## References

1. A. G. Mustafin, I. N. Khalilov, I. B. Abdrakhmanov, and G. A. Tolstikov, *Khimiya Prirod. Soedin.*, 1989, **6**, 816 [*Chem. Nat. Compd.*, 1989 (Engl. Transl.)].
2. A. G. Mustafin, I. N. Khalilov, V. M. Sharafutdinov, D. I. D'yachenko, I. B. Abdrakhmanov, and G. A. Tolstikov, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 630 [*Russ. Chem. Bull.*, 1997, **46**, 608 (Engl. Transl.)].
3. S. Danishefsky and G. B. Phillips, *Tetrahedron Lett.*, 1984, **25**, 3159.
4. USSR Pat. 1830069; *Byull. Izobret.* [*Inventor's Bulletin*], 1993, 27 (in Russian).
5. I. B. Abdrakhmanov, V. M. Sharafutdinov, and G. A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1982, 2160 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1982, **31** (Engl. Transl.)].
6. I. B. Abdrakhmanov, G. B. Shabaeva, N. G. Nigmatullin, and G. A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1986, 1372 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1986, **35**, 1245 (Engl. Transl.)].
7. I. B. Abdrakhmanov, P. P. Gataullin, A. G. Mustafin, G. B. Shabaeva, and G. A. Tolstikov, *Zh. Org. Khim.*, 1991, **27**, 1030 [*J. Org. Chem. USSR*, 1991, **27** (Engl. Transl.)].
8. R. R. Gataullin, T. V. Kazhanova, L. T. Ilyasova, A. A. Fatykhov, L. V. Spirikhin, and I. B. Abdrakhmanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1999, 975 [*Russ. Chem. Bull.*, 1999, **48**, 967 (Engl. Transl.)].
9. Yu. V. Myshko, Ya. B. Kozlikovskii, and V. A. Koshchii, *Zh. Org. Khim.*, 1992, **28**, 950 [*Russ. J. Org. Chem.*, 1992, **28** (Engl. Transl.)].
10. B. I. Ionin, B. A. Ershov, and A. I. Kol'tsov, *YaMR-spektroskopiya v organicheskoi khimii* [*NMR Spectroscopy in Organic Chemistry*], Khimiya, Leningrad, 1983, 170 (in Russian).
11. R. R. Gataullin, I. S. Afon'kin, I. V. Pavlova, and I. B. Abdrakhmanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1999, 398 [*Russ. Chem. Bull.*, 1999, **48**, 396 (Engl. Transl.)].


*Received March 11, 1999;*
*in revised form July 14, 1999*

# Three-component condensation in the synthesis of 4-(2-chlorophenyl)-3-cyano-5-ethoxycarbonyl-6-propyl-3,4-dihydropyridine-2(1*H*)-thione

***S. G. Krivokolysko,[a] V. D. Dyachenko,[a] and V. P. Litvinov[b]****

*[a]Taras Shevchenko Lugansk State Pedagogical University,*
*2 ul. Oboronnaya, 348011 Lugansk, Ukraine.*
*Fax: +38 (064 2) 53 0008. E-mail: kgb@lgpi.lugansk.ua*
*[b]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,*
*47 Leninsky prosp., 117913 Moscow, Russian Federation.*
*Fax: +7 (095) 135 5328. E-mail: vpl@cacr.ioc.ac.ru*

Condensation of 2-chlorobenzaldehyde with cyanothioacetamide and ethyl butyroylacetate results in 4-(2-chlorophenyl)-3-cyano-5-ethoxycarbonyl-6-propyl-3,4-dihydropyridine-2(1*H*)-thione, whose further transformation affords the corresponding substituted 2-methylthio-1,4-dihydropyridine.

**Key words:** 2-chlorobenzaldehyde, cyanothioacetamide, ethyl butyroylacetate, pyridine, condensation.

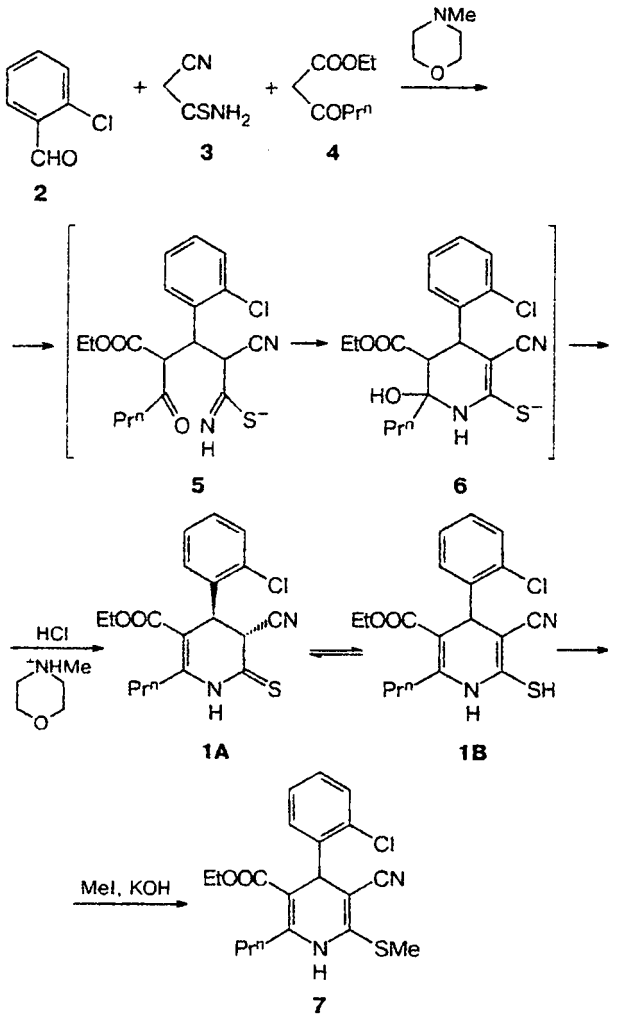
Recently, the synthesis of partially hydrogenated pyridinechalcogenones has become of particular interest because many of their derivatives exhibit biological activity promising for practical purposes.[1,2] Despite a variety of methods for the synthesis of such heterocycles, alkylsubstituted 3,4-dihydropyridine-2(1*H*)-thiones are still poorly studied. In continuation of these investigations,[3–9] we synthesized 4-(2-chlorophenyl)-3-cyano-5-ethoxycarbonyl-6-propyl-3,4-dihydropyridine-2(1*H*)-thione (**1**) by condensation of 2-chlorobenzaldehyde (**2**) with cyanothioacetamide (**3**) and ethyl butyroylacetate (**4**) in ethanol at 20 °C in the presence of *N*-methylmorpholine (Scheme 1). The reaction follows the mechanism of cascade heterocyclization, probably, *via* intermediates **5** and **6**. The reaction mixture was diluted with 10% HCl to isolate thione **1**, whose further treatment

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 1, pp. 173—175, January, 2000.

1066-5285/00/4901-0176 $25.00 

with methyl iodide in an alkaline medium gave the corresponding sulfide **7**.

**Scheme 1**




According to $^1$H NMR spectroscopic data, compound **1** exists in DMSO as a 1 : 2 mixture of tautomers **1A** and **1B**. C(3)H and C(4)H protons in tautomer **1A** manifest themselves as two doublets at δ 4.30 and 4.74, respectively ($^3J_{H(3),H(4)}$ = 3.3 Hz). Based on the previous data[10] for isostructural analogs of compound **1**, one can assume that these protons occupy a *trans*-diequatorial position, the 2-chlorophenyl substituent and the CN group being arranged *trans*-diaxially. In tautomer **1B**, a singlet signal for the C(4)H proton appears at δ 4.99. No signal for the SH proton in this tautomer is probably due to proton exchange with water contained in DMSO-$d_6$. The spectrum of a mixture of tautomers also exhibits a double set of other signals for the protons of compound **1** in the appropriate ranges (see Experimental).

The IR spectrum of compound **1** in Vaseline oil contains a low-intensity band corresponding to nonconjugated CN stretching vibrations at 2260 cm$^{-1}$, which suggests the absence of tautomer **1B** in the crystalline state.

## Experimental

IR spectra were recorded on an IKS-29 spectrophotometer (Vaseline oil). $^1$H NMR spectra were recorded on a Bruker WP-100 SY instrument (100 MHz) in DMSO-$d_6$ with $Me_4Si$ as the internal standard. The course of the reaction was monitored and the purity of compounds was checked by TLC on Silufol UV-254 plates in acetone—hexane (3 : 5).

**4-(2-Chlorophenyl)-3-cyano-5-ethoxycarbonyl-6-propyl-3,4-dihydropyridine-2(1*H*)-thione (1).** A mixture of 2-chlorobenzaldehyde (**2**) (2.25 mL, 20 mmol), cyanothioacetamide (**3**) (2 g, 20 mmol), ethyl butyroylacetate (**4**) (3.2 mL, 20 mmol), and *N*-methylmorpholine (2.02 mL, 20 mmol) in 20 mL of ethanol was stirred at 20 °C for 4 h and then diluted with 10% HCl to pH 5. After 12 h, the precipitate that formed was filtered off and washed with 80% ethanol and hexane to give thione **1** (4.43 g, 61%), m.p. 199—201 °C. IR, ν/cm$^{-1}$: 3330 (NH); 2260 (CN); 1720 (CO). $^1$H NMR, δ: 1.07 (m, 6 H, 2 Me); 1.60, 2.74 (both m, 4 H, $(CH_2)_2$); 3.96 (m, 2 H, $COCH_2$); 4.30 (d, 1 H, C(3)H of tautomer **1A**, $^3J$ = 3.3 Hz); 4.74 (d, 1 H, C(4)H of tautomer **1A**, $^3J$ = 3.3 Hz); 4.99 (s, 1 H, C(4)H of tautomer **1B**); 7.10—7.29 (m, 4 H, Ar); 11.90 (br.s, 1 H, NH of tautomer **1A**); 12.39 (br.s, 1 H, NH of tautomer **1B**). Found (%): C, 59.72; H, 5.41; N, 7.55; S, 9.01. $C_{18}H_{19}ClN_2O_2S$. Calculated (%): C, 59.58; H, 5.28; N, 7.72; S, 8.84.

**4-(2-Chlorophenyl)-3-cyano-5-ethoxycarbonyl-2-methylthio-6-propyl-1,4-dihydropyridine (7).** A 10% aqueous solution of KOH (5.6 mL, 10 mmol) and, after 5 min, methyl iodide (0.62 mL, 10 mmol) were added with stirring to a suspension of thione **1** (3.63 g, 10 mmol) in 20 mL of ethanol. After 3 h, the precipitate that formed was filtered off and washed with 80% ethanol and hexane to give pyridine **7** (3.13 g, 83%), m.p. 178—180 °C. IR, ν/cm$^{-1}$: 3210—3300 (NH); 2200 (CN); 1650, 1695 (CO). $^1$H NMR, δ: 0.95 (m, 6 H, 2 Me); 1.59, 2.74 (both m, 4 H, $(CH_2)_2$); 2.49 (s, 3 H, SMe); 3.90 (q, 2 H, $COCH_2$, $^3J$ = 15.2 Hz); 5.12 (s, 1 H, C(4)H); 7.29 (m, 4 H, Ar); 9.45 (br.s, 1 H, NH). Found (%): C, 60.71; H, 5.85; N, 7.66; S, 8.43. $C_{19}H_{21}ClN_2O_2S$. Calculated (%): C, 60.55; H, 5.62; N, 7.43; S, 8.51.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 99-03-32965).

## References

1. V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 2123 [*Russ. Chem. Bull.*, 1998, **47**, 2053 (Engl. Transl.)].
2. S. G. Krivokolysko, Ph.D. (Chem.) Thesis, Inst. of Organic Chemistry of the RAS, Moscow, 1997, 215 pp.
3. V. D. Dyachenko, S. G. Krivokolysko, and V. P. Litvinov, *Zh. Org. Khim.*, 1998, **34**, 927 [*Russ. J. Org. Chem.*, 1998, **34** (Engl. Transl.)].
4. V. D. Dyachenko, S. G. Krivokolysko, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1997, 1533 [*Chem. Heterocycl. Compd.*, 1997 (Engl. Transl.)].

5. S. G. Krivokolysko, V. D. Dyachenko, and V. P. Litvinov, *Zh. Org. Khim.*, 1997, **33**, 1088 [*Russ. J. Org. Chem.*, 1997, **33** (Engl. Transl.)].
6. V. D. Dyachenko, S. G. Krivokolysko, and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 2016 [*Russ. Chem. Bull.*, 1997, **46**, 1912 (Engl. Transl.)].
7. V. D. Dyachenko, S. G. Krivokolysko, and V. P. Litvinov, *Zh. Org. Khim.*, 1998, **34**, 750 [*Russ. J. Org. Chem.*, 1998, **34** (Engl. Transl.)].
8. V. D. Dyachenko, V. N. Nesterov, S. G. Krivokolysko, and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1997, 785 [*Chem. Heterocycl. Compd.*, 1997 (Engl. Transl.)].
9. S. G. Krivokolysko, V. D. Dyachenko, and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 166 [*Russ. Chem. Bull.*, 1999, **48**, 166 (Engl. Transl.)].
10. L. A. Rodinovskaya, A. M. Shestopalov, and V. N. Nesterov, *Khim. Geterotsikl. Soedin.*, 1996, 1376 [*Chem. Heterocycl. Compd.*, 1996 (Engl. Transl.)].

*Received May 18, 1999;*
*in revised form July 27, 1999*

# Thermodynamic quantities of adsorption described by Freundlich isotherm

***L. D. Asnin, A. A. Fedorov,* and Yu. S. Chekryshkin***

*Institute of Technical Chemistry, Ural Branch of the Russian Academy of Sciences, 13 ul. Lenina, 614000 Perm, Russian Federation.*
*Fax: +7 (343 2) 12 4375. E-mail: cheminst@mpm.ru*

Thermodynamic analysis of the Freundlich adsorption isotherm was performed. Equations describing the thermodynamic characteristics of adsorption as a function of the adsorbed quantity are presented, and relationships between the excess differential and average molar thermodynamic adsorption quantities were obtained. It was shown that the thermodynamic approach does not contradict the molecular statistical theory and provides more general equations. A model of adsorption described by the Freundlich isotherm is discussed.

**Key words:** adsorption, Freundlich adsorption isotherm, thermodynamic quantities.

The Freundlich isotherm (FI) equation describing adsorption on a solid surface has a simple analytical form and is applicable to any convex adsorption isotherm.[1] In studies of adsorption at a solid—gas interface, the FI equation is mainly used only as a convenient approximation formula. At the same time, any isotherm exactly describing experimental data should reflect the thermodynamic properties of the adsorption system. Therefore, it is of interest to consider the FI from the viewpoint of the thermodynamic theory of adsorption.[2]

Thermodynamic analysis can substantially be simplified on going from the adsorption isotherm to the equation of state of the adsorption phase. For this purpose, let us write the FI equation in the form $\Gamma = Cp^{1/n(T)}$, where $\Gamma$ is the excess adsorbed quantity, $p$ is the partial pressure of the adsorbate, $C$ and $n(T)$ are constants independent of $\Gamma$ but dependent on temperature ($T$), and $n(T) > 1$. It is known[2] that

$$\varphi = RT \int_0^p p^{-1} dp,$$

where $\varphi$ is the surface pressure. Inserting the $\Gamma$ value from the FI equation into this expression and integrating it, we obtain the equation of state

$$\varphi = RT\Gamma n(T). \qquad (1)$$

This expression differs from the equation of state of the ideal two-dimensional gas only by the $n(T)$ factor. It follows from it that the surface pressure in the adsorption layer is always higher than that in the case of the ideal two-dimensional gas ($n(T) > 1$). Since $n(T)$ is independent of $\Gamma$, we can conclude that an increase in the surface pressure is related only to enhancement of the adsorbate—adsorbent interaction as compared to the ideal adsorption layer.

To study the dependence of the thermodynamic quantities of $\Gamma$, let us use the following equations[2]:

$$\overline{U}^s = \tilde{U}^s + \varphi\Gamma^{-1} - T\Gamma^{-1} \cdot (\partial\varphi/\partial T)_\Gamma, \qquad (2)$$

$$\overline{S}^s = \tilde{S}^s - \Gamma^{-1} \cdot (\partial\varphi/\partial T)_\Gamma, \qquad (3)$$

$$\overline{U}^s(\overline{S}^s) = \tilde{U}^s(\tilde{S}^s) + \Gamma \cdot (\partial\tilde{U}^s(\partial\tilde{S}^s)/\partial\Gamma)_T. \qquad (4)$$

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 1, pp. 175—177, January, 2000.