A Facile and Convenient Synthesis of 3-Alkylamino-5-arylthiophenes with a Variety of Substituents at C-2 and Studies of Reaction Mechanisms

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Thioaroylketene *S*,*N*-acetals were treated with active methylene compounds including *β*-keto ester, nitromethane, cyanoacetic acid, *p*-toluenesulfonylacetone, 4-nitrophenylacetic acid, and diethyl (2-oxopropyl)phosphonate in the presence of mercury(II) acetate in CH_2Cl_2 at room temperature. These reactions gave 3-alkylamino-5-arylthiophenes containing various substituents, which comprised, respectively, alkoxycarbonyl, nitro, cyano, *p*-toluenesulfonyl, 4-nitrophenyl, and diethylphosphono groups at C-2 in good yields. The reaction of 3-methylamino-3-methylthio-1-phenylthioxopropene with malonic acid or Meldrum's acid under the same conditions gave 3-methylamino-5-phenylthiophene. Similarly, treatment of 3-methylamino-3-methylthio-1-phenylthioxopropene with various enolizable cyclic ketones such as 4-hydroxy-6-methyl-2-pyrone, homophthalic anhydride, 2-hydroxy-1,4-benzoquinone, and 1,3-diethyl-2-thiobarbituric acid gave thieno[3,2-*b*]pyridin-4-one, thieno[3,2-*c*]isoquinolin-5-one, thieno[3,2-*c*]benzazepine-1,6-dione, and thieno[3,2-*d*]pyrimidine-2,4-dione, respectively.

Introduction

Recently, we reported a new and useful synthetic method for 2-acyl- and 2-aroyl-3-alkylamino-5-arylthiophenes **2** and 3-alkylamino-5-aryl-2-(ethoxycarbonyl)thiophenes **3**, which involved the reactions of thioaroylketene *S*,*N*-acetals **1** with 1,3-diketones (X = COR^3, Y = R^4) and *β*-keto ester (X = CO_2Et, Y = Me), respectively, in the presence of $Hg(OAc)_2$ in CH_2Cl_2 at room temperature[1] (Scheme 1).

We have found that compounds **3** were also formed by treatment of **1** with diethyl 1,3-acetonedicarboxylate (X = CO_2Et, Y = CH_2CO_2Et), ethyl 3-nitrobenzoyl acetate (X = CO_2Et, Y = 3-$O_2NC_6H_4$), ethyl methanesulfonyl acetate, methyl phenylsulfinyl acetate, and triethyl phosphonoacetate under the conditions described above. Thus, it would be expected that compounds **1** act as promising starting materials for the synthesis of thiophene derivatives by introduction of one carbon unit to a C_3S chain.

We have extended the foregoing method to a wide variety of compounds bearing active methylene hydrogen atoms. The results are described herein.

Results and Discussion

(A) Synthesis and Structures. The reactions of **1a**−**d** with cyanoacetic acid (X = CN, Y = OH) (2−3 molar equiv) in the presence of $Hg(OAc)_2$ (1.5 molar equiv) in CH_2Cl_2 at room temperature gave 3-alkylamino-5-arylthiophene-2-carbonitriles **4a**−**d**. The reactions of **1a**,**e**,**f** with nitromethane (3 molar equiv) under the same conditions gave 3-alkylamino-5-aryl-2-nitrothiophenes **5a**−**c** (X = NO_2). Similar reaction of **1b** with ethyl nitroacetate (X = NO_2, Y = OEt) gave **5d** (Scheme 1). The results are summarized in Table 1.

Similarly, compound **1a** (Ar = Ph, R^1 = R^2 = Me) reacted with 4-toluenesulfonylacetone (*X* = 4-tosyl, Y = Me), 4-nitrophenylacetic acid (*X* = 4-$O_2NC_6H_4$, Y = OH), and bis(phenylsulfonyl)methane in the presence of $Hg(OAc)_2$ afforded the corresponding thiophenes having 4-tosyl (**6**), 4-nitrophenyl (**7**), and benzenesulfonyl (**8**) (X = $PhSO_2$) groups at C-2 (Table 2). In addition, the reaction with diethyl (2-oxopropyl)phosphonate (X = $PO(OEt)_2$, Y = Me) under the same conditions gave diethyl phosphonate **9**. However, the reaction with malonic acid (X = CO_2H, Y = OH) gave 3-methylamino-5-

Scheme 1

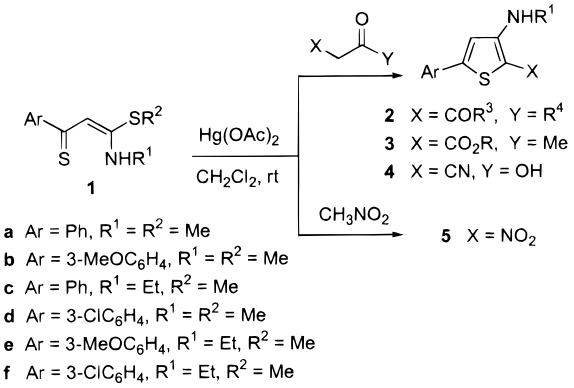

Table 1. Yields and Melting Points of 3-Alkylamino-5-arylthiophene-2-carbonitriles 4 and 3-Alkylamino-5-aryl-2-nitrothiophenes 5

compd	Ar	R^1	X	time (h)	yield[a] (%)	mp[b] (°C)
4a	Ph	Me	CN	3	69	110−111
4b	3-$MeOC_6H_4$	Me	CN	5	88	116−117
4c	Ph	Et	CN	3	71	95−96
4d	3-ClC_6H_4	Me	CN	4	89	146−147
5a	Ph	Me	NO_2	0.5	82	180 (sub)
5b	3-$MeOC_6H_4$	Et	NO_2	0.5	84	102−103
5c	3-ClC_6H_4	Et	NO_2	0.5	80	130−131
5d[c]	3-$MeOC_6H_4$	Me	NO_2	0.5	81	128−130

[a] Isolated yields. [b] Recrystallized from a mixture of EtOAc and *n*-hexane. [c] Compound **5d** was obtained by treatment of ethyl nitroacetate under the same conditions as for **5a**−**c**.

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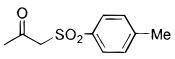
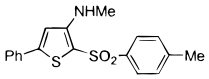
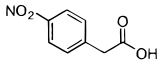
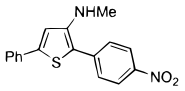
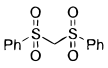
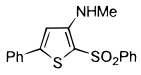
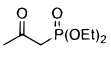
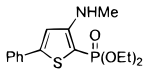
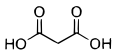
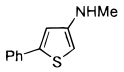
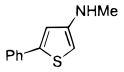
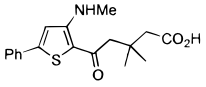
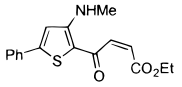
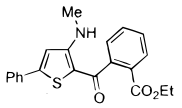
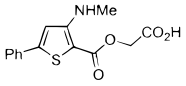
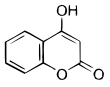
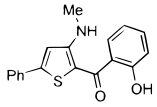
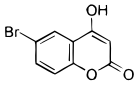
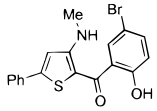
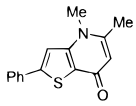
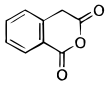
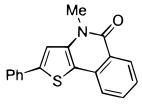
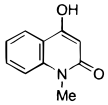
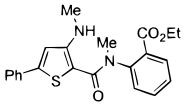
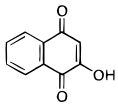
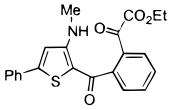
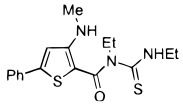
Table 2. Reactions of 1A with Active Methylene Compounds in the Presence of $Hg(OAc)_2$

entry	reagent	time (h)	product	yield[a] (%)	mp[b] (℃)
1		1	**6** 	90	liquid
2		10	**7** 	84	153-154
3		2	**8** 	92	liquid
4		1	**9** 	71	liquid
5		17	**10** 	30	40-41
6		4	**10** 	47	40-41
7		2	**11** 	52	liquid
8		1	**12**[c] 	74	liquid
9		3	**13**[c] 	82	liquid
10		3	**14** 	56	228-230
11		2	**15** 	69	120-121
12		2	**16** 	65	190-191
13		2	**17** 	37	184-185
14		1	**18** 	96	181-182
15		1	**19**[c] 	46	liquid
16		1	**20**[c] 	30	liquid
17		1	**21** 	61	liquid

[a] Isolated yields. [b] Recrystallized from a mixture of EtOAc and *n*-hexane. [c] Products from ethanolysis.

phenylthiophene (**10**) (X = H). Compounds **6**, **8**, and **9** were liquids, and compound **7** was a recrystallizable purple red solid.

Cyclic 1,3-diketones, which have enolizable hydrogen atoms, also undergo analogous reactions to give a variety of thiophene derivatives, **10**−**21**, which are collected in Table 2 (entries 6−17).

The structures of compounds **4**−**21** were determined on the basis of spectroscopic (IR, ^{1}H and ^{13}C NMR, MS) data and elemental analyses. Compounds **4**, **5**, and **10** may be prepared by methods described in the literature. However, it may be difficult to access compounds other than the foregoing, despite the availability of diverse synthetic methods for thiophene derivatives.[2] Treatment of the sodium salt of ethyl cyanoacetate with phenyl isothiocyanate gave the salt of the thioamide, which with bromonitromethane gave 3-amino-2-nitrothiophenes.[3] The method is now known as a practical method for the synthesis of 3-amino-2-nitrothiophenes. β-Chloro-α-cyanocinnamonitrile reacts with alkanethiol in the presence of K_2CO_3 to give 2-substituted 3-aminothiophenes in which the substituents may be CO_2Et, MeCO, PhCO, CN, and NO_2.[4] Treatment of *S*-acetylmercaptoacetonitrile with NaOEt (1 equiv) in EtOH, followed immediately by the addition of β-substituted acetylenic nitriles at −78 °C, gave 3-amino-5-aryl-(or alkyl)thiophene-2-carbonitriles.[5] There exist other methods which may be useful for the synthesis of 2-cyano- and 2-nitrothiophenes.[2] However, the methods are incompatible with the synthesis of compounds of the type **4** and **5**. The formation of thienylphosphonate has been seldom reported. Rearrangement of *O*,*O*-diisopropyl-*S*-(3-thienyl)thiophosphate to diisopropyl (3-mercapto-2-thienyl)phosphonate (47%) may be of practical use for synthesis.[6] However, the method is unrelated to the formation of **9**.

A number of methods have been used for the synthesis of 2-arylthiophenes: reaction of 2-thienylcopper with iodoarenes;[7] treatment of 1,4-diketones with phosphorus sulfide;[8] coupling reactions between 2-thienylmetal derivatives and halobenzenes under catalysts;[9] reaction of 1,4-diarylbutadiynes with arenemethanethiols in DMSO in the presence of KOH;[10] intramolecular reductive coupling of 3-thiapentane-1,5-diones;[11] copper(I) salt-promoted reaction of styryl bromides with dibenzoyl disulfides in a hot aprotic solvent;[12] heating α-bromoketones with Lawesson's reagent in benzene.[13] However, neither of these may be suitable for the synthesis of 3-amino-2-arylthiophenes.

Surprisingly, synthesis of even simple 3-aminothiophene has been achieved by a limited number of methods such as Hofmann rearrangement of thiophene-3-carboxamide,[2b] Beckman rearrangement of the 3-acetylthiophene oxime,[2b] or reduction of 3-nitrothiophene, which is prepared starting from 3-amino-2-thiophenecarboxylate.[14] In addition, the reaction of β-chlorocinnamonitriles with α-mercaptoacetic esters in the presence of a base gave 3-aminothiophenes **3** (R^1 = H, X = CO_2Me, CO_2Et).[15] 2-Alkylthio- or 2-arylthiothiophenes may be prepared by reaction of the lithio derivative with a disulfide.[2b] However, it would be difficult to obtain directly 3-alkylamino-2-arylsulfonylthiophene derivatives such as compounds **6** and **8**.

Compounds **13**, **15**, and **16** belong to the same class of compounds as compound **2**. However, a method for the synthesis of **2** may not be practicable because of the difficulty in synthesizing 1,3-diketones giving rise to the 2-ethoxycarbonylbenzoyl group of **13**, the 2-hydroxybenzoyl group of **15**, and the 5-bromo-2-hydroxybenzoyl group of **16**. There is one report which describes the synthesis of 2-thenoyl-4-ethylphenols from 2-hydroxy-5-ethylbenzoyl chloride and thiophene in the presence of $AlCl_3$ in CS_2. The reported yields were low (3-49%).[16]

(B) Reaction Mechanism. The formation of all of the compounds **4**−**21** may be explained by the same mechanism as that proposed previously for the formation of compounds **2** and **3**, which involved 2,2-disubstituted 3-methylimino-5-phenyl-2,3-dihydrothiophenes **26** as key intermediates.[1] Thus, the mechanism of the reactions with carbonyl compounds having active methylene hydrogen atoms may be described as shown in Scheme 2. Treatment of compound **1a** with $Hg(OAc)_2$ makes complex **22** having an iminothiolester functionality.[17] The electron-deficient imino carbon would be readily attacked by an enolic carbon to give intermediate **23**, which has an amino group and a methylthio group at the same carbon atom. Loss of a methanethiol molecule from **23** gives intermediate **24**, which undergoes tautomerization to give intermediate **25**. Intramolecular nucleophilic attack of the enolic carbon to sulfur, concomitant with the formation of mercury(0) and acetic acid, leads to key intermediate **26**. Subsequent hydrolysis of **26** gives thiophene derivatives.

Thus, compound **6** can be explained by hydrolysis (path a) of the acetyl group of the intermediate **26a** (X =

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(13) (a) Czogalla, C.-D.; Boberg, F. *Phosphorus Sulfur* **1988**, *35*, 67. (b) Boberg, F.; Schulz, J. *15th International Symposium on the Organic Chemistry of Sulfur*, Caen, 1992; Abstract, p 182.

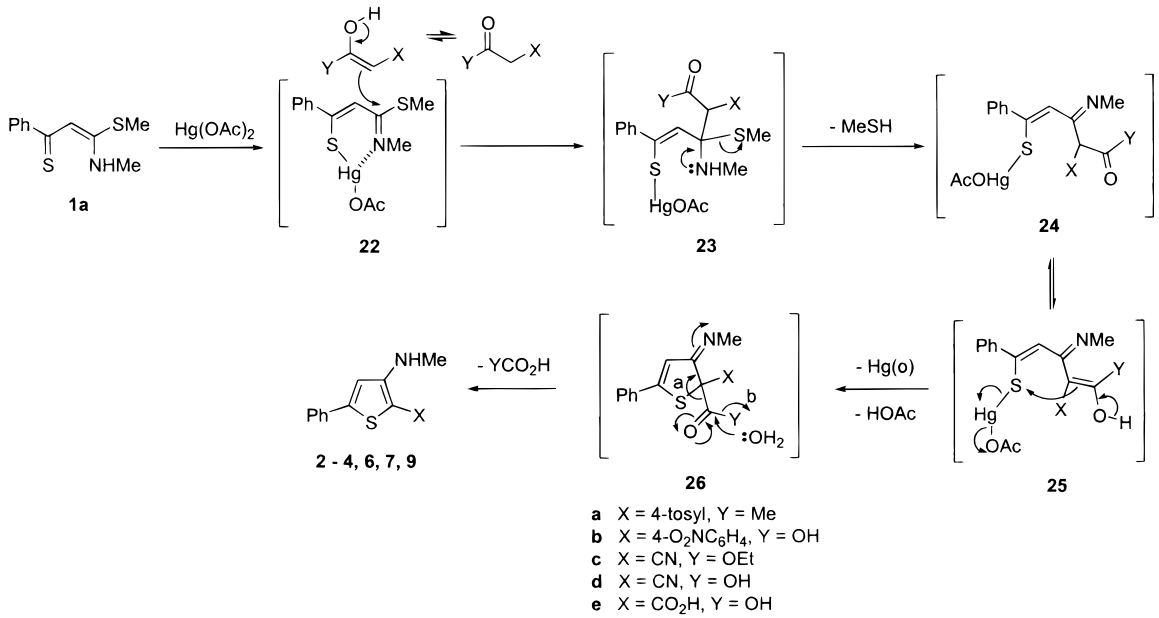
(14) Baker, J. M.; Huddleston, P. R.; Wood, M. L. *Synth. Commun.* **1995**, *25*, 3729.

(15) Hartmann, H. *Synthesis* **1984**, 275.

(16) Evans, D.; Cracknell, M. E.; Saunders: J. C.; Smith, C. E.; Williamson, W. R. N.; Dawson, W.; Sweatman, W. J. F. *J. Med. Chem.* **1987**, *30*, 1321.

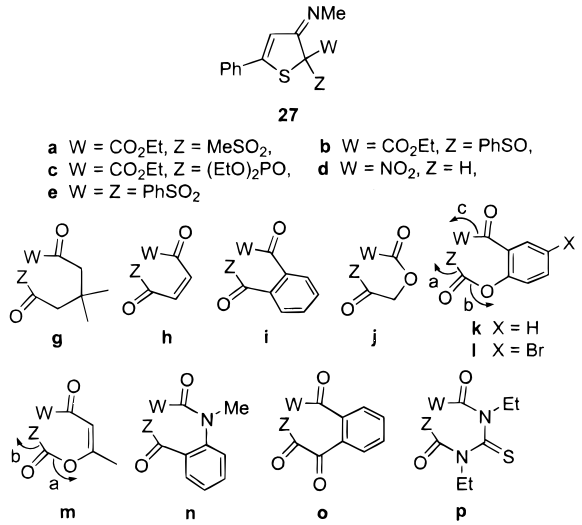
(17) One reviewer suggested an oxidation of **1** by $Hg(OAc)_2$ to a disulfide as an intermediate. The disulfide activated by a second molecule of $Hg(OAc)_2$ might be attacked by the enol.

Scheme 2



4-tosyl, Y = Me). The formation of **7** may be explained by the involvement of the intermediate **26b** (X = 4-$O_2NC_6H_4$, Y = OH), which undergoes decarboxylation (path a) to give **7**. Similarly, the reaction of **1a** with ethyl cyanoacetate (X = CN, Y = OEt) (1 molar equiv) under the same conditions gave 2,3-dihydrothiophene **26c** (96%), which was converted to **4a** (84%) during the chromatographic separation of the reaction mixture. The formation of **4a** via the intermediate **26c** indicates that detachment of an ethoxycarbonyl group in preference to a cyano group from **26c** occurs exclusively. For hydrolysis of **26c**, cleavage of the bond between the carbonyl carbon and C-2 of the thiophene ring to give directly **4a** (path a) is preferable to hydrolysis of the acyl−oxygen bond to give intermediate **26d** (X = CN, Y = OH) (path b). This is because the driving force for the cleavage of the carbon−carbon bond of **26c** leading to aromatic compound **4a** may be more important than hydrolysis leading to the formation of **26d**.

In the meantime, treatment of **1a** with ethyl methanesulfonyl acetate under the same conditions gave 2,3-dihydrothiophene **27a** along with **3a** (Ar = Ph, R^1 = Me)



in 64% and 16% isolable yields, respectively. Compound **27a** was readily converted to **3a** (91%) in stirred aqueous THF. The formation of **3a** via the intermediate **27a** along with a strong acidic solution (pH < 1) indicates that hydrolysis of **27a** takes place exclusively to eliminate the methanesulfonyl group. Similarly, compound **3a** obtained from the reactions with active methylene compounds, i.e., methyl phenylsulfinyl acetate and triethyl phosphonoacetate, may be formed via the formation of dihydrothiophenes **27b**,**c**, respectively. In this context, one can deduce the involvement of the intermediates **27d**,**e**, leading to compounds **5** and **8**, respectively.

The formation of 3-methylamino-5-phenylthiophene (**10**) would be explained by the involvement of the intermediate **26e** (X = CO_2H, Y = OH), which underwent decarboxylation, leading to 3-aminothiophene-2-carboxylic acid (**28**) (Scheme 3). This type of 3-aminothiophene-2-carboxylic acid has never been isolated.[14,18] Consequently, a rapid decarboxylation of **28** via 2,3-dihydrothiophene **29**, a tautomer of **28**, would result in compound **10**.

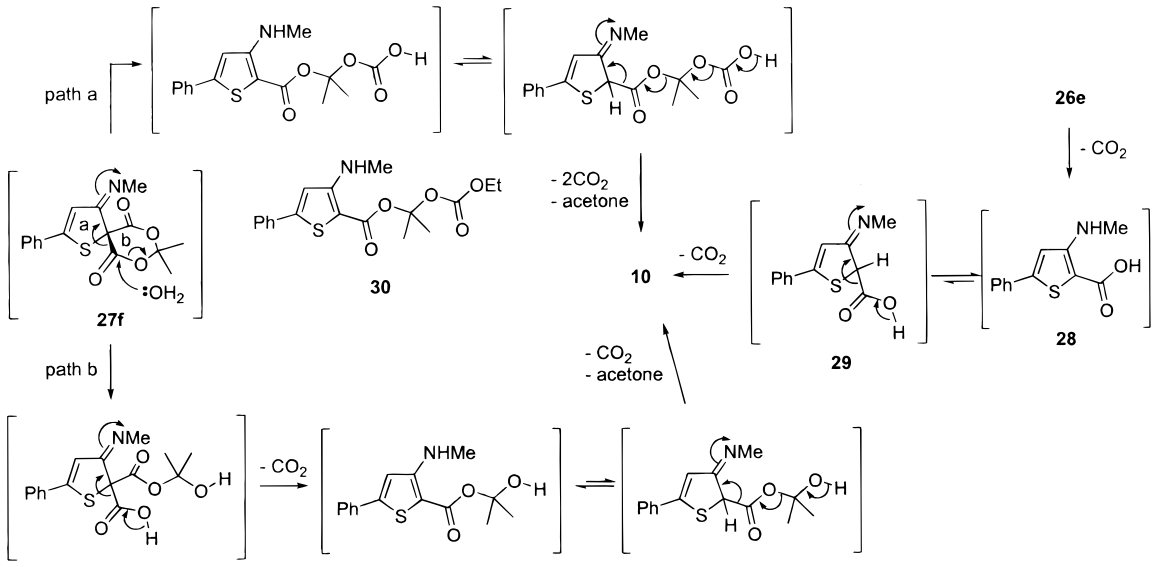
The reaction with Meldrum's acid under the same conditions gave **10** (47%), the formation of which can be explained by cleavage of a carbon−carbon bond (path a) of the intermediate **27f**, followed by decarboxylation and extrusion of acetone (Scheme 3). Alternatively, a series of reactions of the intermediate **27f**, i.e., hydrolysis, decarboxylation, and extrusion of acetone, can also give **10** (path b).

To obtain information about the cleavage of the bonds, EtOH was added to the stirred mixture of **1a**, Meldrum's acid, and $Hg(OAc)_2$ in CH_2Cl_2 for 10 min. The mixture was further stirred for 40 min. From the mixture were isolated **3a** (21%) and diester **30** (28%). The result suggests that both paths a and b are involved in this reaction.

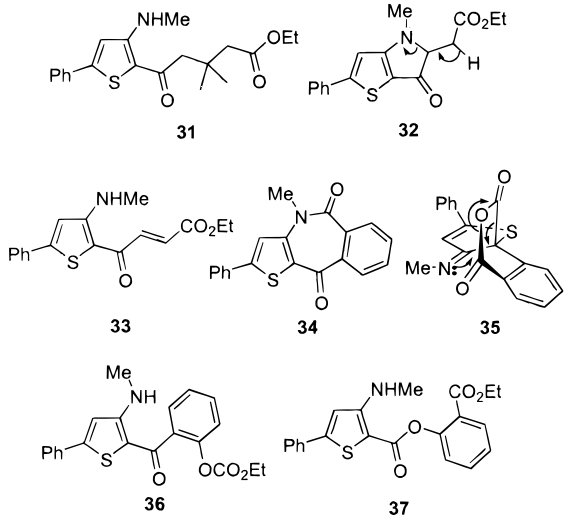
When **1a** was treated with dimedone in CH_2Cl_2 for 2 h under the foregoing conditions, followed by addition of a

(18) (a) 3-*tert*-Butoxyaminothiophene-2-carboxylic acid has been prepared: Galvez, C.; Garcia, F.; Garcia, J. *J. Chem. Res., Synop.* **1985**, 296. (b) Kirsch, G.; Cagniant, M. D.; Cagniant, P. *J. Heterocycl. Chem.* **1982**, *19*, 443.

Scheme 3



mixture of H_2O and THF (1:5), carboxylic acid **11** was isolated in 52% yield along with an unknown mixture. However, upon addition of EtOH to the foregoing mixture, compound **31** analogous to **30** was isolated in 72% yield. The observation can be understood by assuming the involvement of intermediate **27g** which undergoes either hydrolysis or ethanolysis to give **11** and **31**, respectively.



Similarly, treatment of **1a** with 4-cyclopentene-1,3-dione under the foregoing conditions, followed immediately by addition of ethanol, gave γ-keto-α,β-unsaturated ester **12** via the intermediate **27h**. The stereochemistry around the double bond of compound **12** should be retained, as was confirmed by measurement of the coupling constant between vinyl protons ($J_{HH} = 11.9$ Hz). Interestingly, heating **12** in ethanol at reflux caused the isomerization to trans isomer **33**, whose corresponding coupling constant was $J_{HH} = 15.2$ Hz.[19] The isomerization may be achieved by Michael-type intramolecular addition of the methylamino group of **12** to α,β-unsaturated ester to give thienopyrrolidinone **32**, which undergoes ring opening to give trans isomer **33**. This is presumably due not only to the formation of trans isomer being thermodynamically more stable but also to the recovery of delocalization energy in forming a conjugated system.

Treatment of **1a** with 1,3-indandione followed immediately by addition of ethanol gave 2-(2-thenoyl)benzoate **13** (82%) via intermediate **27i**. Heating compound **13** in EtOH at reflux did not give the cyclized product **34** (vide infra).

The reaction with tetronic acid under the foregoing conditions gave an interesting compound, **14** (56%), in which the alcohol oxygen of an ester is connected to the α-carbon of carboxylic acid. The reactions with 4-hydroxycoumarin and 6-bromo-4-hydroxycoumarin under the same conditions gave the 2-(2-thenoyl)phenol derivatives **15** and **16**, respectively.

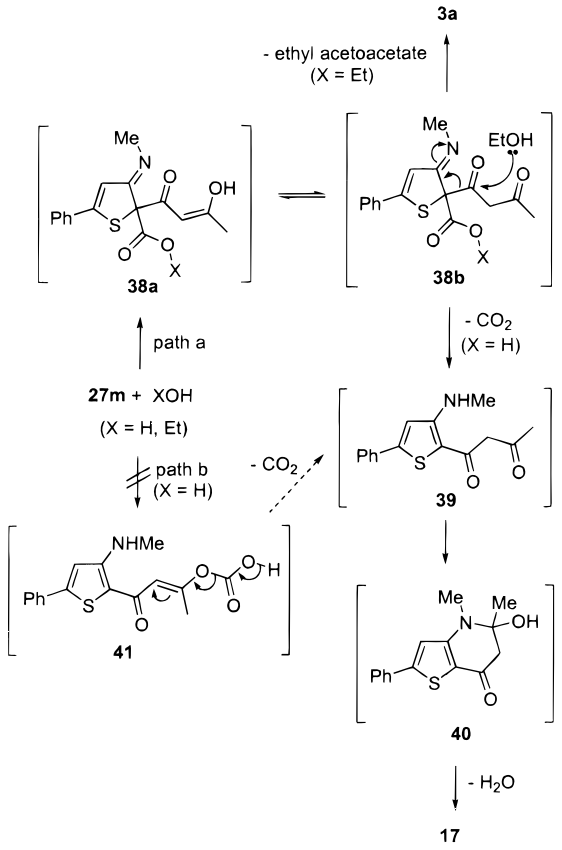
The intermediates **27j**, **27k**, and **27l** are involved in the formation of **14**, **15**, and **16**, respectively. The formation of **14** suggests that when a keto carbonyl and an ester carbonyl group are competitive in hydrolysis, hydrolysis of the former occurs exclusively, as was previously demonstrated in the reaction of **1** with β-keto esters (Scheme 1).[1,20] However, the opposite tendency was observed in the ethanolysis of 4-hydroxycoumarin, namely, that the treatment of **1a** with 4-hydroxycoumarin for 1 min under the foregoing conditions, followed by the addition of EtOH, gave 2-(ethoxycarbonyl)phenyl 2-thiophenecarboxylate **37** (7%) and ethyl carbonate **36** (84%). The result suggests that, for hydrolysis, a water molecule attacks predominantly the ester carbonyl carbon of the dihydrothiophene **27k**, followed by extrusion of CO_2 to give **15** (path a). An alternative path, b, showing the cleavage between the ester carbonyl carbon and phenolic oxygen is unlikely to be involved since no **3a** is isolated in this reaction. The isolation of **37** from the ethanolysis reaction mixture indicates that ethanol also attacks the keto carbonyl carbon (path c). However, an analogous product, benzoic acid derivative, could not be isolated from the hydrolysis reaction mixture.

The formation of **17** could be rationalized on the basis of the hydrolysis of the ester functionality of intermediate **27m**, which resulted in the intermediate **38a** (path a,

(19) Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*, 3rd ed.; McGraw-Hill: London, 1980; p 145.

(20) Harbuck, J. W.; Rapoport, H. *J. Org. Chem.* **1971**, *36*, 853.

Scheme 4

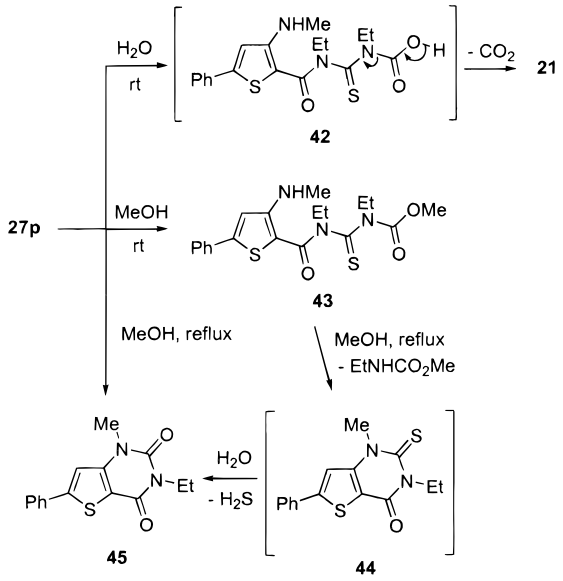


X = H) (Scheme 4). Decarboxylation of **38b** (X = H) concomitant with aromatization would give amino-1,3-diketone **39**. This readily undergoes intramolecular cyclization to give intermediate **40**, dehydration of which would give **17**. However, hydrolysis of **27m** leading to intermediate **41** (path b, X = H) was ruled out on the basis of the result that treatment of **1a** with 4-hydroxy-6-methyl-2-pyrone under the same conditions as for the reaction with 4-hydroxycoumarin involving **27k** gave **3a** (Ar = Ph, R^1 = Me) in 88% yield. This result suggests that the cleavage of the bond by a nucleophilic attack of ethanol follows path a to give intermediate **38** (X = Et), which undergoes ethanolysis to give **3a**. The fashion of the cleavage of the bond of **27m** is in contrast to that shown by intermediate **27k**. The exclusive cleavage of the bond by path a leading to **38b** (X = Et) may be due to the driving mechanism for the formation of 1,3-diketone via enol **38a**. However, for the case of the intermediate **27k**, the π-bond corresponding to the carbon−carbon double bond of **27m** is already part of the stable phenyl ring so that the double bond would not provide the driving force for cleavage by path b.

The formation of thienobenzoisoquinolinone **18** could be achieved via intermediate **35**, which undergoes an intramolecular nucleophilic attack of the imino nitrogen on the carbonyl carbon by forming a six-membered cyclic transition state concomitant with decarboxylation to give the product **18** (96%). The same reaction was performed in the presence of EtOH to trap the intermediate as an ester under the same conditions as in Scheme 3. However, only **18** was obtained in 91% yield.

The formation of *N*-methyl-*N*-(2-ethoxycarbonyl)phenyl-2-thiophenecarboxamide **19** could be achieved by ethanolysis of intermediate **27n**. This result indicates that

Scheme 5



ethanol attacks the keto carbonyl carbon in preference to the amide carbonyl carbon. This is presumably due to the character of the amide carbonyl carbon, which is less electron-deficient than the keto carbonyl carbon because of delocalization of the nonbonding electrons on the nitrogen atom. Similarly, the formation of α-keto ester **20** can be explained by nucleophilic attack of ethanol on the vicinal carbonyl carbon of the intermediate **27o**. Activation of a dipole−dipole repulsion arising from the vicinal carbonyl groups may be responsible for selective ethanolysis.[21] It is noteworthy that heating **20**, which bears an ethylbenzoylformate functional group in EtOH at reflux, leads to thienoazepinedione derivative **34**, whereas heating compound **13**, which has an ethyl benzoate functional group, under the same conditions did not give **34**. The structure of **34** was confirmed by X-ray crystallographic analysis.

Compound **21** is envisaged to be formed by decarboxylation of the intermediate **42**, which is formed by hydrolysis of intermediate **27p** (Scheme 5). However, methanolysis of intermediate **27p** gave two different products, **43** and **45**, depending upon the reaction temperature. Compound **43**, which is a type of carbamate, was formed at room temperature. Heating **43** in MeOH at reflux afforded **45** in 91% yield, presumably via the intermediate **44**. Methanolysis of **27p** at reflux afforded **45** in 43% yield. 3-(2-Hydroxyethyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione, which is analogous to compound **45**, was synthesized from 3-amino-2-(methoxycarbonyl)thiophene with ethyl chloroformate followed by ethanolamine.[22]

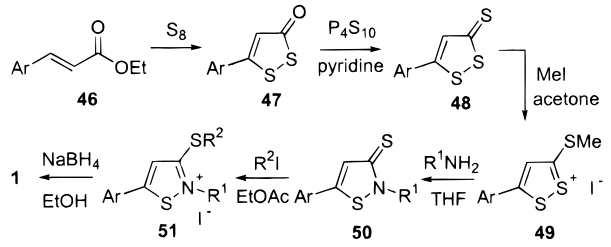
In conclusion, it has been found that thioaroylketene *S*,*N*-acetals are useful starting materials for the synthesis of 3-alkylamino-5-arylthiophenes having various substituents at C-2. Since the enol forms of active methylene compounds participate in the reactions, further study with a variety of enol ethers are worthwhile, and such investigations are in progress.

(21) Refer to equilibrium studies of water to ketones: Burkey, T. J.; Fahey, R. C. *J. Am. Chem. Soc.* **1983**, *105*, 868.

(22) Fukumi, H.; Sugiyama, M.; Sakamoto, T. *Chem. Pharm. Bull.* **1989**, *37*, 1197.

Experimental Section

General Procedures. NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard for ^1H (300 MHz) and solvent as the internal standard for ^{13}C (75 MHz), unless otherwise stated. GC−MS (EI) spectra were obtained at 70 eV. Elemental analyses were determined by the Inter-University Center for Natural Science Research Facilities, Seoul National University. Dichloromethane was distilled from calcium hydride prior to use. Column chromatography was conducted with silica gel (70−230 mesh, ASTM). Thioaroylketene *S*,*N*-acetals **1** were prepared by a procedure which was modified from the literature and described in this section.



5-Aryl-1,2-dithiole-3-ones 47. A mixture of compounds **46** (127−284 mmol) and sulfur (280−561 mmol) was heated for 2 h at 245−255 °C in a sand bath, and then cooled, followed by addition of CH_2Cl_2 (150−200 mL). The mixture was subsequently filtered. After removal of the solvent, the residue was recrystallized from a mixture of CH_2Cl_2 and MeOH (1:1) to give flesh-colored compounds **47** (40−52%).[23a]

5-Aryl-1,2-dithiole-3-thiones 48. A solution of **47** (51−103 mmol) and phosphorus pentasulfide (58−135 mmol) in pyridine (200−300 mL) was refluxed for 4 h, and then the mixture was worked up by the standard literature procedure to give the compounds **48** (79−88%).[23a]

5-Aryl-3-methylthio-1,2-dithiolium Iodides 49. A solution of **48** (45−76 mmol) and iodomethane (134−225 mmol) in acetone (200−250 mL) was stirred for 2 days at room temperature, filtered, and washed with acetone to give orange-colored compounds **49** (86−90%).[23b]

2-Alkyl-5-arylisothiazole-3-thiones 50. To a mixture of **49** (10−57 mmol) and catalytic amounts of iodine in THF (100−200 mL) at −30 °C was added alkylamine (12−68 mmol), and the resulting mixture was stirred for 30 min. The reaction mixture was warmed to room temperature, and extracted with Et_2O (40 mL × 3). After removal of the solvent, chromatography of the residue with a mixture of CH_2Cl_2, EtOAc, and *n*-hexane (1:1:2) gave the compounds **50** (47−63%).[23c]

2-Alkyl-3-alkylthio-5-arylisothiazolium Iodides 51. A solution of **50** (4.8−24 mmol) and alkyl iodide (20−99 mmol) in EtOAc (60−150 mL) was stirred for 2 days at room temperature. The solid formed was filtered and washed with Et_2O to give the yellow compounds **51** (82−88%).[23d]

1-Alkylamino-1-alkylthio-3-arylthioxopropenes 1. To a solution of **51** (4.4−20 mmol) in EtOH (40−100 mL) was added $NaBH_4$ (4.8−25 mmol) at room temperature, and the resulting solution was stirred for 20 min. The reaction mixture was extracted with Et_2O (30 mL × 3). After removal of the solvent, chromatography of the residue with a mixture of EtOAc and *n*-hexane (1:2) gave the compounds **1** (89−93%).[23e]

General Procedure for the Synthesis of 2-Substituted 3-Alkylamino-5-arylthiophenes. (i) To a mixture of ketene *S*,*N*-acetal (0.134−0.475 mmol) and an active methylene compound (0.134−0.476 mmol) in CH_2Cl_2 (8−20 mL) was added a slight excess of a molar equivalent of $Hg(OAc)_2$ (0.201−0.712 mmol). The mixture was stirred for an appropriate time (0.5−17 h) at room temperature, followed by filtration of mercury(0) and unreacted $Hg(OAc)_2$. The solids were washed with CH_2Cl_2. The solution was treated with brine and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was chromatographed on a silica gel column (2 × 20 cm) using a mixture of EtOAc and *n*-hexane (1:4). However, compound **5a** was eluted with a mixture of CH_2Cl_2, EtOAc, and *n*-hexane (1:1:4), compounds **5b**−**d** and **10** were eluted with EtOAc and *n*-hexane (1:2), compounds **7**, **9**, and **19** were eluted with EtOAc and *n*-hexane (1:1), and compound **12** was eluted with EtOAc and MeOH (9:1). All compounds were recrystallized from a mixture of EtOAc and *n*-hexane, except for **15**, which was recrystallized from a mixture of DMSO and Et_2O. (ii) As described in (i), to a mixture of **1**, an active methylene compound, and $Hg(OAc)_2$ in CH_2Cl_2 was additionally added EtOH. The mixture was worked up as usual to give ethyl esters **12**, **13**, **19**, **20**, **30**, **31**, **36**, and **37**. Reaction times, yields, and melting points of compounds **4** and **5** and compounds **6**−**21** are summarized in Tables 1 and 2, respectively.

Ethyl 3-methylamino-5-phenylthiophene-2-carboxylate (3a) was prepared by the general procedure i from 3-methylamino-3-methylthio-1-phenylthioxopropene (**1a**) and enolizable compounds which are diethyl 1,3-acetonedicarboxylate (X = CO_2Et, Y = CH_2CO_2Et), ethyl 3-nitrobenzoyl acetate (X = CO_2Et, Y = 3-$NO_2C_6H_4$), and ethyl methanesulfonyl acetate in 83%, 89%, and 74% yields, respectively: pale yellow solid; mp 55−57 °C; ^1H NMR δ 1.38 (t, J = 7.2 Hz, 3H), 3.04 (d, J = 5.2 Hz, 3H), 4.32 (q, J = 7.2 Hz, 2H), 6.70 (br s, 1H), 6.88 (s, 1H), 7.37−7.44 (m, 3H), 7.64−7.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.0, 32.1, 60.3, 98.3, 112.2, 126.4, 129.3, 129.3, 134.1, 150.0, 157.8, 165.4; IR (KBr) 3373, 1650 cm^{-1}; MS *m*/*z* 261 (M^+, 100). Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36; S, 12.30. Found: C, 64.05; H, 5.81; N, 5.25; S, 12.51.

Methyl 5-(3-anisyl)-3-methylaminothiophene-2-carboxylate (3b) was prepared by the general procedure i from 1-(3-anisyl)-3-methylamino-3-methylthiothioxopropene (**1b**) and methyl phenylsulfinyl acetate in 89% yield: pale yellow solid; mp 49−50 °C; ^1H NMR δ 3.02 (d, J = 5.0 Hz, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 6.67 (br s, 1H), 6.85 (s, 1H), 6.90 (dd, J = 7.8, 2.0 Hz, 1H), 7.14 (d, J = 2.0 Hz, 1H), 7.21−7.34 (m, 2H); IR (KBr) 3374, 1664 cm^{-1}; MS *m*/*z* 277 (M^+, 100). Anal. Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05; S, 11.56. Found: C, 60.56; H, 5.48; N, 5.13; S, 11.43.

Ethyl 5-(3-anisyl)-3-methylaminothiophene-2-carboxylate (3c) was prepared by the general procedure i from 1-(3-anisyl)-3-ethylamino-3-methylthiothioxopropene (**1e**) and triethyl phosphonoacetate in 82% yield: pale yellow solid; mp 77−78 °C; ^1H NMR gd 1.36 (t, J = 7.1 Hz, 3H), 3.02 (d, J = 5.1 Hz, 3H), 4.29 (q, J = 7.1 Hz, 2H), 6.67 (br s, 1H), 6.85 (s, 1H), 6.91 (dt, J = 8.0, 2.5 Hz, 1H), 7.15 (t, J = 2.0 Hz, 1H), 7.22−7.33 (m, 2H); IR (KBr) 3376, 1658 cm^{-1}; MS *m*/*z* 291 (M^+, 100). Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81; S, 11.01. Found: C, 61.76; H, 5.96; N, 4.95; S, 10.89.

3-Methylamino-5-phenylthiophene-2-carbonitrile (4a) was prepared by the general procedure i from **1a** and cyanoacetic acid (X = CN, Y = OH): pale yellow solid; ^1H NMR δ 3.03 (d, J = 5.2 Hz, 3H), 4.54 (br s, 1H), 6.73 (s, 1H), 7.28−7.63 (m, 5H); IR (KBr) 3356, 2178 cm^{-1}; MS *m*/*z* 214 (M^+, 100). Anal. Calcd for $C_{12}H_{10}N_2S$: C, 67.09; H, 4.73; N, 12.92; S, 14.96. Found: C, 67.26; H, 4.70; N, 13.07; S, 14.96.

5-(3-Anisyl)-3-methylaminothiophene-2-carbonitrile (4b) was prepared by the general procedure i from **1b** and cyanoacetic acid: pale yellow solid; ^1H NMR δ 2.96 (d, J = 5.1 Hz, 3H), 3.76 (s, 3H), 4.51 (br d, J = 4.5 Hz, 1H), 6.66 (s, 1H) 6.83−6.85 (m, 1H), 6.98−6.99 (m, 1H), 7.04−7.05 (m, 1H), 7.18−7.23 (m, 1H); IR (KBr) 3320, 2182 cm^{-1}; MS *m*/*z* 244 (M^+, 100). Anal. Calcd for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47; S, 13.12. Found: C, 63.98; H, 4.96; N, 11.42; S, 13.03.

3-Ethylamino-5-phenylthiophene-2-carbonitrile (4c) was prepared by the general procedure i from 3-ethylamino-3-methylthio-1-phenylthioxopropene (**1c**) and cyanoacetic acid: pale yellow solid; ^1H NMR δ 1.25 (t, J = 7.2 Hz, 3H), 3.40 (quintet, J = 7.2 Hz, 2H), 4.52 (br s, 1H), 6.71 (s, 1H), 7.22−7.67 (m, 5H); IR (KBr) 3320, 2180 cm^{-1}; MS *m*/*z* 228 (M^+, 59.9), 213 (100). Anal. Calcd for $C_{13}H_{12}N_2S$: C, 68.39; H, 5.30; N, 12.27; S, 14.04. Found: C, 68.46; H, 5.26; N, 12.14; S, 14.14.

(23) (a) Klingsberg, E. *J. Am. Chem. Soc.* **1961**, *83*, 2934. (b) Böttcher, B.; Lüttringhaus, A. *Annalen* **1947**, *557*, 89. (c) Mckinnon, D. M.; Hassan, M. E.; Chauhan, M. *Can. J. Chem.* **1974**, *52*, 1738. (d) Coustumer, G. L.; Mollier, Y. *Bull. Soc. Chim. Fr.* **1970**, 3076. (e) Kim, S. H.; Lee, Y. Y.; Kim, K.; Kim, J.-H. *Bull. Korean Chem. Soc.* **1994**, *15*, 237.

5-(3-Chlorophenyl)-3-methylaminothiophene-2-carbonitrile (4d) was prepared by the general procedure i from 1-(3-chlorophenyl)-3-methylamino-3-methylthiothioxopropene (**1d**) and cyanoacetic acid: pale yellow solid; ^{1}H NMR δ 3.05 (d, J = 5.2 Hz, 3H), 4.59 (br d, J = 4.1 Hz, 1H), 6.76 (s, 1H), 7.33−7.36 (m, 2H), 7.39−7.44 (m, 1H), 7.53 (m, 1H); IR (KBr) 3344, 2176 cm^{-1}; MS m/z 248 (M$^+$, 100). Anal. Calcd for $C_{12}H_9ClN_2S$: C, 57.95; H, 3.65; N, 11.26; S, 12.89. Found: C, 57.87; H, 3.64; N, 11.22; S, 12.84.

3-Methylamino-2-nitro-5-phenylthiophene (5a) was prepared by the general procedure i from **1a** and nitromethane: yellow solid; ^{1}H NMR δ 3.19 (d, J = 5.3 Hz, 3H), 6.83 (s, 1H), 7.44−7.49 (m, 3H), 7.64−7.68 (m, 2H), 8.07 (br s, 1H); IR (KBr) 3328, 1587 cm^{-1}; MS m/z 234 (M$^+$, 100). Anal. Calcd for $C_{11}H_{10}N_2O_2S$: C, 56.39; H, 4.30; N, 11.96; S, 13.69. Found: C, 56.32; H, 4.36; N, 11.95; S, 13.54.

5-(3-Anisyl)-3-ethylamino-2-nitrothiophene (5b) was prepared by the general procedure i from **1e** and nitromethane: yellow solid; ^{1}H NMR δ 1.37 (t, J = 7.2 Hz, 3H), 3.50 (quintet, J = 7.2 Hz, 2H), 3.86 (s, 3H), 6.79 (s, 1H), 6.99 (dd, J = 8.2, 2.3 Hz, 1H), 7.15 (t, J = 1.8 Hz, 1H), 7.20−7.38 (m, 2H), 8.04 (br s, 1H); IR (KBr) 3328, 1584 cm^{-1}; MS m/z 278 (M$^+$, 100). Anal. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06; S, 11.52. Found: C, 56.23; H, 5.10; N, 10.01; S, 11.44.

5-(3-Chlorophenyl)-3-ethylamino-2-nitrothiophene (5c) was prepared by the general procedure i from 1-(3-chlorophenyl)-3-ethylamino-3-methylthiothioxopropene (**1f**) and nitromethane: yellow solid; ^{1}H NMR δ 1.39 (t, J = 7.2 Hz, 3H), 3.52 (quintet, J = 7.2 Hz, 2H), 6.82 (s, 1H), 7.36−7.44 (m, 2H), 7.49−7.52 (m, 1H), 7.60 (m, 1H), 8.03 (br s, 1H); IR (KBr) 3332, 1585 cm^{-1}; MS m/z 282 (M$^+$, 31.6), 235 (100). Anal. Calcd for $C_{12}H_{11}ClN_2O_2S$: C, 50.98; H, 3.92; N, 9.91; S, 11.34. Found: C, 51.02; H, 4.02; N, 9.82; S, 11.36.

5-(3-Anisyl)-3-methylamino-2-nitrothiophene (5d) was prepared by the general procedure i from **1b** and ethyl nitroacetate (X = NO_2, Y = OEt): yellow solid; ^{1}H NMR δ 3.18 (d, J = 5.2 Hz, 3H), 3.83 (s, 1H), 6.83 (s, 1H), 6.97−6.99 (m, 1H), 7.12−7.13 (m, 1H), 7.20−7.34 (m, 2H), 8.05 (br s, 1H); IR (KBr) 3330, 1585 cm^{-1}; MS m/z 264 (M$^+$, 100). Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60; S, 12.13. Found: C, 54.42; H, 4.55; N, 10.55; S, 12.16.

3-Methylamino-5-phenyl-2-(4-tosyl)thiophene (6) was prepared by the general procedure i from **1a** and 4-toluenesulfonylacetone (X = 4-tosyl, Y = Me): colorless liquid; ^{1}H NMR δ 2.36 (s, 3H), 2.94 (d, J = 5.1 Hz, 3H), 5.95 (br, d, J = 4.9 Hz, 1H), 6.75 (s, 1H), 7.25 (d, J = 8.1 Hz, 2H), 7.31−7.37 (m, 3H), 7.50−7.53 (m, 2H), 7.83 (d, J = 8.1 Hz, 2H); IR (neat) 3392, 1286, 1136 cm^{-1}; MS m/z 343 (M$^+$, 100). Anal. Calcd for $C_{18}H_{17}NO_2S_2$: C, 62.95; H, 4.99; N, 4.08; S, 18.67. Found: C, 63.06; H, 4.94; N, 4.12; S, 18.71.

3-Methylamino-2-(4-nitrophenyl)-5-phenylthiophene (7) was prepared by the general procedure i from **1a** and 4-nitrophenylacetic acid (X = 4-$O_2NC_6H_4$, Y = OH): red solid; ^{1}H NMR δ 2.99 (s, 3H), 4.22 (br s, 1H), 7.03 (s, 1H), 7.35−7.43 (m, 3H), 7.61−7.67 (m, 4H), 8.23 (d, J = 7.1 Hz, 1H); IR (KBr) 3392, 1581, 1546, 1481, 1312, 1104 cm^{-1}; MS m/z 310 (M$^+$, 100), 280 (94.4). Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03; S, 10.33. Found: C, 65.71; H, 4.75; N, 8.79; S, 10.45.

2-Benzenesulfonyl-3-methylamino-5-phenylthiophene (8) was prepared by the general procedure i from **1a** and bis(phenylsulfonyl)methane: colorless liquid; ^{1}H NMR δ 3.52 (s, 3H), 5.03 (br s, 1H), 6.63 (s, 1H), 7.36−7.66 (m, 7H), 8.02 (d, J = 8.1 Hz, 2H); IR (neat) 3375, 1554, 1460, 1283, 1132, 1080 cm^{-1}; MS m/z 329 (M$^+$, 100). Anal. Calcd for $C_{17}H_{15}NO_2S_2$: C, 61.98; H, 4.59; N, 4.25; S, 19.47. Found: C, 61.88; H, 4.65; N, 4.32; S, 19.38.

Diethyl 3-methylamino-5-phenylthienylphosphonate (9) was prepared by the general procedure i from **1a** and diethyl (2-oxopropyl)phosphonate (X = $PO(OEt)_2$, Y = Me): colorless liquid; ^{1}H NMR δ 1.34 (t, J = 7.1 Hz, 6H), 2.95 (s, 3H), 4.1 (m, 4H), 6.09 (br s, 1H), 6.90 (d, J = 4.5 Hz, 1H), 7.31−7.42 (m, 3H), 7.59−7.63 (m, 2H); IR (neat) 3360, 1564, 1398, 1226, 1018 cm^{-1}; MS m/z 325 (M$^+$, 100). Anal. Calcd for $C_{15}H_{20}NO_3PS$: C, 55.37; H, 6.20; N, 4.30; S, 9.86. Found: C, 55.43; H, 6.24; N, 4.24; S, 9.82.

3-Methylamino-5-phenylthiophene (10) was prepared by the general procedure i from **1a** and enolizable compounds, which are malonic acid (X = CO_2H, Y = OH) (entry 5) and Meldrum's acid (entry 6): yellow solid; ^{1}H NMR δ 2.84 (s, 3H), 3.55 (br s, 1H), 5.92 (s, 1H), 6.86 (s, 1H), 7.24−7.40 (m, 3H), 7.54−7.60 (m, 2H); IR (neat) 3392 cm^{-1}; MS m/z 189 (M$^+$, 100). Anal. Calcd for $C_{11}H_{11}NS$: C, 69.80; H, 5.86; N, 7.40; S, 16.94. Found: C, 69.92; H, 5.84; N, 7.31; S, 16.93.

4-(3-Methylamino-5-phenylthenoyl)-3,3-dimethylbutanoic acid (11) was prepared by the general procedure i from **1a** and dimedone: yellow liquid; ^{1}H NMR δ 1.16 (s, 6H), 2.46 (s, 2H), 2.69 (s, 2H), 3.11 (d, J = 5.2 Hz, 3H), 6.89 (s, 1H), 7.38−7.45 (m, 3H), 7.64−7.67 (m, 2H), 8.53 (br s, 1H), 13.20 (br s, 1H); IR (neat) 3312, 2944, 1718, 1582 cm^{-1}; MS m/z 331 (M$^+$, 40.1), 216 (100). Anal. Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23; S, 9.67. Found: C, 65.28; H, 6.41; N, 4.20; S, 9.63.

***cis*-Ethyl 3-(3-methylamino-5-phenylthenoyl)-2-propenoate (12)** was prepared by the general procedure i from **1a** and 4-cyclopentene-1,3-dione: yellow liquid; ^{1}H NMR δ 1.23 (t, J = 7.2 Hz, 3H), 3.06 (d, J = 5.2 Hz, 3H), 4.20 (q, J = 7.2 Hz, 2H), 6.16 (d, J = 11.9 Hz, 1H), 6.73 (d, J = 11.9 Hz, 1H), 6.87 (s, 1H), 7.39−7.43 (m, 3H), 7.61−7.65 (m, 2H), 8.27 (br s, 1H); IR (neat) 3320, 1720, 1584 cm^{-1}; MS m/z 315 (M$^+$, 27.6), 242 (100). Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44; S, 10.17. Found: C, 64.66; H, 5.47; N, 4.39; S, 10.21.

Ethyl 2-(3-methylamino-5-phenylthenoyl)benzoate (13) was prepared by the general procedure ii from **1a** and 1,3-indandione: pale yellow liquid; ^{1}H NMR δ 1.94 (t, J = 7.1 Hz, 3H), 3.10 (d, J = 5.2 Hz, 3H), 4.24 (q, J = 7.1 Hz, 2H), 6.91 (s, 1H), 7.32−7.35 (m, 3H), 7.47−7.60 (m, 5H), 8.03 (br d, J = 8.0 Hz, 1H), 8.27 (d, J = 4.8 Hz, 1H); IR (neat) 3329, 1712, 1590 cm^{-1}; MS m/z 365 (M$^+$, 95.9), 292 (100). Anal. Calcd for $C_{21}H_{19}NO_3S$: C, 69.02; H, 5.24; N, 3.83; S, 8.77. Found: C, 69.15; H, 5.28; N, 3.80; S, 8.75.

3-Methylamino-5-phenyl-2-thenoyloxyacetic acid (14) was prepared by the general procedure i from **1a** and tetronic acid: pale yellow solid; ^{1}H NMR δ 3.06 (d, J = 4.8 Hz, 3H), 4.67 (s, 2H), 6.79 (d, J = 4.7 Hz, 1H), 7.18 (s, 1H), 7.37−7.47 (m, 3H), 7.71−7.74 (m, 2H), 12.86 (br s, 1H); IR (KBr) 3376, 1705, 1651 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81; S, 11.01. Found: C, 57.67; H, 4.51; N, 4.86; S, 11.09.

2-(3-Methylamino-5-phenyl-2-thenoyl)phenol (15) was prepared by the general procedure i from **1a** and 4-hydroxycoumarin: yellow solid; ^{1}H NMR δ 3.12 (d, J = 5.3 Hz, 3H), 6.91−6.93 (m, 1H), 6.92 (s, 1H), 7.00 (dd, J = 8.3, 1.0 Hz, 1H), 7.39−7.43 (m, 4H), 7.67−7.79 (m, 2H), 8.09 (dd, J = 8.0, 1.7 Hz, 1H), 8.85 (br d, J = 4.5 Hz, 1H), 11.72 (s, 1H); ^{13}C NMR δ 32.0, 107.0, 111.4, 118.5, 119.0, 122.6, 126.7, 129.5, 129.5, 130.3, 133.4, 133.9, 154.8, 161.2, 162.0, 188.3; IR (KBr) 3312, 1571 cm^{-1}; MS m/z 309 (M$^+$, 55.9), 189 (100). Anal. Calcd for $C_{18}H_{15}NO_2S$: C, 69.88; H, 4.89; N, 4.53; S, 10.36. Found: C, 69.75; H, 4.88; N, 4.56; S, 10.39.

4-Bromo-2-(3-methylamino-5-phenyl-2-thenoyl)phenol (16) was prepared by the general procedure i from **1a** and 6-bromo-4-hydroxycoumarin: yellow solid; ^{1}H NMR δ 3.15 (d, J = 5.2 Hz, 3H), 6.89 (d, J = 8.8 Hz, 1H), 6.93 (s, 1H), 7.43−7.48 (m, 4H), 7.68−7.72 (m, 2H), 8.18 (d, J = 2.4 Hz, 1H), 8.88 (br d, J = 4.5 Hz, 1H), 11.64 (s, 1H); IR (KBr) 3312, 1570 cm^{-1}; MS m/z 389 (M$^+$ + 2, 11.9), 387 (M$^+$, 11.8), 189 (100). Anal. Calcd for $C_{18}H_{14}BrNO_2S$: C, 55.68; H, 3.63; N, 3.61; S, 8.26. Found: C, 55.66; H, 3.65; N, 3.65; S, 8.19.

1,2-Dimethyl-6-phenylthieno[3,2-*b*]pyridin-4-one (17) was prepared by the general procedure i from **1a** and 4-hydroxy-6-methyl-2-pyrone: white solid; ^{1}H NMR δ 2.38 (s, 3H), 3.73 (s, 3H), 6.41 (s, 1H), 7.26−7.48 (m, 3H), 7.67 (d, J = 7.2 Hz, 2H); ^{13}C NMR δ 20.2, 32.1, 112.6, 116.6, 120.3, 126.5, 129.5, 129.6, 133.8, 144.1, 144.2, 147.6, 163.2; IR (KBr) 1635 cm^{-1}; MS m/z 255 (M$^+$, 100). Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.50; H, 5.12; N, 5.52; S, 12.61.

2-Methyl-4-phenylthieno[3,2-*c*]isoquinolin-1-one (18) was prepared by the general procedure i from **1a** and homophthalic anhydride: white solid; ^{1}H NMR δ 3.74 (s, 3H), 7.20 (s, 1H), 7.35−7.46 (m, 4H), 7.61−7.66 (m, 4H), 8.44 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 31.2, 112.1, 115.8, 121.3, 123.0, 125.1, 125.8, 127.9, 128.5, 128.5, 131.6, 131.8, 132.8, 139.7, 143.5, 161.3; IR (KBr) 1634 cm^{-1}; MS *m*/*z* 291 (M$^+$, 100). Anal. Calcd for $C_{18}H_{13}NOS$: C, 74.20; H, 4.50; N, 4.81; S, 11.01. Found: C, 74.22; H, 4.50; N, 4.77; S, 11.04.

***N*-[2-(Ethoxycarbonyl)phenyl]-*N*-methyl-2-(3-methylamino-5-phenyl)thiophenecarboxamide (19)** was prepared by the general procedure i from **1a** and 4-hydroxy-1-methyl-2(1*H*)-quinolone: colorless liquid; ^{1}H NMR δ 1.29 (t, J = 7.1 Hz, 3H), 2.98 (s, 3H), 3.35 (s, 3H), 4.29 (q, J = 7.1 Hz, 2H), 6.73 (s, 1H), 7.25−7.33 (m, 5H), 7.37−7.40 (m, 1H), 7.49−7.51 (m, 1H), 7.60−7.62 (m, 1H), 7.75 (br s, 1H), 7.99−8.01 (m, 1H); ^{13}C NMR δ 14.1, 31.7, 38.5, 61.5, 99.5, 111.1, 125.8, 128.4, 128.7, 128.7, 130.7, 131.7, 132.0, 133.4, 133.7, 143.4, 147.6, 158.5, 166.1; IR (neat) 3328, 1710, 1582 cm^{-1}; MS *m*/*z* 394 (M$^+$, 22.1), 216 (100). Anal. Calcd for $C_{22}H_{22}N_2O_3S$: C, 66.98; H, 5.62; N, 7.10; S, 8.13. Found: C, 66.92; H, 5.65; N, 7.18; S, 8.10.

Ethyl 2-(3-methylamino-5-phenyl-2-thenoyl)phenyl-oxoacetate (20) was prepared by the general procedure ii from **1a** and 2-hydroxy-1,4-naphthoquinone: yellow liquid; ^{1}H NMR δ 1.18 (t, J = 7.1 Hz, 3H), 3.10 (d, J = 5.2 Hz, 3H), 4.17 (q, J = 7.1 Hz, 2H), 6.94 (s, 1H), 7.40−7.44 (m, 3H), 7.59−7.70 (m, 4H), 7.75−7.77 (m, 1H), 7.99−7.82 (m, 1H), 8.61 (br d, J = 4.8 Hz, 1H); IR (KBr) 3312, 1696, 1584, 1370 cm^{-1}; MS *m*/*z* 393 (M$^+$, 13.4), 320 (100). Anal. Calcd for $C_{22}H_{19}NO_4S$: C, 67.16; H, 4.87; N, 3.56; S, 8.15. Found: C, 67.12; H, 4.85; N, 3.58; S, 8.22.

***N*-Ethyl-*N*′-ethyl-*N*′-(3-methylamino-5-phenyl-2-thenoyl)thiourea (21)** was prepared by the general procedure i from **1a** and 1,3-diethyl-2-thiobarbituric acid: yellow liquid; ^{1}H NMR δ 1.19 (t, J = 7.3 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H), 3.10 (d, J = 4.5 Hz, 3H), 3.66 (m, 2H), 4.40 (q, J = 7.0 Hz, 2H), 6.86 (s, 1H), 7.41−7.44 (m, 3H), 7.61−7.67 (m, 2H); ^{13}C NMR δ 14.2, 14.8, 32.1, 41.5, 46.8, 102.4, 111.5, 126.6, 129.5, 130.3, 133.2, 153.5, 161.4, 169.3, 183.0; IR (neat) 3340, 1594, 1509, 1368 cm^{-1}. Anal. Calcd for $C_{17}H_{21}N_3OS_2$: C, 58.76; H, 6.09; N, 12.09; S, 18.45. Found: C, 58.65; H, 6.05; N, 12.14; S, 18.52.

2-Cyano-2-ethoxycarbonyl-3-methylimino-5-phenyl-2,3-dihydrothiophene (26c). A stirred mixture of **1a** (52 mg, 0.233 mmol), ethyl cyanoacetate (26 mg, 0.230 mmol), and $Hg(OAc)_2$ (102 mg, 0.320 mmol) in CH_2Cl_2 for 1 h was worked up as usual. The mixture was extracted with ethyl ether (30 mL × 2). Evaporation of the solvent gave the crude compound **26c** (64 mg, 96%): colorless liquid; ^{1}H NMR δ 1.34 (t, J = 7.1 Hz, 3H), 3.44 (s, 3H), 4.36 (q, J = 7.1 Hz, 2H), 6.68 (s, 1H), 7.44−7.53 (m, 3H), 7.56−7.59 (m, 2H); IR (neat) 2240, 1747, 1632, 1556, 1229, 1018, 761 cm^{-1}; MS *m*/*z* 286 (M$^+$, 40.6), 213 (100).

2-Ethoxycarbonyl-2-methanesulfonyl-3-methylamino-5-phenyl-2,3-dihydrothiophene (27a). A stirred mixture of **1a** (43 mg, 0.193 mmol), ethyl (methanesulfonyl)acetate (30 mg, 0.181 mmol), and $Hg(OAc)_2$ (92 mg, 0.289 mmol) in CH_2Cl_2 for 3 h was worked up as usual. Chromatography (2 × 10 cm) of the reaction mixture using a mixture of EtOAc and *n*-hexane (2:1) gave **3a** (8 mg, 16%) and **27a** (42 mg, 64%): a colorless liquid; ^{1}H NMR δ 1.30 (t, J = 7.1 Hz, 3H), 3.39 (s, 3H), 3.47 (s, 3H), 4.35 (q, J = 7.1 Hz, 2H), 6.78 (s, 1H), 7.42−7.50 (m, 3H), 7.65−7.67 (m, 2H); IR (neat) 1734, 1310, 1141 cm^{-1}; MS *m*/*z* 339 (M$^+$, 3.8), 214 (100). Compound **27a** (42 mg, 0.124 mmol) was dissolved in a mixture of THF and H_2O (4:1) (5 mL). The pH of the solution was 7 at the beginning. pH = 2−3 in 24 h, and pH < 0 in 48 h. Evaporation of the solvent gave **3a** (29 mg, 58%).

(1-Ethoxycarbonyloxy-1-methyl)ethyl 3-methylamino-5-phenyl-2-thiophenecarboxylate (30) was prepared by the general procedure ii from **1a** and Meldrum's acid in 28% yield: pale yellow liquid; ^{1}H NMR δ 1.32 (t, J = 7.1 Hz, 3H), 1.97 (s, 6H), 3.01 (d, J = 5.2 Hz, 3H), 4.19 (q, J = 7.1 Hz, 2H), 6.68 (br s, 1H), 6.83 (s, 1H), 7.34−7.45 (m, 3H), 7.61−7.64 (m, 2H); IR (neat) 3376, 1752, 1663, 1570, 1133 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_5S$: C, 59.49; H, 5.82; N, 3.85; S, 8.82. Found: C, 59.57; H, 5.79; N, 3.86; S, 8.74.

Ethyl 4-(3-methylamino-5-phenyl-2-thenoyl)-3,3-dimethylbutanoate (31) was prepared by the general procedure ii from **1a** and dimedone in 72% yield: pale yellow liquid; ^{1}H NMR δ 1.19 (s, 6H), 1.27 (t, J = 7.1 Hz, 3H), 2.51 (s, 2H), 2.72 (s, 2H), 3.02 (d, J = 5.2 Hz, 3H), 4.13 (q, J = 7.1 Hz, 2H), 6.87 (s, 1H), 7.38−7.43 (m, 3H), 7.64−7.67 (m, 2H), 8.31 (br s, 1H); IR (neat) 3312, 1727, 1600 cm^{-1}; MS *m*/*z* 359 (M$^+$, 47.6), 216 (100). Anal. Calcd for $C_{20}H_{25}NO_3S$: C, 66.82; H, 7.01; N, 3.90; S, 8.92. Found: C, 66.78; H, 6.99; N, 3.95; S, 8.98.

***trans*-Ethyl 3-(3-Methylamino-5-phenyl-2-thenoyl)-2-propenoate (33).** A solution of **12** (42 mg, 0.133 mmol) in EtOH (15 mL) was heated for 1 day at reflux. Removal of the solvent in vacuo gave a residue which was chromatographed (2 × 20 cm) with a mixture of EtOAc and *n*-hexane (1:4) to give **33** (36 mg, 85%): yellow liquid; ^{1}H NMR δ 1.35 (t, J = 7.1 Hz, 3H), 3.10 (d, J = 5.3 Hz, 3H), 4.28 (q, J = 7.1 Hz, 2H), 6.86 (d, J = 15.2 Hz, 1H), 6.90 (s, 1H), 7.41−7.46 (m, 3H), 7.48 (d, J = 15.2 Hz, 1H), 7.66−7.70 (m, 2H), 8.75 (br s, 1H); IR (neat) 3296, 1715, 1584 cm^{-1}; MS *m*/*z* 315 (M$^+$, 27.8), 242 (100). Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44; S, 10.17. Found: C, 64.72; H, 5.47; N, 4.39; S, 10.21.

2-Methyl-4-phenylthieno[3,2-*c*]benzazepine-1,6-dione (34). A solution of **20** (22 mg, 0.056 mmol) in EtOH (15 mL) was heated for 2 days at reflux. Removal of the solvent in vacuo gave a residue which was chromatographed (2 × 20 cm) with a mixture of EtOAc and *n*-hexane (1:4) to give **34** (11 mg, 61%): white solid; recrystallized from a mixture of EtOAc and *n*-hexane; mp 172−173 °C; ^{1}H NMR δ 3.78 (s, 3H), 7.26 (s, 1H), 7.41−7.45 (m, 3H), 7.64−7.68 (m, 2H), 7.72−7.76 (m, 2H), 8.27−8.29 (m, 1H), 8.43−8.47 (m, 1H); ^{13}C NMR δ 38.3, 118.1, 126.5, 128.5, 129.3, 129.7, 130.2, 132.1, 133.0, 133.1, 133.5, 134.3, 135.3, 142.5, 151.9, 167.0, 181.8; IR (KBr) 1634, 1573 cm^{-1}; MS *m*/*z* 318 (M$^+$, 100). Anal. Calcd for $C_{19}H_{13}NO_2S$: C, 71.45; H, 4.10; N, 4.39; S, 10.04. Found: C, 71.38; H, 4.12; N, 4.36; S, 10.09.

Ethyl 2-(3-methylamino-5-phenyl-2-thenoyl)phenyl carbonate (36) was prepared by the general procedure ii from **1a** and 4-hydroxycoumarin in 84% yield: yellow liquid; ^{1}H NMR δ 1.30 (t, J = 7.1 Hz, 3H), 3.07 (d, J = 5.2 Hz, 3H), 4.26 (q, J = 7.1 Hz, 2H), 6.89 (s, 1H), 7.26−7.36 (m, 5H), 7.45−7.50 (m, 1H), 7.57−7.65 (m, 3H), 7.48 (br d, J = 5.1 Hz, 1H); IR (KBr) 3320, 1762, 1595, 1249 cm^{-1}; MS *m*/*z* 381 (M$^+$, 48.2), 292 (100). Anal. Calcd for $C_{21}H_{19}NO_4S$: C, 66.12; H, 5.02; N, 3.67; S, 8.41. Found: C, 66.24; H, 5.05; N, 3.62; S, 8.32.

2-(Ethoxycarbonyl)phenyl 2-(3-methylamino-5-phenyl)thiophenecarboxylate (37) was prepared by the general procedure ii from **1a** and 4-hydroxycoumarin in 7% yield: pale yellow liquid; ^{1}H NMR δ 1.20 (t, J = 7.1 Hz, 3H), 3.06 (d, J = 5.2 Hz, 3H), 4.27 (q, J = 7.1 Hz, 2H), 6.73 (br s, 1H), 6.91 (s, 1H), 7.21−7.43 (m, 5H), 7.58 (td, J = 7.8, 1.5 Hz, 1H), 7.69 (m, 2H), 8.04 (dd, J = 7.8, 1.7 Hz, 1H); IR (KBr) 3376, 1720, 1672, 1576 cm^{-1}. Anal. Calcd for $C_{21}H_{19}NO_4S$: C, 66.12; H, 5.02; N, 3.67; S, 8.41. Found: C, 66.06; H, 4.98; N, 3.71; S, 8.51.

***N*-Ethyl-*N*-methoxycarbonyl-*N*′-ethyl-*N*′-(3-methylamino-5-phenyl-2-thenoyl)thiourea (43).** To a stirred mixture of **1a** (40 mg, 0.179 mmol), 1,3-diethyl-2-thiobarbituric acid (39 mg, 0.195 mmol), and $Hg(OAc)_2$ (68 mg, 0.213 mmol) in CH_2Cl_2 for 40 min was added MeOH (10 mL). The mixture was stirred for 10 min and then worked up as usual. Chromatography (2 × 10 cm) of the reaction mixture using a mixture of EtOAc and *n*-hexane (1:2) gave **43** (32 mg, 44%): yellow liquid; ^{1}H NMR δ 1.28 (t, J = 7.0 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 3.08 (d, J = 5.2 Hz, 3H), 3.72 (m, 2H), 3.80 (q, J = 7.0 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 6.83 (s, 1H), 7.40−7.43 (m, 3H), 7.60−7.65 (m, 2H); ^{13}C NMR δ 13.1, 14.0, 32.0, 47.9, 48.3, 53.8, 103.6, 111.5, 126.6, 129.5, 130.3, 133.3, 153.4, 154.2, 161.2, 167.6, 187.4; IR (neat) 3344, 1722, 1618 cm^{-1}. Anal. Calcd for $C_{19}H_{23}N_3O_3S_2$: C, 56.27; H, 5.72; N, 10.36; S, 15.81. Found: C, 56.33; H, 5.70; N, 10.28; S, 15.86.

3-Ethyl-1-methyl-6-phenylthieno[3,2-*d*]pyrimidine-2,4-dione (45). (i) A solution of **43** (28 mg, 0.069 mmol) in MeOH (10 mL) was heated for 1 h at reflux, and then the reaction mixture was worked up as usual. Chromatography (1.5 × 20 cm) of the mixture using a mixture of EtOAc and *n*-hexane (1:2) gave **45** (19 mg, 91%). (ii) To a stirred solution of **1a** (41 mg, 0.184 mmol), 1,3-diethyl-2-thiobarbituric acid (40 mg, 0.200 mmol), and $Hg(OAc)_2$ (73 mg, 0.229 mmol) in CH_2Cl_2 for 1 h was added MeOH (10 mL), and the resulting solution was heated for 1.5 h at reflux. Chromatography (1.5 × 20 cm) of the reaction mixture as in i gave **45** (23 mg, 43%): white solid; recrystallized from a mixture of EtOAc and *n*-hexane; mp 209−211 °C; ^{1}H NMR δ 1.29 (t, J = 7.1 Hz, 3H), 3.62 (s, 3H), 4.12 (q, J = 7.1 Hz, 2H), 7.10 (s, 1H), 7.43−7.49 (m, 3H), 7.64−7.67 (m, 2H); ^{13}C NMR δ 13.6, 33.2, 37.4, 111.7, 112.2, 126.7, 129.7, 130.3, 133.0, 146.6, 152.1, 153.5, 158.2; IR (KBr) 1683, 1635 cm^{-1}; MS m/z 286 (M^+, 100). Anal. Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78; S, 11.20. Found: C, 62.88; H, 4.94; N, 9.87; S, 11.11.

X-ray Crystallographic Analysis of Compound 34. Single crystals of **34** were obtained from the concentrated solutions in EtOAc and *n*-hexane. The data were collected on an Enraf-Nomius CAD 4 diffractometer using graphite-monochromated Mo Kα radiation. The structures were inferred by direct methods and subsequent Fourier maps. Refinements were carried out by full-matrix least-squares techniques. Non-hydrogen atoms were anisotropically refined. Atomic scattering factors were taken from the *International Tables for X-ray Crystallography*, Vol IV, 1974. All calculations and drawings were performed using a Micro VAX II computer with an SDP system. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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Supporting Information Available: X-ray crystallographic data of **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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