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Facile one-pot synthesis of thio and selenourea derivatives: A new class of potent urease inhibitors

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Abstract—A facile, one-pot synthesis of thio and selenourea derivatives from amines using tetrathiomolybdate **1** and tetraselenotungstate **2** as sulfur and selenium transfer reagents, respectively, is reported. The compounds were tested for their activity as urease inhibitors and some of the compounds showed potent activity in the nanomolar range towards *jack bean* urease.

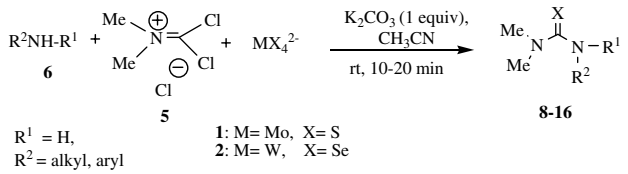
Compounds containing thiourea group are present in many drugs exhibiting antifungal and antibacterial properties[1a,b] and also act as corrosion inhibitors.[2] Plaunotol and its thiourea derivatives **3a**, **b** exhibited antibacterial activity against *Helicobacter pylori* as urease inhibitors.[3] Compounds containing selenocarbonyl group have also been shown to have pharmaceutical significance as kinase inhibitors.[4] It has been shown that the quinazoline derivative **4**[5] exhibits selective inhibitory activity against platelet derived growth factor (PDGF) phosphorylation (Fig. 1).

Generally the thio and selenourea derivatives are prepared in good yield from isothiocyanates or isoselenocyanates by reaction with amines.[6] Another method of synthesis of thiourea derivatives is by thiocarbonylation of amines with thiophosgene in the presence of triethylamine, followed by condensation with a secondary amine.[7] The above methods involve the use of either carbon disulfide or thiophosgene as an isocyanate precursor, and are not easy to work with.

Recently Ishihara et al. reported the conversion of an amine to selenourea using dichloromethylene-dimethyliminium chloride **5**, lithium aluminium hydride and elemental selenium.[8a,b]

Herein, we report a facile one-pot synthesis of thio and selenourea derivatives under mild conditions by the reaction of amines **6** and commercially available Viehe's iminium salt (phosgene iminium chloride) **5**[9] in the presence of benzyltriethylammonium tetrathiomolybdate **1** $[PhCH_2NEt_3]_2MoS_4$[10] as the sulfur transfer reagent or tetraethylammonium tetraselenotungstate **2** $[Et_4N]_2WSe_4$[11] as the selenium transfer reagent, respectively (Scheme 1).

The reaction is generally carried out by the addition of reagent **1** or **2** (1.1 equiv) to the mixture of amine **6** and Viehe's salt **5** (1 equiv, CH_3CN, 28 °C, 10–20 min) in the presence of K_2CO_3 (1 equiv) and in all the cases the corresponding thio/selenourea derivatives were obtained in good yield. The synthesis of a number of thio and selenourea derivatives (**8**–**16**) using this methodology is summarized in Table 1. This methodology is applicable only for primary and secondary amines.



Scheme 1.

Keywords: Thiourea; Selenourea; Urease inhibition; Tetrathiomolybdate; Tetraselenotungstate.
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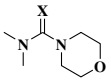
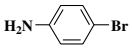
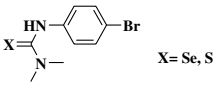
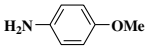
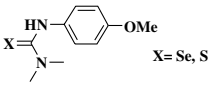
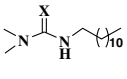
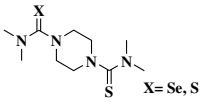
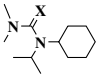
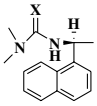
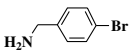
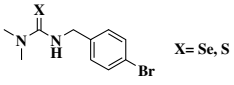
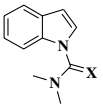
Table 1. Synthesis of Thio and Selenourea Derivatives

Entry	Amine (**6a–i**)	Product (8–16)	Yield
1		 X= Se, S	**8a**; X = S, 64% **8b**; X = Se, 64%
2		 X= Se, S	**9a**; X = S, 60% **9b**; X = Se, (NI)
3		 X= Se, S	**10a**; X = S, 77% **10b**; X = Se, 63%
4		 X= Se, S	**11a**; X = S, 75% **11b**; X = Se, (NI)
5		 X= Se, S	**12a**; X = S, 63% **12b**; X = Se, (NI)
6		 X= Se, S	**13a**; X = S, 61% **13b**; X = Se, 77%
7		 X= Se, S	**14a**; X = S, 70% **14b**; X = Se, 50%
8		 X= Se, S	**15a**; X = S, 76% **15b**; X = Se, 65%
9		 X= Se, S	**16a**; X = S, 78% **16b**; X = Se, NI

NI, not isolable.

It was found that the addition of K_2CO_3 improved the yield of the products formed.

There are two possible pathways proposed for the formation of the urea derivatives. (Schemes 2 and 3) In path A amine **6** acts as a nucleophile and attacks **5** which results in the formation of the intermediate **7a** which on elimination of chloride followed by the attack of tetrathiomolybdate **1** or tetraselenotungstate **2** can furnish the intermediate **7b**. Intermediate **7b** can lead to the formation of the product via the intermediate **7c**. We have reported earlier, a similar reaction in the synthesis of selenoamides from amides via the corresponding chloroiminium salts using tetraselenotungstate **2**.[12]

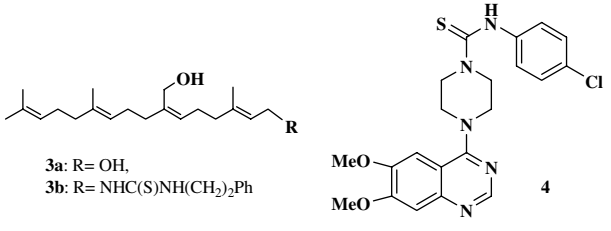
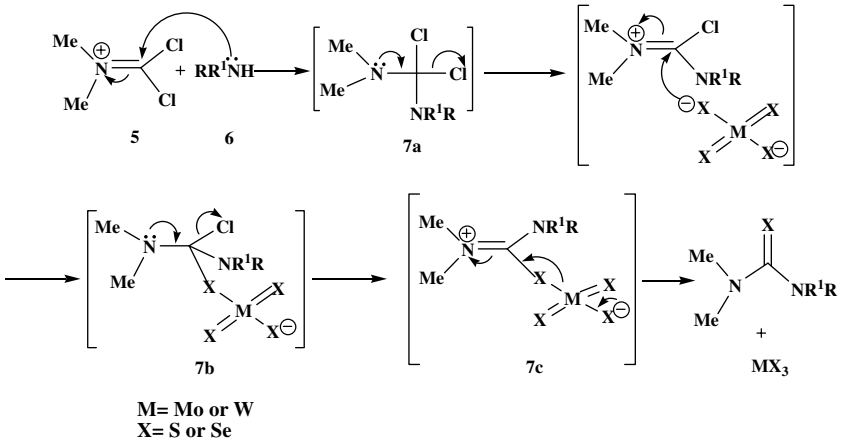


Figure 1.

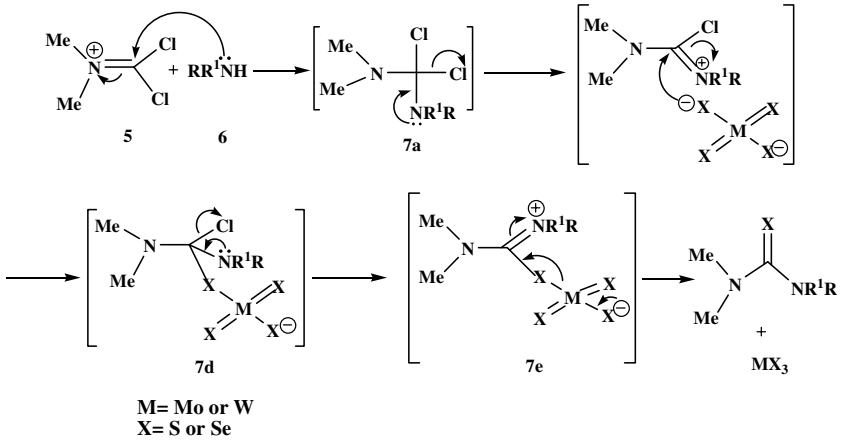
In path B, the amine introduced in the first step can also involve in the displacement of the chloride anion from **7a** to lead to the intermediate **7d**. Intermediate **7d** gets converted to the product via **7e** following a sequence similar to path A (Scheme 3).

A few thio and selenourea derivatives were obtained as crystalline solids whose molecular structures were confirmed by X-ray crystallography. Two of the molecular structures (**16a** and **14b**)[13] are shown below (Fig. 2).

Reaction of piperazine (entry 5) with **1** resulted in the formation of dithiourea derivative **12a** under the same reaction conditions. It was a stable crystalline solid and the molecular structure was confirmed by single crystal X-ray.[13] (Fig. 3) The corresponding selenourea derivative **12b** was not isolable. Similarly compounds **9b** and **11b** were also not isolable and were found to decompose when the crude products were subjected to purification.[14] The reaction of indole (entry 9) with tetraselenotungstate **2** gave a mixture of products which were difficult to purify.



Scheme 2. Path A.



Scheme 3. Path B.

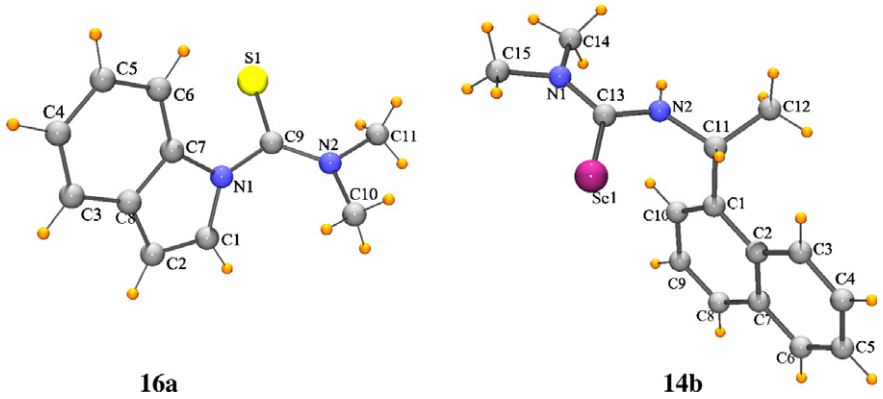


Figure 2. ORTEP diagrams of **16a** and **14b**.

A few of the seleno and thiourea derivatives showed potent inhibitor activity against urease (*jack bean*). Since *jack bean* urease is the most widely studied enzyme and is found to have <50% homology in its sequence with the other known ureases (*Klebsiella aerogenes*, *H. pylori*, etc.) it has been chosen as a model system.[15] The inhibition constants[16,17] (K_i) are given in Table 2. A long chain derivative **11a** was found to be the most potent with the K_i of 124 nM among the thiourea derivatives tested.[18] The K_i for the standard (thiourea) was reported to be 70 mM.[19]

In general, the selenourea derivatives were found to be more potent than the thiourea derivatives and the cyclohexyl derivative **13b** was found to be the most potent among all derivatives tested with the inhibition constant of 25 nM. Morpholine derivatives **8a** and **b** did not show any inhibition.

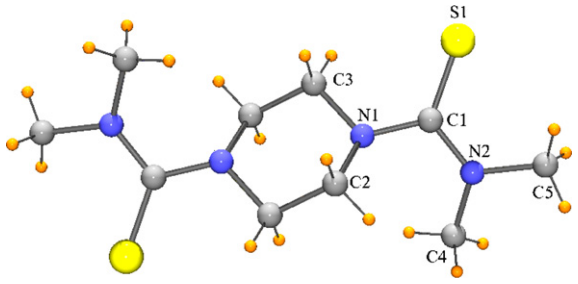
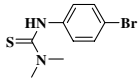
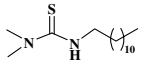
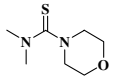
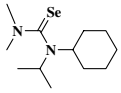
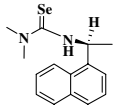
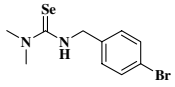
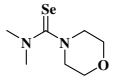


Figure 3. ORTEP diagram of **12a** (other part of the molecule is not labeled for clarity).

Table 2. Inhibitor Activity against urease (*jack bean*)

Compound	Inhibitors	K_i
Control		70 mM
9a		255 nM
11a		124 nM
8a		NI
13b		25 nM
14b		94 nM
15b		135 nM
8b		NI

NI, no inhibition.

In summary, a facile and an efficient one-pot conversion of amines to various thio and selenourea derivatives is demonstrated. A few of the urea derivatives have been shown to be potent inhibitors for *jack bean urease*. Studies of the activity of these compounds as urease inhibitors for *H. pylori* are in progress.

*General experimental procedure for the synthesis of thiourea derivatives: Typical experimental procedure for the synthesis of **11a**:* To a solution of dodecylamine **6d** (0.23 g, 1.23 mmol) and phosgene iminium chloride **5** (0.2 g, 1.23 mmol) in CH_3CN (3 ml) was added K_2CO_3 (0.17 g, 1.23 mmol) and the mixture was stirred for 5 min at 28 °C. To this mixture tetrathiomolybdate **1** (1.2 equiv, 0.9 g, 1.48 mmol) was added and immediate colour change from red to black was observed. After stirring for 10 min at 28 °C, diethyl ether (3 ml) was added to the reaction mixture and filtered through a Celite pad. The black residue was extracted with CH_2Cl_2/Et_2O (1:9, 5× 20 ml) and filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (230–400 mesh, elution with hexane/ethyl acetate 7:3) to furnish the thiourea derivative **11a** (0.25 g, 75%) as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.30 (br s, 1H), 3.66–3.60 (m, 2H), 3.26 (s, 6H), 1.66–1.56 (m, 2H), 1.26 (br s, 20H), 0.88 (t, J_1 = 6.6 Hz, J_2 = 13.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 181.9, 46.4, 40.3, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 26.9, 22.6, 14.1; HR-MS (*m*/*z*): Calculated for $C_{17}H_{38}N_2S$ ($M+H^+$): 273.2364; Observed ($M+H^+$): 273.2364.

*General experimental procedure for the synthesis of selenourea derivatives: Typical experimental procedure for the synthesis of **13b**:* To a solution of isopropyl cyclohexylamine **6f** (0.17 g, 1.23 mmol) and phosgene iminium chloride **5** (0.2 g, 1.23 mmol) in CH_3CN (2 ml) was added K_2CO_3 (0.12 g, 1.23 mmol) and the mixture was stirred for 5 min at 28 °C. To this mixture tetraselenotungstate **2** (1.1 equiv, 1.1 g, 1.48 mmol) was added and immediate colour change from maroon to black was observed. After stirring for 10 min at 28 °C, diethyl ether (3 ml) was added to the reaction mixture and filtered through a Celite pad. The black residue was extracted with CH_2Cl_2/Et_2O (1:9, 5× 20 ml) and filtered. The filtrate was concentrated and the crude product was purified by flash column chromatography on silica gel (230–400 mesh, elution with hexane/ethyl acetate 4:1) to furnish the selenourea derivative **13b** (0.26, 77%) as a viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.07 (qu, J_1 = 7.2 Hz, J_2 = 6.9 Hz, J_3 = 14.1 Hz, 1H), 3.66 (tt, J_1 = 3.6 Hz, J_2 = 8.4 Hz 1H), 3.18 (s, 6H), 1.96–1.67 (m, 6H), 1.38 (s, 3H), 1.35 (s, 3H), 1.26–1.32 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 223.1, 63.4, 53.2, 45.2, 32.0, 26.5, 25.8, 21.8; ^{77}Se NMR (76 MHz, $CDCl_3$): δ 453; HR-MS (*m*/*z*): Calculated for $C_{12}H_{24}N_2Se$ ($M+Na^+$): 299.1002; Observed ($M+Na^+$): 299.1002.

Acknowledgments

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13. CCDC numbers for compound **16a**: CCDC 642511, Compound **14b**: CCDC 642510, compound **12a**: CCDC 644845: Crystallographic data (excluding structure factors) for the structure in this paper have been deposited to the Cambridge Crystallographic Data Centre as supplementary publication. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk or via www.ccdc.cam.ac.uk/conts/.
14. The reason for the instability of compounds **9b**, **11b** and **12b** is not clear.
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17. The inhibitor solution (varied concentrations from 1 to 100 nm), urea (1 mM), cresol red (sodium salt and 50 mg/50 ml of buffer) and the buffer solution (Tris–Cl, 10 mM, pH 7.6) were taken in a test tube. The enzyme urease (3 nM) was added and the activity was measured at the zeroth minute and the measurements have been taken up to the 7th minute at regular intervals. All the solutions were kept in the incubator prior to the measurements. The OD measurements have been taken in triplicate by varying the concentration of the substrate and the inhibitors. The precise K_i value was derived from nonlinear least-squares fits of the data and the double reciprocal analysis (Dixon plot) established that the inhibitor was competitive.
It been reported that the urea derivatives are likely to be stabilized by coordination to the enzyme via neutral hydrogen bond donor than by coordination via one of the nickel ions.[19]
18. A few of the urea derivatives have not been tested for their activity due to their poor solubility in the buffer solution.
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