Indian Journal of Chemistry
Vol. 37B, February 1998, pp. 135 - 138

Utilities of saccharinyl acetyl isothiocyanate in synthesis of non-condensed polynuclear heterocyclic compounds of expected biological activity

M S Amine* & M M H Arief
Chemistry Department, Faculty of Science, Benha University, Benha-Egypt

Received 17 June 1997; accepted (revised) 22 January 1998

The title compound **1** has been reacted with nitrogen nucleophiles phenylhydrazine, acetylhydrazines, benzoylhydrazine, sodium azide, anthranilic acid and oxygen nucleophile as *o*-aminophenol, and amino acid as glycine. Also the reaction of **1** with phenyl isocyanate and active methylene compounds has been investigated and it was found that all these reactions proceeds via isothiocyanate heterocyclization to furnish non-condensed heterocyclic compounds **2-14**.

It has been well established that thiazole, triazole, benzoxazole, azlactone, quinazoline, oxadiazine and oxazine derivatives have a great application in the field of manufacturing of drugs and as a chemotherapeutic agents. This prompted us to synthesise those nuclei in a molecule bearing saccharin moiety as a building block aiming to increase their biological activities.

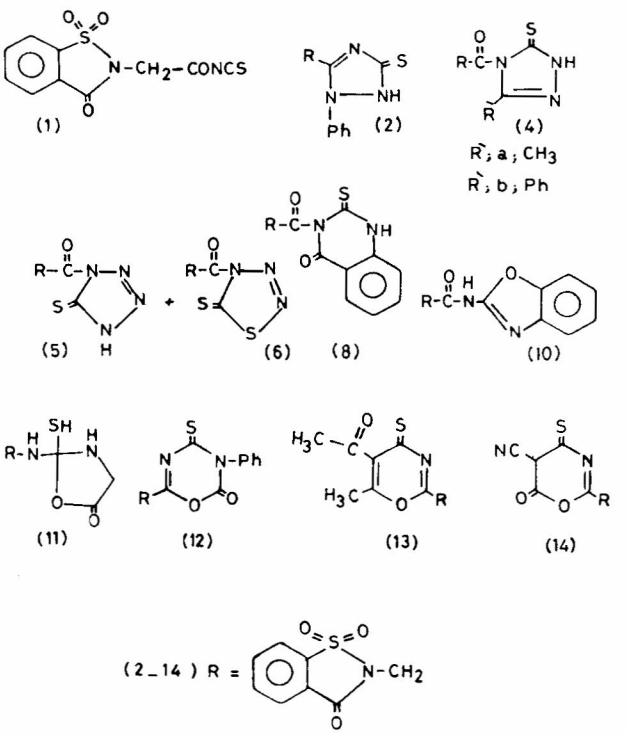
Isothiocyanate provide an easy access to non-condensed polyheterocyclic systems. Thus the title compound **1** was made to react with some nitrogen nucleophiles, oxygen nucleophiles and active methylene compounds in order to obtain some new interesting heterocycles. The results are reported in the present paper.

The isothiocyanate **1** was obtained by treating acid chloride of saccharinylacetic acid, in acetone with ammonium thiocyanate[1,2] and the solution obtained was used *in situ* to prevent it's decomposition. Thus when compound **1** was allowed to react with phenylhydrazine *in situ* it afforded the triazole derivative[3] **2**.

Reaction of **1** with acetylhydrazine and/or benzoylhydrazine gave the thiosemicarbazide derivatives **3a, b** respectively which when treated with polyphosphoric acid afforded the respective triazole derivatives **4a, b**.

Sodium azide reacted with isothiocyanate[4,5] in boiling acetone and gave a mixture of tetrazole derivative **5** and thiatriazole derivative **6**. On the other hand anthranilic acid reacted with isothiocyanate **1** and afforded the thiourea derivative **7** which on treatment with polyphosphoric acid cyclized by dehydration to quinazoline derivative **8.**

Amident nucleophiles as *ortho*-aminophenol reacted with isothiocyanate **1** in refluxing acetone and gave the thiocarbamate derivative **9**.



When thiocarbamate **9** was heated above it's melting point by 20-30°C, H_2S gas evolved and the compound was cyclized to furnish the benzoxazole derivative **10**.

The hitherto-unknown reaction of amino acids[6,7] with compound **1** is illustrated, thus when it is reacted with glycine in the presence of pyridine as a base, azlactone derivative **11** is obtained.

The isothiocyanate **1** reacts with phenylisocyanate[8] *via* [2+4] π-electron cycloaddition reaction to produce oxadiazine derivative **12**.

As a point of interest in this investigation was the behaviour of isothiocyanate **1** toward active methylene compound[9] under Michael reactions conditions, thus when **1** was treated with acetylacetone in presence of ammonium acetate or triethylamine it afforded **13**.

Similarly isothiocyanate **1** reacted with ethyl cyanoacetate under the same reaction conditions to afford the oxazine derivative **14**.

Experimental Section

All melting points are uncorrected. IR spectra (KBr) were recorded on PYE Unicam spectrophotometer SP 1200 wafer technique and ^{1}HNMR spectra on a Perkin-Elmer 90 MHz spectrometer (chemical shifts are δ, ppm) using TMS as an internal standard, $CDCl_3$ and DMSO as solvents. Mass spectra were recorded on G-S/MS Finnigan-MAT, Tremetrics 9000 Series gas chromatography for compounds **2, 11** and on EI+QIMS LMR VP LR for compounds **5-7** and **13**. The antimicrobial activity were determined *in vitro* using the cut plate and filter paper disc diffusion method[10,11]. Four different species of gram positive and gram negative bacteria were examined; the culture medium was normal nutrient agar NA and the solvent used was acetone water mixture (10%). Antimicrobial activity data are listed in Table I.

Synthesis of saccharinyl acetyl isothiocyanate 1. To a stirred solution of saccharinyl *N*-acetyl chloride[12] (0.01 mole) in dry acetone (50 mL), solid ammonium thiocyanate (0.01 mole) was added. The reaction mixture was stirred for 1 hr at room temperature. Ammonium chloride was precipitated during the progress off the reaction, which was filtered off to leave a clear solution of saccharinyl-*N*-acetyl isothiocyanate **1** in acetone.

Reaction of isothiocyanate 1 with phenylhydrazine: Formation of phenyl-3-saccharinyl-methyl-1, 2, 4-triazoline-5-thione 2. A solution of isothiocyanate **1** (0.01 mole) in dry acetone and phenylhydrazine (0.01 mole) was heated under reflux for half an hour, a solid crystal of **2** was obtained which crystallized from pet. ether 60-80°, yield 82%, m.p. 92-94° (Found: C, 51.43; H, 3.12; N, 15.00. $C_{16}H_{12}N_4O_3S_2$ requires C, 51.61; H, 3.23; N, 15.05%); IR: 3200 (NH), 1620 (C=N), 1240 cm^{-1} (C=S); MS: m/z 373 (M^++1) (2%), 152 (100%).

Reaction of isothiocyanate 1 with acid hydrazide: Formation of *N*-acyl-*N*-saccharinyl acety thiosemicarbazide 3a, b. The solution of

Table I—Microbiological activities data*

Compd	*B. subtilis*		*B. mycoides*		*B. cereus*		*E. coli*	
	A	*MIC*	*A*	*MIC*	*A*	*MIC*	*A*	*MIC*
2	++	500	+	125	++	500	+	250
4b	+	250	+	250	++	500	++	500
4b	—	—	+	250	+	250	+	125
5	—	—	—	—	+	125		125
6	+	125	++	250	+++	500	++	500
8	+	125	+++	250	+	250	+	125
12	+	125	++	250	+++	250	+	250
13	+	125	++	250	++	500	+	125

A—Antimicrobial activity of tested compounds
MIC—Minimum inhibitory concentration.
+ >5 mm slightly.
++ >7 mm moderately.
+++ >9 mm highly active.
*The data were determined in Botany Department, Faculty of Science, Benha University, Benha, Egypt.

isothiocyanate **1** (0.01 mole) in dry acetone (50 mL) and acylhydrazine namely acetylhydrazine or benzoyl hydrazine (0.01 mole) was heated under reflux for 1 hr. The solid product was filtered off and recrystallized from ethanol-toluene mixture to give **3a** and from ethanol to give **3b**.Compound **3b**, yield 63% had m.p. 220-21° (Found: C, 40.32; H, 3.30; N, 15.62. $C_{12}H_{12}N_4O_5S_2$ requires C, 40.45; H, 3.37; N, 15.73%); IR: 3270, 3200 (NH), 1670 (C=O), 1270 cm^{-1} (C=S); **3b**, yield 87%, m.p. 139-40° (Found: C, 48.63; H, 2.70; N, 13.21. $C_{17}H_{14}N_4O_5S_2$ requires C, 48.80; H, 3.35; N, 13.40%); IR: 3230, 3180 (NH), 1670 (C=O), 1280 cm^{-1} (C=S).

Cyclization of thiosemicarbazide 3a, b with polyphosphoric acid: Formation of 3-methyl-4-(saccharinyl acetyl)-Δ^2-1, 2, 4-trizol and/or phenyline-5-thione 4a, b. The solution of **3a, b** (0.01 mole) in acetic acid (20 mL) was added dropwise to (20 mole) of polyphosphoric acid at (60°C). After complete addition the solution was left overnight at room temperature and then diluted with water. The solid product was filtered off and crystallized from ethanol-benzene mixture to get **4a** and from pet. ether 60-80° to get **4b.** Compound **4a**, had yield 52%, m.p. 155-57° (Found: C, 42.70; H, 3.08; N, 16.60. $C_{12}H_{10}N_4O_4S_2$ requires C, 42.60; H, 2.96; N, 16.57%); IR: 3190 (NH), 1670 (C=O), 1280 cm^{-1} (C=S); ^{1}HNMR: δ 1.0 (3H, methyl protons), 4.6 (2H, methylene protons), 5.7 (1H, NH exchangeable with D_2O), 8.3 (m, 4H, ArH); **4b**, yield 63%, m.p. 112-14° (Found: C, 50.8; H, 2.66; N, 13.40. $C_{17}H_{12}N_4O_4S_2$ requires C, 51.0; H, 3.70; N, 14.0); IR: 3210 (NH), 1680 (C=O), 1270 cm^{-1} (C=S).

Reaction of isothiocyanate 1 with sodium azide: Formation of 4-(saccharinyl acetyl) tetrazolo-5-thione 5 and 4-(saccharinyl acetyl)-thiatriazolo-5-thione 6. To a solution of isothiocyanate **1** in dry acetone (30 mL) (0.5 mole of sodium azide was added and the mixture refluxed for 8 hr. The product was then poured onto cold water. The solid that obtained after filtration was dissolved in cold methanol and filtered off to give **5**. The filtrate was concentrated to give **6**. Compound **5** crystallised from methanol, yield 42%, m.p. 120-22° (Found: C, 37.00; H, 2.10; N, 21.42. $C_{10}H_7N_5O_4S_2$ requires C, 36.92; H, 2.15; N, 21.54%); IR showed the characteristic bands of tetrazole moiety[13] at 3100 (NH, 1720) (C=O) and 1260 cm^{-1} (C=S); ^{1}HNMR: δ 4.8 (2H, methylene protons), 6.4 (s, 1H, NH exchangeable with D_2O), 8.4 (m, 4H, Ar-H); MS: m/z M^+ 325 (2%), (M+2) 327 (0.33%), 196 (100%). Compound **6** crystallized from xylene, yield 38%, m.p. 230-32° (Found: C, 34.92; H, 1.69; N, 16.13. $C_{10}H_6N_4O_4S_3$ requires C, 35.09; H, 1.75; N, 16.37%); IR showed no NH band and MS: m/z M^+ 342 (4%) and (M^+ 2) 244 (0.2%), 196 (100%).

Reaction of isothiocyanate 1 with anthranilic acid: Formation of *N*-sacchrinyl acetyl)-*N*(*o*-carboxyphenyl)thiourea 7. To a solution of isothiocyanate **1** (0.01 mole) in 30 mL of dry acetone anthranilic acid (0.01 mole) was added. The reaction mixture was refluxed for 1 hr, then cooled and the precipitated solid was filtered off and crystallized from ethanol-benzene mixture to give **7**, yield 84%, m.p. 197-98° (Found: C, 48.92; H, 3.06; N, 10.13. $C_{17}H_{13}N_3O_6S_2$ requires C, 48.69; H, 3.10; N, 10.02%).

Cyclization of 7 with PPA: Formation of 3-(saccharinyl acetyl)-quinazolin-4-one-2-thione 8. A solution of **7** (0.01 mole) in PPA (30 mL) was allowed to stand at room temperature overnight, then diluted with 20 mL water. The solid product that separated out was filtered off, crystallized from methanol to give **8** yield 53%, m.p. 125-27° (Found: C, 50.55; H, 3.82; N, 10.27. $C_{17}H_{11}N_3O_5S_2$ requires C, 50.87; H, 2.74; N, 10.47); IR: 3220 (NH), 1720 (C=O), 1280 cm^{-1} (C=S); MS: m/z M^+ 401 (0.4%), 164 (100%).

Reaction of isothiocyanate 1 with *o*-aminophenol: Formation of *N*-(saccharinyl acetyl)-2-aminophenyl thiocarbamate 9. To a solution of isothiocyanate **1** (0.01 mole) in 30 mL of dry acetone, *o*-aminophenol (0.01 mole) was added. The reaction mixture was refluxed for 1 hr. After cooling the solid product obtained, was crystallized from xylene to give **9**, yield 78%, m.p. 180-82° (Found: C, 49.20; H, 3.23; N, 10.69. $C_{16}H_{13}N_3O_5S_2$ requires C, 49.10; H, 3.23; N, 10.74%); IR: 3200 (NH), 1740 (C=O), 1620 cm^{-1} (C=N); MS: m/z (M^++1) 392 (4%), 109 (100%).

Cyclization of the thiocarbamate derivative 9 to 2-(saccharinyl acetamido)-1, 3-benzoxazole 10. The thiocarbamate derivative **9** was heated above its melting point by 20-30°C when H_2S gas liberated during the fusion process. After evolution

of all H_2S gases, the reaction mixture was left to cool, a solid product of **10** was obtained and crystallized from ethanol, yield 62%, m.p. 135-37° (Found: C, 53.56; H, 3.21; N, 11.82. $C_{16}H_{11}N_3O_5S$ requires C, 53.78; H, 3.08; N, 11.76%); IR: 3200 (NH), 1740 (C=O), 1620 cm^{-1} (C=N); ^{1}HNMR: δ 3.6 (2H, methylene protons), 7.6 (m, 8H, Ar-H), 8.4 (1H, NH, exchangeable with D_2O); MS: m/z M^+ 357 (2%), (M^++2) 359 (0.6%), 196 (100%).

Reaction of isothiocyanate 1 with glycine: Formation of 2-(*N*-saccharinyl acetamido)-1, 3-oxazolidin-5-one-2-thiol 11. To a solution of isothiocyanate **1** (0.01 mole) in dry acetone (30 mL), glycine (0.01 mole) and few drops of pyridine was added. The reaction mixture was refluxed for 1 hr. the solid product was precipitated after cooling which was filtered off, washed with water, and recrystallized from methanol to give **11**, yield 76%, m.p. 165-67° (Found: C, 40.32; H, 3.1; N, 11.4. $C_{12}H_{11}N_3O_6S_2$ requires C, 40.34; H, 3.00; N, 12.77%); IR: 1760, 1690 (C=O), 2500 (SH), 3350-3200 cm^{-1} (NH's).

Reaction of isothiocyanate 1 with phenyl-isocyanate: Formation of 2-(saccharinylmethyl)-5-phenyl-1, 3, 5-oxadiazin-6-one-4-thione 12. To a solution of isothiocyanate **1** (0.01 mole) phenyl isocyanate (0.1 mole) was added and the mixture refluxed for 1 hr. The solid product that obtained was crystallized from xylene to give **12,** yield 84%, m.p. 188-89° (Found: C, 50.93; H, 2.66; N, 10.52. $C_{17}H_{11}N_3O_5S_2$ requires C, 50.87; H, 2.74; N, 10.47%); IR: 1750 (C=O), 1620 (C=N), 1260 cm^{-1} (C=S); ^{1}HNMR: δ 4.6 (2H, methylene protons), 7.7 (m, 9H, Ar).

Reaction of isothiocyanate 1 with acetylacetone and/or ethyl cyanoacetate: Formation of 2-(saccharinyl-methyl)-5-acetyl-6-methyl-1, 3-oxazine-4-thione 13 and/or 2-(saccharinyl methyl)-5-cyano-1, 3-oxazin-6-one-4-thione 14. To a solution of isothiocyanate **1** (0.01 mole) in dry acetone (30 mL), acetylacetone and/or ethyl cyanoacetate (0.01 mole) and ammonium acetate or triethylamine (0.1 mole) were added and the mixture was refluxed for 3 hr. The hot reaction mixture was then poured onto ice and the precipitate obtained was collected and crystallized from xylene to give **13** and/or **14**. Compound **13** was obtained in 77% yield, m.p. 190-92° (Found: C, 49.57; H, 3.20; N, 7.56. $C_{15}H_{12}N_2O_5S_2$ requires C, 49.45; H, 3.30; N, 7.69%); IR: 1710 (C=O), 1615 (C=N), 1270 cm^{-1} (C=S); MS: m/z M^+ 364 (30%), (M^+ 2) 366 (0.1%), 184 (100%). Compound **14** was obtained in 62% yield, m.p. 270-72° (Found: C, 44.91; H, 2.08; N, 11.82. $C_{15}H_{11}N_3O_5S_2$ requires C, 44.70; H, 2.01; N, 12.03%); IR: 2100 cm^{-1} (C≡N).

References

1 Baeger M & Drabck J, *Ger Offen DE,* 3,504,016 (1985); *Chem Abstr,* 103, 215196 (1985).
2 Hull R & Seden J P, *Synth Commun,* 10, **1981,** 489.
3 Mishra V K, Bahel S C & Akin B, Bobai, 13,351 (1985); *Chem Abstr,* 105, **1986,** 4980.
4 Neidlein R & Tauber J, *Chem Ber,* 100, **1967,** 736.
5 Van Look E, Vandennsovel J M, Labbe G & Smeto G, *J Org Chem,* 38, **1973,** 2916.
6 Carraway J L, *J Chem Soc,* **1961,** 3733.
7 Bahadur S & Saxena M, *J Chem Soc Pak,* 4, **1982,** 141.
8 Rotton S, Moyne J & Longeray R, *Bull Soc Chem Fr,* **1981,** 28.
9 Dehne H & Krey P, *J Prakt Chem,* 324, **1982,** 915.
10 Vincent J G & Vincent H W, *Proc Soc Exptl Biol Med,* 55, **1944,** 162.
11 Calson H J, *J Bact,* 55, **1948,** 607.
12 Arief M M H, *Phosphorus, Sulfur & Silicon,* 114, **1996,** 129.
13 Ballmy L, *The infrared spectra of complex molecules* (London), **1966,** p. 284.