Investigation of the Cyclization of *N*-(2-Hydroxyethyl)-*N'*-phenylthioureas: Mitsunobu Conditions *vs* TsCl/NaOH System

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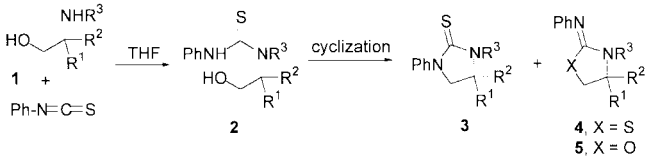
The Mitsunobu reaction is a mild way to convert an alcohol into a wide range of functionality.[1] In general, this method proves efficacious for the acidic component (p*Ka* ~ 8) of the form of amides,[2] phthalimides,[3] *N*-alkylsulfonamides,[4] *N*-methyltrifluoro methanesulfonamides,[5] or hydrazoic acid,[6] providing useful yields under neutral reaction conditions. In the intramolecular Mitsunobu reaction of *N*-(2-hydroxyethyl)amides and *N*-(2-hydroxyethyl)thioamides having ambident nucleophile, *O*-cyclized products[7] and *S*-cyclized product[7b] are generally obtained in preference to *N*-cyclized products, respectively. Recently we reported that 2-phenylamino-2-oxazolines were prepared by the cyclization of *N*-(2-hydroxyethyl)-*N'*-phenylthioureas using TsCl and NaOH.[8] This reaction proceeded *via* cyclodesulfurization to regiocontrolled *O*-alkylation products. To the best of our knowledge, no Mitsunobu reaction of *N*-(2-hydroxyethyl)-*N'*-phenylthioureas has been reported in the literature so far.[9] Therefore, the behavior of ambident nucleophile in the Mitsunobu-mediated intramolecular cyclization of *N*-(2-hydroxyethyl)thioureas **2** was investigated to compare the results using TsCl and NaOH (Scheme 1). In addition, mechanistic investigation of Mitsunobu conditions and TsCl/NaOH system was also disclosed.

N-(2-hydroxyethyl)thioureas **2** as substrates were readily prepared from reaction of the corresponding 1,2-amino-alcohols with phenyl isothiocyanate in THF at room temperature in good yields.[10] The Mitsunobu reaction was achieved with diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in THF. The reactions were complete within 30 min at room temperature. The intramolecular Mitsunobu reaction of various substrates **2a-2h** was examined. The results are shown in Table 1. The Mitsunobu reaction furnished mainly the mixture of *N*- and *S*-cyclization (entries 1-8). In the case of **2d** and **2e** a small amount of *O*-alkylation products were formed (entries 4-5). On the other hand, using TsCl and NaOH the regioselectivity of cyclization was depending on the *N*-substituted group. That is, **2a-2e**



Scheme 1

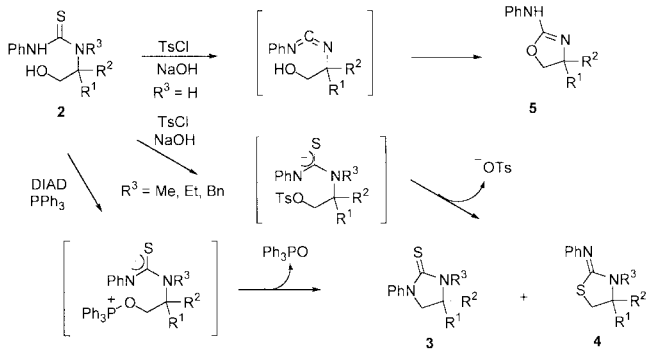
Table 1. Cyclization of *N*-(2-hydroxyethyl)-*N'*-phenylthioureas **2**

Entry	Sub-strate	R1	R2	R3	Product ratios[a]		
						Mitsunobu reaction	TsCl/ NaOH[b]
1	**2a**	H	H	H	**3a/4a/5a**	69/31/0	0/0/100
2	**2a**	Me	H	H	**3b/4b/5b**	72/28/0	0/0/100
3	**2c**	Et	H	H	**3c/4c/5c**	79/21/0	0/0/100
4	**2d**	(*S*)-*i*-Pr	H	H	**3d/4d/5d**	70/13/17	0/0/100
5	**2e**	Me	Me	H	**3e/4e/5e**	51/32/17	0/0/100
6	**2f**	H	H	Me	**3f/4f/5f**	80/20/0	57/43/0
7	**2g**	H	H	Et	**3g/4g/5g**	89/11/0	70/30/0
8	**2h**	H	H	Bn	**3h/4h/5h**	95/5/0[c]	69/31/0

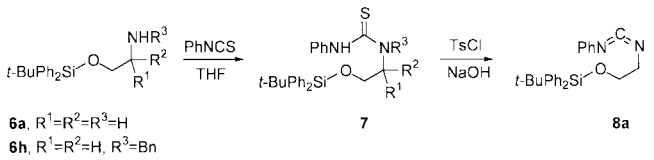
[a]The ratio of the crude mixtures was determined by ^{1}H NMR. [b]For isolated yields, see: Ref. 8. [c]For procedure for Mitsunobu reaction, see: Ref. 14.

prepared from *N*-unsubstituted aminoalcohols (R^3 = H) proceeded to the regiocontrolled *O*-cyclization (entries 1-5) and **2f-2h** prepared from *N*-substituted aminoalcohols gave the mixture of *N*- and *S*-cyclization as the Mitsunobu reaction rather than *O*-cyclization (entries 6-8). The significant difference of the reaction pathway of various thioureas **2** was unique to TsCl/NaOH system and was not observed in the Mitsunobu condition.

Mitsunobu of thioureas such as **2** almost might proceed through *N*- or *S*-nucleophilic attack of thiourea upon the oxyphosphonium intermediate to produce the mixture of *N*- and *S*-alkylation product as delineated in Scheme 2. A small amount of *O*-alkylation in **2d-2e** might occur through carbodiimide intermediate.[9] Using TsCl and NaOH the mechanism



Scheme 2



Scheme 3

for the formations of *O*-, *N*-, and *S*-cyclized products could be proposed as follows. The reaction might proceed to two directions such as the cyclodesulfurization or the cyclodehydration to be strongly influenced by the R^3 group of thioureas (Scheme 2): (i) in the case of **2a-2e** (R^3=H), the reaction pathway of carbodiimide[11] intermediate is leading to oxazoline derivatives **5**. (ii) in the case of **2f-2h** (R^3=Me, Et, and Bn), the tosylate is formed and anion delocalized on nitrogen and sulfur can attack the tosylate to provide the mixture of *N*-cyclized product **3** and *S*-cyclized product **4**. The remarkable *O*-cyclization selectivity in *N*-phenylthioureas **2a-2e** may be due to a carbodiimide intermediate because a carbodiimide intermediate can be formed only in case of R^3=H. To confirm the proposed pathway, O-*t*-butyldiphenylsilyl (TBDPS) protected thiourea **7** was prepared from O-TBDPS protected aminoalcohols **6** and phenyl isothiocyante.[12] followed by cyclization using TsCl and NaOH (Scheme 3). In the case of **7a** the carbodiimide intermediate was isolated as expected.[13] With **7h** no reaction such as tosylation occurred and the starting material was recovered. Thus, **7h** prepared from *N*-substituted aminoalcohols did not provide carbodiimide or tosylated thiourea. From these results our proposed reaction mechanism in TsCl and NaOH might be possible.

In conclusion, our study on *N*-(2-hydroxyethyl)-*N'*-phenylthioureas demonstrates the main formation of *N*-cyclized product from thioureas **2** under Mitsunobu conditions. Cyclization of **2a-2e** under TsCl/NaOH results in regiocontrolled 2-amino-2-oxazolines *via* carbodiimide intermediate.

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12. Preparation of *N*-(*t*-butyldiphenylsilanyloxyethyl)thiourea **7a**. To a stirred solution of 2-(*t*-butyldimethylsilanyloxy)ethylamine **6a** (0.21 g, 0.63 mmol) in THF (5 mL) under nitrogen at room temperature was added and triethylamine (0.11 mL, 0.76 mmol) and phenyl isothiocyanate (0.08 mL, 0.76 mmol). The reaction mixture was stirred for 5 min and evaporated. The crude product was purified by column chromatography to give the requisite product **7a**. Yield 90%; R_f = 0.5 (ethyl acetate/hexane 1 : 4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (1H, bs, PhNH), 7.54-7.25 (15H, m, 3Ph), 6.67 (1H, bs, NH), 3.82-3.76 (4H, m, C_2H_4), 0.92 (9H, s, $(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.4, 136.0, 135.3, 130.2, 129.9, 127.8, 127.3, 125.3, 62.0, 47.5, 26.6, 19.0.
13. Phenyl *t*-buthyldiphenylsilanyloxyethylcarbodiimide **8a**. To a stirred solution of thiourea **7a** (0.10 g, 0.23 mmol) in THF (5 mL) at room temperature was added a solution of NaOH (0.02 g, 0.55 mmol) in water (1 mL) and TsCl (0.05 g, 0.28 mmol) in THF (2 mL) dropwise for 5 min with a syringe. The reaction mixture was stirred for 1 h at room temperature, quenched with water (20 mL), and extracted with ether (20 mL × 3). The organic layer was dried, filtered, evaporated, and purified by flash column chromatography to give the carbodiimide product **8a**. Yield 70%; R_f = 0.8 (ethyl acetate/hexane 1 : 4); IR ($CDCl_3$, cm^{-1}) 2142 (N=C=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.65 (4H, m, 2Ph), 7.42-7.32 (6H, m, 2Ph), 7.28-7.22 (2H, m, Ph), 7.13-7.08 (3H, m, Ph), 3.84 (2H, t, OCH_2, J = 5.4 Hz), 3.48 (2H, t, CH_2N, J = 5.4 Hz), 1.02 (9H, s, $(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 136.9, 135.6, 133.3, 129.7, 129.2, 127.7, 124.5, 123.8, 63.8, 49.0, 26.7, 19.1.
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