Study on Reaction of α-Benzoylhemithioacetal with Alkylamines

ZOU, Jian-Ping[*,a](邹建平) **LIU, Xian-Jun**[b](刘现军) ZHANG, Jian[a](张健)
LU, Zhong-E[a](陆忠娥)
[a] *Department of Chemistry, Suzhou University, Suzhou, Jiangsu 215006, China*
[b] *Department of Chemistry, Fudan University, Shanghai 200437, China*

α-Benzoylhemithioacetal (1) reacted with alkylamines under mild conditions to give 2-alkylamino-2-thiomethyl acetophenones (3) in good yields.

Keywords α-Benzoylhemithioacetal, 2-alkylamino-2-thiomethyl acetophenone, reaction

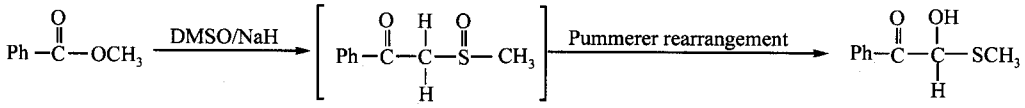
Introduction

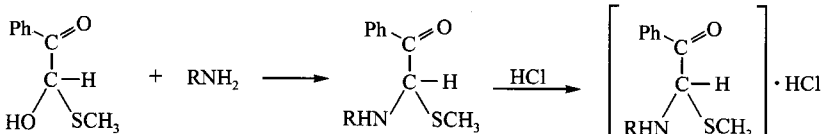
The rearrangement of aromatic α-sulfinyl carboxylic acids to hemithioacetals or other derivatives of glyoxylic acid under the action of acids (or acidic reagents) was first reported by Pummerer.[1] Later, Russell and coworkers applied this rearrangement to β-ketosulfoxides to synthesize α-ketohemithioacetal,[2] which can then be transformed to α-keto alcohol and aldehyde, as well as α-hydroxy alcohol and acid.[3] Furthermore, Hall and Poet reported that α-ketohemithioacetal could be rearranged to the corresponding α-hydroxythioester in the presence of magnesium nitrate and sodium acetate or tertiary amine.[4]

We reported the reaction of α-ketohemithioacetal with ureas in slightly acidic medium to form 2, 4-imidazolidinediones in good yields.[5] In contrast, when the reaction of α-benzoylhemithioacetal (**1**) with alkylamines in ethanol was carried out, the amino group substituted the hydroxy of **1** to afford 2-alkylamino-2-thiomethyl acetophenones (**3**). This reaction is very attractive, which may be used in synthesis of nitrogen-containing glucoside and aminonation of sacchride. The further exploration is in progress now. Herein, we report this reaction and the structural determination of the products.

Results and discussion

α-Benzoylhemithioacetal (**1**) was readily prepared by the reaction of methyl benzoate and DMSO in the presence of sodium hydride, followed by acidification to pH = 1. Compound **1** reacted with alkylamines in ethanol at 20—30℃ to give 2-alkylamino-2-thiomethyl acetophenones (**3**) easily.





1 2 3 4

R: **a**, $CH_3(CH_2)_6$; **b**, $CH_3(CH_2)_7$; **c**, $CH_3(CH_2)_9$; **d**, $CH_3(CH_2)_{11}$; **e**, $CH_3(CH_2)_{13}$; **f**, $CH_3(CH_2)_{15}$

E-mail: jpzou@suda.edu.cn
Received April 7, 2000; accepted September 28, 2000.
Project (No. 95094) supported by the Natural Science Foundation of Jiangsu Education Committee of China.

Compounds **3a**—**3e** are oils, while **3f** is solid. All compounds are unstable at above 40℃ and in air. Therefore, we failed to purify these compounds by chromatography or distillation under vaccum. However, when dilute hydrochloric acid was added to the reaction mixture, high purity of 2-alkylamino-2-thiomethyl acetophenone hydrochlorides (**4**) were precipitated, which can be further purified by recrystallization from 95% ethanol to give pure compounds **4**. The HCl salts **4** are stable below 100℃ and in air, suitable for a variety of analyses. The structures of **4** were characterized by MS, ^{1}H NMR, IR spectra and elemental analysis.

In conclusion, when **1** reacted with alkylamine, the amino group selectively substituted the hydroxy group, while thiomethyl and carbonyl groups of **1** remained unchanged.

Experimental

Melting points were determined with an Electrothermal Eng. Ltd. Digital Melting Point apparatus and are uncorrected. The infrared spectra were recorded on a Mattson Alpha-Centauri FT-IR spectrometer. The ^{1}H NMR spectra were recorded on a Varian 400 spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard. The mass spectra were determined with a VG-ZAB-HS mass spectrometer.

Synthesis of α-benzoylhemithioacetal (**1**)

A dry 500 mL three-necked flask was fitted with a mechanical stirrer, a pressure-equalizing addition funnel and a mineral oil bubble trap which served to close the system to the atmosphere. 80% sodium hydride (5.4 g, 0.18 mol) and dry DMSO (240 mL) were placed in the flask in a nitrogen atmosphere and the mixture was stirred with heating at 60—65℃ for 2—2.5 h until sodium hydride had dissolved and no bubble produced. After cooling the mixture to 15℃, methyl benzoate (20 mL, 0.16 mol) was added dropwise and the mixture was allowed to react for 1—1.5 h at room temperature. Then the mixture was dissolved in 400 mL of cold water. The aqueous solution was extracted with ether for three times, then acidified to pH = 1 by addition of concentrated hydrochloric acid, and allowed to stand at room temperature for 48 h. The white precipitate was formed. After filtration, the precipitate was washed with water and dried to give **1**.

1 Colorless crystal (23.3 g, 80%), m.p. 100—101℃ (recrystallized from anhydrous ethanol) (Lit.[3] 104—106℃). ^{1}H NMR δ: 7.30—8.31 (m, 5H, C_6H_5), 6.17 (s, 1H, COCH), 4.42 (s, 1H, OH), 2.01 (s, 3H, SCH_3).

Preparation of compounds **4a**—**e**

General procedure To a solution of **1** (2.2 mmol) in ethanol (20 mL) was added alkylamine (2.2 mmol). The mixture was stirred for 3 h at 20—30℃ (TLC monitors the reaction), then dilute hydrochloric acid (10 mL) was added dropwise to the mixture. A white precipitate was formed, filtered, washed with water and ether, dried and recrystallized from ethanol to give pure compounds **4a**—**e** in 60—72% yield.

4a Colorless crystal (72%), m.p. 155—158℃. ^{1}H NMR δ: 9.8 (br, 2H, N^+H_2), 7.4—8.2 (m, 5H, C_6H_5), 6.4 (s, 1H, CH), 1.4—3.2 (m, 12H, $6\times CH_2$), 1.3 (s, 3H, SCH_3), 0.9 (t, J = 7 Hz, 3H, CH_3). IR ν: 3410, 1687 cm^{-1}. MS *m/z* (%): 232 (M^+ − HCl − SCH_3, 48). Anal. Calcd for $C_{16}H_{26}ClNOS$: C 60.86, H 8.24, N 4.44; Found: C 60.65, H 8.20, N, 4.41.

4b Colorless crystal (69%), m.p. 146—148℃. ^{1}H NMR δ: 9.8 (br, 2H, N^+H_2), 7.5—8.2 (m, 5H, C_6H_5), 6.4 (s, 1H, CH), 1.0—3.2 (m, 14H, $7\times CH_2$), 1.3 (s, 3H, SCH_3), 0.9 (t, J = 7 Hz, 3H, CH_3). IR ν: 3451, 1690 cm^{-1}. MS *m/z* (%): 246 (M^+ − HCl − SCH_3, 25). Anal. Calcd for $C_{17}H_{28}ClNOS$: C 61.91, H 8.50, N 4.25; Found: C 61.62, H 8.48, N 4.22.

4c Colorless crystal (69%), m.p. 138—140℃. ^{1}H NMR δ: 9.8 (br, 2H, N^+H_2), 7.5—8.2 (m, 5H, C_6H_5), 6.4 (s, 1H, CH), 1.0—3.2 (m, 18H, $9\times CH_2$), 1.3 (s, 3H, SCH_3), 0.9 (t, J = 7 Hz, 3H, CH_3). IR ν: 3451, 1688 cm^{-1}. MS *m/z* (%): 274 (M^+ − HCl − SCH_3, 14). Anal. Calcd for $C_{19}H_{32}ClNOS$: C 63.78, H 8.95, N 3.92; Found: C 63.48, H 8.90, N 3.90.

4d Colorless crystal (63%), m.p. 116—118℃. ^{1}H NMR δ: 9.8 (br, 2H, N^+H_2), 7.4—8.2 (m, 5H, C_6H_5), 6.4 (s, 1H, CH), 1.0—3.2 (m, 22H, $11\times CH_2$), 1.3 (s, 3H, SCH_3), 0.9 (t, J = 7 Hz, 3H, CH_3). IR δ: 3451, 1688 cm^{-1}. MS *m/z*

(%): 302 (M^+ – HCl – SCH_3, 3). Anal. Calcd for $C_{21}H_{36}ClNOS$: Calcd C 65.37, H 9.34, N 3.63; Found: C 65.00, H 9.33, N 3.59.

4e Colorless crystal (65%), m. p. 112—114℃. ^1H NMR δ: 9.8 (br, 2H, N^+H_2), 7.4—8.2 (m, 5H, C_6H_5), 6.3 (s, 1H, CH), 1.0—3.2 (m, 26H, 13 × CH_2), 1.2 (s, 3H, SCH_3), 0.9 (t, J = 7 Hz, 3H, CH_3). IR ν: 3452, 1674 cm^{-1}. MS *m/z* (%): 330 (M^+ – HCl – SCH_3, 2). Anal. Calcd for $C_{23}H_{40}ClNOS$: C 66.75, H 9.67, N 3.39; Found: C 66.54, H 9.65, N 3.36.

Preparation of compounds **3f** *and* **4f**

To a solution of **1** (0.3 g, 1.6 mmol) in ethanol (20 mL) was added *n*-hexadecylamine (0.4 g, 1.6 mmol). The mixture was stirred for 3.5 h at 20—30℃. A white precipitate was formed, filtered, dried by vacuum to give **3f** (0.3 g, yield 46%). Then, dilute hydrochloric acid (10 mL) was added to the filtrate, another white precipitate was formed, filtered, washed with water and ether, dried and recrystallized from ethanol to give **4f** (0.2 g, 28 %). Compound **3f** is unstable to air, when it is allowed to stand at atmosphere about one week, it becomes yellow slowly and finally, becomes yellow oil.

3f Colorless crystal (46%), m. p. 44—46℃. ^1H NMR δ: 7.4—8.1 (m, 5H, C_6H_5), 5.8 (s, 1H, CH), 3.3 (s, 1H, NH), 1.0—2.8 (m, 30H, 15 × CH_2), 1.2 (s, 3H, SCH_3), 0.9 (t, J = 7 Hz, 3H, CH_3). ^1H NMR δ: 3410, 1685 cm^{-1}. MS *m/z* (%): 358 (M^+ – SCH_3, 5). Anal. Calcd for $C_{25}H_{43}NOS$: C 74.07, H 10.62, N 3.46; Found: C 73.85, H 10.59, N 3.44.

4f Colorless crystal (24%), m. p. 108—110℃. ^1H NMR δ: 9.7 (br, 2H, N^+H_2), 7.4—8.2 (m, 5H, C_6H_5), 6.4 (s, 1H, CH), 1.1—3.2 (m, 30H, 15 × CH_2), 1.3 (s, 3H, SCH_3), 0.9 (t, J = 7 Hz, 3H, CH_3). IR ν: 3400, 1700 cm^{-1}. MS *m/z* (%): 358 (M^+ – HCl – SCH_3, 5). Anal. Calcd for $C_{25}H_{44}ClNOS$: C 67.95, H 9.97, N 3.17; Found: C 67.45, H 9.94, N 3.14.

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(E200004086 SONG, J.P.; LING, J.)