Investigation of Isothiocyanate Addition to Alkylidene Derivatives of Malononitrile and Cyanoacetic Acid Esters

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Addition of arylisothiocyanates to active methylene compounds leads to a variety of compounds depending on the structure of the starting material and conditions used to conduct the addition. Addition of arylisothiocyanate to **1c** leads to a pyrido[2,3-*d*]pyrimidine resulting from addition of a second mole of cyanate to the initial adduct. Addition of arylisothiocyanate to **1b** led to a mixture of pyridine and thiopyran adducts, while addition to **1a** led to open chain structures.

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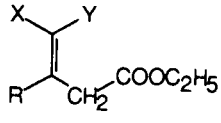
Introduction.

Active methylene compounds **1a-1c** have received a great deal of attention as reactive synthones in a variety of cycloaddition and condensation reactions yielding potentially biologically active compounds [1-6]. We became interested in the reactivity of these compounds toward phenylisothiocyanate, expecting that the resulting addition



1a X=$COOC_2H_5$, Y=CN, R=NH_2

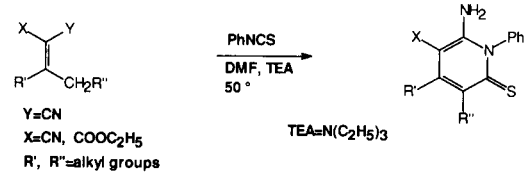
1b X=$COOC_2H_5$, Y=CN, R=CH_3

X=CN, Y=$COOC_2H_5$, R=CH_3

1c X=CN, Y=CN, R=CH_3

products may serve as useful reagents in heterocyclic synthesis. Addition of phenylisothiocyanate to certain alkylidene malononitriles, structurally similar to **1a-1c** were first investigated by Gewald and coworkers [7] (Scheme I). According to their report, reaction of phenylisothiocyanate with alkylidene malononitrile derivatives resulted in initial addition followed by subsequent cyclization leading

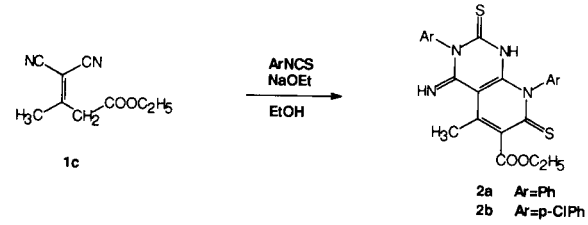
Scheme I



exclusively to pyridine derivatives. In contrast, our experiments have shown a greater variety of products of phenylisothiocyanate addition to **1a-1c** under similar reaction conditions. In this work we describe two different methods used to affect addition of phenylisothiocyanate to compounds **1a-1c**: (Method A) sodium ethoxide in absolute ethanol with the base at a stoichiometric proportion to the substrate and (Methods B and B') *N*,*N*-dimethylformamide and triethylamine catalyzed in stoichiometric and excess quantities. We further show some of the diverse reaction pathways available to the initial addition products.

Results and Discussion.

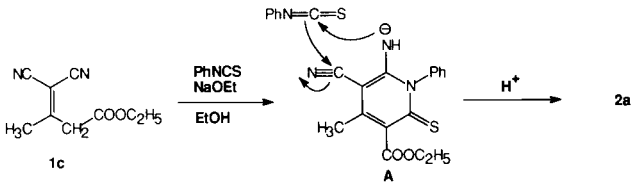
Initial studies were carried out by the addition of either phenylisothiocyanate or *p*-chlorophenylisothiocyanate to **1c**. It was found that the addition was best conducted by using a stoichiometric amount of sodium ethoxide in absolute ethanol to induce reaction. Attempts to use other methods of addition led to complex mixtures of products. Using sodium ethoxide, the reaction proceeded smoothly yielding the pyrido[2,3-*d*]pyrimidine derivatives, **2a** or **2b** depending on starting isothiocyanate. This product most likely results from initial addition to form the pyridine



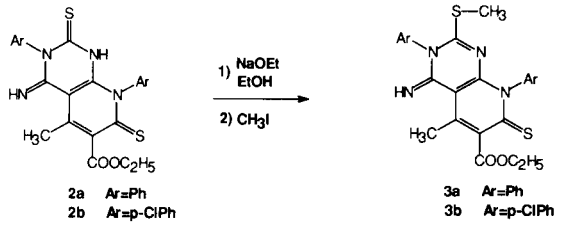
derivative **A**. Addition of a second mole of phenylisothiocyanate to **A** then leads to the observed product (Scheme II).

The structures of **2a** and **2b** are fully supported by spectral data. The ^{13}C-nmr spectrum of both compounds show resonances at 178.4 and 182.5 ppm. These resonances are consistent with the two thiocarbonyl groups present. Cyclization in the C-S direction leading to a thiopyran quite possibly could have occurred, however the presence of two

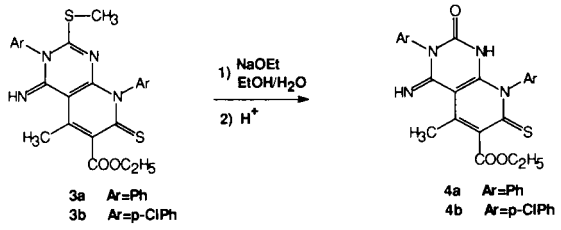
Scheme II



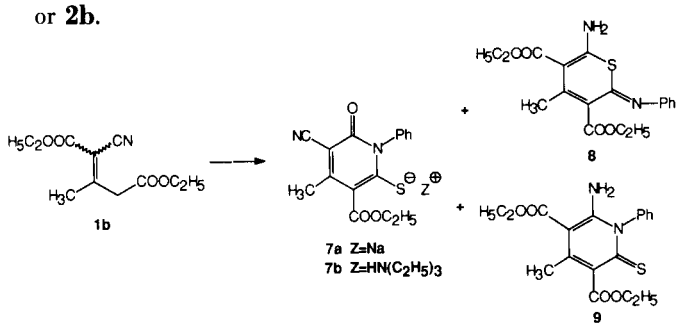
thiocarbonyl groups precludes this possibility. Methylation of either **2a** or **2b** led to **3a** or **3b**, respectively. In both derivatives, **3a** and **3b**, the ^{13}C-nmr spectra show a loss of one of the thiocarbonyl resonances due to sulfur methylation and imine formation.



Mass spectral analysis of compounds **2a**, **2b**, **3a**, and **3b** all gave spectra with abundant M^+ ions. Compounds **3a** and **3b** showed production of a fragment ion at m/z 150 and m/z 184 respectively. This ion was identified as $[Ar-N\equiv C-S-CH_3]^+$ thus confirming the pyrimidine ring structure of **3a** and **3b**. In addition to the above mentioned data, a NOESY spectrum of compound **3b** indicated a close proximity of the hydrogen atoms on the aryl and thiomethoxy group. Finally, desulfurization of either **3a** or **3b** with water/ethanol/sodium hydroxide produced either

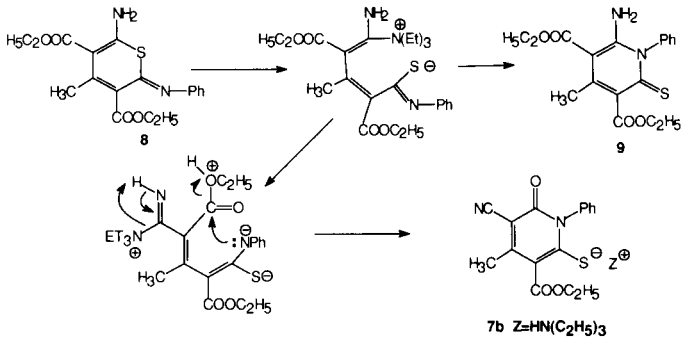


4a or **4b**. Either product could not be methylated under the same conditions used to methylate **2a** or **2b**. Thus due to the hindered nature of the second thiocarbonyl group, this sulfur cannot be easily methylated as is the case in **2a** or **2b**.

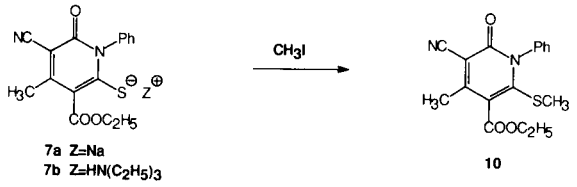


Reaction of **1b** (a 2:1 *Z*:*E* mixture of geometric isomers) with phenylisothiocyanate produced a mixture of three compounds, the composition of which depended on reaction conditions. The three products were: a pyridine derivative **7a** or **7b**, a thiopyran derivative **8**, and an aminopyridine derivative **9**. Reaction of **1b** using ethoxide to effect addition led exclusively to **7a**. When a mixture of triethylamine [7] and *N*,*N*-dimethylformamide was used to induce addition, a mixture of all three products, **7b**, **8**, and **9** resulted. When excess triethylamine was used, the yields of **7b** and **9** increased while only trace amounts of **8** were produced. These results indicate that it is probable the thiopyran, **8**, was a precursor of the rearranged products **7** and **9**. To investigate this possibility, compound **8** was treated with a mixture of phenylisothiocyanate and excess triethylamine in DMF. It was found that **8** was indeed transformed into a mixture of **7** and **9** under these reaction conditions. One possible mechanism which explains the transformation of **8** into a mixture of **7** and **9** is outlined in Scheme III.

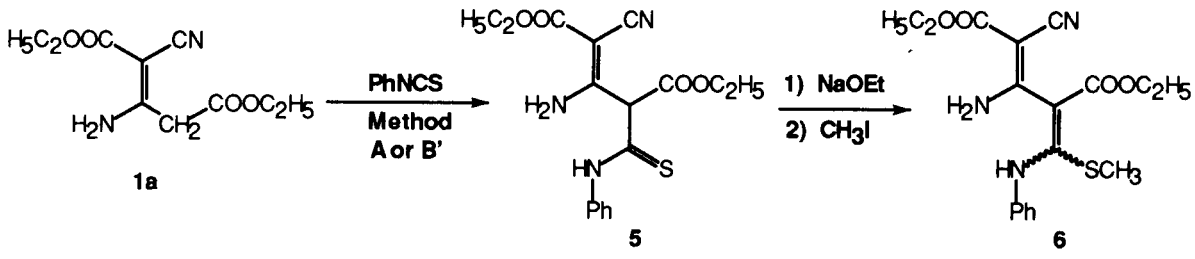
Scheme III



Assignment of structure to compounds **7a**, **7b**, **8**, and **9** was confirmed by spectral data. The thiopyran **8** can easily be distinguished from the isomeric **9** by virtue of its characteristic mass spectrum which shows an abundant peak at m/z 257 corresponding to the loss of a $C_6H_5NC\cdot$ radical. The resultant thiophene cation formed in this process has been shown to be a major peak in the spectra of 6-amino-2-phenyliminothiopyrans [9,10]. Methylation of **7a** or **7b** under mild conditions employing methyl iodide gave the methylated derivative **10**, thus confirming the presence of the thiolate function. Compound **9** did not react with methyl iodide due to the reduced reactivity of the thiocarbonyl group compared to the thiolate anion.



Unlike compounds **1b** and **1c**, **1a** reacted with phenylisothiocyanate to produce an open chain product **5** in ex-



cellent yield. Compound **5** could be further methylated using sodium ethoxide/ethanol/methyl iodide to produce **6**. Attempts to cyclize either **5** or **6** under elevated temperature have been unsuccessful so far.

Conclusions.

Compound **5** is the only open chain product that was isolated from the series of phenylisothiocyanate additions. The formation of **5** can be explained by the results of a comprehensive study on the reactivity and structure of **1a** by Junek and coworkers [12] which showed that **1a** exists predominately as the *Z* isomer (*Z*/*E* ratio was found to be 95:5). This is in good agreement with X-ray experiments which indicate that the amino group of **1a** and its derivatives are hydrogen bound with the *cis* carboxyl group oxygen [11,12]. Intramolecular hydrogen bonding would be expected to be a significant factor in stabilizing the open chain compounds **5** and **6**. These observations could, in turn, explain the differences in reactivity between **1a** and **1b** and **c** towards phenylisothiocyanates. In contrast to **1a**, compound **1c** possesses two cyano groups coupled with a double bond and gives no opportunity for hydrogen bonding in the acyclic adduct, thus making cyclization favorable. In solution the intermediate thiopyridine most probably exists as a reactive anion capable of intercepting a second molecule of phenylisothiocyanate to give the pyrido[2,3-*d*]pyrimidines **2a-b**.

Finally, comparing the product distribution of the phenylisothiocyanate addition reactions, it can be seen that the reaction catalyzed by ethoxide (Method A) lead to high yields of a single main product, while the triethylamine catalyzed reactions (Method B) lead to a more diverse mixture of products.

The phenylisothiocyanate adducts and their methylated derivatives, **5-10**, are potentially interesting synthons for heterocyclic synthesis and we are currently investigating their reactions further.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a Mattson 4020 Galaxy FT-IR as potassium bromide pellets. The ^{1}H and ^{13}C-nmr spectra were recorded on a Bruker AC 300 spectrometer in deuteriochloroform, DMSO-d_6 or a 1:1 mixture of deuteriochloroform:DMSO-d_6 (TMS was added as an internal standard). Mass spectra were obtained using a Finnigan TSQ-45 quadrupole mass spectrometer. Compounds **1a** [14], **1b** [13], and **1c** [1] were prepared by known methods.

Method A. General Procedure.

To a cooled (0°) solution of 0.05 mole of **1a** or **b**, 0.05 mole of arylisothiocyanate (0.1 mole of arylisothiocyanate was used to react with **1c**) in 100.0 ml of absolute ethanol and 0.05 mole of sodium ethoxide was added with stirring. After 12 hours of stirring at room temperature the solvent was removed under reduced pressure.

Isolation of **2a-b** and **5**.

The material remaining after solvent removal was mixed with 300 ml of ice water and neutralized with 2 *M* hydrochloric acid. The solid material remaining was collected, dried and recrystallized from a mixture of *N*,*N*-dimethylformamide/ethanol, **2a-b**, or ethanol, **5**.

2,7-Dithioxo-3,8-diphenyl-4-imino-5-methyl-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carboxylic Acid Ethyl Ester (**2a**).

This compound was obtained as an orange crystalline solid, mp 215°, yield 91%; ^{1}H-nmr (1:1 deuteriochloroform-DMSO-d_6): δ 1.32 (t, 3H), 2.49 (s, 3H), 4.28 (q, 2H), 7.14-7.61 (m, 12H); ^{13}C-nmr (1:1 deuteriochloroform-DMSO-d_6): δ 13.74 (CH_3CH_2O), 18.52 (CH_3), 60.97 (CH_3CH_2O), 97.13, 127.85, 128.49, 128.65, 129.06, 129.38, 130.28, 132.99, 137.92, 138.58, 140.39, 151.97, 155.65, 165.89, 178.40 (PhN*C*=S), 181.98 (NH*C*=S); ms: m/z 448 (100%, M^+), 390 (12.8%, M^+-SCN), 375 (50.8%, M^+-$COOC_2H_5$); ir: ν 3450, 3322, 3218 (NH), 1725 (C=O).

Anal. Calcd. for $C_{23}H_{20}N_4O_2S_2$ (448.57): C, 61.59; H, 4.49; N, 12.49. Found: C, 61.30; H, 4.47; N, 12.57.

2,7-Dithioxo-3,8-di(*p*-chlorophenyl)-4-imino-5-methyl-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carboxylic Acid Ethyl Ester (**2b**).

This compound was obtained as an orange solid, mp 220-221°, yield 93%; ^{1}H-nmr (1:1 deuteriochloroform-DMSO-d_6): δ 1.33 (t, 3H), 2.49 (s, 3H), 4.29 (q, 2H), 7.13-7.71 (m, 10H); ^{13}C-nmr (1:1 deuteriochloroform-DMSO-d_6): δ 13.84 (CH_3CH_2O), 18.77 (CH_3), 61.19 (CH_3CH_2O), 97.16, 129.28, 130.31, 130.39, 130.66, 133.00, 133.56, 134.73, 136.63, 138.31, 139.05, 152.20, 155.70, 165.94, 178.52 (*p*-PhN*C*=S), 182.47 (NH*C*=S); ms: m/z 516 (58.7%, M^+), 458 (12.8%, M^+-SCN), 443 (50.8%, M^+-$COOC_2H_5$); ir: ν 3465, 3353, 3240 (NH), 1720 (C=O), 1660 (C=N).

Anal. Calcd. for $C_{23}H_{18}N_4O_2S_2Cl_2$ (517.45): C, 53.39; H, 3.51; N, 10.83. Found: C, 53.20; H, 3.59; N, 10.97.

3-Amino-2-cyano-4-phenylthiocarbamoyl-2-pentenedioic Acid Diethyl Ester (**5**).

This compound was obtained as a yellow crystalline solid, mp 128°, yield 95%; ^{1}H-nmr (deuteriochloroform): δ 1.26 (t, 3H), 1.32

(t, 3H), 4.20 (q, 2H), 4.29 (q, 2H), 5.41 (s, 1H), 7.26-7.84 (m, 5H), 8.38 (s, 1H), 9.69 (s, 1H), 10.7 (s, 1H); ^{13}C-nmr (deuteriochloroform): δ 13.83 (2 x CH_3CH_2O), 14.27, 61.53, 60.87 (2 x CH_3CH_2O), 63.13 (CH), 72.33, 119.24, 123.38, 127.47, 128.88, 138.32, 164.34, 165.21, 167.46, 189.75 (C=S); ms: m/z 361 (2.3%, M^+), 226 (21.2%, M^+-PhNCS), 152 (55.7%), 135 (100%, $PhNCS^+$); ir: ν 3354, 3254, 3204 (NH), 2207 (C≡N), 1751 (C=O), 1648 (conjugated H-bound C=O), 1614 (C=C).

Anal. Calcd. for $C_{17}H_{19}N_3O_4S$ (361.42): C, 56.50; H, 5.30; N, 11.63. Found: C, 56.54; H, 5.28; N, 11.71.

Isolation of the Sodium Salt of 5-Cyano-4-methyl-6-oxo-1-phenyl-2-thiolo-1,6-dihydropyridine-3-carboxylic Acid Ethyl Ester (**7a**).

The oily residue was dissolved in approximately 10 ml of boiling ethanol. A crystalline product precipitated on addition of 200 ml of diethyl ether as a bright yellow salt. This material was recrystallized from a small amount of absolute ethanol yielding a yellow crystalline solid, mp 180° dec, yield 85%; ^{1}H-nmr (DMSO-d_6): δ 1.22 (t, 3H), 2.03 (s, 3H), 4.12 (q, 2H), 6.96-7.40 (m, 5H); ^{13}C-nmr (DMSO-d_6): δ 13.83 (CH_3CH_2O), 17.90 (CH_3), 60.01 (CH_3CH_2O), 85.55, 119.16, 120.06, 126.67, 128.35, 128.98, 141.30, 146.03, 161.92, 167.48, 177.58; ir: ν 2211 (C≡N), 1725 (C=O).

Method B [7]. General Procedure.

Compound **1b** (43 mmoles), phenylisothiocyanate (43 mmoles) and 19 mmoles of triethylamine were dissolved in 9.0 ml of *N,N*-dimethylformamide. The reaction mixture was stirred at 47-50° for one hour, then left for two hours at room temperature. The solvent and other volatile materials were removed *in vacuo* (0.5 Torr, 40°). The semi-solid product was triturated with diethyl ether (200 ml). The crystalline product **7b** was separated and recrystallized from absolute ethanol. The ether solution was condensed to 50 ml and left for 2 days. The semi-crystalline product was collected and purified by liquid chromatography on silica gel using chloroform as solvent to isolate compounds **8** and **9**.

Triethylammonium Salt of 5-Cyano-4-methyl-6-oxo-1-phenyl-2-thiolo-1,6-dihydropyridine-3-carboxylic Acid Ethyl Ester (**7b**).

This compound had mp 168-169°, yield 36%, orange solid; ^{1}H-nmr (deuteriochloroform): δ 1.06 (t, 9H), 1.36 (t, 3H), 2.24 (s, 3H), 2.85 (q, 6H), 4.33 (q, 2H), 7.09-7.53 (m, 5H); ^{13}C-nmr (deuteriochloroform): δ 8.82 (($CH_3CH_2)_3N^+H$), 14.15 (CH_3CH_2O), 18.54 (CH_3), 46.75 (($CH_3CH_2)_3N^+H$), 61.25 (CH_3CH_2O), 86.88, 119.24, 123.42, 127.71, 128.60, 129.00, 141.22, 147.23, 164.09, 168.36, 178.25; ms: m/z 314 (9.5%, M^+-$N(C_2H_5)_3$), 268 (30.6%), 267 (34.5%), 86 (100.0%, $CH_2N^+(C_2H_5)_2$); ir: ν 2203 (C≡N), 1713 (C=O).

Anal. Calcd. for $C_{22}H_{29}N_3O_3S$ (415.56): C, 63.59; H, 7.03; N, 10.11. Found: C, 63.71; H, 6.92; N, 10.11.

6-Amino-4-methyl-2-phenylimino-2*H*-thiopyran-3,5-dicarboxylic Acid Diethyl Ester (**8**).

This compound was obtained as a yellow crystalline solid, mp 134-135°, yield 12%; ^{1}H-nmr (deuteriochloroform): δ 1.28 (t, 3H), 1.32 (t, 3H), 2.21 (s, 3H), 4.23 (q, 2H), 4.31 (q, 2H), 6.81-7.36 (m, 7H); ^{13}C-nmr (deuteriochloroform): δ 14.01 (CH_3CH_2O), 14.24 (CH_3CH_2O), 22.47 (CH_3), 60.74 (CH_3CH_2O), 61.46 (CH_3CH_2O), 96.82, 120.05, 121.62, 124.36, 129.47, 144.18, 149.91, 150.29, 159.28, 167.58, 168.08; ms: m/z 360 (9.0%, M^+), 257 (100.0%, M^+-PhNC) [9,10], 211 (98%, M^+-PhNC-C_2H_5OH), 135 (22.1%); ir: ν 3388, 3299 (NH), 1709 (C=O), 1675 (conjugated H-bound C=O).

Anal. Calcd. for $C_{18}H_{20}N_2O_4S$ (360.43): C, 59.98; H, 5.59; N, 7.77. Found: C, 60.11; H, 5.59; N, 7.74.

6-Amino-4-methyl-1-phenyl-2-thioxo-1,2-dihydropyridine-3,5-dicarboxylic Acid Diethyl Ester (**9**).

This compound had mp 172-173°, yield 6.4%, yellow solid; ^{1}H-nmr (deuteriochloroform): δ 1.35 (t, 3H), 1.39 (t, 3H), 2.39 (s, 3H), 4.32 (q, 2H), 4.36 (q, 2H), 6.90-7.62 (m, 7H); ^{13}C-nmr (deuteriochloroform): δ 14.02 (CH_3CH_2O), 14.24 (CH_3CH_2O), 21.23 (CH_3), 61.35 (CH_3CH_2O), 61.52 (CH_3CH_2O), 96.43, 128.26, 129.69, 130.15, 130.98, 137.72, 144.59, 155.03, 167.61, 168.05, 178.22 (C=S); ms: m/z 360 (100.0%, M^+), 315 (20.8%, M^+-C_2H_5O), 287 (65.5%, M^+-$COOC_2H_5$), 241 (59.7%, M^+-$COOC_2H_5$-C_2H_5OH); ir: ν 3476, 3291 (NH), 1721 (C=O), 1674 (conjugated H-bound C=O).

Anal. Calcd. for $C_{18}H_{20}N_2O_4S$ (360.43): C, 59.98; H, 5.59; N, 7.77. Found: C, 60.03; H, 5.57; N, 7.70.

Method B′. General Procedure.

Compounds **1a** or **1b** (19 mmoles), phenylisothiocyanate (19 mmoles) and 28 mmoles of triethylamine were dissolved in 7.0 ml of *N,N*-dimethylformamide. The solution was stirred at 47-50° for two hours. The products were isolated and purified as was described previously for Method B, yielding: **7b**, 53%, **8**, trace and **9**, 15%. The reaction of **1a** with phenylisothiocyanate yielded, upon solvent removal *in vacuo* and base neutralization, 85% of **5**.

Rearrangement of **8**.

Compound **8** (1.9 mmoles) and 2.8 mmoles of triethylamine were mixed with 2.0 ml of *N,N*-dimethylformamide and treated as described in Method B′, yielding **7b**, 60% and **9**, 16%.

Methylation. General Procedure.

To a cooled (0°) solution of 10 mmoles of compounds **2**, **5**, or **7** in 50 ml of absolute ethanol, 11 mmoles of methyl iodide in 20 ml of absolute ethanol was added with stirring. The reaction mixture was stirred at room temperature for three hours. The solvent was then removed under reduced pressure. The resulting solid was washed with water, dried and recrystallized; **3a-b** and **10** from *N,N*-dimethylformamide/ethanol and **6** from ethanol.

3,8-Diphenyl-4-imino-2-methylthio-5-methyl-7-thioxo-3,4,7,8-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylic Acid Ethyl Ester (**3a**).

This compound was obtained as a yellow solid, mp 213-214°, yield 96%; ^{1}H-nmr (deuteriochloroform): δ 1.39 (t, 3H), 1.69 (s, 3H), 2.68 (s, 3H), 4.42 (q, 2H), 6.70 (broad s, 1H), 7.19-7.61 (m, 11H); ^{13}C-nmr (deuteriochloroform): δ 14.03 (SCH_3), 14.84 (CH_3CH_2O), 21.02 (CH_3), 61.66 (CH_3CH_2O), 104.88, 128.03, 128.21, 129.23, 129.61, 130.97, 131.26, 133.63, 136.88, 141.28, 143.04, 151.15, 152.94, 164.03, 167.17, 179.85 (C=S); ms: m/z 462 (50.5%, M^+), 389 (35.3%, M^+-$COOC_2H_5$), 150 (31.3%, $PhNSCH_3^+$); ir: ν 3297, 3353, 3240 (NH), 1730 (C=O).

Anal. Calcd. for $C_{24}H_{22}N_4O_2S_2$ (462.59): C, 62.31; H, 4.79; N, 12.11. Found: C, 62.15; H, 4.90; N, 12.16.

3,8-Bis(*p*-chlorophenyl)-4-imino-2-methylthio-5-methyl-7-thioxo-3,4,7,8-tetrahydropyrido[2,3-*d*]pyrimidine-6-carboxylic Acid Ethyl Ester (**3b**).

This compound was obtained as a yellow solid, mp 218-219°, yield 97%; ^{1}H-nmr (deuteriochloroform): δ 1.37 (t, 3H), 1.78 (s, 3H), 2.65 (s, 3H), 4.41 (q, 2H), 6.70 (broad s, 1H), 7.12-7.61 (m,

11H); ^{13}C-nmr (deuteriochloroform): δ 14.03 (S*C*H$_3$), 14.95 (*C*H$_3$-CH$_2$O), 20.94 (*C*H$_3$), 61.74 (CH$_3$*C*H$_2$O), 104.84, 129.52, 129.57, 131.09, 131.30, 132.10, 134.04, 136.91, 137.44, 139.62, 143.10, 150.99, 152.61, 164.13, 166.91, 179.47 (C=S); ms: m/z 530 (31.5%, M$^+$), 457 (19.9%, M$^+$-COOC$_2$H$_5$), 184 (31.3%, *p*-ClPhNS-CH$_3^+$), 111 (60.7%, *p*-ClPh); ir: ν 3306 (NH), 1728 (C=O).

Anal. Calcd. for $C_{24}H_{20}N_4O_2S_2Cl_2$ (531.48): C, 54.24; H, 3.79; N, 10.54. Found: C, 54.40; H, 3.69; N, 10.37.

3-Amino-4-(anilinothiomethylmethylidene)-2-cyano-2-pentenedioic Acid Diethyl Ester (**6**).

This compound was obtained as a white crystalline solid, mp 150°, yield 96%; ^{1}H-nmr (deuteriochloroform): δ 1.24 (t, 3H), 1.34 (t, 3H), 1.97 (s, 3H), 4.18 (q, 2H), 4.23 (q, 2H), 7.14-7.37 (m, 5H), 9.27 (s, 1H), 10.85 (s, 1H); ^{13}C-nmr (deuteriochloroform): δ 14.37 (2 x *C*H$_3$CH$_2$O), 16.48 (S*C*H$_3$), 60.55 (CH$_3$*C*H$_2$O), 60.70 (CH$_3$-*C*H$_2$O), 99.91, 118.71, 119.38, 123.80, 125.60, 129.27, 139.16, 160.70, 165.91, 167.36, 168.25; ms: m/z 375 (2.7%, M$^+$), 328 (38.4%, M$^+$-SCH$_3$), 254 (28.6%), 150 (100%, PhNCSCH$_3^+$); ir: ν 3379, 3256, 1729 (NH), 2203 (C≡N), 1672, 1656 (conjugated H-bound C=O), 1616 (C=C).

Anal. Calcd. for $C_{18}H_{21}N_3O_4S$ (375.45): C, 57.58; H, 5.64; N, 11.19. Found: C, 57.76; H, 5.62; N, 11.42.

5-Cyano-4-methyl-2-methylthio-6-oxo-1-phenyl-1,6-dihydropyridine-3-carboxylic Acid Ethyl Ester (**10**).

This compound was obtained as a colorless crystalline solid, mp 146-147°, yield 90%; ^{1}H-nmr (DMSO-d$_6$): δ 1.29 (t, 3H), 2.14 (s, 3H), 2.38 (s, 3H), 4.34 (q, 2H), 7.41-7.56 (m, 5H); ^{13}C-nmr (DMSO-d$_6$): δ 13.70 (*C*H$_3$CH$_2$O), 18.99 (S*C*H$_3$), 19.19 (*C*H$_3$), 62.05 (CH$_3$*C*H$_2$O), 103.91, 114.95, 120.65, 128.52, 129.08, 129.22, 137.43, 149.38, 155.24, 159.13, 164.57; ms: m/z 328 (90.9%, M$^+$), 253 (100.0%), 150 (6.5%, PhNCSCH$_3^+$), 143 (14.1%, PhNCCCO); ir: ν 1729 (C=O), 1663 (C=O, amide).

Anal. Calcd. for $C_{17}H_{16}N_2O_3S$ (328.39): C, 62.18; H, 4.91; N, 8.53. Found: C, 61.99; H, 4.93; N, 8.45.

Preparation of **4a-b**.

A mixture of 2.2 mmoles of **3**, 30 ml of ethanol and 12 g of a 25% sodium hydroxide solution were refluxed for 3 hours. The solution was then neutralized with 2 *M* hydrochloric acid. The resulting precipitate was collected on a Büchner funnel, dried and recrystallized from a small amount of *N,N*-dimethylformamide.

3,8-Diphenyl-4-imino-5-methyl-2-oxo-7-thioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carboxylic Acid Ethyl Ester (**4a**).

This compound was obtained as an orange solid, mp 300-303°, yield 50%; ^{1}H-nmr (1:1 deuteriochloroform-DMSO-d$_6$): δ 1.29 (t, 3H), 2.46 (s, 3H), 4.25 (q, 2H), 6.80-7.57 (m, 12H); ^{13}C-nmr (1:1 deuteriochloroform-DMSO-d$_6$): δ 13.75 (*C*H$_3$CH$_2$O), 18.83 (*C*H$_3$), 60.78 (CH$_3$*C*H$_2$O), 93.76, 127.52, 128.39, 128.52, 128.96, 129.39, 130.13, 131.03, 134.72, 138.89, 140.96, 151.88, 157.36, 157.61, 166.21, 181.82 (C=S); ms: m/z 432 (77.2%, M$^+$), 359 (36.4%, M$^+$-COOC$_2$H$_5$), 77 (84.5%, Ph$^+$); ir: ν 3354, 3365 (NH), 1729 (C=O), 1675 (C=O, amide).

Anal. Calcd. for $C_{23}H_{20}N_4O_3S$ (432.50): C, 63.8; H, 4.66. Found: C, 63.83; H, 4.70.

3,8-Bis(*p*-chlorophenyl)-4-imino-5-methyl-2-oxo-7-thoixo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carboxylic Acid Ethyl Ester (**4b**).

This compound was obtained as an orange solid, mp 221-225° dec, yield 52%; ^{1}H-nmr (1:1 deuteriochloroform-DMSO-d$_6$): δ 1.33 (t, 3H), 2.52 (s, 3H), 4.30 (q, 2H), 7.20-7.78 (m, 10H); ^{13}C-nmr (1:1 deuteriochloroform-DMSO-d$_6$): δ 13.80 (*C*H$_3$CH$_2$O), 18.90 (*C*H$_3$), 60.96 (CH$_3$*C*H$_2$O), 94.20, 129.37, 130.48, 130.75, 130.96, 132.41, 133.98, 134.34, 139.66, 139.98, 151.92, 157.71, 166.36; ms: m/z 500 (65.4%, M$^+$), 427 (37.6%, M$^+$-COOC$_2$H$_5$), 111 (100%, *p*-ClPh$^+$); ir: ν 3448, 3391 (NH), 1721 (C=O), 1686 (C=O, amide), 1655 (C=N).

Anal. Calcd. for $C_{23}H_{18}N_4O_3SCl_2$ (501.39): C, 55.09; H, 3.61. Found: C, 54.62; H, 3.47.

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