Nucleophilic Substitution of 1,2,4-Triazines [1]

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The reaction of 3-(methylthio)-5-carbethoxy-1,2,4-triazine (**5**) with ammonia was found to yield products from not only ammonia but also methanethiolate displacements. An account of the transformations and the products observed is given. The 3-position of 3,6-bis(methylthio)-5-carbamoyl-1,2,4-triazine (**7**) was shown to be more reactive than the 6-position toward nucleophilic substitution. Reduction at the 4,5 positions of triazine **5** occurred upon treatment with methanethiol under basic and neutral conditions.

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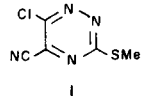
The reactions of the 1,2,4-triazine system toward nucleophiles have been studied by some groups [3], and it has been found that the positional reactivity of this π-deficient heteroaromatic system is dependent on the nature of the reagent and the reaction conditions [4].

The isomeric triazines **1** and **2** were recently synthesized and shown to be readily hydrolyzed to yield **3** and **4**, respectively [5]. These results indicate that the 5-position, being *para* to a ring nitrogen, is the most reactive site. In order to investigate the reactivity of the remaining 3- and 6-positions, the 5-carbethoxy derivative **5** [5] was reacted with a number of different nucleophiles. This paper describes these interesting findings.



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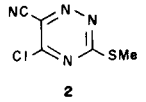

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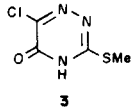

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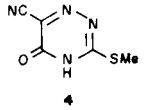

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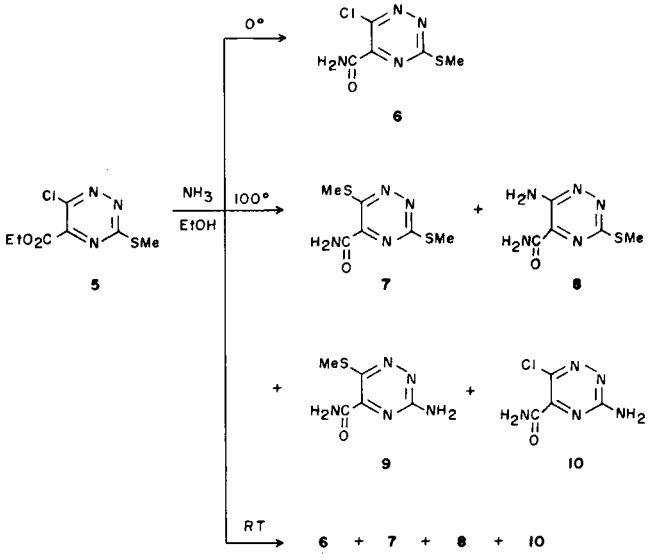
Reaction of **5** with the simplest amine, ammonia, was performed at different temperatures. At 0°, only the ester function, as expected, was affected by ammonia to yield the corresponding 5-carbamoyl derivative **6**. At 100°, four products **7-10** were isolated. At room temperature, compounds **6-8,10** were formed (Scheme I).

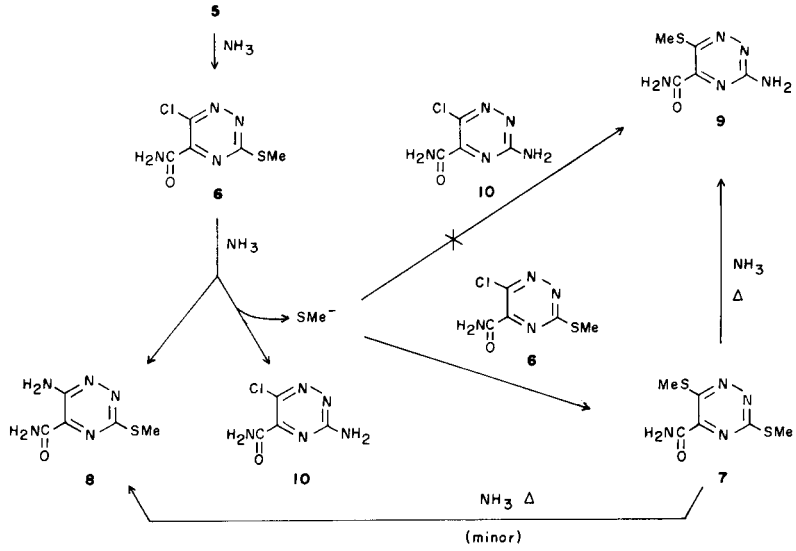
The two isomeric amino-methylthio derivatives **8** and **9** could be readily differentiated by the SCH_3 protons located at the 3-position in **8**, resonating at δ 2.59 and at the 6-position in **9** appearing at a higher field δ 2.48 (both in perdeuteriodimethylsulfoxide). The electron-impact mass spectral fragments $H_2N\text{-}C\equiv C\text{-}CONH_2$ (m/z 84, 100%) and $H_2N\text{-}C\equiv C\text{-}C\equiv O$ (m/z 68, 51%) support the structure of compound **8** having the NH_2 substituent at the 6-position (see Experimental). Similarly, the fragments $CH_3S\text{-}C\equiv C\text{-}CONH_2$ (m/z 115, 44%) and $CH_3S\text{-}C\equiv C\text{-}C\equiv O$ (m/z 99, 58%) support the structure of **9** with the SCH_3 group at the 6-position. Chemically, the structure for **9** was evident by the reaction of 3-amino-6-chloro-5-carbamoyl-1,2,4-triazine (**10**) with sodium methanethiolate that unambiguously gave the corresponding 6-methylthio triazine **9**. It is noteworthy that in compound **7** the methylthio protons at the 3-position are shifted upfield from δ 2.67 to 2.59 in **8** by 0.08 ppm and at the 6-position are shifted from 2.55 to 2.48 in **9** by 0.07 ppm when a *para* methylthio substituent of **7** is replaced by NH_2. It deserves mentioning that all the above 5-carbamoyl triazines **6-10** show mass spectral fragments of $X\text{-}C\equiv C\text{-}CONH_2$ (X = Cl, SCH_3, NH_2) and $X\text{-}C\equiv C\text{-}C\equiv O$ resulting from rupture of the N(1)-C(6) and N(4)-C(5) bonds.

Scheme I



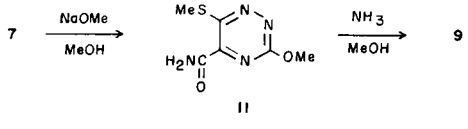
Reaction of the 3,6-bis(methylthio) derivative **7** with ammonia at room temperature after 24 hours mainly gave the unreacted starting material; at 100°, however, this reaction was found to give the 3-amino derivative **9** and a minor amount of the 6-amino isomer **8**, suggesting that the 3-position is more reactive than the 6-position toward amination. Thus in the reaction of 3-(methylthio)-5-carb-

Scheme II



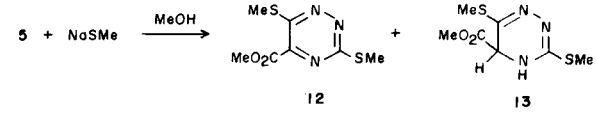
ethoxy-6-chloro-1,2,4-triazine (**5**) with ammonia it could be envisioned that 3-amino-5-carbamoyl-6-chloro-1,2,4-triazine (**10**) is formed initially; the leaving methylthio group then attacks at the 6-position and displaces the chloro substituent of the 3-(methylthio)-6-chloro compound **6**, rather than the existing 3-amino-6-chloro compound **10**, to give the 3,6-bis(methylthio) derivative **7**. This preferential displacement may be rationalized in terms of a *para* amino group being a stronger electron-donating substituent than an alkylthio substituent in the resonance effect as is evident in the nmr spectral analysis of compounds **7-8**; thus the amino group severely decreases the susceptibility of the 6-position toward the incoming nucleophile. One can conclude that the 3-amino-6-(methylthio) compound **9** must be derived from the reaction of the 3,6-bis(methylthio) compound **7** with ammonia, and that the formation of the 3-(methylthio)-6-amino compound **8** is the combined result of this pathway and more importantly the displacement reaction of the 6-chloro substituent of **6** by ammonia (Scheme II).

Reaction of 3,6-bis(methylthio)-5-carbamoyl-1,2,4-triazine (**7**) with excess sodium methoxide gave only the 3-substituted product **11**. This finding with respect to positional reactivity is consistent with that observed in the ammonia reaction. The structure for the 3-methoxy product **11** was



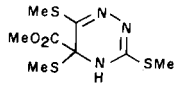
suggested by the presence of mass spectral fragments of $CH_3S\text{-}C\equiv C\text{-}CONH_2$ (m/z 115, 45%) and $CH_3S\text{-}C\equiv C\text{-}C\equiv O$ (m/z 99, 66%) accompanied by S_{34} isotope peaks, and confirmed by its conversion to the known 3-amino-5-carbamoyl-6-(methylthio)-1,2,4-triazine (**9**) upon reaction with ammonia.

Treatment of 3-(methylthio)-5-carbethoxy-6-chloro-1,2,4-triazine (**5**) with methanolic sodium methanethiolate gave 3,6-bis(methylthio)-5-carbomethoxy-1,2,4-triazine (**12**). Interestingly, excess methanethiolate gave additionally a reduction product **13** as suggested by the elemental analysis



and mass spectrometric molecular weight. The ^{1}H-nmr spectrum of this compound in deuteriochloroform solution revealed five singlets at δ 2.38, 2.50, 3.76, 4.84 and 7.9 (broad), respectively, with an intensity ratio of 3:3:3:1:1. Clearly, the three-proton peak at δ 3.76 is ascribed to the carbomethoxy protons. The two peaks at δ 2.38 and 2.50 are due to the two methylthio groups at the 6- and 3-positions, respectively; they were at somewhat higher fields than δ 2.68 and 2.71 in the corresponding heteroaromatic compound **12**. The δ 4.84 signal was assigned to the proton on C-5 of the triazine ring on the grounds that addition of a proton on C-3 or C-6 would have shifted the methylthio group attached to the resulting sp^3 carbon to a higher field than observed. The remaining one-proton signal was therefore assigned to NH at the 4-position [6].

The formation of the dihydro derivative **13** presumably involves initial covalent addition of methanethiol to form the intermediate **14**, in which the methylthio substituent



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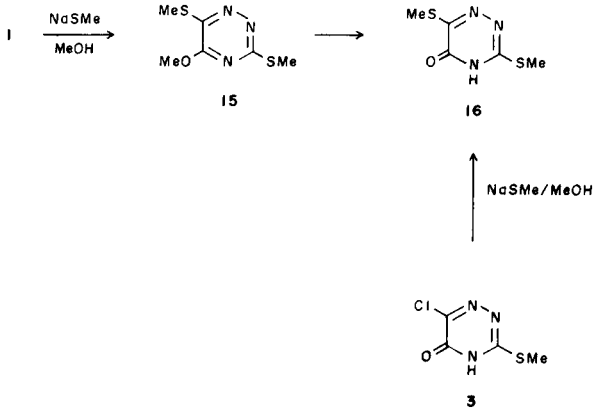
at the 5-position is then attacked by another methanethiolate nucleophile to form dimethyl disulfide and the final dihydro product after abstracting a proton from the solvent [7]. Direct reaction of **12** with methanethiolate at room temperature or with neutral methanethiol at an elevated temperature successfully gave the reduced product. Aromatization of the dihydro derivative was accomplished by reaction with *p*-chloranil.

Reaction of the 5-cyano derivative **1** with sodium methanethiolate however gave only a simple substitution product **15**, which was hydrolyzed to afford **16**. Compound **16** could also be obtained by reaction of 3-(methylthio)-6-chloro-5-oxo-4,5-dihydro-1,2,4-triazine (**3**) with methanolic sodium methanethiolate.



Reduction of C=N at the 4,5 positions of some 1,2,4-triazines with neutral *p*-thiocresol has been reported [8]. Other heterocyclic compounds are also known to undergo this type of reaction [9].

EXPERIMENTAL

Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Electron-impact mass spectra were measured on a Varian MAT CH5 mass spectrometer at an ionizing voltage of 70 eV. The ^{1}H-nmr spectra were obtained with a Varian HA-100 or an FT-80A spectrometer. Chemical shifts are reported as δ (ppm) downfield from tetramethylsilane (TMS). The elemental analyses were performed by Atlantic Microlab Inc., Atlanta, Georgia.

Reaction of 3-(Methylthio)-5-carbethoxy-6-chloro-1,2,4-triazine (**5**) with Ammonia.

At 0°. One hundred milligrams (0.4 mmole) of **5** [5] in 5 ml of dry ethanol was saturated with ammonia gas at 0°. The resulting solution was kept in a refrigerator for 6 hours. The solvent was evaporated under reduced pressure without heating. The residue was recrystallized from ethyl acetate to give 65 mg (74%) of 3-(methylthio)-5-carbamoyl-6-chloro-1,2,4-triazine (**6**), mp 161-163°; ms: m/z 206 (25, M$^+$, ^{37}Cl), 204 (66, M$^+$), 189 (2), 187 (5, M - NH_3), 178 (9), 176 (22, M - N_2), 141 (15, M - N_2 -Cl), 129 (11), 117 (11), 106 (33), 105 (11), 104 (100, Cl-C≡C-C(OH)NH_2), 103 (26, Cl-C≡C-$CONH_2$), 89 (21), 87 (71, Cl-C≡C-C≡O), 75 (15), 74 (13), 73 (25), 59 (15), 47 (21, SCH_3), 46 (14), 45 (21), 44 (35, H_2NC≡O), 28 (18, N_2); ir (nujol): 1680 cm^{-1} (C=O), 3180-3380 (NH); ^{1}H-nmr (deuteriochloroform): δ 2.72 (s, 3H, SCH_3), 5.9 (b, 1H, NH), 7.3 (b, 1H, NH).

Anal. Calcd. for $C_5H_5ClN_4OS$: C, 29.35; H, 2.46; N, 27.37. Found: C, 29.36; H, 2.49; N, 27.37.

At 100°. A solution of 500 mg (2.1 mmoles) of **5** in 10 ml of dry ethanol was saturated with ammonia gas, and the resulting solution was sealed and heated at 100° (oil bath). After 2 hours, the solution was cooled and the solvent was evaporated to dryness. The residue was chromatographed on silica gel with chloroform followed by 5%, 10% and 15% of methanol in chloroform to give the pure compounds corresponding to the third and fourth spots of the reaction mixture. The fractions containing a mixture of the first two components were combined and again chromatographed on silica gel with chloroform to give the pure products. The four products isolated from the reaction mixture were, in the order of increasing polarity (on silica gel), as follows:

The first component was further recrystallized from ethyl acetate to give 70 mg of yellow solid 3,6-bis(methylthio)-5-carbamoyl-1,2,4-triazine (**7**), mp 215-216°; ms: m/z 216 (100, M$^+$), 199 (15, M - NH_3), 173 (18), 115 (80, CH_3S-C≡C-$CONH_2$), 99 (44, CH_3S-C≡C-C≡O), 72 (36), 47 (12, SCH_3), 45 (21), 44 (15, H_2N-C≡O); ^{1}H-nmr (deuteriochloroform): δ 2.65 (s, 3H, SCH_3), 2.72 (s, 3H, SCH_3), 5.3 (b, 1H, NH), 7.5 (b, 1H, NH); ^{1}H-nmr (DMSO-d_6): δ 2.55 (s, 3H, SCH_3), 2.67 (s, 3H, SCH_3), 8.15 (b, 1H, NH), 9.40 (b, 1H, NH).

Anal. Calcd. for $C_6H_8N_4OS_2$: C, 33.32; H, 3.73; N, 25.90; S, 29.65. Found: C, 33.43; H, 3.77; N, 25.91; S, 29.76.

The second component was recrystallized from ethyl acetate to give 30 mg of yellow solid 3-(methylthio)-5-carbamoyl-6-amino-1,2,4-triazine (**8**), mp 207-208°; ms: m/z 185 (80, M$^+$), 168 (8, M - NH_3), 112 (19), 84 (100, H_2N-C≡C-$CONH_2$), 74 (14), 68 (51, H_2N-C≡C-C≡O), 67 (13), 47 (14, SCH_3), 46 (20), 44 (33, H_2N-C≡O); ^{1}H-nmr (deuteriochloroform): δ 2.66 (s, 3H, SCH_3), 5.7 (b, 1H, NH), 6.5 (b, 2H, NH_2), 7.7 (b, 1H, NH); ^{1}H-nmr (DMSO-d_6): δ 2.59 (s, 3H, SCH_3), 7.51 (b, 2H, NH_2), 8.10 (b, 1H, NH), 8.40 (b, 1H, NH).

Anal. Calcd. for $C_5H_7N_5OS$: C, 32.43; H, 3.81; N, 37.81. Found: C, 32.43; H, 3.82; N, 37.82.

The third component was recrystallized from methanol to give 14 mg of yellow solid 3-amino-5-carbamoyl-6-(methylthio)-1,2,4-triazine (**9**), mp 268-269°; ms: m/z 185 (100, M$^+$), 168 (91, M - NH_3), 142 (21), 115 (44, CH_3S-C≡C-$CONH_2$), 99 (58, CH_3S-C≡C-C≡O), 98 (17), 87 (10), 72 (44), 71 (22), 70 (16), 47 (11, SCH_3), 45 (24), 44 (25, H_2N-C≡O); ^{1}H-nmr (DMSO-d_6): δ 2.48 (s, 3H, SCH_3), 7.1 (b, 2H, NH_2), 7.8-8.0 (b, 2H, NH_2).

Anal. Calcd. for $C_5H_7N_5OS$: C, 32.43; H, 3.81; N, 37.81. Found: C, 32.53; H, 3.82; N, 37.80.

Compound **9** was also obtained by reaction of 3-amino-5-carbamoyl-6-chloro-1,2,4-triazine (**10**) (see below) with methanolic sodium methanethiolate at room temperature as determined by tlc analysis.

The fourth component (60 mg) was brownish yellow solid 3-amino-5-carbamoyl-6-chloro-1,2,4-triazine (**10**), mp 192-194°; ms: m/z 175 (31, M$^+$, ^{37}Cl), 173 (100, M$^+$), 147 (1.6), 145 (4.9, M - N_2), 110 (19), 105 (6), 104 (19), 103 (20, Cl-C≡C-$CONH_2$), 89 (22), 87 (67, Cl-C≡C-C≡O), 77 (19), 75 (61), 67 (25), 66 (32), 47 (13, SCH_3), 44 (48, H_2N-C≡O), 43 (66), 42 (22), 28 (24, N_2).

Anal. Calcd. for $C_4H_4ClN_5O$: C, 27.68; H, 2.32; N, 40.35. Found: C, 27.63; H, 2.37; N, 40.19.

At room temperature. When the above reaction was carried out at room temperature, tlc analysis (Whatman MK6F and EM 60F silica gel plates with chloroform:methanol/9:1 and 8:2 solvent sytems) showed the presence of **7**, **6**, **8** and **10**, but no **9** was detected.

Reaction of **7** with Ammonia.

A mixture of 800 mg of **7** in 80 ml of methanol was saturated with am-

monia and heated at 100° (in a steel bomb) for 14 hours. After cooling to room temperature, the precipitate was filtered to give 380 mg of yellow solid, identical to **9**. The filtrate was evaporated to dryness. Chromatography of the residue on silica gel with 5% and then 10% methanol in chloroform gave 50 mg of **8** and additionally 60 mg of **9**.

3-Methoxy-5-carbamoyl-6-(methylthio)-1,2,4-triazine (**11**).

To a suspension of 400 mg (1.85 mmoles) of **7** in 80 ml of methanol was added 8.5 ml of 0.43 *N* methanolic sodium methoxide (3.7 mmoles). After stirring at room temperature for 5 hours the resulting reaction mixture was evaporated to dryness. The residue was recrystallized from methanol to give 260 mg (70%) of yellow solid **11**, mp 221-222°; ms: m/z 200 (100, M^+), 183 (91, M - NH_3), 157 (24), 155 (16), 115 (45, CH_3S-C≡C-$CONH_2$), 99 (66, CH_3S-C≡C-C≡O), 72 (60), 71 (20), 70 (27), 47 (12, SCH_3), 45 (22), 44 (40, H_2N-C≡O); ^{1}H-nmr (deuteriochloroform): δ 2.54 (s, 3H, SCH_3), 4.11 (s, 3H, OCH_3), 8.12 (b, 1H, NH), 8.43 (b, 1H, NH).

Anal. Calcd. for $C_6H_8N_4O_2S$: C, 35.99; H, 4.03; N, 27.98. Found: C, 35.83; H, 4.08; N, 27.86.

Heating **11** with methanolic ammonia in a steel bomb at 100° for 24 hours gave **9** as determined by tlc analysis and quantitative uv: **9**, λ max 276 nm at *p*H 1, 268 nm at *p*H 13; **11**, λ max 268 nm at *p*H 1, 260 nm at *p*H 13.

3,6-Bis(methylthio)-5-carbomethoxy-1,2,4-triazine (**12**) and 3,6-Bis(methylthio)-5-carbomethoxy-4,5-dihydro-1,2,4-triazine (**13**).

To a solution of 500 mg (2.14 mmoles) of **5** in 5 ml of methanol was added 7 ml (3.0 mmoles) of 0.43 *N* methanolic sodium methanethiolate. The resulting solution was stirred at room temperature under nitrogen for 4 hours. The precipitate which had formed was filtered to give 155 mg of greenish yellow solid **12**, mp 145-147°; ms: m/z 231 (67, M^+), 188 (27, M -N_2 - CH_3), 174 (24), 130 (100, CH_3S-C≡C-CO_2CH_3), 114 (17), 100 (23), 99 (100, CH_3S-C≡C-C≡O), 85 (42), 72 (38), 44 (17); ^{1}H-nmr (deuteriochloroform): δ 2.68 (s, 3H, SCH_3), 2.71 (s, 3H, SCH_3), 4.02 (s, 3H, CO_2CH_3).

Anal. Calcd. for $C_7H_9N_3O_2S_2$: C, 36.35; H, 3.92; N, 18.17; S, 27.72. Found: C, 36.26; H, 3.93; N, 18.13; S, 27.65.

The filtrate was evaporated to dryness. The residue was dissolved in water, neutralized with dilute aqueous hydrochloric acid and extracted with chloroform. The chloroform solution was washed with water, dried over sodium sulfate, and evaporated to dryness. Chromatography of the residue on silica gel with chloroform gave an additional 160 mg (total 64%) of **12** followed by 143 mg (29%) of light yellow solid **13**, mp 134-136°; ms: m/z 233 (3, M^+), 174 (100), 101 (16), 74 (43); ^{1}H-nmr (deuteriochloroform): δ 2.38 (s, 3H, SCH_3), 2.50 (s, 3H, SCH_3), 3.76 (s, 3H, CO_2CH_3), 4.84 (s, 1H, C-H), 7.9 (b, 1H, NH).

Anal. Calcd. for $C_7H_{11}N_3O_2S_2$: C, 36.04; H, 4.75; N, 18.01; S, 27.48. Found: C, 36.10; H, 4.75; N, 17.98; S, 27.59.

When excess (4 equivalents) sodium methanethiolate was used in the above reaction, only **13** was obtained. Reaction with 1 equivalent of methanethiolate gave only **12** and a trace of unreacted **13**.

Reaction of **12** with methanethiol in the presence of triethylamine (4 equivalents) in methanol at room temperature for 24 hours also gave **13**.

Heating **12** with methanethiol in methanol at 100° (in a steel bomb) for 24 hours gave **13**.

Reaction of **13** with *p*-chloranil in acetic acid at reflux for 2 hours gave **12**.

Reaction of **12** with Ammonia.

Into an ice-water cooled suspension of 600 mg (2.59 mmoles) of **12** in 200 ml of methanol was bubbled ammonia gas. The resulting mixture was kept at 0° for 24 hours. Evaporation of the reaction mixture under reduced pressure gave 530 mg (95%) of a yellow solid, identical (mp and infrared spectrum) with **7**.

3,6-Bis(methylthio)-5-methoxy-1,2,4-triazine (**15**) and 3,6-Bis(methylthio)-5-oxo-4,5-dihydro-1,2,4-triazine (**16**).

To a solution of 100 mg (0.54 mmole) of 100 mg (0.54 mmole) of **1** [5] in 1 ml of methanol was added 3 ml of 0.43 *N* methanolic sodium methanethiolate (1.29 mmoles). After stirring at room temperature for 24 hours the solution was evaporated to dryness. The residue was suspended in water and extracted with chloroform. The chloroform solution was dried over magnesium sulfate and evaporated to dryness. The residue was recrystallized from petroleum ether (30-60°) to give 35 mg (32%) of a white solid **15**, mp 101-102°; ms: m/z 203 (100, M^+), 188 (11, M - CH_3), 102 (41, CH_3S-C≡C-OCH_3), 87 (71, CH_3S-C=C=O); ^{1}H-nmr (deuteriochloroform): δ 2.62 (s, 3H, SCH_3), 2.63 (s, 3H, SCH_3), 4.06 (s, 3H, OCH_3).

Anal. Calcd. for $C_6H_9N_3OS_2$: C, 35.45; H, 4.46; N, 20.67. Found: C, 35.50; H, 4.49; N, 20.67.

The aqueous filtrate was neutralized with 1*N* hydrochloric acid to give 15 mg (15%) of a white precipitate **16**, mp 229-231°; ms: m/z 189 (87, M^+), 142 (14, M - SCH_3), 116 (15, M - CH_3SCN), 74 (80, CH_3SC=NH), 69 (100, M - CH_3SCN - CH_3S), 48 (51, CH_3SH); ^{1}H-nmr (DMSO-d_6): δ 2.32 (s, 3H, SCH_3), 2.50 (s, 3H, SCH_3).

Anal. Calcd. for $C_5H_7N_3OS_2$: C, 31.73; H, 3.73; N, 22.20. Found: C, 31.86; H, 3.77; N, 22.17.

When the above reaction was heated at reflux for 2 hours, only **16** was obtained.

Treatment of 3-(methylthio)-5-oxo-6-chloro-4,5-dihydro-1,2,4-triazine (**3**) [5] with methanolic sodium methanethiolate at room temperature for 24 hours also gave **16**.

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