ACTION OF ALKALI METALS IN LIQUID AMMONIA ON SUBSTITUTED THIOPHENES.

COMMUNICATION 9. PREPARATION OF 5-MERCAPTO-4-KETOALKANOIC ACIDS BY REDUCTIVE CLEAVAGE OF 4-ACETYLAMINO- AND 4-NITROTHIOPHENE-2-CARBOXYLIC ACIDS

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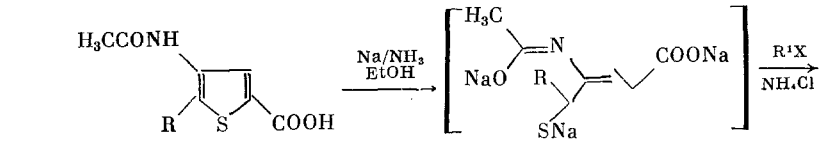
It has already been shown [1] that in 2-thiophenecarboxylic acids the thiophene ring is selectively opened by the action of solvated electrons with the formation of 5-mercapto-3(Z)-alkenoic acids. In the case of 5-dialkylaminoalkyl-2-thiophenecarboxylic acids, the specific influence of the substituted amino group, removed from the ring by one of two C atoms, favors the elimination of the S atom, which leads to the formation of dialkylamino-s-trans-2(E),4(E)-alkadienoic acids [2].

It was interesting to study the influence of the amino group located in the ring and not in the side chain, and the direction of its opening under the action of solvated electrons. We selected 4-acetylamino-2-thiophenecarboxylic acids (I), since they are readily available [3]. Also, if ring opening proceeds by the same scheme as in the case of 2-thiophenecarboxylic acids that do not contain other functional substituents, the cleavage products will be enamino derivatives, which are readily hydrolyzed in the presence of a free NH_2 group, but are more stable in the case of acylamino substituent. The experiments confirmed these assumptions.

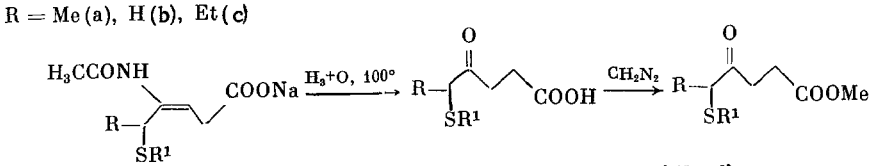
In the treatment of 4-acetylamino-5-methyl-2-thiophenecarboxylic acid (Ia) with 4.5 equivalents of Na in liquid NH_3 and in alcohol, followed by the action of 2,4-dinitrochlorobenzene (DNCB), the Na salt of 5-(2,4-dinitrophenylthio)-4-acetylamino-3-hexenoic acid (IIa) was isolated in a 65% yield. Its structure was confirmed by spectral data (see Experimental). Hence, firstly, reduction of the thiophene ring is observed, and the acetylamino group is not affected, although according to the data in [4] it may also be reduced. Also, 29% of bis(2,4-dinitrophenyl) sulfide was isolated. The formation of this compound indicates a side process of splitting the sulfur atom, but products that do not contain sulfur could not be isolated.

After acidifcation and boiling in aqueous solution, the salt (IIa) hydrolyzes to 5-(2,4-dinitrophenylthio)-4-oxocaproic acid (IIIa). The last compound was also obtained from (Ia) in a 45% yield without intermediate separation of (IIa). The reaction of acid (Ia) with Na in NH_3 and alcohol, subsequent alkylation with benzyl chloride, acid hydrolysis of alkylation products, and esterification of the acid obtained (IIIa) by diazomethane give methyl 5-benzylthio-4-oxocaproate (IVb) in a 75% yield. Similarly, by reductive cleavage of 4-acetylamino-2-thiophenecarboxylic acid (Ib), alkylation with benzyl chloride and subsequent saponification,



(I)

R = Me (a), H (b), Et (c)



(II)

R = Me, R^2 = 2,4-dinitrophenyl (a)

(III) (IVa-d)

R = Me, R^1 = 2,4-dinitrophenyl (a). R = Me, R^1 = CH_2Ph (b), R = H, R^1 = CH_2Ph (c), R = Et, R^1 = CH_2Ph (d)

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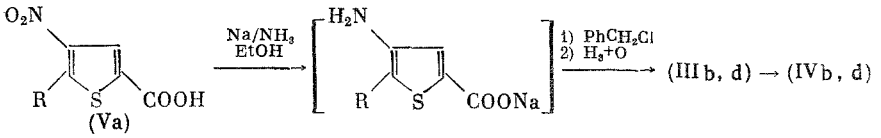
5-benzylthio-4-oxovaleric acid (IIIc) was obtained in a 53% yield, and from 5-ethyl-4-acetylamino-2-thiophenecarboxylic acid (Ic), as the result of the above transformations and esterification by CH_2N_2, methyl 5-benzylthio-4-oxoenanthate (IVd) was obtained in a 72% yield.

Thus, reductive opening of the ring in acids (I) proceeds similarly to the reduction of 2-thiophenecarboxylic acids with no acetylamino group. The only difference is that the main cleavage products are N-acetylenamines (II), which are smoothly transformed into mercaptoketo acids (III).

The initial acids (I) are obtained by reductive acetylation of the corresponding nitrocarboxylic acids (V) [3] and since the nitro group is readily reduced by Na in NH_3 [5], it is advisable to combine these two stages into one.



R = Me (a), R = Et (b).

By the action of eleven equivalents of Na in liquid NH_3 and ethanol on 4-nitro-5-methyl-2-thiophenecarboxylic acid (Va), followed by alkylation with benzyl chloride, acid (IIIb) was obtained in a yield of 45%, and in the analogous reduction of 4-nitro-5-ethyl-2-thiophenecarboxylic acid (Vb), 67% of acid (IIId) were obtained. It is interesting to note that the initially formed type (II) salt hydrolyzes on addition of water.

Since acids (V) are obtained in one stage of nitration of 5-alkyl-2-thiophenecarboxylic acids, the above transformation can be considered as a basis for a simple two-stage method of synthesis of 5-mercapto-4-ketoalkanoic acids from readily available thiophene derivatives.

EXPERIMENTAL

The IR spectra were run on the UR-20 spectrophotometer (in a film or in KBr tablets). The mass spectra were obtained on the "Varian CH-6" apparatus. The PMR spectra were run on the "Tesla BS-467" spectrometer (60 MHz), with reference to TMS as internal standard. The GLC was carried out on the LKhM-8MD chromatograph (carrier gas helium, 20 ml/min, 180-230°C). Column (100 × 0.3 cm) with 6% SE-30 on N-AW-HMDS Chromatone, 0.125-0.160 mm. The melting points were determined on a microscopic stage "Boetius."

Na Salt of 5-(2,4-Dinitrophenylthio)-4-acetylaminohexen-3-oic Acid (IIa). A 1.06-g portion (0.045 g-atom) of finely cut sodium was added slowly at −40°C to a solution of 1.99 g (0.01 mole) of (Ia) [3] in 3.7 g of absolute ethanol in 150 ml of liquid NH_3. The mixture was stirred for 50 min, and then 1.08 g (0.02 mole) of NH_4Cl were added. Ammonia was evaporated, and 80 ml of absolute alcohol were added to the residue to form a suspension. After the mixture was stirred, 4.1 g (0.01 mole) of DNCB in 50 ml of alcohol were gradually added to the solution, and stirring was continued at the boiling point for 20 min. The mixture was cooled and filtered from the bis(2,4-dinitrophenyl) sulfide formed [1.05 g (29%), mp 198-200 °C]. The filtrate was evaporated, and the residue was repeatedly washed with absolute ether and recrystallized from i-PrOH. Yield, 65%, mp 148-151°C. Found, %: C 42.59; H 3.77; N 10.97; S 7.95. $C_{14}H_{14}NaN_3O_7S$. Calculated, %: C 42.97; H 3.61; N 10.74; S 8.19. PMR spectrum [in $(CD_3)_2SO$, δ, ppm]: 1.53 d (3H, CH_3, J = 7.0 Hz), 1.92 s (3H, CH_3CO), 3.36 d (2H, CH_2, J = 7.8 Hz), 4.91 q (1H, CHS, J = 7.0 Hz), 6.09 t (1H, =CH, J = 7.8 Hz), 7.89 d (1H, H^6, J_o = 8.8 Hz), 8.39 d.d (1H, H^5, J_o = 8.8, J_m = 2.9 Hz), 8.80 d (1H, H^3, J_m = 2.9 Hz).

5-(2,4-Dinitrophenylthio)-4-oxocaproic Acid (IIIa). A 1.99-g portion of acid (Ia) was reduced by the method described above. After evaporation of NH_3, the residue was dissolved (under N_2) in a mixture of 25 ml of alcohol and 10 ml of water and the solution was added slowly to a solution of DNCB in 50 ml of alcohol. The mixture was stirred for 30 min and boiled for 20 min. When cool, it was filtered from bis(2,4-dinitrophenyl) sulfide which precipitated (0.64 g, 18%). One-third of the filtrate was evaporated, then diluted by water to 300 ml, extracted by ether, and acidified. The precipitate was separated and boiled for 2.5 h, with 250 ml of water containing 1 ml of concentrated HCl. Yield, 1.47 g (45%) of (IIIa), mp 168-170°C. Found, %: C 43.95; H 3.69; N 8.56; S 9.71. $C_{12}H_{12}N_2O_7S$. Calculated, %: C 43.90; H 3.69; N 8.53; S 9.77. PMR spectrum (in C_5D_5N, δ, ppm): 1.68 d (3H, CH_3, J = 7.4 Hz), 2.64-3.32 m (4H, CH_2CH_2), 4.74 q (1H, CH, J = 7.4 Hz), 7.84 d (1H, H^6, J_o = 9.0 Hz), 8.30 d.d (1H, H^5, J_o = 9.0, J_m = 2.8 Hz), 8.94 d (1H, H^3, J_m = 2.8 Hz). IR spectrum (ν, cm^{-1}): 1710 and 1700 (C=O), 1590, 1510 (C–C_{arom}), 1535, 1345, 740 (C_{arom}–NO_2), 1250 (C–O).

Methyl 5-Benzylthio-4-oxocaproate (IVb). a) A 1.15-g portion (0.05 g-atom) of sodium was gradually added to a solution of 1.99 g (0.01 mole) of (Ia) and 2.76 g (0.06 mole) of absolute alcohol in 100 ml liquid NH_3, stirred at −40°C in an inert gas atmosphere. After 40 min, 2.7 g (0.05 mole) of NH_4Cl, and at −73°C, 1.9 g (0.015 mole) of benzyl chloride were added to the mixture, which was then stirred for 30 min. The cooling was stopped and NH_3 was evaporated. The residue was acidified by dilute HCl and extracted by ether. The extract was evaporated, and the residue was boiled for 5 h with 30 ml of water, and then extracted by ether. The extract was dried over $MgSO_4$, concentrated to a small volume, and treated with an ether solution of CH_2N_2. After evaporation of the solvent, 2.0 g (75%) of ester (IVb) were obtained, bp 160-170°C (0.05 mm) (bath temperature). Found, %: C 63.08; H 6.85; S 12.14. $C_{14}H_{18}O_3S$. Calculated, % : C 63.13; H 6.81; S 12.04. PMR spectrum ($CDCl_3$, δ, ppm): 1.33 d (2H, CH_3—C, J = 7.1 Hz), 2.40-3.00 m (4H, CH_2CH_2), 3.32 q (1H, CH), 3.6 br. s (5H, CH_3O and CH_2S), 7.27 m (5H, C_6H_5). Mass spectrum, m/z (relative intensity, %), fragment: 266(4) M^+, 151(37) $[PhCH_2S(CH_3)CH]^+$, 123(21)$[PhCH_2S]^+$, 115(68) $[CH_2OCO(CH_2)_2CO]^+$, 91(100) $[PhCH_2]^+$. IR spectrum (ν, cm^{-1}): 1700 (C=O), 1735 (COOMe), 1500, 1600 (C—C_{arom}).

b) By reducing 1.87 g (0.01 mole) of 5-methyl-4-nitro-2-thiophenecarboxylic acid (Va) by means of 0.11 g-atom of Na and 0.15 mole of alcohol, and alkylation with 0.015 mole of benzyl chloride by method a), 1.95 g of crude acid (IIIb) were obtained, and after treatment with CH_2N_2 and distillation, 1.2 g (45%) of methyl ester (IVb) were obtained. According to IR and PMR spectra, the product was identical with the above sample.

5-Benzylthio-4-oxovaleric acid (IIIc). A 1.85-g portion (0.01 mole) of (Ib), 1.15 g (0.05 g-atom), 2.76 g (0.06 mole) of alcohol, and 1.5 g (0.015 mole) of benzyl chloride were treated by the method described for (IIIb). After evaporation of the ether extract, 1.26 g (53%) of (IIIc) were obtained, mp 76-78°C (from 20% alcohol). Found, %: C 60.06; H 5.69; S 13.50. $C_{12}H_{14}O_3S$. Calculated, %: C 60.48; H 5.92; S 13.46. PMR spectrum ($CDCl_3$, δ, ppm): 2.40-2.98 m (4H, CH_2CH_2), 3.10 s (2H, SCH_2CO), 3.63 s (2H, $PhCH_2S$), 7.21 m (5H, C_6H_5), 10.08 s (1H, COOH).

Methyl ester IVc was obtained by the action of CH_2N_2 on (IIIc) in ether, bp 180-210°C (0.05 mm) (bath temperature). Mass spectrum, m/z (relative intensity, %), fragment: 252(13) M^+, 123(13) $[PhCH_2S]^+$, 91(100) $[PhCH_2]^+$. IR spectrum (ν, cm^{-1}): 1702 (C=O), 1737 (COOMe), 1270, 1050 (COC), 1500-1600 (C—C_{arom}). Phenylsemicarbazone of acid (IIIc): mp 165-168°C (from aqueous alcohol). Found, %: C 62.02; H 5.55; N 11.06; S 8.68. $C_{19}H_{21}N_3O_3S$. Calculated, %: C 61.43; H 5.70; N 11.31; S 8.63.

Methyl 5-Benzylthio-4-oxoenanthate (IVd). a) A 2.13-g portion (0.01 mole) of Ic, 1.15 g of Na, 3.22 g of alcohol, and 1.9 of benzyl chloride were treated by the above method for (IVb) to yield 2.02 g (72%) of ester (IVd), bp 180-200°C (0.05 mm) (bath temperature). Found, %: C 64.28; H 7.26; S 11.31. $C_{15}H_{20}O_3S$. Calculated, %: C 64.25; H 7.19; S 11.43. PMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 0.93 t (3H, CH_3, J = 7.2 Hz), 1.50-2.10 m (2H, CH_2 in C_2H_5, J = 7.2 Hz), 2.45-3.00 m (4H, CH_2CH_2), 3.16 t (1H, CH, J = 7.2 Hz), 3.62 s (3H, CH_3O), 3.67 s (2H, $PhCH_2S$), 7.28 br. s (5H, C_6H_5). Mass spectrum m/z (relative intensity, %), fragment: 280(1.5) M^+, 165(10) $[PhCH_2S(Et)CH]^+$, 123(4) $[PhCH_2S]^+$, 115(21) $[CH_3OCO—(CH_2)_2CO]^+$, 91(100) $[PhCH_2]^+$. IR spectrum (ν, cm^{-1}): 1702 (C=O), 1737 (COOMe), 1500, 1600 (C—C_{arom}).

b) Ester (IVd) was obtained by reducing 5-ethyl-4-nitro-2-thiophenecarboxylic acid (Vb) by Na and alcohol in liquid NH_3, followed by treatment with benzyl chloride and CH_2N_2 in the same way as ester (IVb), in a yield of 67%.

CONCLUSIONS

1. Opening of the thiophene ring in acetylamino-2-thiophenecarboxylic acids by the action of Na in liquid ammonia leads to salts of 4-acetylamino-5-mercaptoalkenoic acid. After alkylation and saponification these salts are converted to 5-alkylthio-4-ketoalkanoic acids.

2. A preparative method has been developed for the synthesis of 5-alkylthio-4-ketoalkanoic acids by reductive cleavage of 4-nitro-2-thiophenecarboxylic acids.

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REACTION OF COMBINATION OF TRIMETHYLVINYLSILANE WITH ORGANIC HALIDES CATALYZED BY PALLADIUM DERIVATIVES

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The reactions of cleavage of the Si—C bonds by the action of transition metal complexes open up new paths for using organosilicon compounds in organic synthesis and catalysis [1]. Recently, research workers have paid great attention to the vinylation reactions of organic halides by means of organometallic compounds, catalyzed by transition metal complexes [2-4]. Interest in the synthesis of vinyl compounds is due to their wide use in practice.

In the present work, we carried out the vinylation of halides of the benzene, naphthalene, pyridine, and carborane series by reaction with trimethylvinylsilane in the presence of catalytic amounts of Pd complexes at 100°C in DMFA or in hexametapol (HMPT).

$$Me_3SiCH{=}CH_2 + RX \xrightarrow{Cat} RCH{=}CH_2 + Me_3SiX \xrightarrow{1/2\,H_2O} Me_3SiOSiMe_3 + HX$$

Table 1 shows that, in the case of halo-derivatives of pyridine, the bromide is more active than the iodide, while for halides of the naphthalene series, the opposite is observed.

The vinylation reaction is catalyzed not only by bis-π-allylpalladium chloride, but also by a wide range of Pd(II) and Pd(0) derivatives: $LiPdCl_3$, $(PhCN)_2PdCl_2$, $(MeCN)_2PdCl_2$, $(Ph_3P)_4Pd$, Pd/C. According to their activity in the vinylation reaction, the Pd complexes can be arranged in the following sequence:*

*The yields of styrene at 100°C after 5 h are given in brackets.

TABLE 1. Reactions of Combination of $Me_3SiCH{=}CH_2$ with RX Catalyzed by $(\pi\text{-}C_3H_5PdCl)_2$ (DMFA, 100°, 5 h, molar ratio silane: RX:catalyst = 2:1:0.1)

RX	Yield of RCH = CH_2, % based on RX	RX	Yield of RCH = CH_2, % based on RX
α-Iodonaphthalene	55	Iodobenzene	35
α-Bromonaphthalene	2	Iodobenzene	53*
9-Iodo-m-carborane	4	p-Ethoxyiodobenzene	14
α-Bromopyridine	30	p-Nitroiodobenzene	10
α-Iodopyridine	23	p,p'-Diiodobenzene	5

*In the presence of Et_3N, after 15 h.

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