Efficient Synthesis of Isothiocyanates Based on the Tandem Staudinger/aza-Wittig Reactions and Mechanistic Consideration of the Tandem Reactions

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The tandem and stepwise Staudinger/aza-Wittig reactions of several azides were examined in detail. The tandem reaction method (Method I) exhibited superior results in the yield of the corresponding isothiocyanates bearing an electron-withdrawing group than the conventional stepwise method (Method II) which involves the sequential treatment of the azides with triphenylphosphine and then carbondisulfide. The mechanistic consideration for both reaction methods was proposed on the basis of the ^{1}H-NMR analyses.

Key words isothiocyanate; Staudinger reaction; phosphazide; azaylide; carbapenem antibiotic; L-084

The reaction of organic azides with trivalent phosphorous compounds to afford the corresponding azaylides is known as the Staudinger reaction.[1)] This reaction proceeds *via* a primary imination adduct, phosphazide, which spontaneously decomposes into azaylide and nitrogen in most cases.[2)] The azaylide product can usually be isolated as a stable compound, which can be used to prepare various amines, imines, amides, isocyanates, isothiocyanates,[3,4)] and so forth,[5)] as a versatile synthetic intermediate. As for the isothiocyanate synthesis, a convenient one-pot procedure was reported by Tsuge *et al.* in 1984 as is to say the tandem Staudinger/aza-Wittig reaction.[6,7)] They used carbon disulfide (CS_2) as the co-solvent in the reaction of only (trimethylsilyl)methylazide with triphenylphosphine (PPh_3),[6)] and the yield of the corresponding isothiocyanate was superior to that obtained from a stepwise method[8)] in which CS_2 was added to the primary reaction mixture containing the azaylide product. Especially, the tandem method was recently utilized in a carbohydrate field in order to effectively obtain isothiocyanate-functionalized sugars.[9—11)] Herein, we investigated the substrate generality of the tandem and stepwise Staudinger/aza-Wittig reactions and their reaction mechanisms utilizing a ^{1}H-NMR analysis.

Results and Discussion

Our first target was to prepare chloroethylisothiocyanate (**3a**), because **3a** was an indispensable material for the synthesis of 3-mercapto-1-(1,3-thiazolin-2-yl)azetidine (**1**), useful for the pendant moiety of the oral carbapenem antibiotic L-084 (Chart 1).[12)] In recent years, the development of new antibiotics has attracted the attention in the clinical realm for the treatment of severe infectious diseases. L-084 is one of several promising candidates for oral administration and is now under clinical trials. During the course of our synthetic study of L-084, we established an efficient synthetic route for **1** from **2** and **3a**,[13)] but to the best of our knowledge, there was no application to prepare **3a** without using the harmful and toxic thiophosgene.[14,15)] Thus, we planned to develop an effective and harmless synthetic route for **3a** in which scale-up production would be possible. Chloroethylisothiocyanate (**3a**) was initially prepared from the reaction of chloroethylazide (**5a**)[16)] and PPh_3 followed by the aza-Wittig reaction with CS_2, but **3a** was obtained in only 16% yield from **5a** due to the decomposition of the unstable intermediate **8a** (Entry 1 in Table 1). As a result of the optimization of the reaction conditions, we found that the yield of **3a** dramatically increased to 83% when CS_2 was used as the co-solvent in the reaction of **5a** with Ph_3P, compared to the above stepwise method.

At this point, we investigated in detail the tandem Staudinger/aza-Wittig reactions (Method I) and the stepwise reactions (Method II), as shown in Table 1. Namely, several azides **5b**—**g** were treated with Ph_3P in a mixed solvent of CS_2 and $CHCl_3$ to afford the corresponding isothiocyanates in good yields except for the case of diphenylmethylisothiocyanate (**3e**). As the control, we also attempted a stepwise addition protocol (Method II) for the same compounds and obtained results almost similar to those of Method I in Entries 3—7. Besides, the yield of **3b** using Method II was only 27% (Entry 2), because the product **8b** might be unstable just like that of **8a** in Entry 1. Interestingly, a labile byproduct **6** was concomitantly isolated in 15% yield for the Method II reaction of **5b**. The plausible mechanism to afford **6** from **5b** is illustrated in Chart 2. This side reaction is thought to occur *via* a seven-membered cycloaddition in which the chloro atom was readily substituted by a sulfur atom from CS_2. In contrast, no byproduct **6** was obtained using the Method I reaction (Entry 2).

For the purpose of exploring why the yield was improved in Entry 1 of Method I, we carefully checked the reactions used by both methods (Methods I and II) based on a ^{1}H-NMR analysis.[17)] In the case of the stepwise procedure

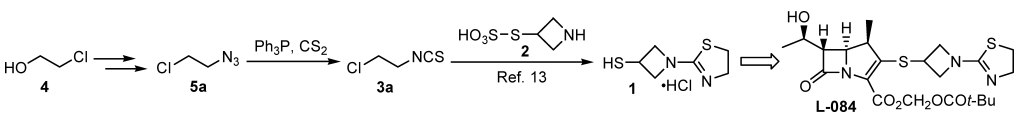

Chart 1

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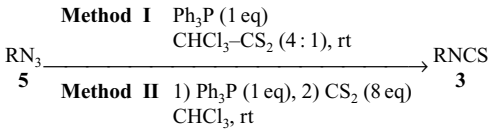
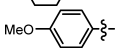
Table 1. Isothiocyanate Syntheses by Two Methods



Entry	R	RN_3	RN=PPh_3	RNCS[a]	Method I		Method II		
					Time (h)	Yield[b] (%)	Time (h)		Yield[b] (%)
							Ph_3P	CS_2	
1		**5a**[16]	**8a**	**3a**[14]	1	83[c]	0.5	3	16[c]
2		**5b**	**8b**	**3b**	3[d]	90	3	1	27
3		**5c**[20]	**8c**	**3c**[23]	2	75	2	1	66
4		**5d**[20]	**8d**	**3d**[24]	2	71	4	1	54
5		**5e**[21]	**8e**	**3e**[25]	2[e]	0	2[e]	2	0
6		**5f**[20]	**8f**	**3f**[26]	22	67	6	16	64
7		**5g**[22]	**8g**	**3g**[27]	1.5	75	1.5	1	77

a) Spectral data (NMR and IR) of each isothiocyanate were in accord with the reported ones. *b*) Isolated yield after preparative thin layer chromatography. *c*) THF was used as a solvent instead of $CHCl_3$. *d*) Reacted at 50 °C for 3 h. *e*) Evolution of nitrogen was observed and **5e** was consumed within 0.5 h.

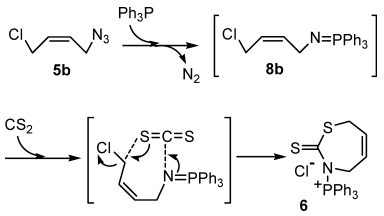


Chart 2. The Plausible Mechanism for Formation of **6**

(Method II) in $CDCl_3$, the reaction of chloroethylazide (**5a**) (0.5 mmol) with Ph_3P (0.5 mmol) afforded the azaylide **8a** with the evolution of nitrogen gas as a first step [see (a) and (b) in Fig. 1]. During the second step, CS_2 (4.0 mmol) was added to the solution of **8a**, and the formation of the isothiocyanate **3a** was observed in the ^{1}H-NMR spectrum along with a small amount of the remaining azaylide **8a** after stirring for 3 h [see (c) in Fig. 1]. On the other hand, no azaylide **8a** formation was recognized when Ph_3P was added to the solution of **5a** (0.5 mmol) and CS_2 (4.0 mmol) in $CDCl_3$ [see (d) in Fig. 1]. Based on the outcome described above, we assumed that the tandem reactions (**5a**→**3a**) proceeded *via* the phosphazide **7a** followed by its direct addition to CS_2 without generation of the azaylide **8a**, whereas the well-known mechanism is a concomitant process of the Staudinger reaction and aza-Wittig reaction *via* a four-membered cycloaddition reaction **A**, as shown in Chart 3.[5] Thus, we propose a plausible mechanism for the tandem reaction (**5a**→**3a**) *via* a [4+2] type of cycloaddition reaction **B** followed by elimination of nitrogen *via* **B′** in Method I.[10,18] This proposed mechanism rationally explains the increase in the yield of **3a** for Method I without generation of the unstable intermediate **8a** (Chart 3). As for the reason for the hard formation of azaylide **8a**, it must be considered that nitrogen elimination *via* **C** is prevented by the effect of the electron-withdrawing chloro substituent. Moreover, no formation of the byproduct **6** during the Method I reaction of **5b** also demonstrated that the exclusive precursor, phosphazide,[19] must be directly converted into the corresponding isothiocyanate **3b** *via* a six-membered cycloaddition reaction like **B** followed by the elimination of nitrogen.

In addition, all of the Method I reactions shown in Table 1 were evaluated by ^{1}H-NMR in the same way as for Entry 1. In the case of Entries 6 and 7, we confirmed the formation of the azaylide intermediates **8f** and **8g** based on the ^{1}H-NMR spectrum for each reaction. To rationalize these results, we realized that the tandem Staudinger/aza-Wittig reaction (Method I) proceeded through two kinds of competitive routes. One is the route *via* the commonly known four-membered cycloaddition like **A** and the other can be explained by the proposed direct conversion of the phosphazide like **7a** to **3f** and **3g** *via* a six-membered cycloaddition like **B** followed by the elimination of nitrogen. The differentiation between Entries 1 and 2 and Entries 6 and 7 in the Method I reactions may be due to the corresponding substituent effect as follows. The formation of **8f** or **8g** seems to be accelerated due to the effect of the electron-donating substituent, and these intermediates are stable enough to be monitored by each ^{1}H-NMR spectrum. On the other hand, the formation of **8a** or **8b** would be retarded by the electoron-withdrawing effect of the chloro atom as already discussed.

Conclusion

The efficient synthesis of several isothiocyanates was achieved by utilizing the tandem Staudinger/aza-Wittig reactions of the corresponding azides. It was demonstrated that the reaction mechanism for the tandem reactions of **3a** and **3b** is different from that for the conventional stepwise ones based on a comparison of the ^{1}H-NMR spectrum of each reaction solution with that of the related compounds.

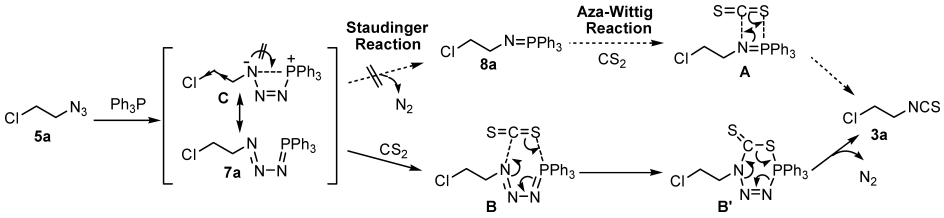


Chart 3. The Proposed Mechanism for the Tandem Staudinger/aza-Wittig Reactions to Produce **3a**

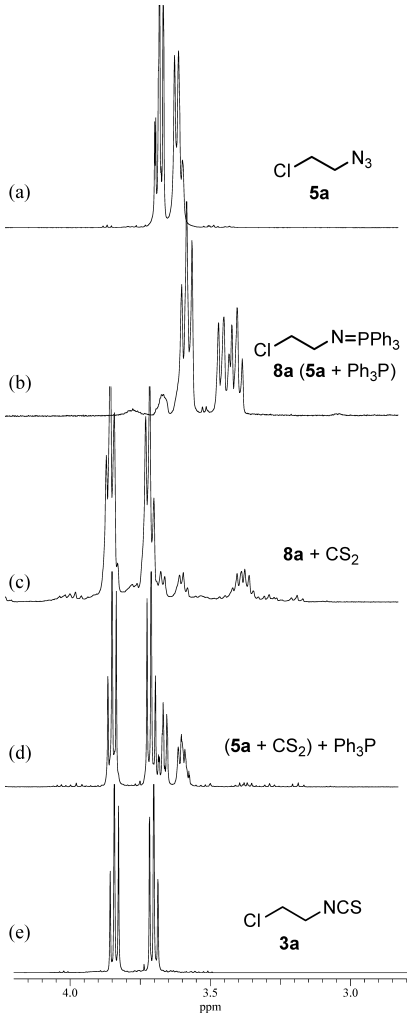


Fig. 1. ^{1}H-NMR Spectrum (400 MHz, $CDCl_3$) of Chloroethylazide (**5a**), Some Reaction Mixtures, and Chloroethylisothiocyanate (**3a**) in the Range between 3 and 4 ppm

(a) The chart of **5a**, (b) that of the reaction mixture after 0.5 h when Ph_3P was added to a solution of **5a**, (c) that of the reaction mixture after 3.0 h when CS_2 was added to the mixture of **5a** and Ph_3P, (d) that of the reaction mixture after 0.5 h when Ph_3P was added to a premixed solution of **5a** and CS_2, and (e) that of **3a** are depicted. All reactions were carried out at room temperature.

Experimental

The NMR spectra were obtained using a Bruker Avance DPX400 (400 MHz) spectrometer with tetramethylsilane (TMS) as the internal standard. The IR spectra were recorded by a JASCO FT-IR (VALOR-III) spectrometer. The Mass spectra were recorded using a JMS-SX102A spectrometer.

(*Z*)-1-Azido-4-chlorobut-2-ene (5b) To a solution of (*Z*)-4-azidobut-2-en-1-ol[28] (2.5 g, 22.1 mmol) and pyridine (1.95 ml, 24.3 mmol) in CH_2Cl_2 (22 ml) was added $SOCl_2$ (1.77 ml, 24.3 mmol) at 5 °C, and the mixture was stirred for 30 min. The reaction mixture was then treated with excess saturated aqueous ammonium chloride. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography ($CHCl_3$/*n*-Hexane = 1 : 3) to afford **5b** as a colorless oil (0.78 g, 27%). ^{1}H-NMR ($CDCl_3$) δ: 3.81 (2H, d, J = 5.8 Hz), 4.09 (2H, d, J = 5.8 Hz), 5.10—5.90 (2H, m). ^{13}C-NMR ($CDCl_3$) δ: 44.06, 52.10, 128.07, 130.89. IR (neat) cm^{-1}: 2102, 1442, 1350, 1255, 971. FAB-MS *m*/*z*: 131.0275 (Calcd for $C_4H_6ClN_3$: 131.0250). MS *m*/*z*: 131 (M^+).

General Procedure Utilizing Method I for the Preparation of ((*E*)-3-Isothiocyanatoprop-1-enyl)benzene (3c)[23] To a solution of ((*E*)-3-azidoprop-1-enyl)benzene **5c** (78.5 mg, 0.5 mmol) and CS_2 (0.24 ml, 4.0 mmol) in $CHCl_3$ (1.0 ml) was added Ph_3P (131.1 mg, 0.5 mmol) at room temperature. The mixture was stirred for 1.5 h, and the reaction mixture was directly subjected to preparative TLC with AcOEt–hexane (1 : 10, v/v) to give **3c** as a colorless oil (65.4 mg, 75%). ^{1}H-NMR ($CDCl_3$) δ: 4.31 (2H, d, J = 5.5 Hz), 6.17 (1H, dd, J = 5.5, 15.7 Hz), 6.66 (1H, d, J = 15.7 Hz), 7.25—7.39 (5H, m). IR (neat) cm^{-1}: 3027, 2093, 1495, 1448, 1350, 964. EI-MS *m*/*z*: 175.0351 (Calcd for $C_{10}H_9NS$: 175.0456). MS *m*/*z*: 175 (M^+).

(*Z*)-1-Chloro-4-isothiocyanatobut-2-ene (**3b**): Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 4.09 (2H, d, J = 6.5 Hz), 4.18 (2H, d, J = 4.9 Hz), 5.82 (1H, dt, J = 4.9, 15.1 Hz), 5.97 (1H, dt, J = 6.5, 15.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 43.77, 46.17, 127.02, 129.55, 133.25. IR (neat) cm^{-1}: 2120, 1437, 1348, 1297, 1252. EI-MS *m*/*z*: 146.9919 (Calcd for C_5H_6ClNS: 146.9909). MS *m*/*z*: 147 (M^+).

Spectral data of the known compounds **3a**,[14] **3d**,[24] **3e**,[25] **3f**,[26] and **3g**[27] agree with those of the disclosed data.

General Procedure Utilizing Method II for the Preparation of ((*E*)-3-Isothiocyanatoprop-1-enyl)benzene (3c)[23] To a solution of ((*E*)-3-azidoprop-1-enyl)benzene **5c** (78.5 mg, 0.5 mmol) in $CHCl_3$ (1.0 ml) was added Ph_3P (131.1 mg, 0.5 mmol) at room temperature, and the mixture was stirred for 2 h. To the reaction mixture was added CS_2 (0.24 ml, 4.0 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was directly subjected to preparative TLC with AcOEt–hexane (1 : 10, v/v) to give **3c** (58.0 mg, 66%).

(*Z*)-2-Thioxo-1,3-thiazepin-3(2*H*,4*H*,7*H*)-yltriphenylphosphonium chloride (**6**) was obtained from the reaction of **5b** (77.9 mg, 0.59 mmol) as a colorless oil (39.9 mg, 15%). ^{1}H-NMR ($CDCl_3$) δ: 3.69—3.74 (2H, m), 3.89 (2H, d, J = 7.0 Hz), 5.50 (1H, dt, J = 7.0, 15.3 Hz), 5.86—5.93 (1H, m), 7.61—7.66 (6H, m), 7.69—7.71 (3H, m), 7.74—7.86 (6H, m). ^{13}C-NMR ($CDCl_3$) δ: 43.87, 44.51, 121.64, 122.66, 128.55, 130.15, 130.29, 132.17, 133.90, 134.01, 135.06. IR (neat) cm^{-1}: 2929, 1588, 1440, 1116. FAB-MS *m*/*z*: 366 (M^++H−Ph), 330 (M^++H−Ph−Cl).

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