Synthesis of 2-alkyl-2-(3-cyanopyridin-2-ylthio)propionic acids

V. K. Zav´alova, A. A. Zubarev, and V. P. Litvinov*†

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (499) 135 5328. E-mail: zvk@ioc.ac.ru

Derivatives of 2-alkyl-2-mercaptopropionic acid were synthesized based on the substituted 3-cyanopyridin-2(1*H*)-thiones. The synthesis was carried out by the heating of a mixture of thione, alkyl methyl ketone, and chloroform in the presence of a base. The reaction proceeds readily for acetone, whereas alkyl methyl ketones require a prolonged heating in the presence of a phase-transfer catalyst. Methyl esters were prepared from the acids obtained.

Key words: 3-cyanopyridin-2(1*H*)-thiones, alkyl methyl ketones, 2-alkyl-2-mercaptopropionic acids, ketoform reaction, phase-transfer catalyst.

2-(Aryloxy)isobutyric acids are known to have a pronounced biological activity. Clofibrate[1,2] and Clofenapate,[3] alkyl esters of 2-(aryloxy)isobutyric acids, used for the atherosclerosis treatment, can serve as the examples. The replacement of the chlorine atom in clofibrat structure by electron-withdrawing heterocyclic fragment, such as pyrimidin-4-yl and 5-chloro-2-thienyl, increases hypolipidemic activity (the ability to decrease the cholesterol level in blood).[3]

Thiophenol derivatives of 2-mercaptoisobutyric acids also showed a high hypocholesterolemic activity.[2] Though on the whole, derivatives of 2-mercaptopropionic and 2-mercaptoisobutyric acids with hypolipidemic properties are far less studied than the corresponding oxygen-containing compounds, they are of much interest from the point of view of their biological activity. The data, obtained for the 5-(arylthioalkyl)- and 5-(aryloxyalkyl)tetrazole derivatives, can serve as the confirmation of this: they also show hypocholesterolemic properties with the mechanism of action similar to that of Clofibrate.[4] It was found that the activity of (arylthioalkyl)tetrazoles, as a rule, is higher, whereas the toxicity is lower, than those in the corresponding oxygen-containing compounds.

Judging from the foregoing, it seems prospective to synthesize 2-mercaptoisobutyric acid derivatives on the basis of the substituted 3-cyanopyridin-2(1*H*)-thiones, which are used in the synthesis of biologically active substances.[5] These compounds contain, on one hand, electron-withdrawing cyanopyridine fragment, on the other hand, the active sulfur atom, being, at the same time, easily available.

† Deceased.

Results and Discussion

Substituted 2-hydroxy-, 2-mercapto-, and 2-aminoisobutyric acids can be synthesized, as a rule, by three methods: upon alkylation of a substrate with 2-bromoisobutyric acid, upon treatment with 1,1,1-trichloro-2-methyl-2-propanol, obtained from acetone and chloroform, as well as upon direct treatment with acetone, chloroform, and an alkali (the ketoform reaction).[2,3] In our case, the ketoform reaction was used as the most simple and convenient method of the synthesis.

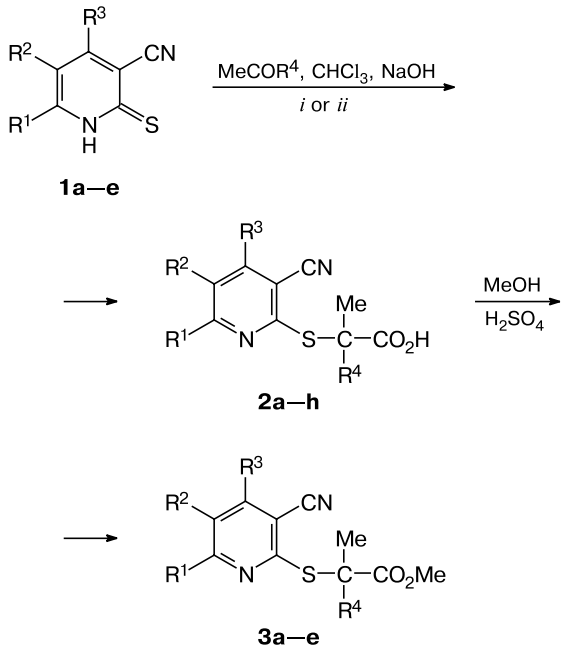
We found that the reaction of chloroform, alkyl methyl ketone, sodium hydroxide, and substituted 3-cyanopyridin-2(1*H*)-thiones **1a—e** leads to the formation of acids **2a—h** in good yields (Scheme 1 and Table 1).

In case of acetone, a reflux of a mixture of thione, $CHCl_3$, and NaOH with acetone in excess as the solvent for 2 h was found to be the optimal. When other alkyl methyl ketones were used under these conditions, isolation of the target acids failed. In case of butan-2-one, even a prolonged heating gives only traces of acid **2**, returning unchanged thione **1**, which, apparently, can be explained both by the decreasing solubility of the reagents (thiolate and sodium hydroxide) in the ketone and by lower accessibility of the reaction center, carbonyl group.

We used a phase-transfer catalyst, tetra-*n*-butylammonium bromide, in the reaction with alkyl methyl ketones. In case of acetone, the reaction proceeds at room temperature, whereas for ethyl methyl, methyl propyl, and isobutyl methyl ketones the optimal conditions were 45 °C during 10 h. The higher methyl ketones, for example, nonan-2-one, do not react in the presence of tetra-*n*-butylammonium bromide even under the more drastic conditions: prolonged heating and high temperature.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 1967—1970, October, 2007.

Scheme 1



i. Excess of $MeCOR^4$ (R^4 = Me), reflux, 2 h.
ii. Excess of $MeCOR^4$ (R^4 = Et, Pr^n, Bu^i), Bu_4NBr, 45 °C, 10 h

Compound	R^1 ($R^1 + R^2$)	R^2	R^3	R^4
1a, 2a	Me	H	H	Me
1b, 2b	Me	H	Me	Me
1c, 2c	Pr^n	H	H	Me
1d, 2d	Bu^i	H	H	Me
1e, 2e	$(CH_2)_4$		H	Me
2f	Me	H	H	Et
2g	Me	H	H	Pr^n
2h	Me	H	H	Bu^i

Acids **2a—h** were obtained as yellow or light brown crystalline substances with precise melting points. Their structures were confirmed by IR and ^{1}H NMR spectroscopic, as well as by mass spectrometric data (Table 2). In the IR spectra of acids **2a—h**, there is an absorption band of the carboxy group in the region 1700 cm^{-1} and of the nitrile group at 2224 cm^{-1}. In the ^{1}H NMR spectra, a singlet in the region 1.6—1.7 ppm of two methyl groups ($\underline{Me}_2CCO_2H$) with the total intensity of six protons or of one methyl group ($R\underline{Me}CCO_2H$) is characteristic of compounds **2a—e** and of acids **2f—h**, respectively.

Methyl esters **3a—e** were synthesized from the acids obtained, the structures of which were confirmed by IR and ^{1}H NMR spectroscopy. The optimal conditions for the synthesis of the methyl esters (see Table 2) include a reflux of acids **2a—e** in excess methanol (10 mL of MeOH per 1 g of acid) in the presence of sulfuric acid (1 mL of concentrated H_2SO_4 per 10 mL of MeOH) for 8 h. When the concentration of sulfuric acid or the reaction time were increased, a side product from the hydrolysis of the nitrile group to carboxy group with its subsequent esterification is formed along with the ester. Thus, after reflux for 15 h, the content of methyl 2-methyl-2-(3-methoxycarbonylpyridin-2-ylthio)propionate in the final product was 8%, which was confirmed by the ^{1}H NMR spectrum: a signal of the second methoxycarbonyl group appeared downfield shifted from the main peak.

Thus, we showed the reaction of alkyl methyl ketones and chloroform with substituted 3-cyanopyridin-2(1*H*)-thiones in the presence of a base leads to the formation of the substituted 2-mercaptopropionic acids. In case of acetone, the reaction proceeds quite readily, whereas alkyl methyl ketones require a prolonged heating in the presence of a phase-transfer catalyst. The higher alkyl methyl

Table 1. Characteristics of compounds **2a—h** and **3a—e**

Compound	Mol. weight	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)			Molecular formula
				C	H	N	
2a	236	80	197—200 (AcOEt)	<u>56.14</u> 55.92	<u>5.09</u> 5.12	<u>11.94</u> 11.86	$C_{11}H_{12}N_2O_2S$
2b	250	77.5	182—184 (AcOEt)	<u>57.70</u> 57.58	<u>5.60</u> 5.64	<u>11.23</u> 11.19	$C_{12}H_{14}N_2O_2S$
2c	264	74.5	168.5—169.5 (AcOEt)	<u>59.21</u> 59.07	<u>6.04</u> 6.10	<u>10.68</u> 10.60	$C_{13}H_{16}N_2O_2S$
2d	278	71	167—169 (AcOEt)	<u>60.55</u> 60.41	<u>6.54</u> 6.52	<u>10.15</u> 10.06	$C_{14}H_{18}N_2O_2S$
2e	276	78	225—227 (AcOEt)	<u>60.93</u> 60.85	<u>5.82</u> 5.84	<u>10.18</u> 10.14	$C_{14}H_{16}N_2O_2S$
2f	250	72	160—161 (AcOEt)	<u>57.71</u> 57.58	<u>5.60</u> 5.64	<u>11.26</u> 11.19	$C_{12}H_{14}N_2O_2S$
2g	264	79.5	151—153 (AcOEt)	<u>59.22</u> 59.07	<u>6.14</u> 6.10	<u>10.52</u> 10.60	$C_{13}H_{16}N_2O_2S$

(*to be continued*)

Table 1 (*continued*)

Compound	Mol. weight	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)			Molecular formula
				C	H	N	
2h	278	36	160—162 (AcOEt)	60.58 / 60.41	6.47 / 6.52	10.14 / 10.06	$C_{14}H_{18}N_2O_2S$
3a	250	80	95—96 (C_6H_{14})	57.70 / 57.58	5.60 / 5.64	11.26 / 11.19	$C_{12}H_{14}N_2O_2S$
3b	264	81	79—80 (C_6H_{14})	59.22 / 59.07	6.15 / 6.10	10.53 / 10.60	$C_{13}H_{16}N_2O_2S$
3c	278	78.5	39.5—41 (C_6H_{14})	60.56 / 60.41	6.49 / 6.52	10.16 / 10.06	$C_{14}H_{18}N_2O_2S$
3d	292	80	57—59 (C_6H_{14})	61.80 / 61.62	6.83 / 6.89	9.65 / 9.58	$C_{15}H_{20}N_2O_2S$
3e	290	85	155—156 (C_6H_{14})	62.12 / 62.04	6.23 / 6.25	9.70 / 9.65	$C_{15}H_{18}N_2O_2S$

Table 2. Spectral characteristics of compounds **2a—h** and **3a—e**

Compound	IR spectrum, ν/cm^{-1}	MS, m/z (I (%))	^{1}H NMR spectrum (δ, J/Hz)
2a	1704 (CO_2H); 2228 (CN)	236 $[M]^+$ (3.2), 192 (26.1), 177 (18.1), 159 (62.8), 150 (100), 117 (15.4), 106 (34.0), 90 (16.8), 69 (9.6), 59 (23.9), 41 (40.4)	1.70 (s, 6 H, CMe_2); 2.55 (s, 3 H, C(6)Me); 7.08 (d, 1 H, H(5), J = 7.4); 7.82 (d, 1 H, H(4), J = 7.4)
2b	1708 (CO_2H); 2224 (CN)	250 $[M]^+$ (2.9), 192 (20.6), 164 (100), 131 (19.5), 104 (37.1), 69 (8.4), 59 (38.2), 41 (32.4)	1.68 (s, 6 H, CMe_2); 2.42 (s, 6 H, C(4)Me, C(6)Me); 6.77 (s, 1 H, H(5))
2c	1704 (CO_2H); 2224 (CN)	264 $[M]^+$ (1.2), 220 (27.3), 205 (23.5), 187 (90.8), 163 (29.6), 150 (100), 116 (20.1), 105 (10.1), 69 (13.4), 59 (32.3), 45 (24.1), 41 (75.6), 39 (48.5)	0.85 (t, 3 H, Me-γ, J = 7.5); 1.63 (s, 6 H, CMe_2); 1.70 (m, 2 H, C(2)H_2); 2.69 (t, 2 H, C(1)H_2, J = 7.3); 7.15 (d, 1 H, H(5), J = 7.4); 8.15 (d, 1 H, H(4), J = 7.4)
2d	1708 (CO_2H); 2228 (CN)	234 (1.8), 192 (8.2), 177 (6.9), 150 (34.3), 116 (5.1), 86 (11.3), 64 (6.2), 44 (100), 41 (42.4), 39 (40.9)	0.85 (d, 6 H, Me_2CH, J = 6.5); 1.63 (s, 6 H, CMe_2); 2.15 (m, 1 H, CH); 2.59 (d, 2 H, CH_2, J = 6.6); 7.12 (d, 1 H, H(5), J = 7.4); 8.06 (d, 1 H, H(4), J = 7.4)
2e	1712 (CO_2H); 2220 (CN)	276 $[M]^+$ (0.9), 232 (30.8), 217 (27.1), 199 (100), 190 (94.5), 162 (24.1), 158 (17.4), 77 (13.8), 74 (10.9), 69 (9.7), 59 (27.8), 45 (22.7), 41 (59.1), 39 (38.8)	1.60 (s, 6 H, CMe_2); 1.72 (m, 2 H, C(7)H_2); 1.80 (m, 2 H, C(5)H_2); 2.69 (t, 2 H, C(8)H_2, J = 3.0); 2.77 (t, 2 H, C(5)H_2, J = 3.1); 7.89 (s, 1 H, H(4))
2f	1708 (CO_2H); 2228 (CN)	250 $[M]^+$ (1.9), 191 (5.8), 178 (45.2), 150 (100), 132 (5.3), 117 (11.1), 106 (19.2), 90 (10.8), 64 (12.1), 55 (23), 39 (18.4)	1.05 (t, 3 H, $MeCH_2$, J = 7.4); 1.66 (s, 3 H, Me); 2.08 (m, 2 H, CH_2Me); 2.58 (s, 3 H, C(6)Me); 7.09 (d, 1 H, H(5), J = 7.4); 7.82 (d, 1 H, H(4), J = 7.4)
2g	1692 (CO_2H); 2228 (CN)	264 $[M]^+$ (0.9), 205 (1.9), 187 (8.6), 178 (68.8), 150 (100), 117 (12.5), 106 (19.2), 90 (12), 69 (22.7), 59 (14.2), 41 (46.2)	0.92 (t, 3 H, $MeCH_2CH_2$, J = 6.9); 1.48 (m, 2 H, $MeCH_2CH_2$); 1.69 (s, 3 H, Me); 2.00 (m, 2 H, $MeCH_2CH_2$); 2.60 (s, 3 H, C(6)Me); 7.10 (d, 1 H, H(5), J = 7.4); 7.84 (d, 1 H, H(4), J = 7.4)
2h	1708 (CO_2H); 2224 (CN)	243 (1.4), 233 (2.7), 202 (3.7), 191 (4.1), 178 (24.3), 150 (100), 137 (30.6), 117 (12.9), 106 (54.6), 86 (60.5), 69 (40.4), 55 (53.1), 45 (25.6)	0.92 (d, 3 H, MeCHMe, J = 6.6); 0.98 (d, 3 H, MeCHMe, J = 6.6); 1.70 (s, 3 H, Me); 1.90 (m, 2 H, CH_2); 2.08 (m, 1 H, CH); 2.61 (s, 3 H, C(6)Me); 7.12 (d, 1 H, H(5), J = 7.4); 7.84 (d, 1 H, H(4), J = 7.4)

(*to be continued*)

Table 2 (*continued*)

Compound	IR spectrum, ν/cm^{-1}	MS, m/z (I (%))	^1H NMR spectrum (δ, J/Hz)
3a	1724 (CO_2Me); 2228 (CN)	250 $[M]^+$ (8.5), 191 (37.1), 150 (100), 117 (6.5), 90 (6.5), 73 (8.4), 59 (14.5), 41 (20.3)	1.70 (s, 6 H, CMe_2); 2.49 (s, 3 H, C(6)Me); 3.70 (s, 3 H, CO_2Me); 6.92 (d, 1 H, H(5), J = 7.4); 7.67 (d, 1 H, H(4), J = 7.4)
3b	1728 (CO_2Me); 2224 (CN)	264 $[M]^+$ (5.5), 205 (22.6), 164 (100), 131 (10.8), 104 (10.4), 73 (20.7), 59 (46.2), 41 (39.4)	1.68 (s, 6 H, CMe_2); 2.42 (s, 6 H, C(4)Me, C(6)Me); 3.68 (s, 3 H, CO_2Me); 6.78 (s, 1 H, H(5))
3c	1724 (CO_2Me); 2224 (CN)	278 $[M]^+$ (35), 263 (2.1), 250 (9.8), 219 (86.3), 178 (100), 163 (17.1), 150 (64.2), 116 (9.3), 59 (24.8), 41 (23.9)	0.93 (t, 3 H, Me-γ, J = 7.5); 1.70 (s, 6 H, CMe_2); 1.72 (m, 2 H, $C(2)H_2$); 2.69 (t, 2 H, $C(1)H_2$, J = 7.3); 3.67 (s, 3 H, CO_2Me); 6.90 (d, 1 H, H(5), J = 7.4); 7.78 (d, 1 H, H(4), J = 7.4)
3d	1728 (CO_2Me); 2228 (CN)	292 $[M]^+$ (4.1), 277 (8.1), 250 (20.4), 233 (53.2), 193 (78.5), 177 (35.2), 150 (100), 122 (10.2), 116 (8), 90 (7.6), 69 (19.7), 58 (9.1), 43 (23.1)	0.90 (d, 6 H, $\underline{Me}_2CH$, J = 6.5); 1.68 (s, 6 H, CMe_2); 2.12 (m, 1 H, CH); 2.58 (d, 2 H, CH_2, J = 6.6); 3.67 (s, 3 H, CO_2Me); 6.87 (d, 1 H, H(5), J = 7.4); 7.68 (d, 1 H, H(4), J = 7.4)
3e	1732 (CO_2Me); 2220 (CN)	290 $[M]^+$ (4.6), 231 (17.7), 190 (100), 162 (5.8), 59 (8.8), 41 (16.3)	1.67 (s, 6 H, CMe_2); 1.82 (m, 4 H, $C(6)H_2$ + $C(7)H_2$); 2.70 (t, 2 H, $C(8)H_2$, J = 3.0); 2.82 (t, 2 H, $C(5)H_2$, J = 3.1); 3.70 (s, 3 H, CO_2Me); 7.47 (s, 1 H, H(4))

ketones can not be involved into the reaction. Methyl esters were synthesized from the acids obtained.

Experimental

Melting points were determined on the Kofler heating table. IR spectra were recorded on a Specord M-80 spectrometer in KBr pellets, ^1H NMR spectra were recorded on a Bruker WM 250 spectrometer (250.13 MHz) in $CDCl_3$. The residual signal of $CHCl_3$ (δ_H = 7.25) was used as the internal standard. Mass spectra were recorded on a Finnigan MAT INCOS-50 instrument (energy of ionization was 70 eV).

2-(3-Cyanopyridin-2-ylthio)-2-methylpropionic acids (2a—e) (general procedure). Chloroform (0.6 g, 5 mmol) and NaOH (0.6 g, 15 mmol) were added to a suspension of thione **1a—e** (3 mmol) in acetone (10 mL). The resulting mixture was refluxed for 2 h and cooled, acetone was evaporated, the residue was dissolved in water (40 mL) and washed with ether. The aqueous layer was acidified with HCl, the precipitate formed was filtered off and recrystallized from ethyl acetate. Acids **2a—e** were obtained as light yellow crystalline powders in 70—80% yield.

2-Alkyl-2-(3-cyanopyridin-2-ylthio)propionic acids (2f—h) (general procedure). Chloroform (0.6 g, 5 mmol), NaOH (0.6 g, 15 mmol), and Bu_4NBr (0.05 g, 0.15 mmol) were added to a suspension of thione **1a** (0.45 g, 3 mmol) in alkyl methyl ketone (15 mL). The resulting mixture was stirred for 10 h at 45 °C. Acids **2f—h** were isolated similarly to preceding procedure as light yellow crystalline powders in 40—80% yield.

Methyl 2-(3-cyanopyridin-2-ylthio)-2-methylpropionates (3a—e) (general procedure). A mixture of acid **2a—e** (2 mmol), MeOH (7 mL), and H_2SO_4 (0.7 mL) was refluxed for 8 h. The excess of MeOH was evaporated from the reaction mixture, the residue was diluted with water and extracted with ether. The extract was washed with aqueous soda solution and water, dried with $MgSO_4$ and concentrated. Esters **3a—e** were obtained as colorless crystalline powders in 80—85% yield.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 05-03-32031).

References

1. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Medicines*], Meditsina, Moscow, 1984, V. **2**, p. 90 (in Russian).
2. F. Andreani, R. Andrisano, and A. Andreani, *Il Farmaco*, 1975, **30**, 847.
3. S. Gronowitz, R. Svenson, G. Bondesson, O. Magnusson, and N. E. Stjernstrom, *Acta Pharm. Suec.*, 1974, **11**, 211.
4. R. L. Buchanan, V. Sprancmanis, and R. A. Partyka, *J. Med. Chem.*, 1969, **12**, 1001.
5. Yu. A. Sharanin, V. K. Promonenkov, V. P. Litvinov, *Itogi nauki i tekhniki, Organicheskaya khimiya* [*Results of Science and Technique, Organic Chemistry*], VINITI, Moscow, 1991, V. **20** (2), p. 73 (in Russian).

Received 1 February, 2007;
in revised form 13 September, 2007