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2-Amino-3-cyanothiophenes were reacted with ethyl aminocrotonate in the presence of catalytic amounts of *p*-toluensulfonic acid. The intermediates 2-[*N*-(3′-ethoxycarbonyl-2′-propenylamino]-3-cyanothiophenes obtained were cyclized with sodium ethoxide to give the desired ethyl 4-aminothieno[2,3-*b*]pyridine-5-carboxylate. Hydrolysis of the latter aminoesters afforded 4-aminothieno[2,3-*b*]pyridine-5-carboxylic acid. The overall yields were about 80%.

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In connection with a research program on the synthesis of polyheterocyclic compounds and polyazasteroids (2-6), 4-aminothieno[2,3-*b*]pyridine-5-carboxylic acids (**5**) were required.

Recently, Zimmermann, *et al.*, (7) have shown that 2-amino-3-cyanopyrroles and ethyl acetoacetate in the presence of *p*-toluensulfonic acid followed by base catalyzed cyclization of the intermediates would afford ethyl 4-aminopyrrolo[2,3-*b*]pyridine-5-carboxylates.

Attempts to prepare fused pyridines through the interaction of ethyl acetoacetate with aromatic and heterocyclic compounds having adjacent aminocyano groups, failed. In fact, 2-aminobenzonitrile, 2-amino-3-cyanofurans, 2-amino-3-cyanothiophenes, and 5-amino-4-cyanoisoxazoles upon reaction with ethyl acetoacetate in the presence of catalytic amounts of *p*-toluensulfonic acid in refluxing benzene, toluene, xylene or in the presence of sodium ethoxide in ethanol, did not give the [*N*-(3′-ethoxycarbonyl-2′-propenylamino)]-cyano adducts or the corresponding fused pyridine derivatives. The structure elucidation of the compounds formed is under investigations.

In spite of failure of the reaction with ethyl acetoacetate, when substituted 2-amino-3-cyanothiophenes (**1**) prepared according to the method of Gewald (8) were reacted with ethyl aminocrotonate (**2**) in the presence of catalytic amounts of *p*-toluensulfonic acid in refluxing benzene, high yields of the corresponding 2-[*N*-(3′-ethoxycarbonyl-2′-propenylamino]-3-cyanothiophenes (**3a-d**) were obtained. This reaction was accompanied by the evolution of ammonia. This could be used as a control of the reaction progress. The recrystallized intermediates **3** and equimolar quantities of sodium ethoxide in refluxing ethanol led to the formation of substituted ethyl 4-aminothieno[2,3-*b*]pyridine-5-carboxylates (**4**). The amino esters **4** were hydrolyzed to give 4-aminothieno-[2,3-*b*]pyridine-5-carboxylic acids (**5**). The overall yields were about 75-85%.

Scheme I

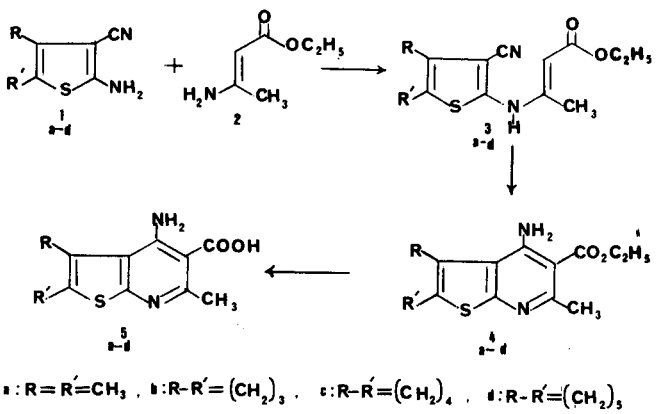
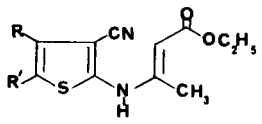



Table I



| Compound | R | R′ | M.p. °C | Yield % | Formula | Analyses C % Calcd. | C % Found | H % Calcd. | H % Found | N % Calcd. | N % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | Me | Me | 73-75 | 91 | $C_{13}H_{16}N_2O_2S$ | 59.09 | 58.88 | 6.06 | 6.17 | 10.60 | 10.44 |
| **3b** | -$(CH_2)_3$- | | 79-83 | 86 | $C_{14}H_{16}N_2O_2S$ | 60.86 | 60.93 | 5.79 | 5.77 | 10.14 | 10.28 |
| **3c** | -$(CH_2)_4$- | | 68-70 | 96 | $C_{15}H_{18}N_2O_2S$ | 62.06 | 62.15 | 6.20 | 6.30 | 9.65 | 9.52 |
| **3d** | -$(CH_2)_5$- | | 78-80 | 89 | $C_{16}H_{20}N_2O_2S$ | 63.15 | 63.06 | 6.57 | 6.43 | 9.21 | 9.40 |

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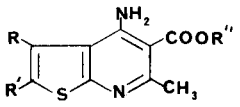
Table II



| Compound | R | R′ | R″ | M.p. °C | Yield % | Formula | Analyses C % Calcd. | C % Found | H % Calcd. | H % Found | N % Calcd. | N % Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **4a** | Me | Me | Et | 115-117 | 85 | $C_{13}H_{16}N_2O_2S$ | 59.05 | 59.11 | 6.06 | 6.02 | 10.60 | 10.77 |
| **4b** | -(CH$_2$)-$_3$ | | Et | 129-131 | 78 | $C_{14}H_{16}N_2O_2S$ | 60.86 | 60.76 | 5.79 | 5.49 | 10.14 | 10.38 |
| **4c** | -(CH$_2$)-$_4$ | | Et | 120-124 | 94 | $C_{15}H_{18}N_2O_2S$ | 62.06 | 61.92 | 6.20 | 6.29 | 9.65 | 9.77 |
| **4d** | -(CH$_2$)-$_5$ | | Et | 137-139 | 72 | $C_{16}H_{20}N_2O_2S$ | 63.15 | 63.33 | 6.57 | 6.50 | 9.21 | 9.11 |
| **5a** | Me | Me | H | 225-226 | 92 | $C_{11}H_{12}N_2O_2S$ | 55.93 | 56.06 | 5.08 | 5.23 | 11.86 | 11.69 |
| **5b** | -(CH$_2$)-$_3$ | | H | 235-238 | 95 | $C_{12}H_{12}N_2O_2S$ | 58.60 | 58.21 | 4.83 | 4.74 | 11.29 | 11.11 |
| **5c** | -(CH$_2$)-$_4$ | | H | 219-223 | 91 | $C_{13}H_{14}N_2O_2S$ | 59.54 | 59.45 | 5.34 | 5.48 | 10.68 | 10.89 |
| **5d** | -(CH$_2$)-$_5$ | | H | 162-164 | 85 | $C_{14}H_{16}N_2O_2S$ | 60.86 | 60.56 | 5.79 | 5.97 | 10.14 | 10.24 |

Further confirmation of the structures of compounds **3**, **4** and **5** was obtained through the nmr, ir and mass spectroscopy and supported by elemental analysis.

This new reaction is illustrated in Scheme I.

The physical properties of compounds **3**, **4** and **5** are reported in Tables I and II.

## EXPERIMENTAL

Melting points were determined with a hot stage microscope and are uncorrected. Ir spectra were recorded using a Perkin-Elmer model 267 spectrograph. The nmr spectra were recorded on a Varian T-60A spectrometer and chemical shifts ($\delta$) are in ppm relative to tetramethylsilane. Mass spectra were run on a Varian-Mat Ms-311 spectrometer at 70 eV.

4,5-Dimethyl-2-[*N*-(3′-ethoxycarbonyl-2′-propenylamino)]-3-cyanothiophene (**3a**).

A mixture of 7.6 g. (0.05 mole) of 4,5-dimethylamino-3-cyanothiophene (8), 6.45 g. (0.05 mole) of ethyl aminocrotonate and 0.5 g. *p*-toluensulfonic acid monohydrate in 100 ml. of benzene was refluxed for 10 hours. Ammonia was formed during the reaction time. The solvent was evaporated under reduced pressure and the crystaline residue was recrystallized (charcoal) from 95% ethanol to give 12 g. (91%) of **3a** as cream plates, m.p. 73-75°; nmr (deuteriochloroform): 1.33 (t, 3H, J = 4 Hz, $CH_3$), 2.16 (s, 3H, $CH_3$), 2.37 (s, 3H, $CH_3$), 4.20 (q, 2H, J = 4 Hz, $CH_2$), 4.70 (b, 1H, NH) and 4.91 (s, 1H, CH); molecular weight by mass spectroscopy m/e 264.

Compounds **3b-d** were prepared similarly. The physical properties of compounds **3** are reported in Table I.

Ethyl 2,3,6-Trimethyl-4-aminothieno[2,3-*b*]pyridine-5-carboxylate (**4a**).

A solution of 5.28 g. (0.02 mole) of **3a** in 50 ml. of ethanol containing 0.2 mole of sodium ethoxide was refluxed for 8 hours. The reaction mixture was concentrated to one half of the original volume and diluted with water. The brown crystaline mass was recrystallized (charcoal) from 50 % ethanol to give 4.48 g. (85%) of amino ester **4a**, m.p. 115-117°; ir (potassium bromide): 3525, 3345, 2979, 2920, 1673, 1585, 1565, 1523, 1451, 1422, 1377, 1349, 1300, 1238, 1183, 1100, 1075, 1031, 930 and 804 cm$^{-1}$; nmr (deuteriochloroform): 1.37 (t, 3H, J = 4.5 Hz, $CH_3$), 2.33 (s, 3H, $CH_3$), 2.47 (s, 3H, $CH_3$), 2.65 (s, 3H, $CH_3$), 4.39 (q, 2H, J = 4.5 Hz, $CH_2$), and 6.57 (b, 2H, $NH_2$); ms m/e: 264 $M^+$ (100%), 219 (M-OEt) (63%), 190 (M-$CO_2$Et) (100%).

Compounds **4b-d** were prepared similarly. The physical properties of compounds **4** are reported in Table II.

2,3,6-Trimethyl-4-aminothieno[2,3-*b*]pyridine-5-carboxylic Acid (**5a**).

The amino acid **4a**, 2.64 g. (0.01 mole) in 25 ml. of a 10% solution of sodium hydroxide in 50% ethanol was refluxed for 4 hours. After cooling, the solution was acidified with hydrochloric acid and the precipitate was recrystallized from aqueous ethanol to give 2.17 g. (92%) of amino acid **5a**, m.p. 225-226°, molecular weight by mass spectroscopy m/e 236; ir (potassium bromide): 3460, 3305, 2620, 1690, 1600, 1548, 1453, 1390, 1300, 1261, 1049, 899, and 810 cm$^{-1}$.

Compounds **5b-d** were prepared similarly. The physical properties of compounds **5** are reported in Table II.

Acknowledgment.

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