3-(2-Methylthiopyridin-3-yl)-3-oxopropionic esters

A. A. Zubarev, V. K. Zav´yalova, and A. M. Shestopalov*

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

A reaction of alkyl bromoacetates with substituted 3-cyano-2-methylthiopyridines in the presence of zinc dust furnishes 3-amino-3-(2-methylthiopyridin-3-yl)propenoic esters. Their hydrolysis under mild conditions leads to 3-(2-methylthiopyridin-3-yl)-3-oxopropionic esters. The latter were used in the synthesis of pyridine-substituted pyrazolones.

Key words: 3-cyano-2-methylthiopyridines, methyl bromoacetate, ethyl bromoacetate, zinc dust, 3-(2-methylthiopyridin-3-yl)-3-oxopropionic acids, hydrazine, dinitrophenylhydrazine, pyridylpyrazolones, the Blaise reaction.

Substituted compounds of pyridine series are key building blocks frequently used in the synthesis of biologically active compounds and for preparation of new fused heterocyclic systems. Earlier, working on the methods for functionalization of a nitrile group in substituted 3-cyanopyridine-2(1*H*)-thiones and their alkylthio derivatives, we studied their reaction with alkyllithium compounds.[1—3] The carbonyl compounds obtained, as well as the products of their bromination were found to be convenient reagents for the synthesis of fused heterocyclic systems and 3-hetaryl-substituted 2-alkylthiopyridines.[1,3] In continuation of these studies, it seems promising to develop methods for the synthesis of more complex pyridine-2(1*H*)-thions substituted at position 3 and their alkylthio derivatives containing several reactive groups. Substituted 3-pyridoylacetic esters are of interest from this point of view. Such compounds are widely used in the preparation of annulated heterocyclic systems and 3-hetaryl-substituted pyridines displaying biological activities of various kinds.[4,5]

Separate examples of synthesis of 2-alkylthio-3-pyridoylacetic esters are based on the transformation of corresponding nicotinic acids using organolithium compounds or metallic sodium.[6,7]

At the same time, another method for the synthesis of β-keto esters from nitriles by the Blaise reaction which uses zinc and bromoacetic ester found wide application in the synthetic practice.[8] The use of this method in the present work seems promising, since it allows us to use easily available 3-cyano-2-methylthiopyridines for the synthesis of the target compounds. It should be especially noted that the intermediately obtained 3-amino-3-(pyridin-3-yl)propenoic esters are not virtually described in the literature (there are only several publications[9—11] on these compounds unsubstituted at the pyridine ring), though they can also be of certain interest as starting compounds in the synthesis of β-amino acids and some heterocyclic compounds.

Results and Discussion

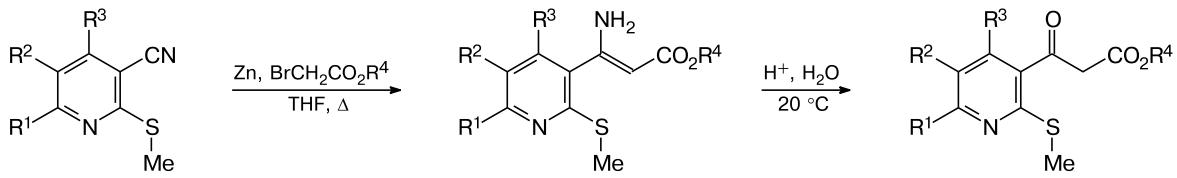
The reaction of 3-cyano-2-methylthiopyridines **1a—e** with ethyl- or methyl bromoacetate in the presence of activated zinc dust upon reflux in THF leads to enamino esters **2a—f** in good yields (Scheme 1). We found that optimum yield of compounds **2a**,**d—f** obtained from pyridines **1a**,**d**,**e** is reached at the ratio of the starting reagents 1 : 4 : 6. In the case of pyridines **1b**,**c**, such a ratio of reagents leaves up to 25% of the starting compound in the reaction products (the ^{1}H NMR data). Apparently, this is due to the steric effect of the substituent at position 4 of the pyridine ring. The ratio of reagents 1 : 6 : 10 is the optimum for pyridines **1b,c**, but even in this case the content of the starting pyridine in **2b** is no less than 15%. In this connection, enamino ester **2b** was characterized in the form of oxalate.

Enamino esters **2a—f** are white or light yellow crystalline powders, whose structures were confirmed by IR and ^{1}H NMR spectroscopy and mass spectrometry. The IR spectra of compounds **2a—f** exhibit two absorption bands of the amino group in the region 3300—3450 cm^{-1} and an absorption band of the conjugated ester group at 1660—1668 cm^{-1}. The ^{1}H NMR spectra are characterized by the presence of signals for the protons of the alkyl group of the ester fragment, as well as a signal for the proton of the fragment C=CH as a singlet with the intensity of one proton at δ 4.6—4.8 (Table 1).

Enamino esters **2a**,**d—f** are easily and in high yields hydrolyzed in THF in the presence of dilute HCl at 20 °C to the corresponding β-keto esters **3a**,**d—f**. At the same time, compounds **2b**,**c** do not hydrolyze under these conditions.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 514—519, March, 2011.

Scheme 1



1a—e **2a—f** **3a,d—f**

1, **2**	R^1	R^2	R^3	R^4
a	Me	H	H	Et
b	Me	H	Me	Et
c	Ph	H	Ph	Et
d	Et	Me	H	Et
e	3,4-$(OCH_2O)C_6H_3$	H	H	Et
f	Me	H	H	Me

3	R^1	R^2	R^3	R^4
a	Me	H	H	Et
d	Et	Me	H	Et
e	3,4-$(OCH_2O)C_6H_3$	H	H	Et
f	Me	H	H	Me

Table 1. Spectroscopic characteristics of compounds **1d,e**, **2a—f**, **3a,d—f**, **4a,d,e**, **5a,d,e**, and **6a,d**

Compound	IR, ν/cm^{-1}	MS, m/z (I (%))	^{1}H NMR, δ (J/Hz)
1d[a]	2212 (CN)	192 $[M]^+$ (100), 177 (21.7), 159 (88.1), 146 (67.1), 132 (19.9), 116 (33.4), 102 (13.3), 96 (6.3)	1.24 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.1); 2.23 (s, 3 H, Me(5)); 2.60 (s, 3 H, SMe); 2.79 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.1); 7.90 (s, 1 H, H(4))
1e[a]	2220 (CN)	270 $[M]^+$ (100), 255 (19.0), 225 (20.6), 179 (29.9), 165 (24.5), 140 (17.8), 131 (64.3), 105 (36.0), 77 (52.4)	2.68 (s, 3 H, SMe); 6.11 (s, 2 H, OCH_2O); 7.04 (d, 1 H, C_6H_3 (H(5)), J = 8.2); 7.70—7.80 (m, 3 H, H(4) + + C_6H_3 (H(2) + H(6))); 8.12 (d, 1 H, H(5), J = 8.1)
2a[b]	3408, 3304 (NH_2); 1660 (C=CH, CO_2Et)	252 $[M]^+$ (43.4), 237 (57.3), 207 (17.5), 205 (42.6), 191 (29.4), 179 (37.1), 165 (100), 146 (31.5), 119 (28.7), 105 (41.3)	1.29 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.1); 2.53 (s, 3 H, SMe); 2.55 (s, 3 H, Me(6)); 4.18 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.1); 4.76 (s, 1 H, CH); 6.86 (d, 1 H, H(5), J = 7.7); 7.40 (d, 1 H, H(4), J = 7.7)
2b[b]	3440, 3324 (NH_2); 1668 (C=CH, CO_2Et)	266 $[M]^+$ (49.7), 251 (100), 221 (39.5), 219 (49.8), 205 (34.9), 193 (74.8), 179 (87.3), 164 (30.4), 151 (30.7), 145 (40.6), 132 (33.3), 107 (26.6)	1.29 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.1); 2.25 (s, 3 H, Me(4)); 2.47 (s, 3 H, SMe); 2.51 (s, 3 H, Me(6)); 4.17 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.1); 4.62 (s, 1 H, CH); 6.72 (s, 1 H, H(5))
2c[b]	3444, 3324 (NH_2); 1664 (C=CH, CO_2Et)	390 $[M]^+$ (5.2), 375 (100), 345 (8.4), 317 (21.0), 302 (31.1), 160 (31.8), 98 (33.4)	1.27 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.1); 2.68 (s, 3 H, SMe); 4.13 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.1); 4.77 (s, 1 H, CH); 7.40—7.55 (m, 9 H, 4-Ph (H(2)—H(6)) + 6-Ph (H(3)—H(5)) + H(5)); 8.12 (d, 2 H, 6-Ph (H(2), H(6)), J = 7.8)
2d[b]	3448, 3328 (NH_2); 1668 (C=CH, CO_2Et)	280 $[M]^+$ (6.3), 265 (21.8), 233 (69.7), 219 (14.0), 205 (28.7), 193 (100), 178 (11.3), 146 (10.3), 102 (20.3)	1.28 (m, 6 H, $CO_2CH_2C\underline{H}_3$ + $CH_2C\underline{H}_3$); 2.22 (s, 3 H, Me(5)); 2.53 (s, 3 H, SMe); 2.77 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.1); 4.15 (q, 2 H, $CO_2C\underline{H}_2CH_3$, J = 7.1); 4.74 (s, 1 H, CH); 7.24 (s, 1 H, H(4))
2e[b]	3412, 3296 (NH_2); 1668 (C=CH, CO_2Et)	358 $[M]^+$ (26.6), 343 (100), 311 (21.7), 285 (32.2), 270 (88.1), 101 (58.7)	1.31 (t, 3 H, $CH_2C\underline{H}_3$, J = 7.1); 2.65 (s, 3 H, SMe); 4.19 (q, 2 H, $C\underline{H}_2CH_3$, J = 7.1); 4.83 (s, 1 H, CH); 6.04 (s, 2 H, OCH_2O); 6.91 (d, 1 H, C_6H_3 H(5), J = 8.2); 7.38 (d, 1 H, H(4), J = 7.9); 7.54—7.62 (m, 3 H, H(5) + C_6H_3 (H(2) + H(6)))
2f[b]	3424, 3312 (NH_2); 1668 (C=CH, CO_2Me)	238 $[M]^+$ (24.5), 223 (71.3), 191 (66.4), 179 (34.3), 164 (100), 136 (12.6), 118 (21.0),	2.52 (s, 3 H, SMe); 2.53 (s, 3 H, Me(6)); 3.70 (s, 3 H, CO_2Me); 4.76 (s, 1 H, CH); 6.86 (d, 1 H, H(5), J = 7.7); 7.39 (d, 1 H, H(4), J = 7.7)

(*to be continued*)

Table 1 (*continued*)

Compound	IR, ν/cm^{-1}	MS, *m/z* (*I* (%))	^{1}H NMR, δ (*J*/Hz)
3a[b]	1740 (CO_2Et); 1672 (C=O)	253 $[M]^+$ (16.8), 238 (11.2), 219 (23.1), 207 (14), 179 (37.8), 165 (100), 135 (47.9), 91 (54.5)	1.25 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.1); 2.52 (s, 3 H, SMe); 2.57 (s, 3 H, Me(6)); 3.94 (s, 2 H, $COC\underline{H}_2$); 4.20 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.1); 6.92 (d, 1 H, H(5), *J* = 8.0); 7.92 (d, 1 H, H(4), *J* = 8.0)
3d[b]	1716 (CO_2Et); 1672 (C=O)	281 $[M]^+$ (12.6), 266 (11.9), 249 (34.3), 236 (11.7), 208 (26.6), 193 (100), 177 (13.8), 164 (16.3), 160 (29.0), 146 (16.2), 121 (13.8), 91 (18.9)	1.23—1.35 (m, 6 H, $CO_2CH_2C\underline{H}_3$ + $CH_2C\underline{H}_3$); 2.29 (s, 3 H, Me(5)); 2.53 (s, 3 H, SMe); 2.82 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.1); 3.94 (s, 2 H, $COC\underline{H}_2$); 4.19 (q, 2 H, $CO_2C\underline{H}_2CH_3$, *J* = 7.1); 7.73 (s, 1 H, H(4))
3e[b]	1724 (CO_2Et); 1672 (C=O)	359 $[M]^+$ (23.9), 344 (18.6), 327 (43.4), 313 (37.1), 285 (44.8), 272 (100), 254 (43.3), 229 (21.0), 170 (22.4), 140 (21.4), 127 (23.9), 113 (22.2)	1.27 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.1); 2.62 (s, 3 H, SMe); 3.97 (s, 2 H, $COC\underline{H}_2$); 4.22 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.1); 6.04 (s, 2 H, OCH_2O); 6.92 (d, 1 H, C_6H_3 (H(5)), *J* = 8.8); 7.42 (d, 1 H, H(4), *J* = 8.3); 7.64—7.67 (m, 2 H, C_6H_3 (H(2) + H(6))); 8.06 (d, 1 H, H(5), *J* = 8.3)
3f[b]	1740 (CO_2Me); 1668 (C=O)	239 $[M]^+$ (14.7), 224 (9.8), 207 (37.1), 206 (39.9), 192 (19.2), 180 (54.9), 166 (100), 150 (25.2), 136 (48.3), 123 (14.9), 106 (14.6), 92 (44.1)	2.51 (s, 3 H, SMe); 2.56 (s, 3 H, Me(6)); 3.73 (s, 3 H, CO_2Me); 3.96 (s, 2 H, $COCH_2$); 6.92 (d, 1 H, H(5), *J* = 8.0); 7.92 (d, 1 H, H(4), *J* = 8.0)
4a[a]	1616 (CO)	221 $[M]^+$ (100), 206 (10.8), 188 (58.0), 177 (48.3), 163 (26.4), 150 (55.9), 145 (39.8), 118 (20.8), 101 (9.2)	2.47 (s, 3 H, SMe); 2.48 (s, 3 H, Me(6)); 5.86 (s, 1 H, H(4′)); 7.03 (d, 1 H, H(5), *J* = 7.7); 7.63 (d, 1 H, H(4), *J* = 7.7); 9.90 (br.s, 1 H, N(2)H); 11.90 (br.s, 1 H, N(1)H)
4d[a]	1620 (CO)	249 $[M]^+$ (12.7), 216 (8.7), 203 (11.1), 188 (15.4), 178 (100), 158 (20.3), 146 (22.5), 131 (14.8), 125 (12.7)	1.25 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.2); 2.23 (s, 3 H, Me(5)); 2.48 (s, 3 H, SMe); 2.74 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.2); 5.86 (s, 1 H, H(4′)); 7.52 (s, 1 H, H(4)); 10.90 (br.s, 2 H, 2 NH)
4e[a]	1616 (CO)	327 $[M]^+$ (100), 294 (26.6), 270 (13.3), 251 (23.8), 238 (12.0), 224 (14.7), 133 (13.3), 121 (41.3), 101 (21.3)	2.59 (s, 3 H, SMe); 5.95 (s, 1 H, H(4′)); 6.09 (s, 2 H, OCH_2O); 7.03 (d, 1 H, C_6H_3 (H(5)), *J* = 8.4); 7.65—7.85 (m, 4 H, C_6H_3 (H(2) + H(6)), H(5), H(4)); 10.15 (br.s, 1 H, N(2)H); 11.88 (br.s, 1 H, N(1)H)
5a[a]	3292 (NH); 1736 (CO_2Et); 1516 (NO_2); 1332 (NO_2)	433 $[M]^+$ (25.2), 418 (12.8), 237 (37.8), 205 (18.2), 177 (17.8), 164 (100), 118 (60.1), 101 (71.3)	1.31 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.1); 2.58 (s, 3 H, SMe); 2.60 (s, 3 H, Me(6)); 3.90 (s, 2 H, CH_2); 4.29 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.1); 6.97 (d, 1 H, H(5), *J* = 8.0); 7.71 (d, 1 H, H(4), *J* = 8.0); 8.39 (m, 2 H, C_6H_3 (H(5) + H(6))); 9.16 (d, 1 H, C_6H_3 (H(3)), *J* = 2.4); 11.83 (s, 1 H, NH)
5d[a]	3288 (NH); 1732 (CO_2Et); 1516 (NO_2); 1328 (NO_2)	461 $[M]^+$ (16.8), 282 (32.2), 264 (37.2), 249 (45.9), 209 (49.7), 194 (100), 177 (46.2), 164 (44.4), 118 (24.6), 104 (29.2)	1.20 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.1); 1.28 (t, 3 H, $CO_2CH_2C\underline{H}_3$, *J* = 7.1); 2.29 (s, 3 H, Me(5)); 2.51 (s, 3 H, SMe); 2.80 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.1); 4.13 (s, 2 H, CH_2); 4.17 (q, 2 H, $CO_2C\underline{H}_2CH_3$, *J* = 7.1); 7.73 (s, 1 H, H(4)); 8.23 (d, 1 H, C_6H_3 (H(6)), *J* = 9.6); 8.48 (dd, 1 H, C_6H_3 (H(6)), J_3 = 9.6, J_4 = 2.7); 8.89 (d, 1 H, C_6H_3 (H(3)), *J* = 2.7); 11.37 (s, 1 H, NH)
5e[a]	3292 (NH); 1732 (CO_2Et); 1500 (NO_2); 1336 (NO_2)	539 $[M]^+$ (5.1), 270 (100), 165 (9.1), 149 (8.7), 101 (25.9)	1.21 (t, 3 H, $CO_2CH_2C\underline{H}_3$, *J* = 7.1); 2.63 (s, 3 H, SMe); 4.16 (m, 4 H, CH_2 + $CO_2C\underline{H}_2CH_3$); 6.10 (s, 2 H, OCH_2O); 7.05 (d, 1 H, C_6H_3 (H(5)), *J* = 7.8); 7.72—7.87 (m, 3 H, C_6H_3 (H(2) + H(6)), H(4)); 8.02 (d, 1 H, H(5), *J* = 8.3); 8.28 (d, 1 H, 2,4-$(NO_3)_2C_6H_3$ (H(6)), *J* = 9.5); 8.50 (dd, 1 H, 2,4-$(NO_3)_2C_6H_3$ (H(5)), J_3 = 9.5, J_4 = 2.6); 8.91 (d, 1 H, 2,4-$(NO_3)_2C_6H_3$ (H(3)), *J* = 2.7); 11.40 (s, 1 H, NH)
6a[a]	1748 (CO); 1540 (NO_2); 1340 (NO_2)	387 $[M]^+$ (48.9), 358 (10.8), 341 (9.9), 277 (20.3), 178 (97.2), 164 (100), 148 (55.7), 118 (74.1), 92 (65.4)	2.48 (s, 3 H, SMe); 2.54 (s, 3 H, Me(6)); 6.04 (s, 1 H, CH); 7.07 (d, 1 H, H(5), *J* = 7.8); 7.81 (d, 1 H, H(4), *J* = 7.8); 8.11 (d, 1 H, C_6H_3 (H(6)), *J* = 8.9); 8.65 (dd, 1 H, C_6H_3 (H(5)), J_3 = 8.9, J_4 = 2.5); 8.79 (d, 1 H, C_6H_3 (H(3)), *J* = 2.5)

(*to be continued*)

Table 1 (*continued*)

Compound	IR, ν/cm^{-1}	MS, *m/z* (*I* (%))	^{1}H NMR, δ (*J*/Hz)
6d[a]	1748 (CO); 1532 (NO_2); 1340 (NO_2)	415 $[M]^+$ (100), 206 (17.5), 191 (9.4), 173 (8.4), 146 (4.9), 104 (5.0)	1.27 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7.2); 2.26 (s, 3 H, Me(5)); 2.51 (s, 3 H, SMe); 2.77 (q, 2 H, $C\underline{H}_2CH_3$, *J* = 7.2); 6.04 (s, 1 H, CH); 7.69 (s, 1 H, H(4)); 8.09 (d, 1 H, C_6H_3 (H(6)), *J* = 8.9); 8.64 (d, 1 H, C_6H_3 (H(5)), *J* = 8.9); 8.78 (s, 1 H, C_6H_3 (H(3)))

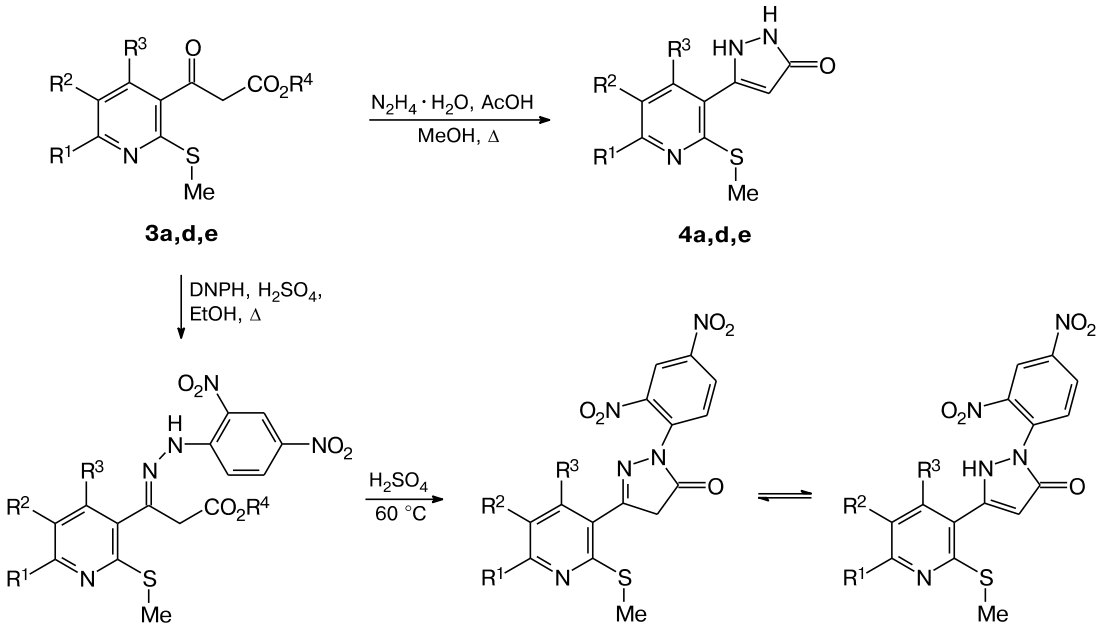
[a] ^{1}H NMR spectra were obtained for solutions in DMSO-d_6.
[b] ^{1}H NMR spectra were recorded for solutions in $CDCl_3$.

β-Keto esters **3a**,**d**—**f** are light yellow low-melting crystalline compounds, their structures were confirmed by IR and ^{1}H NMR spectroscopy and mass spectrometry. The IR spectra of compounds **3a**,**d**—**f** exhibit an absorption band of the ester group at 1715—1740 cm^{-1} and an absorption band of the carbonyl group at 1668—1672 cm^{-1}. The ^{1}H NMR spectra are characterized by the presence of the signals for the protons of the methylene group of the β-keto ester fragment as a singlet with the intensity of two protons at δ 3.94—3.97 (see Table 1).

Compounds **3a**,**d**,**e** as typical β-keto esters react with hydrazine and its 2,4-dinitrophenyl derivative on heating in ethanol in the presence of an acidic catalyst. In the case of hydrazine hydrate, pyrazolones **4a**,**d**,**e** were obtained in good yields (Scheme 2). The reaction with dinitrophenylhydrazine under similar conditions stops at the step of formation of hydrazones **5a**,**d**,**e**. Pyrazolones **6a**,**d** were synthesized by heating compounds **5a**,**d** with concentrated sulfuric acid (see Scheme 2).

Pyrazoles **4a,d,e** are colorless crystals, whereas compounds **5a,d,e** and **6a,d** are red and dark yellow crystalline powders, respectively. Their structures were confirmed by IR and ^{1}H NMR spectroscopy and mass spectrometry. The IR spectra of compounds **5a,d,e** exhibit absorption

Scheme 2



3—6	R^1	R^2	R^3	R^4
a	Me	H	H	Et
d	Et	Me	H	Et
e	3,4-$(OCH_2O)C_6H_3$	H	H	Et

DNPH is 2,4-dinitrophenylhydrazine

bands of the NH group at 3288—3292 cm^{-1}, the ester group at 1732—1736 cm^{-1}, and characteristic absorption bands of the nitro group in the regions 1500 and 1330 cm^{-1}. The ^1H NMR spectra are characterized by the presence of the signal for the NH group as a singlet with the intensity of one proton at δ 11.4—11.8 It is known that pyrazol-5-ones can exist as different tautomeric forms,[12] however, compounds unsubstituted at the nitrogen atom exist as 1,2-dihydropyrazol-5-ones, which was confirmed by X-ray diffraction analysis.[13] The spectral characteristics of obtained by us pyrazoles **4a,d,e** are analogous to those published earlier,[14] that allows us to assign to them the structure of 1,2-dihydropyrazol-5-ones. The IR spectra of pyrazoles **4a,d,e** exhibit an absorption band of the conjugated carbonyl group at 1616—1620 cm^{-1}. The ^1H NMR spectra of pyrazoles **4a,d,e** are characterized by the presence of the signal for the proton at position 4 of the pyrazole ring as a singlet with the intensity of one proton in the region δ 5.86—6.09, as well as the signals for the protons of two NH groups as broad singlets with the intensity of one proton each or as a very broad singlet with the intensity of two protons in the region δ 9.90—11.90.

Unlike for pyrazoles **4a,d,e**, a strong absorption band of the endocyclic amide group at 1748 cm^{-1} is observed in the IR spectra of pyrazoles **6a,d**, that indicates that these compounds in the solid phase exist as 1,4-dihydropyrazol-5-ones, which also agrees with the literature data.[15] However, in DMSO these compounds exist as 1,2-dihydropyrazol-5-ones, and this is confirmed by the ^1H NMR spectroscopic data. Like in the case of pyrazoles **4a**,**d**,**e**, a signal for the proton at position 4 of the pyrazole ring is present as a singlet with the intensity of one proton at δ 6.04.

In conclusion, we synthesized 3-amino-3-(2-methylthiopyridin-3-yl)propenoic esters by the Blaise reaction.[8] The compounds obtained easily hydrolyze to the corresponding β-keto carboxylic esters, which are of interest as building blocks in the synthesis of substituted pyridylpyrazoles.

Experimental

Melting points were determined on a Kofler heating stage. IR spectra were recorded on a Specord M-82 spectrophotometer in KBr pellets, ^1H NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz) in DMSO-d_6 and $CDCl_3$. The solvent signals were used as references (δ_H = 2.5 and 7.27, respectively). Mass spectra were obtained on a Finnigan MAT INCOS-50 instrument (70 eV). Compounds **1a—e** were synthesized similarly to the method described[3] for the preparation of compound **1a**. Physicochemical and spectroscopic characteristics of compounds **1a—c** are identical to those reported earlier,[3,16,17] such characteristics of compounds **1d,e** are given in Tables 1 and 2.

Synthesis of alkyl 3-amino-3-(pyridin-3-yl)prop-2-enoates 2a—f (general procedure). Ethyl or methyl bromoacetate (5 drops out of 12 mmol) was added to a boiling suspension of activated[5] zinc dust (1.2 g, 18 mmol) in THF (10 mL), followed by reflux until the mixture turned light green (~10 min). In the case of

Table 2. Physicochemical characteristics of compounds **1d,e**, **2a—f**, **3a,d—f**, **4a,d,e**, **5a,d,e**, and **6a,d**

Compound	Mol. weight	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)				Molecular formula
				C	H	N	S	
1d	192	91	103—104 (hexane)	62.22 / 62.46	6.32 / 6.29	14.43 / 14.57	16.44 / 16.68	$C_{10}H_{12}N_2S$
1e	270	84	202—204 (AcOEt)	61.94 / 62.21	3.76 / 3.73	10.27 / 10.36	11.59 / 11.86	$C_{14}H_{10}N_2O_2S$
2a	252	92	98—100 (hexane—AcOEt)	56.24 / 57.12	6.33 / 6.39	10.84 / 11.10	12.62 / 12.71	$C_{12}H_{16}N_2O_2S$
2b*	266	81	95—98 (Et_2O)	45.04 / 45.74	4.97 / 4.97	6.34 / 6.27	6.48 / 7.18	$C_{13}H_{18}N_2O_2S$
2c	390	95	152—154 (AcOEt)	70.41 / 70.74	5.75 / 5.68	6.98 / 7.17	8.04 / 8.21	$C_{23}H_{22}N_2O_2S$
2d	280	94	52—56 (hexane)	59.82 / 59.97	7.24 / 7.19	9.91 / 9.99	11.19 / 11.43	$C_{14}H_{20}N_2O_2S$
2e	358	85.5	150.5—152.5 (hexane—AcOEt)	59.68 / 60.32	5.16 / 5.06	7.57 / 7.82	8.72 / 8.95	$C_{18}H_{18}N_2O_4S$
2f	238	90	123.5—124.5 (hexane—AcOEt)	55.27 / 55.44	6.14 / 5.92	11.45 / 11.76	13.37 / 13.45	$C_{11}H_{14}N_2O_2S$
3a	253	100	32—34 (hexane)	57.01 / 56.90	5.93 / 5.97	5.65 / 5.53	12.43 / 12.66	$C_{12}H_{15}NO_3S$

(*to be continued*)

Table 2 (*continued*)

Compound	Mol. weight	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)				Molecular formula
				C	H	N	S	
3d	281	91.5	44—46 (hexane)	59.62 59.76	6.77 6.81	5.11 4.98	11.23 11.39	$C_{14}H_{19}NO_3S$
3e	359	82	112—114 (AcOEt)	60.28 60.16	4.72 4.77	3.86 3.90	8.74 8.92	$C_{18}H_{17}NO_5S$
3f	239	100	56—58 (hexane)	55.30 55.21	5.60 5.48	5.72 5.85	13.20 13.40	$C_{11}H_{13}NO_3S$
4a	221	68	244.5—245.5	54.04 54.28	5.06 5.01	18.90 18.99	14.34 14.49	$C_{10}H_{11}N_3OS$
4d	249	58	216—217	57.23 57.81	6.28 6.06	16.69 16.85	12.09 12.86	$C_{12}H_{15}N_3OS$
4e	327	66	245—248	58.49 58.71	4.12 4.00	12.68 12.84	9.51 9.79	$C_{16}H_{13}N_3O_3S$
5a	433	62.5	175—178 (AcOEt)	50.12 49.88	4.36 4.42	16.24 16.16	7.24 7.40	$C_{18}H_{19}N_5O_6S$
5d	461	77	177.5—179	51.81 52.05	5.08 5.02	15.08 15.18	6.79 6.95	$C_{20}H_{23}N_5O_6S$
5e	539	65	192—195	53.06 53.43	4.04 3.92	12.74 12.98	5.65 5.94	$C_{24}H_{21}N_5O_8S$
6a	387	62	214—217	49.34 49.61	3.45 3.38	17.87 18.08	8.14 8.28	$C_{16}H_{13}N_5O_5S$
6d	415	80	217—220	51.78 52.04	4.19 4.12	16.96 16.86	7.57 7.72	$C_{18}H_{17}N_5O_6S$

* Was isolated as a complex with oxalic acid, melts with decomposition.

synthesis of compounds **2b**,**c**, 1.95 g (30 mmol) of zinc dust and 18 mmol of the corresponding bromo ester were used. Nitrile **1a—e** (3 mmol) was added to the reaction mixture, then, while refluxing, the rest of bromo ester was added dropwise over 1.5 h. The mixture was refluxed for another 10 min, cooled, diluted with THF (20 mL) and 50% aqueous K_2CO_3 (5 mL), and stirred for 30 min. The organic layer was separated, the residue was washed with THF. A combined organic phase was dried with $MgSO_4$, the solvent was evaporated *in vacuo*. The product was recrystallized from hexane—AcOEt (5 : 1) to obtain esters **2a—f** as colorless or light yellow crystals in 80—95% yields (see Table 2).

Synthesis of alkyl 3-pyridoylacetates 3a,d—f (general procedure). A 10% aq. HCl (3 mL) was added to a solution of compound **2a**,**d—f** (2.5 mmol) in THF (20 mL), the mixture obtained was vigorously stirred for 50 min at ~20 °C, then made basic with aq. K_2CO_3, the organic layer was separated, washed with water, and dried with $MgSO_4$. The solvent was evaporated *in vacuo* to obtain esters **3a,d—f** as clear light yellow oils, which crystallized on standing, the yields were 80—100% (see Table 2).

Synthesis of 3-(pyridin-3-yl)-1,2-dihydropyrazol-5-ones 4a,d,e (general procedure). Acetic acid (2 drops) and 64% aq. hydrazine hydrate (0.1 mL, 2 mmol) were added to a solution of keto ester **3a,d,e** (2 mmol) in methanol (5 mL). The solution was refluxed for 3 h and cooled. A precipitate formed was filtered off and washed with hot methanol to obtain pyrazolones **4a,d,e** as colorless crystals in 60—70% yields (see Table 2).

Synthesis of alkyl 3-pyridoylacetate 2,4-dinitrophenylhydrazones 5a,d,e (general procedure). A solution of 2,4-dinitrophenylhydrazine (0.3 g) in ethanol (5 mL) containing sulfuric acid (3 drops) was added to a solution of keto ester **3a,d,e** (1.5 mmol) in ethanol (5 mL), the mixture was refluxed for 1 h. The solution obtained was cooled, a precipitate formed was filtered off. The product was washed with water and recrystallized from AcOEt to obtain hydrazones **5a,d,e** as red crystalline powders in 60—80% yields (see Table 2).

Synthesis of 1-(2,4-dinitrophenyl)-3-(pyridin-3-yl)-1,4-dihydropyrazol-5-ones 6a,d (general procedure). A solution of phenylhydrazone **5a,d** (0.4 mmol) in concentrated sulfuric acid (3 mL) was heated with stirring at 60 °C for 1 h. The solution obtained was cooled, poured into water (10 mL) and neutralized with sodium hydrogen carbonate. Precipitates formed were filtered off, washed with water, and recrystallized from aq. alcohol to obtain compounds **6a,d** in 60—80% yields (see Table 2).

This work was partially financially supported by the Russian Foundation for Basic Research (Project No. 09-03-00349a).

References

1. V. K. Zav´yalova, A. A. Zubarev, V. P. Litvinov, *Izv. Akad. Nauk*, *Ser. Khim.*, 2008, 1504 [*Russ. Chem. Bull.*, *Int. Ed.*, 2008, **57**, 1534].

2. V. K. Zav´yalova, A. A. Zubarev, A. M. Shestopalov, *Izv. Akad. Nauk, Ser. Khim.*, 2008, 2303 [*Russ. Chem. Bull., Int. Ed.*, 2008, **57**, 2349].
3. V. K. Zav´yalova, A. A. Zubarev, A. M. Shestopalov, *Izv. Akad. Nauk, Ser. Khim.*, 2009, 1878 [*Russ. Chem. Bull., Int. Ed.*, 2009, **58**, 1939].
4. M. Fray, D. Bull, K. Cooper, M. Parry, M. Stefaniak, *J. Med. Chem.*, 1995, **38**, 3524.
5. K. Tomita, Y. Tsuzuki, K. Shibamori, M. Tashima, F. Kajikawa, Y. Sato, S. Kashimoto, K. Chiba, K. Hino, *J. Med. Chem.*, 2002, **45**, 5564.
6. S. McCombie, S. Lin, J. Tagat, *Heterocycles*, 1993, **35**, 93.
7. P. I. Abramenko, V. G. Zhiryakov, *Khim. Geterotsikl. Soedin.*, 1972, 1539 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1972].
8. S. Hannick, Y. Kishi, *J. Org. Chem.*, 1983, **48**, 3833.
9. T. Hiyama, K. Kobayashi, *Tetrahedron Lett.*, 1982, **23**, 1597.
10. Y. Hsiao, N. Rivera, T. Rosner, S. Krska, E. Njolito, F. Wang, Y. Sun, J. Armstrong, E. Grabowski, R. Tillyer, F. Spindler, C. Malan, *J. Am. Chem. Soc.*, 2004, **126**, 9918.
11. N. L. Racheva, Z. G. Aliev, M. A. Belova, I. V. Mashevskaya, A. N. Maslivets, *Zh. Org. Khim.*, 2008, **44**, 710 [*Russ. J. Org. Chem.* (*Engl. Transl.*), 2008, **44**, 701].
12. V. I. Ivanskii, *Khimiya Geterotsiklicheskikh Soedinenii* [*Chemistry of Heterocyclic Compounds*], Vysshaya Shkola, Moscow, 1978, p. 171 (in Russian).
13. W. De Camp, J. Stewart, *Acta Crystallogr.*, 1971, **27**, 1227.
14. B. Burja, M. Kocevar, S. Polanc, *Tetrahedron*, 2009, **65**, 8690.
15. Y. Huang, H. Lin, K. Cheng, W. Su, K. Sung, T. Lin, J. Huang, S. Lin, F. Wong, *Tetrahedron*, 2009, **65**, 9592.
16. L. S. Liebeskind, J. Srogi, *Org. Lett.*, 2002, **4**, 979.
17. A. A. Krauze, Yu. E. Pelcher, Z. A. Kalme, G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, 1984, 1140 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1984, **20**, 935].

Received November 8, 2010