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Sulfenocyclization of Unsaturated Ureas and Thioureas

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Summary. A general method for the formation of cyclic sulfenylated 2-oxazoline, 2-thiazolines, 5,6-dihydro-4*H*-1,3-oxazines, and 5,6-dihydro-4*H*-1,3-thiazines is described. The procedure employs arylsulfenyl chloride and ethyldiisopropylamine to generate an episulfonium ion intermediate from which the cyclic products arise by internal nucleophilic displacement.

Keywords. Sulfenocyclization; 2-Oxazoline; 2-Thiazoline; 5,6-Dihydro-1,3-oxazine; 5,6-Dihydro-1,3-thiazine.

Sulfenocyclisierung ungesättigter Harnstoffe und Thioharnstoffe

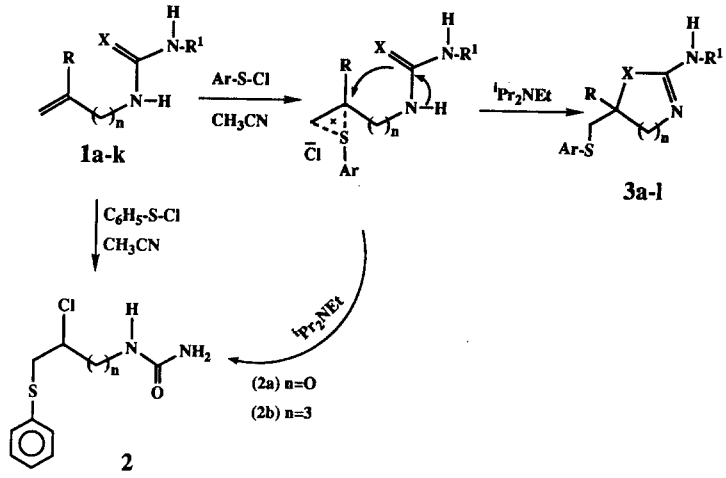
Zusammenfassung. Eine allgemeine Methode zur Herstellung cyclischer sulfenylierter 2-Oxazoline, 2-Thiazoline, 5,6-Dihydro-4*H*-1,3-oxazine und 5,6-Dihydro-4*H*-1,3-thiazine wird beschrieben. Aus Arylsulfenylchlorid und Ethyldiisopropylamin entsteht ein Episulfoniumion als Zwischenprodukt; dieses bildet durch nucleophile Umlagerung die cyclischen Produkte.

Introduction

Organosulphur compounds play an important role in modern organic synthesis, not only because they constitute a particularly useful class of synthons [1] but also because they are of great biological interest [2]. The electrophilic addition of sulfur electrophiles to alkenes appears to be one of the most efficient ways to transform alkenes into synthetically useful products [3, 4]. Previously, we have developed a methodology [5, 9] for the functionalization of alkenes by sulfur electrophiles generated *in situ* from organic disulfides based on the use of manganese(III) salts in trifluoroacetic acid. This method has been used as a new route to different heterocyclic systems [10, 11]. However, the excessive amount of trifluoroacetic acid required for the reaction is undesirable in sensitive cases and may lead to destruction of the products. Therefore, we wish to report that an intramolecular regioselective sulfenocyclization of unsaturated ureas and thioureas could be achieved in good yields when the usaturated alkenes were treated with arylsulfenyl chloride. This study is related to our previous reports [10, 11] which employed the oxidation of organic disulfides as a source of sulfur electrophiles.

Results and Discussion

By reaction of unsaturated urea (**1a–g**) or thiourea (**1i–k**) derivatives with arylsulfenyl chloride in presence of ethyldiisopropylamine ($^{i}Pr_2NEt$) and dry acetonitrile, cyclization by oxygen or sulphur proceeded to form heterocycles (**3a–l**) bearing an arylsulfenylmethyl moiety (Scheme 1). The outstanding feature of these additions is the good regiochemical control which is of *Markovnikov* type.



Scheme 1

Reaction conditions were briefly examined using N-allylurea (**1a**) as starting material; the results are summarized in Table 1. No cyclization, but only addition of phenylsulfenyl chloride to the double bond [12] leading to the adduct **2a** was observed. The presence of ethyldiisopropylamine is essential for the sulfenocyclization reactions. Cyclisation proceeded in dry pyridine as well, but in a lower yield.

Under proper conditions (see Experimental), 2-amino-5-arylthiomethyl-2-oxazolines (**3a–c**) were formed in good yields using different arylsulfenyl chlorides (Table 2). These results are consistent with the initial formation of an episulfonium

Table 1. Cyclisation of **1a** under various conditions[a]

Solvent	Temp.	Additive[b]	Product	Yield %[c]
CH_2Cl_2	0 °C	-	**2a**	75
CH_3CN	25 °C	-	**2a**	78
CH_2Cl_2	25 °C	$^{i}Pr_2NEt$	**3a**	76
CH_3CN	25 °C	$^{i}Pr_2NEt$	**3a**	84
THF	25 °C	$^{i}Pr_2NEt$	**3a**	74
CH_3CN	25 °C	Pyridine	**3a**	72

[a]Carried out using **1a** (3 mmol) and phenylsulfenyl chloride (3 mmol) in various solvents (15 ml); [b]amount of additive; 5 mmol; [c]isolated yield after column chromatography

Table 2. Sulfenocyclization of unsaturated ureas and thioureas for *X* and *N*, see Scheme 1

Substrate	R	R^1	Ar	*X*	*N*	Product	Yield%[a]
1a	H	H	C_6H_5	O	1	**3a**	84
1a	H	H	4-$CH_3OC_6H_4$	O	1	**3b**	87
1a	H	H	4-ClC_6H_4	O	1	**3c**	82
1b	H	C_6H_5	C_6H_5	O	1	**3d**	82
1c	CH_3	C_6H_5	C_6H_5	O	1	**3e**	88
1d	H	4-ClC_6H_4	C_6H_5	O	1	**3f**	81
1e	H	4-$CH_3OC_6H_4$	C_6H_5	O	1	**3g**	86
1f	H	H	C_6H_5	O	2	**3h**	78
1g	H	C_6H_5	C_6H_5	O	2	**3i**	79
1h	H	C_6H_5	C_6H_5	O	3	**2b**	82
1i	H	H	C_6H_5	S	1	**3j**	84
1j	H	C_6H_5	C_6H_5	S	1	**3k**	86
1k	H	C_6H_5	C_6H_5	S	2	**3l**	80

[a] Isolated yield after chromatographic separation

ion intermediate [13] which is displaced by the internal oxygen nucleophile (Scheme 1). The cyclized products arise *via* a prefered 5-*exo-tet* mode of **1a**. Neither the alternative 6-*endo-tet* mode of ring closure to an dihydrooxazine nor the cyclization by nitrogen atom participation to form dihydroimidazole derivatives was observed. This agrees well with analogous examples in the literature. A close parallel is the organoselenium induced cyclization of allylic ureas to give 2-oxazoline derivatives [14]. An earlier study [15] also reports this cyclization under acidic conditions. The formation of 2-(N-arylamino)-5-phenylthiomethyl-2-oxazolines (**3d–g**) from N-allyl-N-arylureas (**1b–e**) shows the generality of the formation of sulfenylated 2-oxazolines from derivatives of N-allylurea.

The length of the alkenyl chain in the starting material was changed to test the limitations of the cyclization reaction. Table 2 shows that N-homoallylic ureas (**1f, g**) behave in an analogous manner to afford 2-amino- and 2-(N-phenylamino)-6-phenylthiomethyl-5,6-dihydro-4*H*-1,3-oxazines (**3h,i**) *via* a *Markovnikov* intramolecular oxygen cyclization. Again, the formation of 1,3-diazines was not observed. It is worth mentioning that the products **3h** and **3i** were very unstable on silica and has to be chromatographed on alumina.

Furthermore, chain extension allows competition between the formation of a seven membered ring through oxygen or the formation of a tetrahydropyrrole ring through nitrogen. Starting with N-(4-pentenyl)-urea (**1h**), no cyclization occurred. Instead, the adduct N-(4-chloro-5-phenylthiopentyl)-urea (**2b**) was isolated as the sole product.

With unsaturated thioureas (**1i–k**), the cyclization proceeds *via* a 5-*exo* mode to give 2-amino- and 2-(N-phenylamino)-5-phenylthiomethyl-2-thiazolines (**3i, k**) and *via* a 6-*exo* mode to afford 2-(N-phenylamino)-6-phenylthiomethy-5,6-dihydro-4*H*-1,3-thiazine (**3l**). Although the formation of sulfenylated thiazoline and dihydrothiazine derivatives has not been studied, related cyclizations are reported from the iodination of allyl and homoallyl thioureas, respectively [16].

Table 3. Physical and spectroscopic data of sulfenylated 2-oxazoline (**3a–g**), 2-thiazoline (**3j, k**), 5,6-dihydro-4**H**-1,3-oxazine (**3h, i**), and thiazine (**3l**) derivatives

Compd.	Melting point[a] °C	Molecular formula (M.W.)	Analyses (%) calcd/found C	H	N	IR (KBr) $\nu_{max}(cm^{-1})$
3a	110–112	$C_{10}H_{12}N_2OS$ (208.3)	57.67 57.7	5.81 5.8	13.45 13.4	3450 (NH_2), 1670 (C=N), 1600 (C=C)
3b	124–126	$C_{11}H_{14}N_2O_2S$ (238.3)	55.44 55.4	5.92 6.0	11.76 11.7	3450 (NH_2), 1675 (C=N), 1600 (C=C)
3c	136–138	$C_{10}H_{11}ClN_2OS$ (242.7)	49.48 49.6	4.57 4.6	11.54 11.5	3450 (NH_2), 1670 (C=N), 1595 (C=C)
3d	109–111	$C_{16}H_{16}N_2OS$ (248.4)	67.57 67.4	5.67 5.6	9.85 9.9	3435 (NH), 1675 (C=N), 1595 (C=C)
3e	140–142	$C_{17}H_{18}N_2OS$ (298.4)	68.43 68.4	6.08 6.0	9.39 9.2	3445 (NH), 1660 (C=), 1600 (C=C)
3f	116–118	$C_{16}H_{15}ClN_2OS$ (318.8)	60.28 60.4	4.74 4.7	8.79 8.8	3445 (NH), 1675 (C=N), 1600 (C=C)
3g	120–122	$C_{17}H_{18}N_2OS$ (314.4)	65.01 64.9	5.77 5.7	8.91 9.0	3445 (NH), 1675 (C=), 1600 (C=C)
3h	107–109	$C_{11}H_{14}N_2OS$ (222.3)	59.43 59.3	6.35 6.3	12.60 12.7	3445 (NH), 1685 (C=N), 1600 (C=C)
3i	120–122	$C_{17}H_{18}N_2OS$ (298.4)	68.43 68.3	6.08 6.1	9.39 9.5	3440 (NH), 1685 (C=N), 1595 (C=C)
3j	113–115	$C_{10}H_{12}N_2S_2$ (224.3)	53.54 53.2	5.39 5.5	12.49 12.5	3420 (NH), 1635 (C=N), 1595 (C=C)
3k	128–130	$C_{16}H_{16}N_2S_2$ (300.1)	63.97 64.1	5.37 5.3	9.32 9.4	3425 (NH), 1640 (C=N), 1595 (C=C)
3l	88–90	$C_{17}H_{18}N_2S_2$ (314.5)	64.93 64.8	5.77 5.8	8.91 9.0	3420 (NH), 1620 (C=N), 1590 (C=C)

Compd.	^{1}H NMR (δ in ppm)
3a	3.05 (dd, J = 14; 6 Hz, 1H, CH_2S), 3.27 (dd, J = 14; 7 Hz, 1H, CH_2S), 3.60 (dd, J = 12; 6 Hz, 1H, CH_2N), 3.91 (dd, J = 12; 9 Hz, 1H, CH_2N) 4.40 (s, 2H, NH_2), 4.70 (m, 1H, CH-O), 6.85–7.40 (m, 5H, Ar–H)
3b	3.07 (dd, J = 14; 7 Hz, 1H, CH_2S), 3.29 (dd, J = 14; 6 Hz, 1H, CH_2S), 3.60 (dd, J = 12; 6 Hz, 1H, CH_2N), 3.74 (s, 3H, OCH_3), 3.87 (dd, J = 12; 6 Hz, 1H, CH_2N), 4.10 (s, 2H, NH_2), 4.68 (m, 1H, CH–O), 6.90–7.40 (m, 4H, Ar–H)
3c	3.06 (dd, J = 14; 7 Hz, 1H, CH_2S), 3.27 (dd, J = 14; 6 Hz, 1H, CH_2S), 3.58 (dd, J = 12; 6 Hz; 1H, CH_2N), 3.70 (s, 2H, NH_2), 3.90 (dd, J = 12; 6 Hz, 1H, CH_2N), 4.65 (m, 1H, CH–O), 6.89–7.45 (m, 4H, Ar–H)
3d	3.05 (dd, J = 14; 7 Hz, 1H, CH_2S), 3.27 (dd, J = 14; 7 Hz, 1H, CH_2S), 3.62 (dd, J = 12; 6 Hz, 1H, CH_2N), 3.93 (dd, J = 12; 9 Hz, 1H, CH_2N), 4.20 (s, 1H, NH), 4.67 (m, 1H, CH–O), 6.93–7.50 (m, 10H, Ar–H)
3e	1.55 (s, 3H, CH_3), 3.27 (d, J = 14 Hz, 1H, CH_2S), 3.35 (d, J = 14 Hz, 1H, CH_2S), 3.53 (d, J = 12Hz, 1H, CH_2N), 3.95 (s, 1H, NH), 4.80 (d, J = 12Hz, 1H, CH_2N), 6.95–7.45 (m, 10H, Ar–H)

(*continued*)

Table 3 (*Continued*)

Compd.	^{1}H MR (δ in ppm)
3f	3.08 (dd, J = 14; 7 Hz, 1H, CH_2S), 3.30 (dd, J = 14; 6 Hz, 1H, CH_2S), 3.60 (dd, J = 12; 6 Hz, 1H, CH_2N), 3.89 (m, 1H, CH_2N), 4.67 (m, 1H, CH–O), 5.40 (s, 1H, NH), 6.80–7.40 (m, 9H, Ar–H)
3g	3.07 (dd, J = 14; 7 Hz, 1H, CH_2S), 3.27 (dd, J = 14; 6 Hz, 1H, CH_2S), 3.65 (dd, J = 12; 6 Hz, 1H, CH_2N), 3.75 (s, 3H, OCH_3), 3.92 (complex, 2H, CH_2N and NH), 4.69 (m, 1H, CH–O), 6.80–7.45 (m, 9H, Ar–H)
3h	1.75 (m, 1H, CH_2), 2.10 (m, 1H, CH_2), 3.04 (dd, J = 14; ' Hz, 1H, CH_2S), 3.24 (dd, J = 14; 7 Hz, 1H, CH_2S), 3.40 (m, 2H, CH_2N), 3.90 (s, 2H, NH_2), 4.30 (m, 1H, CH–O), 6.70–7.35 (m, 5H, Ar–H).
3i	1.77 (m, 1H, CH_2), 2.06 (m, 1H, CH_2), 3.0 (dd, J = 14; 7 Hz, 1H, CH_2S), 3.30 (dd, J = 14; 7 Hz, 1H, CH_2S), 3.42 (m, 2H, CH_2N), 4.35 (complex, 2H, CH–O, NH), 6.85–7.50 (m, 10H, Ar–H)
3j	3.15 (m, 2H, CH_2S), 3.79 (m, 3H, CH–S, CH_2N), 4.2 (s, 2H, NH_2), 7.0–7.45 (m, 5H, Ar–H)
3k	3.14 (m, 2H, CH_2S), 3.78 (m, 3H, CH–S, CH_2N), 4.75 (s, 1H, NH), 7.0–7.40 (m, 10H, Ar–H)
3l	1.79 (m, 1H, CH_2), 2.25 (m, 1H, CH_2), 3.10 (m, 2H, CH_2S), 3.35–3.55 (m, 3H, CH–S, CH_2N), 4.95 (s, 1H, NH), 6.85–7.40 (m, 10H, Ar–H)

[a] Compounds **3a–d**, **3f–h**, and **3g, k** were crystallized from chloroform/hexane; compounds **3i, l** were crystallized from chloroform/pentane; **3f** was crystallized from ethyl acetate/petroleum ether

All sulfenylated 2-oxazolines, 2-thiazolines, dihydrooxazine, and dihydrothiazine derivatives were characterized spectroscopically (IR and ^{1}H NMR) and gave satisfactory elemental analyses (Table 3).

Experimental

Melting points: open glass capillaries, uncorrected. IR spectra were recorded as KBr pellets on a Pye-Unicam SP 1100 infrared spectrophotometer (ν_{max} in cm^{-1}). ^{1}H NMR spectra were taken in *DMSO*-d_6 on a Varian EM-390 90 MHz NMR spectrometer using *TMS* as internal standard (chemical shifts in δ (ppm)). Microanalyses were performed at University College, London. Purity of the compounds was checked by paper chromatography using ethyl acetate/petroleum ether (b.p. 40–60 °C) as eluant. Flash column chromatography was performed according to the procedure of *Still* and co-workers [17] using Macherey-Nagel Kieselgel 60 (230–400 mesh). For gravity column chromatography, Aldrich neutral alumina (grade III) was used. The starting unsaturated urea and thiourea derivatives (**1**) were prepared by standard procedures [15].

General sulfenocyclization procedure

A solution of arylsulfenyl chloride (6 mmol) in dry acetonitrile (10 ml) was added dropwise to a magnetically stirred solution of the corresponding unsaturated ureas or thioureas (6 mmol) in dry acetonitrile (10 ml) at room temperature. Stirring was continued for 30 minutes. After addition was complete, a solution of ethyldiisopropylamine (1.2 ml, 6.9 mmol) in acetonitrile (5 ml) was added. The reaction mixture was stirred for further 30 minutes. The reaction mixture was concentrated under reduced pressure, extracted with ether (3 × 50 ml), washed with saturated aqueous ammonium chloride (2 × 50 ml), dried, filtered, and concentrated. The product was purified by column chromatography

(ethyl acetate petroleum ether = 1:1) to give the corresponding sulfenylated heterocycles. Yields are given in Table 2. Physical data, elemental analyses, and spectroscopic data (IR and ^{1}H NMR) are recorded in Table 3.

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