Thiophene Systems. 10.
The Synthesis and Chemistry of some Thienopyridinols [1]

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Substituted thieno[2,3-*c*]-, thieno[3,2-*c*]- and thieno[3,4-*c*]pyridinols have not been described despite the fact that a few descriptions of the parent ring systems have appeared in the literature. As part of our ongoing program to investigate the synthesis of thiophene derivatives with potential biological activity, we became interested in the preparation of the various thienopyridinols. Syntheses of the title compounds **2a**, **3** and **25** were achieved starting from thiophene-3-acetic acid and 3-acetylthiophene. The two isomeric systems **2a** and **3** were reacted with electrophiles to give products substituted at the position α to the hydroxy group on the pyridine ring (the 4- and 6-positions, respectively). Lack of stability of **25** precluded studies on this system. Compounds **2a**, **3** and **25** reacted with acetic anhydride to give *O*-acetyl derivatives while reaction of the anion of **2a** and **3** with methyl iodide gave mixtures of *O*- and *N*-methylation. The *N*-methylated products are the novel thienopyridones **45** and **47**.

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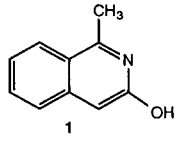
Isoquinolines have been known for over 100 years. Their synthesis and medicinal value [2] have been well documented. While the corresponding thienopyridines [3] have been known as far back as 1951, some of the hydroxy substituted thienopyridines remain unknown. Because of our interest in preparing novel thiophene analogs of biologically active benzo compounds, we set out to synthesize the thiophene analogs of 3-hydroxy-1-methylisoquinolines **1** which have been shown to be active as cardiovascular agents [4]. All three of the thiophene isosteres, **2a**, **3** and **4**, require synthesis, since large differences in biological activity between thiophene isosteres, in a variety of systems, have frequently been observed [5].



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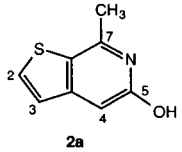
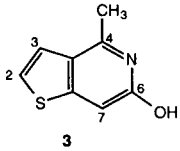


2a



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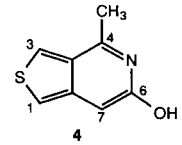
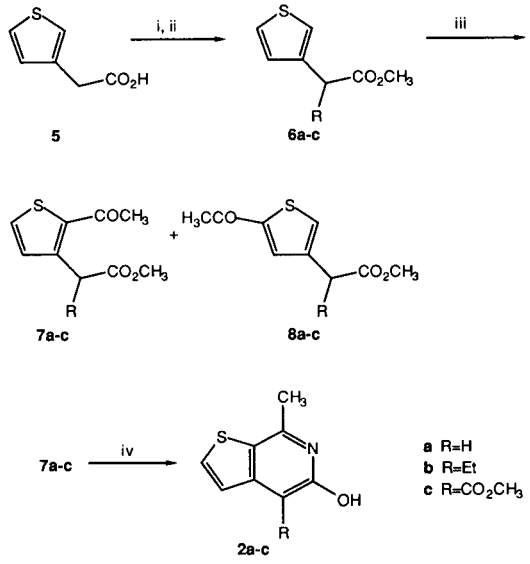


4

7-Methylthieno[2,3-*c*]pyridin-5-ol (**2a**) was synthesized from commercially available 3-thiopheneacetic acid (**5**, Scheme 1) by a method similar to that used by Dorofeenko in the synthesis of 3-hydroxy-6,7-dimethoxy-1-methylisoquinoline [6]. Compound **5** was converted quantitatively to methyl ester **6a** with methanol and a catalytic amount of sulfuric acid. Treatment of **6a** with acetic anhydride and one equivalent of perchloric acid did **not** result in the formation of a pyrylium salt corresponding to the benzene analogue as described by Dorofeenko [6], but rather, two acylated products, namely methyl 2-acetyl-3-thiopheneacetate (**7a**) and methyl 2-acetyl-4-thiopheneacetate (**8a**). The conversion was quantitative with an isomer ratio of 3:2 for **7a**:**8a** as determined by ^{1}H nmr analysis; these isomers were easily separable by flash chromatography. Preferably, acylation of **6a** was achieved with perchloric acid catalyst in acetic anhydride; acetyl chloride/tin(IV) chloride or boron trifluoride and acetic anhydride/phosphoric acid also gave a similar product ratio but in lower overall yields. Acylation at the more hindered α-position may arise partly from the "*ortho*" directing influence of the 3-alkyl substituent and/or by catalyst coordination on the ester carbonyl causing delivery to the vicinal position.

Scheme 1



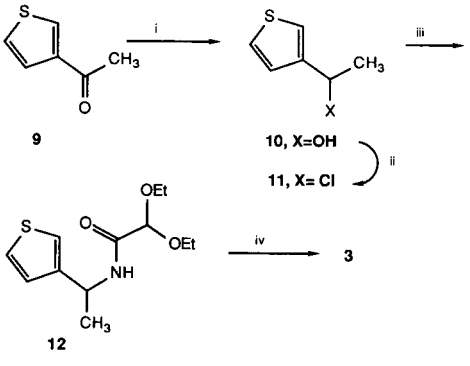
(i) CH_3OH/H_2SO_4,
(ii) LDA/CH_3CH_2I or LDA/CH_3OCOCl, omit (ii) for R = H,
(iii) $Ac_2O/HClO_4$,
(iv) NH_4OAc (molten)

Conversion of **7a** to the ring closed product **2a** with molten ammonium acetate was straightforward and achievable in large scale with product isolation by filtration from aqueous media. Furthermore, we found that separation of intermediate **7a** from **8a** was unneccessary since cyclization of the mixture of **7a** and **8a** in molten ammonium acetate with the same workup conditions gave **2a** in identical overall yield.

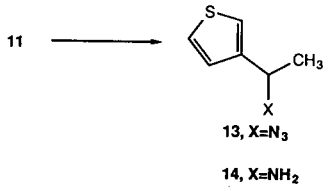
Methyl thiopheneacetate **6a** was deprotonated with lithium diisopropylamide and the anion alkylated with ethyl iodide to give methyl 2-(thien-3-yl)butanoate (**6b**). Treatment of **6b** with acetic anhydride and perchloric acid gave a quantitative mixture of methyl 2-(2-acetylthien-3-yl)-butanoate (**7b**) and methyl 2-(2-acetylthien-4-yl)butanoate (**8b**) in a ratio of 1:1. The increase of the undesired isomer **8b** presumably arises from increased steric demands of the ethyl substitution on the side chain adjacent to the desired site of reaction. The mixture of **7b** and **8b** was treated with molten ammonium acetate to produce the desired 4-ethyl-7-methylthieno[2,3-*c*]pyridin-5-ol (**2b**). The anion of **6a** could also be reacted with methyl chloroformate to give **6c** which was acetylated to give **7c**:**8c** in a ratio of 2:3. Compound **7c** was separated by flash chromatography prior to cyclization to the thieno[2,3-*c*]pyridinol **2c**.

Preparation of 4-methylthieno[3,2-*c*]pyridin-6-ol (**3**) was envisoned using Pomerantz-Fritsch type synthesis [7], which required the synthesis of the intermediate amide acetal **12** (Scheme 2). The initial preparation of this intermediate was accomplished by lithium aluminum hydride (LAH) reduction of 3-acetylthiophene (**9**) to the corresponding alcohol **10** and conversion to the chloride **11** with thionyl chloride. Special care was taken to avoid heat when working with **11** which tended to eliminate hydrogen chloride to form 3-vinylthiophene, a volatile nonpolar material previously reported [8]. Displacement of chloride from **11** with the sodium salt of diethoxyacetamide gave **12** in 45% yield. The major impurity was again 3-vinylthiophene which formed as a result of competitive dehydrochlorination of **11**.

Scheme 2

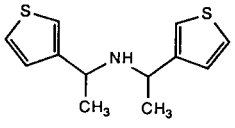


An alternative method to synthesize **12**, which avoids this elimination problem, utilizes amine **14** as an intermediate (Equation 1). Successful preparation of **14** was achieved by treating chloride **11** with sodium azide and reducing the resulting azide with LAH (Equation 1). When **14** was treated with trimethyl aluminum and ethyl diethoxyacetate using the procedure of Weinreb [11], amide **12** formed in good yield. Although this method of synthesizing **12** requires two additional steps as compared to that shown in Scheme 2, it is accomplished in higher overall yield without chromatographic purification of any of the intermediates.



(eq 1)

Several conventional methods to prepare amines from ketones proved unsuccessful for the synthesis of **14**. For example, treatment of **9** with sodium cyanoborohydride and ammonium acetate [9] gave bis[1-(3-thienyl)ethyl]-amine (**15**) presumably by reductive amination of the ketone group of **9** with the desired amine **14** which formed *in situ*. Reducton of the oxime of **9** with LAH gave similar results, while catalytic reduction resulted only in recovery of starting material, and zinc in acetic acid caused decomposition. Treatment of the oxime with titanium tetrachloride/sodium borohydride [10] gave a mixture of chlorinated products rather than the desired **14**.

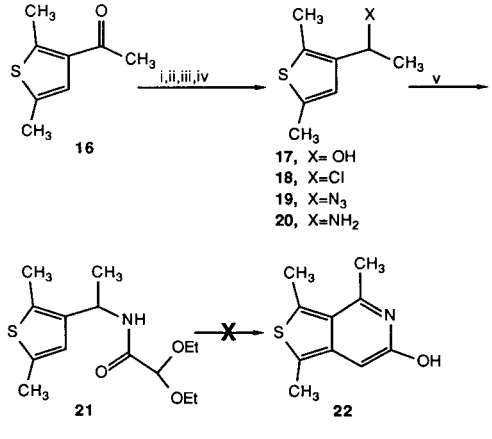


Lewis acids were not effective in cyclizing **12** to the thienopyridinol **3**. Starting material was recovered essentially quantitatively when **12** was treated with tin(IV) chloride, tin(II) chloride or boron trifluoride at room temperature, while higher temperatures caused decomposition. The same was true when dilute protic acids such as hydrochloric acid and sulfuric acid were used and concentrated sulfuric acid slowly decomposed the starting material. These failures to directly close **12** to **3** led to an attempt to hydrolyze the acetal to an aldehyde which might then be more amenable to closure to **3**. When **12** was heated in 48% aqueous hydrobromic acid and acetic acid in this attempt,

somewhat surprisingly, the hydrobromic acid salt of **3** precipitated directly from the reaction solution in 70% yield; presumably, the aldehyde forms and immediately cyclizes.

Synthesis of the 4-methylthieno[3,4-*c*]pyridin-6-ol (**4**) proved to be the most challenging of the three systems. Since electrophilic substitution reactions and metalation are known to occur predominantly on the 2- and 5-positions of thiophene [12], these positions were blocked by using 2,5-dimethyl-3-acetylthiophene (**16**) as a starting material. An approach similar to that for synthesis of **3** from 3-acetylthiophene was expected to give **22** (Scheme 3). LAH reduction of ketone **16** gave alcohol **17** which was extremely unstable at room temperature. Fortunately, isolation of the alcohol was unnecessary and direct conversion *in situ* to chloride **18** could be accomplished by quenching the reduction reaction with aqueous sodium hydroxide, removing the resultant aluminum salts and treating the dried solution with thionyl chloride at 0°. The chloride was isolated by evaporating the solvent *in vacuo* at **low** temperature since it also is extremely labile and volatile. Although **18** could be stored for short periods of time at $<0°$, it was advantageous to convert to **19** with sodium azide in *N,N*-dimethylformamide immediately after isolation of **18**. Azide **19** was stable at room temperature and could be stored for several months without noticeable decomposition. Reduction of **19** to the equally stable amine **20** was accomplished with LAH. The penultimate amide **21** formed in good yield by treating **20** with trimethylaluminum and ethyl diethoxyacetate. Unfortunately, all attempts to cyclize **21** to the desired thieno[3,4-*c*]pyridinol **22** failed. Numerous Lewis acids and protic acids under a large variety of reaction conditions caused only slow decomposition of the starting material with no evidence of desired product formation.

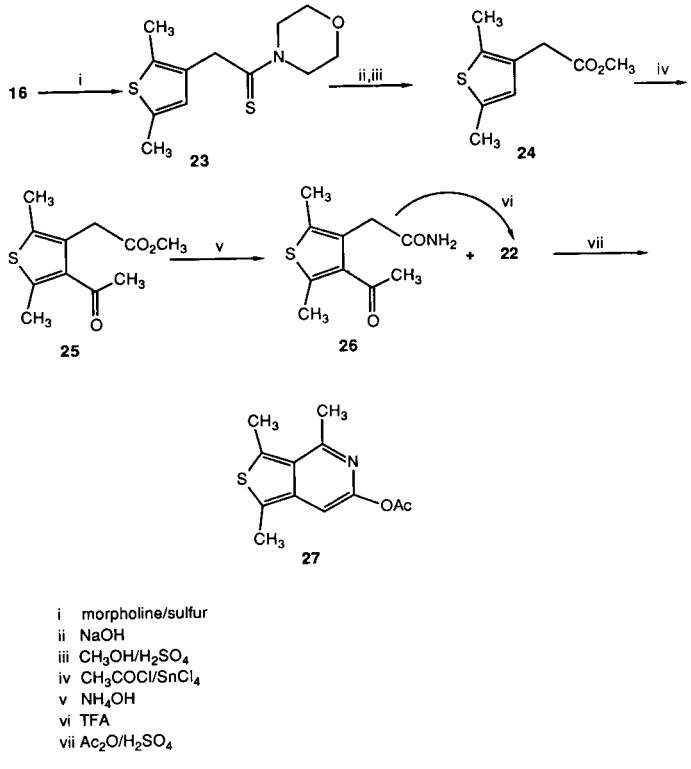
Scheme 3



In an alternative procedure (Scheme 4), ketone **16** was treated with sulfur and morpholine under Willgerodt conditions [13] to give thioamide **23** which hydrolyzed to the acid with aqueous sodium hydroxide [14]. Esterification of the acid to **24** was straight forward. Attempts to form this ester directly by treating **16** with thallium(III) nitrate and trimethyl formate in methanol, conditions useful for the preparation of phenylacetic acid esters from acetophenones [15], failed. Acylation of **24** with acetyl chloride and tin(IV) chloride gave **25** in good yield.

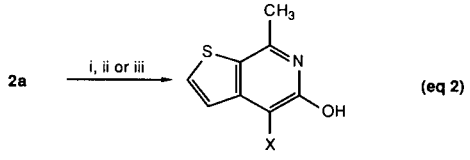
Treatment of **25** with concentrated ammonium hydroxide resulted in the formation of amide **26** contaminated with some **22**. Cyclization of **26** to the desired thieno-[3,4-*c*]pyridinol **22** was smoothly effected in trifluoroacetic acid at room temperature while the reaction was monitored by ^{1}H nmr analysis. To our knowledge, these mild conditions represent a novel method to effect the formation of a pyridine derivative. Thin layer chromatographic (tlc) analysis proved inadequate to follow the course of this reaction since a multispot mixture proved to be an artifact of decomposition of **22** on silica gel (demonstrated by 2-dimensional tlc methods). Treatment of **25** with molten ammonium acetate gave only a moderate yield of material while work-up was less effective than the trifluoroacetic acid procedure on **26** which was preferable for our work. When **22** was treated with acetic anhydride with sulfuric acid catalyst, the stable *O*-acyl compound **27** formed in modest yields.

Scheme 4



The instability of thieno[3,4-*c*]pyridinol **22**, relative to related thienopyridinols, **2** and **3**, might be attributable to both electronic and steric factors. The [2,3-*c*] and the [3,2-*c*] systems have 11 classical resonance structures two of which have no localized charges. The [3,4-*c*]thienopyridinol has 10 classical resonance structures only one of which is uncharged. As a consequence, the two former structures might be expected to be electronically more stable than the latter. This expectation is supported by quantum mechanics calculations [16]. While direct comparisons of **2, 3** and **22** are impossible due to energy differences resulting from the presence of the methyl groups in **22**, MNDO was used to optimize the geometry of **2a, 3** and **4**, and calculated heats of formation revealed that **2a** and **3** were of equal energy (−18.2 kcal and −18.1 kcal, respectively) while **4** was thermodynamically less stable (−6.7 kcal). When the calculations were repeated for **22** and the related dimethyl analogues of **2a** and **3**, similar results (albeit with different energies) were obtained, presumptive of the lesser stability of the [3,4-*c*] system. In addition, the 1,3-dimethyl groups of **22** may cause steric crowding not present in the other two systems which might kinetically activate the system to facile hydrolytic opening. As a result of the synthetic difficulties as well as the apparent instability of this system, preparation of **4**, the desmethyl analogue of **22**, was not attempted.

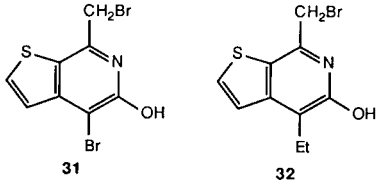
Since 7-methylthieno[2,3-*c*]pyridin-5-ol (**2a**) was formed most expediently, the chemistry of this system was extensively studied (Equation 2). Despite the electron-rich nature of thiophene which usually facilitates electrophilic substitution chemistry on this ring [12], the C-4 adjacent to the 5-hydroxy group is most susceptible to electrophilic attack similar to the chemistry observed for isoquinolin-3-ols [4]. When **2a** was treated with one equivalent of bromine in acetic acid containing sodium acetate, **28** formed in 60% yield. Use of *N*-chlorosuccinimide in acetic acid on **2a** gave chloride **29** in good yield while sulfuryl chloride effected incomplete conversion (18%). When sodium acetate buffering was used with sulfuryl chloride, no reaction occured. Reaction of **2a** with two equivalents of bromine led to a second bromine incorporation onto the 7-methyl group to give **31** rather than reaction on the thiophene ring. A similar result was observed for the monobromination of 4-ethyl-7-methylthieno[2,3-*c*]pyridin-5-ol (**2b**) in which the 4-position is blocked by an ethyl group to give **32**.



(eq 2)

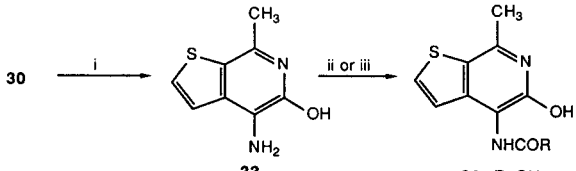
28, X=Br
29, X=Cl
30, X=NO_2

i Br_2/NaOAc/AcOH, ii NCS/AcOH, iii HNO_3/AcOH



31 **32**

Nitration of **2a** using nitric acid in acetic acid gave 4-nitro compound **30** in good yield. No additional products were detected regardless of the amount of nitrating agent used. The nitro derivative was easily reduced to amine **33** in methanol or acetic acid with palladium-on-carbon as the catalyst (Equation 3). Amine **33** is stable and could be stored for at least several weeks without decomposition. The corresponding amide **34** could be made by treating the amine with acetic anhydride while the urea **35** formed by reaction of **33** with sodium isocyanate. No evidence of *O*-acylation was observed.



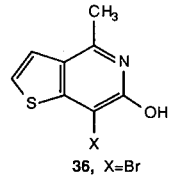
(eq 3)

33

34 R=CH_3
35 R=NH_2

i H_2/Pd-C/MeOH, ii Ac_2O, iii NaNCO

The chemistry of 4-methylthieno[3,2-*c*]pyridin-6-ol (**3**) was similar to that of **2a**. Bromination, chlorination and nitration went cleanly to form the corresponding 7-substituted thienopyridinol derivatives **36**, **37** and **38**, respectively. Unlike the chemistry of **2a**, however, reaction with two equivalents of bromine gave an intractable mixture of mono- and polybrominated material as evidenced by mass spectral analysis.



36, X=Br
37, X=Cl
38, X=NO_2

This difference in observed electrophilic substitution chemistry is predicted from the MNDO calculated eigenvectors of **2a** and **3** (discussed earlier) [16]. The HOMO coefficients of the aromatic positions susceptible to electrophilic attack are shown in Figure 1. The position α to the hydroxyl substituent has the highest coefficient indicating high electron density for the HOMO and hence high reactivity. After monobromination, however, clear differences between the two systems are evident. While **28** has very low coefficients on either of the thiophene positions, the coefficients of **36** suggest that substitution on the thiophene ring is likely. While **2a** reacts with one equivalent of

electrophile on the aromatic system, the next addition occurs cleanly on the methyl group (presumably by a different mechanism). In the case of **3**, after initial reaction to give **36**, the aromatic positions are still quite reactive and mixtures of products arise by competitive mechanisms.

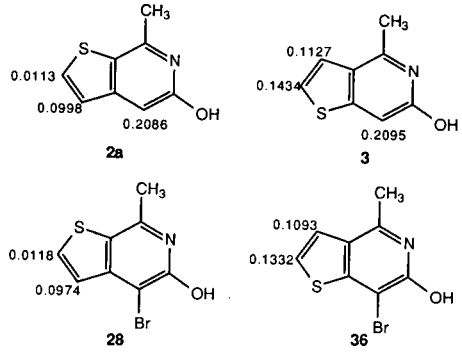
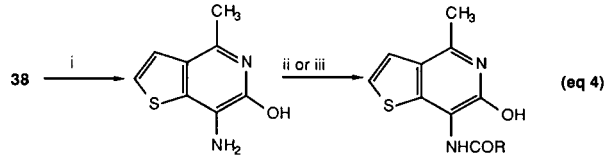


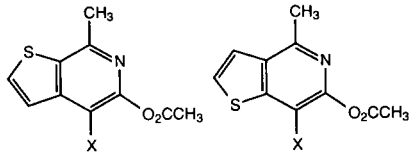
Figure 1. Homo Coefficients of **2a**, **3**, **28** and **36**

The reduction of nitro compound **38** also was unlike that of the [2,3-*c*] analogue **30** (Equation 4). Reduction required the presence of acetic acid; use of methanol as solvent (as for **30**) for the catalytic reduction resulted only in recovery of **38**. Also unlike the [2,3-*c*] amine **33**, amine **39** is sensitive to heat and decomposes on storage. Although it can be isolated, it is far more expedient to convert **39** directly to the corresponding amide **40** or urea **41** *in situ* by adding acetic anhydride or sodium isocyanate to the reduction medium.

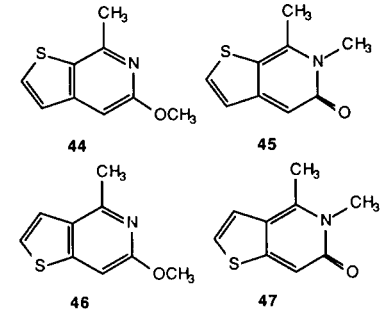


i H_2/Pd-C/AcOH, ii Ac_2O, iii NaNCO

Treating the three isosteric thienopyridinols **2a**, **3** and **22** with acetic anhydride using a catalytic amount of sulfuric acid gives the corresponding *O*-acetylated products **42a**, **43a** and **27**, respectively; acetylation of the ethyl or bromo compounds **2b**, **28** and **36** works equally well to produce **42b,c** and **43b**, respectively. In general, these esters slowly decompose on silica gel (evidenced by two dimensional thin layer chromatography) but they are sufficiently stable to survive flash chromatography. The acetates slowly revert to the hydroxy compounds on standing under ambient conditions.



The anion of the thienopyridinol **2a** forms with sodium hydride. As expected of such ambident anions, quenching with methyl iodide gives a mixture of the *O*-alkyl **44** and *N*-alkyl **45** products in the ratio of 1:2, respectively. These products were separable by chromatography. Similarly, the anion of **3** formed under these conditions reacts with methyl iodide to give the *O*-alkyl **46** and *N*-alkyl **47** in approximately the same ratio although in lower overall yields. The pyridone systems **45** and **47** are also novel and we are currently investigating some of their chemistry.



While systems **2a**, **3** and **22** and their derivatives may exist in several tautomeric forms (especially dependent on solvent polarity- see discussion and references in [4]), most of the chemistry observed in our studies may be explained in terms of the pyridinol structures depicted. There is some evidence from ir analysis (absorptions in the vicinity of 1640 cm^{-1}) that the pyridone tautomers may also exist in these series. Whether they may be isolated or further reacted in their "pyridone" or other tautomeric forms may be the subject of further study.

In conclusion, the three isosteric [2,3-*c*], [3,2-*c*] and [3,4-*c*] thienopyridinol systems **2a**, **3** and **22** were prepared and some electrophilic substitution chemistry was investigated. Differences in stability between the systems precluded a thorough comparison but electrophilic reaction occurs initially on the pyridine ring α- to the hydroxyl moiety in all cases studied. The resulting nitro compounds could be reduced and functionalized without reaction on the hydroxy group. The ambident anions of **2a** and **3** were prepared and alkylation gave mixtures of *O*- and *N*-substituted products. The initial goal of this work was to prepare thiophene isosteres of reported cardiotonic agents [4]. In this regard, the compounds in this report have good activity in our biological assays, many as good as their benzo-fused isosteres.

EXPERIMENTAL

Melting point determinations were done on either a Mel-Temp® or Thomas-Hoover capillary melting point apparatus and are uncorrected.

All compounds had spectra (ir, uv, ^{1}H nmr and ms) consistent with their assigned structures and were homogeneous by thin layer chromatography (tlc). The ^{1}H nmr spectra were determined on a Varian T60 or Brucker WP-100 FT spectrometer in deuteriochloroform unless otherwise noted. The ir spectra were determined on potassium bromide pellets unless otherwise noted.

Methyl 3-Thienylacetate (**6a**).

A solution of 3-thiopheneacetic acid (45 g, 0.316 mole) and sulfuric acid (4 ml) in methanol (400 ml) was stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue was diluted with water. The aqueous layer was extracted with methylene chloride and the organic extract was washed with saturated sodium bicarbonate, dried over magnesium sulfate and concentrated to give **6a** as an amber oil, 49 g (99%), which was used without further purification; ^{1}H nmr: δ 3.67 (s, 2H), 3.71 (s, 3H), 7.2 (m, 3H).

Methyl 2-Acetyl-3-thienylacetate (**7a**) and Methyl 2-Acetyl-4-thienylacetate (**8a**).

Acetic anhydride (13.0 ml, 0.147 mole) was added dropwise to a mixture of 70% perchloric acid (1.25 g, 8.7 mmoles) and **6a** (19.15 g, 0.123 mole) at 0° and the mixture was stirred at 0° for 1 hour. The reaction mixture was treated with 5% aqueous sodium bicarbonate. The product was extracted into methylene chloride, the extract dried over magnesium sulfate and purified by flash chromatography on silica gel 60 (450 g) and eluted with 15% ethyl acetate in hexanes to give **7a** as a solid, 10.4 g (43%), mp 53-54°; ir: 1735 and 1655 cm^{-1}; ms: m/z 198 (M$^+$); ^{1}H nmr: δ 2.53 (s, 3H), 3.70 (s, 3H), 4.05 (s, 2H), 7.07 (d, J = 5 Hz, 1H) and 7.47 (d, J = 5 Hz, 1H).

Anal. Calcd. for $C_9H_{10}O_3S$: C, 54.53; H, 5.08. Found: C, 54.63; H, 5.06.

Compound **8a** was obtained from a later fraction from the column as an amber oil, 6.3 g (25%); ^{1}H nmr: δ 2.55 (s, 3H), 3.66 (s, 3H), 3.73 (s, 2H), 7.47 (m, 1H) and 7.64 (d, J = 1.5 Hz, 1H).

7-Methylthieno[2,3-*c*]pyridin-5-ol (**2a**).

Compound **7a** (3.65 g, 18.4 mmoles) was added to molten ammonium acetate (46 g) at 130°. Anhydrous ammonia was bubbled into the reaction mixture maintained at 130° for 30 minutes. The hot mixture was poured into ice water and the pale green precipitate was collected by filtration and washed with water. The solid was recrystallized from isopropanol to give **2a** (1.89 g, 62%) as an off-white solid, mp 230-231° dec; ir: 2638, 1645, 1490, 1455 cm^{-1}; ms: m/z 165 (M$^+$); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.52 (s, 3H), 6.70 (s, 1H), 7.21 (d, J = 5 Hz, 1H), 7.87 (d, J = 5 Hz, 1H).

Anal. Calcd. for C_8H_7NOS: C, 58.16; H, 4.27; N, 8.48; S, 19.41. Found: C, 57.92; H, 4.26; N, 8.36; S, 19.18.

Methyl 2-(3-Thienyl)butanoate (**6b**).

n-Butylithium (1.6 *M*, in hexanes, 21 ml, 33.6 mmoles) was added to a solution of diisopropylamine (5.0 ml, 36.2 mmoles) in tetrahydrofuran (40 ml) at −10° under nitrogen and stirred for 30 minutes. The solution was cooled to −78°, and at this temperature a solution of **6a** (5.14 g, 32.9 mmoles) in tetrahydrofuran (10 ml) was added slowly. A yellow precipitate formed. The mixture was stirred at −78° for 1 hour. Ethyl iodide (3.0 ml, 37.5 mmoles) was added and the mixture was stirred at −78° for an additional ½ hour. The mixture was allowed to warm to room temperature over ½ hour, stirred 1 hour at room temperature, and poured into methylene chloride containing 1-3 g of ice. The separated organic layer was washed with 1*N* hydrochloric acid, dried over magnesium sulfate and evaporated *in vacuo* to yield 5.6 g of a yellow oil. The oil was purified by flash chromatography on silica gel 60 (100 g) using 3% ethyl acetate in hexanes as the eluant to give **6b** (4.62 g, 76%) as a colorless oil; ir (neat): 2958, 1736 cm^{-1}; ms: m/z 184 (M$^+$); ^{1}H nmr: δ 0.90 (t, J = 8 Hz, 3H), 1.65-2.23 (m, 2H), 3.59 (t, J = 7.5 Hz, 1H), 3.65 (s, 3H), 6.90-7.28 (m, 3H).

Anal. Calcd. for $C_9H_{12}O_2S$: C, 58.67; H, 6.56. Found: C, 58.91; H, 6.72.

4-Ethyl-7-methylthieno[2,3-*c*]pyridin-5-ol (**2b**).

Acetic anhydride (2.8 ml, 29.4 mmoles) was added to a solution of **6b** (4.33 g, 23.5 mmoles) in perchloric acid (70%, 230 mg, 1.61 mmoles) at 0°. The reaction was stirred at room temperature for ½ hour, diluted with methylene chloride and washed with saturated aqueous sodium bicarbonate. The organic phase was dried over magnesium sulfate and evaporated *in vacuo* to give an oil which is a mixture of acetyl thiophenes **7b** and **8b** (5.1 g, 96%) and was used without purification in the next step; ir (neat): 2960, 1730 and 1660 cm^{-1}; ms: m/z 226 (M$^+$; ^{1}H nmr: δ 0.90 (t, J = 8 Hz, 3H), 1.60-2.27 (m, 2H), 2.53 (s, 3H), 3.65 and 3.68 (each s, total of 3H), 4.78 (t, J = 7 Hz, 1H), 7.00 to 7.63 (m, 2H).

The mixture of **7b** and **8b** (5.1 g, 22.5 mmoles) was added to molten ammonium acetate (50 g) at 120°. Ammonia was bubbled into the mixture and the temperature was maintained at 120° for 40 minutes. The hot mixture was poured into 400 ml of ice water, and a sticky semisolid precipitated. The water was decanted, the semisolid was dissolved in hot isopropanol (40 ml) and the product, which crystallized upon cooling, was collected by filtration and triturated with diethyl ether to give **2b** (1.3 g, 29% from **6b**) as a yellow solid, mp 187-189°; ir: 1630 cm^{-1}; ms: m/z 193 (M$^+$); ^{1}H nmr (trifluoroacetic acid): δ 1.37 (t, J = 8 Hz, 3H), 2.97 (s, 3H), 3.12 (q, J = 8 Hz, 2H), 7.63 and 8.27 each (d, J = 5 Hz, 1H).

Anal. Calcd. for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25; S, 16.59. Found: C, 62.28; H, 5.91; N, 7.17; S, 16.51.

Dimethyl 3-Thienylmalonate (**6c**).

The anion of **6a** (10.0 g, 64 mmoles) was prepared as in the preparation of **6b** using *n*-butylithium (1.6 *M*, 40.4 ml, 64.6 mmoles) and diisopropylamine (9.4 ml, 67 mmoles) in tetrahydrofuran (110 ml total volume). Methyl chloroformate (5.7 ml, 73.6 mmoles) was slowly added (the temperature rose to −55°) and the mixture was stirred at −78° for ½ hour, warmed to room temperature and stirred for 2 hours. The mixture was poured into methylene chloride containing some ice and the separated organic phase was washed with 1*N* hydrochloric acid and dried over magnesium sulfate. The solvent was removed *in vacuo*. The crude material was purified by flash chromatography on silica gel 60 (350 g) and eluted with 8% ethyl acetate in hexanes to give **6c** (8.0 g, 58%) as an oil; ir (neat): 3115, 2960, 1740 and 1435 cm^{-1}; ms: m/z 214 (M$^+$); ^{1}H nmr: δ 3.73 (s, 6H), 4.75 (s, 1H), 7.03 to 7.30 (m, 3H).

Anal. Calcd. for $C_9H_{10}O_4S$: C, 50.46; H, 4.70. Found: C, 50.25; H, 4.49.

Dimethyl 2-Acetyl-3-thienylmalonate (**7c**) and 4-Carbomethoxy-7-methylthieno[2,3-*c*]pyridin-5-ol (**2c**).

Dimethyl 3-thienylmalonate (5.86 g, 27.4 mmoles) and perchloric acid (70%, 260 mg, 1.8 mmoles) were treated with acetic anhydride (3.1 ml, 32.8 mmoles) at 0°. The mixture was stirred at room temperature for 45 minutes. Workup as for **7b** gave an oil which was purified by flash chromatography on silica gel 60 (250 g) and eluted with 25% ethyl acetate in hexanes to give **7c** (1.6 g, 23%) as an oil which was used without further purification; ^{1}H nmr: δ 2.55 (s, 3H), 3.77 (s, 6H), 5.98 (s, 1H), 7.25 and 7.51 each (d, J = 5 Hz, 1H). Compound **8c** was obtained as an oil from later fractions of the chromatography, 2.4 g (34%); ^{1}H nmr: δ 2.57 (s, 3H), 3.79 (s, 6H), 4.79 (s, 1H), 7.66 and 7.79 each (d, J = 1.4 Hz, 1H).

Compound **7c** (1.64 g, 6.4 mmoles), was dissolved in 2-propanol (*ca.* 20 ml) and added to molten ammonium acetate at 140°. The reaction mixture was stirred 35 minutes at 130-140° and the melt was poured into ice water. The precipitate was collected by filtration, washed with water and recrystallized from 2-propanol to give **2c** (0.702 g, 49%) as a yellow solid; mp 187-190°; ir: 1710 and 1595 cm^{-1}; ms: m/z 223 (M$^+$); ^{1}H nmr: δ 2.73 (s, 3H), 4.05 (s, 3H), 7.70 and 7.83 each (d, J = 5 Hz, 1H), 12.08 (br s, 1H, exchanges with deuterium oxide).

Anal. Calcd. for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06; N, 6.27. Found: C, 53.75; H, 4.07; N, 6.28.

1-(3-Thienyl)ethanol (**10**).

Ketone **9** (100 g, 0.790 mole) in diethyl ether (600 ml) was added dropwise to a suspension of LAH (15.3 g, 0.403 mole) in diethyl ether (400 ml) over a 1 hour period. The mixture was heated to reflux for 1 hour, cooled to room temperature; water (16 ml) was slowly added followed by 15% aqueous sodium hydroxide (16 ml) and water (50 ml). The inorganic pre-

cipitate was removed by filtration and washed with diethyl ether. The combined diethyl ether filtrates were dried over magnesium sulfate and evaporated *in vacuo* to give **10** (101 g, 100%) as an oil which was used without further purification; ir (neat): 2990 and 3040 to 3700 cm^{-1}; ms: m/z 128 (M^+); ^1H nmr: δ 1.52 (d, J = 6 Hz, 3H), 2.08 (br s, 1H, exchanges with deuterium oxide), 4.95 (q, J = 6 Hz, 1H), 6.98-7.38 (m, 3H).

1-(3-Thienyl)chloroethane (**11**).

Thionyl chloride (95 ml, 0.819 mole) was added to **10** (100 g, 0.780 mole) at 0° over a 1 hour period, and the mixture was stirred at room temperature for 2.5 hours and ice water was added to the mixture. Extraction with diethyl ether and subsequent treatment of the combined organic phases with magnesium sulfate and charcoal and removal of the solvent *in vacuo* at 40° gave **11** (99.6 g, 87%) as an amber oil which was used without further purification; ir (neat): 3100, 2980, 2940, 1440 and 1420 cm^{-1}; ^1H nmr: δ 1.85 (d, J = 6 Hz, 3H), 5.23 (q, J = 6 Hz, 1H), 7.03-7.38 (m, 3H).

N-[1-(3-Thienyl)-1-ethyl]diethoxyacetamide (**12**).

2,2-Diethoxyacetamide (106.4 g, 0.723 mole) was added in portions to a suspension of sodium hydride (60% in oil-prewashed with pentane, 29.0 g, 0.726 mole) in tetrahydrofuran (500 ml). Chloride **11** (99.1 g, 0.676 mole) dissolved in tetrahydrofuran (200 ml) was added dropwise to this solution. Sodium iodide (10 g, 66.7 mmoles) was added and the mixture was heated to reflux for 24 hours. The solvent was evaporated *in vacuo*. Water was added to the oily residue and extracted with methylene chloride. The combined organic phases were dried over magnesium sulfate and the solvent was evaporated *in vacuo* to give an oil (155 g) which was purified by flash chromatography on silica gel 60 (1 kg) and eluted with 25% ethyl acetate in hexanes to give **12** (70 g, 38%) as an oil; ir (neat): 3440, 3320, 3000, 1690 and 1520 cm^{-1}; ms: m/z 257 (M^+); ^1H nmr: δ 1.22 and 1.23 each (t, J = 7 Hz, 3H), 1.57 (d, J = 7 Hz, 3H), 3.63 and 3.67 each (q, J = 7 Hz, 2H), 4.77 (s, 1H), 5.00-5.50 (m, 1H), 6.73 (br s, 1H), 6.97-7.37 (m, 3H).

Anal. Calcd. for $C_{12}H_{19}NO_3S$: C, 56.01; H, 7.44; N, 5.44; S, 12.46. Found: C, 56.06; H, 7.76; N, 5.37; S, 12.70.

4-Methylthieno[3,2-*c*]pyridin-6-ol (**3**, Method I).

Acetal **12** [12.0 g, 46.6 moles) was heated to reflux in 47% aqueous hydrobromic acid (40 ml) and glacial acetic acid (80 ml) for 15 minutes. The mixture was cooled to room temperature and a purple solid precipitated which was collected by filtration, washed with acetic acid and diethyl ether. It was then suspended in water, neutralized with solid sodium bicarbonate, filtered, washed with water and recrystallized from isopropanol. Product **3** was washed with isopropanol and diethyl ether to give an off-white solid, 2.6 g (34%), mp 225-227°; ir: 2300-3060, 1640 and 1585 cm^{-1}; ms: m/z 165 (M^+); ^1H nmr (trifluoroacetic acid): δ 3.05 (s, 3H), 7.60 and 7.75 each (d, J = 6 Hz, 1H), 7.65 (s, 1H).

Anal. Calcd. for C_8H_7NOS: C, 58.16; H, 4.27; N, 8.48; S, 19.41. Found: C, 58.09; H, 4.45; N, 8.24; S, 19.70.

1-(3-Thienyl)ethylazide (**13**).

A mixture of **11** (5.0 g, 34 mmoles) and sodium azide (2.65, 41 mmoles) in *N,N*-dimethylformamide was stirred at room temperature for 3 days. The reaction mixture was poured into water and extracted with methylene chloride. The organic extracts were washed with water, dried over magnesium sulfate and concentrated *in vacuo* to give **13** (5.02 g, 96%) as a brown oil which was used without further purification; ir (neat): 2110 cm^{-1}; ^1H nmr: δ 1.55 (d, J = 7 Hz, 3H), 4.67 (q, J = 7 Hz, 1H), 6.98-7.43 (m, 3H).

1-(3-Thienyl)ethylamine (**14**).

A solution of **13** (5.0 g, 32.6 mmoles) in diethyl ether (80 ml) was added to a suspension of LAH (1.7 g, 44.8 mmoles) in diethyl ether (80 ml) under a nitrogen atmosphere at such a rate as to maintain a gentle reflux. The reaction mixture was heated to reflux for an additional hour, water (2 ml), 15% sodium hydroxide (2 ml) and water (6 ml) were used in a standard workup to give **14** (3.7 g, 90%) as an amber oil; ir (neat): 1590, 2760-3660 and 2990 cm^{-1}; ms: m/z 127 (M^+); ^1H nmr: δ 1.42 (d, J = 6 Hz, 3H), 1.62 (s, 2H, exchanges with deuterium oxide), 4.20 (q, J = 6 Hz, 1H), 7.00-7.40 (m, 3H).

4-Methylthieno[3,2-*c*]pyridin-6-ol (**3**, Method II).

A standard solution of trimethylaluminum (2*N* in hexanes, 10 ml, 20 mmoles) was syringed into a solution of **14** (2.5 g, 20 mmoles) in methylene chloride (40 ml) at 0-5°. The solution was allowed to warm to room temperature over ½ hour. Ethyl 2,2-diethoxyacetate (3.6 ml, 20 mmoles) was added by syringe, the mixture was heated to reflux for 2 hours and 1*N* hydrochloric acid was carefully added until effervescence ceased. The organic layer was washed with water, 1*N* hydrochloric acid and dried over magnesium sulfate. The solvent was removed *in vacuo* to give an oil (5.05 g) as a mixture of **12** and ethyl 2,2-diethoxyacetate in a ratio of 3:1 as judged by tlc and ^1H nmr: analysis. This mixture, without further purification, was treated with 48% hydrobromic acid (20 ml) and glacial acetic acid (40 ml) and heated to reflux for 15 minutes. The mixture was cooled to room temperature and a precipitate was collected by filtration, washed with acetic acid and triturated with diethyl ether to give the hydrobromide salt of the product (2.7 g, 67% from **14**) as an off-white solid. The solid was suspended in water and neutralized with solid sodium bicarbonate. An off-white solid was collected by filtration, washed with water and triturated with refluxing isopropanol to give the **3** (1.45 g, 44% from **14**), mp 225-227°.

Bis[1-(3-thienyl)ethyl]amine (**15**).

Sodium cyanoborohydride (2.79 g, 44.5 mmoles) was added to a mixture of 3-acetylthiophene (6.23 g, 49.4 mmoles) and ammonium acetate (19 g, 0.25 mole) in methanol (200 ml). The mixture was stirred at room temperature for 16 hours, concentrated *in vacuo* and diluted with water. The aqueous layer was washed with methylene chloride and the combined organic layer was washed with water, dried over magnesium sulfate and concentrated. The residue was purified by medium pressure chromatography on silica gel 60 using 3% methanol in methylene chloride as the eluant to give **15** as an amber oil, 2.4 g (20%); ir (neat): 1449, 2965 cm^{-1}; ms: (DCI) m/z 238 (MH^+); ^1H nmr: δ 1.29 and 1.36 each (d, J = 6 Hz, 3H), 1.50 (br s, 1H, exchanges with deuterium oxide), 3.72 and 3.91 each (q, J = 6 Hz, 1H), 7.02-7.27 (m, 6H).

Anal. Calcd. for $C_{12}H_{15}NS_2$: C, 60.72; H, 6.37; N, 5.90. Found: C, 60.43; H, 6.45; N, 6.05.

1-(2,5-Dimethylthien-3-yl)chloroethane (**18**).

A solution of 2,5-dimethyl-3-acetylthiophene (**16**, 3.3 g, 21.7 mmoles) in diethyl ether (20 ml) was added slowly to a mixture of LAH (1.1 g, 2.9 mmoles) in diethyl ether (20 ml). The mixture was stirred 1 hour at room temperature and water (1.2 ml), 15% aqueous sodium hydroxide (1.2 ml) and water (3.5 ml) were added dropwise. The precipitate was removed by filtration and the filtrate dried over magnesium sulfate. The ethereal solution was treated with thionyl chloride (2.0 ml, 25.3 mmoles) and stirred at room temperature for 1 hour. The solution was extracted with saturated aqueous sodium bicarbonate and dried over magnesium sulfate. Removal of the solvent *in vacuo* at 25-30° gave **18** (3.6 g, 95%) as a brown oil; ir (neat): 2975, 2921 and 1445 cm^{-1}; ^1H nmr: δ 1.79 (d, J = 6 Hz, 3H), 2.34 (s, 3H), 2.39 (s, 3H), 5.13 (q, J = 6 Hz, 1H), 6.74 (s, 1H). This material was used in the next step without further purification.

1-(2,5-Dimethylthien-3-yl)ethylazide (**19**).

A solution of **18** (3.6 g, 20.6 mmole) and sodium azide (3.5 g, 53.8 mmoles) in *N,N*-dimethylformamide (50 ml) was stirred at room temperature for 3 days. The mixture was poured into water and the aqueous layer was extracted with diethyl ether; the organic layer was washed with water and dried over magnesium sulfate. Removal of the solvent *in vacuo* gave **19** as an amber oil which was used without further purification, 2.7 g (69%); ir (neat): 2977, 2921, 2101 and 1425 cm^{-1}; ^1H nmr: δ 1.44 (d, J = 7 Hz, 3H), 2.34 (s, 3H), 2.40 (s, 3H), 4.63 (q, J = 7 Hz, 1H), 6.65 (s, 1H).

1-(2,5-Dimethylthien-3-yl)ethylamine (**20**).

A solution of **19** (2.6 g, 14.3 mmoles) in diethyl ether (20 ml) was added

dropwise to a suspension of LAH (0.65 g, 17.1 mmole) in diethyl ether (30 ml). The mixture was heated at reflux for 1 hour and water (0.7 ml), 15% aqueous sodium hydroxide (0.7 ml) and water (2 ml) were used in a standard workup to give **20** as an oil which was used without further purification, 2.2 g (99%). Ms m/z 155 (M^+); ^1H nmr: δ 1.32 (d, J = 6 Hz, 3H), 1.42 (s, 2H, exchanges with deuterium oxide), 2.33 (s, 3H), 2.40 (s, 3H), 4.13 (q, J = 6 Hz, 1H), 6.67 (s, 1H).

N-[1-(2,5-Dimethylthien-3-yl)-1-ethyl]diethoxyacetamide (**21**).

A solution of trimethylaluminum in hexanes (2.0*N*, 6.8 ml, 13.6 mmoles) was added by syringe to a solution of **20** (2.1 g, 13.5 mmoles) in methylene chloride (30 ml) at 0-5°. After the mixture stirred for 0.5 hour, ethyl diethoxyacetate (2.5 ml, 13.6 mmoles) was added by syringe and the combined mixture was heated at reflux for 2 hours. Workup as for **3** in Method II gave a residue which was purified by flash chromatography on silica gel 60 using 25% ethyl acetate in hexanes to give **21** as a yellow oil, 2.3 g (60%). The analytical sample was prepared by distallation in a Kugelrohr apparatus at 183° (0.25 mm Hg); ir (neat): 3320, 2976, 2924, 1681 and 1516 cm^{-1}; ms (DCI): m/z 286 (MH^+); ^1H nmr: δ 1.23 (t, J = 7 Hz, 3H), 1.27 (t, J = 6 Hz, 3H), 1.44 (d, J = 6 Hz, 3H), 2.38 (s, 3H), 2.41 (s, 3H), 3.60 (m, 4H), 4.76 (s, 1H), 5.10 (m, 1H), 6.58 (s, 1H), 6.67 (br d, 1H, exchanges with deuterium oxide).

Anal. Calcd. for $C_{14}H_{23}NO_3S$: C, 58.92; H, 8.12; N, 4.91. Found: C, 58.94; H, 8.22; N, 5.01.

2-(2,5-Dimethyl-3-thienyl)-1-morpholino-1-thioxoethane (**23**).

A mixture of **16** (10.0 g, 64.8 mmoles), sulfur (3.35 g, 0.109 mole) and morpholine (13 ml, 0.149 mole) was heated to reflux for 16 hours. The mixture was poured into 1*N* hydrochloric acid and the product was extracted into methylene chloride, washed with 1*N* hydrochloric acid and dried over magnesium sulfate. The solvent was removed *in vacuo* to give an oil (17 g) which was purified by flash chromatography on silica gel 60 (300 g) and eluted with 15% ethyl acetate in hexanes to give thioamide **23** (11.5 g, 69%) as a yellow solid, mp 82-84°, lit[14] mp 76-77°; ir: 1487 and 1435 cm^{-1}; ms: m/z 255 (M^+); ^1H nmr: δ 2.30 (s, 3H), 2.37 (s, 3H), 3.32-3.85 (m, 6H), 4.08 (s, 2H), 4.25-4.45 (m, 2H), 6.55 (s, 1H).

Anal. Calcd. for $C_{12}H_{17}NOS_2$: C, 56.43; H, 6.71; N, 5.48; S, 25.11. Found: C, 56.75; H, 6.85; N, 5.27; S, 25.11.

Methyl 2,5-Dimethyl-3-thienylacetate (**24**).

A solution of **23** (79 g, 0.309 mole) and 50% aqueous sodium hydroxide (150 ml) in methanol (500 ml) was heated to reflux for 5 hours. The reaction mixture was concentrated *in vacuo*, diluted to 500 ml with water, and acidified with concentrated hydrochloric acid with cooling to give a yellow precipitate which was collected by filtration, washed with water and air dried to give the acid (34.4 g, 65%) as a yellow solid, mp 62-65° (lit [14 mp 69-70°); ir: 1705 cm^{-1}; ms: m/z 170 (M^+); ^1H nmr: δ 2.31 (s, 3H), 2.38 (s, 3H), 3.46 (s, 2H), 6.53 (s, 1H), 11.08 (br s, 1H, exchanges with deuterium oxide).

Anal. Calcd. for $C_8H_{10}O_2S$: C, 56.45; H, 5.92; S, 18.84. Found: C, 56.28; H, 5.98; S, 19.09.

A solution of 2,5-dimethyl-3-thiopheneacetic acid (34 g, 0.200 mole) and concentrated sulfuric acid (1.0 ml) in methanol (500 ml) was esterified using the procedure for **6a** to give **24** (33.2 g, 90%) as an oil; ir (neat): 1750 cm^{-1}; ms: m/z 184 (M^+); ^1H nmr: δ 2.32 (s, 3H), 2.38 (s, 3H), 3.45 (s, 2H), 3.67 (s, 3H), 6.53 (s, 1H).

Anal. Calcd. for $C_9H_{12}O_2S$: C, 58.67; H, 6.56; S, 17.40. Found: C, 58.77; H, 6.65; S, 17.29.

Methyl 2,5-Dimethyl-4-acetyl-3-thienylacetate (**25**).

A solution of **24** (33.2 g, 0.18 mole) in methylene chloride (150 ml) was added to a solution of acetyl chloride (15.5 ml, 0.216 mole) and tin(IV) chloride (23.2 ml, 0.198 mole) in methylene chloride at 0-5° over a 15 minute period. The solution became a deep red color and was stirred at 0-5° for 2 hours. Water was added to the mixture and the organic layer was separated, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate and treated with activated charcoal. The solvent was removed *in vacuo* to give **25** (40.2 g, 99%) as an oil which crystallized slowly on standing, mp 68-71°; ir: 1745 and 1650 cm^{-1}; ms: m/z 226 (M^+); ^1H nmr: δ 2.30 (s, 3H), 2.47 (s, 3H), 2.60 (s, 3H), 3.67 (s, 5H).

Anal. Calcd. for $C_{11}H_{14}O_3S$: C, 58.38; H, 6.24; S, 14.17. Found: C, 58.35; H, 6.02; S, 14.04.

1,3,4-Trimethylthieno[3,4-*c*]pyridin-6-ol (**22**) and 2,5-Dimethyl-4-acetyl-3-thiopheneacetamide (**26**).

A suspension of **25** (20.0 g, 88.4 mmoles) in concentrated ammonium hydroxide (250 ml) was stirred at room temperature for 5 days. A solid was collected by filtration and washed with water to give **22** (2.4 g, 14%) as a solid which was used without further purification, mp 226-230° dec; ir: 1640 cm^{-1}; ms (DCI): m/z 194 (MH^+); ^1H nmr (trifluoroacetic acid): δ 2.67 (s, 3H), 3.10 (s, 3H), 3.20 (s, 3H), 6.90 (s, 1H).

The aqueous filtrate was diluted to 200 ml with water and extracted with methylene chloride. The combined organic phase was dried over magnesium sulfate and concentrated to 200 ml, hexanes (100 ml) were added and the solution was cooled in an ice bath. Amide **26** (5.1 g, 27%) crystallized as a colorless solid, mp 123-125°; ir: 3410 and 1660 cm^{-1}; ms: (DCI) m/z 212 (MH^+); ^1H nmr: δ 2.38 (s, 3H), 2.52 (s, 3H), 2.60 (s, 3H), 3.48 (s, 2H), 5.60 (br s, 1H), 6.75 (br s, 1H).

Anal. Calcd. for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63; S, 15.18. Found: C, 56.61; H, 6.34; N, 6.58; S, 15.12.

1,3,4-Trimethylthieno[3,4-*c*]pyridin-6-ol (**22**).

A solution of **26** (2.4 g, 11.4 moles) in trifluoroacetic acid (25 ml) was stirred at room temperature for 16 hours. The solvent was removed *in vacuo*. The gummy residue was treated with water and neutralized with solid sodium bicarbonate. The brown solid was collected by filtration, washed with water and air dried to give **22** (2.1 g, 94%) identical to that isolated in the above procedure.

6-Acetoxy-1,3,4-trimethylthieno[3,4-*c*]pyridine (**27**).

A solution of **22** (5.7 g, 29.5 mmoles) and concentrated sulfuric acid (0.2 ml) in acetic anhydride (55 ml) was stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the residue was treated with a saturated aqueous sodium bicarbonate. The product was extracted into methylene chloride, washed with saturated aqueous sodium bicarbonate and dried over magnesium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel 60 (100 g) using 1% methanol in methylene chloride as eluant to give **27** (1.25 g, 18%); mp 127-130°; ir: 1755 and 1590 cm^{-1}; ms: (DCI) m/z 236 (MH^+); ^1H nmr: δ 2.33 (s, 3H), 257 (s, 3H), 2.83 (s, 3H), 2.90 (s, 3H), 6.76 (s, 1H).

Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.19; H, 5.72; N, 5.95.

4-Bromo-7-methylthieno[2,3-*c*]pyridin-5-ol (**28**).

Bromine (0.65 ml, 12.7 mmoles) was added to a solution of **2a** (2.00 g, 12.1 mmoles) and sodium acetate (1.5 g, 18.7 mmoles) in acetic acid (30 ml) at room temperature. A yellow solid precipitated. The reaction was stirred 1 hour at room temperature, the precipitate collected by filtration and was washed with acetic acid. The solid was triturated successively in water, acetone, and diethyl ether, collected by filtration and dried *in vacuo* to give **28** (1.72 g, 58%) as a yellow solid, mp 196-198° dec; ir: 1640 cm^{-1}; ms: m/z 243 (M^+); ^1H nmr: (trifluoroacetic acid); δ 3.00 (s, 3H), 7.71 and 8.45 each (d, J = 5 Hz, 1H).

Anal. Calcd. for C_8H_6BrNOS: C, 39.36; H, 2.48; N, 5.74; S, 13.14; Br, 32.73. Found: C, 39.17; H, 2.49; N, 5.62; S, 13.21; Br, 32.64.

4-Chloro-7-methylthieno[2,3-*c*]pyridin-5-ol (**29**).

N-Chlorosuccinimide (2.5 g, 18.7 mmoles) was added to a solution of **2a** (3.0 g, 18.2 mmoles) in acetic acid (50 ml) and the mixture was stirred for 4 hours. Solvent was removed *in vacuo*, the residue was triturated with water and collected by filtration. Trituration of the solid with hot ethanol gave **29**, 3.3 g (91%), as a yellow solid, mp 272-275°; ir: 1645, 1620, 1490 and 1460 cm^{-1}; ms: m/z 199 (M^+); ^1H nmr (dimethyl sulfoxide-d_6): δ 2.52 (s, 3H), 7.20 (d, J = 5 Hz, 1H), 8.07 (d, J = 5 Hz, 1H), 12.10 (br

s, 1H).

Anal. Calcd. for C_8H_6ClNOS: C, 48.13; H, 3.03; N, 7.02. Found: C, 48.13; H, 3.00; N, 7.02.

7-Methyl-4-nitrothieno[2,3-*c*]pyridin-5-ol (**30**).

Nitric acid (90%, 3.2 ml, 75 mmoles) was added over a period of 3 minutes to a solution of **2a** (2.0 g, 12.1 mmoles) in acetic (25 ml) at 15°. A yellow solid precipitated. The mixture was stirred at room temperature for 20 minutes. The precipitate was collected by filtration, washed sparingly with acetic acid, triturated in diethyl ether, filtered and dried *in vacuo* to give **30** (1.70 g, 67%) as a bright yellow solid, mp 275-278° dec; ir: 1660, 1600 and 1490 cm^{-1}; ms: m/z 210 (M^+); ^1H nmr (trifluoroacetic acid): δ 3.28 (s, 3H), 8.65 and 8.95 each (d, J = 5 Hz, 1H).

Anal. Calcd. for $C_8H_6N_2O_3S$: C, 45.71; H, 2.88; N, 13.33; S, 15.25. Found: C, 45.64; H, 2.89; N, 13.26; S, 15.19.

7-Bromomethyl-4-bromothieno[2,3-*c*]pyridin-5-ol (**31**).

Bromine (1.3 ml, 25.4 mmoles) was added dropwise to a solution of **2a** (2.0 g, 12.1 mmoles) and sodium acetate (6.6 g, 48.5 mmoles) in acetic acid (45 ml). Within minutes a yellow solid had precipitated. The reaction mixture was stirred at room temperature for 2 hours, and the solid was collected by filtration, washed with acetic acid, diethyl ether and air dried to give **31** (1.78 g, 46%) as a yellow solid, mp 185-186° dec; ir: 1625, 1590 and 1540 cm^{-1}; ms: m/z 321 (M^+); ^1H nmr (dimethylsulfoxide-d_6): δ 4.78 (s, 2H), 7.33 and 8.17 each (d, J = 5 Hz, 1H).

Anal. Calcd. for $C_8H_5Br_2NOS$: C, 29.75; H, 1.56; N, 4.34. Found: C, 29.43; H, 1.24; N, 4.23.

7-Bromomethyl-4-ethylthieno[2,3-*c*]pyridin-5-ol (**32**).

Bromine (0.42 ml, 8.19 mmoles) was added dropwise to a solution of **2b** (1.5 g, 7.76 mmoles) and sodium acetate (1.58 g, 11.6 mmoles) in acetic acid (40 ml). The solution was stirred at room temperature for 0.5 hour, the solvent was removed *in vacuo* and the residue was triturated with water and air dried. After trituration with diethyl ether and refluxing ethanol, the solid was dried *in vacuo* to give **32** (1.1 g, 52%) as yellow needles, mp 164-166°; ir: 2975, 1645, 1630, 1580 and 1410 cm^{-1}; ms: m/z 271 (M^+); ^1H nmr (dimethyl sulfoxide-d_6): δ 1.13 (t, J = 7 Hz, 3H), 2.82 (q, J = 7 Hz, 2H), 4.75 (s, 2H), 7.47 and 7.98 each (d, J = 5 Hz, 1H), 9.57 (br s, 1H).

Anal. Calcd. for $C_{10}H_{10}BrNOS$: C, 44.13; H, 3.70; N, 5.15; S, 11.78; Br, 29.36. Found: C, 43.89; H, 3.67; N, 5.23; S, 11.98; Br, 29.01.

4-Amino-7-methylthieno[2,3-*c*]pyridin-5-ol (**33**).

Compound **30** (2.5 g, 11.9 mmoles) was suspended in methanol (150 ml) containing Pd/C (10%, 250 mg) and was hydrogenated at 40 psi for 30 minutes in a Parr apparatus. The mixture was filtered through celite, and the collected solid was washed with methanol. The filtrates were concentrated to 50 ml *in vacuo* and a solid crystallized from solution. The yellow crystals were collected by filtration, washed with cold methanol and air dried to give **33** (1.4 g, 64%) as a tan solid, mp 203-205° dec; ir: 1635 and 1440 cm^{-1}; ms: m/z 180 (M^+); ^1H nmr (dimethyl sulfoxide-d_6): δ 2.33 (s, 3H), 5.23 (br s exchanges in deuterium oxide, 2H), 7.28 and 7.48 each (d, J = 6 Hz, 1H), 11.8 (br s, exchanges in deuterium oxide, 1H).

Anal. Calcd. for $C_8H_8N_2OS \cdot \frac{1}{4}H_2O$: C, 52.02; H, 4.64; N, 15.16. Found: C, 52.18; H, 4.49; N, 15.05.

4-Acetamido-7-methylthieno[2,3-*c*]pyridin-5-ol (**34**).

Acetic anhydride (1.1 ml, 11.7 mmoles) was added to a solution of **33** (2.0 g, 11.1 mmoles) in acetic acid (15 ml). The solultion was stirred ½ hour at room temperature and the solvent removed *in vacuo* at 40°. The yellow solid residue was triturated successively with acetone, refluxing methanol and diethyl ether to give **34** (1.8 g, 72%) as a yellow solid, mp >290°; ir: 3280, 1635 and 1530 cm^{-1}; ms: m/z 222 (M^+); ^1H nmr (trifluoroacetic acid): δ 2.58 (s, 3H), 3.02 (s, 3H), 7.68 and 8.37 each (d, J = 5 Hz, 1H).

Anal. Calcd. for $C_{10}H_{10}N_2O_2S \cdot \frac{1}{4}H_2O$: C, 52.97; H, 4.67; N, 12.35. Found: C, 53.38; H, 4.39; N, 12.30.

5-Hydroxy-7-methyl-4-ureido[2,3-*c*]pyridine (**35**).

Sodium cyanate (0.865, 13 mmoles) was added to a solution of **33** (2.00 g, 11.1 moles) in acetic acid (25 ml). A yellow solid precipitated within 5 minutes. The mixture was stirred for 20 minutes and filtered. The solid product was triturated successively with water, acetone and diethyl ether and dried *in vacuo* to give **35** (1.81 g, 73%) as a yellow solid, mp 261-265° dec; ir: 3425, 3255, 1630 and 1540 cm^{-1}; ms: (DCI) m/z 224 (MH^+); ^1H nmr (trifluoroacetic acid): δ 3.02 (s, 3H), 8.25 (br s, 1H), 7.68 and 8.38 each (d, J = 5 Hz, 1H).

Anal. Calcd. for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82; S, 14.36. Found: C, 48.19; H, 3.86; N, 18.76; S, 14.40.

7-Bromo-4-methylthieno[3,2-*c*]pyridin-6-ol (**36**).

Bromine (0.45 ml, 8.77 mmoles) was added to a solution of **3** (1.38 g, 8.35 mmoles) and sodium acetate (1.7 g, 12.5 mmoles) in acetic acid. The mixture was worked up in a manner similar to that for **28** to give **36** (0.680 g, 32%) as an off-white solid, mp 206-208° dec; ir: 2300-3020, 1635 and 1540 cm^{-1}; ms: m/z 243 (M^+); ^1H nmr (trifluoroacetic acid): δ 3.00 (s, 3H), 7.73 (s, 2H).

Anal. Calcd. for C_8H_6BrNOS: C, 39.36; H, 2.48; N, 5.74; S, 13.14; Br, 32.73. Found: C, 39.54; H, 2.55; N, 5.74; S, 13.40; Br, 32.44.

7-Chloro-4-methylthieno[3,2-*c*]pyridin-6-ol (**37**).

N-Chlorosuccinimide (2.02 g, 15.1 mmoles) was added to a solution of **3** (2.5 g, 15.1 mmoles) in acetic acid (50 ml) and the mixture was worked up using the procedure for **29**. Trituration with hot ethanol gave **37** as an off-white solid, 2.35 g (78%), mp 258-260°; ir: 1649 cm^{-1}; ms: (DCI) m/z 200 (MH^+); ^1H nmr (trifluoroacetic acid): δ 3.06 (s, 3H), 7.67 (d, J = 6 Hz, 1H), 7.83 (d, J = 6 Hz, 1H).

Anal. Calcd. for C_8H_6ClNOS: C, 48.13; H, 3.03; N, 7.02; S, 16.06; Cl, 17.76. Found: C, 48.28; H, 3.14; N, 7.03; S, 16.00; Cl, 17.84.

4-Methyl-7-nitrothieno[3,2-*c*]pyridin-6-ol (**38**).

A solution of nitric acid (90%, 2.6 ml, 61 mmoles) in glacial acetic acid (5 ml) was added to a solution of **3** (2.15 g, 13.0 mmoles) in glacial acetic acid (30 ml) at 15-20°. A yellow solid precipitated immediately. The mixture was stirred for 15 minutes. The solid was collected by filtration, washed with acetic acid, triturated with refluxing ethanol, diethyl ether and dried *in vacuo* to give **38** (1.66 g, 61%), mp 260-273° dec; ir: 2500-3040, 1675 and 1610 cm^{-1}; ms: m/z 210 (M^+); ^1H nmr (trifluoroacetic acid): δ 3.20 (s, 3H), 7.82 and 7.98 each (d, J = 5 Hz, 1H).

Anal. Calcd. for $C_8H_6N_2O_3S$: C, 45.71; H, 2.88; N, 13.33; S, 15.25. Found: C, 45.76; H, 2.96; N, 13.33; S, 15.46.

7-Amino-4-methylthieno[3,2-*c*]pyridin-6-ol (**39**).

A suspension of **38** (6.5 g, 30.9 mmoles) in acetic acid (100 ml) was hydrogenated using 10% Pd/C as catalyst in a Parr shaker at 40 psi for 20 minutes. The catalyst was removed by filtration from the reaction mixture, and the solvent was removed *in vacuo* to give crude **39** (4.7 g, 84%) as a tan solid; ir: 1610, 1660 and 2300-3600 cm^{-1}; ms: m/z 180 (M^+); ^1H nmr (trifluoroacetic acid): δ 1.32 (s, 3H), 7.43-7.77 (m, 2H). This material was used directly in subsequent reactions without further purification.

7-Acetamido-4-methylthieno[3,2-*c*]pyridin-6-ol (**40**).

A suspension of **38** (3.0 g, 14.3 mmoles) and 10% Pd/C (300 mg) in acetic acid (25 ml) and acetic anhydride (25 ml) was treated with hydrogen at 40 psi in a Parr apparatus for 6 hours. The mixture was filtered, the filtrate concentrated *in vacuo* and diluted with water and the aqueous mixture was neutralized with aqueous sodium bicarbonate. The solid was collected by filtration, washed with water, air dried and eluted through silica gel 60 with 10% methanol in methylene chloride to give **40** as a pale yellow solid, 1.2 g (37%), mp 295-299°; ir: 1630, 1530 cm^{-1}; ms: (DCI) m/z 223 (MH^+); ^1H nmr (trifluoroacetic acid): δ 2.23 (s, 3H), 3.07 (s, 3H), 7.62 and 7.78 each (d, J = 6 Hz, 1H).

Anal. Calcd. for $C_{10}H_{10}N_2O_2 \cdot \frac{1}{4}H_2O$: C, 52.97; H, 4.67; N, 12.35; S, 14.14. Found: C, 52.82; H, 4.63; N, 12.20; S, 14.17.

6-Hydroxy-4-methyl-7-ureido[3,2-*c*]pyridine (**41**).

Sodium cyanate (0.50 g, 7.69 mmoles) was added to a solution of crude **39** (1.26 g, 7.00 mmoles) in acetic acid (30 ml) and an off-white solid precipitated. This mixture was stirred for 1 hour at room temperature. The solid was collected by filtration, washed with acetic acid, triturated with refluxing methanol, then refluxing diethyl ether and dried *in vacuo* to give **41** as a yellow solid, 0.798 g (51%), mp 294-297° dec; ir: 1525, 1620 and 2300-3100 cm^{-1}; ms: m/z 223 (M^+); ^1H nmr (trifluoroacetic acid): δ 3.02 (s, 3H), 7.63 and 7.77 each (d, J = 6 Hz, 1H).

Anal. Calcd. for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82. Found: C, 48.39; H, 4.31; N, 18.38.

5-Acetoxy-7-methylthieno[2,3-*c*]pyridine (**42a**).

A solution of **2a** (5.0 g, 30.3 mmoles) and concentrated sulfuric acid (3 drops) in acetic anhydride (50 ml) was stirred at room temperature for 16 hours. The mixture was poured into ice water, neutralized with sodium bicarbonate and was extracted with methylene chloride. The organic layer was washed with a saturated solution of sodium bicarbonate, dried over magnesium sulfate and treated with activated charcoal and evaporated *in vacuo* to give **42a** (3.9 g, 62%) as an amber oil; ir (neat): 3090, 1770 and 1585 cm^{-1}; ms: m/z 207 (M^+); ^1H nmr: δ 2.35 (s, 3H), 2.75 (s, 3H), 7.28 (d, superimposed on s, J = 5 Hz, 2H), 7.67 (d, J = 5 Hz, 1H).

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 57.95; H, 4.38; N, 6.76. Found: C, 57.70; H, 4.33; N, 6.72.

5-Acetoxy-4-ethyl-7-methylthieno[2,3-*c*]pyridine (**42b**).

A solution of **2b** (0.50 g, 2.59 moles) and concentrated sulfuric acid (1 drop) in acetic anhydride (5 ml) was stirred at room temperature for 16 hours. Extractive workup and elution through a magnesium silicate column gave an eluate which was concentrated to 10 ml, diluted with hexanes (20 ml) and the resultant solid was collected by filtration and washed with hexanes to give **42b** (0.36 g, 59%) as a colorless solid, mp 69-71°; ir: 3070 and 1770 cm^{-1}; ms: m/z 235 (M^+); ^1H nmr: δ 1.23 (t, J = 7 Hz, 3H), 2.38 (s, 3H), 2.27 (s, 3H), 2.82 (q, J = 7 Hz, 2H), 7.40 (d, J = 5 Hz, 1H), 7.68 (d, J = 5 Hz, 1H).

Anal. Calcd. for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57: N, 5.95; S, 13.63. Found: C, 61.09; H, 5.23; N, 5.98; S, 13.57.

5-Acetoxy-4-bromo-7-methylthieno[2,3-*c*]pyridine (**42c**).

A solution of **28** (3.0 g, 12.3 mmoles) and concentrated sulfuric acid (2 drops) in acetic anhydride (25 ml) was stirred at room temperature for 3 days. The reaction mixture was poured into ice water. A colorless solid precipitated which was collected by filtration, washed with water and air dried. This solid was dissolved in methylene chloride, treated with charcoal and precipitated by adding hexanes to give **42c** (2.14 g, 61%) as a colorless solid, mp 132-133°; ir: 3120 and 1770 cm^{-1}; ms: m/z 243 (M^+-$COCH_3$); ^1H nmr: δ 2.42 (s, 3H), 2.73 (s, 3H), 7.47 (d, J = 5 Hz, 1H), 7.78 (d, J = 5 Hz, 1H).

Anal. Calcd. for $C_{10}H_8BrNO_2S$: C, 41.98; H, 2.82; N, 4.89; Br, 27.92; S, 11.21. Found: C, 41.78; H, 2.86; N, 4.82; Br, 27.99; S, 11.13.

6-Acetoxy-4-methylthieno[3,2-*c*]pyridine (**43a**).

A solution of **3** (1.35 g, 8.17 mmoles) and concentrated sulfuric acid (2 drops) in acetic anhydride (10 ml) was stirred 16 hours at room temperature. Typical extractive workup gave an oil which crystallized slowly over several days. The solid was triturated in hexanes and collected by filtration to give **43a** (0.49 g, 29%), mp 38-40°; ir: 1765 cm^{-1}; ms: (DCI) m/z 208 (MH^+); ^1H nmr: δ 2.37 (s, 3H), 2.80 (s, 3H), 7.42 (s, 3H).

Anal. Calcd. for $C_{10}H_9NO_2S$: C, 57.95; H, 4.38; N, 6.76; S, 15.47. Found: C, 58.12; H, 4.39; N, 6.75; S, 15.37.

6-Acetoxy-7-bromo-4-methylthieno[3,2-*c*]pyridine (**43b**).

A mixture of **36** (1.8 g, 7.37 mmoles) and sulfuric acid (1 drop) in acetic anhydride (25 ml) was treated as for **43a** to give, after flash chromatography on silica gel 60 using 20% ethyl acetate in hexanes as the eluant, **43b** as a colorless solid, 1.1 g (53%); ir: 1764, 1567 cm^{-1}; ms: (DCI) m/z 286 (MH^+); ^1H nmr: δ 2.45 (s, 3H), 2.80 (s, 3H), 7.50 (s, 2H).

Anal. Calcd. for $C_{10}H_8BrNO_2S$: C, 41.98; H, 2.82; N, 4.89. Found: C, 41.58; H, 2.86; N, 4.86.

5-Methoxy-7-methylthieno[2,3-*c*]pyridine (**44**) and 6,7-Dimethyl-5-thieno[2,3-*c*]pyridone (**45**).

A mixture of **2a** (2.1 g, 12.7 mmoles) and sodium hydride (60% suspension in mineral oil, 520 mg, 13.0 mmoles, prewashed with hexanes) in *N,N*-dimethylformamide (30 ml) was stirred for 1 hour at room temperature. Methyl iodide was added, the mixture stirred 1 hour and poured into water. The aqueous layer was extracted with methylene chloride and the combined organic layer was washed with water, dried over magnesium sulfate and concentrated to give a semi-solid. Trituration with diethyl ether gave the pyridone **45** as a yellow solid, 1.2 g (52%), mp 184-186°; ir: 1640, 1535 cm^{-1}; ^1H nmr: δ 2.59 (s, 3H), 3.68 (s, 3H), 6.73 (s, 1H), 6.89 (d, J = 5.5 Hz, 1H), 7.44 (d, J = 5.5 Hz, 1H); ms: m/z 179 (M^+); Calcd. for C_9H_9NOS: 179.0398; Found: 179.0391.

The diethyl ether solution was evaporated *in vacuo* to give **44** as an amber oil, 0.6 g (28%); ir: 1595, 1560 cm^{-1}; ms: m/z 179 (M^+); ^1H nmr: δ 2.70 (s, 3H), 3.97 (s, 3H), 6.90 (s, 1H), 7.18 (d, J = 6 Hz, 1 Hz), 7.57 (d, J = 6 Hz, 1H).

Anal. Calcd. for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.31; H, 5.13; N, 7.60.

6-Methoxy-4-methylthieno[3,2-*c*]pyridine (**46**) and 4,5-Dimethyl-6-thieno-[3,2-*c*]pyridone (**47**).

A mixture of **3** (4.3 g, 26 mmoles), sodium hydride (60% suspension in mineral oil, 1.1 g, 27.5 mmoles, prewashed with hexanes) and methyl iodide (1.79 ml, 28.7 mmoles) in DMF (50 ml) was reacted as above to give pyridone **47** as a yellow solid after trituration with diethyl ether and chromatography on silica gel 60 using 3% methanol in methylene chloride, 1.7 g (36%), mp 128-131°; ir: 1643, 1561 cm^{-1}; ms: (DCI) m/z 180 (MH^+); ^1H nmr: δ 2.64 (s, 3H), 3.68 (s, 3H), 6.81 (s, 1H), 6.88 (d, J = 6 Hz, 1 Hz), 6.96 (d, J = 6 Hz, 1H).

Anal. Calcd. for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.31; H, 5.09; N, 7.63.

The diethyl ether solution from trituration was evaporated *in vacuo* to give the ether **46** as an oil which crystallized slowly on standing, 1.0 g (21%), mp 45-48°; ir: 1593, 1549 cm^{-1}; ms: (DCI): m/z 180 (MH^+); ^1H nmr: δ 2.74 (s, 3H), 3.97 (s, 3H), 7.01 (s, 1H), 7.19 (d, J = 5 Hz, 1 Hz), 7.30 (d, J = 5 Hz, 1H). Exact mass Calcd. for C_9H_9NOS: 179.040; Found: 179.039.

Anal. Calcd. for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.95; H, 5.36; N, 7.97.

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