

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

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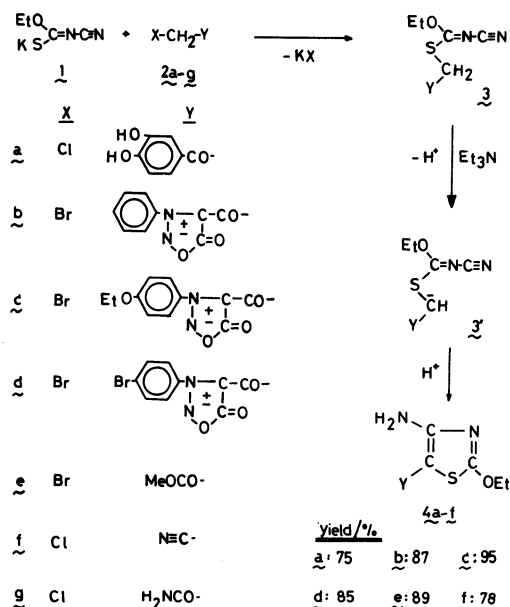
Synopsis. α -Halo derivatives of ketones, ester, and nitrile reacted readily with potassium ethoxythiocarbonylcyanamide to provide the corresponding 4-amino-2-ethoxythiazole compounds in good yields, while α -halo amide did not. In a similar manner, α,α' -dihalo ketone reacted with 2 equiv of alkoxythiocarbonylcyanamide 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 studies¹⁻⁷⁾ 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 studies⁸⁾ 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



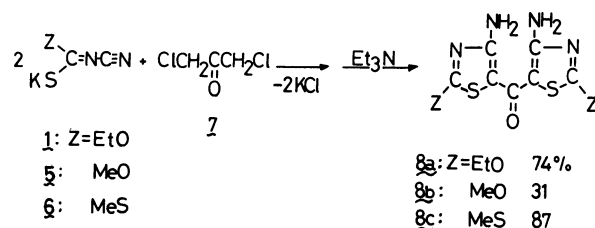
Scheme 1.

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.

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

Although 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)sydnones¹¹⁾ could be prepared in our previous works. In this point, the reaction of **1** with 3-aryl-4-(bromoacetyl)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-aryl-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, CH₃CH₂), 4.37 (q, 2H, CH₃CH₂), 6.58–7.00 (m, 3H, Ar-H), 7.90 (s, 2H, NH₂), and 9.00 (broad s, 2H, OH). Found: C, 51.42; H, 4.01; N, 9.97%. Calcd for C₁₂H₁₂N₂O₄S: 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-phenylsydnone¹² 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, CH₃CH₂), 4.40 (q, 2H, CH₃CH₂), 7.50 (s, 5H, Ar-H), and 8.00 (s, 2H, NH₂); MS *m/e* 332 (M⁺). Found: C, 50.50; H, 3.59; N, 16.73%. Calcd for C₁₄H₁₂N₄O₄S: 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, CH₃CH₂), 4.08 (q, 2H, CH₂OC₆H₄), 4.43 (q, 2H, CH₃CH₂), 7.02 (d, 2H, Ar-H), 7.52 (d, 2H, Ar-H), and 8.10 (s, 2H, NH₂); MS *m/e* 376 (M⁺). Found: C, 50.95; H, 4.18; N, 14.75%. Calcd for C₁₆H₁₆N₄O₅S: 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, CH₃CH₂), 4.42 (q, 2H, CH₃CH₂), 7.65 (q, 4H, Ar-H), and 8.19 (s, 2H, NH₂); MS *m/e* 410 (M⁺) and 412 (M⁺+2). Found: C, 40.98; H, 2.47; N, 13.61%. Calcd for C₁₄H₁₁N₄O₄SBBr: 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 (CDCl₃) δ =1.37 (t, 3H, CH₃CH₂), 3.65 (s, 3H, CH₃O), 4.35 (q, 2H, CH₃CH₂), and 5.70 (broad s, 2H, NH₂); MS *m/e* 202 (M⁺). Found: C, 41.30; H, 4.81; N, 13.65%. Calcd for C₇H₁₀N₂O₃S: 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 (CDCl₃) δ =1.43 (t, 3H, CH₃CH₂), 4.44 (q, 2H, CH₃CH₂), and 4.90 (broad s, 2H, NH₂); MS *m/e* 169 (M⁺). Found: C, 42.65; H, 3.90; N, 24.91%. Calcd for C₆H₇N₃OS: 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 C₆H₉N₃O₂S: 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, CH₃) and 7.57 (s, 4H, NH₂); MS *m/e* 286 (M⁺). Found: C, 38.04; H, 3.49; N, 19.38%. Calcd for C₉H₁₀N₄O₃S₂: 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, CH₃) and 7.66 (s, 4H, NH₂); MS *m/e* 318 (M⁺). Found: C, 33.83; H, 3.05; N, 17.58%. Calcd for C₉H₁₀N₄OS₄: C, 33.95; H, 3.17; N, 17.59%.

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