Synthesis of Sulfenamides from Aminoesters and their Stability

[1]MUHAMMAD IRFAN ASHIQ, [1]ISHTIAQ HUSSAIN* [1]MUHAMMAD ILYAS TARIQ,
[2]JEREMY KILBURN AND [3] HAMID LATIF SIDDIQUI
[1]*Department of Chemistry, University of Sargodha, Sargodha-40100, Pakistan.*
[2]*Queen Mary University of London, Mile End Road, London, E1 4NS, U.K.*
[3]*Institute of Chemistry, University of the Punjab, Lahore-54590, Pakistan.*
dr_research@uos.edu.pk*

(Received on 12th April 2011, accepted in revised form 2nd August 2012)

Summary: A series of sulfenamides is derived from α-amino esters for the first time. Stabilities of synthesized compounds are studied and attempts have been made to increase their half-lives.

Keywords: Sulfenamides, Amino esters, Sulfenyl halides.

Introduction

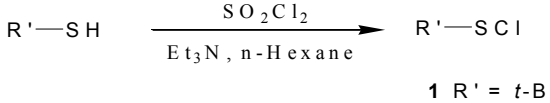
Organosulphur compounds are very important part of biological systems and have been reported to play important functions in different metabolic processes [1]. These compounds are being widely used in pharmaceutical industry; the examples of drugs containing such compounds are dapsone (leprosy drug), feldene (arthritis drug), glutathione (scavenger for oxidising agents), cysteine and sulphur containing penicillin family of drugs [2]. The organosulphur compounds derived from natural sources (garlic and onion) also reflect anticancer properties [3-5]. Compounds containing sulphur-nitrogen bond, especially sulfenamides show diverse applications in pharmaceutical and agricultural areas [6-9]. Sulfenamides derived from α-amino esters are reported as a source of α-aminyl radicals [10]. The α-aminyl radicals containing alkene side chains are found to undergo 5-exo-trig cyclisation reaction to yield nitrogen containing heterocycles. In sulfenamides, the single N-S bond, containing bivalent sulphur atom, is polarised in such a way that sulphur atom bears partial positive charge and nitrogen atom bears partial negative charge. As a result compounds are highly susceptible towards both nucleophilic and electrophilic attack. Consequently, this property contributes un-stability and high reactivity to compounds. The high susceptibility of sulfenamides towards nucleophilic attack has made them useful as pro-drugs for NH-acidic drugs.[7] The neucleophilic attack on sulphur atom breaks N-S bond resulting the formation of NH-acid product. The interesting properties of sulfenamides and the importance of amino acids in biological processes have developed our interest to study the properties of a new class of sulfenamides derived from α-amino esters.

Several methods have been reported for the synthesis of sulfenamides including the reaction of sulfenyl chlorides with amines and the reaction of haloamides with thiols [11]. A few of them has been successfully used for the conversion of amines into corresponding sulfenamides. These methods appeared to be futile in the conversion of amino acids/esters. These compounds can also be obtained in good yields by silver catalysed reaction of disulfides with amines [12].

Here, we have reported the synthesis of novel sulfenamides by using the reaction of sulfenyl chlorides with α-amino esters. The stability of compounds synthesised by this method has been studied and attempts are made to increase their half-life.

Results and Discussion

The literature procedure [11] was used for the synthesis of sulfenyl chlorides (Scheme. 1). Thiols were treated with sulfuryl chloride to yield corresponding sulfenyl chlorides **1** and **2**. The compounds were found to be highly unstable and were used without further purification after work-up the product.

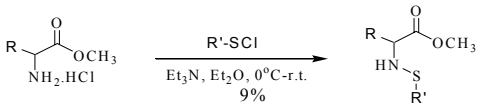


Scheme 1

Sulfenamides (**3-7**) were obtained by the reaction of aminoacids hydrochloride in the presence of Et_3N with sulfenyl chloride **1** (Scheme. 2). The yields and stability of compounds were found to be poor. It could be due to highly reactive and relatively weak N-S bond [13]. The both atoms of N-S bond behave as electrophilic and nucleophilic centers. They (**3-7**) are highly susceptible towards electrophilic and nucleophilic reactions.

*To whom all correspondence should be addressed.

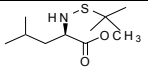
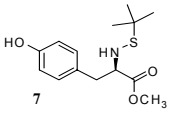
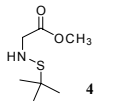
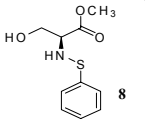
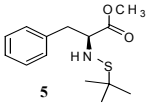
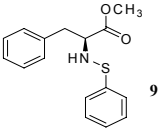
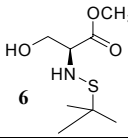
In order increase the stability of compound and to reduce the nucleophilicity of sulphur atom in N-S bond, the sulfenamides were derived from thiophenol in which sulphur atom is directly attached to the phenyl group. It was believed that the electron pairs present on the sulphur atom will delocalize on the phenyl ring and eventually lead to the less nucleophilic character of sulphur atom. This decrease in the neucleophilic character of S-atom was supposed to be helpful in reducing the reactivity of the resulting sulfenamides **8** and **9** (Scheme 2). However, no significant difference was observed in the half-lives of compounds **8**, **9**, which contains phenyl ring directly attached to the S-atom as compared to compounds **3-7**. The half-lives of all the compounds were observed to be less than 24 hours. However, it was also observed that the decomposition of these compounds is relatively slower in solvent ($CDCl_3$) which allowed their characterisation by NMR, IR and mass spectrometry. Presumably, in the absence of solvent, rapid oxidation/hydrolysis of sulfenamides take place, which is responsible for their very short half-lives. Results have been summarised in Table-1.



3 R = CH_3-CH-CH_3, R' = *t*-Bu
4 R = H, R' = *t*-Bu
5 R = Ph-CH_2, R' = *t*-Bu
6 R = OH-CH_2, R' = *t*-Bu
7 R = OH-Ph-CH_2, R' = *t*-Bu
8 R = OH-CH_2, R' = Ph
9 R = Ph-CH_2, R' = Ph

Scheme 2

Table-1: Sulfenamides synthesised and their % yields.

Sulfenamide	Yield (%)	Sulfenamide	Yield (%)
 **3**	**17**	 **7**	**23**
 **4**	**9**	 **8**	**13**
 **5**	**27**	 **9**	**25**
 **6**	**17**		

Experimental

Solvents and reagents were of commercial grade and were used without further purification. However, they were distilled prior to use wherever necessary. The petroleum ether fractions boiling between 40°C–60°C were used. Flash column chromatography was performed on Sorbsil C60, 40-60 mesh silica. Experiments were conducted at room atmosphere unless otherwise specified. Reactions requiring dry atmosphere were carried out under dried nitrogen atmosphere.

^{1}H-NMR spectra were obtained at 300 MHz on a Bruker AC 300 and at 400 MHz on a Bruker DPX 400 spectrometer. ^{13}C-NMR spectra were recorded at 75 MHz on a Bruker AC 300 and at 100 MHz on a Bruker DPX 400 spectrometer. Spectra were referenced to the solvent residual peak for the deutrated solvent. Infra-red spectra were recorded on BIORAD Golden Gate FTS 135. Mass spectra were obtained on a VG analytical 70-250 SE normal geometry double focusing mass spectrometer. All electron ionisation spectra were recorded on a ThermoQuest Trace MS single quadrupole GC-MS mass analyser with an electron ionisation ion source using DCM as solvent.

General Procedure for the Synthesis of Sulfenyl Chlorides **1-2**

Thiol (44.4 mmol) was dissolved in n-Hexane (15 mL) and cooled to 0 °C. Et_3N (0.04 g, 0.44 mmol) was added dropwise followed by the addition of sulfuryl chloride (6.9 g, 51 mmol). It was warmed to room temperature and stirred for 1.5 h. The solvent was removed *in vacuo* (1 mm Hg) at 0 °C to give desired product as yellowish orange oil. It was used without further purification because of its highly reactive nature.

General Synthesis of Sulfenamides

Amino ester hydrochloride (1.5 mmol) and Et_3N (1.1 mg, 1.5 mL) were dissolved in Et_2O (15 mL). The reaction mixture was cooled to 0 °C before addition of sulfenyl chloride (1.5 mmol). It was warmed to room temperature and stirred for 16 h, filtered through celite™ and washed with Et_2O (25 mL). The filtrate was concentrated *in vacuo*, purification by column chromatography (PE) gave the desired compound as yellowish oil.

2-tert-Butylsulfanylamino-4-methyl-pentanoic acid methyl ester **3**

Yield: 17%; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm): 3.71 (3H, s, OCH_3), 3.60 (1H, m,

CH_2CHNH), 3.27 (1H, d, *J* = 7.3 Hz, CHN*H*S), 1.75-1.59 (1H, m, $(CH_3)_2CH$), 1.45 (2H, dd, *J* = 7.1, 7.0 Hz, $CHCH_2CH$), 1.33 (9H, s, $3CH_3$), 0.88 (6H, d, *J* = 5.5 Hz, $(CH_3)_2CH$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 175.48 (C=O), 62.92 (CH_3), 52.36 (CH), 48.42 (C), 42.61 (CH_2), 30.60 (CH_3), 30.02 (CH_3), 24.75 (CH_3), 22.85 (CH_3), 22.24 (CH_3); MS (ES^+): *m/z* (%) = 234.2 (70) $[M + H]^+$; IR ν_{max} (film) cm^{-1}: 3331 (m), 2957 (s), 2869 (m), 1737 (s), 1456 (m), 1167 (s), 614 (m).

Tert-Butylsulfanylamino-acetic acid methyl ester **4**

Yield: 9%; ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm): 4.07 (2H, m, CH_2NH), 3.72 (3H, s, OCH_3), 1.58 (1H, m, N*H*), 1.42 (9H, s, $3CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 170.14 (C=O), 63.76 (CH_2), 52.26 (CH_3), 48.42 (C), 30.95 (CH_3); MS (ES^+): *m/z* (%) = 178.1 (95) $[M + H]^+$; IR ν_{max} (film) cm^{-1}: 3391 (m), 2956 (s), 2854 (m), 1739 (s), 1459 (m), 1149 (s), 707 (m).

2-tert-Butylsulfanylamino-3-phenyl-propionic acid methyl ester **5**

Yield: 27%; ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm): 7.18 (5H, m, 5C*H*), 3.89 (1H, m, C*H*NH), 3.65 (3H, s, OCH_3), 3.22 (1H, m, CHN*H*), 2.94 (2H, dd, *J* = 7.6, 5.7 Hz, $PhCH_2$), 1.20 (9H, s, $3CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 173.69 (C=O), 136.62 (C), 129.51 (CH), 128.62 (CH), 127.04 (CH), 63.90 (CH), 52.37 (CH_3), 48.47 (C), 38.74 (CH_2), 30.35 (CH_3); MS (ES^+): *m/z* (%) = 290 (100) $[M + Na]^+$; IR ν_{max} (film) cm^{-1}: 3332 (m), 2958 (s), 2859 (m), 1737 (s), 1455 (m), 1165 (s), 700 (m).

2-tert-Butylsulfanylamino-3-hydroxy-propionic acid methyl ester **6**

Yield: 17%; ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm): 3.91 (1H, m, CH_2CHNH), 3.73 (3H, s, OCH_3), 3.66 (1H, m, O*H*), 2.30 (1H, m, N*H*S), 1.33 (9H, s, $3CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 172.33 (C=O), 63.61 (CH), 61.50 (CH_2), 52.75 (CH_3), 48.70 (C), 30.62 (CH_3); MS (ES^+): *m/z* (%) = 230 (90) $[M + Na]^+$; IR ν_{max} (film) cm^{-1}: 3336 (m), 2957 (m), 2895 (m), 1733 (s), 1456 (m), 1165 (s), 733 (m).

2-tert-Butylsulfanylamino-3-(4-hydroxy-phenyl)-propionic acid methyl ester **7**

Yield: 23%; ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm): 7.00 (2H, d, *J* = 8.4 Hz, 2C*H*), 6.71 (2H, d, *J* = 8.4 Hz, 2C*H*), 4.10 (1H, m, CH_2CHNH), 3.68 (3H, s, OCH_3), 3.24 (1H, m, N*H*), 2.90 (2H, m, $PhCH_2$), 1.24 (9H, s, $3CH_3$); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 173.91 (C=O), 154.79 (C), 130.67 (CH), 128.48 (C), 115.49 (CH), 64.08 (CH_3), 52.40 (CH), 48.48 (C), 37.87 (CH_2), 30.52 (CH_3); MS (ES^+): *m/z* (%) = 306 (100) $[M + Na]^+$; IR ν_{max} (film) cm^{-1}: 3333 (m), 2956 (m), 1725 (m), 1614 (s), 1515 (s), 1441 (m), 1170 (s), 1108 (m).

3-Hydroxy-2-phenylsulfanylamino-propionic acid methyl ester **8**

Yield: 13%; ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm): 7.38 (5H, m, 5C*H*), 4.21 (1H, td, *J* = 5.5, 1.8 Hz, CH_2CHNH), 3.85 (2H, m, CH_2CHNH), 3.48 (3H, s, OCH_3), 1.92 (1H, t, *J* = 6.6 Hz, O*H*); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 170.75 (C=O), 139.18 (C), 129.21 (CH), 128.93 (CH), 127.96 (CH), 127.34 (CH), 125.45 (CH), 77.68 (CH_3), 62.54 (CH_2), 52.31 (CH); MS (ES^+): *m/z* (%) = 228.2 (100) $[M + H]^+$; IR ν_{max} (film) cm^{-1}: 3467 (b), 2950 (m), 1735 (s), 1437 (m), 1047 (m), 737 (m).

3-Phenyl-2-phenylsulfanylamino-propionic acid methyl ester **9**

Yield: 25%; ^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm): 7.27-6.97 (10H, m, 10C*H*), 3.70 (1H, m, C*H*), 3.62 (3H, s, OCH_3), 3.22 (1H, m, N*H*), 3.75 (2H, dd, *J* = 7.7, 5.5 Hz, CH_2); ^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm): 173.99 (C=O), 141.13 (C), 136.75 (C), 129.54 (CH), 129.41 (CH), 129.07 (CH), 128.79 (CH), 128.68 (CH), 127.08 (CH), 125.57 (CH), 124.45 (CH), 123.72 (CH), 66.05 (CH_3), 52.23 (CH), 39.62 (CH_2); MS (ES^+): *m/z* (%) = 288.3 (100) $[M + H]^+$; IR ν_{max} (film) cm^{-1}: 3329 (b), 2950 (m), 1736 (s), 1438 (m), 1101 (m), 739 (s).

Conclusion

A series of novel sulfenamides have been synthesised successfully but they are found to be highly unstable. Attempts have been made to increase their stability by reducing nucleophilicity of sulphur in the N-S linkage but it was found to be un-effective.

Acknowledgement

We are thankful to the University of Southampton, UK, to provide laboratory facilities and spectroscopic analysis.

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