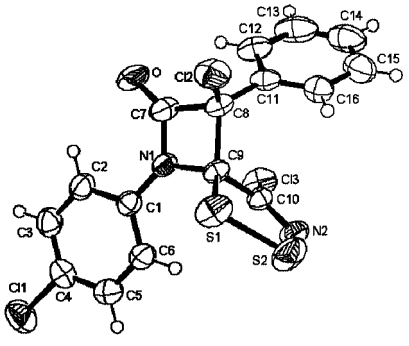


Fig. 1 ORTEP drawing of (3*S*,4*R*)-3-chloro-1-(4-chlorophenyl)-3-phenylazetidin-2-one-4-spiro-5′-(4′-chloro-5′*H*-1′,2′,3′-dithiazole) **2d**.

† Electronic supplementary information (ESI) available: spectral and analytical data for **2** and **4**–**8**. See http://www.rsc.org/suppdata/cc/b1/b103974c/

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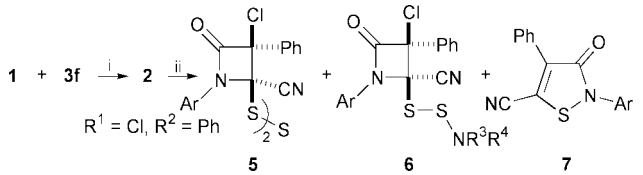
Table 2 Reaction times and yields of compounds **5**, **6** and **7**

Entry	Compound	Ar	R^3R^4NH	Time (*t*/h)	Yield[a] (%) **5**	**6**	**7**
1	**2b**	4-$MeOC_6H_4$	*n*-$PrNH_2$	0.7	**b** 93 (93–98)[c]		
2	**2b**	4-$MeOC_6H_4$	*t*-$BuNH_2$	42	**b** 77	**b** 7	
3	**2c**	4-MeC_6H_4	*n*-$PrNH_2$	0.7	**c** 80 (103–107)[c]	**c** 4	
4	**2c**	4-MeC_6H_4	*t*-$BuNH_2$	4	**c** 77	**d** 6	
5	**2c**	4-MeC_6H_4	*n*-Pr_2NH	2	**c** 61	**e** 16	**c** 6 (170–171)[d]
6	**2c**	4-MeC_6H_4	$PhNH_2$	24[b]			
7	**2d**	4-ClC_6H_4	*n*-$PrNH_2$	0.2	**d** 69 (110–115)[c]	**f** 10	**d** 19 (181–182)[d]
8	**2d**	4-ClC_6H_4	*t*-$BuNH_2$	16	**d** 73	**g** 8	
9	**2f**	4-$O_2NOC_6H_4$	*n*-$PrNH_2$	0.2	**e** 90 (160–165)[d]		

[a] Isolated yields. [b] Reflux time. [c] Recrystallized from a mixture of CH_2Cl_2 and EtOH. [d] Recrystallized from a mixture of *n*-hexane and CH_2Cl_2.

2d. Trisulfides of azetidin-2-ones have never been reported despite the existence of numerous methods for the synthesis of a variety of trisulfides.[6] Compounds **6** and **7** are also new. The stereochemistry at C-3 and C-4 of **5** and **6** are believed to be intact. Reaction times and yields of trisulfides **5**, disulfides **6**, and isothiazol-3-ones **7** are summarized in Table 2.

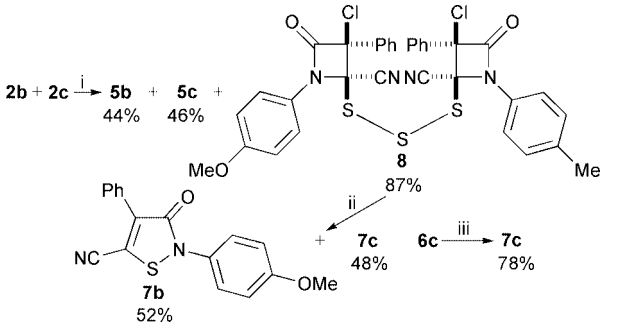


Scheme 2 *Reagents and conditions*: i, Et_3N, CH_2Cl_2, rt; ii, R^3R^4NH, CH_2Cl_2, rt.

Table 2 shows that **2** react with both primary (entries 1–4 and 7–9) and secondary (entry 5) alkylamines to give **5** but not with arylamine even at reflux temperature over a prolonged reaction time (entry 6). Among primary alkylamines, *i.e.* *n*-$PrNH_2$ and *t*-$BuNH_2$, the reactions with *n*-$PrNH_2$ proceeded more rapidly than those with *t*-$BuNH_2$, presumably due to the steric effect of a bulky *tert*-butyl group.

For a mechanistic study, a mixture of equal molar amounts of **2b** (0.253 mmol) and **2c** (0.253 mmol) was treated with *n*-$PrNH_2$ (2.07 mmol) for 3 h under the foregoing conditions. From the reaction were isolated **5b** (44%), **5c** (46%), and unsymmetrical trisulfide **8** (87%) (Scheme 3). The isolation of unsymmetrical trisulfide **8** coupled with its yield, which is approximately twice of that of either **5b** or **5c**, indicates that trisulfides **5** are formed *via* an intermolecular reaction. Furthermore, when the mixture of **2b** (0.070 mmol) and **2c** (0.069 mmol) was treated with a large exccss of *n*-$PrNH_2$ (1.1 mmol) for 24 h under the same conditions, isothiazol-3-ones **7b** (58%) and **7c** (62%) along with unknown mixtures were obtained. No trisulfides **5b** and **5c** were detected. The results indicate that **2** are converted to **7** *via* **5** in the presence of a large excess of *n*-$PrNH_2$ over a prolonged reaction time. In addition, the fact that **7c** (78%) together with an unknown mixture as obtained from the reaction of disulfide **6c** (Ar = 4-MeC_6H_4, R^3 = H, R^4 = *n*-Pr) (0.11 mmol) with *n*-$PrNH_2$ (0.49 mmol) in CH_2Cl_2 for 26 h indicates that **6** also act as intermediates for the formation of **7**.

In conclusion we have found that 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles reacted with (chloro)phenylketene in CH_2Cl_2 at rt to give spiro compound **2**, which undergoes a decomposition reaction in the presence of primary and secondary alkylamines in CH_2Cl_2 at rt, giving bis(2-oxo-azetidin-4-yl) trisulfides as major products. Study of the mechanism and scope of the reactions is in progress.



Scheme 3 *Reagents and conditions*: i, *n*-$PrNH_2$ (8 equiv.), CH_2Cl_2, rt, 3 h; ii, *n*-$PrNH_2$, (8 equiv.), CH_2Cl_2, rt, 24 h; iii, *n*-$PrNH_2$ (4 equiv.), CH_2Cl_2, rt, 26 h.

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Notes and references

‡ *Crystal data* for **2d**: $C_{16}H_9Cl_3N_2OS_2$, M = 415.72, monoclinic, a = 16.946(2), b = 7.4460(5), c = 15.026(3) Å, β = 113.080(10)°, U = 1744.2(4) Å^3, T = 293 K, $P2/k$, Z = 4, μ(Mo-Kα) = 0.770 mm^{-1}, λ = 0.71070 Å, 3189 reflections measured, 3057 unique (R_{int} = 0.0088) which were used in all calculations. Final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0455, $wR2$ = 0.1156. CCDC 165871. See http://www.rsc.org/suppdata/cc/b1/b103974c/ for crystallographic data in CIF or other format.

Spectral data for **2d**: ν(neat)/cm^{-1} 3056, 1782, 1490, 1442, 1366, 1158, 1117, 1109, 1051, 1010; δ_H(300 MHz, $CDCl_3$) 7.36 (s, 4H), 7.38-7.44 (m, 3H), 7.59 (br, 2H); δ_C(75 MHz, $CDCl_3$) 82.9, 102.1, 119.2, 126.6, 129.2, 129.8, 130.2, 131.8, 132.9, 133.1, 142.0, 160.3.

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