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Tributylphosphine-Catalyzed Cycloaddition of Aziridines with Carbon Disulfide and Isothiocyanate

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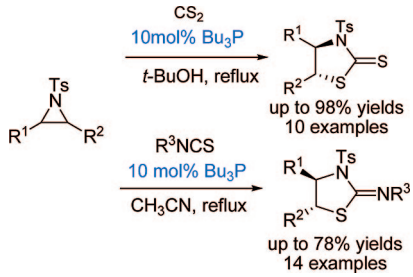

Aziridines underwent cyclization reaction with carbon disulfide and isothiocyanate in the presence of organophosphine to afford thiazolidinone derivatives in good to high yields. The mechanistic study revealed that organophosphine serves as a catalyst in the reaction.

Aziridines are versatile intermediates for the synthesis of biologically important compounds due to their ability to function as carbon electrophiles.[1,2] Many transformations of activated and unactivated aziridines have well been documented, and the ring-opening reactions are among the most studied ones. On the other hand, there are many reports on the reaction of epoxides with heterocumulenes, such as carbon disulfide and isothiocyanate, to form heterocycles.[3] However, a relatively limited number of reports on the reaction of aziridines with heterocumulenes have appeared.[4] Most of the reactions proceeded in the presence of a metal catalyst,[4b−d] and few of them used organo-molecules as the catalyst. During the studies on the transformation of aziridines,[5] we found that organophosphines played a role as a trigger to initiate the ring-opening reaction of aziridines[6a−c] as well as the transformation of aziridines to conjugated dienes.[6d] Upon the basis of these results, further investigations on the reaction of aziridines using organophosphine were carried out. In this paper, we disclose the organophosphine-catalyzed reaction of aziridines with carbon disulfide and isothiocyanate to produce 1,3-thiazolidine derivatives, which are commonly used as potential intermediates in pharmaceutical chemistry and organic synthesis.[7] Furthermore, a plausible mechanism is proposed.

TABLE 1. Reaction of Aziridine 1a with CS_2 in the Presence of Organophosphine[a]

entry	solvent	catalyst	yield (%)[b]
1	THF	PPh_3	none
2	toluene	PPh_3	20
3	CCl_4	PPh_3	trace
4	EtOH	PPh_3	81
5	*t*-BuOH	PPh_3	83
6	*t*-BuOH	PCy_3	78
7	*t*-BuOH	PBu_3	92
8	*t*-BuOH	PBu_3[c]	78

[a] Molar ratio of **1a**:CS_2:organophosphine = 1:6.6:0.1, run in 2 mL of solvent. [b] Isolated yield, the structure was determined by ^1H NMR. [c] 50 mol % of PBu_3 was used.

At the beginning, the reaction of aziridine **1a** with CS_2 in the presence of Bu_3P was studied (eq 1). The solvent has great impact on the reaction (Table 1). No product was obtained when the reaction was carried out in THF using triphenylphosphine as a catalyst (entry 1). 1,3-Thiazolidine **2a** was afforded in 20% yield when the reaction was carried out in toluene (entry 2), while only a trace of the desired product was isolated with CCl_4

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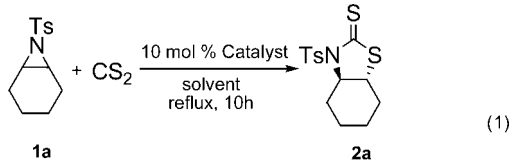
TABLE 2. Cycloaddition of CS_2 with Aziridines Catalyzed by Bu_3P[a]

entry	aziridine	R^1, R^2, R^3	product	yield %[b]
1	**1a**	-$(CH_2)_4$-, H	**2a**	92
2	**1b**	-$(CH_2)_3$-, H	**2b**	trace[c]
3	**1c**	-$(CH_2)_5$-, H	**2c**	41
4	**1d**	-$(CH_2)_6$-, H	**2d**	−
5	**1e**	*n*-C_4H_9, H, H	**2e**	98
6	**1f**	*n*-C_6H_{13}, H, H	**2f**	90
7	**1g**	*n*-$C_{16}H_{33}$, H, H	**2g**	83
8	**1h**	Bn, H, H	**2h**	93
9	**1i**	*n*-C_3H_7, H, CH_3	**2i**	91
10	**1j**	Ph, H, H	**2j**:**2j'** = 1:1[d]	98

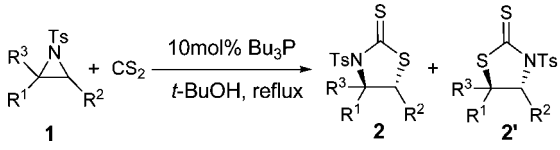
[a] Reaction conditions: aziridine (0.25 mmol), CS_2 (0.1 mL, 1.65 mmol), and Bu_3P (6.25 μL, 0.025 mmol). [b] Isolated yield based upon aziridine. [c] Indicated by TLC. [d] Products ratio was determined by ^1H NMR.

as the solvent (entry 3). The yield of **2a** increased dramatically to 81% and 83% when EtOH and *t*-BuOH were the solvent, respectively (entries 4 and 5). The influence of organophosphines on the reaction was also investigated. The yield of **2a** was 92% when Bu_3P was used (entry 7), while 78% and 83% yield of the product was obtained using Cy_3P and PPh_3 as the catalyst, respectively (entries 6 and 5). An increase of the amount of organophosphine did not improve the yield of product (entry 8 vs entry 7). The *trans*-structure of product **2a** was determined by the coupling constant of the two bridgehead hydrogens (J = 11.7 Hz) and confirmed further by the X-ray analysis (see Supporting Information).



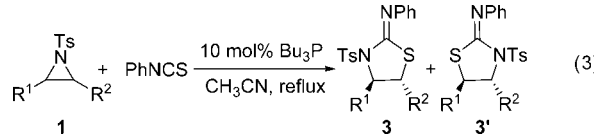
1a **2a** (1)

Under the optimized reaction conditions, the scope of the reaction was examined (eq 2, Table 2). Excellent yields were obtained from the reactions of aziridine **1a** derived from cyclohexene and **1e**−**j** derived from acyclic alkenes (entries 1 and 5−10). However, no product was obtained from aziridine **1b** derived from cyclopentene (entry 2) because of the high strain energy of *trans*-stereochemistry of the product. For the reaction of **1c** derived from cycloheptene, only 41% yield of the desired product was afforded (entry 3) likely due to the steric hindrance of the substrate. Only the products formed by the attack of the S-atom of CS_2 at the terminal carbon were detected by ^1H NMR from the reaction of monoalkyl-substituted aziridines **1e**−**h** and *gem*-disubstituted aziridine **1i** (entries 5−8 and 9). For the phenyl-substituted aziridine **1j**, the terminal- and benzylic-attacked products were formed in a ratio of 1:1 (entry 10) caused by the interference of the electronic and steric effect. The regioselectivity of the reaction is in accordance with that of aziridines with other nucleophiles reported in the literature.[1,2]



1 **2** **2'** (2)

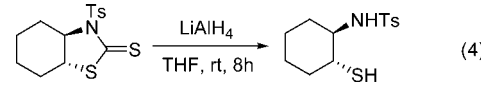
To extend the scope of this organophosphine-catalyzed cyclization reaction, the reaction of aziridines with isothiocyanates was tested (eq 3). Optimization of the reaction conditions showed that Bu_3P was still the best catalyst, while a trace of product was afforded if Ph_3P was used. In addition, CH_3CN was the choice among common solvents tested, including THF, DMF, ^{t}BuOH, and $CHCl_3$. Under the conditions described in eq 3, the scope of aziridines was investigated (Table 3).



1 **3** **3'** (3)

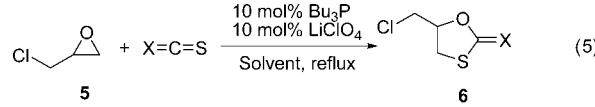
Good yields were obtained from the reaction of aziridine **1a** and **1m** derived from cyclohexene and cyclohexadiene, respectively, with phenyl isothiocyanate (entries 1 and 11), while **3b** was obtained in 16% yield with the same reason as that in the reaction with CS_2 (entry 2). Aziridine **1c** derived from cycloheptene gave the product in 47% yield (entry 3), while no product was obtained when aziridine **1d** derived from cyclooctene was used (entry 4). Substrates **1j** and **1k** derived from styrene and internal aliphatic alkene, respectively, afforded the corresponding heterocycles in good yields (entries 8 and 9), while **1e**−**g** derived from terminal alkenes gave moderate yields (entries 5−7). The reaction of other disubstituted aziridines **1l** and **1n** provided the products in lower yields (entries 10 and 12). A moderate yield of product **3p** was afforded when butyl isothiocyanate was used (entry 14), but a lower yield of **3o** was obtained when naphthyl isothiocyanate was the reagent (entry 13). The reactions have the same regiochemistry as that with CS_2 (vide supra).

The thiol group plays a vital role in the function of a large number of biopolymers. The active sites of enzymes, subunit interactions, and certain membrane functions may also involve mercapto groups. For this reason, numerous attempts have been made to develop highly specific thiol group reagents. To demonstrate the utility of the current reactions, we found that the treatment of compound **2a** with $LiAlH_4$ overnight at room temperature afforded β-thio amine **5** in nearly quantitative yield (eq 4).



2a **4** 99% yield (4)

This organophosphine-catalyzed reaction of heterocumulenes can also be extended to that with epoxides, providing corresponding heterocycles in good yields (eq 5). However, oligomerization of phenyl isocyanate was observed in the reaction of aziridine **1a** with it.



5 **6** (5)

a. X = NPh, 88% yield (in MeCN)
b. X = S, 74% yield (in *t*-BuOH)

To understand the role of organophosphine in this reaction, the study of ^{31}P NMR was performed. As we reported before, the mixture of aziridine **1a** and Bu_3P in benzene at 25 °C in a molar ratio of 1:1 gave a signal at δ 31.07 ppm from the ^{31}P NMR spectrum.[6a] No product was detected when CS_2 was added to the above solution and after the resulting mixture was refluxed

TABLE 3. Cycloaddition of Isothiocyanate with Aziridines Catalyzed by Bu_3P[a]

entry	aziridine	R^1, R^2	product	yield %[b]
1	**1a**	-$(CH_2)_4$-	**3a**	78
2	**1b**	-$(CH_2)_3$-	**3b**	16
3	**1c**	-$(CH_2)_5$-	**3c**	47
4	**1d**	-$(CH_2)_6$-	**3d**	−
5	**1e**	*n*-C_4H_9, H	**3e**	39
6	**1f**	*n*-C_6H_{13}, H	**3f**	53
7	**1g**	*n*-$C_{16}H_{33}$, H	**3g**	56
8	**1j**	Ph, H	**3j**:**3j** = 5:2[c]	78
9	**1k**	*n*-C_5H_{11}, CH_3	**3k** + **3k'**	62
10	**1l**	Ph, CO_2Me	**3l**	27
11	**1m**	-CH_2CH=$CHCH_2$-	**3m**	77
12	**1n**	Ph, Me	**3n**	38
13	**1a**	-$(CH_2)_4$-	**3o**[d]	23
14	**1a**	-$(CH_2)_4$-	**3p**[e]	55

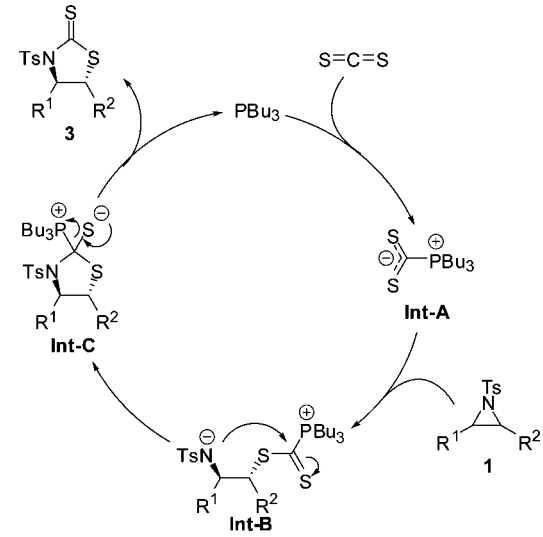
[a] Reaction conditions: aziridine (0.5 mmol), isothiocyanate (1 mmol), and Bu_3P (6.25 μL, 0.05 mmol). [b] Isolated yield based upon aziridine. [c] Product ratio was determined by ^1H NMR. [d] 1-Naphthyl isothiocyanate was used. [e] Butyl isothiocyanate was used.

for 24 h. On the other hand, when CS_2 and Bu_3P were mixed in benzene in a ratio of 1:1, a signal at δ 15.35 ppm from the ^{31}P NMR spectrum appeared, indicating the formation of a zwitterion.[8] Product **2a** was afforded when aziridine **1a** was added and refluxed for 12 h, while the signals at 15.76 and −30.90 ppm were detected from the ^{31}P NMR spectrum, which showed the reproduction of Bu_3P.

From these clues, a plausible reaction mechanism is proposed (Scheme 1). Phosphine attacks CS_2 to form zwitterion **Int-A**,[8] which reacts with aziridine **1** to give ring-opened intermediate **Int-B**. Ring closure of this intermediate affords product **3** and reproduces Bu_3P to complete the catalytic cycle. This mechanism differs from that of organophosphine-mediated ring-opening reaction of aziridines with nucleophiles,[6a] in which organophosphine just serves as a trigger to initiate the reaction.

In summary, we have developed an efficient organophosphine-catalyzed ring-opening reaction of carbon disulfide and isothiocyanates with aziridines as well as with epoxides, which provides a simple and convenient way to the synthesis of thiazolidinone derivatives. The mechanistic study reveals that the organophosphine serves as catalyst in the reaction.[9] Further investigations on the asymmetric version of the reaction as well as the further applications of this organophosphine-catalyzed reaction of heterocumulene in organic synthesis are in progress.

SCHEME 1. Plausible Mechanism of the P-Catalyzed Reaction of Aziridine 1 with CS_2



Experimental Section

Representative Procedure for the Phosphine-Catalyzed Reaction of Aziridine 1a with Phenyl Isothiocyanate. In a Schlenk tube equipped with condenser, Bu_3P (6.25 μL, 0.025 mmol) was added to a stirring mixture of aziridine **1a** (62.75 mg, 0.25 mmol), phenyl isothiocyanate (60 μL, 0.5 mmol), and anhydrous acetonitrile (2 mL) under argon at rt. Then the mixture was heated to reflux for 24 h until the substrate disappeared and monitored by TLC. After that, the mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using PE/EtOAc (10:1) as eluent to give **3a** as solid, 75.3 mg, 78% yield. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.35−1.57 (m, 3H), 1.68−1.86 (m, 2H), 1.93−2.03 (m, 2H), 2.45 (s, 3H), 3.13−3.26 (m, 2H), 3.62 (td, J = 3.3 Hz, 11.1 Hz, 1H), 6.55 (d, J = 7.8 Hz, 2H), 7.04 (t, J = 7.2 Hz, 1H), 7.12 (m, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 21.7 (Ar−CH_3), 24.4 (CH_2), 25.3 (CH_2), 29.4 (CH_2), 32.7 (CH_2), 49.1 (S−CH), 70.6 (N−CH), 120.5 (Ar−C), 124.3 (Ar−C), 128.9 (Ar−C), 129.0 (Ar−C), 129.1 (Ar−C), 135.2 (Ar−C), 144.5 (Ar−C), 150.0 (Ar−C), 154.8 (N=C). IR: 1641, 1594, 1359, 1174, 1087. Anal. Calcd for $C_{20}H_{22}N_2O_2S_2$: C, 62.15; H, 5.74; N, 7.25. Found: C, 61.98; H, 5.76; N, 7.19.

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Supporting Information Available: Full experimental procedures, characterization data, copies of ^1H and ^{13}C NMR spectra of products, and X-ray analysis data of compounds **2a** and **3a** (cif file). This material is available free of charge via the Internet at http://pubs.acs.org.

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