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Chalcogeno Ureas Derived from Bis(1,3-diazepan-2-ylidene)

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A series of new electron rich olefins (=$\overline{\mathrm{CNR(CH_2)_4NR}}$)$_2$, **3**, (**a**; R = $CH_2C_6H_5$, **b**; R = $CH_2C_6H_4$-OMe-*p*, **c**; R = $CH_2C_6H_4$-NMe_2-*p*) was generated via the condensation of $RNH(CH_2)_4NHR$ with $Me_2NCH(OMe)_2$. The C=C bond cleavage reactions of **3** with S_8 and Se provide a simple and straightforward method for the synthesis of 1,3-diazepan-2-chalcogenones **4** and **5,** respectively.

Key Words: Thio- and selenoureas, 1,3-diazepan derivatives, electron rich olefins

Introduction

Thioureas and their cyclic derivatives are an important class of compounds with a wide variety of applications. They are used as analytical reagents[1], flotation aids for sulfidic ores[2], complexing agents[1] and bath additives in electroplating processes[3]. Some of them exhibit biological activity[4] against bacteria, fungi and parasitic worms. Derivatives of imidazole-2-thiones are used to treat hyperthyroidism[5]. On the other hand, heterocycles containinig a selenium atom occupy a special place among organoselenium compounds[6].

Due to their broad spectrum of application, these compounds have received a great deal of attention in connection with their synthesis. Different synthetic routes to thio- and selenourea have been reported in the literature. They include: (i) condensation of polymethylenediamines, $RNH(CH_2)_mNHR$, with carbon disulfide in aqueous ethanol to form thiocarbamic acid intermediates, which are heated continuously to give thioureas[7]; (ii) treatment of *N*-heterocarbenes (NHCs) with chalcogens[8]; (iii) in situ use of a $HC(OEt)_3$, $RNH(CH_2)_mNHR$ mixture with Se to prepare selenoureas (m = 2 or 3)[9]; and (iv) the reaction of sulfur with cyclic formaldehyde aminals[10].

However, many of these methodologies are associated with some shortcomings, such as long reaction times, harsh reaction conditions, low product yields, occurrence of side products and lack of versatility. Moreover, some of the reagents employed are expensive. Although method (i) is a general one, the lengthening of the alkyl chain (m) between the N atoms and/or the branching of N-alkyl substituent on the diamines leads to a decrease in the cyclization tendency. For instance, the thiocarbamic acid intermediate of $RNH(CH_2)_4NHR$ (R = CH_3) failed to cyclize[10,11]. A simple and straightforward entry is therefore desirable.

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For our part, we developed the synthesis of 1,3-heterocyclic ureas via C=C bond cleavage of cyclic electron rich olefins (ero's) ($m = 2$ or 3) by dioxygen or chalcogens[12]. Following a similar synthetic approach based on a C=C cleavage reaction, we prepared a new series of benzyl substituted 1,3-diazepan-2-thio- and selenourea derivatives (Scheme 1). To the best of our knowledge this benzyl substituted 7-membered skeleton is not well known in the literature[13]. Nevertheless, a closed structure ($m = 4$, R = Me) was elaborated using another pathway by Lien and Kumler[14] and Li et al.[11].

Results and Discussion

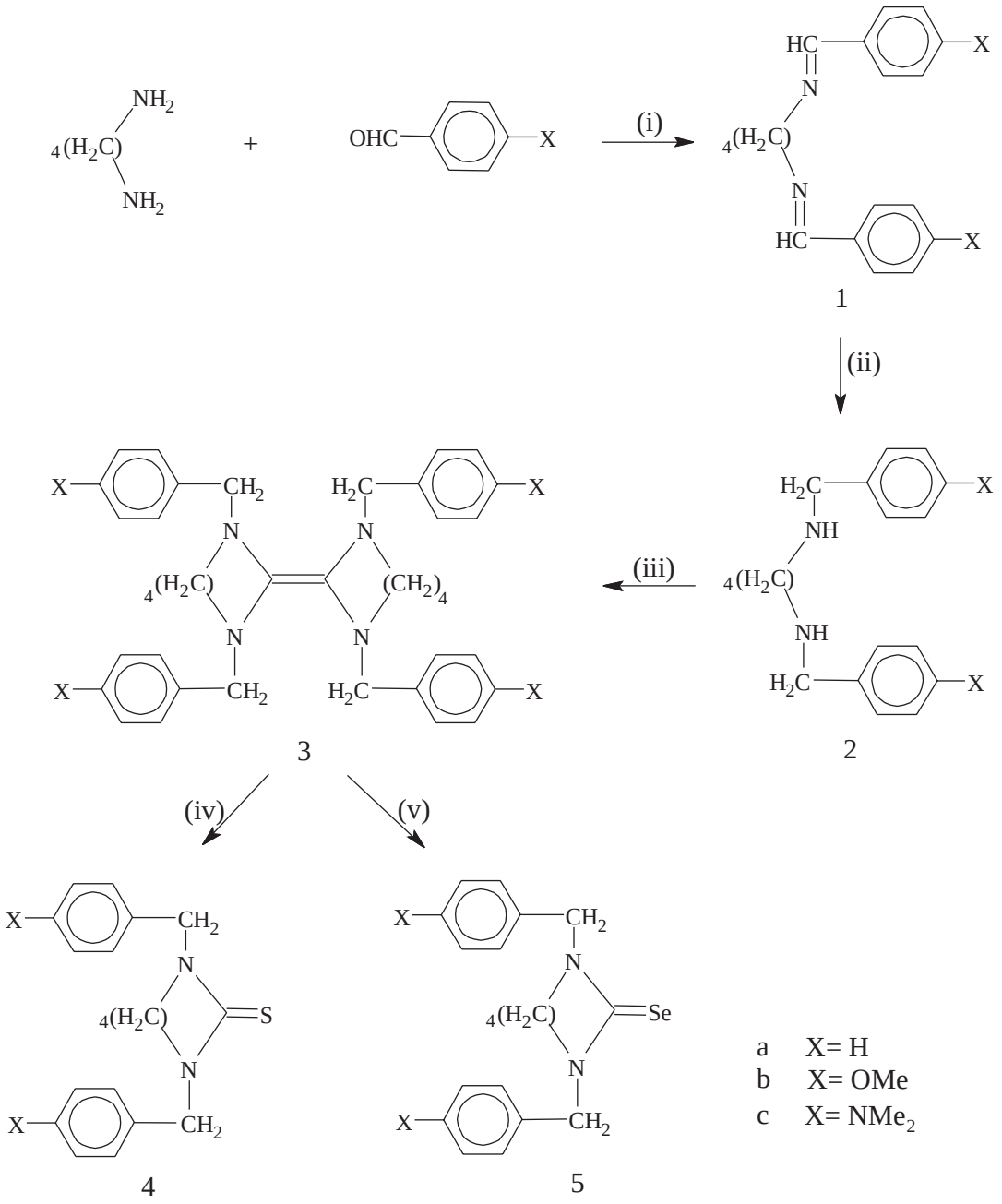
Although the ease of condensation of $Me_2NCH(OMe)_2$ with unhindered N, N'-dialkyldiamines, $RNH(CH_2)_m$ NHR, to give exocyclic ero's of the type $[=CN(R)(CH_2)_mNR]_2$ ($m = 2$ or 3) is well documented[15], very little is known about larger analogues, i.e. $m > 4$. A study to extend this condensation to N, N'-dialkyl-1,4-diamines for the preparation of **3** (R = benzyl or *p*-substituted benzyl) was initiated. Then the use of **3** was successfully employed to prepare cyclic chalcogenoureas **4** and **5**.

The synthesis of the desired compounds started from benzaldehyde or *p*-substituted benzaldehydes (Scheme 1). Following a standard protocol for the synthesis of symmetrical 1,4-diamines, the aldehydes were treated with 0.5 mol of 1,4-diaminobutane and the resulting Schiff bases were reduced with H_2/Pd in high yields. The amines obtained were then reacted with the acetal to afford ero's, **3**. Since the ero's are air- and moisture-sensitive, they were not characterized as it was not necessary. The final step involves the reaction of ero's with the chalcogens sulfur and selenium. The desired compounds **4** and **5** are colorless, air-stable crystalline solids. The elemental analyses and spectroscopic data are consistent with the proposed structures. Both thio- and selenoureas exhibit characteristic υ(C=S) and υ(C=Se) bands typically at 1490-1517 cm^{-1} that compare well with the 1510 cm^{-1} found for the 5-membered ureas. The ^1H NMR spectra exhibit pronounced chemical shifts for the benzylic protons at δ = 4.91-5.38 ppm. ^{13}C chemical shifts, which are a useful diagnostic tool for urea compounds, show that C=S (or C=Se) is substantially deshielded. Values of δ (C=S) are in the range 190-193 ppm and similar to those found for 5-membered urea analogues[12]. The final structural proof was obtained by single X-ray analysis of selenourea **5c**[13]. It is also worth noting that the identities of air-sensitive ero's (**3**) were firmly established by their conversion to the corresponding chalcogenones **4** and **5**.

Experimental

All reactions were performed using Schlenk-type flasks under argon and standard vacuum- line techniques. Solvents were analytical grade and distilled under argon from sodium benzophenone (toluene, hexane). FTIR spectra were recorded in the 4000-400 cm^{-1} region on a Matson-1000 spectrometer. Samples were prepared as KBr disks. ^1H and ^{13}C NMR spectra were recorded using a Varian 360 L or a Bruker AC spectrometer (250 MHz). *J*values are given in Hz. Melting points were recorded using an electrothermal melting point apparatus and are uncorrected.

Elemental analyses were performed by TÜBITAK (the Scientific and Technical Research Council of Turkey), Ankara. Commercial reagents were used as supplied and other reagents were prepared by literature methods.



Scheme 1. Synthesis of 1,3-diazepan-2-chalcogenones. Reaction conditions: (i) EtOH, 76 °C; (ii) Pd/C (5%), H_2; (iii) $CH(OMe)_2NMe_2$, 100-130 °C; (iv) S_8, toluene, 110 °C; (v) Se, toluene, 110 °C.

General procedure for the synthesis of 1,4-bis(*p*-substitutedbenzylideneamino) butane (1)

1,4-Diaminobutane (1.0 mmol) was added dropwise to *p*-substituted benzaldehyde (2.0 mmol) in 20 mL of absolute alcohol, and the mixture was heated under reflux. After 1 h, the clear solution was cooled to 25 °C. The light yellow crystals obtained were filtered off and washed with Et_2O (3 x 20 mL).

1,4-Bis(benzylideneamino)butane (1a) Yield: 65%, mp. 42-43 °C. ^{1}H-NMR ($CDCl_3$), δ: 1.65-1.85(m, 4H, (CH_2)$_4$), 3.52-3.72 (m, 4H, (CH_2)$_4$), 7.20-7.83 (m, 10H, C_6H_5), 8.26 (s, 2H, C*H*=N).

1,4-Bis(*p*-methoxybenzylideneamino)butane (1b) Yield: 92%, mp. 117-118 °C; found: C, 73.10; H, 6.74; N, 7.89; calcd: C, 74.07; H, 7.41; N, 8.64. ^{1}H-NMR ($CDCl_3$), δ: 1.78 (br s, 4H, (CH_2)$_4$), 3.62 (br s, 4H, (CH_2)$_4$), 3.83 (s, 6H, OCH_3), 6.87 (d, 4H, J = 8.2, C_6H_4), 7.71 (d, 4H, J = 8.2, C_6H_4), 8.20 (s, 2H, C*H*=N); ^{13}C-NMR ($CDCl_3$), δ: 29.4, 56.1 ((CH$_2$)$_4$), 62.24 (OCH$_3$), 115, 130.4, 130.7, 161.6 (C_6H$_4$), 162.8 (CH).

1,4-Bis(*p*-dimethylaminobenzylideneamino)butane (1c) Yield: 90%, mp. 132-133 °C; found: C, 75.70; H, 7.91; N, 16.05; calcd: C, 75.43; H, 8.56; N, 16.00. ^{1}H-NMR ($CDCl_3$), δ: 1.75 (br s, 4H, (CH_2)$_4$), 3.70 (br s, 4H, (CH_2)$_4$), 2.94 (s, 12H, N(CH_3)$_2$), 6.65 (d, 4H, J = 8.5, C_6H_4), 7.59 (d, 4H, J = 8.5, C_6H_4), 8.17 (s, 2H, C*H*); ^{13}C-NMR ($CDCl_3$), δ: 29.63, 62.35 ((CH$_2$)$_4$), 40.89 (NMe$_2$), 112.7, 125.7, 130.6, 153.2 (C_6H$_4$), 162.2 (CH).

General procedure for the synthesis of disecondary amines (2)

1,4-Bis(*p*-substitutedbenzylideneamino)butane, Pd/C (5%) and dry toluene were placed in a reactor and H_2 gas was applied at 340 psi pressure. Decantation at Pd/C was followed by distillation of the excess toluene. Oily residue was distilled under vacuum or recrystallized from toluene/n-hexane (5/10 mL).

1,4-Bis(benzylamino)butane (2a) Yield: 68%, bp. 140-145 °C (0.3 mmHg). ^{1}H-NMR ($CDCl_3$), δ: 1.32-1.54 (m, 4H, (CH_2)$_4$), 2.46-2.54 (m, 4H, (CH_2)$_4$), 1.96 (s, 2H, N*H*), 3.72 (s, 4H, C$H_2C_6H_5$), 7.16 (s, 10H, C_6H_5).

1,4-Bis(*p*-methoxybenzylamino)butane (2b) Yield: 80%, mp. 51-52 °C; found: C, 73.01; H, 9.74; N, 8.53; calcd: C, 73.17; H, 8.53; N, 8.53. ^{1}H-NMR ($CDCl_3$), δ: 1.58 (t, 4H, J = 6.2, (CH_2)$_4$), 2.63 (t, 4H, J = 6.2, (CH_2)$_4$), 1.30 (s, 2H, N*H*), 3.72 (s, 6H, OCH_3), 3.79 (s, 4H, C$H_2C_6H_5$), 6.86 (d, 4H, J = 8.5, C_6H_4), 7.23 (d, 4H, J = 8.5, C_6H_4); ^{13}C-NMR ($CDCl_3$), δ: 28.49, 49.92 ((CH$_2$)$_4$), 54.15 (CH$_2$C$_6$H$_5$), 62.24 (OCH$_3$), 115, 130.4, 130.7, 161.6 (C_6H$_4$).

1,4-Bis(*p*-dimethylaminobenzylamino)butane (2c) Yield: 66%, mp. 59-60 °C; found: C, 74.91; H, 9.64; N, 16.00; calcd: C, 74.57; H, 9.60; N, 15.81. ^{1}H-NMR ($CDCl_3$), δ: 1.56 (br s, 4H, (CH_2)$_4$), 2.65 (br s, 4H, (CH_2)$_4$), 1.55 (s, 2H, N*H*), 2.95 (s, 12H, NMe$_2$), 3.17 (s, 4H, C$H_2C_6H_5$), 6.74 (d, 4H, J = 8.4, C_6H_4), 7.21 (d, 4H, J = 8.4, C_6H_4); ^{13}C-NMR ($CDCl_3$), δ: 28.54, 49.94 ((CH$_2$)$_4$), 41.47 (NMe$_2$), 54.28 (CH$_2$C$_6$H$_5$), 113.8, 129.8, 130.3, 151.1 (C_6H$_4$).

General procedure for the generation of bis[(1,3-dialkyl)-1,3-diazepan-2-ylidene] (3)

A stirred solution of $N,N-$dimethylformamide dimethyl acetal (1.0 mmol) and N,N'-dialkyl-1,4-diaminobutane (1.0 mmol) in dry toluene (20 mL) was heated for 3 h at 90 °C under an argon atmosphere. The reaction mixture was then heated for 1 h at 120 °C under distillation conditions, allowing the produced dimethylamine and methanol to escape. From the resultant product, unreacted starting materials were eliminated in vacuo. The white solid was recrystallized from a mixture of toluene (5 mL) and *n*-hexane (10

mL) at –20 °C. However, the ero's obtained in this study could not be characterized by elemental analyses or NMR spectroscopy due to their air sensitivity.

General procedure for the synthesis of 1,3-dialkyl-1,3-diazepan-2-thione (4)

A mixture of **3** (1.0 mmol) and sulfur S_8 (2.0 mmol) in toluene was heated under reflux for 2 h. Then the mixture was cooled to room temperature and filtered to remove unreacted sulfur and volatiles were removed in vacuo (0.01 mmHg). The crude solid was crystallized from toluene/n-hexane (1/2) upon cooling to –20 °C.

1,3-Dibenzyl-1,3-diazepan-2-thione (4a) Yield: 60%, mp. 105-106 °C; ν_{CS} (cm^{-1}): 1490.8; found: C, 71.17; H, 8.24; N, 8.97; S, 10.02 calcd: C, 73.53; H, 7.14; N, 9.02; S, 10.33. ^{1}H-NMR ($CDCl_3$), δ: 1.43 (br s, 4H, (CH_2)$_4$), 3.32 (br s, 4H, (CH_2)$_4$), 5.18 (s, 4H, $CH_2C_6H_5$), 7.28-7.41 (m, 10H, C_6H_5); ^{13}C-NMR ($CDCl_3$), δ: 24.9, 52.5((CH$_2$)$_4$), 59.3 (CH$_2$C$_6$H$_5$), 127.4, 128.4, 128.5, 137.8 (C_6H_5), 193.2 (C=S).

[1,3-di(*p*-methoxybenzyl)]-1,3-diazepan-2-thione (4b) Yield: 79%, mp. 137-138 °C; ν_{CS} (cm^{-1}): 1510.1; found: C, 67.85; H, 5.99; N, 7.44; S, 8.22; calcd: C, 68.08; H, 7.07; N, 7.56; S, 8.65. ^{1}H-NMR ($CDCl_3$), δ: 1.38 (br s, 4H, (CH_2)$_4$), 3.26 (br s, 4H, (CH_2)$_4$), 3.78 (s, 6H, OCH_3), 4.96 (s, 4H, $CH_2C_6H_5$), 6.85 (d, 4H, J = 8.6, C_6H_4), 7.32 (d, 4H, J = 8.6, C_6H_4); ^{13}C-NMR ($CDCl_3$), δ: 25, 52.3 ((CH$_2$)$_4$), 58.6 (CH$_2$C$_6$H$_5$), 55.2 (OCH$_3$), 113.9, 129.8, 129.9, 159 (C_6H_4), 193 (C=S).

[1,3-(*p*-dimethylaminobenzyl)]-1,3-diazepan-2-thione (4c) Yield: 67%, mp. 155-156 °C; ν_{CS} (cm^{-1}): 1523.6; found: C, 68.62; H, 7.62; N, 14.11; S, 7.26; calcd: C, 69.66; H, 8.14; N, 14.14; S, 8.07. ^{1}H-NMR ($CDCl_3$), δ: 1.33 (br s, 4H, (CH_2)$_4$), 3.24 (br s, 4H, (CH_2)$_4$), 2.90 (s, 12H, NMe_2), 4.91 (s, 4H, $CH_2C_6H_5$), 6.66 (d, 4H, J = 8.4, C_6H_4), 7.25 (d, 4H, J = 8.4, C_6H_4); ^{13}C-NMR ($CDCl_3$), δ: 25.1, 43.5 ((CH$_2$)$_4$), 52.2 (NMe_2), 58.6 (CH$_2$C$_6$H$_5$), 112.4, 125.4, 129.6, 150 (C_6H_4), 192.5 (C=S).

General procedure for the synthesis of 1,3-dialkyl-1,3-diazepan-2-selenone (5)

Bis[1,3-dialkyl)-1,3-diazepan-2-ylidene], **3**, (1.0 mmol) was heated with elemental selenium (2.0 mmol) in refluxing toluene (20 mL) for 2 h. The resulting solution was cooled to room temperature and then filtered to remove the excess selenium. The volume of the filtrate was reduced to ca. 10 mL and *n*-hexane (10 mL) was added. Upon cooling the solution to –20 °C cream crystals of the title compound were obtained.

1,3-dibenzyl-1,3-diazepan-2-selenone (5a) Yield:60%, mp. 101-102 °C; ν_{CSe} (cm^{-1}): 1504.3; found: C, 65.43; H, 5.00; N, 8.04; calcd: C, 63.87; H, 6.19; N, 7.82. ^{1}H-NMR ($CDCl_3$), δ: 1.42 (br s, 4H, (CH_2)$_4$), 3.34 (br s, 4H, (CH_2)$_4$), 5.20 (s, 4H, $CH_2C_6H_5$), 7.27-7.42 (m, 10H, C_6H_5); ^{13}C-NMR ($CDCl_3$), δ: 24.0, 52.5((CH$_2$)$_4$), 62 (CH$_2$C$_6$H$_5$), 127.6, 128.5, 128.6, 137.2 (C_6H_5), 192 (C=Se).

[(1,3-di(*p*-methoxybenzyl)]-1,3-diazepan-2-selenone (5b) Yield: 65%, mp.133-134 °C; ν_{CSe} (cm^{-1}): 1510.1; found: C, 60.50; H, 6.08; N, 6.80; calcd: C, 60.27; H, 6.27; N, 6.70. ^{1}H-NMR ($CDCl_3$), δ: 1.39 (br s, 4H, (CH_2)$_4$), 3.30 (br s, 4H, (CH_2)$_4$), 3.79 (s, 6H, OCH_3), 5.12 (s, 4H, $CH_2C_6H_4$), 6.86 (d, 4H, J = 8.5, C_6H_4), 7.34 (d, 4H, J = 8.5, C_6H_4); ^{13}C-NMR ($CDCl_3$), δ: 24.3, 52.5 ((CH$_2$)$_4$), 61.4 (CH$_2$C$_6$H$_5$), 55.29 (OCH$_3$), 114.0, 129.3, 129.8, 159.8 (C_6H_4), 192 (C=Se).

Conclusion

In summary, the following conclusions can be drawn from this study:

(i) The novel ero's, bis[(1,3-dialkyl)-1,3-diazepan-2-ylidene] (**3**), are accessible via a condensation reaction between $Me_2NCH(OMe)_2$ and N,N'-dialkyldiamines, $RNH(CH_2)_4NHR$.

(ii) The C=C bond cleavage reactions represent a simple and high yielding route to 1,3-diazepan-2-chalcogenones with various benzyl substituents on the N atoms and thus are suitable for the preparation of a wide variety of derivatives.

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