Studies of Cyanamide Derivatives. Part 109. A Convenient Method for Preparation of 4-Aminothiazole Compounds from Alkoxythiocarbonylcyanamide Salts

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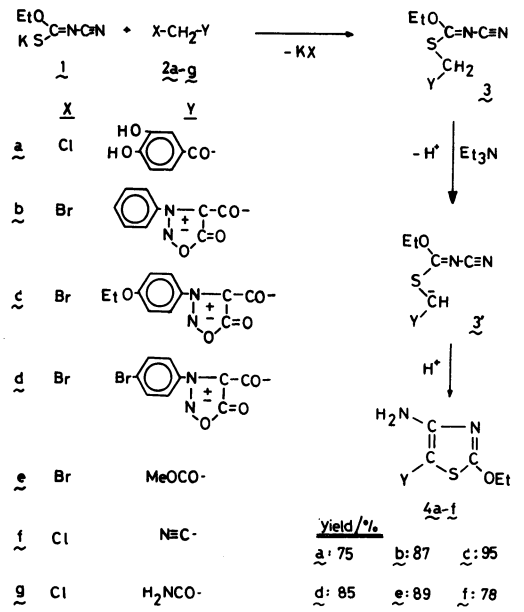
Synopsis. α-Halo derivatives of ketones, ester, and nitrile reacted readily with potassium ethoxythiocarbonylcyanamide to provide the corresponding 4-amino-2-ethoxythiazole compounds in good yields, while α-halo amide did not. In a similar manner, α,α′-dihalo ketone reacted with 2 equiv of alkoxythiocarbonylcyanamide and *S*-methyl *N*-cyanocarbamodithioate salts to give the corresponding bis(4-amino-5-thiazolyl) ketones.

Cyanamide derivatives are very useful for synthesis of heterocyclic compounds having nitrogen atoms. In the course of our synthetic studies[1-7] of heterocyclic compounds using cyanamide derivatives, we have found a novel synthetic reaction of 4-aminothiazole compounds from potassium ethoxythiocarbonylcyanamide (**1**) and α-halo ketones.[7] The reaction should be interesting from an aspect that few studies[8] on the synthesis of 4-aminothiazoles have been reported, while a number of 2-aminothiazoles have been known. In addition, the reaction may be useful for the preparation of 4-aminothiazoles having unstable substituents, since it can proceed under quite mild reaction conditions.

In this work, we attempted some extensions of the reaction to more complicated α-halo ketones and α-halo derivatives of compounds other than ketones.

Results and Discussion

The reaction of **1** with **2** easily proceeded at room temperature eliminating potassium halide to form stable intermediate (**3**), and then **3** underwent the base-catalyzed cyclization to be converted into the final product (**4**), as shown in Scheme 1. In the course of the reaction, **3** was not isolated from the reaction mixture and one-pot reaction was carried out.

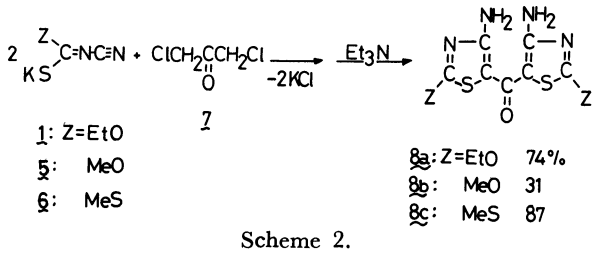


Scheme 1.

4-Aminothiazole (**4a**) having hydroxyl groups could be obtained in a fairly good yield from the corresponding α-halo ketone (**2a**).

Althogh sydnone compounds are generally interesting in their chemical, physical and biological properties,[9] their syntheses seem to be limited.[10,11] For instance, a few works dealing with the successful synthesis of sydnones having heterocyclic substituents have been reported: Only 4-(4-thiazolyl)[12] and 4-(1,2,4-oxadiazol-3-yl)sydnones[11] could be prepared in our previous works. In this point, the reaction of **1** with 3-aryl-4-(bromoacethyl)sydnone (**2b—d**) under such mild conditions, where a sydnone ring itself did not decompose, was successfully tried to prepare the corresponding 4-amino-5-thiazolyl 3-ary-4-sydnonyl ketones (**4b—d**).

The reaction was also extended to α,α′-dihalo ketone (1,3-dichloro-2-propanone, **7**) and consequently the corresponding bis(4-amino-5-thiazolyl)ketones (**8a—c**) were obtained in 31—87% yields using 2 equiv of cyanamide salts (**1**, **5**, and **6**), as shown in Scheme 2.



Scheme 2.

At the second stage of the investigation, the reaction was also extended to α-halo derivatives of compounds other than ketones. As shown in Scheme 1, α-halo ester (**2e**) and nitrile (**2f**) reacted with **1** to give the corresponding 4-aminothiazole compounds (**4e, f**) in high yields, while α-halo amide (**2g**) gave only the intermediate (**3g**) which could not cyclize under the conditions used. Since the initiation step of the cyclization seems to be carbanion (**3′**) formation from **3** by base-catalyzed proton abstraction, no occurrence of the cyclization of **3g** may be due to weaker electron-withdrawing effect of an amide group than the others.

Experimental

*3,4-Dihydroxyphenyl 2-Ethoxy-4-amino-5-thiazolyl Ketone (**4a**).*

To a stirred solution of 0.84 g (5 mmol) of potassium ethoxythiocarbonylcyanamide (**1**)[13] in 5 ml of acetone was gradually added a solution of 0.93 g (5 mmol) in 10 ml of acetone at room temperature. After 2 h of stirring, 0.31 ml of triethylamine was added to the reaction mixture. After additional 2 h of stirring, the reaction mixture was evaporated to dryness and the residue was mixed with water. The insoluble oily material was solidified with small amount of methanol and the resulting solid was collected by filtration. The yield was 1.05 g (75%). Recrystallization from aq. methanol provided 0.90 g (64%) of pure **4a**: mp 201—202 °C; IR (KBr) 1640 cm^{-1} (C=O); NMR (DMSO-d_6) δ=1.33 (t, 3H, $C\underline{H}_3CH_2$), 4.37 (q, 2H, $CH_3C\underline{H}_2$), 6.58—7.00 (m, 3H, Ar-H), 7.90 (s, 2H, $N\underline{H}_2$), and 9.00 (broad s, 2H, O<u>H</u>). Found: C, 51.42; H, 4.01; N, 9.97%. Calcd for $C_{12}H_{12}N_2O_4S$: C, 51.42; H, 4.32; N, 9.99%.

*4-Amino-2-ethoxy-5-thiazolyl 3-Phenyl-4-sydnonyl Ketone (**4b**).* To a stirred solution of 0.42 g (2.5 mmol) of **1** in 5 ml of acetone was gradually added a solution of 0.71 g (2.5 mmol) of 4-bromoacetyl-3-phenylsydnone[12] in 10 ml of acetone at room temperature. After 1 h of stirring, 0.1 ml of triethylamine was added to the reaction mixture. After additional 0.5 h of stirring, the reaction mixture was evaporated to dryness under reduced pressure. The residue was mixed with water and insoluble material was collected by filtration. The yield was 0.72 g (87%). Recrystallization from methanol provided 0.60 g (72%) of pure **4b** as yellow needles: mp 172—173 °C; IR (KBr) 1775 and 1605 cm^{-1} (C=O); NMR (DMSO-d_6) δ=1.37 (t, 3H, $C\underline{H}_3CH_2$), 4.40 (q, 2H, $CH_3C\underline{H}_2$), 7.50 (s, 5H, Ar-H), and 8.00 (s, 2H, $N\underline{H}_2$); MS *m/e* 332 (M^+). Found: C, 50.50; H, 3.59; N, 16.73%. Calcd for $C_{14}H_{12}N_4O_4S$: C, 50.60; H, 3.70; N, 16.86%.

*4-Amino-2-ethoxy-5-thiazolyl 3-(p-Ethoxyphenyl)-4-sydnonyl Ketone (**4c**).* In a similar manner, **4c** was obtained from **2c** in 95% yield. Recrystallization from ethanol provided pure **4c** as yellow needles: mp 171—172 °C; IR (KBr) 1775 and 1605 cm^{-1} (C=O); NMR (DMSO-d_6) δ=1.37 (t, 6H, $C\underline{H}_3CH_2$), 4.08 (q, 2H, $C\underline{H}_2OC_6H_4$), 4.43 (q, 2H, $CH_3C\underline{H}_2$), 7.02 (d, 2H, Ar-H), 7.52 (d, 2H, Ar-H), and 8.10 (s, 2H, $N\underline{H}_2$): MS *m/e* 376 (M^+). Found: C, 50.95; H, 4.18; N, 14.75%. Calcd for $C_{16}H_{16}N_4O_5S$: C, 51.06; H, 4.29; N, 14.89%.

*4-Amino-2-ethoxy-5-thiazolyl 3-(p-Bromophenyl)-4-sydnonyl Ketone (**4d**).* In a similar manner, **4d** was obtained in 85% yield. Recrystallization from ethanol provided pure **4d** as yellow needles: mp 163—164 °C; IR (KBr) 1775 and 1605 cm^{-1} (C=O); NMR (DMSO-d_6) δ=1.33 (t, 3H, $C\underline{H}_3CH_2$), 4.42 (q, 2H, $CH_3C\underline{H}_2$), 7.65 (q, 4H, Ar-H), and 8.19 (s, 2H, $N\underline{H}_2$): MS *m/e* 410 (M^+) and 412 (M^++2). Found; C, 40.98; H, 2.47; N, 13.61%. Calcd for $C_{14}H_{11}N_4O_4SBr$: C, 40.89; H, 2.70; N, 13.62%.

*4-Amino-2-ethoxy-5-methoxycarbonylthiazole (**4e**).* By the procedure similar to the preparation of **4b**, **4e** was obtained from methyl bromoacetate. The yield was 89%. Recrystallization from 20% aq methanol provided pure **4e** as colorless needles (83%): mp 80 °C; IR (KBr) 1620 cm^{-1} (C=O); NMR ($CDCl_3$) δ=1.37 (t, 3H, $C\underline{H}_3CH_2$), 3.65 (s, 3H, $C\underline{H}_3O$), 4.35 (q, 2H, $CH_3C\underline{H}_2$), and 5.70 (broad s, 2H, $N\underline{H}_2$); MS *m/e* 202 (M^+). Found: C, 41.30; H, 4.81; N, 13.65%. Calcd for $C_7H_{10}N_2O_3S$: C, 41.58; H, 4.98; N, 13.85%.

*4-Amino-5-cyano-2-ethoxythiazole (**4f**).* By the same procedure described above, **4f** was obtained from chloroacetonitrile. The yield was 78%. Recrystallization from methanol provided pure **4f** (60%); mp 148—149 °C IR (KBr) 2180 cm^{-1} (C≡N); NMR ($CDCl_3$) δ=1.43 (t, 3H, $C\underline{H}_3CH_2$), 4.44 (q, 2H, $CH_3C\underline{H}_2$), and 4.90 (broad s, 2H, $N\underline{H}_2$); MS *m/e* 169 (M^+). Found: C, 42.65; H, 3.90; N, 24.91%. Calcd for $C_6H_7N_3OS$: C, 42.59; H, 4.17; N, 24.83%.

*Reaction of **1** with Chloroacetamide.* The reaction was performed in a similar manner. After the reaction, the precipitating salt (KCl) was removed by filtration and the filtrate was concentrated to dryness provided **3g** in 100% yield. Recrystallization from methanol provided pure **3g**; mp 163—164 °C; IR (KBr) 2210, 2180 (C≡N) and 1660 cm^{-1} (C=O); MS *m/e* 187 (M^+). Found: C, 38.10; H, 4.84; N, 22.07%. Calcd for $C_6H_9N_3O_2S$: C, 38.49; H, 4.85; N, 22.44%.

*Bis(4-amino-2-ethoxy-5-thiazolyl) Ketone (**8a**).* The preparative procedure was described in the previous paper.[7]

*Bis(4-amino-2-methoxy-5-thiazolyl) Ketone (**8b**).* By the procedure similar to the preparation of **4** and **8a**, the reaction was carried out using 0.62 g (4 mmol) of potassium methoxythiocarbonylcyanamide (**5**),[3] 0.25 g (2 mmol) of 1,3-dichloro-2-propanone, and 0.1 ml of triethylamine in 10 ml of acetone. After the reaction, the reaction mixture was evaporated and the remaining residue was mixed with water. The insoluble oily material was separated from water and the oil was solidified with methanol, giving 0.18 g (31%) of crude **8b**. Recrystallization from DMF provided pure **8b**: mp 208—209 °C; IR (KBr) 3380, 3280 (NH) and 1600 cm^{-1} (C=O); NMR (DMSO-d_6) δ=3.97 (s, 6H, $C\underline{H}_3$) and 7.57 (s, 4H, $N\underline{H}_2$); MS *m/e* 286 (M^+). Found: C, 38.04; H, 3.49; N, 19.38%. Calcd for $C_9H_{10}N_4O_3S_2$: C, 37.75; H, 3.52; N, 19.57%.

*Bis(4-amino-2-methylthio-5-thiazolyl) Ketone (**8c**).* In a similar manner as above, the reaction was carried out using 1.70 g (10 mmol) of potassium *S*-methyl *N*-cyanocarbamodithioate (**6**),[3] 0.64 g (5 mmol) of 1,3-dichloro-2-propanone, and 0.4 ml of triethylamine. After work-up, 1.39 g (87%) of crude **8c** was obtained. Recrystallization from DMF-methanol provided pure **8c**: mp 250—251 °C; IR (KBr) 3480, 3370, 3300, 3250 (NH) and 1580 cm^{-1} (C=O); NMR (DMSO-d_6) δ=2.70 (s, 6H, $C\underline{H}_3$) and 7.66 (s, 4H, $N\underline{H}_2$); MS *m/e* 318 (M^+). Found: C, 33.83; H, 3.05; N, 17.58%. Calcd for $C_9H_{10}N_4OS_4$: C, 33.95; H, 3.17; N, 17.59%.

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