# Substituted Ethyl 2-Acyl-3-amino-6-methylthieno[2,3-*b*]pyridine-4-carboxylates as Synthons for Novel Heterocycles



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Received November 5, 1996

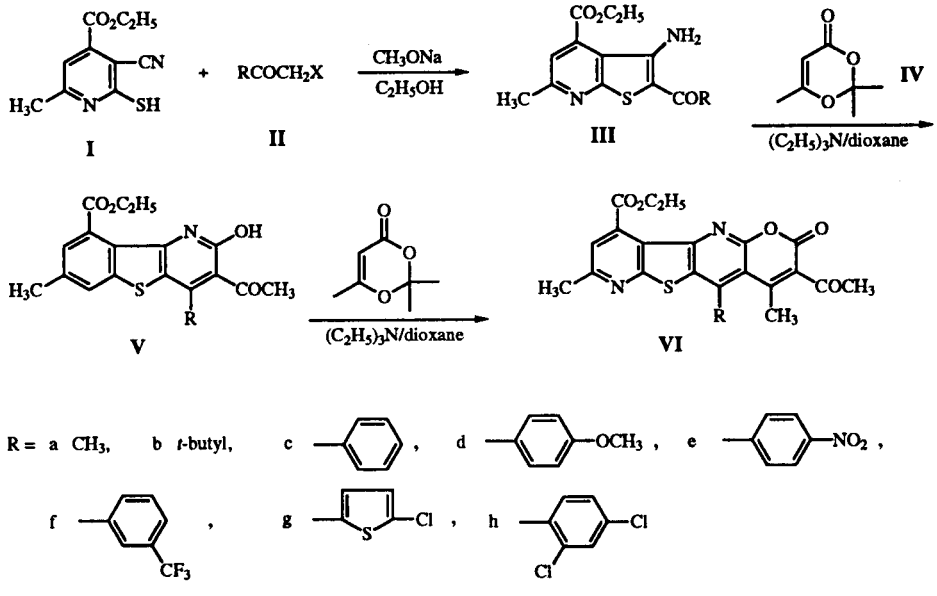
The triethylamine-catalyzed reaction of 4-substituted ethyl 2-acyl-3-amino-6-methylthieno[2,3-*b*]pyridine-4-carboxylates **IIIa-h** with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **IV** gave 4-substituted ethyl 3-acetyl-2-hydroxy-7-methylthieno[2,3-*b*:4,5-*b'*]dipyridine-9-carboxylates **Va-h**. Some of the thienodipyridines (**V**) reacted with excess **IV** to give 5-substituted ethyl 3-acetyl-4,8-dimethyl-2-oxo-2H-pyrano[2,3-*b*]-pyrido[3',2':4,5]thieno[2,3-*e*]pyridine-10-carboxylates **VI**.

*J. Heterocyclic Chem.*, **34**, 729 (1997).

The use of diketene as a synthon for the preparation of heterocyclic compounds is known in the literature [1]. For example, 3'-amino-5',6',7',8'-tetrahydro-2-acetonaphthone reacted with diketene to give 3-acetyl-4-methyl-6,7,8,9-tetrahydrobenzo[*g*]quinolin-2(1*H*)-one [2]. Other 2-aminoketones react in a similar fashion [3] to give fused heterocycles.

Several investigators reacted substituted 3-cyano-2-mercaptopyridines with 2-chloroacetamide, 2-haloketones and ethyl chloroacetate to give 3-aminothieno[2,3-*b*]-pyridines [4,5]. The latter compounds were used to prepare polycyclic heterocycles [6,7,8,9,10].

Our interest in the synthesis of novel heterocyclic compounds for evaluation as agrochemicals and pharmaceuticals prompted us to prepare several 4-substituted ethyl 2-acyl-3-amino-6-methylthieno[2,3-*b*]pyridine-4-carboxylates **IIIa-h** by the condensation of ethyl 3-cyano-2-mercapto-6-methylpyridine-4-carboxylate with 2-bromoketones in the presence of sodium methoxide [4,5], and to investigate the reaction of **IIIa-h** with diketene-acetone adduct [2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**IV**)]. The reaction of **IIIa-h** with **IV** in the presence of triethylamine in dioxane gave the novel 4-substituted ethyl 3-acetyl-2-hydroxy-7-methylthieno[2,3-*b*:4,5-*b'*]dipyridine-9-carboxylates **Va-h**. The tricyclic compounds **Va-h** reacted further with **IV** to give 5-substituted ethyl 3-acetyl-4,8-dimethyl-2-oxo-2*H*-pyrano[2,3-*b*]pyrido[3',2':4,5]-thieno[2,3-*e*]pyridine-10-carboxylates **VI**. Only ethyl 3-acetyl-4-(*tert*-butyl)-2-hydroxy-7-methylthieno-[2,3-*b*:4,5-*b'*]dipyridine-9-carboxylate (**Vb**) did not give **VIb**. Compounds of type **VI** are examples of a novel heterocyclic system that is easily accessible from readily available intermediates.




## EXPERIMENTAL

Melting points were determined with a Thomas Hoover capillary melting point apparatus and are reported uncorrected. The

Table 1

| Compound | mp | Formula | Anal. Calcd. (Found) | | $^1$H NMR (deuteriochloroform) | Yield |
|---|---|---|---|---|---|---|
| | (°C) | C | H | N | δ, J ( Hz) | (%) |
| **IIIb** | 144-146 | $C_{16}H_{20}N_2O_3S$ | | | 1.42 (s, 9H), 1.46 (t, J = 7.0 Hz, 3H), 2.70 | 52 |
| | | 59.98 | 6.29 | 8.75 | (s, 3H), 4.48 (q, J = 7.0 Hz, 2H), 7.59 | |
| | | (59.82 | 6.27 | 8.70) | (s, 1H), 8.56 (br s, 2H) | |
| **IIId** | 191-193 | $C_{19}H_{18}NO_4S$ | | | 1.47 (t, J = 7.1 Hz, 3H), 2.70 (s, 3H), 3.88 | 48 |
| | | 61.60 | 4.90 | 7.56 | (s, 3H), 4.50 (q, J = 7.1 Hz, 2H), 6.97 | |
| | | (61.53 | 5.03 | 7.55) | (d, J = 9.0 Hz, 2H), 7.64 (s, 1H), 7.88 | |
| | | | | | (d, J = 9.0 Hz, 2H), 8.60 (br s, 2H) | |
| **IIIe** | 201-202 | $C_{18}H_{15}N_3O_5S$ | | | 1.49 (t, J = 7.0 Hz, 3H), 2.71 (s, 3H), 4.52 | 70 |
| | | 56.10 | 3.92 | 10.90 | (q, J = 7.0 Hz, 2H), 7.71 (s, 1H), 7.96 | |
| | | (56.33 | 3.94 | 10.69) | (d, J = 8.5 Hz, 1H), 8.32 (d, J = 8.5 Hz, 1H), | |
| | | | | | 8.98 (br s, 2H) | |
| **IIIf** | 137-138 | $C_{19}H_{15}F_3N_2O_3S$ | | | 1.47 (t, J = 7.3 Hz, 3H), 2.68 (s, 3H), 4.48 | 61 |
| | | 55.88 | 3.70 | 6.66 | (q, J = 7.3 Hz, 2H), 7.61 (t, J = 7.8 Hz, 1H), | |
| | | (55.81 | 3.67 | 6.85) | 7.66 (s, 1H), 7.77 (d, J = 7.8 Hz, 1H), 8.03 | |
| | | | | | (d, J = 7.8 Hz, 1H), 8.12 (s, 1H), 8.87 (br s, 2H) | |
| **IIIg** | 218-221 | $C_{16}H_{13}ClN_2O_3S_2$ | | | 1.48 (t, J = 7.0 Hz, 3H), 2.74 (s, 3H), 4.51 | 89 |
| | | 50.45 | 3.44 | 7.36 | (q, J = 7.0 Hz, 2H), 7.00 (d, J = 4.0 Hz, 1H), | |
| | | (50.51 | 3.37 | 7.27) | 7.69 (s, 1H), 7.77 (d, J = 4.0 Hz, 1H) 8.82 | |
| | | | | | (br s, 2H) | |
| **IIIh** | 168-170 | $C_{18}H_{14}Cl_2N_2O_3S$ | | | 1.47 (t, J = 7.0 Hz, 3H), 2.68 (s,3H), 4.50 (q, J = 7.0 Hz, | 65 |
| | | 52.82 | 3.42 | 6.85 | 2H), 7.34 (dd, J = 2.0, 8.3 Hz, 1H), 7.41 (d, | |
| | | (52.83 | 3.56 | 6.53) | J = 8.3 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.66 | |
| | | | | | (s, 1H), 8.81 (br s, 2H) | |

Table 2

| Compound | mp | Formula | Anal. Calcd. (Found) | | $^1$H NMR (deuteriochloroform) | Yield |
|---|---|---|---|---|---|---|
| | (°C) | C | H | N | δ , J (Hz) | (%) |
| **Va** | 213-216 | $C_{17}H_{16}N_2O_4S$ | | | 1.53 (t, J = 7.0 Hz, H), 2.42 | 72 |
| | | 59.29 | 4.68 | 8.14 | (s, 3H), 2.66 (s, 3H), 2.77 (s, 3H), 4.58 | |
| | | (59.38 | 4.65 | 8.31) | (q, J = 7.0 Hz, 2H), 7.87 (s, 1H), 12.41 (s, 1H) | |
| **Vb** | 201-205 | $C_{20}H_{22}N_2O_4S$ | | | 1.51 (t, J = 7.0 Hz, 3H), 1.59 | 45 |
| | | 62.15 | 5.74 | 7.25 | (s, 9H), 2.67 (s, 3H), 2.78 (s, 3H), 4.57 | |
| | | (62.33 | 5.76 | 7.33) | (q, J = 7.0 Hz, 2H), 7.91 (s, 1H), 12.82 (s, 1H) | |
| **Vc** | 236-238 | $C_{22}H_{18}N_2O_4S$ | | | 1.52 (t, J = 7.1 Hz, 3H), 2.40 (s, 3H), | 64 |
| | | 65.01 | 4.46 | 6.89 | 2.74 (s,3H), 4.55 (q, J = 7.1 Hz, 2H), | |
| | | (64.93 | 4.49 | 6.96) | 7.41-7.52 (m, 5H), 7.90 (s, 1H), 12.63 (s, 1H) | |
| **Vd** | 166-168 | $C_{23}H_{20}N_2O_5S$ | | | 1.52 (t, J =7.1 Hz, 3H), 2.37 | 53 |
| | | 63.29 | 4.62 | 6.42 | (s, 3H), 2.77 (s, 3H), 3.88 (s, 3H), 4.59 (q, J = | |
| | | (62.89 | 4.71 | 6.13) | 7.1 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 7.41 | |
| | | | | | (d, J = 8.7 Hz, 2H), 7.92 (s, 1H), 12.67 (s, 1H) | |
| **Ve** | 238-241 | $C_{22}H_{17}N_3O_6S$ | | | 1.54 (t, J = 7.0 Hz, 3H), 2.53 | 33 |
| | | 58.53 | 3.80 | 9.31 | (s, 3H), 2.77 (s, 3H), 4.61 (q, J = 7.0 Hz, 2H), | |
| | | (58.64 | 3.87 | 9.52) | 7.60 (d, J = 8.8 Hz, 2H), 7.95 (s, 1H), 8.36 | |
| | | | | | (d, J = 8.8 Hz, 2H), 12.82 (s, 1H) | |
| **Vf** | 184-185 | $C_{23}H_{17}F_3N_2O_4S$ | | | 1.53 (t, J = 7.3 Hz, 3H), 2.50 (s, 3H), | 66 |
| | | 58.22 | 3.61 | 5.91 | 2.77 (s, 3H), 4.60 (q, J = 7.3 Hz, 2H), 7.64-7.77 | |
| | | (57.92 | 3.80 | 5.69) | (m, 4H), 7.95 (s, 1H), 12.82 (s, 1H) | |
| **Vg** | 223-227 | $C_{20}H_{15}ClN_2O_4S_2$ | | | 1.53 (t, J = 7.0 Hz, 3H), 2.48 (s, 3H) | 29 |
| | | 53.75 | 3.38 | 6.27 | 2.77 (s, 3H), 4.58 (q, J = 7.0 Hz, 2H), 7.00 (d, J = | |
| | | (53.39 | 3.37 | 6.05) | 4.0 Hz, 1H), 7.14 (d, J = 4Hz, 1H), 7.93 (s, 1H), | |
| | | | | | 12.67 (s, 1H) | |
| **Vh** | 217-219 | $C_{22}H_{16}Cl_2N_2O_4S$ | | | 1.53 (t, J = 7.0 Hz, 3H), 2.57 (s, 3H), | 37 |
| | | 55.59 | 3.39 | 5.89 | 2.76 (s, 3H), 4.60 (q, J = 7.0 Hz, 2H), 7.32 | |
| | | (55.58 | 3.52 | 5.89) | (d, J = 8.3 Hz, 1H), 7.44 (dd, J = 2.0, 8.3 Hz, 1H), | |
| | | | | | 7.52 (d, J = 2.0 Hz, 1H), 12.80 (s, 1H) | |

Table 3

| Compound | mp | Formula | Anal. Calcd. (Found) | | $^1$H NMR (deuteriochloroform) | Yield |
|---|---|---|---|---|---|---|
| | (°C) | C | H | N | δ, J (Hz) | (%) |
| **VIa** | 248-251 | $C_{21}H_{18}N_2O_5S$ | | | 1.50 (t, J = 7.1Hz, 3H), 2.60 (s, 3H), | 12 |
| | | 61.45 | 4.39 | 6.82 | 2.65 (s, 3H), 2.79 (s, 3H), 3.02 (s, 3H), | |
| | | (61.36 | 4.47 | 6.96) | 4.67 (q, J = 7.0 Hz, 2H), 7.39 (s, 1H) | |
| **VIc** | 190-194 | $C_{26}H_{20}N_2O_5S$ | | | 1.53 (t, J = 7.2 Hz, 3H), 1.81 (s 3H), 2.54, | 47 |
| | | 66.09 | 4.27 | 5.93 | (s, 3H), 2.74 (s, 3H), 4.68 (q, J = 7.2 Hz, | |
| | | (65.80 | 4.39 | 5.71) | 2H), 7.38 (s, 1H), 7.41-7.52 (m, 5H) | |
| **VId** | 211-212 | $C_{27}H_{22}N_2O_6S$ | | | 1.53 (t, J = 7.0 Hz, 3H), 1.83 (s, 3H), 2.55 (s, 3H), | 53 |
| | | 64.53 | 4.41 | 5.58 | 2.75 (s, 3H), 3.98 (s, 3H), 4.69 (q, J = 7.0 Hz, | |
| | | (64.32 | 4.49 | 5.55) | 2H), 7.09 (d, J = 8.8 Hz, 2H), 7.32 | |
| | | | | | (d, J = 8.8 Hz, 2H), 7.38 (s, 1H) | |
| **VIe** | >270 | $C_{26}H_{19}N_3O_7S$ | | | 1.53 (t, J = 7.3 Hz, 3H), 1.79 (s, 3H), 2.55 | 75 |
| | | 60.34 | 3.70 | 8.12 | (s, 3H), 2.76 (s, 3H), 4.70 (q, J = 7.3 Hz, 2H), | |
| | | (60.35 | 3.40 | 8.03) | 7.42 (s, 1H), 7.65 (d, J = 8.8 Hz, 2H), | |
| | | | | | 8.48 (d, J = 8.8 Hz, 2H) | |
| **VIf** | 208-210 | $C_{27}H_{19}F_3N_2O_5S$ | | | 1.52 (t, J = 7.3 Hz, 3H), 1.78 (s, 3H), 2.55 | 45 |
| | | 59.99 | 3.54 | 5.18 | (s, 3H), 2.74 (s, 3H), 4.68 (q, J = 7.3 Hz, 2H), | |
| | | (60.06 | 3.65 | 5.39) | 7.40 (s, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.73 (s, 1H), | |
| | | | | | 7.79 (t, J = 7.8 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H) | |
| **VIg** | 223-225 | $C_{24}H_{17}ClN_2O_5S_2$ | | | 1.51 (t, J = 7.1 Hz, 3H), 2.12 (s, 3H), 2.57 | 48 |
| | | 56.19 | 3.34 | 5.46 | (s, 3H), 2.77 (s, 3H), 4.68 (q, J = 7.1 Hz, 2H), | |
| | | (55.88 | 3.41 | 5.40) | 7.01 (d, J = 3.8 Hz, 1H) 7.09 (d, J = 3.8 Hz, 1H), | |
| | | | | | 7.40 (s, 1H) | |
| **VIh** | 198-200 | $C_{26}H_{18}Cl_2N_2O_5S$ | | | 1.54 (t, J =7.1 Hz, 3H), 1.87 (s, 3H), 2.56 (s, 3H), | 50 |
| | | 57.68 | 3.35 | 5.18 | 2.76 (s,3H), 4.70 (q, J = 7.1 Hz, 2H), 7.31 | |
| | | (57.73 | 3.46 | 4.77) | (d, J = 8.3 Hz), 7.40 (s, 1H), 7.51(dd, J = 2.0, 8.3 Hz, | |
| | | | | | 1H), 7.66 (d, J = 2.0 Hz, 1H) | |

$^1$H nmr spectra were recorded using a Varian Unity Plus 300 and a Varian VXRS 400. Chemical shift values are reported in parts per million on the δ scale. The nmr spin multiplicities are indicated by the symbols s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, New Jersey, U.S.A. The ethyl 3-cyano-2-mercapto-6-methylpyridine-4-carboxylate (I) used in this investigation was purchased from Maybridge Chemical Company Ltd.

General Procedure for the Preparation of 4-Substituted Ethyl 2-Acyl-3-amino-6-methylthieno[2,3-*b*]pyridine-4-carboxylates **IIIa-h**.

In a nitrogen atmosphere, ethyl 3-cyano-2-mercapto-6-methylpyridine-4-carboxylate (6.6 g, 30 mmoles) was added to a stirred solution of sodium methoxide (30 mmoles) in ethanol (150 ml). The resulting mixture was heated at 50° for 20 minutes then cooled to room temperature. A substituted 2-bromoketone (30 mmoles) was added and the reaction mixture was heated under reflux for three hours and then cooled to ambient temperature. An additional quantity (30 mmoles) of sodium methoxide was added. Within seconds a heavy precipitate formed. The reaction mixture was stirred for 3 hours at room temperature, diluted with ice/water (150 ml) and the solid product was removed by filtration, washed with water, and crystallized from acetonitrile. In the case of compound **IIIb** the reaction mixture was heated under reflux for 6 hours after the addition of the second quantity of sodium methoxide. Compounds **IIIa** and **IIIc** are known, mp 165-168° and 154-157° (reported mp 170-172° and 161-163° [5]).

Data for all the new compounds are listed in Table I.

General Procedure for the Preparation of 4-Substituted Ethyl 3-Acetyl-2-hydroxy-7-methylthieno[2,3-*b*:4,5-*b'*]dipyridine-9-carboxylates **Va-h**.

A few drops (3-4 drops) of triethylamine were added to a 4-substituted ethyl 2-acyl-3-amino-6-methylthieno[2,3-*b*]pyridine-4-carboxylate (20 mmoles) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (30 mmoles) in dioxane (50-75 ml). The reaction mixture was stirred and heated under reflux for 6 hours then cooled to room temperature. The product that crystallized from the reaction mixture was removed by filtration and recrystallized from acetonitrile. If the product did not crystallize out, the dioxane was removed under vacuum and the residue was crystallized from acetonitrile. Data for all the compounds prepared are listed in Table II.

General Procedure for the Preparation of 5-Substituted Ethyl 3-Acetyl-4,8-dimethyl-2-oxo-2*H*-pyrano[2,3-*b*]pyrido[3',2':4,5]-thieno[2,3-*e*]pyridine-10-carboxylates **VI**.

A few drops (3-4 drops) of triethylamine were added to a 4-substituted ethyl 3-acetyl-2-hydroxy-7-methylthieno[2,3-*b*:4,5-*b'*]dipyridine-9-carboxylate (2 mmoles) and 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (20 mmoles) in dioxane (15 ml). The reaction mixture was stirred and heated under reflux for 4 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the product was purified by column chromatography (silica gel, eluting with 3/2 hexane: ethyl acetate). Compound **Vb** failed to give **VIb** under the above reaction conditions. Data for all the compounds synthesized are listed in Table III.

Acknowledgment.

We thank Mr. T. D. Elmer for his technical assistance, and Mrs. G. L. Blankenship and Mr. J. C. Groce, Jr., for recording the nmr spectra.

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