Reaction of Substituted Selenoureas with Dimethyl Acetylenedicarboxylate (1)

A. Shafiee, F. Assadi

Department of Chemistry, College of Pharmacy, Tehran University, Tehran, Iran

and

V. I. Cohen

Department of Chemistry, Sciences Faculty, Ferdosi University, Mashhad, Iran

Received July 27, 1977

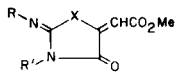
Mono and 1,3-disubstituted selenoureas react with dimethyl acetylenedicarboxylate to give in high yield substituted 3,4-dihydro-4-oxo-2*H*-1,3-selenazines whose structures were established by spectroscopic methods.

J. Heterocyclic Chem., 15, 39 (1978)

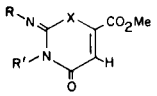
In continuation of our study on the chemistry of selenium heterocyclic compounds (2-5) and in view of their possible pharmacological activity (6,7), we have studied the reaction of substituted selenoureas with dimethyl acetylenedicarboxylate (DMAD).

Reaction of DMAD with substituted thioureas has been claimed to give thiazolidines (I, X = S) (8). However, the correct structure was later shown to be the substituted 3,4-dihydro-4-oxo-2*H*-1,3-selenazines (II, X = S) (9,10).

Reaction of thiobenzamide with DMAD was also shown to give methyl 2-phenyl-4-oxo-4*H*-1,3-thiazine-6-carboxlate (11).

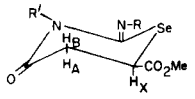


I, X = S, Se

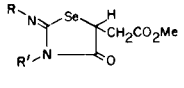


II, X = S, Se

1,3-Dimethylselenoureas reacted with one mole of DMAD in methanol giving a colorless crystalline compound, $C_8H_{10}N_2O_3Se$, in 90% yield; ir (potassium bromide): 1705 (ester), 1655 cm^{-1} (amide). The nmr spectrum showed a singlet at δ 7.30 (1H, ethylenic), 3.90 (3H, OCH_3), 3.39 and 3.36 ppm (6H, NCH_3). These data are consistent with either structure I (X = Se, R = R′ = Me) or II (X = Se, R = R′ = Me) which are both possible on mechanistic grounds. The adduct absorbed 1 mole of hydrogen on hydrogenation over 10% palladium on charcoal, giving a white solid, $C_8H_{12}N_2O_3Se$. The ir spectrum exhibited an ester and an amide absorption. The nmr spectrum, in addition to two *N*-methyl and one *O*-methyl groups, exhibited a new ABX pattern with coupling constant of J_{AX} = 4, J_{BX} = 11 and J_{AB} = 17 Hz. These data are consistent with structure III (R = R′ = Me) shown below.



III



IV

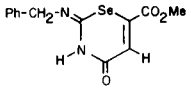
The observation of J_{BX} with a coupling constant of 11 Hz, resulting from fully trans coupling between the two adjacent hydrogens precludes structure IV (R = R′ = Me) for the compound resulting from hydrogenation.

The mass spectrum fragmentation pattern of compound II (X = Se, R = R′ = Me) and III (R = R′ = Me) is in good agreement with the suggested structure II (X = Se, R = R′ = Me) for the adduct.

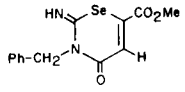
In addition, it was recently reported that the reaction of DMAD with 2-aminobenzothiazole gave only methyl 2-oxopyrimido[2,1-*b*]benzothiazole-4-carboxylate whose structure was confirmed by X-ray analysis (12). This result is also in a good agreement with our finding.

Reaction of 1,3-diarylselenoureas with one mole of DMAD gave also methyl 2-arylimino-3-aryl-3,4-dihydro-4-oxo-2*H*-1,3-selenazines (II, X = Se, R = R′ = aryl).

The reaction of monosubstituted thioureas with DMAD was reported to give methyl 2*H*-3-alkyl(or aryl)imino-1,3-thiazine-6-carboxylates (10). Reaction of 1-benzylselenourea with one mole of DMAD gave one compound whose ir and mass spectrum were consistent with either structure V or VI. However, the nmr spectrum was in favor of structure V.

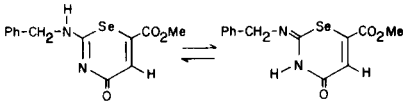


V



VI

In dimethylsulfoxide the benzylic protons appeared as a doublet at 4.82 ppm which was collapsed to a singlet by the deuterium oxide addition. This fact demonstrates that the adduct exist as Va and Vb in solution.



Vb Va

The structure elucidation of all substituted methyl 3,4-dihydro-4-oxo-2*H*-1,3-selenazines were done by analytical and spectroscopic methods and in the case of a known compound by comparison with an authentic sample (13).

The physical data of all the compounds prepared are summarized in Table I.

Table I

R	R′	M.p. °C (a)	Yield %	Formula	C%		H%		N%	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
$C_6H_5CH_2$-	H	213-215	70	$C_{13}H_{12}N_2O_3Se$	48.30	48.45	3.72	3.91	8.67	8.58
C_6H_5-	H	215-216	90	$C_{12}H_{10}N_2O_3Se$	46.60	46.52	3.24	3.35	9.06	9.25
p-ClC_6H_4-	H	244-246	95	$C_{12}H_9ClN_2O_3Se$	41.92	41.75	2.62	2.81	8.15	8.02
p-BrC_6H_4-	H	237-240	93	$C_{12}H_9BrN_2O_3Se$	37.11	37.02	2.32	2.11	7.22	7.05
p-$CH_3C_6H_4$-	H	232-234	94	$C_{13}H_{12}N_2O_3Se$	48.30	48.15	3.72	3.90	8.67	8.52
p-$CH_3OC_6H_4$-	H	230-232	96	$C_{13}H_{12}N_2O_4Se$	46.02	46.15	3.54	3.71	8.26	8.41
p-$C_2H_5OC_6H_4$-	H	245-247	87	$C_{14}H_{14}N_2O_4Se$	47.59	47.68	3.97	3.99	7.93	8.07
CH_3-	CH_3-	159-160	90	$C_8H_{10}N_2O_3Se$	36.78	36.96	3.83	3.95	10.73	10.55
C_6H_5-	C_6H_5-	115-117	70	$C_{18}H_{14}N_2O_3Se$	56.10	56.26	3.64	3.47	7.27	7.39
p-ClC_6H_4-	p-ClC_6H_4	128-130 (b)	65	$C_{18}H_{12}Cl_2N_2O_3Se$	47.58	47.74	2.64	2.79	6.17	6.34
p-BrC_6H_4-	p-BrC_6H_4-	118-120 (b)	68	$C_{18}H_{12}Br_2N_2O_3Se$	39.78	39.63	2.21	2.04	5.16	5.33
p-$CH_3C_6H_4$-	p-$CH_3C_6H_4$-	134-136 (b)	80	$C_{20}H_{18}N_2O_3Se$	58.11	58.30	4.36	4.52	6.78	6.62
p-$CH_3OC_6H_4$-	p-$CH_3OC_6H_4$-	68-70 (b)	75	$C_{20}H_{18}N_2O_5Se$	53.93	53.81	4.04	4.21	6.29	6.37
p-$C_2H_5OC_6H_4$-	p-$C_2H_5OC_6H_4$-	93-95 (b)	70	$C_{22}H_{22}N_2O_5Se$	55.81	55.98	4.65	4.47	5.92	6.09

(a) All compounds, unless otherwise mentioned, were crystallized from methanol. (b) This compound was crystallized from ether-petroleum ether.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and are uncorrected. The ir spectra were obtained on a Perkin-Elmer Model 267 spectrograph. Nmr spectra were determined using a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian MAT-311 spectrometer at 70 eV.

Reaction of Selenourea with Dimethyl Acetylenedicarboxylate.

To a solution of selenourea (246 mg., 2 mmoles) in 30 ml. of methanol a solution of dimethyl acetylenedicarboxylate (284 mg., 2 mmoles) in 1 ml. of methanol was added. After 10 minutes the precipitate was filtered to give methyl 2-imino-3,4-dihydro-4-oxo-2*H*-1,3-selenazine-6-carboxylate (II, X = Se, R = R′ = H, 443 mg., 95%)(13); m.p. 254-256°; ir (potassium bromide): 3210 (amine), 1690 (ester), 1655 cm^{-1} (amide); nmr (trifluoroacetic acid): 7.70 (s, 1H, ethylenic), 4.10 (s, 3H, OCH_3); mass spectrum m/e (%): 234 (M^+, 50), 192 (100), 164 (67), 105 (48), 64 (43) and 59 (93).

Anal. Calcd. for $C_6H_6N_2O_3Se$: C, 30.90; H, 2.58; N, 12.02. Found: C, 30.75; H, 2.39; N, 12.19.

Acetylation of Methyl 2-Imino-3,4-dihydro-4-oxo-2*H*-1,3-selenazine-6-carboxylate (II, X = Se, R = R′ = H).

A solution of 234 mg. of II (X = Se, R = R′ = H; 1 mmole) in 5 ml. of acetic anhydride was refluxed for 6 hours. After cooling the precipitate was filtered to give methyl 2-acetylimino-3,4-dihydro-4-oxo-2*H*-1,3-selenazine-6-carboxylate (II, X = Se, R = CH_3CON, R′ = H; 80%); m.p. 277-279°; ir (potassium bromide): 1715 (ester), 1690 cm^{-1} (amide); nmr (trifluoroacetic acid): 7.66 (s, 1H, ethylenic), 4.07 (s, 3H, OCH_3), and 2.60 ppm (s, 3H, CH_3CO); ms m/e (%): 276 (M^+, 28), 261 (24), 192 (31), 164 (32), 69 (27), 59 (30), 43 (100).

Anal. Calcd. for $C_8H_8N_2O_4Se$: C, 34.91; H, 2.91; N, 10.18. Found: C, 34.83; H, 2.75; N, 10.29.

Reaction of 1,3-Dimethylselenoureas with Dimethyl Acetylenedicarboxylate.

To a solution of 1,3-dimethylselenourea (151 mg., 1 mmole) in 20 ml. of methanol, dimethyl acetylenedicarboxylate (142 mg., 1 mmole) in 1 ml. of methanol was added. It was allowed to stand at room temperature for 2 hours and the precipitate was filtered to give 236 mg. of methyl 2-methylimino-3-methyl-3,4-dihydro-4-oxo-2*H*-1,3-selenazine-6-carboxylate (II, X = Se, R = R′ = CH_3, 90%); m.p. 159-160°; ir (potassium bromide): 1705 (ester), 1655 cm^{-1} (amide); nmr (deuteriochloroform): 7.30 (s, 1H, ethylenic), 3.90 (3H, OCH_3), 3.39 (s, 3H, NCH_3) and 3.36 ppm (s, 3H, NCH_3); ms m/e (%): 262 (M^+, 100), 260 (28), 221 (5), 203 (10), 192 (91), 190 (45), 164 (65), 134 (7), 133 (12), 113 (11), 106 (4), 105 (12) and 103 (17).

Anal. Calcd. for $C_8H_{10}N_2O_3Se$: C, 36.78; H, 3.83; N, 10.73. Found: C, 36.96; H, 3.95; N, 10.55.

Methyl 2-Phenylimino-3-phenyl-3,4-dihydro-4-oxo-2*H*-1,3-selenazine-6-carboxylate (II, X = Se, R = R′ = Ph).

To a solution of 1,3-diphenylselenourea (275 mg., 1 mmole) in 30 ml. of methanol, dimethyl acetylenedicarboxylate (142 mg., 1 mmole) in 1 ml. of methanol was added. The mixture was allowed to stand at room temperature for a week. The solvent was evaporated and the residue was purified by tlc (silica gel, $CHCl_3$) and crystallized from methanol to give 270 mg. (70%) of II (X = Se, R = R′ = C_6H_5); m.p. 115-117° (ethanol); ir (potassium bro-

mide): 1695 (ester), 1632 cm^{-1} (amide); nmr (deuteriochloroform): 7.57-6.83 (m, 11H, aromatic and ethylenic), 3.83 ppm (s, 3H, OCH_3); ms m/e (%): 386 (M^+, 22), 267 (13), 195 (18), 194 (100), 91 (25), 77 (52), 59 (11), 51 (26), and 39 (10).

Anal. Calcd. for $C_{18}H_{14}N_2O_3Se$: C, 56.10; H, 3.64; N, 7.27. Found: C, 56.26; H, 3.47; N, 7.39.

Other methyl 2-arylimino-3-aryl-3,4-dihydro-4-oxo-2*H*-1,3-selenazine-6-carboxylates were prepared similarly (See Table I).

Hydrogenation of Methyl 2-Methylimino-3-methyl-3,4-dihydro-4-oxo-2*H*-1,3-selenazine-6-carboxylate (II, X = Se, R = R′ = CH_3).

A solution of II (X = Se, R = R′ = CH_3, 261 mg., 1 mmole) in 150 ml. of ethyl acetate was hydrogenated over *ca.* 200 mg. of 10% palladium on charcoal overnight. The solution was filtered through celite to remove the catalyst, and the solvent was evaporated under reduced pressure. The tlc of the residue showed to be a mixture of starting material and the product which were separated by preparative tlc (silica gel, chloroform: petroleum ether; 1:1). The product was crystallized from methanol to give III (R = R′ = CH_3, 158 mg., 60%); m.p. 58-60°; ir (potassium bromide): 1725 (ester), 1692 cm^{-1} (amide); nmr (deuteriochloroform): 4.47 (q, 1H, *CH*COOMe, J_{AX} = 4 Hz, J_{BX} = 11 Hz), 3.72 (s, 3H, OCH_3), 3.33-2.77 (m, 2H, CH_2-CO, part AB of ABX pattern, J_{AB} = 17 Hz), 3.20 (s, 3H, NCH_3) and 3.12 ppm (s, 3H, NCH_3); ms m/e (%): 264 (M^+, 45), 233 (18), 204 (15), 150 (22), 121 (6), 112 (16), 71 (100), 70 (15), 58 (28), 55 (18), 42 (28).

Anal. Calcd. for $C_8H_{12}N_2O_3Se$: C, 36.50; H, 4.56; N, 10.65. Found: C, 36.35; H, 4.73; N, 10.51.

Methyl 2-Benzylimino-3,4-dihydro-4-oxo-2*H*-1,3-selenazine-6-carboxylate (V).

To a solution of 1-benzylselenourea (213 mg., 1 mmole in 20 ml. of methanol, dimethyl acetylenedicarboxylate (142 mg., 1 mmole) in 1 ml. of methanol was added. After one hour the precipitate was filtered to give V (226 mg., 70%); m.p. 213-215°; ir (potassium bromide): 1680 (ester), 1635 cm^{-1} (amide); nmr (dimethylsulfoxide-d_6): 9.90 (broad s, 1H, NH), 7.47 (s, 5H, C_6H_5), 7.10 (s, 1H, ethylenic), 4.87 (d, 2H, CH_2, collapsed to a singlet with deuterium oxide) and 3.87 ppm (s, 3H, OCH_3); nmr (trifluoroacetic acid): 7.60 (s, 1H, ethylenic), 7.47 (s, 5H, C_6H_5), 4.88 (s, 2H, CH_2) and 4.03 ppm (s, 3H, OCH_3); mass spectrum m/e (%): 324 (M^+, 15), 192 (8), 164 (10), 131 (11), 119 (7), 91 (100), 69 (23) and 65 (26).

Anal. Calcd. for $C_{13}H_{12}N_2O_3Se$: C, 48.30; H, 3.72; N, 8.67. Found: C, 48.45; H, 3.91; N, 8.58.

Methyl 2-Phenylimino-3,4-dihydro-4-oxo-2*H*-1,3-selenazine-6-carboxylate (II, X = Se, R = Ph, R′ = H).

This compound was prepared similarly; m.p. 215-216°; ir (potassium bromide): 1690 (ester), 1655 cm^{-1} (amide): nmr (dimethylsulfoxide-d_6): 8.0-7.0 (m, 6H, Ph and ethylenic) and 3.82 ppm (s, 3H, OCH_3); ms m/e (%): 310 (M^+, 39), 192 (40), 164 (33), 118 (100), 91 (25), 77 (24), 59 (23), 51 (17) and 39 (16).

Anal. Calcd. for $C_{12}H_{10}N_2O_3Se$: C, 46.60; H, 3.24; N, 9.06. Found: C, 46.52; H, 3.35; N, 9.25.

Other methyl 2-arylimino-3,4-dihydro-4-oxo-2*H*-1,3-selenazine-6-carboxylates were prepared similarly (See Table I).

Hydrogenation of Methyl 2-Phenylimino-3,4-dihydro-4-oxo-2*H*-1,3-selenazine-6-carboxylate (II, X = Se, R = Ph, R′ = H).

A solution of II (X = Se, R = Ph, R′ = H, 309 mg., 1 mmole) in 150 ml. of ethyl acetate was hydrogenated over *ca.* 200 mg. of 10% palladium on charcoal overnight. The solution was filtered through celite and the solvent was evaporated under reduced pressure. The residue was purified by tlc (silica gel, chloroform: petroleum ether; 1:1). The product was crystallized from ethanol to give III (R = C_6H_5, R′ = H, 225 mg., 70%); m.p. 136-138°; nmr (deuteriochloroform): 7.57-7.00 (m, 5H, C_6H_5), 4.50 (q, 1H, *H*C-CO OMe, J_{AX} = 4 Hz, J_{BX} = 11 Hz), 3.70 (s, 3H, OCH_3), and 3.47-2.57 ppm (m, 2H, *CH*2-CO, AB part of ABX, J_{AB} = 18.5 Hz); ms m/e (%): 312 (M^+, 44), 281 (8), 252 (4), 194 (9), 166 (26), 119 (100), 118 (93), 90 (33), 77 (28).

Acknowledgment.

This work was supported by a grant from Research Development Council of Tehran University.

REFERENCES AND NOTES

(1) A preliminary account of the work was presented in the 6th International Congress of Heterocyclic Chemistry, Tehran, Iran, July 1977.

(2) I. Lalezari, A. Shafiee and M. Yalpani, *Tetrahedron Letters*, 5105 (1969).

(3) I. Lalezari, A. Shafiee, and M. Yalpani, *J. Org. Chem.*, **38**, 338 (1973).

(4) A. Shafiee and I. Lalezari, *J. Heterocyclic Chem.*, **12**, 675 (1975): *ibid.*, **8**, 1011 (1971).

(5) I. Lalezari and A. Shafiee, *ibid.*, **8**, 835 (1971).

(6) A. Shafiee, I. Lalezari, S. Yazdani and A. Pounorouz, *J. Pharm. Sci.*, **62**, 839 (1973).

(7) I. Lalezari, A. Shafiee and S. Yazdani, *ibid.*, **63**, 628 (1974).

(8) L. K. Mushkalo and G. YA. Yangol, *Ukr. Khim. Zh.*, **21**, 732 (1955); *Chem. Abstr.*, 50 (1956).

(9) E. Winterfeldt and J. M. Nelke, *Chem. Ber.*, **100**, 3671 (1967).

(10) J. W. Lown and J. C. N. Ma, *Can. J. Chem.*, **45**, 939 (1967).

(11) C. M. Hall, The Abstracts of the Vth International Congress of Heterocyclic Chemistry, Ljublajana, Yugoslavia, July, 1975, p. 353.

(12) C. K. Chan, J. C. N. Ma and T. C. W. Mak, *J. Chem. Soc., Perkin Trans. II*, 1070 (1977).

(13) E. G. Kataev, L. K. Konovalova, and E. G. Yarkova, *Zh. Org. Khim.*, **5**, 621 (1969); *Chem. Abstr.*, **71**, 21668e (1969).